

Edited by  
Alan B. Ettinger and  
Deborah M. Weisbrot

# Neurologic Differential Diagnosis

## A Case-Based Approach



[STORMRG]

# **Neurologic Differential Diagnosis**

**A Case-Based Approach**

---

# **Neurologic Differential Diagnosis**

## **A Case-Based Approach**

*Edited by*

Alan B. Ettinger, MD, MBA

*Epilepsy Director, Neurological Surgery P.C., Rockville Center, New York;  
Director of the Epilepsy Wellness Program, Winthrop University Hospital,  
Mineola, New York;*

*Director of EEG and Epilepsy, Huntington Hospital, Huntington, New York; and  
Professor of Clinical Neurology, Albert Einstein College of Medicine, Bronx,  
New York, USA*

Deborah M. Weisbrod MD

*Associate Professor of Clinical Psychiatry and Director, Child & Adolescent  
Psychiatry, Outpatient Clinic,  
Department of Psychiatry and Behavioral Sciences, Stony Brook University  
Medical Center, New York, USA*



**CAMBRIDGE**  
UNIVERSITY PRESS

[STORMRG]



University Printing House, Cambridge CB2 8BS, United Kingdom

Cambridge University Press is part of the University of Cambridge.  
It furthers the University's mission by disseminating knowledge in the pursuit of  
education, learning and research at the highest international levels of excellence.

[www.cambridge.org](http://www.cambridge.org)

Information on this title: [www.cambridge.org/9781107014558](http://www.cambridge.org/9781107014558)

© Cambridge University Press 2014

This publication is in copyright. Subject to statutory exception and to the provisions of relevant collective licensing agreements, no reproduction of any part may take place without the written permission of Cambridge University Press.

First published 2014

Printed and bound in the United Kingdom by TJ International Ltd. Cornwall

*A catalogue record for this publication is available from the British Library*

ISBN 978-1-10701455-8 Hardback

Cambridge University Press has no responsibility for the persistence or accuracy of URLs for external or third-party internet websites referred to in this publication, and does not guarantee that any content on such websites is, or will remain, accurate or appropriate.

Every effort has been made in preparing this book to provide accurate and up-to-date information which is in accord with accepted standards and practice at the time of publication. Although case histories are drawn from actual cases, every effort has been made to disguise the identities of the individuals involved.

Nevertheless, the authors, editors and publishers can make no warranties that the information contained herein is totally free from error, not least because clinical standards are constantly changing through research and regulation. The authors, editors and publishers therefore disclaim all liability for direct or consequential damage resulting from the use of material contained in this book. Readers are

**uamages resulting from the use of material contained in this book. Readers are strongly advised to pay careful attention to information provided by the manufacturer of any drugs or equipment that they plan to use.**

*This book is dedicated to our sons, Joshua and Jonathan Ettinger, with love. They have been our greatest teachers along the journey of life.*

# Contents

---

*List of contributors*

*Foreword*

*Preface*

*Acknowledgments*

## **Section 1 Differential Diagnosis of Abnormal Symptoms and Signs**

### **1 Introduction: localization and differential diagnosis in neurology**

Alan B. Ettinger and Deborah M. Weisbrot

### **2 Agitation**

Angela Scicutella and Durga Roy

### **3 Agnosias**

Marlene Behrman and Maxim D. Hammer

### **4 Anxiety and panic**

Kenneth R. Kaufman

### **5 Aphasia**

Gad E. Klein and Dragana Micic

### **6 Apraxia**

Jasvinder Chawla and Noam Epstein

### **7 Ataxia, acute or subacute**

Jay Elliot Yasen

### **8 Ataxia, subacute or chronic**

Amanda J. Thompson and S. H. Subramony

### **9 Attentional problems**

Lenard A. Adler, Thomas M. Boes, David M. Shaw, and Samuel Alperin

### **10 Autonomic failure or syndromes**

Rajpal Singh and Joe Colombo

### **11 Bulbar and pseudobulbar palsy**

Eric R. Eggenberger and David Clark

### **12 Catatonic-like states**

Edward Firouztaie

### **13 Chorea**

Ruth H. Walker

- 14 Coma**  
Galen V. Henderson and Alan B. Ettinger
- 15 Dementia**  
Howard Crystal and Diana Rojas-Soto
- 16 Depression**  
Yelizaveta Sher and John J. Barry
- 17 Diplopia**  
Deborah I. Friedman
- 18 Dissociative disorder**  
Danielle G. Koby and W. Curt LaFrance, Jr.
- 19 Dizziness**  
Martin Gizzi and Manpreet Multani
- 20 Drop attacks**  
Lourdes Bello-Espinosa
- 21 Dysarthria**  
David B. Rosenfield
- 22 Dysphagia**  
Jessica A. Shields and Anne L. Foundas
- 23 Dystonia**  
Ritesh A. Ramdhani and Steven J. Frucht
- 24 Eating disorders**  
Nina Kirz and Vandana Aspen
- 25 Eye movements, abnormal**  
Heather E. Moss
- 26 Falls**  
Christyn M. Edmundson and Steven A. Sparr
- 27 Foot drop**  
Pinky Agarwal and Ryan J. Zehnder
- 28 Gait abnormalities**  
Michael A. Williams and Scott E. Brown
- 29 Hallucinations, visual**  
Victoria S. Pelak
- 30 Headache**  
Ira M. Turner and Richard B. Lipton
- 31 Hearing deficit**  
David A. Gudis and Michael J. Ruckenstein
- 32 Hypersomnolence**  
Jeffrey S. Durmer and Heidi D. Riney
- 33 Incontinence**

- Cara Tannenbaum and Nelly Faghani
- 34 Mania and bipolar symptoms  
Christopher P. Kogut and James L. Levenson
- 35 Medically unexplained symptoms  
Eve G. Spratt and Ryan R. Byrne
- 36 Memory loss and cognitive decline – acute and subacute amnesia  
Max C. Rudansky, Jacques Winter, Alan Mazurek, Fawaz Al-Mufti, and Alan B. Ettinger
- 37 Mental status change, acute [and delirium]  
G. Bryan Young, Teneille G. Gofton, and Alan B. Ettinger
- 38 Movement disorders in psychiatric disorders  
Gregory M. Pontone
- 39 Movements, facial  
Kevin M. Biglan and Annie Killoran
- 40 Movements, focal, clonic  
Daniel J. Luciano and Siddhartha Nadkarni
- 41 Movements, complex motor activity  
Siddhartha Nadkarni and Daniel J. Luciano
- 42 Movements during sleep  
Michael J. Thorpy
- 43 Movements, tonic-clonic type  
Daniel J. Luciano and Siddhartha Nadkarni
- 44 Mutism  
Gaia Donata Oggioni and Alberto J. Espay
- 45 Myalgia, cramps  
Gary P. Kaplan and Rina Caprarella
- 46 Myoclonus  
Venkat Ramani, David Elliott Friedman, and Mehri Songhorian
- 47 Myotonia  
Beth Stein and Steven Herskovitz
- 48 Nystagmus  
Sarita B. Dave and Patrick J. M. Lavin
- 49 Ophthalmoparesis, gaze conjugate lateral deficit and conjugate vertical deficit  
Matthew J. Thurtell
- 50 Pain, arm  
Robert Duarte
- 51 Pain, back  
Michael Ronthal

- 52 Pain, eye**  
Mark Beyer and Deepak Grover
- 53 Pain, face**  
Egilius L. H. Spierings
- 54 Pain, neck**  
Louis J. Goodrich and Ajay Berdia
- 55 Papilledema**  
Don C. Bienfang
- 56 Paresthesias**  
George D. Baquis and Anant M. Shenoy
- 57 Parkinson's disease and related extrapyramidal syndromes**  
Oded Gerber, Fawaz Al-Mufti, and Alan B. Ettinger
- 58 Proptosis [exophthalmos]**  
Luis J. Mejico and Laryssa A. Huryn
- 59 Psychosis, thought disorder**  
Ramses Ribot and Andres M. Kanner
- 60 Ptosis**  
Andrew R. Harrison, Ali Mokhtarzadeh, and Juwan Park
- 61 Pupil constriction and Horner's syndrome**  
Robert C. Sergott and Scott Uretsky
- 62 Pupil dilation**  
Jade S. Schiffman, Rosa Ana Tang, Anastas F. Pass, and L. Anne Hayman
- 63 Respiratory difficulties, neurologic causes**  
Wan-Tsu W. Chang and Paul A. Nyquist
- 64 Retardation, mental**  
Tal Gilboa, Varda Gross-Tsur, Rolla Nuoman, and Alan B. Ettinger
- 65 Seizure**  
David J. Anschel
- 66 Sensory deficits and abnormal sensations**  
Paul W. Brazis
- 67 Sensory deficits in the face**  
Jeffrey A. Brown and Alan B. Ettinger
- 68 Smell deficit**  
Richard L. Doty and Hakan Tekeli
- 69 Spasm, hemifacial**  
Jagga Rao Alluri
- 70 Stroke and hemorrhage syndromes**  
George C. Newman and Aparna M. Prabhu

- 71 Stroke in adults, etiologies**  
Susan W. Law and Daniel M. Rosenbaum
- 72 Stroke in the young, etiologies**  
Walter J. Molofsky
- 73 Syncope**  
Todd J. Cohen
- 74 Tinnitus**  
Eric E. Smouha and Grace M. Charles
- 75 Tremor**  
Odi Oguh, Esther Baldinger, and Tanya Simuni
- 76 Vertigo**  
Maroun T. Semaan
- 77 Visual field deficits**  
Scott Uretsky
- 78 Visual loss, acute bilateral**  
Robert M. Mallory and Misha L. Pless
- 79 Visual loss, monocular**  
Jeffrey Peterson, Rehan Ahmed, and Rod Foroozan
- 80 Weakness, generalized acute**  
Denis Ostrovskiy
- 81 Weakness, hemiparesis**  
Amit M. Shelat, Shicong Ye, and Malcolm H. Gottesman
- 82 Weakness in the intensive care unit**  
John J. Halperin
- 83 Weakness, monomelic**  
Casey A. Chamberlain and Michael Andary
- 84 Weakness, neck**  
Sindhu Ramchandren and Aashit K. Shah
- 85 Weakness, paraparesis**  
Friedhelm Sandbrink
- 86 Weakness, proximal**  
Georgios Manousakis and Glenn Lopate

## **Section 2 Differential Diagnosis within Specific Localizations**

- 87 Cavernous sinus syndrome**  
Vladimir Dadashev, Jonathan L. Brisman, and John Pile-Spellman
- 88 Facial nerve palsy**  
Philip Ragone
- 89 Fourth nerve palsy**  
.....

Kristina Y. Pao and Mark L. Moster

[\*\*90 Myelopathy\*\*](#)

Amanda R. Bedford and Randall J. Wright

[\*\*91 Nerve, cranial: multiple deficit\*\*](#)

David Solomon and Jee Bang

[\*\*92 Neuropathy, axonal versus demyelinating\*\*](#)

Michael T. Pulley and Alan R. Berger

[\*\*93 Neuropathy, femoral\*\*](#)

Eva Sahay

[\*\*94 Neuropathy, median and carpal tunnel\*\*](#)

Huiying Yu

[\*\*95 Neuropathy, radial\*\*](#)

Padmaja Aradhya

[\*\*96 Neuropathy, sciatic\*\*](#)

Julius Bazan and Pedro J. Torrico

[\*\*97 Neuropathy, tibial\*\*](#)

Reema Maindiratta

[\*\*98 Neuropathy, ulnar\*\*](#)

Steven Ender

[\*\*99 Plexopathy, brachial\*\*](#)

Michael Amoashiy, Prajwal Rajappa, and Caitlin Hoffman

[\*\*100 Plexopathy, lumbar\*\*](#)

Jean Robert Desrouleaux and Alan B. Ettinger

[\*\*101 Radiculopathy\*\*](#)

Amtul Farheen and Bashar Katirji

[\*\*102 Sixth nerve palsy\*\*](#)

Scott Uretsky

[\*\*103 Third nerve palsy\*\*](#)

Claire A. Sheldon and Jason J. S. Barton

[\*\*\*Index\*\*\*](#)

## **Contributors**

---

### **Lenard A. Adler, MD**

Professor of Psychiatry and Child and Adolescent Psychiatry, NYU School of Medicine, New York, NY, USA

### **Pinky Agarwal, MD**

Attending Neurologist, Booth Gardner Parkinson's Center at Evergreen Hospital, Kirkland, WA, USA

### **Rehan Ahmed, MD**

Cullen Eye Institute, Baylor College of Medicine, Houston, TX, USA

### **Jagga Rao Alluri, MD**

Clinical Neurophysiologist, ABK Neurological Associates, Forest Hills, NY, USA

### **Fawaz Al-Mufti, MD**

Chief Resident, Department of Neurology, State University of New York at Stony Brook, Stony Brook University Medical Center, Stony Brook, NY, USA

### **Samuel Alperin, BS**

Department of Psychiatry, NYU School of Medicine, and Mental Health Research Service, VA NY Harbor Healthcare System, New York, NY, USA

### **Michael Amoashiy, MD, PhD**

Assistant Professor of Clinical Neurology, Weill Cornell Medical College, Brooklyn, NY, USA

### **Michael Andary, MD**

Professor and Residency Program Director, Michigan State University College of Osteopathic Medicine Department of Physical Medicine and

Rehabilitation, East Lansing, MI, USA

**David J. Anschel, MD**

Director, Comprehensive Epilepsy of Long Island, St Charles Hospital, Port Jefferson, NY, USA

**Padmaja Aradhy, MD**

Neurologist, Bethpage, NY, USA

**Vandana Aspen, PhD**

Postdoctoral Scholar, Stanford University, Stanford, CA, USA

**Esther Baldinger, MD**

Clinical Assistant Professor of Neurology, SUNY Downstate Medical Center, Brooklyn, NY, USA

**Jee Bang, MD**

Chief Resident, Department of Neurology, Johns Hopkins Hospital, Baltimore, MD, USA

**George D. Baquis, MD**

Head – Neuromuscular Section, Baystate Medical Center and Associate Clinical Professor of Neurology, Tufts University School of Medicine, Springfield, MA, USA

**John J. Barry, MD**

Professor of NeuroPsychiatry and Behavioral Science, Stanford University Medical Center, Stanford, CA, USA

**Jason J. S. Barton, MD, PhD, FRCPC**

Professor, Departments of Ophthalmology and Visual Sciences, Medicine (Neurology), and Psychology, University of British Columbia, Vancouver, Canada

**Julius Bazan, MD**

Neurologist, Rockville Centre, NY, USA

**Amanda R. Bedford, MA**

University of Houston-Clear Lake, American Washington University  
College of Law, Houston, TX, USA

**Marlene Behrman, PhD**

Professor, Department of Psychology and Center for the Neural Basis of Cognition, Carnegie Mellon University, Pittsburgh, PA, USA

**Lourdes Bello-Espinosa, MD**

Assistant Professor of Neurology and Pediatrics, Stony Brook University, Stony Brook, NY, USA

**Ajay Berdia, MD**

Neurologist, Rochester, NY, USA

**Alan R. Berger, MD**

Professor and Chairman, Department of Neurology, Interim Chairman, Department of Neurosurgery, Associate Dean for Research, University of Florida College of Medicine – Jacksonville, and Director, Neuroscience Institute, Shands Jacksonville, FL, USA

**Mark Beyer, DO**

Resident in Ophthalmology, Philadelphia College of Osteopathic Medicine, Philadelphia, PA

**Don C. Bienfang, MD**

Director of Neuro-ophthalmology, Brigham and Women's Hospital Assistant Professor, Harvard Medical School, Boston, MA, USA

**Kevin M. Biglan, MD, MPH**

Associate Chair for Clinical Research, Associate Professor of Neurology, Director, National Parkinson Foundation Center of Excellence, Director, Huntington Disease Society of America Center of Excellence, University of Rochester School of Medicine and Dentistry, Rochester, NY, USA

**Thomas M. Boes, MD**

Department of Psychiatry, NYU School of Medicine, New York, NY, USA

**Paul W. Brazis MD**

Professor of Neurology and Consultant in Neuro-Ophthalmology and Neurology, Departments of Neurology and Ophthalmology, Mayo Clinic, Jacksonville, FL, USA

**Jonathan L. Brisman, MD**

Neurological Surgery PC, Rockville Center, NY, USA

**Jeffrey A. Brown, MD**

Neurological Surgery, PC, Great Neck, NY, USA Regional Director, TNA-Facial Pain Organization, Neurosurgery Director of the Winthrop-University Hospital CyberKnife® Program and Chief of Neurosurgery at Mercy Medical Center, Rockville Centre, New York, NY, USA

**Scott E. Brown, MD**

Chief, Department of Physical Medicine and Rehabilitation, Sinai Hospital of Baltimore, Baltimore, MD, USA

**Ryan R. Byrne, MD**

Assistant Professor of Psychiatry and Behavioral Medicine, Medical College of Wisconsin (MCW), Milwaukee, WI, USA

**Rina Caprarella, MD**

Chief of Neurology, ProHealth, Lake Success, NY, USA

**Casey A. Chamberlain, DO**

Physiatrist, Michigan State University College of Osteopathic Medicine, Department of Physical Medicine and Rehabilitation, East Lansing, MI, USA

**Wan-Tsu W. Chang, MD**

Clinical Fellow, Neurosciences Critical Care Division, Department of Anesthesiology and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Grace M. Charles, BA**

Mount Sinai School of Medicine, New York, NY, USA

**Jasvinder Chawla, MD, MBA, FAAN**

Chief, Neurology Service, Edward Hines, Jr. VA Hospital, Hines, IL, USA

**David Clark, DO**

Neuro-ophthalmology Fellow, Michigan State University, East Lansing, MI, USA

**Todd J. Cohen MD FACC FHRS**

Director of Electrophysiology Director of the Pacemaker Arrhythmia Center, Winthrop University Hospital, Mineola, NY, USA

**Joe Colombo, PhD**

Medical Director, Ansar Medical Technologies, Philadelphia, PA, USA

**Howard Crystal, MD**

Professor of Neurology, Pathology, and Psychiatry, SUNY Downstate Medical Center, Brooklyn, NY, USA

**Vladimir Dadashov, MD**

Neurosurgeon, Neurological Surgery PC, Rockville Center, NY, USA

**Sarita B. Dave, MD**

Senior Resident, Ophthalmology, Vanderbilt Eye Institute, Nashville, TN, USA

**Jean Robert Desrouleaux, MD**

Neurologist, Hempstead NY, USA

**Richard L. Doty, PhD**

Professor and Director, Smell and Taste Center, University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA

**Robert Duarte, MD**

Director, Pain Center Assistant Professor of Neurology, Hofstra North Shore-LIJ

School of Medicine, Manhasset, NY, USA

**Jeffrey S. Durmer, MD, PhD**

Chief Medical Officer, Fusion Health and Fusion Sleep, Atlanta, GA, USA

**Christyn M. Edmundson**

Medical Student, Albert Einstein College of Medicine, Bronx, NY, USA

**Eric R. Eggenberger, DO, MSEpi**

Professor and Vice-Chairman, Michigan State University Department of Neurology & Ophthalmology, East Lansing, MI, USA

**Steven Ender, DO**

Assistant Clinical Professor of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA

**Noam Epstein, MD, MS**

Staff Neurologist and Researcher, Edward Hines, Jr. VA Hospital, Hines, IL, USA

**Alberto J. Espay, MD, MSc, FAAN**

Associate Professor of Neurology and Director of Clinical Research, UC Neuroscience Institute, Department of Neurology, Gardner Family Center for Parkinson's Disease and Movement Disorders, University of Cincinnati, Cincinnati, OH, USA

**Alan B. Ettinger, MD, MBA**

Epilepsy Director, Neurological Surgery P.C., Rockville Center; Director of the Epilepsy Wellness Program, Winthrop University Hospital, Mineola; Director of EEG and Epilepsy, Huntington Hospital, Huntington; and Professor of Clinical Neurology, Albert Einstein College of Medicine, Bronx, NY, USA

**Niloofer (Nelly) Faghani, PT**

Physiotherapist/Clinical Director/Owner, Aurora Prime Physiotherapy and Sports Rehabilitation Centre, Richmond Hill, ON, Canada

**Amtul Farheen, MD**

Neuromuscular Center, Neurological Institute, University Hospitals Case Medical Center, Case Western Reserve University, School of Medicine,

Cleveland, OH, USA

**Edward Firouztaie, DEngSc, DO**

South Shore Neurologic Associates, Patchogue, NY, USA

**Rod Foroozan, MD**

Associate Professor of Ophthalmology, Cullen Eye Institute, Baylor College of Medicine, Houston, TX, USA

**Anne L. Foundas, MD**

Professor and Chair, Department of Neurology and Cognitive Neuroscience, University of Missouri-Kansas City School of Medicine, Kansas City, MO, USA

**David Elliot Friedman, MD**

Medical Director, Winthrop Comprehensive Epilepsy Center, Mineola, NY, USA

**Deborah I. Friedman, MD, MPH**

Professor, Departments of Neurology and Ophthalmology, University of Texas Southwestern Medical Center, Dallas, TX, USA

**Steven J. Frucht, MD**

Professor of Neurology and Director, Movement Disorders Division, Mount Sinai School of Medicine, New York, NY, USA

**Oded Gerber, MD**

Associate Professor, Department of Neurology at Stony Brook University Hospital, Stony Brook, NY, USA

**Tal Gilboa, MD**

Pediatric Epilepsy Clinic Director, Shaare-Zedek Medical Center, Jerusalem, Israel

**Martin Gizzi, MD, PhD**

Professor and Chairman, NJ Neuroscience Institute, Seton Hall University JFK Medical Center, Edison, NJ, USA

**Teneille G. Gofton, MD, MSc, FRCPC**

Department of Clinical Neurological Sciences, London Health Sciences Centre – University Hospital, The University of Western Ontario, London, ON, Canada

**Louis J. Goodrich**

Medical Student, Nova Southwestern University, Davie, FL, USA

**Malcolm H. Gottesman, MD, FACP, FAAN**

Professor of Clinical Neurology, Stony Brook University School of Medicine Chief, Division of Neurology, Winthrop-University Hospital, Mineola, NY, USA

**Varda Gross-Tsur, MD**

Associate Professor, Pediatrics (Neurology), Faculty of Medicine, Hebrew University Director, Neurodevelopment Unit, Shaare Zedek Medical Center, Jerusalem, Israel

**Deepak Grover, DO**

Ophthalmologist, Philadelphia, PA, USA

**David A. Gudis, MD**

Resident Physician, Department of Otorhinolaryngology: Head and Neck Surgery, University of Pennsylvania Health System, Philadelphia, PA, USA

**John J. Halperin, MD, FAAN, FACP, FRCP(E)**

Professor of Neurology & Medicine, Mount Sinai School of Medicine Chair; Department of Neurosciences, Overlook Medical Center, Summit, NJ, USA

**Maxim D. Hammer, MD**

Assistant Professor of Neurology, University of Pittsburgh Medical Center, Pittsburgh, PA, USA

**Andrew R. Harrison, MD**

Departments of Ophthalmology & Visual Neurosciences and Otolaryngology Director, Ophthalmic Plastic and Reconstructive Surgery Service Co-Director, Center for Thyroid Eye Disease, Associate Professor, University of Minnesota, Minneapolis, MN, USA

**L. Anne Hayman, MD**

Clinical Director Neuro-Radiology, Anatom-e Information Systems, Ltd., Houston, TX, USA

**Galen V. Henderson, MD**

Director of Neuro ICU, Brigham and Women's Hospital, Boston, MA, USA

**Steven Herskovitz, MD**

Professor of Clinical Neurology and Director of the Neuromuscular Division and EMG Lab, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

**Caitlin Hoffman, MD**

Department of Neurological Surgery, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY, USA

**Laryssa A. Huryn, MD**

Resident in Ophthalmology, Department of Ophthalmology, Syracuse, NY, USA

**Andres M. Kanner, MD**

Professor of Clinical Neurology, Director, Comprehensive Epilepsy Center and Chief, Epilepsy Section, University of Miami Miller School of Medicine, Miami, FL, USA

**Gary P. Kaplan, MD, PhD**

Clinical Associate Professor of Neurology, Hofstra North Shore-LIJ School of Medicine, Hempstead, NY, USA

**Bashar Katirji, MD**

Director, Neuromuscular Center and EMG Laboratory, University Hospitals Case Medical Center Program Director, Neuromuscular Medicine, University Hospitals Case Medical Center Professor, Neurology, Case Western Reserve University School of Medicine, Cleveland, OH, USA

**Kenneth R. Kaufman, MD, MRCPsych**

Professor of Psychiatry, Neurology, and Anesthesiology, Departments of Psychiatry, Neurology, and Anesthesiology, Rutgers – Robert Wood Johnson Medical School, New Brunswick, NJ, USA

**Annie Killoran, MD MSc**

Assistant Professor of Neurology, Director of the WVU Movement Disorders Clinic, Robert C. Byrd Health Sciences Center, West Virginia University, Morgantown, WV, USA

**Nina Kirz, MD**

Clinical Instructor, Child and Adolescent Psychiatry, Stanford University, Stanford, CA, USA

**Gad E. Klein, PhD**

Neurological Surgery PC, Lake Success, New York, USA

**Danielle G. Koby, PhD**

Staff Psychologist, Division of Health Psychology, The Institute of Living, Departments of Neurology and Neurosurgery, Comprehensive Epilepsy Center, Hartford Hospital, Hartford, CT, USA

**Christopher P. Kogut, MD**

Assistant Professor, Department of Psychiatry, Virginia Commonwealth University, Richmond, VA, USA

**W. Curt LaFrance Jr, MD, MPH**

Assistant Professor of Psychiatry and Neurology (Research), Alpert Medical School, Brown University, Director of Neuropsychiatry and Behavioral Neurology, Rhode Island Hospital, Providence, RI, USA

**Patrick J.M. Lavin, MD**

Professor of Neurology and Ophthalmology, Vanderbilt University Medical Center, Nashville, TN, USA

**Susan W. Law, DO**

Neurology Resident, SUNY Downstate Medical Center Long Island College Hospital, Brooklyn, NY, USA

**James L. Levenson, MD**

Vice Chair, Department of Psychiatry, Chair, Division of Consultation-Liason Psychiatry and Professor of Psychiatry, Medicine and Surgery, Virginia Commonwealth University School of Medicine, Richmond, VA, USA

**Richard B. Lipton, MD**

Edwin S. Lowe Professor and Vice Chair of Neurology, Professor of Epidemiology and Population Health and Professor of Psychiatry and Behavioral Sciences, Albert Einstein College of Medicine, Bronx, NY, USA

**Glenn Lopate, MD**

Associate Professor, Department of Neurology, Division of Neuromuscular Diseases, Washington University School of Medicine; Consulting Staff, Department of Neurology, Barnes-Jewish Hospital, St. Louis, MO, USA

**Daniel J. Luciano, MD**

Director of the Clinical Epilepsy Program at the NYU Comprehensive Epilepsy Center and Director of the Out Patient EEG Epilepsy Service, NYU School of Medicine, NY, USA

**Reema Maindiratta, MD**

Neurologist, Babylon, NY, USA

**Robert M. Mallery, MD**

Resident in Neurology, Harvard Medical School, Massachusetts General Hospital, and Brigham and Women's Hospital, Boston, MA, USA

**Georgios Manousakis, MD**

Assistant Professor, University of Minnesota, Minneapolis, MN, USA

**Alan Mazurek, MD**

Assistant Clinical Professor of Neurology at Mt. Sinai Medical Center and Director of Rockville Center Neurology, Rockville Centre, NY, USA

**Luis J. Mejico, MD**

Associate Professor of Neurology and Ophthalmology, SUNY Upstate Medical University, Syracuse, NY, USA

**Dragana Micic, MA, PhD**

Department of Psychology, Queens College, The City University of New York, NY, USA

**Ali Mokhtarzadeh, MD**

Fellow, Oculoplastic and Orbital Surgery University of Minnesota Minneapolis, MN, USA

**Walter J. Molofsky, MD**

Associate Professor of Neurology, Albert Einstein College of Medicine, Chief, Pediatric Neurology, Beth Israel Medical Center, New York, NY, USA

**Heather E. Moss, MD, PhD**

Assistant Professor in Ophthalmology, Department of Ophthalmology & Visual Sciences, University of Illinois at Chicago, Chicago, IL, USA

**Mark L. Moster, MD**

Professor of Neurology and Ophthalmology, Neuro-Ophthalmology Service, Wills Eye Institute, Thomas Jefferson University School of Medicine, Philadelphia, PA, USA

**Manpreet Multani, MD**

NJ Neuroscience Institute, Seton Hall University, Edison, NJ, USA

**Siddhartha Nadkarni, MD**

Assistant Professor of Neurology, Director of the Epilepsy HOS Clinic and Epilepsy Fellowship Program, NYU School of Medicine, New York, NY, USA

**George C. Newman, MD, PhD**

Professor and Chairman, Neurosurgery Sciences, Director, Stroke Program, Albert Einstein Medical Center, Philadelphia, PA, USA

**Rolla Nuoman, MD**

Pediatric Resident, Woodhull Medical Center, New York University, Brooklyn, NY, USA

**Paul A. Nyquist, MD, MPH**

Associate Professor, Department of Neurology, Anesthesiology and Critical Care Medicine, Neurosurgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA

**Gaia Donata Oggioni, MD**

UC Neuroscience Institute, Department of Neurology, Gardner Family Center for Parkinson's Disease and Movement Disorders, University of Cincinnati, Cincinnati, OH, USA Department of Neurology, Università del Piemonte Orientale A. Avogadro, Novara, Italy

**Odi Oguh, MD**

University of Florida Jacksonville Assistant Professor, Department of Neurology Jacksonville FL, USA

**Denis Ostrovskiy, MD**

Assistant Clinical Professor of Neurology, Hofstra North Shore-LIJ School of Medicine, Hempstead Assistant Clinical Professor of Neurology, Mount Sinai School of Medicine, New York, NY, USA

**Kristina Y. Pao, MD**

Ophthalmology Resident, Wills Eye Institute at Thomas Jefferson University, Philadelphia, PA, USA

**Juwen Park**

Oculoplastic Surgeon, Republic of Korea

**Anastas F. Pass, OD, MS, JD**

University of Houston – University Eye Institute, Co-Director: Neuro-Ophthalmology Service, Ocular Diagnostic and Medical Eye Service, University of Houston – University Eye Institute, Houston, TX, USA

**Victoria S. Pelak, MD**

Associate Professor of Neurology and Ophthalmology, University of Colorado School of Medicine, Aurora, CO, USA

**Jeffrey Peterson, MD, PhD**

Cullen Eye Institute, Baylor College of Medicine, Houston, TX, USA

**John Pile-Spellman, MD**

Neurological Surgery PC, Rockville Center, NY, USA

**Misha L. Pless, MD**

Chief, Divisions of General Neurology and Neuro-ophthalmology Neurology Department, Massachusetts General Hospital Associate Professor, Harvard Medical School, Neuro-ophthalmology, Multiple Sclerosis and General Neurology, Boston, MA, USA

**Gregory M. Pontone, MD**

Assistant Professor and Director, Movement Disorders Psychiatry Clinic, John Hopkins University School of Medicine, Baltimore, MD, USA

**Aparna M. Prabhu, MD**

Attending Neurologist, Albert Einstein Medical Center, Philadelphia, PA, USA

**Michael T. Pulley, MD, PhD**

Clinical Associate Professor of Neurology, Director EM6 Laboratory, University of Florida, Jacksonville, FL, USA

**Philip Ragone, MD**

Neurologist, Great Neck, NY, USA

**Prajwal Rajappa, MD**

Fellow, Department of Neurological Surgery, Weill Cornell Medical College, New York Presbyterian Hospital, New York, NY, USA

**Venkat Ramani, MD**

Professor of Neurology at New York Medical College Chief of Section of Epilepsy and Clinical Neurophysiology Laboratory at Westchester Medical Center, Valhalla, NY, USA

**Sindhu Ramchandren, MD, MS**

Assistant Professor of Neurology, Director of the Pediatric and Adult CMT and MDA Clinic, University of Michigan, Ann Arbor, MI, USA

**Ritesh A. Ramdhani, MD**

Fellow, Movement Disorders Division, Department of Neurology, Mount Sinai School of Medicine, New York, NY, USA

**Ramses Ribot, MD**

Fellow in Clinical Neurophysiology, Department of Neurological Sciences, Rush Medical College at Rush University and Rush University Medical Center, Chicago, IL, USA

**Heidi D. Riney, MD, D. ABPN**

Sleep Medicine Medical Director, Fusion Sleep, Atlanta, GA, USA

**Diana Rojas-Soto, MD**

Stroke Fellow, Department of Neurology SUNY Downstate Medical Center, Brooklyn, NY, USA

**Michael Ronthal, MD**

Professor of Neurology, Harvard Medical School, Boston, MA, USA

**Daniel M. Rosenbaum, MD**

Professor and Chairman, Department of Neurology, SUNY Downstate Medical Center, SUNY Downstate Stroke Center, Brooklyn, NY, USA

**David B. Rosenfield, MD**

Director, Speech and Language Center, Director, EMG and Motor Control Laboratory, Neurological Institute, The Methodist Hospital Professor, Weill Medical College of Cornell University, Houston, TX, USA

**Durga Roy, MD**

Assistant Professor Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine Baltimore, MD, USA

**Michael J. Ruckenstein, MD**

Professor and Vice Chairman, Department of Otorhinolaryngology: Head and Neck Surgery, University of Pennsylvania Health System, Philadelphia, PA, USA

**Max C. Rudansky, MD, FACP**

Clinical Assistant Professor of Neurology, Hofstra North Shore-LIJ School of Medicine Emeritus Chief and Director of Stroke Unit, Huntington Hospital, Huntington, NY, USA

**Eva Sahay, MD**

Consultant Neurology and Neurophysiology, Sahay Medical Group PC, Garden City, NY, USA

**Friedhelm Sandbrink, MD**

Assistant Clinical Professor of Neurology, Georgetown University, Washington, DC; Director EMG Laboratory and Chief Pain Clinic, Department of Neurology, Washington VA Medical Center, Washington, DC, USA

**Jade S. Schiffman, MD, FAAO, FAAN**

Professor of Ophthalmology and Neuro-Oncology, Director of Neuro-Ophthalmology, Head & Neck Surgery, Section of Ophthalmology, and Co-Director of MS EyeCARE, The University of Texas MD Anderson Cancer Center, Houston, TX, USA

**Angela Scicutella, MD, PhD**

Attending Neuropsychiatrist, Clinical Associate Professor in Psychiatry, Hofstra North Shore – Long Island Jewish School of Medicine at Hofstra University, Hempstead, NY, USA

**Maroun T. Semaan, MD**

Clinical Assistant Professor of Otolaryngology at University Hospitals Case Medical Center and the Louis Stokes Cleveland Department of Veteran Affairs Medical Center, Case Western Reserve University, Cleveland, OH, USA

**Robert C. Sergott, MD**

Director, Neuro-Ophthalmology Wills Eye Hospital; Professor of

Ophthalmology, Neurology, and Neurosurgery, Thomas Jefferson University, Philadelphia, PA, USA

**Aashit K. Shah, MD, FAAN, FANA**

Professor and Associate Chair Wayne State University Department of Neurology; Director, Comprehensive Epilepsy Program Director, Clinical Neurophysiology Fellowship, Wayne State University Detroit; Medical Center Chief of Neurology, Harper University Hospital

**David M. Shaw, BA**

Department of Psychiatry, NYU School of Medicine, New York, NY  
Department of Psychology, Fordham University, Bronx, NY, USA

**Amit M. Shelat, DO, MPA, FACP**

Assistant Professor of Clinical Neurology, Stony Brook University School of Medicine and Attending Neurologist, Winthrop-University Hospital, Mineola, NY, USA

**Claire A. Sheldon, MD, PhD, FRCSC**

Department of Ophthalmology and Visual Sciences, University of British Columbia, VC, Canada

**Anant M. Shenoy, MD**

Neurology Attending, Baystate Medical Center and Assistant Professor of Neurology, Tufts University School of Medicine, Springfield, MA, USA

**Yelizaveta Sher, MD**

Instructor, Psychosomatic Medicine, Stanford University Medical Center Stanford, CA, USA

**Jessica A. Shields, PhD**

Brain & Behavior Program, Department of Neurology, Cell Biology & Anatomy, Louisiana State University Health Sciences Center, New Orleans, LA, USA

**Tanya Simuni, MD**

Arthur C. Nielson Professor of Neurology, Director, Parkinson's Disease and Movement Disorders Center, Northwestern University Feinberg School of Medicine, Chicago, IL, USA

**Rajpal Singh, MD**

Neurology, Hollis, NY, USA

**Eric E. Smouha, MD**

Associate Professor and Director of Otology-Neurotology, Department of Otolaryngology, Mount Sinai School of Medicine, New York, NY, USA

**David Solomon, MD, PhD**

Assistant Professor of Neurology and Otolaryngology Head and Neck Surgery, CSF Disorders Program, Johns Hopkins Hospital, Baltimore, MD, USA

**Mehri Songhorian, MD**

Neurologist, Great Neck, NY, USA

**Steven A. Sparr, MD, FAAN**

Professor of Clinical Neurology and Assistant Professor of Rehabilitation Medicine, Albert Einstein College of Medicine, Bronx, NY, USA

**Egilus L. H. Spiersings, MD, PhD**

Associate Clinical Professor of Neurology, Brigham and Women's Hospital, Harvard Medical School; Associate Clinical Professor of Craniofacial Pain, Tufts University School of Dental Medicine; Director, Headache and Face Pain Program, Tufts Medical Center, Boston, MA, USA

**Eve G. Spratt, MD**

Professor of Psychiatry, Medical University of South Carolina, Mount Pleasant, SC, USA

**Beth Stein, MD**

Assistant Professor of Neurology, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

**S.H. Subramony, MD**

Professor, Department of Neurology, University of Florida College of Medicine, Gainesville, FL, USA

**Rosa Ana Tang, MD, MPH, MBA**

Director, Neuro-Ophthalmology Service and Co-Director, MS EyeCARE,  
University of Houston – University Eye Institute, Houston, TX, USA

**Cara Tannenbaum, MD, MSc**

Associate Professor of Medicine, Institut universitaire de gériatrie, Université de  
Montréal, QC, Canada

**Hakan Tekeli, MD**

Neurology Department, Kasimpasa Military Hospital, Istanbul, Turkey

**Amanda J. Thompson, MD**

Adjunct Clinical Post-Doctoral Fellow, University of Florida Center for  
Movement Disorders and Neurorestoration, Gainesville, FL, USA

**Michael J. Thorpy, MD**

Director, Sleep-Wake Disorders Center, Montefiore Medical Center, Albert  
Einstein College of Medicine, Bronx, NY, USA

**Matthew J. Thurtell, BSc(Med), MBBS, MSc(Med), FRACP**

Assistant Professor of Ophthalmology and Neurology, Department of  
Ophthalmology and Visual Sciences, University of Iowa, Iowa City, IA, USA

**Pedro J. Torrico, MD**

Department of Neurology, North Shore Medical Group of the Mount Sinai  
School of Medicine, Huntington, NY, USA

**Ira M. Turner, MD**

The Center for Headache Care and Research, Island Neurological Associates PC,  
Plainview, NY, USA

**Scott Uretsky, MD**

Director, Neuro-Ophthalmology Division, Neurological Surgery PC, Lake  
Success, NY, USA

**Ruth H. Walker, MB, ChB, ASS, PhD**

Department of Neurology, James J. Peters Veterans Affairs Medical Center,  
Bronx, NY and Mount Sinai School of Medicine, New York City, NY, USA

**Deborah M. Weisbrot, MD**

Associate Professor of Clinical Psychiatry and Director, Child & Adolescent Psychiatry Outpatient Clinic, Department of Psychiatry and Behavioral Sciences, Stony Brook University Medical Center, New York, USA

**Michael A. Williams, MD, FAAN**

Medical Director, The Sandra and Malcolm Berman Brain & Spine Institute Director, Adult Hydrocephalus Center, Sinai Hospital of Baltimore, Baltimore, MD, USA

**Jacques Winter, MD**

Neurologist Huntington, New York, NY, USA

**Randall J. Wright, MD**

Clinical Assistant Professor, UT Health, Department of Neurosurgery, Mischer Neuroscience Associates, Houston, TX, USA

**Jay Elliot Yasen, MD**

Director Stroke Service, Associate Professor of Clinical Neurology, School of Medicine, State University of New York at Stony Brook, NY, USA

**Shicong Ye, MD**

Assistant Professor of Clinical Neurology, Stony Brook University School of Medicine, and Attending Neurologist, Winthrop-University Hospital, Mineola, NY, USA

**G. Bryan Young, MD, FRCPC**

Department of Clinical Neurological Sciences, London Health Sciences Centre – University Hospital, The University of Western Ontario, London, ON, Canada

**Huiying Yu, MD**

Director of Neurodiagnostic Laboratory, Winthrop University Hospital, Mineola, NY, USA

**Ryan J. Zehnder, MD**

Physical Medicine and Rehabilitation, Evergreen Rehabilitation, Kirkland, WA,  
USA

## **Foreword**

---

There is an apocryphal story of an eminent neurology professor who was asked to provide a differential diagnosis. He allegedly quipped: “I can't give you a differential diagnosis. If you wish I will give you a list of wrong diagnoses followed by the right diagnosis.” Sadly, this sort of arrogance pervaded our field, particularly in the era before there were accurate diagnostic methods and effective treatments of neurological diseases. Fortunately, this sort of pomposity is now relegated to the past and remains only as an antique reminder of a type of hubris that precluded discovery and progress in diseases of the nervous system.

Fortunately, the era of therapeutic nihilism in neurology is over, but now we are faced with a different problem. There is simply too much information for any one person to accommodate. In the twentieth century, internal medicine responded to this explosion of knowledge by differentiating itself into an array of subspecialties, such as cardiology, endocrinology, nephrology, hematology, oncology, gastroenterology, infectious diseases, pulmonology, and many more. The internist of the 1950s took care of patients with cardiological and hematological problems. In the year 2000, no one can imagine a hematologist performing a cardiac catheterization or a nephrologist managing hepatitis C. Similarly, in the twenty-first century neurology now is a group of fields, such as stroke, movement disorders, epilepsy, cancer neurology, neuromuscular disease, headache, multiple sclerosis, cognitive and behavioral neurology, neuroophthalmology and many more. Just as, in internal medicine, the Parkinson's disease expert cannot be expected to undertake the treatment of brain tumors or complex epilepsy.

But because of the changes in the way medical care is delivered, neurology, as internal medicine, has experienced a renaissance of the generalist in the form of divisions of general and hospital neurology. After all, someone must decode the non-specific neurological complaint, such as dizziness, headache, and confusion, and determine the nature of the problem so the evaluation and treatment can be undertaken in an effective and efficient manner. Obtaining an unfocused array of neurodiagnostic tests is not only inordinately expensive, but it is potentially dangerous, as it may disclose an incidentaloma, the irrelevant finding on a blood

test or image that can lead to unnecessary and even life-threatening interventions. Also the availability of an enormous amount of medical information to the lay public, some of which is useful but most of which is misleading and often terrifying for the patient, greatly complicates the care of patients who may come to the doctor with a strongly held theory of their own problem.

It was in this context that Alan Ettinger and Deborah Weisbrod conceived of the idea of a practical, easily accessible source for the clinician to generate a rapid differential diagnosis when faced with the most common neurological complaints. This is a bold and ambitious endeavor as the number of such complaints is enormous. Entire textbooks have been written about virtually all of the major subjects and a huge literature lurks in the background for every problem. Rather than try to create simply another textbook, Drs Ettinger and Weisbrod have disciplined their large array of authors to follow a strict format. For each chapter, there is a brief description of the symptom, sign, or condition, followed by a summary of the relevant anatomy, physiology, and pathophysiology. The heart of each chapter is a differential diagnosis table, which is consistent throughout the book. For each item, the differential diagnosis is divided by the basic nature of the problem, followed by specific types, etiologies, and clinical features. For example, for the dilated pupil, the several major categories of the table are toxic, pressure, degenerative, vascular, traumatic, inflammatory, ictal, and congenital. For toxic types, anticholinergic and adrenergic are listed as the subtypes. For anticholinergic, scopolamine, cosmetics, glaucoma treatments are listed as etiologies and for scopolamine, special clinical features such as accidental instillation into the eye of an agent being used for the prevention of motion sickness. Following the table, there is an illustrative clinical vignette. For the dilated pupil, a case of a male who was using scopolamine to prevent sea sickness is recounted.

Using this stereotyped method the reader can know exactly how to look up a particular symptom (e.g. dizziness) or sign (e.g. the dilated pupil) and quickly obtain a reasonable differential diagnosis which will aid in ordering studies, starting treatment, and referring to the appropriate specialist. The book will be valuable to multiple different types of readers depending on their specific needs and level of sophistication. The student will use the book to begin to understand the assessment of the patient with a neurological complaint. The non-neurologist, including other specialists and physician extenders, will be aided in approaching such patients and referring those who need it to the appropriate specialist. The general neurologist will use it to refresh memory of the many

different subspecialties of the field and the subspecialist will find it invaluable to deal with problems outside their area of special competence. Those taking certifying examinations can use it as a study guide for the major neurological problems faced in the practice of medicine, whether it be in the office, the hospital, or the emergency department.

Ettinger and Weisbrot's *Neurologic Differential Diagnosis: A Case-Based Approach* is likely to become a must-have for any doctor or other healthcare provider who must assess neurologic symptoms and signs, and that is just about everyone.

Martin A. Samuels, M.D.

## Preface

---

There is certainly no paucity of general and specialty neurology textbooks, so why produce yet another one? This book was inspired by our experiences as neurology and psychiatry residents many years ago, and has been reinforced decades later as senior clinicians. Nowadays, in the era of managed care, clinicians are expected to see increasing numbers of patients in shorter amounts of time; how can the clinician ensure that important diagnoses are not missed?

It seems to us that it is unlikely that the busy neurologist or neurology resident will have the time or inclination to pore through voluminous textbooks in the office or emergency room, looking for clarification of differential diagnosis. A smaller collection of textbooks specifically devoted to differential diagnosis is available; however, many of these are essentially bare-bone lists of diagnoses while others seem too basic or superficial.

What we seek to provide in *Neurologic Differential Diagnosis: A Case-Based Approach*, is a highly accessible and pragmatic guide to the vast array of potential etiologies for neurologic and psychiatric symptoms. Clinicians can readily find, in the alphabetized arrangement of topics, immediate references that remind the clinician of items to check for when faced with complaints of “dizziness,” “mental status change,” “diplopia,” or “psychosis.” Instead of simple lists of potentially responsible causes for symptoms, each diagnostic possibility is linked to reminders of key elements that will help the clinician decide whether the specific patient's presentation fits with each possible etiology. In addition, each chapter includes case studies that exemplify a systematic approach to differential diagnosis of each symptom.

Who will find the book useful? Both experienced and junior neurologists should find the content written by the expert authors to be invaluable. The non-neurologist such as the internist or general or family practitioner, emergency room physician, physician assistant, and nurse practitioner who finds the subject of neurology to be esoteric and difficult to conceptualize, will find the organized tables in each chapter to be readily comprehensible. Many chapters are devoted to psychiatric symptoms and will find good use in the hands of the psychiatrist performing the essential task of ruling out compelling medical diagnoses.

presenting as psychiatric conditions. Neurologists and psychiatrists preparing for their board examinations will also find *Neurologic Differential Diagnosis* to be invaluable, particularly because of the inclusion of case examples and the discussion of the organized approach to diagnosing each symptom.

As academic clinicians teaching residents in neurology and psychiatry, we have had the opportunity to pilot the use of numerous chapters as teaching guides for physicians-in-training. We have been very gratified by the enthusiastic and positive feedback that we have received from our student physicians as well as our colleagues. We sincerely hope that this book will find an important place on the shelves of clinicians everywhere.

## Acknowledgments

---

This ambitious project would not have been possible without the kind and dedicated efforts of numerous individuals. We would like to acknowledge the many authors who, in spite of daily clinical and academic demands, contributed invaluable chapters to this book. We extend our special thanks to Dr. Bashar Katirji who provided additional assistance in reviewing the chapters related to peripheral nerve disease. We also thank Dr. Richard Libman for his helpful comments.

We would also like to thank the many colleagues who provided administrative assistance or helped procure medical articles utilized in formulating this book. These include Rosemary Valdez, Chaomei Wu, Gilda Davis, Kathy Grzymala, Anna Dushenkov, Erica Jalal, Susan Simpson, Debra Rand, Shifra Atik, Barbara Sacks, and Rita Feigenberg.

We would also like to acknowledge individuals who have played special roles in our lives. First, Dave Jones, LCSW, for sharing his extraordinary wisdom and insight. Second, our friend John Mangione, for providing musical diversion during the long process of preparing this book and for his generous spirit raising funds to help children with devastating neurological disorders. Finally, Omri Adut, for bringing the great joy of horseback riding into Deborah's life and enabling her to fulfill her most treasured childhood dream.

We extend our special thanks to Nicholas Dunton, Jane Seakins, Sarah Payne, Lesley Bennun, and Arindam Bose at Cambridge University Press, who were very helpful throughout the publication process.

Finally, we thank our patients, who shared their lives and struggles with us and taught us the true value of patiently taking a thorough history when generating the differential diagnosis.

Alan B. Ettinger, MD, MBA

Deborah M. Weisbrot, MD

# **Section 1 Differential Diagnosis of Abnormal Symptoms and Signs**

---

# **1 Introduction: localization and differential diagnosis in neurology**

---

Alan B. Ettinger and Deborah M. Weisbrot *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

## **Introduction**

Generating a neurologic differential diagnosis can be very challenging. In contrast to many other fields of medicine, neurologic differential diagnosis requires the initial step of localizing abnormalities along the complex neuro-axis, before generating a list of potential etiologies. That step is predicated upon an appreciation of neuroanatomy and the associated symptoms and signs that apply to disturbances of specific parts of the neuro-axis. While numerous discussions may be found on this topic, often diffused among specific chapters in standard neurology texts, many students and even seasoned clinicians may be overwhelmed with the intricacies of neurologic localization. Some clinicians attempt to skip the logical thought processes involved in generating a differential diagnosis by immediately ordering numerous tests, hoping that the elusive explanatory lesion will demonstrate itself. This is unfortunate, since the most accurate diagnoses emerge from following a step-by-step approach which in turn guides the rational selection of specific tests.

The process of deriving a differential diagnosis can even precede the first face-to-face encounter between doctor and patient and truly begins with the clinician's receipt of any information about the patient. Even a requisition listing a reason for referral can lead to preparations for questioning that is relevant to generating a differential diagnosis. Rather than deferring the active thought process about possible localizations and causes until after the data from a generic history and examination are derived, proper procedure requires active consideration of localization and diagnostic possibilities from the very beginning. This process continues throughout the taking of the history and performance of the examination. The clinician should inquire about specific

diagnostic hypotheses with answers to each query by the clinician, leading to further clarification achieved by issuing subsequent questions. The clinician should avoid focusing only on the early hypotheses about explanatory diagnoses and should keep an open mind about the diverse range of diagnostic possibilities. This book is designed to help with this process, providing descriptions of possible causes that can be integrated into the history and pursuit of abnormalities on examination that will support or discourage each diagnostic possibility.

## The neurologic history

Information elicited through the history and examination is essential not only for localizing the abnormality but also for identifying possible etiologies. A focused history begins with clarification of the chief complaint. Patients' descriptions of their symptoms need to be clarified by the clinician as what is stated may not be equivalent to what is actually meant. For example, many patients will use the term numbness when they really mean weakness. A complaint of dizziness may actually mean gait unsteadiness.

Particularly crucial to generating a list of diagnostic possibilities is knowledge about the “whats, wheres, hows, etc.” that give context to the symptom or sign, and are usually a part of the history of present illness (HPI) portion of the history.

For example [1]:

- When: When did the symptom begin? When did it stop? Did it recur? How often does it happen? How long does it last? Has it changed over time?
- What: What happens? (Step-by-step description is often helpful.) What do others see? What does it feel like? What brings it on? What makes it worse? What makes it better?
- Where: Where on the body do the symptoms occur? Where does it radiate to? Where was the patient and what was the patient doing when the symptoms developed, what were the circumstances?
- How: How severe is it? How does it affect daily life?
- Why: What does the patient believe is causing the symptoms? What are their greatest fears about the symptoms?

Beyond these more generic questions, specific questions that relate to

elements of the differential diagnosis should be asked to either support or discourage possibilities that could explain a symptom. These questions can be generated by referring to the differential diagnosis table included in each chapter of this book. For example, if a migraine headache is a possibility, the clinician may not only ask the generic question about what brings it on, but may also inquire about possible precipitants such as sleep deprivation or ingestion of wine, or other questions that specifically relate to migraine headaches. Active history-taking is a balancing act between guiding the patient to provide the relevant information and permitting the patient to provide the most spontaneous account without “leading the witness.”

Past medical and psychiatric history provide a context in which symptoms occur. The patient with an established history of breast cancer who presents with progressive hemiparesis raises the concern about possible metastasis. Review of systems provides additional background information that may not be elicited on the more focused, earlier portions of history-taking. It also embraces the concept that concomitant illnesses may not only predispose the patient to neurologic disorders but also may be the result of or impacted by neurologic disease [2].

Family history may also provide important clues about diagnostic possibilities. A family history of a condition or specific genetic disorder may heighten suspicion of a distinct diagnosis, and may also lead to recommendations to examine other family members. Social history is replete with potentially invaluable clues to diagnostic possibilities. History of substance abuse, or stressors, may be very relevant toward symptoms.

The history should also go beyond the patient's own account of symptoms. Witnesses' accounts and review of prior records and prior diagnostic work-up can be invaluable.

## The neurologic examination

Abnormalities along the neuro-axis are further clarified by seeking the presence or absence of findings on examination. While the examination is traditionally performed after a thorough history is obtained, in fact the experienced clinician begins the examination from the moment of the first encounter with each patient, observing a potential multitude of signs that will be evident in the way the patients present themselves. During the formal examination, the seasoned neurologist is able to identify and accurately classify examination findings such as movement abnormalities or what exceeds the normal variations in findings

among different individuals. Performing a rote detailed neurologic examination for every patient irrespective of presenting symptoms is a suboptimal way of attaining relevant data and is frankly not feasible for the typical busy clinician. More desirable is a hypothesis-driven focused neurologic exam that is supplemented by a general screening neurologic exam to ensure that important additional findings have not been ignored.

Examination includes elements of the general examination that are relevant to neurologic disorders such as vital signs, neurocutaneous abnormalities, heart exam, presence or absence of bruits, etc. Abnormalities found on the neurologic examination should lead to hypotheses about localization that are supported or dismissed by symptoms on history and additional findings sought on examination. Validation of subtle abnormalities is supported by asking the patient to perform additional tasks that test similar function. Additional signs should also be sought that would make sense to be abnormal in the face of dysfunction of that portion of the neuro-axis.

## **Localizing abnormalities along the neuro-axis**

The reader is directed to the diverse anatomical diagrams featured in each of the chapters of this book. As most symptoms or signs may be explained by deficits at different points of the neuro-axis, it is helpful to systematically consider the specific features of different neurologic sites. For example, unilateral paresis may arise from a problem in the cortex or as distal as the neuromuscular junction or muscle itself. What leads the neurologist to favor one localization over another is an understanding of what to expect with problems at each site along the neuro-axis.

Neurologic localization of the deficit is made more complex by the fact that the origin of the disturbance may not necessarily be directly within the area where the deficit appears to come from. For example, deficits in one region may arise from compressive effects from an expanding mass, from cerebrospinal outflow problems, or poorly localized inflammatory or neurodegenerative processes of neurons or their axonal components [3]. For example, while most neurologic localization tends to be contralateral to a central nervous system (CNS) hemispheric lesion, compressive effects in transtentorial herniation can affect the contralateral cerebral peduncles causing hemiparesis ipsilateral to the side of a hemispheric mass lesion [4]. Localization is also challenging if the site of suspected disturbance cannot be adequately explained by one specific localization site and hence is deemed multifocal, or if the process represents a

diffuse disturbance such as toxic–metabolic systemic effects [3].

The clinician takes each symptom and sign and considers its potential sites of localization. Then, applying principles of parsimony, the clinician considers among the diverse list of localization sites, a common area that could explain most or all symptoms or signs. Further evidence for the responsible site of localization can be sought by pursuing more queries in the history or performing specific examination maneuvers that support that site of localization.

One particularly challenging aspect of performing a history and examination occurs in the individual with a primary psychiatric disorder or when there is significant psychiatric comorbidity of neurologic disease. Active pursuit of higher integrative functions may be performed in individuals with memory complaints but it is also important to enquire about and look for signs of depression. Individuals with conversion disorder or malingering may exhibit abnormal signs on examination and careful examination of potential inconsistencies and other classic functional signs such as Hoover's sign, non-physiologic visual fields, or one of many types of functional gait may be elicited. Clinicians should be especially careful to avoid misidentifying aphasia as psychotic thinking, or misattributing altered behavior due to diffuse or bilateral hemispheric lesions as merely part of a primary psychiatric disease.

While a comprehensive discussion of neuroanatomy is beyond the scope of this chapter, selective features of anatomical sites and anticipated findings are noted below. The typical neurologist will not compare the constellation of symptoms and signs of the individual patient against each and every possible localization site but rather begin with consideration of broad categories of neurologic localization. A typical starting point will be deciding between localization in the CNS versus peripheral nervous system (PNS). Longstanding CNS deficits may be associated with cognitive or language difficulties , visual field cuts, and upper motor neuron signs such as hyperreflexia and the Babinski sign . Problems in the PNS may feature muscular atrophy , fasciculations , and diminished reflexes [4]. If the lesion is focal and suspected to be within the CNS, the next question is whether the lesion is intra-axial or extra-axial. If intra-axial, major areas to be considered would include the cerebral hemisphere, ventricular pathways, basal ganglia, brainstem, cerebellum, or spinal cord. Extra-axial lesions should also be considered including those emanating from surrounding bone or the meningeal space such as epidural, subdural, or subarachnoid regions [5].

## **Lesions involving the cerebral hemispheres including the cerebral cortex**

These localizations may be cortical, subcortical, or combinations. Hemispheric lesions that involve the pyramidal (corticospinal) tracts are evidenced by upper motor neuron injury signs including usually contralateral paresis , spasticity , increased deep tendon reflexes , and the Babinski sign. The corticospinal tract may be affected further down its long pathway and therefore other cerebral hemispheric signs help the clinician identify the localization in the cerebral hemispheres. Upper motor neuron injury is distinguished from peripheral nerve disturbances; the latter associated with weakness in the company of loss of tone and atrophy, diminished reflexes, and absence of the Babinski sign [6]. Hemisensory loss , hemifield visual field cuts , and partial seizures are other clues to hemispheric insults.

Many lesions of the cerebral cortex that show classic “cortical signs” are in fact often not restricted to the superficial cortex but also involve subcortical regions. A classic example is the large vessel territory stroke . Findings that suggest involvement of the cortex include higher-level deficits such as agnosia or apraxia syndromes. Aphasia may occur if the dominant hemisphere (usually left) is affected. Other dominant hemisphere syndromes depending on the site of disturbance include alexia without agraphia , and the Gerstmann syndrome . In the non-dominant hemisphere, more subtle signs including denial , neglect , and constructional apraxia are elicited by examination and less likely through taking the history alone. Cortical deficits associated with affection of either hemisphere include the superimposition of “cortical sensory” deficits on top of primary modality sensory loss. Examples include problems in two-point discrimination , graphesthesia , and stereognosis . Dramatic syndromes such as the alien hand syndromes point to a cortical localization. While some “cranial nerve” deficits such as unilateral facial sensation loss may occur with cortical lesions, there is usually preservation of functions of cranial nerves II (pupillary response), VIII (hearing), along with IX, X, and XI. With cortical lesions, corticospinal fibers are less consolidated and therefore lesions are more likely to produce more variability in the severity of weakness in the face, upper and lower extremity.

With regard to lateralized deficits, it is useful to consider whether findings suggest a specific lobe or lobes, or specific vascular territories. The effects of deficits in specific lobes of the brain are highlighted in [Table 1.1](#).

**Table 1.1 Localization of forebrain lesions.**

Site	Finding
Left frontal lobe	Anterior aphasia (Broca's transcortical motor), aphemia Ideomotor apraxia Voluntary rightward saccades, left gaze preference Right hemiparesis , deep tendon reflex, and Babinski sign
Right frontal lobe	Motor neglect of left world Ideomotor apraxia Voluntary leftward saccades, right gaze preference Left hemiparesis, deep tendon reflex, and Babinski sign
Bilateral frontal lobes	Perseveration, impersistence, stimulus-bound responses Impaired executive functions : planning, sequencing, judgment, insight, abstract reasoning Impaired motor (Luria) sequencing Snout, root, grasp, and palmomental reflexes Gegenhalten (paratonic rigidity )
Orbitofrontal	Disinhibition, aggressive impulsivity Anosmia Memory disturbance
Frontal convexity	Abulia – akinetic mutism Incontinence “Magnetic” gait
Midline frontal	Bilateral leg weakness Behavioral changes (cingulate gyrus)

Left parietal lobe	<p>Right cortical sensory loss (astereognosis, agaphesthesia , two-point discrimination)</p> <p>Anomic aphasia, transcortical sensory aphasia, dysgraphia, dyscalculia, left–right disorientation , finger agnosia</p> <p>Right inferior quadrantanopsia</p>
Right parietal lobe	<p>Left cortical sensory loss (as above)</p> <p>Left-sided neglect, anosognosia , asomatognosia</p> <p>Constructional apraxia , dressing apraxia</p> <p>Left inferior quadrantanopsia</p>
Left temporal lobe	<p>Posterior aphasia (Wernicke's, transcortical sensory)</p> <p>Conduction aphasia</p> <p>Amnesia for verbal material (usually bilateral lesions)</p> <p>Right superior quadrantanopsia</p>
Right temporal lobe	<p>Dysprosody , amusia, non-verbal auditory agnosia</p> <p>Amnesia for non-verbal material (usually bilateral lesions)</p> <p>Left superior quadrantanopsia</p>
Bilateral temporal lobes, medial perisylvian	<p>Amnesia</p> <p>Cortical deafness</p> <p>Auditory agnosia</p>
Occipital lobe	Contralateral homonymous hemianopsia (macular sparing)
Left	Alexia without agraphia (requires lesion of splenium of corpus callosum)
Parieto-occipital	Balint syndrome (simultanagnosia, optic ataxia, ocular apraxia), impaired visuospatial localization

Temporo-occipital	Visual agnosias (including prosopagnosia, color agnosia, achromatopsia) Visual amnesia Confusional state
-------------------	--

Modified from Table 1–1 in [7] with permission.

**Table 1.2** *Localization of brainstem lesions.*

Site	Finding
Midbrain tectum and prepectum	Parinaud syndrome (large pupils with near-light dissociation, convergence–retraction nystagmus, impaired upgaze, eyelid retraction)
Tegmentum	Abnormal pupils: midrange, unequal, irregularly shaped Impaired vertical eye movements Anterior INO Skew deviation Decreased arousal Nuclear CN III lesions (including bilateral ptosis and superior rectus deficits) Nuclear CN IV lesions (contralateral CN IV deficit)
Cerebral peduncles	Weber syndrome (ipsilateral CN III, contralateral hemiparesis)
Red nucleus	Benedikt's syndrome (ipsilateral CN III, contralateral tremor)
Ascending cerebellar fibers	Claude's syndrome (ipsilateral CN III, contralateral cerebellar ataxia)
Pons tegmentum	Ipsilateral gaze palsy (“wrong-way eyes”) Internuclear ophthalmoplegia One-and-a-half syndrome

	Skew deviation CN V, VI, VII, and VIII lesions
Basis pontis	Contralateral hemiparesis Contralateral ataxia Dysarthria
Medulla lateral	Wallenberg syndrome (ipsilateral CN V, ipsilateral Horner's syndrome, contralateral loss of pain and temperature below the neck [spinothalamic tract], vertigo and ipsilateral nystagmus, ipsilateral CN IX and X deficits, skew deviation)
Medial	Ipsilateral CN XII deficit, contralateral hemiparesis, contralateral medial lemniscus deficit (joint position and vibration)

CN, cranial nerve: INO, internuclear ophthalmoplegia.

Reprinted from [7] with permission.

**Table 1.3 Localization of spinal cord lesions.**

Site	Finding
Spinal cord	Bilateral signs LMN signs at the level of the lesion UMN signs below the lesion Marked spasticity with Babinski signs Absent jaw jerk Sensory level at or below the level of the lesion
Craniocervical junction	Neck pain, head tilt Downbeating nystagmus UMN signs of all four extremities
Cervical spinal cord	Neck pain Root signs at the dermatomal level of the lesion in the neck, shoulders, or arms

	<p>Long tract signs below the level of the lesion (usually bilateral)</p> <p>Sensory level at or below the level of the lesion</p> <p>Spastic bowel and bladder (later)</p>
Thoracic spinal cord	<p>Back pain</p> <p>Root signs at the level of the lesion</p> <p>Paraparesis: long tract signs below the level of involvement</p> <p>Sensory level below the level of involvement</p> <p>Spastic bowel and bladder</p>
Conus medullaris (S3--Coc1)	<p>Early bowel, bladder, and sexual dysfunction; usually areflexic (LMN) bladder outlet obstruction.</p> <p>Early perineal hypesthesia</p> <p>No motor signs in legs (if pure)</p> <p>Distal motor signs with loss of ankle jerks (if epiconus, L4--S2)</p>
Cauda equina anterior cord syndrome	<p>AHC (LMN) involvement at the level of the lesion</p> <p>Corticospinal tract involvement below the lesion</p> <p>Spinothalamic tract involvement below the lesion</p> <p>Sparing of the dorsal columns</p> <p>Spastic bowel and bladder</p>
Central cord syndrome	<p>Segmental loss of pain and temperature at the level of the lesion</p> <p>UMN signs below the lesion</p> <p>Sparing of dorsal column modalities</p> <p>Sacral sparing</p>
Brown–Sequard (hemicord) syndrome	<p>Ipsilateral corticospinal tract signs below the lesion</p> <p>Ipsilateral loss of vibration and joint position sense below the lesion</p> <p>Contralateral loss of pain and temperature below the lesion</p> <p>Band of ipsilateral hypesthesia to all modalities at the level of the lesion</p>

---

AHC, anterior horn cell; LMN, lower motor neuron; UMN, upper motor neuron.

Reprinted with permission from [7].

**Table 1.4 Localization of lower motor neuron lesions.**

Site	Finding
Anterior horn cells	Evolves to involve all four extremities (may not at first) – LMN involvement of the lower extremities may distinguish it from cervical spondylosis – in ALS Atrophy, fasciculations , and weakness Hypotonicity and loss of reflexes Tongue and other involvement above the neck (in ALS) Usually with associated UMN signs (in ALS)
Roots	Dermatomal pain and paresthesias Unilateral (unless multiple, as in GBS) Dermatomal sensory loss Myotomal weakness Isolated DTR
Cauda equina	Low back and perineal pain LMN deficits of the lower extremities (may be asymmetric) Early areflexic bladder and bowel
Nerve mononeuropathy	Pain and paresthesias in sensory nerve distribution (light touch loss typically involves greater area than pinprick loss) Sensory and motor deficit characteristic of a peripheral nerve
Polyneuropathy	Usually distally predominant stocking--glove distribution <small>Deficit gradient from distal to proximal</small>

**Distribution from distal to proximal**

Symmetric deficits

Loss of motor, sensory, or autonomic function,  
depending on the nerves involved

Loss of ankle jerks in most

---

ALS, amyotrophic lateral sclerosis; DTR, deep tendon reflex; GBS, Guillain–Barré syndrome; LMN, lower motor neuron; UMN, upper motor neuron.

Reprinted with permission from [7].

Alternative distributions that may affect portions of one lobe or involve more than one lobe of the brain include classic vascular territory lesions of the cerebral cortex and subcortical regions. For example, middle cerebral artery territory deficits which include subcortical regions classically produce contralateral deficits of arm and face more than leg, and contralateral sensory loss with increased reflexes. If originating in the dominant hemisphere, aphasia will be apparent. Other findings include apraxia, contralateral field deficits, and early on there may be gaze deviations to the side of the lesion. Anterior cerebral artery territory lesions cause deficits of contralateral leg more than arm and face. There may be contralateral cortical sensory loss in the leg, and increased deep tendon reflexes . Additionally, incontinence and frontal lobe signs may be present. Posterior cerebral artery territory deficits may produce a homonymous hemianopia, contralateral sensory loss, and sometimes visual agnosia or alexia without agraphia. Borderzone vascular territory syndromes termed watershed syndromes, such as the bilateral anterior watershed territory (man in a barrel syndrome) ischemic syndromes, can be particularly challenging to identify.

## **Subcortical white matter disturbances**

Consolidation of pyramidal tract fibers makes it feasible that even small lesions can produce substantial deficits (Box 1.1). While affection of the corona radiata may elicit more variability in degree of paresis among face, arm, and leg, lesions of the posterior limb of the internal capsule may produce a uniform deficit throughout the contralateral side. Sufficiently large subcortical lesions often produce visual field deficits.

Examples of subcortical lesions include lacunar strokes .

---

### **Box 1.1 Subcortical white matter disturbances.**

Syndrome	Localization	Findings
Dysarthria clumsy hand syndrome	Junction internal capsule and corona radiata (also seen with pontine lesions)	Facial paresis, dysarthria, mild paresis and clumsiness of contralateral hand
Ataxic hemiparesis syndrome	Posterior limb of internal capsule, pons	Contralateral dysmetria and distal lower extremity paresis
Pure motor stroke	Corona radiata, genu or posterior limb of internal capsules. (Also seen with lesion in pons or medullary pyramids)	Contralateral paresis or plegia without sensory deficits, cortical signs or visual field deficits

Bilateral subcortical processes commonly connote demyelinating disease.

### **Subcortical gray matter lesions**

Thalamic lesions should be considered in the face of profound contralateral primary modality sensory deficits. Many other thalamic-related symptoms have been reported depending upon the specific nucleus affected. These include contralateral severe pain, transcortical aphasia , or acute agitation .

Basal ganglia affection should be considered with findings of Parkinsonian symptoms (e.g. pill-rolling resting tremor , bradykinesia , festinating gait ,

postural loss ), hemiballismus , chorea , or athetoid movements . Patients may also complain of swallowing difficulties , and alterations of speech articulation and gait.

## **Diffuse or bilateral hemispheric disturbances**

The category of diffuse cortical involvement may be applied to situations in which there is no clear-cut lateralization to findings. This may be associated with depressed mentation either with altered sensorium as in a toxic–metabolic encephalopathy or with preserved sensorium but altered cognition as in a dementia . Bilateral corticobulbar tract disturbances can produce a pseudobulbar palsy characterized by dysarthria , loss of inhibition of emotional expression, and hyperactive bulbar reflexes .

## **Brainstem syndromes**

Lesions of the brainstem are usually suspected when there are crossed deficits, usually with ipsilateral motor or sensory deficits on the face but contralateral deficits in the rest of the body, or in company with specific cranial nerve deficits such as those subserving eye movements, facial sensation, facial movements, or swallowing [4]. Depending on the site of brainstem involvement, patients may complain of varying combinations of double vision , speech articulation difficulties , vertigo , facial numbness , or facial weakness contralateral to limb weakness . The ocular motility disorder internuclear ophthalmoplegia (INO) indicates a disturbance of the medial longitudinal fasciculus in the brainstem.

## **Cerebellar syndromes**

These are traditionally divided into the appendicular type referring to lateral cerebellar hemispheric problems and characterized by ipsilateral signs of ataxia including dysmetria and intention tremor , dysdiadochokinesia and diminished tone in the ipsilateral limbs. Truncal or midline cerebellar deficits are suggested by a wide-based gait , scanning speech , and truncal titubation . Affectation of the floccular-nodular lobe is associated with vestibulocerebellar ataxia characterized by many ocular findings including nystagmus , distortion of smooth and saccadic pursuits , ocular malalignment , diplopia , and oscillopsia , along with episodes of vertigo, gait and motor ataxia along with head tilting [8].

## **Spinal cord syndromes**

These should be suspected when the face is spared and with motor and sensory deficits at levels below the lesion [4]. Sphincter dysfunction due to autonomic fiber involvement is another clue to spinal cord localization.

Lesions of the high cervical area are the exception to the facial sparing rule and should be considered in the presence of upper and lower extremity upper motor neuron signs in the absence of hemispheric or brainstem deficit signs.

Pyramidal tract involvement is associated with upper motor neuron type deficits such as spasticity which may be perceived as stiffness in the lower extremities . Distal weakness tends to exceed proximal weakness. Classically, there is a sensory “level” representing a sharp line below which there is diminished sensation.

The nature of the deficits in spinal cord lesions depends not only upon the lesion localization in the rostro-caudal plane but also in the transverse plane, since there are many and diverse motor and sensory tracts running perpendicularly at different antero-postero and lateral regions along the transverse plane. Upon suspecting a myelopathic localization, the clinician should then consider specific spinal cord patterns. For example, a complete transverse cord syndrome of the thoracic cord will produce paresis of both lower extremities, a sensory level and sphincter problem . An anterior cord syndrome such as that due to anterior spinal artery insufficiency affects the lateral spinothalamic tracts and hence creates a sensory level for pain and temperature sensation but spares the dorsal columns that subserve joint position and vibration. A motor deficit may also occur.

Posterior column syndromes, such as with tabes dorsalis or vitamin B12 deficiency, spare pain and temperature but create joint position and vibration sensory loss. The hemicord Brown–Séquard syndrome causes ipsilateral paresis due to affection of lateral corticospinal tracts and anterior horn cells, and ipsilateral pain and temperature of only one segment due to effects on the nerve root entering the cord and crossing to the contralateral spinothalamic tract. Contralaterally, there is pain and temperature deficit below the affected level.

A “suspended” sensory level may occur with involvement of inner laminations of the spinothalamic tract and crossing fibers traveling to each spinothalamic tract and creating pain and temperature sensory deficits in a cape, unilateral limb, or in multiple adjacent segments.

Affection of the anterior horn cell region spares upper motor neurons and creates muscle atrophy , flaccid paresis , and diminished deep tendon reflexes .

Another classically cited distinction is made between lesions that are intramedullary (where dissociation of pain and temperature deficits from joint position and vibration is more common) and extramedullary (upper motor neuron signs tend to occur later, radicular pain is less likely, and sphincter loss is more common). Extramedullary lesions are further classified as extra-or intradural.

The lowest spinal cord lesions, involving the conus medullaris (associated with lower sacral root sensory loss – perianal hypesthesia, less intense radicular pain, and L5–S1 motor deficits such as ankle paresis) are distinguished from the cauda equina syndrome characterized by saddle hypesthesia , lower motor often asymmetric paraparesis , multiple sensory dermatomal loss, later sphincteric dysfunction, and marked radicular pain [9].

## **Lower motor neuron syndromes**

### ***Dorsal root ganglion***

Sensory neuronopathies may be confused with sensory polyneuropathies. Sensory neuronopathies are characterized by profoundly diminished vibration and proprioceptive loss, profound sensory ataxia, and loss of reflexes that may be worse in hands compared with feet. Pain and temperature modalities are less affected.

### ***Nerve root***

This is suggested by the finding of specific dermatomal sensory loss and myotomal deficits that fit the distribution of a nerve root. Radiating pain often in association with neck or back pain is common.

### ***Plexus***

A plexus lesion should be suspected when sensory motor deficits suggest a distribution that goes beyond a single nerve. Classic types of brachial plexopathies include the Erb–Duchenne upper trunk C5–C6 plexopathy where the upper extremity assumes a dangling limp extended posture. There are many other varieties of complete or partial brachial or lumbosacral plexopathies.

### ***Specific nerves***

Mononeuropathies are suspected when motor and sensory deficits fit within the distribution of a single nerve. Specific examples of mononeuropathies are highlighted in specific chapters of this book. Some mononeuropathies involve nerves consisting of primary sensory fibers and hence produce sensory deficits such as on the thigh seen with meralgia paresthetica due to problems of the lateral femoral cutaneous nerve.

Mononeuropathy multiplex is characterized by involvement of multiple nerves, often in random areas. Over time, progressive involvement of more nerves and increased severity of deficits lead to the potential confusion with polyneuropathies.

## ***Peripheral neuropathies***

Generalized neuropathies are associated with usually distal sensory loss (classically a “stocking--glove distribution”), distal paresis , atrophy , fasciculations , and diminished reflexes . Classic neuropathies are length dependent and typically begin in distal extremities and climb more proximally. The many varieties of polyneuropathies , such as those that are predominantly sensory or predominantly motor, are discussed in detail in the chapter on this topic.

## **Syndromes with combined upper and lower motor neuron deficits**

This combination, summarized under the term “motor neuron disease,” is the hallmark of amyotrophic lateral sclerosis (ALS) and is distinguished from pure upper motor neuron diseases such as primary lateral sclerosis and purely lower motor neuron disease such as the spinal muscular atrophies . Motor neuron disease displays combinations of upper motor neuron deficit signs such as spasticity and hyperreflexia with lower motor neuron deficit signs such as muscle atrophy and fasciculations. Progressive diffuse weakness , along with speech, swallowing, and respiratory difficulties occur in ALS.

Motor neuron disease should be distinguished from cervical lesions such as spondylosis or neoplasms in which there are lower motor neuron signs in the upper extremities due to nerve root compression but myelopathic upper motor neuron signs such as spasticity evident in the lower extremities.

## **Syndromes with combined spinal cord and peripheral nerve lesions**

Subacute combined degeneration associated with vitamin B12 deficiency is an example where the problem involves two sites of the neuro-axis. Peripheral neuropathy is an often painful sensory or sensorimotor neuropathy while affection of the lateral and dorsal columns of the spinal cord produces severe proprioceptive sensory deficits along with spasticity and paraparesis . Involvement of other sites in the nervous system can lead to other symptoms such as dementia or visual deficits .

## ***Neuromuscular junction***

This is often suspected in the presence of fluctuating weakness , usually with exacerbation with use of the affected musculature (unless a Lambert–Eaton variant), and typically improving with rest. Sensory loss is absent. Examination often documents fatigability usually of proximal muscle groups and often includes facial, especially ocular, musculature. Bulbar musculature involved in the neuromuscular junction (NMJ) syndrome of botulism can be confused with brainstem lesions such as stroke which will present more static classic combinations of findings that fit with specific vascular syndromes. Acute inflammatory demyelinating polyneuropathy (AIDP; Guillain–Barré syndrome) may also look like a NMJ disease but the latter usually presents with bulbar symptoms earlier on and lacks the classic ascending paralysis pattern. Bulbar involvement in NMJ disorders helps distinguish it from myopathies.

## ***Muscle***

Myopathy is often suggested by the presentation of fairly symmetric proximal weakness in the absence of sensory complaints. Depending on the type of myopathy, symptoms may develop acutely, or more gradually, and may or may not be associated with muscle pain and tenderness. Proximal muscle weakness often comes to medical attention as the patient begins to observe difficulty climbing stairs, getting up from a chair, or combing hair. Examination may show evidence of muscle atrophy.

## ***Generating a differential diagnosis***

As discussed earlier, traditional approaches in neurology promote the concept of

identifying the salient symptoms and signs and then applying parsimony in localizing neurologic deficits. Once one generates an idea of where the deficit arises, and then places it in the context of the history, one can then generate a succinct “synthesis statement” which captures the essence of the case. This in turn leads to the consideration of the broad list of categories that apply to that specific region of the neuro-axis (e.g. toxic, metabolic, ischemic) that explain how the deficit or dysfunction occurred. We have found the following list of categories of pathologic processes, with examples of specific etiologies, to be useful in thinking about differential diagnosis:

- Structural (congenital or acquired).
- Toxic (medication/drugs, toxic substances, withdrawal states).
- Infective/post-infective (meningitis, encephalitis, sinus, osteomyelitis, abscess); viral, bacterial, parasitic/protozoal, mycobacterial, fungal, spirochete, prion, post-infective.
- Pressure effects (increased intracranial pressure, herniation, hypertension, entrapment, decreased pressure).
- Psychiatric.
- Inflammatory (post-radiation therapy, granulomatous, collagen vascular, auto-immune).
- Neoplastic/paraneoplastic.
- Degenerative (acquired or heredofamilial such as dysgenetic syndromes, neurophakomatoses).
- Vascular (ischemia, hemorrhage), including aberrations in vessels, vasculitis, vascular spasm, hematologic, embolic, thrombosis.
- Metabolic (electrolyte/liver function test abnormality, endocrine, enzyme defect/deposition disease [lysosomal and other] mitochondrial, nutrient deficiency).
- Movement disorder (such as dystonia, chorea, dyskinesia).
- Sleep disorder.
- Congenital.
- Heredofamilial.
- Traumatic.
- Ictal.
- Demyelinating.
- Other, idiopathic.

The choice of the most likely etiologies is often dictated by knowledge about

other features of the symptoms and signs such as timing issues (frequency, duration, nature of onset, and termination) or circumstances of their occurrence. For example, transient neurologic events involving altered awareness or altered behaviors conjure up very specific types of diagnostic possibilities such as seizures, conditions that cause transient increased intracranial pressure, transient ischemic attacks (TIAs), movement disorders, syncope, or psychiatric symptoms. Etiologies for symptoms that develop slowly and become progressively worse suggest expanding lesions such as a neoplasm whereas acute onset symptoms may suggest an acute ischemic stroke or intracerebral hemorrhage.

Fundamental features about the patient, such as age and gender, often play crucial roles in narrowing down diagnostic possibilities. Some diagnoses may be sex-linked genetic disorders. Some diseases only afflict patients in childhood. Other risk factors are integrated into the clinician's diagnostic process such as race, prior or current illnesses, occupation and exposures, among many other factors. On the other hand, the clinician should be cautious to avoid a narrow view about the likely diagnosis simply based upon a compelling past medical history of a given condition.

Probability dictates that more common disorders, even with more unusual presentations, are more likely to explain symptoms compared with a common presentation of a rare disorder [10]. A narrowed list of possibilities is then subjected to further clarification through the use of additional testing.

Similar to the parsimonious approach taken in trying to find the least number of explanatory localization sites, a unifying etiology is promoted wherever possible, as the most likely explanation of even diverse symptoms and signs [10]. Sometimes, a patient's symptoms and signs are best explained as a manifestation of a syndrome, which represents a convenient way of looking at characteristic features that often go together and may lend itself to a set of uniform treatments or typical prognosis. For example, myoclonus may be explained by an epilepsy syndrome termed juvenile myoclonic epilepsy which may have diverse genetic etiologies. Some syndromes that are in a differential diagnosis may have currently unknown causes.

The narrowed-down list of differential diagnosis possibilities can be classified according to what is most likely, what is less likely, and important diagnoses that should be excluded even if less likely [11]. For example, a neoplasm may be unlikely but still possible; missing it could have devastating consequences.

Generating and refining the list of diagnostic possibilities is a cyclical process. Similar to the scientific method in studying research questions, hypotheses are generated and then tested through additional history, examination findings, and then formal testing procedures. Based upon these results, the clinician returns to the list of diagnostic possibilities and seeks further clarification on history, exam, and other tests when needed. Not infrequently, specific diagnoses to explain a patient's problems may not be successfully derived; however, even the exclusion of serious diagnostic causes represents an achievement of carefully thinking through the differential diagnosis.

## Conclusions

Generating a neurologic differential diagnosis requires a logical and thoughtful approach. Following a step-wise procedure of localizing the lesion, and then considering the wide range of diagnostic possibilities for that site of localization, is an optimal way to generate the most likely diagnostic possibilities. The chapters of this book can aid the clinician in performing the challenging task of generating the differential diagnosis pertaining to the presenting phenomenology.

## References

1. Ettinger AB, Weisbrod DM. *The Essential Patient Handbook; Getting the Health Care You Need – From Doctors Who Know*. New York, NY: Demos Medical Publishers, 2004.
2. Ettinger AB, Devinsky O. *Managing Epilepsy and Co-Existing Disorders*. Boston, MA: Butterworth Heinemann, 2002.
3. Waxman SG. Introduction to clinical thinking: The relationship between neuroanatomy and neurology. In: *Clinical Neuroanatomy*, 25th edn. New York, NY: Lange Medical Books/McGraw-Hill, 2003: 35–44.
4. Aminoff MJ, Greenberg DA, Simon RP. Neurologic history and examination. In *Clinical Neurology*, 6th edn. New York, NY: Lange Medical Books/McGraw-Hill, 2005.
5. Biller J, Gruener G, Eds. *A Synopsis of the Neurologic Investigation and a Formulary of Neurodiagnosis*, 6th edn. New York, NY: McGraw-Hill Professional, 2011.

6. Kaufman DM. Central nervous system disorders. In *Clinical Neurology for Psychiatrists*, 6th edn. Philadelphia, PA: W.B. Saunders, 2007: 5–17.
7. Feske SK. Neurologic history and examination. In *Office Practice of Neurology*, 2nd edn. Philadelphia, PA: Churchill Livingstone, 2003: 2–35.
8. Waxman SG. The brainstem and cerebellum. In *Clinical Neuroanatomy*. New York, NY: McGraw Hill Medical, 2010: 79–98.
9. Marshall RS, Mayer SA. *On Call Neurology*, 3rd edn. Philadelphia, PA: Saunders/Elsevier, 2007.
10. Daroff RB, Bradley WG. *Bradley's Neurology in Clinical Practice*, 6th edn. Philadelphia, PA: Elsevier/Saunders, 2012.
11. Stern SDC, Cifu AS, Altkorn D. *Symptom to Diagnosis: An Evidence-based Guide*, 2nd edn. New York, NY: McGraw-Hill Medical, 2010.

## 2 Agitation

---

Angela Scicutella and Durga Roy *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Agitation is defined as a cluster of behaviors marked by poorly organized, excessive, repetitious, and inappropriate motor or verbal activities which can fluctuate over time and are observed in diverse medical and psychiatric conditions. Key features of the syndrome include irritability, heightened response to stimuli, and sleep disruption. Aggression, which is socially inappropriate physical or verbal behavior directed towards another individual or object, and self-injurious behaviors can both be observed within the spectrum of agitation [1].

The neuroanatomy of agitation is not completely understood but is hypothesized to be a result of disruption either structurally or neurochemically in the cortico-striatal-thalamic circuitry; the motor aspect of agitation may be accounted for by pathology in prefrontal cortex or striatal regions (caudate, putamen, dorsal pallidum) whereas the emotional component of agitation may be explained by damage to cortical areas (orbitofrontal, temporal, or cingulate), limbic areas (amygdala, nucleus accumbens, ventral pallidum), or the hypothalamus [2].

### Case vignette

A 55-year-old man with a history of Down's syndrome was noted by staff at his residence to be more forgetful over the past year, with a decline in his ability to independently perform routine chores, and his usual cheerful demeanor was replaced by irritability. His roommate had recently been transferred to a nursing home, so the patient's symptoms were attributed to depression and an antidepressant was prescribed. There was not much improvement in mood, and over the next 6 months he was noted to be more confused, functionally

compromised, and belligerent when staff assisted him with toileting and dressing. He then underwent neurologic evaluation and with no evidence of stroke or tumor on neuroimaging, a diagnosis of Alzheimer's disease was made. Over the course of the next year, his sleep pattern changed and he was observed to be talking to himself and wandering around the house in the early morning hours. He was placed on neuroleptic medication to calm his agitation with some improvement, but several months later an acute change in this new baseline mental status was noted. Over a few days he exhibited increased confusion, incoherent speech, and combative behavior and was taken to the emergency room where medical evaluation revealed a urinary tract infection.

## Acknowledgment

The authors would like to acknowledge Dr. Pam Hoffman who assisted in formatting aspects of this chapter.

**Table 2.1 Agitation and aggressive behavior in patients with dementia or developmental disability.**

Item	Subdivision	Specific entity	Clinic
Toxic: Medications [3,4]	Anticholinergics	Benztropine trihexyphenidyl	Confusion disinhibition perception disturbance disorientation mydriasis xerostomia urinary hypotension
	Medications with anticholinergic side effects	Diphenhydramine Olanzapine Oxybutynin Tricyclic antidepressants	As per
	Antiepileptic drugs	Levetiracetam	Aggression

## (AEDs)

anxiety  
psychotic  
hostile  
occurs monthly  
treatment  
dose related

Barbiturates\*  
Gabapentin\*  
Topiramate\*

Disinhibition  
syndrome  
characteristic  
hyperactivity  
aggressive  
behavior  
impulsiveness  
Auditory  
visual hallucinations  
severe psychoses  
agitation

## Sedative-hypnotics (Benzodiazepines – BZDs)

Lorazepam (BZD)  
Alprazolam (BZD)  
Clonazepam (BZD)  
Zolpidem (non-BZD)

Paradoxical effects  
disinhibition  
confusion  
increased sensitivity  
impulsiveness  
mania  
Interpersonal  
symptoms  
insomnia

## Beta-blockers (in elderly demented)

Metoprolol  
Propranolol

Agitation  
aggression  
hallucinations  
paranoia  
bradycardia  
hypotension

Opiates	Morphine Fentanyl Dilaudid	Confusion anxiety psychosis nausea constipation
Agents for Parkinson's disease	Levodopa/carbidopa	Confusion disinhibition hallucinations paranoia dyskinetic movements chorea alternating movement dystonia dizziness vomiting insomnia orthostatic hypotension
	Amantadine	Edema hypotension confusion hallucinations more common in elderly
Serotonergic agents	SSRIs	Gastrointestinal symptoms headache may see mood changes behavioral changes increased sweating and agitation the first few weeks treatment
Steroids	Prednisone SoluMedrol	Mania irritability

			decreased energy, for sleepiness, pressure ulcers, delusions, hallucinations, and aggression
	Stimulants	Methylphenidate Dextroamphetamine	Decreased appetite, tachycardia, anxiety, aggression, paranoid delusions, hallucinations, and tics
Toxic: Withdrawal states	Benzodiazepine/ETOH withdrawal		Anxiety, agitation, psychosis, confusion, hypertension, tachycardia, tremor, nausea, seizures
	Opiate withdrawal	Morphine Fentanyl Dilauidid	Anxiety, lacrimation, myalgia, insomnia, rhinorrhea, yawning, vomiting
Infective/post-infective [3]	Encephalitis	Herpes encephalitis	Fever, nuchal rigidity, hallucinations, memory impairment

		erratic person change partial
	Meningitis	West Nile virus
	Neurosyphilis	Argyll pupils, forgetf irritabi person change delusio
	Pneumonia	Fever, crackl wheez
	Urinary tract infection	Fever, urinary and ur
Pressure effects [3]	Hypertensive encephalopathy	Severe hypert associ confus headac vomiti disturb seizure
Psychiatric [5,6]	Alcohol intoxication	Disinh bellige ~~~~~

		aggres slurrec ataxia
Anxiety	Generalized anxiety	Nervo shakin associ exagge and we fatigue tension palpita
Attention deficit hyperactivity disorder (ADHD) *		Inatter impuls hypera
Delirium	Hyperactive delirium	Menta chang over h and sy tend to wane i marked attention disorga thinkin disorie difficu memo psycho sympt chang restles worse increas activit of line sleep

Impulse control disorder      Intermittent explosive disorder\*      Violent combative behavior by env trigger proportionate stressc

Mood disorders      Depression      Tearful, enjoy sad feelings, worthlessness, somatic complaints, and apathy, and suicidal thoughts, depression, wringing, delusions, wrong

Mania      Irritable mood, need for pressure, racing thoughts, increased directness, impulsiveness, paranoid, hostile, judgment

Psychosis      Dementia      Delusions, money

posses  
missin  
(b) spc  
unfaith  
unwelc  
are liv  
house;  
is an i  
(Capg  
syndrc  
audito  
halluci  
paranc

### Schizophrenia

Comp  
persec  
delusio  
paranc  
commu  
audito  
halluci  
disorg  
behavi  
impuls

Neoplastic [3]      Brain tumor

Frontal/temporal  
cortex  
Limbic structures

Tumoi  
left he  
more r  
growir  
and in  
intracr  
pressu  
associ  
manic  
psycho  
irritabi  
increas  
agitati  
seizure  
.....

			<p>headache vomiting deficit motor/sensory may be focal</p>
Paraneoplastic [3]	Limbic encephalitis	Small cell lung carcinoma	<p>Subacute onset disorganized behavior agitation and sleep problems seizures communicative hallucinations preceded by other issues</p>
Degenerative [5]	Alzheimer's dementia	Aging Down's syndrome patients	<p>Gradual onset and functional decline irritability psychotic symptoms behavioral disturbances</p>
Vascular [7]	Stroke	Posterior cerebral artery infarct (mainly left-sided)	<p>Sensorimotor deficits visual field deficits communicative often right-sided signs/symptoms are often subtle hyperreflexia extremity weakness and agitation vivid dreams hallucinations delusions</p>

		Right hemisphere infarcts (orbitofrontal, basotemporal)	Hypotension Depression Delusions Irritability Inattention Distraction Extreme behavior May have hemia hemiparesis
Other [5,6]	Environmental	(a) Personal care (washing, dressing, toileting) (b) Lack of structure or change in routine (c) Stressors (noise, hunger, thirst, relationships)	Further history recent patient psychological status. to touch yelling attempt to leave oneself off clothes injury
	Functional decline	Deficits in vision, hearing, ambulation, continence, or communication skills (aphasia)	Due to frustration tolerance lower energy lead to behavioral changes above
	Pain	Dental problem, hip fracture, fecal impaction, reflux esophagitis, urinary retention, dysmenorrhea*	Facial stiffness contortion increased irritability yelling

guard  
physic  
and be  
above

Metabolic [3,11]	Dehydration	Dry m increas decrea output weakn
	Electrolyte abnormalities	Hypernatremia  Restles irritabi hyperr flushed oliguri
		Hyponatremia  Nause vomiti restles irritabi weakn cramp seizure
	Enzyme defects	Lesch–Nyhan syndrome (X-linked recessive trait; defect in purine metabolism)  Micro spastic chorec severe disabil male; l syndrc mutila includ fingers
		Sanfilippo Type B (deficiency of <i>N</i> - acetyl-alpha-D-

	glucosaminidase)	hyper aggres behavi and slē disturb
Encephalopathy	Hepatoencephalopathy	Asteri hyperr confus disinhi aggres behavi
	Uremic encephalopathy	Muscl myoclo tremor restles crawlin sensati limbs*
Hypoxia		Restle motor incoor inatter disorie associ respira hypote
Porphyrias	Acute intermittent porphyria (abnormality of porphobilinogen deaminase)	Abdor nausea constip fever, neurop restles paranc halluci more c female

~~common~~  
40; can  
precipi  
AEDs

Endocrine

Hypoglycemia

Sweati  
tachyc  
hypert  
tremor  
psychic

Hyperglycemia

Blurre  
thirst,  
mouth  
restles  
headac  
dizzine  
polyur

Hypothyroidism  
(myxedema)

Cold int  
constip  
brittle  
muscle  
with per  
change  
psychic

Hyperthyroidism

Heat int  
sweati  
diarrhe  
tachyc  
palpita  
hyperac  
irritabi  
pressur  
psychic

Vitamin deficiencies

Thiamine deficiencies

Anore  
cramps  
—  
—  
—  
—  
—

			paresu irritabi psycho anxiet impair
Movement disorders [8]	Akathisia	(a) Acute (within hours) (b) Tardive (delayed onset 3 months) (c) Chronic (persists for more than 3 months) (d) Withdrawal (within 6 weeks of medication discontinuation)	In assoc with h neuroleptic inabilit still, irrestless frantic constipation
	Catatonia	Excited type	In assoc with psychotropic medications neuroleptic disorders excess purposeful repetitive hyperactivity becomes stuporous exhausted leading to death
	Neuroleptic malignant syndrome		In assoc with neuroleptic or abrupt cessation of dopamine agonist

depur  
therap  
eleme  
leadpi  
rigidit  
hypert  
autonc  
instabi  
agitati  
confus  
deliriu

Serotonin syndrome	Use of two or more serotonergic agents; interaction between serotonergic agents and MAOIs, TCAs	Usually within medical administration. Three main types: (1) restlessness, agitation, confusion, fever, tachypnoea, diaphoresis, tremor, and myoclonus. Nausea and diarrhoea may also be observed.
Stereotypy*		Repetitive, purposeless, complex, rhythmic, involuntary movements of the body, face, slurred speech, incessant washing

Tic		Tourette's*	Rapid, stereotyped movements and vocalizations Motor: arm jerks, stomping, kicking Vocal: grunting, coprolalia, echolalia
Sleep disorder [9,10]	Circadian misalignment	Intrinsic circadian rhythm disorder (sundowning)	Occurs afternoons, evenings, increases confusion, wandering, agitation
		Irregular sleep--wake cycle	Advanced phase with first daytime leads to nocturnal with hallucinations, awake desire to get dressed early in morning
Dyssomnia		Insomnia	Difficulty initiating and maintaining sleep

disrup  
behavi  
crying  
and sc  
well as  
mainta  
which  
irritabi  
fatigue  
aggres  
the da

	Parasomnia	Rapid eye movement (REM) sleep behavior disorder	Male prepor occurs half of interm of ator REM s dream (i.e. pu kickin to inju partne assoc diffuse body c
Congenital [11]	Fragile X syndrome	Trinucleotide repeat mutation on X chromosome	More males female intelle disabil head, l ears, macro in mal
	Prader–Willi syndrome	Small deletion in chromosome 15	Short s small

Symptoms	Chromosome 15	Similar to
Trauma [3]	Focal brain injury Contusion Subdural hematoma Subarachnoid hemorrhage	Hyperdelirium; post-traumatic amnesia with agitation, akathisia, disinhibition. Residual symptoms: orbitofrontal lesions, disinhibition, impulsivity, sexual inappropriateness, behavioral obsessions and frequent signs; temporal lobe lesions, mania.
Demyelinating [11]	Leukodystrophies Metachromatic leukodystrophy (adult) (deficiency of lysosomal arylsulfatase A)	Behavioral changes; impairment, psychosis, disinhibition, motor dysfunction.

## Myoclonic seizures

Epilepsy [12]	Simple or partial complex or secondary generalized	Frontal lobe seizures	Pelvic pedal mover thrash and leg someti obscen vocaliz short r post-ic seizure cluster at nigh
	Complex partial or secondary generalized	Post-ictal psychosis	Occurs cluster seizure paranc delusio as agg behavi can be toward others
	Non-epileptic events		Uncoo violenc disorg motor which longer seizure discret stop” (
	Non-convulsive status		Often or elde

past se  
history  
abrupt  
bizarre  
change  
halluci  
and pa  
which  
days to

---

MAOIs, monoamine oxidase inhibitors; SSRIs, selective serotonin reuptake inhibitors; TCA, tricyclic antidepressant.

\* May see in patients with intellectual or developmental disability.

\*\* Please see description of delirium under Psychiatric subdivision.

## References

1. Lindenmayer JP. The pathophysiology of agitation. *J Clin Psychiatry* 2000; 61[suppl 14]:5–10.
2. Sachdev P, Kruk J. Restlessness: the anatomy of a neuropsychiatric symptom. *Aust NZ J Psychiat* 1996; 30:38–53.
3. Haskell RM, Frankel HL, Rotondo MF. Agitation. *AACN Clinical Issues* 1997; 8:335–50.
4. Ettinger AB. Psychotropic effects of antiepileptic drugs. *Neurology* 2006; 67:1916–25.
5. Kahn D, Gwyther LP, Frances A *et al*. Treatment of dementia and agitation: a guide for families and caregivers. *Postgrad Med Special Report* January 2005:101–9.
6. Antonacci DJ, Manuel C, Davis E. Diagnosis and treatment of aggression in individuals with developmental disabilities. *Psychiatr Q* 2008; 79:225–47.
7. Caplan LR. Delirium: a neurologist's view – the neurology of agitation and overactivity. *Rev Neurol Dis* 2010; 7:111–18.

8. Jackson N, Doherty J, Coulter S. Neuropsychiatric complications of commonly used palliative care drugs. *Postgrad Med J* 2008; 84:121–6.
9. Bombois S, Derambure P, Pasquier F *et al.* Sleep disorders in aging and dementia. *JNHA* 2010; 14:212–17.
10. Boyle A, Melville CA, Morrison J *et al.* A cohort of the prevalence of sleep problems in adults with intellectual disabilities. *J Sleep Res* 2010; 19:42–53.
11. Sedel F, Baumann N, Turpin JC *et al.* Psychiatric manifestations revealing inborn errors of metabolism in adolescents and adults. *J Inherit Metab Dis* 2007; 30:631–641.
12. Ettinger AB, Steinberg AL. Psychiatric issues in patients with epilepsy and mental retardation. In Ettinger AB, Kanner AM, Eds. *Psychiatric Issues in Epilepsy: A Practical Guide to Diagnosis and Treatment*. Philadelphia, PA: Lippincott Williams & Wilkins, 2001: 181–99.

## 3 Agnosias

---

Marlene Behrmann and Maxim D. Hammer *Neurologic Differential Diagnosis*,  
ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge  
University Press. © Cambridge University Press 2014.

### Introduction

Agnosia (agnosis, or loss of knowledge) refers to a class of neuropsychological impairments in which the affected individual is unable to recognize an object successfully. This recognition failure can occur in the visual, auditory, or tactile modality, and arises despite preserved sensory information in that modality. In other words, the primary sensory modalities are preserved but there is impairment of higher-order representations of objects in the affected domain. The recognition impairment is neither attributable to an anomia or to a semantic deficit (or lack of knowledge about objects in general) because patients can successfully identify the same object presented in a different sensory modality. The preserved long-term representation of objects can also be revealed as, for example, patients with visual agnosia may be able to visualize a particular object in their “mind’s eye” but, presented with the same object, may fail to identify it.

### Visual agnosias

Because visual agnosia is the best-studied instance of the agnosias, we focus more specifically on this impairment here. Patients with visual agnosia may have fully, or at least relatively, preserved visual acuity [1] and sensory vision (e.g. contrast sensitivity or brightness discrimination) and fall into one of at least three subtypes. Apperceptive agnosia corresponds to the breakdown at the stage of visual processing at which the elementary features of the stimulus are processed and a structural description of the input is derived – a relatively early stage of the visual recognition system (see [Table 3.1](#) for description of all agnosia types as well as neuropathologic basis and clinical manifestation). Not surprisingly, a person with apperceptive agnosia fails to produce a coherent copy of a target stimulus and fails to match a visual target against a set of choice objects. In contrast, a person with associative agnosia cannot use the well-specified

perceptual representation to access the stored knowledge of the object's functions and associations – for example, such an individual is able to copy and match a target object while still unable to identify the object (this disorder is often described as “perception stripped of meaning”). Whether perception is entirely normal in associative agnosia remains somewhat controversial. Finally, integrative agnosia, recognized more recently than the other subtypes and likely lying intermediate between the two other types, refers to the impairment in grouping disparate elements of the display into a coherent whole, with a piecemeal approach to perception [2,3]. Such individuals may be able to copy and match a target object but this is done in a slow, segmental, and laborious fashion, perhaps feature-by-feature.

**Table 3.1 *Classification of visual agnosias, underlying neuropathology, and clinical manifestation.***

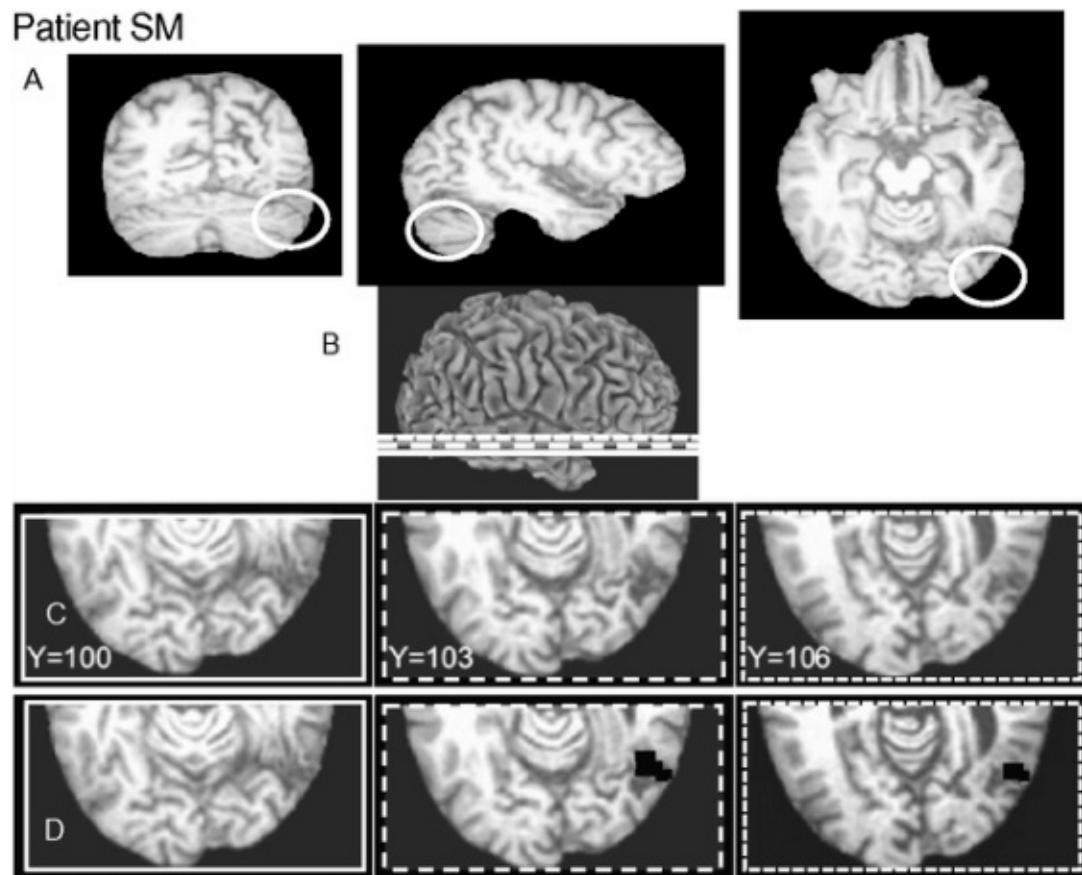
Type	Neuropathology	Clinical manifestation
Apperceptive agnosia	Stroke, anoxia, carbon monoxide poisoning affecting occipital, parietal, or posterior temporal regions bilaterally	Unable to copy, match, or identify visual stimuli
Associative agnosia	Usually bilateral infarction of the posterior cerebral arteries but unilateral temporo-occipital damage may suffice	Able to copy and match stimuli, may even be able to provide verbal description of aspects but still fails to recognize the object
Integrative agnosia	Extensive extrastriate damage bilaterally or to the right	Fails to piece the components of an object together, so oversegments or perceives in segmental fashion

## hemisphere

Prosopagnosia	Acquired form: bilateral inferomesial visual association cortices (lingual and fusiform gyri) and subjacent white matter	Failure to recognize faces
Agnosia for words	Left occipitotemporal cortex	“Pure” alexia – fails to read words normally in the face of normal language and sensory visual function
Agnosia for scenes	Bilateral or right posterior artery infarction involving the fusiform and lingual gyri, extending to the parahippocampal gyrus	Failure to recognize landmarks or known scenes
Developmental agnosia	No obvious neural concomitant on clinical scanning	Difficulty in acquiring mastery over word, face, or object recognition (developmental dyslexia or developmental/congenital prosopagnosia) or even in forming mental maps of their environment
Posterior cortical agnosia	Focal right temporal and/or occipital lobe atrophy	Progressive decline in complex visual functions and recognition

It is thought that these subtypes of agnosia reflect a spectrum of impairments in the different stages in object recognition and localization of lesion [4]. Thus, apperceptive agnosia has been associated with more posterior diffuse lesions resulting from mercury or lead poisoning or from carbon monoxide inhalation whereas the higher-order forms of agnosia are associated with more focal lesions situated more anteriorly in the visual system. [Figure 3.1](#) depicts the lesion of a patient, SM, who sustained damage to the right occipitotemporal lobe and who suffers from integrative agnosia. SM can match and copy objects albeit in a slavish fashion. Like other agnosic individuals, SM's failure to recognize objects occurs under a whole range of conditions and is independent of whether the stimulus is presented as a real three-dimensional object, black-and-white line drawing, or as a photograph [5]. Dramatically, SM's perceptual failures occur despite normal or near-normal elementary visual function, along with normal semantic and memory functioning. SM, like other agnosic individuals, also has intact alertness, intelligence, and language, thus setting aside questions about whether agnosia is simply a manifestation of reduced elementary visual function and intelligence.

Patient SM



**Figure 3.1** (A) Coronal, sagittal, and axial views of SM's lesioned right hemisphere in anatomical space and (B) inflated view. The markings of the overlaid slices correspond to the axial slices shown in (C)–(D). The white line/outline indicates the bottom slice, the large-dash line/outline indicates the middle slice, and small-dash line/outline indicates the top slice. Note that the bottom slice is inferior to the lesion, whereas the middle and top slices cover the lesion site. (C) Axial view of the lesion site and Talairach coordinates. The slices were cut along the temporal poles for enlarged representation of occipitotemporal cortex. (D) Axial view of the lesion site as marked (in black). Reproduced from Konen C, Behrmann M, Nishimura M, Kastner, S. The functional neuroanatomy of object agnosia: a case study. *Neuron* 2011;71:49–60.

Although agnosias are usually acquired in adulthood as a consequence of a stroke, tumor, trauma (as in SM's case), or other form of brain damage, there are a few cases of agnosia reported in individuals who have sustained a brain lesion early in life, a disorder referred to as “developmental agnosia.” Agnosia may also be evident in individuals who are apparently impaired at object recognition from birth but in the absence of any obvious neurologic concomitant [6, 7] (see Table 3.1). Finally, agnosia can occur in the context of a progressive deterioration of perceptual skills, as in the case of visually selective progressive posterior cortical atrophy [8].

Visual agnosia can be general, affecting the recognition of all visual stimuli or, in the higher-order form of the disorder, it can be more specific [9]: for example, there are agnosias that are relatively selective for objects, or for body parts, or for colors [10]. Topographic agnosia is another variant in which patients have difficulties with scene perception and different subtypes exist including landmark agnosia (the failure to recognize buildings and scenes), problems in cognitive map formation , or heading disorientation (a failure to discern the relationship between objects in the environment). The lesion in such cases may implicate the fusiform and lingual gyri, extending to the parahippocampal gyrus.

Prosopagnosia , in which there is failure to recognize familiar faces or even discriminate between novel faces, is typically associated with normal voice and face recognition. In many instances, these patients can describe the face in detail, including the age and gender of the person, but still be unable to say whose face it is. The ability to extract information about emotional expression is preserved in some cases but not in others. The prosopagnosia deficit is typically perceptual

in nature, rather than arising from a memory (although there are prosopamnesic cases for whom this is the core of the deficit) or semantic deficit, nor from a failure to label the face (an anomia). The acquired form of the disorder usually results from a lesion to the right fusiform gyrus although some more anterior lesions could produce the same outcome (also, for left versus right lesions, see [11]). The developmental or congenital variant of prosopagnosia has received considerable recent attention, with growing recognition that there is a familial component and that the incidence may be as high as 2% in the population [12]. Prosopagnosia, especially the congenital form, must be differentially diagnosed from autism spectrum disorder and other social disorders.

Patients with left posterior lesions, usually to the so-called visual word form area of the fusiform gyrus, evince a deficit in word recognition with intact writing abilities (and hence the failure to read what she herself has written), termed pure alexia or agnosic alexia. The deficit may extend beyond the ability to recognize text per se, impairing the recognition of other alphanumeric stimuli, too, and even affecting object recognition [13]. These patients have normal language function and may be able to spell words out loud.

The agnosias catalogued above all implicate problems in visual shape perception but there have also been occasional reports of patients who have preserved shape processing but impaired perception of material properties, such as texture [14].

Finally , the disorder of simultanagnosia, an inability to “see” more than one object at a time, which often accompanies Balint's syndrome, results from lesion to the dorsal (occipitoparietal) pathway. Such patients fail to recognize multiple aspects of a scene simultaneously and may fail to extract the gist or holistic nature of the scene. This is also commonly seen following certain right hemispheric strokes, and in such cases, “visual field testing” (presentation of one object at a time to different visual areas) is normal, but presentation of simultaneous visual stimuli to both the right and the left hemifields results in “visual extinction” of the object presented to the patient's left side.

One final note of caution is necessary: although, as outlined here, there are cases who evince fairly “pure” forms of these various agnosias, there are many reported cases in whom more than one type of agnosia occurs (see Table 3.1 for forms of agnosia).

## Other agnosias

Auditory agnosias refer to a spectrum of disorders of auditory processing, with preserved perception of auditory input. *Non-verbal auditory agnosia* refers to the inability to recognize common objects by their sounds. For example, a patient with this disorder might hear the sound of a telephone ringing, but may mistakenly identify the object as a car horn. *Pure word deafness* and *cortical deafness* are closely related disorders in which verbal auditory language is not recognized, while non-verbal auditory input is preserved, as are all other modalities of language function (including reading comprehension). Cortical deafness is usually caused by injury to one or both mesial temporal lobes. In *phonagnosia*, patients may lose the ability to recognize familiar voices.

Tactile agnosia, which refers to the disorder of object recognition by touch, is difficult to assess and its existence is controversial. However, a form of tactile agnosia, *simultagnosia*, is commonly seen following certain right hemispheric strokes, and is analogous to visual extinction. In such cases, sensory testing is normal, but presentation of simultaneous sensory stimuli to both the right and the left sides results in “sensory extinction” of the object presented to the patient's left side.

Anosagnosia is the unawareness of illness, and refers primarily to patients who have had a massive right hemispheric stroke resulting in not only severe left hemiparesis , but unawareness of the hemiparesis. Anosagnosia is poorly understood, although it has been postulated to be a disorder of body image or representation.

## References

1. Farah MJ. *Visual Agnosia*, 2nd edn. Cambridge, MA: MIT Press, 2004.
2. Riddoch MJ, Humphreys GW. A case of integrative visual agnosia. *Brain* 1987; 110:1431–62.
3. Riddoch MJ, Humphreys GW. Visual agnosia. *Neurol Clin*. 2003; 21:501–20.
4. Behrmann M. The neuropsychology of perceptual organization. In Rhodes G, Peterson M, Eds. *The Perception of Faces, Objects and Scenes: Analytic and Holistic Processes*. New York, NY: Oxford University Press, 2003.
5. Konen CS, Behrmann M, Nishimura M, Kastner S. The functional neuroanatomy of object agnosia: a case study. *Neuron* 2011; 71:49–60.

6. Gilai-Dotan S, Perry A, Bonneh Y, Malach R, Bentin S. Seeing with profoundly deactivated mid-level visual areas: non-hierarchical functioning in the human visual cortex. *Cereb Cortex* 2009; 19:1687–703.
7. Germine L, Cashdollar N, Duzel E, Duchaine B. A new selective developmental deficit: impaired object recognition with normal face recognition. *Cortex* 2011; 47:598–607.
8. Migliaccio R, Agosta F, Toba MN *et al*. Brain networks in posterior cortical atrophy: A single case tractography study and literature review. *Cortex* 2012; 48:1298–309.
9. Barton JJS. Disorder of higher visual function. *Curr Opin Neurol* 2011; 24:1–5.
10. Nijboer TC, te Pas SF, van der Smagt MJ. Detecting gradual visual changes in colour and brightness agnosia: a double dissociation. *NeuroReport* 2011; 22:175–80.
11. Gainotti G, Marra C. Differential contribution of right and left temporo-occipital and anterior temporal lesions to face recognition disorders. *Front Hum Neurosci* 2011; 5:55.
12. Mitchell KJ. Curiouser and curioser: genetic disorders of cortical specialization. *Curr Opin Genet Dev* 2011; 21:271–7.
13. Starrfelt R, Behrmann M. Number reading in pure alexia – a review. *Neuropsychologia* 2011; 49:2283–98.
14. Cavina-Pratesi C, Kentridge RW, Heywood CA, Milner AD. Separate processing of texture and form in the ventral stream: evidence from fMRI and visual agnosia. *Cereb Cortex* 2010; 20:433–46.

## 4 Anxiety and panic

---

Kenneth R. Kaufman *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

### Definition

Anxiety (an emotional state of feeling anxious or nervous) and panic (extreme anxiety associated with fear, apprehension, and even terror) are cardinal symptoms associated with anxiety disorders. DSM–IV–TR anxiety disorders include: (1) panic disorder with or without agoraphobia ; (2) agoraphobia without history of panic disorder; (3) specific phobia ; (4) social phobia (social anxiety disorder ); (5) obsessive-compulsive disorder ; (6) post-traumatic stress disorder ; (7) acute stress disorder ; (8) generalized anxiety disorder ; (9) anxiety disorder due to a general medical condition; (10) substance-induced anxiety disorder (both intoxication and withdrawal); (11) anxiety disorder not otherwise specified [1]. These disorders with associated anxiety and panic symptoms may be chronic (generalized anxiety disorder) or episodic (panic disorder) and may include other features including palpitations, shortness of breath, diaphoresis, hypervigilance, avoidance, muscle tension, and insomnia [1]. Anxiety is also prominent in the following adjustment disorders: (1) adjustment disorder with anxiety; (2) adjustment disorder with mixed anxiety and depressed mood [1].

Thus, the presence of anxiety and panic symptoms in patients with neurologic disorders may have multiple etiologies: (1) the presence of a primary psychiatric disorder; (2) the neurologic disorder or other comorbid general medical conditions; (3) coping with the neurologic process or other comorbid general medical conditions; and (4) medications used to treat neuropsychiatric and medical conditions.

### Prevalence

When considering the lifetime prevalence of anxiety and panic symptoms in the general population, the lifetime prevalence for anxiety disorders can serve as a baseline. The retrospective national cohort comorbidity replication survey ( $N = 9,282$ ) reported a lifetime prevalence of 28.8% for anxiety disorders [2]. A recent prospective birth cohort study noted that by age 32, 49.5% ( $N = 1,000$ ) had an anxiety disorder diagnosis [3]. The prospective study clearly noted that retrospective studies may significantly underestimate lifetime prevalence rates.

## Neuroanatomy and neurotransmitters

As determined by neuroimaging (functional magnetic resonance imaging, fMRI; magnetic resonance imaging, MRI; positron emission tomography, PET; single photon emission computed tomography, SPECT; magnetic resonance spectroscopy, MRS) and pharmacologic challenge, anxiety disorders and anxiety and panic symptoms are associated with multiple neurocircuits including the amygdala, hippocampus, insular cortex, medial prefrontal cortex, frontal cortex, rostral anterior cingulate cortex, dorsal anterior cingulate cortex, striatum, septum, thalamus, hypothalamus, and brainstem [4,5]. Neurotransmitter and neuromodulator imbalances implicated in anxiety and panic symptoms include gamma-amino butyric acid, serotonin, noradrenaline, dopamine, glutamate, histamine, acetylcholine, cannabinoids, neuropeptides, glucocorticoids, cytokines, and neurosteroids [5,6]. Medical, psychiatric, and neurologic disorders impacting neurocircuitry in these neuroanatomic regions, whether by directly or indirectly impacting specific structures or neurotransmitters/neuromodulators in those structures, may result in the development of anxiety and panic symptoms.

## Summary of etiologies

Etiologies for anxiety and panic symptoms have been summarized into greater than 100 conditions in 10 key divisions [7]. Table 4.1 selectively addresses specific illnesses and substances that induce anxiety and panic with associated clinical features.

**Table 4.1 Differential diagnosis of anxiety and panic symptoms.**

Item	Subdivision	Specific entity
Toxic substances &	Hallucinogens	Altered acid (TCA)
Medications		
Medical conditions		
Psychiatric conditions		
Substances of abuse		
Other		

Toxic substances or abuse and

medications [7–26]

Acute, chronic, low dose, high dose, overdose impact adverse clinical features

Hallucinogens

*α*-Lysergic Acid (LSA)

Mescaline (Peyote)

Mushrooms

(Psilocybin)

Cannabis

Dissociative agents

Phencyclidine (PCP)

Ketamine (Special K)

Stimulant-hallucinogens

Ecstasy (MDMA with active metabolite MDA)

Stimulants

Amphetamine  
Methamphetamine  
Ephedra alkaloids  
Methylphenidate

Caffeine

## Cocaine

Anticholinergics and medications with anticholinergic adverse effects	Benztropine Trihexyphenidyl Diphenhydramine Biperiden, Procyclidine Jimson weed Tricyclic antidepressants Antipsychotics
Opiates	Heroin, Morphine Oxycodone Hydromorphone, Hydrocodone, Meperidine, Fentanyl Methadone
Sedative-hypnotics [Benzodiazepines/non-benzodiazepines]	Alprazolam [BZD] Lorazepam [BZD] Clonazepam [BZD] Temazepam [BZD] Diazepam [BZD] Midazolam [BZD] Triazolam [BZD]  Zolpidem [non-BZD]

Corticosteroids	Prednisone Methylprednisolone
Anabolic--androgenic steroids	Testosterone Methyltestosterone Nandrolone
Anti-Parkinson's disease drugs	Amantadine, pergolide, apomorphine, lisuride, bromocriptine, ropinirole, cabergoline, pramipexole
Cardiovascular drugs	Clonidine, sulfonamides, thiazides, nitrates/nitrites, quinidine
Immunomodulators	Aspirin, non-steroidal anti-inflammatory drugs (adverse effects may be associated with acute and chronic toxicity)
	Cyclosporine A Tacrolimus
Anti-migraine drugs	Sumatriptan
Serotonergic antidepressants	Fluoxetine, paroxetine, citalopram, escitalopram, sertraline, fluvoxamine, venlafaxine, duloxetine, <del>desvenlafaxine</del>

## Psychotropic drugs

	Atypical antipsychotics	Clozapine, olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, asenapine, lurasidone
	Antiepileptic drugs	Ethosuximide
		Felbamate
		Levetiracetam
	Antibacterial antimicrobial	Penicillins
	Antiviral antimicrobial	Acyclovir, ganciclovir
	Antimalarial antimicrobial	Chloroquine, mefloquine, quinine
	Antiretroviral agents	Ritonavir, didanosine, lopinavir + ritonavir, saquinavir, enfuvirtide
	Skeletal muscle relaxants	Dantrolene Baclofen
Toxic: Withdrawal states [7,8,17,26,27]	Stimulants	Amphetamines, methylphenidate
	Cannabis	
	Opiates	Heroin, morphine

oxycodone,  
hydromorphone,  
hydrocodone,  
meperidine, fentanyl,  
methadone

Sedative-hypnotics  
[Benzodiazepines/non-  
benzodiazepines]

Benzodiazepines  
Zolpidem  
Barbiturates

Alcohol

Antidepressant  
discontinuation  
syndrome

SSRIs/SNRIs

Infective/post-  
infective  
[7,17,26,28–35]

Viral

Human  
immunodeficiency  
virus (HIV)/acquired  
immunodeficiency  
syndrome (AIDS)

Herpes simplex  
encephalitis

West Nile virus

Hepatitis C

Epstein Barr  
(mononucleosis and  
meningitis/encephalitis)

Mycobacterial

Tuberculous meningitis

Leprosy

Bacterial

Meningitis – includes  
post-infective sequelae

Brucellosis

Parasitic protozoan

Malaria

Spirochete

Neurosypilis

		Lyme meningitis
Fungal	CNS histoplasmosis	
	Prion diseases (transmissible spongiform encephalopathies)	Creutzfeldt--Jakob disease
Pressure effects [26,36]	Hydrocephalus	Normal pressure
	Hypertensive encephalopathy	
Psychiatric [1]	Anxiety disorders	Panic disorder with/without agoraphobia
		Specific phobias
		Social phobia

Generalized anxiety disorder

Obsessive-compulsive disorder

Acute stress disorder

Post-traumatic stress disorder

Anxiety disorder due to a general medical condition

Inflammatory disorders [17,26]

Auto-immune

Systemic lupus erythematosus

Rheumatoid arthritis

Scleroderma

Neoplastic [7,17,26]      Brain tumor (primary)      L > R for depression

and metastatic) R > L for mania

Paraneoplastic [7,17,26,37]	Limbic encephalitis	Small cell lung carcinoma (also reported with testicular, breast, gastrointestinal, ovarian tumors; neuroblastoma, lymphoma, thymoma)
Degenerative [7,26,38,39] [See movement disorders]	Alzheimer's disease	
	Frontotemporal dementia	Younger onset than Alzheimer's disease
Vascular [7,17,26,38,39]	Stroke	Depression associated with left frontal infarcts Mania/hypomania associated with right hemispheric infarcts

Subarachnoid  
hemorrhage

Vasculitis

Temporal arteritis

Other [7,17,26,39]

Environmental

Heavy metals

Pain

Terminal illness

Pregnancy/post-  
pregnancy

Myasthenia gravis

Auto-immune

Metabolic

[7,17,26,40]

Endocrine

Diabetes

Hyperthyroidism

Hypothyroidism

Hyperparathyroidism  
(predominantly  
parathyroid gland  
adenoma)

Hypoparathyroidism

Cushing's syndrome

Addison's disease

Pheochromocytoma

Hyperprolactinemia  
(pituitary adenoma)

Electrolyte  
abnormalities

Hypokalemia

Hyponatremia

Hypomagnesemia

Encephalopathy

Uremic encephalopathy

Porphyrias

Acute intermittent  
porphyria (autosomal  
dominant)

Respiratory  
compromise

Chronic obstructive  
pulmonary disease

Mitochondrial

MELAS (mitochondrial  
encephalopathy, stroke-  
like episodes and lactic  
acidosis)

Vitamin deficiencies

B12 deficiency  
Pernicious anemia

Pellagra

Movement disorders  
[7,17,26,38,39,41,42]

Parkinson's disease

Neurodegenerative

Huntington's disease

Neurodegenerative  
autosomal dominant  
(increased CAG triplet  
repeats on chromosome  
4p16)

Wilson's disease

Autosomal recessive

Tic

Gilles de la Tourette  
syndrome

Sleep disorder [7,17,26]	Dyssomnia	Insomnia (multiple psychiatric, medical, and drug etiologies)
	Parasomnia	Non-rapid eye movement, rapid eye movement, and diffuse sleep disorders
Congenital (not listed elsewhere) [7,17]	Cystic fibrosis	Autosomal recessive
	Turner's syndrome	45, X
	Sickle cell anemia	Autosomal recessive
	Fragile X syndrome	Trinucleotide repeats (full syndrome 200+CGG repeats; premutation allele 59–200 repeats)
Traumatic brain injury [7,17,38,39]	Focal traumatic brain injury	Neuropsychiatric presentation is secondary to general and focal effects from traumatic brain injury

Ictal [7,17,26,39,40,43]	Simple or complex partial seizures with or without secondary generalization Generalized seizures NCSE PNES	Neuropsychiatric symptoms associated with epilepsy may be ictal, postictal, or interictal, confounding differentiation from primary psychiatry disorder – video EEG for electrographic/clinical correlation may be required
Demyelinating disorders [7,17,26,38]	Multiple sclerosis	

---

ADHD, attention deficit hyperactivity disorder; CVA, cerebrovascular accident; DIC, disseminated intravascular coagulation; EPS, extrapyramidal symptoms; MI, myocardial infarction; NCSE, nonconvulsive status epilepticus; PNES, psychogenic non-epileptic seizures; PTSD, post-traumatic stress disorder; TIA, transient ischemic attack.

## Case vignette

An anxious and depressed 64-year-old female presented for psychiatric consultation. Prior to her diagnosis of Parkinson's disease (PD) at age 52, she described an excellent premorbid psychiatric history endorsing only excessive worrying (Generalized Anxiety Disorder) and situational anxiety (Anxiety Not

Otherwise Specified). The patient specifically denied pre-PD psychiatric features associated with depression, mania, psychosis, panic disorder/panic attacks, obsessive-compulsive disorder, phobias, impulsive behaviors, eating disorder, and/or self-mutilation. Her past medical history was pertinent for eye surgery with complications and migraines; her family medical history included a grandparent with PD with dementia.

Since PD diagnosis, the patient had developed depressive episodes and when seen in consultation she endorsed decreased energy/appetite/concentration/memory with self-deprecatory thoughts, guilt, passive suicidal ideation, and depressed mood (Mood Disorder Due to a General Medical Condition with Major Depressive-Like Episode). She acknowledged that her anxiety had worsened as PD symptom severity progressed with the development of panic features during “on–off fluctuations” (Anxiety Due to a General Medical Condition) and her expectation of “going off and being frozen.” The patient did not associate worsening of anxiety or periods of panic with PD pharmacotherapy though these medications are associated with anxiety (see [Table 4.1](#)). During treatment with pramipexole, the patient noted new-onset psychosis, impulsive gambling, and excessive shopping which resolved once pramipexole was discontinued. The patient also noted development of persistent visual illusions and hallucinations that were related to PD, PD pharmacotherapy (carbidopa–levodopa, amantadine, and entacapone), and visual defects associated with eye surgery.

Sertraline, citalopram, escitalopram, venlafaxine, duloxetine, amoxapine, and bupropion had limited benefit in treating depressive or anxiety features. The patient has shown modest benefit with low-dose benzodiazepines for anxiety and low-dose quetiapine for psychotic features. Due to her exquisite sensitivity to medications, psychiatric treatment has focused on cognitive behavioral therapy with positive response.

Within the past several years, there had been a more rapid decline with word-finding difficulties and memory impairment (Cognitive Loss Due to General Medical Condition) in addition to decreased mobility (cane progressing to four-wheel walker and wheelchair). The patient summarized her condition as a dramatic change in Quality of Life (QOL), continued difficulty in accepting the illness process (Adjustment Disorder), and apprehension of what the future will bring, especially in light of family history of PD dementia.

This intriguing case addresses the multiple etiologies of anxiety in patients with a neurologic disorder (PD): (1) primary psychiatric illness (premorbid

Generalized Anxiety Disorder); (2) neurologic disorder (panic features during “on–off fluctuations” consistent with Anxiety Due to a General Medical Condition); (3) coping with the neurologic disease (Adjustment Disorder with anxiety features associated with coping with diagnosis, progressive loss of QOL, and apprehension of potential PD dementia); (4) medication-induced anxiety (PD pharmacotherapy is associated with anxiety and this needed to be excluded during assessment of patient). This case also addresses the potential for the development of other neuropsychiatric disorders with PD and PD pharmacotherapy.

## References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revision)* (DSM-IV-TR). Washington, DC: American Psychiatric Association, 2000.
2. Kessler RC, Berglund P, Demier O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; 62:593–602.
3. Moffitt TE, Caspi A, Taylor A *et al.* How common are common mental disorders? Evidence that lifetime prevalence rates are doubled by prospective versus retrospective ascertainment. *Psychol Med* 2010; 40:899–909.
4. Shin LM, Liberzon I. The neurocircuitry of fear, stress and anxiety disorders. *Neuropsychopharmacology* 2010; 35:169–91.
5. Millan MJ. The neurobiology and control of anxious states. *Prog Neurobiol* 2003; 70:83–244.
6. Johnson PL, Truitt W, Fitz SD *et al.* A key role for orexin in panic anxiety. *Nat Med* 2010; 16:111–15.
7. Stern TA, Fritchionne GL, Cassem NH, Jellinek MS, Rosenbaum JF, Eds. *Massachusetts General Hospital Handbook of General Hospital Psychiatry*, 5th edn. Philadelphia, PA: Mosby, 2004.
8. Lowinson JH, Ruiz P, Millman RB, Langrod JG, Eds. *Substance Abuse*, 4th edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2005.
9. Turjanski N, Lloyd GG. Psychiatric side-effects of medications: recent

- developments. *Adv Psychiatr Treat* 2005; 11:58–70.
10. Chakraborty K, Neogi R, Basu D. Club drugs: review of “rave” with a note of concern for the Indian scenario. *Indian J Med Res* 2011; 133:594–604.
  11. Krasnova IN, Cadet JL. Methamphetamine and messengers of death. *Brain Res Rev* 2009; 60:379–407.
  12. Meehan TJ, Bryant SM, Aks SE. Drugs of abuse: the highs and lows of altered mental status in the emergency department. *Emerg Med Clin North Am* 2010; 28:663–82.
  13. Carvalho M, Carmo H, Costa VM *et al*. Toxicity of amphetamines: an update. *Arch Toxicol* 2012; 86:1167–231.
  14. Mancuso CE, Tanzi MG, Gabay M. Paradoxical reactions to benzodiazepines: literature review and treatment options. *Pharmacotherapy* 2004; 24:1177–85.
  15. Inagaki T, Miyaoka T, Tsuji S, Thami Y, Nichida A, Horiguchi J. Adverse reactions to zolpidem: case reports and a review of the literature. *Prim Care Companion J Clin Psychiatry* 2010; 12. pii: PCC.09r00849.
  16. Hoque R, Chesson AL. Zolpidem-induced sleep walking, sleep related eating disorder, and sleep-driving: fluorine-19-fluorodeoxyglucose positron emission tomography analysis, and a literature review of other unexpected clinical effects of zolpidem. *J Clin Sleep Med* 2009; 5:471–6.
  17. Levenson JL, Ed. *The American Psychiatric Publishing Textbook of Psychosomatic Medicine*. Washington, DC: American Psychiatric Publishing, 2005.
  18. Fardet L, Petersen I, Nazareth I. Suicidal behavior and severe neuropsychiatric disorders following glucocorticoid therapy in primary care. *Am J Psychiatry* 2012; 169:491–7.
  19. Kanayama G, Hudson JI, Pope HG. Long-term psychiatric and medical consequences of anabolic-androgenic steroid abuse. *Drug Alcohol Depend* 2008; 98:1–12.
  20. Ferguson JM. SSRI antidepressant medications: adverse effects and tolerability. *Prim Care J Clin Psychiatry* 2001; 3:22–7.
  21. Amsterdam JD, Garcia-Espana F, Goodman D, Hooper M, Hornig-Rohan

- M. Breast enlargement during chronic antidepressant therapy. *J Affect Disord* 1997; 46:151–6.
22. Kaufman KR, Levitt MJ, Schiltz JF, Sunderram J. Neuroleptic malignant syndrome and serotonin syndrome in the critical care setting: case analysis. *Ann Clin Psychiatry* 2006; 18:201–4.
23. Kaufman KR, Stern L, Mohebati A, Olsavsky A, Hwang J. Ziprasidone induced priapism requiring surgical treatment. *Eur Psychiatry* 2006; 21:48–50.
24. Kaufman KR. Antiepileptic drugs in the treatment of psychiatric disorders. *Epilepsy Behav* 2011; 21:1–11.
25. Tashman A, Kay J, Lieberman JA, Ed. *Psychiatry*. Philadelphia, PA: W.B. Saunders Company, 1997.
26. David AS, Fleminger S, Kopelman MD, Lovestone S, Mellers JDC, Eds. *Lishman's Organic Psychiatry*, 4th edn. Chichester: Wiley–Blackwell, 2009.
27. Haddad PM, Anderson IM. Recognizing and managing antidepressant discontinuation symptoms. *Adv Psychiatr Treat* 2007; 13:447–57.
28. Caparros-Lefebvre D, Girard-Buttaz I, Reboul S *et al.* Cognitive and psychiatric impairment in herpes simplex encephalitis suggest involvement of the amygdalo-frontal pathways. *J Neurol* 1996; 243:248–56.
29. Davis LE, DeBiasi R, Goade DE *et al.* West Nile virus neuroinvasive disease. *Ann Neurol* 2006; 60:286–300.
30. Navines R, Castellvi P, Moreno-Espana J *et al.* Depressive and anxiety disorders in chronic hepatitis C patients: reliability and validity of the Patient Health Questionnaire. *J Affect Disord* 2012; 138:343–51.
31. Ezurum S, Kalavsky SM, Watanakunakorn C. Acute cerebellar ataxia and hearing loss as initial symptoms of infectious mononucleosis. *Arch Neurol* 1983; 40:760–2.
32. Bhatia MS, Chandra R, Bhattacharya SN, Imran M. Psychiatric morbidity and pattern of dysfunctions in patients with leprosy. *Indian J Dermatology* 2006; 51:23–5.
33. Barbosa IG, Vale TC, de Macedo DL, Gomez RS, Teixeira AL. Neurosyphilis presenting as mania. *Bipolar Disord* 2012; 14:309–12.

34. Cormia FE. Syphilophobia and allied anxiety states. *Can Med Assoc J* 1938; 39:361–6.
35. Talbot MD, Morton RS. Neurosyphilis: the most common things are most common. *Genitourin Med* 1985; 61:95–8.
36. Kito Y, Kazui H, Kubo Y et al. Neuropsychiatric symptoms in patients with idiopathic normal pressure hydrocephalus. *Behav Neurol* 2009; 21:165–74.
37. Grisold W, Giometto B, Vitaliani R, Oberndorfer S. Current approaches to the treatment of paraneoplastic encephalitis. *Ther Adv Neurol Disord* 2011; 4:237–48.
38. Lyketsos CG, Kozauer N, Rabins PV. Psychiatric manifestations of neurologic disease: where are we headed? *Dialogues Clin Neurosci* 2007; 9:111–24.
39. Lyketsos CG, Rabins PV, Lipsey JR, Slaveney PR. *Psychiatric Aspects of Neurologic Diseases*. Oxford: Oxford University Press, 2008.
40. Kaufman KR, Zuber N, Rueda-Lara MA, Tobia A. MELAS with recurrent complex partial seizures, nonconvulsive status epilepticus, psychosis, and behavioral disturbances: case analysis with literature review. *Epilepsy Behav* 2010; 18:494–7.
41. Ebmier KP, O'Brien JT, Taylor J-P, Eds. *Psychiatry of Parkinson's Disease*. Basel: S Karger AG, 2012.
42. Akil M, Brewer GJ. Psychiatric and behavioral abnormalities in Wilson's disease. *Adv Neurol* 1995; 65:171–8.
43. Ettinger AB, Kanner AM, Eds. *Psychiatric Issues in Epilepsy: A Practical Guide to Diagnosis and Treatment*. Philadelphia, PA: Lippincott Williams & Wilkins, 2007.

## 5 Aphasia

---

Gad E. Klein and Dragana Micic *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Aphasia is a neurogenic disorder of linguistic processing in which expression and comprehension of written and spoken language are compromised due to damage to specific regions of the cerebral hemisphere dominant for language. Injury to these regions can disrupt the symbols and grammatical relationships that constitute language, leading to deficits in fluency, comprehension, repetition, naming, and impairments in reading and writing. Impairment to these functions can severely impact the ability to communicate. However, the detrimental effect of a primary language deficit such as aphasia is not limited only to communication; cognitive functions that are even in part verbally mediated (e.g. memory, executive function) can be affected, leading to devastating impairments in daily functioning and quality of life [1–6].

### Etiology

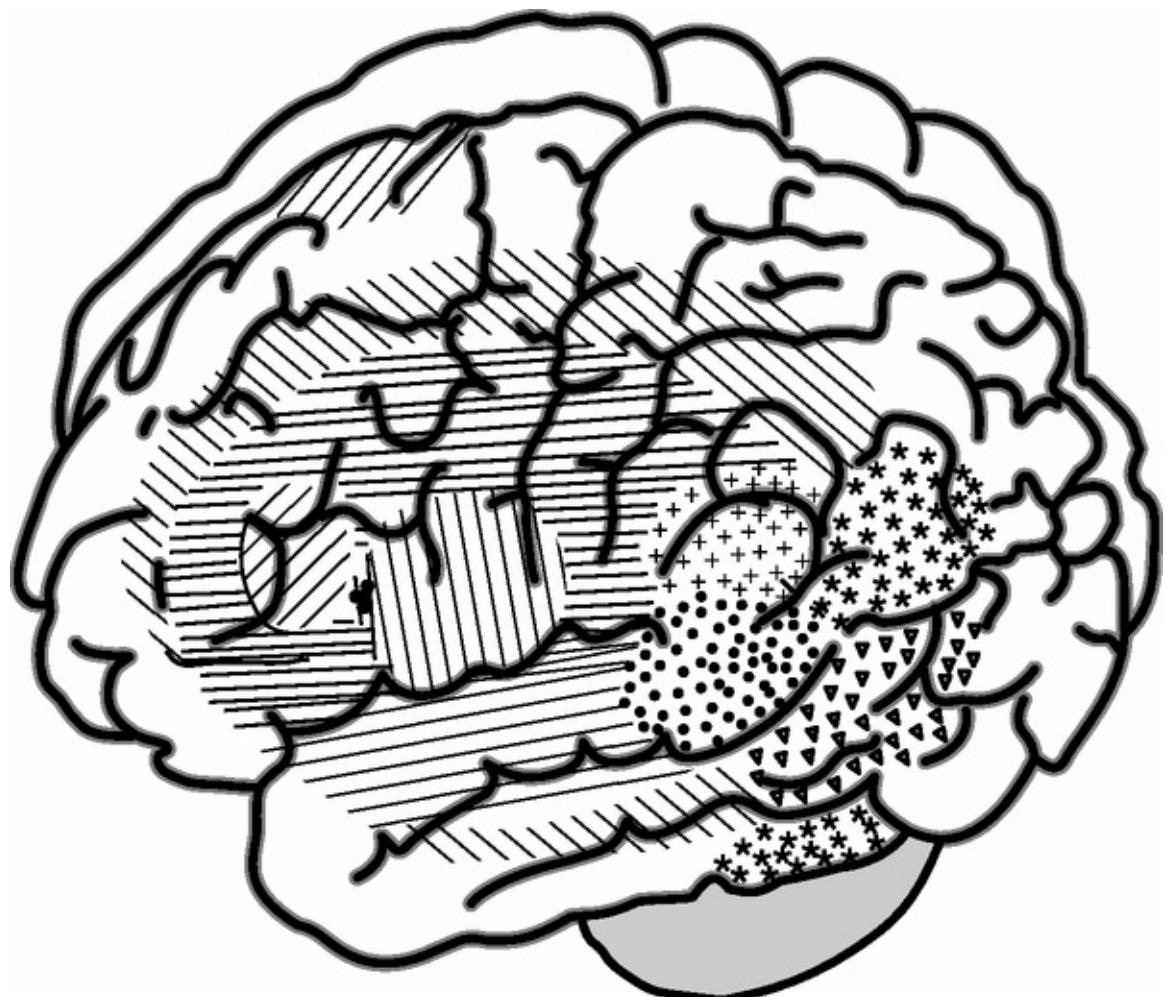
Depending on the nature of the underlying brain damage, aphasias can be acute or progressive. The most common cause of aphasia is cerebral infarct. However, sudden onset of aphasia can also be seen in cerebral contusion, subdural or epidural hematoma, and both ictally and post-ictally due to seizure discharges in or adjacent to cortical language areas. In contrast to acute aphasias, slowly developing progressive aphasias can occur as a result of degenerative cortical dementias, brain tumors, and acquired epileptiform aphasia. Transient aphasia may occur in transient ischemic attacks, and seizures [2].

Aphasia can result from damage to any portion of the language processing neural network: Broca's area and adjacent frontal cortices, temporal cortices adjacent to and including Wernicke's area, inferior portion of the parietal lobule, and pathways running as a part of or in parallel with the arcuate fasciculus [3].

An important principle to be aware of is that language lateralizes to the left hemisphere of the brain in over 95% of right-handed people and in most left-handed people, as studies examining hemispheric language lateralization in left-handers report varied figures of left language dominance ranging from 70% to over 90% [4,5]. However, patients can also present with “crossed dominance” or bi-hemispheric language representation, and this should always be considered when a patient is presenting with aphasic symptomatology. Another important principle is that aphasia is *not* due to a disturbance in motor skills required for phonation, articulation, or writing. However, these deficits can often co-occur with aphasia, making a clear diagnosis difficult.

## Differential assessment of aphasic syndromes

There are eight classic aphasic syndromes that present with overlapping symptoms ([Figure 5.1](#)). These can be differentiated using a simple approach evaluating three important components of language: fluency, comprehension, and repetition, in that order ([Table 5.1](#)). While this approach is sufficient for a rapid classification of aphasic syndromes, a more detailed language assessment is needed to accurately determine the severity of deficits and to adequately direct the rehabilitative process. This can be accomplished at bedside using a six-step approach popularized by Benson and Geschwind [2,5] involving assessment of (1) spontaneous speech (fluency, prosody, grammar and meaning, paraphasias, and articulation); (2) naming (visual confrontation naming, responsive naming, objects and parts, nouns, verbs, proper nouns, colors, etc.); (3) comprehension (commands simple to complex, yes/no questions and multiple choice, point to objects, syntax-dependent meaning); (4) repetition (single words, simple sentences, complex sentences); (5) reading (aloud, comprehension); (6) writing (patient's name, copy sentence, spontaneous sentence). Whenever possible, assessment of language function should be performed in the patient's primary language.



**Figure 5.1** Aphasias due to anterior lesion:  Broca's aphasia,  Transcortical motor aphasia,  Global aphasia,  Mixed transcortical aphasia; Aphasias due to posterior lesion:  Wernicke's aphasia,  Transcortical sensory aphasia,  Conduction aphasia,  Anomic aphasia.

**Table 5.1** *Characteristics of nonfluent and fluent aphasia .*

		Nonfluent aphas		
Clinical syndrome		Global	Mixed transcortical	Trans motor
Key func	Fluent?	No	No	No

<b>features</b>				
<b>assessment</b>	<b>Comprehends?</b>	<b>No</b>	<b>No</b>	<b>Yes</b>
	<b>Repeats?</b>	<b>No</b>	<b>Yes</b>	<b>Yes</b>
Typical pattern of spontaneous speech	Scant, reduced to few words. Mutism is also possible	Telegraphic: short, missing function words, reduced to brief noun–verb combinations	Nonfl	
Associated features	Right hemiparesis, hemi-sensory loss, homonymous hemianopia	Right-sided weakness or sensory loss	Leg w	
Features of diagnostic and therapeutic concern	Stock expletives often used appropriately. Poorer comprehension of complex sentences	Repetition without comprehension	Akinet tende perse Abili	
Differential diagnosis and rule outs	Impaired comprehension, reading and writing differentiates from mutism	Poor comprehension differentiates from Broca's and good repetition from global	Intact repeti differ from	

Prognosis (when vascular)	Poor	Poor, but variable	Good resolution anom aphas
Localization of lesion	Large perisylvian, both anterior and posterior eloquent cortex, sometimes from large infarcts surrounding anterior eloquent cortex	Isolated damage to anterior and posterior eloquent cortex	Surrogate Broca anterior association cortic

## Fluent aphasias

Word groupings of over five to six words articulated effortlessly but erroneously, with numerous errors of word choice and sound substitutions, indicate aphasia of a fluent type [6], in which anterior linguistic cortex is intact, but posterior linguistic cortex is damaged [3,7]. Fluent aphasias occur due to lesions of temporal--parietal cortical regions and white matter supplied by the posterior distribution of the middle cerebral artery (MCA) and by the posterior cerebral artery (PCA). Paraphasic errors are common in fluent aphasias and can be either phonemic (e.g. “shawl” instead of “ball”), or semantic (e.g. “tent” instead of “house”).

## Wernicke's aphasia

Striking deficits in auditory comprehension and repetition severely limit the ability of patients with Wernicke's aphasia to communicate using language

despite their intact ability to speak fluently. Their speech is fluent, often logorrheic (excessive talkativeness) but incomprehensible both to the listener and the patient. Conversational speech approximates normal speech in terms of fluency, articulatory agility, and phrase length but has little communicative value due to absence of clear content, extensive presence of semantic and phonemic paraphasias, and neologisms (new, meaningless words). Circumlocutions are frequent due to word-finding difficulty. Reading and writing skills are affected, mirroring the deficits of the conversational speech. Patients with Wernicke's aphasia often lack awareness of their deficits, a condition known as anosognosia. They can therefore become frustrated when others do not understand what they are trying to say [1,6].

Assessment should focus on comprehension and repetition and both functions should progress from single words to phrases to more complex grammatical constructs. Preservation or deficit in repetition will help differentiate between Wernicke's aphasia and transcortical sensory aphasia.

## **Conduction aphasia**

This subtype is notable for severe deficits in repetition of speech. The speech of patients with conduction aphasia is fluent, but filled with errors so that it can resemble the speech of patients with Wernicke's aphasia. However, these patients tend to make more phonemic paraphasias, fewer neologisms, and attempt to self-correct more often than patients with Wernicke's aphasia. Naming is also poor in these patients, but comprehension of spoken and written language is intact, as is reading. Conduction aphasia has been attributed to damage to arcuate fibers, but more recent evidence indicates that damage to the dominant supramarginal gyrus and underlying white matter can also present with these deficits [8].

Assessment of conduction aphasia should focus on the pattern of fluent speech as these patients may make a large number of inconsistent literal paraphasias, attempt to correct themselves often by repeated approximations of the intended word, and may use fewer neologisms than Wernicke's aphasia. Reading and writing are intact as compared with Wernicke's and transcortical sensory aphasias and therefore assessment of these modalities is critical. Severely impaired repetition, even of single words, is the predominant feature.

## **Transcortical sensory aphasia**

Transcortical sensory aphasia (TSA) is most simply thought of as Wernicke's aphasia with preserved repetition. Thus, comprehension of spoken and written language is impaired, as is reading. Interestingly, because they can echo their conversational partner, TSA patients can sound as if they understand language (e.g. Asked: "Did you like your dinner?" Answer: "Like dinner."), but these patients do not understand what they are repeating. In addition to intact purposeful repetition they can also present with almost compulsive repetition known as echolalia. Large MCA–PCA watershed infarcts can be associated with this constellation of symptoms.

Assessment of repetition is critical as TSA patients can be misdiagnosed with Wernicke's aphasia because of their pattern of fluent, but empty, speech and impaired comprehension. The ability to repeat in the absence of the ability to understand what is being repeated is the primary and most easily assessed factor that differentiates between these two subtypes of fluent aphasia.

## Anomic aphasia

Patients with anomic aphasia produce fluent, syntactically and grammatically correct speech but often struggle to find an appropriate word or the name of an object. They can also make occasional semantic and phonemic paraphasias. Because their ability to comprehend and repeat speech is almost always near normal, they are usually able to recognize and repeat the word they are searching for if it is provided for them or if they are given a verbal or visual cue. Their writing skills can follow the same pattern of difficulties in speech, while reading is typically intact. Anomia is associated with many of the aphasic syndromes. However, anomia or dysnomia alone can be associated with damage to various different areas of the dominant hemisphere and subcortical structures. It is also often the last lingering symptom in a resolving aphasia [7].

Assessment of naming should include both high-frequency words (e.g. ear, shirt) and low-frequency words (e.g. lobe, cuff) as patients may only have difficulty with the latter category and may easily pass brief mental status screening measures.

## Nonfluent aphasias

Short word groupings consisting of no more than three to four words in a breath group, usually produced laboriously [9], indicate aphasias of the nonfluent type

seen due to lesions of the anterior speech areas, such as Broca's aphasia. Nonfluent aphasias typically occur due to lesions of the frontal lobe supplied by the superior distribution of the MCA and the anterior cerebral artery (ACA) [3,5].

## **Broca's aphasia**

Patients with Broca's aphasia experience a severe difficulty in producing speech while they are generally able to understand spoken language. Their speech, as well as writing and reading aloud, has a slow, effortful, and agrammatical quality. Although in severe cases they may initially be mute and unable to produce any speech, when they can speak they typically produce fewer than five words between breaths, have difficulties both articulating and finding words, use disproportionately more content words (nouns and verbs) than function words (e.g. the, is, on) and do not use melodic intonation (prosody) to convey the message of their utterances. Articulation of automatized sequences and exclamations may be unaffected (e.g. profanity). Writing deficits commonly mirror speech deficits, while comprehension of spoken and written language is generally only mildly impaired. Gestural communication may also be intact [6,9].

Assessment should include evaluation of both auditory and written comprehension to differentiate from global aphasia, and reading/writing to differentiate from mutism.

## **Global aphasia**

All aspects of language are severely impaired in global aphasia due to extensive damage to both anterior and posterior language areas. Patients may be able to articulate stereotypical utterances but not much more. For these patients the prognosis is generally poor.

Assessment should include measures of both simple and complex comprehension to differentiate from Broca's and transcortical motor aphasia, and measures of repetition to differentiate from mixed transcortical aphasia.

## **Transcortical motor aphasia**

Transcortical motor aphasia (TcMA) is most simply thought of as Broca's aphasia with preserved repetition. Therefore, patients with TcMA have relatively good auditory comprehension and preserved repetition but poor fluency. In

contrast to Broca's aphasics who attempt to communicate, TcMA patients may be abulic, thus failing to attempt to initiate spontaneous speech.

Assessment of repetition is critical as TcMA patients can be misdiagnosed with Broca's aphasia because of their pattern of dysfluent speech. The ability to repeat in the absence of other fluent expressive speech is the primary and most easily assessed factor that differentiates between these two subtypes of nonfluent aphasia.

## **Mixed transcortical aphasia**

Mixed transcortical aphasia (MTcA) is most simply thought of as global aphasia with preserved repetition. Conversational speech is similar to that of global aphasia; the ability to form meaningful verbal expressions is severely reduced or entirely lost. The ability to understand spoken language is severely impaired even at the level of single words. Therefore, even though they can repeat phrases and sentences, MTcA patients do not understand what they had just heard or said.

Assessment of repetition is critical as this is the only preserved language function in these patients. It will allow quick differentiation from global aphasia.

## **Subcortical aphasia**

Aphasia can also occur due to lesions that spare the cortex. Although still not fully understood, these types of aphasia are thought to occur due to damage to white matter tracts interrupting typical cortical connections involved in speech. The thalamus is a common site for aphasia with variable symptoms including fluent but reduced speech output, anomia, paraphasic errors, variable comprehension, and preserved repetition. Lesions to regions of the basal ganglia and other white matter pathways can also result in aphasic symptoms. However, these are variable and can include fluent paraphasic or nonfluent agrammatic speech. Articulation and prosody can also be affected.

## **Primary progressive aphasia**

The primary progressive aphasias are a group of degenerative dementias whose most striking characteristic is a clinical syndrome of insidiously declining language function affecting expression and comprehension. Although many

dementias eventually present with some level of language impairment, the presence of at least 2 years of predominant language decline without significant impairment in other cognitive domains differentiates primary progressive aphasias from other cortical dementias such as Alzheimer's disease.

There are several recognized variants of primary progressive aphasia. In *semantic dementia*, articulation is intact and speech is fluent, comprehension and naming are severely impaired, and patients often lose not only the ability to name objects but also the conceptual knowledge of the object they are trying to name. In *nonfluent progressive aphasia* there are agrammatisms in speech production accompanied by halting speech, effortful articulation, variable degrees of anomia and phonemic paraphasias in the presence of relatively preserved word comprehension. This often progresses to a full nonfluent aphasic syndrome. The *logopenic variant* of progressive aphasia presents with severe word-finding difficulties and slowed speech due to frequent word-finding pauses [9,10].

## Differential diagnoses

Aphasia is a disorder which can coexist with deficits in hearing, vision, and articulation but is not caused by impairments in these modalities. It is neither a disorder of perception and movement, nor a result of a disordered thought process. Therefore, it is essential to differentiate aphasia from several disorders that affect language but are not disorders of language.

*Dysarthria* is a disorder of articulation due to motor weakness of the muscles required for speech production. Therefore, while a dysarthric patient may find it difficult to articulate speech their deficits are distinct from those seen in nonfluent aphasics who present with halting speech, reduced phrase length, and agrammatisms. Additionally, dysarthria presents with intact comprehension, reading, and writing which easily differentiates it from the fluent aphasias.

*Mutism* is the inability to produce any speech that can occur in a number of neurologic and psychologic disorders (e.g. depression, severe frontal lobe injury). Patients with severe expressive aphasia may be mute at least for a period of time. However, an assessment of some of the language skills that do not require expressive speech (e.g. written expression, verbal, and written comprehension) will differentiate this disorder from nonfluent aphasias.

*Agnosia* is the inability to identify an object in a specific sensory modality without primary impairment in that modality. For example, visual agnosia is the

inability to identify an object that is presented visually, with intact ability to identify that same object using a different modality. Thus, visual agnosia can easily be confused with anomia if a patient is asked to identify an object by sight only. If a patient is presenting with difficulty visually naming objects, having the patient attempt to identify the object by touch can help distinguish between aphasia and agnosia. (The reader may want to refer to [Chapter 3](#), this volume, on agnosia.) *Apraxia of speech* is a deficit in the motor planning or programming needed for speech production. It exists in the absence of motor weakness and non-speech related oromotor planning. It can often co-occur with aphasia and therefore may be hard to differentiate. Patients with this disorder can present with speech that is labored and halting, clear articulatory groping, and inconsistent errors in speech even on the same word. They make phonemic substitution errors especially with less common phonemes, and have more difficulty with multi-syllabic words and nonsense words. Unless there is comorbid aphasia, these patients will present with intact comprehension, reading, and writing. (The reader may want to refer to [Chapter 6](#), this volume, on apraxia.) *Pure word deafness* is the inability to comprehend or repeat spoken language in the presence of preserved expressive speech, spontaneous writing, and reading comprehension. There is no hearing deficit and non-speech sounds can be heard with no difficulty. The presence of intact reading comprehension and written expression differentiates it from Wernicke's aphasia. This syndrome typically arises from bilateral lesions of the posterior aspect of the superior temporal gyrus interrupting connections between the primary auditory cortices and association cortices.

*Alexia* and *agraphia* refer to deficits in reading and writing, and they are often comorbid in patients with aphasia. However, these deficits can also occur individually. Agraphia can occur with a lesion to the inferior parietal lobule and especially the angular gyrus. This deficit is often comorbid with other features of Gerstmann's syndrome including acalculia , finger agnosia , and right-left disorientation . When alexia is present alone it is known as alexia without agraphia or sometimes "pure word blindness." Oftentimes patients cannot read their own writing. Reading of simple words can be accomplished by sequential single letter recognition. This syndrome is most typically the result of a lesion affecting the dominant visual cortex and extending to the splenium of the corpus callosum. Thus, visual information from the right visual field cannot be processed, and visual information from the left visual field cannot be transferred to the language-dominant left hemisphere due to damage to the splenium. An assessment of verbal expression and comprehension will distinguish these

syndromes from aphasia.

*Schizophrenia* can sometimes present with syntactic and prosodic but incomprehensible speech patterns that can be mistaken for those seen in Wernicke's aphasia. Both can include paraphasic errors and neologisms, and patients with both disorders often seem unaware of their deficits. While there are certainly differences, there is no clear consensus on an easy way to differentiate these expressive speech patterns. However, the expressive speech pattern is less important clinically as verbal comprehension should be significantly more impaired in patients with receptive aphasia than in patients with schizophrenia. Thus, in most cases a thorough assessment of auditory and written comprehension should assist in this differential.

## Case vignette

A 72-year-old female with a history of hypertension and diabetes presented to the emergency room with a slightly irregular pulse. Her daughter reported that while at home, her mother suddenly began "talking nonsense" and was "confused." Examination revealed fluent but meaningless speech filled with paraphasia errors and neologisms: "She was in...flying in a splee that she goed. It's in you know...uh...that's what they're sayin' but it's not I know." This was in the context of normal prosody. She was unable to follow one-step commands and even single-word repetition was impaired. The following is a portion of a writing sample: "The ling gru yy to the cat in the fistral to the house." She was not able to read what she wrote, nor was she able to read any other written material. Her affect was euthymic and she seemed genuinely unconcerned about her condition, although briefly got upset at her daughter who did not respond to her when she asked her what sounded like a question. The remainder of her work-up was normal.

Overall, the examination revealed the presence of fluent meaningless speech, impaired comprehension, impaired repetition, and impaired reading and writing. Computed tomography (CT) revealed a left MCA infarct in the posterior-superior temporal lobe and left parietal lobe. Taken together these findings are highly consistent with a Wernicke's aphasia. The patient was stabilized and sent to acute inpatient rehabilitation where reading and writing improved markedly. Over time and with outpatient rehabilitation her speech improved significantly with lingering paraphasic errors, word-finding difficulties, and some difficulty with grammatically complex commands.

## References

1. Damasio AR, Geschwind N. The neural basis of language. *Ann Rev Neurosci* 1983; 7:127–47.
2. Beeson PM, Rapcsak SZ. The aphasias. In Snyder PJ, Nussbaum PD, Robins DL, Eds. *Clinical Neuropsychology – A Pocket Handbook for Assessment*. Washington, DC: American Psychiatric Association, 2006; 436–59.
3. Glasser MF, Rilling J. DTI tractography of the human brain's language pathways. *Cerebral Cortex* 2008; 18:2471–82.
4. Festa JR, Lazar RM, Marshall RS. Ischemic stroke and aphasic disorders. In Morgan JE, Ricker JH, Eds. *Textbook of Clinical Neuropsychology*. New York, NY: Taylor & Francis, 2008; 363–83.
5. Blumenfeld H. *Neuroanatomy through Clinical Cases*. Sunderland, MA: Sinauer Associates, 2002.
6. Damasio AR. Aphasia. *N Engl J Med* 1992; 326:531–9.
7. Goodglass H. *The Assessment of Aphasia and Related Disorders*. Austin, TX: Pro-Ed, 2002.
8. Benson DF, Sheremata WA, Buchard R *et al*. Conduction aphasia. *Arch Neurology* 1973; 28:339–46.
9. Mesulam MM. Primary progressive aphasia – a language-based dementia. *N Engl J Med* 2003; 349:1535–42.
10. Mendez MF, Clark DG, Shapira JS, Cummings JL. Speech and language in progressive nonfluent aphasia compared with early Alzheimer's disease. *Neurology* 2003; 28:1108–13.

## 6 Apraxia

---

Jasvinder Chawla and Noam Epstein *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Apraxia is a cortical dysfunction of motor planning not caused by paresis, loss of coordination, sensation, comprehension, or a movement disorder. Heilman defined apraxia in negative terms, characterizing it as “a disorder of skilled movement not caused by weakness, akinesia, deafferentation, abnormal tone or posture, movement disorders such as tremors or chorea, intellectual deterioration, poor comprehension, or uncooperativeness.” To simplify matters, apraxia can be considered a form of a motor agnosia. Patients are not paretic but have lost information about how to perform skilled movements.

The most clinically significant disability due to apraxia is the loss of the ability to use tools which then impairs a patient's activities of daily living (ADL). Apraxia is one of the most debilitating and least understood of the major behavioral neurology syndromes. Apraxia has a neurologic cause that usually localizes predominantly to the left inferior parietal lobule, or the frontal lobes (especially the premotor cortex, supplementary motor area, and convexity), or the corpus callosum.

Stroke and dementia are the most common causes, although any disease involving the above-mentioned brain areas can cause apraxia. Apraxia is one of the best localizing signs of the mental status examination and, unlike aphasia, also predicts disability in patients with stroke or dementia. Interestingly, callosal apraxia is rare after callosotomy and is much more common with anterior cerebral artery strokes or collosal tumors. No good data exist concerning the occurrence of apraxia in different age groups. However, it is more common in older age groups, as they typically have higher frequencies of stroke and dementia.

## Case vignette

A 69-year-old male was brought to medical attention by his family for history of progressively worsening gait and falls. The patient had a history of hypertension, diabetes, and stroke due to a subcortical infarct. He denied any history of subarachnoid hemorrhage, meningitis, brain irradiation, intracranial surgery, or head trauma. Despite his severe gait disorder, the patient had no signs or symptoms suggestive of primary sensory or motor loss or any incoordination. On examination, the patient was able to stand but had marked difficulty in lifting his feet off the ground and walked as if his feet were glued to the floor. Arm swing during walking was relatively smooth and well preserved. He did not have resting tremor, bradykinesia, or rigidity. Turning was cautious and required several small steps. His gait difficulties and falling episodes continued despite a therapeutic trial of levodopa/carbidopa. An unenhanced magnetic resonance imaging (MRI) scan of the brain revealed ventricular enlargement out of proportion to his cortical atrophy.

The patient also had neuropsychological evaluation and a large-volume (approximately 50 cc of cerebrospinal fluid [CSF]) lumbar puncture with measurement of the opening pressure. Gait and Folstein mini-mental status exams were assessed before and after the lumbar puncture. After the lumbar puncture both his gait and mental status improved significantly. The patient and family were informed of the likely diagnosis and possible treatment of normal pressure hydrocephalus (NPH).

A clinical improvement of gait predicts a good response to shunting. Our patient had a magnetic gait. This type of gait may be caused by bilateral lesions of the medial frontal cortex, bilateral ischemic lesions of the white matter, or severe hydrocephalus. Normal pressure hydrocephalus is a clinical entity seen in older subjects and is characterized by ventriculomegaly and normal CSF opening pressure. The clinical triad consists of gait apraxia, urinary incontinence, and dementia. Gait impairment is the most prominent and often the earliest manifestation of NPH. Distinguishing the gait disorder encountered among patients with NPH from other disorders can sometimes be challenging (see [Table 6.4](#) for the differential diagnosis of NPH).

**Table 6.1 Apraxia subtypes.**

Type	Deficit
------	---------

Ideational apraxia	Sequencing multistep tasks
Ideomotor apraxia	Gesturing and pantomime
Limb kinetic apraxia	Limb
Gaze apraxia	Extraocular movements
Speech apraxia	Speech
Magnetic gait	Gait
Conceptual apraxia	Tool types and actions
Conduction apraxia	Gesture imitation

---

**Table 6.2 Tests for apraxia .**

Test	Examples
Intransitive limb gestures	Salute Wave goodbye
Intransitive buccofacial gestures	Stick your tongue out Blow whistle
Transitive limb gestures	Use a toothbrush Use a hammer
Transitive buccofacial gestures	Suck on a straw Blow out a match
Serial acts	Show how you would make a sandwich Show how you would write and mail a letter

---

**Table 6.3** *Differential diagnosis of apraxia.*

Item	Subdivision	Specific entity	Possible clinical features
Structural	Obstructive	Hydrocephalus	Headache, nausea, vomiting and lethargy. Gait instability, Parinaud's palsy, dementia, and urinary incontinence
Infectious	Meningitis	Bacterial or viral	Fever, headache, lethargy, meningismus, and CSF lymphocytosis or pleocytosis
		Neurocysticercosis	Seizure, headaches, ring enhancing cystic CT/MRI lesions
Post- infectious	Acute demyelinating encephalitis		Post-infectious, contrast enhancing MRI and CSF findings
Psychiatric	Malingering		No biological cause and secondary gain
	Schizophrenia	Abulia	Poor motivation, reduced spontaneous

			movement, and flat affect
Neoplastic	Tumor	Glioma	Gradually progressive neurologic deficit, enhancing parenchymal lesion on MRI
	Para-neoplastic	No primary tumor	Anti-hu or anti-Ma antibodies
Degenerative	Dementia	CBD	Akinetic-rigid, alien hand syndrome
	Alzheimer's disease		Memory and ADL loss without other etiology
	Frontotemporal dementia		Social disinhibition, executive dysfunction, and bizarre behavior
	CJD		Rapidly progressive dementia with myoclonus. Characteristic cortical ribbon sign on diffusion MRI
Vascular	Stroke	Ischemic	Anterior cerebral artery territory common. Often includes neglect

and a change in personality

	Hemorrhagic	Dorsal or paramedian thalamic. Hyperintensity on CT head
Aneurysm	Subarachnoid hemorrhage	Headache and nuchal rigidity. Xanthochromia on lumbar puncture
Arterial venous malformation		Headache, seizure, progressive neurologic deficit, MRI/angiography
Subdural	Chronic subdural hemorrhage	Common in the elderly, anticoagulation and falls are risk factors
Idiopathic	Primary progressive apraxia	Apraxia of the limb or gait without dementia
Metabolic	Vitamin B12 deficiency	Gait problems, mental status changes, large fiber neuropathy, and anemia
Movement	Parkinson's	Rigidity, cog

disorder	disease	wheeling, and bradykinesia with or without tremor
	PSP	Extraocular movement limitations and characteristic extended neck posture
	Multi-system atrophy	Autonomic dysfunction and movement disorder
	Huntington's disease	Chorea, behavioral problems, family history, and CAG repeats
	Dystonia	Limb/head posture which may be intermittent
Trauma associated	Post concussive	History of head trauma
Ictal	Subtle status	EEG findings
Demyelinating	Multiple sclerosis	Limb apraxia. Anterior callosal disconnection syndrome

---

ADL, activities of daily living; CSF, cerebrospinal fluid; CT, computerized tomography; EEG, electroencephalogram; MRI, magnetic

resonance imaging.

**Table 6.4 Differential diagnosis of gait apraxia and normal pressure hydrocephalus (NPH) .**

Item	Specific type	Specific etiology	Clinical features may include
Toxic	Manganese	Chronic exposure required	Initial presentation neuropsychiatric symptoms; later parkinsonism; action rather than rest tremor; cerebellar dysfunction
	Carbon monoxide	History of exposure	Diffuse nervous system dysfunction with parkinsonism; CT head or MRI brain reveal bilateral globus pallidus necrosis
	Carbon disulfide		Parkinsonism, dementia, neuropathies seen with chronic exposure
	Cyanide		Parkinsonism in cyanide

**Cyanoacrylate  
poisoning  
survivors**

Pharmacologic causes	Various drugs	Neuroleptics, reserpine, tetrabenazine, alpha-methyl dopa	Parkinsonism
MPTP	Intravenous drugs		Young adults; use of intravenous synthetic heroin
Degenerative	Other degenerative conditions	Primary pallidal atrophy	Juvenile onset, progressive parkinsonism with chorea and dystonia
		Idiopathic dystonia parkinsonism	Juvenile and adult onset, diurnal fluctuations of parkinsonism dystonia
	CBGD		Onset in midlife; clinical features of cortical and basal ganglia involvement; unilateral
	LBD		Synchronous onset of parkinsonism and dementia, prominent gait

	impairment with subcortical dementia
PSP	Parkinsonism with supranuclear gaze palsy, pseudobulbar signs, and severe gait difficulty
OPCA	Gait ataxia, kinetic tremors and dysarthria. Parkinsonism at later stages
MSA or Shy– Drager syndrome	Drug-resistant parkinsonism with predominant autonomic features
Hemiparkinsonism	Late complication of hemiatrophy due to injury in early life
ALS– parkinsonism– dementia	Endemic occurrence in Guam; signs of ALS, parkinsonism, and dementia

	Alzheimer's and Pick's disease	Primary dementing conditions, parkinsonism possibly seen in later stages of the disease
CJD		Dementing condition with subacute onset and rapid course; wide central nervous system involvement, including basal ganglia
GSSD		Onset in midlife; ataxia, pyramidal signs, dementia, later parkinsonism
Central nervous system disorders	Brain tumors	Parkinsonism possibly seen with brain tumors; neuroimaging diagnostic
	Trauma	Rare, chronic traumatic encephalopathy of boxers
Metabolic causes	Hypoparathyroidism and basal ganglia calcification	Disorders of calcium metabolism

		possibly resulting in basal ganglia calcification and sometimes parkinsonism
	Chronic hepatocerebral degeneration	Seen in some patients with repeated episodes of hepatic coma
Hereditary conditions	Wilson's disease	Onset in adolescence; reduced serum ceruloplasmin and copper and increased 24- hour excretion of copper are diagnostic
	Huntington's chorea	Juvenile onset; hyperkinetic disorder, possibly with primary parkinsonism features

---

ALS, amyotrophic lateral sclerosis; CBGD, corticobasal ganglionic degeneration; CJD, Creutzfeldt–Jakob disease; CT, computerized tomography; GSSD, Gerstman–Straussler–Scheinker disease; LBD, Lewy body dementia; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MRI, magnetic resonance imaging; MSA, multi-system atrophy; OPCA, olivopontocerebellar atrophy; PSP, progressive supranuclear palsy.

## Further reading list

- Adams RD, Fisher CM, Hakim S *et al.* Symptomatic occult hydrocephalus with “normal” cerebrospinal fluid pressure. a treatable syndrome. *N Engl J Med* 1965; 273:117–26.
- Dovern A, Fink GR, Weiss PH. Diagnosis and treatment of upper limb apraxia. *J Neurol* 2012; 259:1269–83.
- Gillon GT, Moriarty BC. Childhood apraxia of speech: children at risk for persistent reading and spelling disorder. *Semin Speech Lang* 2007; 28:48–57.
- Goldenberg G. Apraxia and the parietal lobes. *Neuropsychologia* 2009; 47:1449–59.
- Hermsdörfer J, Li Y, Randerath J, Roby-Brami A, Goldenberg G. Tool use kinematics across different modes of execution. Implications for action representation and apraxia. *Cortex* 2013; 49:184–99.
- Morgan AT, Vogel AP. Intervention for childhood apraxia of speech. *Cochrane Database Syst Rev* 2008; 3:CD006278.
- Vanbellingen T, Lungu C, Lopez G, Baronti F, Müri R, Hallett M, *et al.* Short and valid assessment of apraxia in Parkinson's disease. *Parkinsonism Relat Disord* 2012; 18: 348e350.
- Wambaugh JL, Nessler C, Cameron R, Mauszycki SC. Acquired apraxia of speech: the effects of repeated practice and rate/rhythm control treatments on sound production accuracy. *Am J Speech Lang Pathol* 2012; 21:S5–27.
- Whiteside SP, Inglis AL, Dyson L *et al.* Error reduction therapy in reducing struggle and grope behaviours in apraxia of speech. *Neuropsychol Rehabil* 2012; 22:267–94.

## 7 Ataxia, acute or subacute

---

Jay Elliot Yasan *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

The word ataxia is from the Greek “a” “taxis,” meaning absence of order. In clinical practice, ataxia means incoordination of movement due to cerebellar dysfunction. Gait ataxia encompasses a wide spectrum of imbalance. The patient may describe walking “as if drunk.” As the cerebellum also modulates speech, eye, and limb movements, the patient may experience slurred speech, diplopia, oscillopsia (jiggling of the environment), or tremor.

It is important to distinguish cerebellar gait ataxia from other causes of unsteadiness. For example, sensory ataxia (SA) refers to unsteadiness attributable to a loss of proprioceptive feedback. Patients with SA are more dependent upon visual feedback to maintain their balance; they sway and fall once their eyes are closed (Romberg testing). Patients with cerebellar ataxia tend to fall even with their eyes open. Sensory ataxia is due to a significant sensory neuropathy or dorsal column dysfunction. Examples of the latter are tabes dorsalis (syphilis) or multiple sclerosis. In general, patients with SA do not have oculomotor symptoms and signs such as nystagmus, while patients with cerebellar ataxia may also have these. Other less common localizations which may give rise to a hemi-sensory ataxia are the parietal lobe or thalamus. Some of the more important sensory ataxias are included in [Tables 7.1](#) and [7.2](#).

**Table 7.1** *Differential diagnosis of episodic ataxias* .

---

Age of onset	Specific entity	Clinical features
Late infancy, early childhood	Hartnup disease, autosomal recessive	Unsteady gait, intention tremor, dysarthria; intermittent rash, developmental delay; triggered

Category	Type	Description
Adolescence–adult	Episodic ataxia (EA 1–6) autosomal dominant	Acute-onset ataxia, triggered by stress, exposure to sunlight, and sulfonamides; intestinal malabsorption of tryptophan with increased excretion of amino acids
	EA-1	Episodes of ataxia and dysarthria; Some also have vertigo, dysarthria, diplopia, tinnitus, and seizures; precipitated by stress
	EA-2	Frequent spells (15×/day) lasting seconds–minutes, with interictal hand or periorbital myokymia; no interictal ataxia; provoked by sudden movement or startle; onset childhood–teens
	Episodic ataxia with paroxysmal choreoathetosis and spasticity	Spells of ataxia and dysarthria last hours–days; some have nausea, headache, dystonia, or hemiplegia; interictal gaze-evoked or upbeat nystagmus; interictal nystagmus and limb ataxia may become persistent; provoked by caffeine, alcohol, phenytoin; associated with migraine; onset childhood–teens, but can occur up to 40s; more common than EA-1
	Basilar migraine	Lasts 20 min, dystonia of limbs and burning in legs and around mouth
		Usually b/l occipital headache, nausea/vomiting; accompanied

		by visual sx, vertigo, diplopia, tinnitus, diminished hearing, drop attacks, altered level of arousal; can have prolonged aura; definitive dx = complex partial seizures
Adult	Carbamoyl phosphate synthetase type I deficiency, autosomal recessive	Presents with ataxia, seizures, and tremor in early–mid adulthood; elevated ammonia level. Check blood amino acid and urine organic acid analyses
	Late onset ornithine transcarbamylase deficiency (OTCD)	F > M; post-prandial headaches, seizures, spells of ataxia, vomiting, psychiatric sx, unexplained change in mental status can last days, coma with brain edema; sx due to high ammonia; spells triggered by high-protein meals or infection; check serum and urine amino acid studies; liver biopsy, DNA testing for definitive dx
	Multiple sclerosis	Abrupt and recurrent spells of dysarthria and ataxia; seconds to minutes; usually during relapsing–remitting phase, not presenting feature
	Vascular	Vertebrobasilar TIA
Variable age	Pyruvate dehydrogenase deficiency (lactic and pyruvate acidemia with	Spells including hypoglycemia and seizures; may mimic subacute necrotizing encephalopathy (Leigh's disease). Serum and urine

episodic ataxia and weakness)	studies show hyperalaninemia
Intracranial hypertension	Episodic-persistent ataxia; including idiopathic intracranial hypertension (IIH); headache, papilledema
Radiation vasculopathy	Complicated migraine-like spells, sometimes with ataxia, which may precede stroke; can be due to micro-or macro- angiopathy (which vessels were in field of radiation?); MRI brain with white matter changes, BG Ca++; Also, check CTA or MRA

CTA, computerized tomography angiography; dx, diagnosis; MRA, magnetic resonance angiography; sx, symptoms.

Another cause of unsteadiness which needs to be distinguished from cerebellar ataxia is the unsteadiness due to labyrinthine ataxia. When a patient complains of dizziness, one needs to play psychiatrist, and ask what he means by dizzy. Patients may use the word dizzy to describe a wide spectrum of symptoms, ranging from vertigo to lightheadedness, or even confusion. True vertigo involves an illusory sense of movement. It is important to distinguish the unsteadiness which results from a peripheral vestibulopathy (e.g. benign positional vertigo or labyrinthitis) from cerebellar ataxia. Labyrinthine ataxia causes impaired balance; however, it does not cause alteration of speech or appendicular ataxia. However, with posterior circulation strokes, the brainstem and cerebellum and their connections are often involved, and the patient often experiences vertigo and cerebellar ataxia, as well as other symptoms. With an acute vestibular syndrome, it can be difficult to distinguish central versus peripheral causes of vertigo. The head thrust test can be used to distinguish between a cerebellar infarction and a vestibular neuritis. This test evaluates how well the eyes maintain fixation during a rapid head turn. This is called the vestibular-ocular response (VOR). Since a cerebellar stroke will not affect the

VOR, the head thrust test will be negative; that is, there will be no “catch-up” re-fixation. This is a vastly under-utilized test.

Myelopathy also causes imbalance; however, this should be easily distinguished from cerebellar ataxia based upon the presence of myelopathic signs and the absence of signs referable above the neck, such as dysarthria.

On examination, one may find “scanning” speech – deliberate articulation of each syllable. Eye movements demonstrate saccadic (broken up) pursuit, ocular dysmetria (under-or overshoot of the visual target), and nystagmus. Appendicular (limb) ataxia indicates a lesion of the ipsilateral cerebellar hemisphere. This is due to the double decussation of cerebellar pathways. Patients take a wide base , with irregular steps. Milder cases show inability to tandem gait, tending to fall to the side of the lesion. Even while sitting, the patient tends to lean to the side of the lesion. Isolated truncal ataxia (without appendicular ataxia) localizes to the cerebellar vermis (midline). Dysdiadochokinesia (impaired rapid alternating movements), intention tremor , or a coarse tremor may also be seen. Hypotonia or slowness of the affected limb may be present, especially acutely. There is often an exaggerated rebound or overshoot of the limb.

Cerebellar signs may be accompanied by signs related to compression of nearby structures. For example, a cerebellar hemorrhage may cause compression of the medulla, leading to respiratory compromise . Mass effect on the pons may lead to cranial nerve palsies , especially the sixth and seventh nerves.

**Table 7.2 Differential diagnosis of non-episodic ataxia.**

Category	Subdivision	Specific entity	Clinical features Include
Toxic	Toxins	Acute alcohol toxicity	ETOH abuse; dysarthria; screen
		Alcoholic cerebellar degeneration (subacute–chronic)	Develops over months; dysmetria; nystagmus not absent; focal anterior-superior

can be seen in

	Mercury, lead, thallium, solvents (paint thinner), pesticides, toluene (glue sniffing, spray paint)	Mercury may cause permanent damage and persist even after removal. High mercury levels are associated with memory loss, confusion and hallucinations.
Medications	Phenytoin toxicity (subacute) Other medications: (subacute–chronic) carbamazepine, valproic acid, vigabatrin, phenobarbital, barbiturates, lithium, metronidazole, amiodarone, procainamide, isoniazid, fluorouracil, cisplatin, cytarabine, cyclosporine, intrathecal methotrexate, methoxetamine (ketamine derivative)	Nystagmus, ataxia > dysarthria; level of consciousness Check medications and levels
Deficiencies	B1 (thiamine) deficiency (Wernicke's disease)	Ophthalmoplegia, nystagmus, confusion “Korsakoff’s syndrome” (amnesia/confusion) may occur after alcohol withdrawal

		follow with primarily bu in alcoholics of bariatric s MRI: symme thalamic, periaqueductal hyperintensi B1 deficiency cause acute o bilateral vest failure
	B12 deficiency Sensory ataxia: primarily due to dorsal column disease (subacute)	Neuropsychi subacute cor degeneration cord and bra corticospinal dorsal column vibration, propriocepti Romberg); o peripheral ne often due to anemia
	Vitamin E deficiency (subacute–chronic)	Malabsorpti alcoholism, i failure
	Zinc deficiency (subacute–chronic)	Irritability, t sometimes c ataxia
Infectious	Cerebellar infection/abscess (subacute)	Headache; t cryptococcal fungal, herpes Barr virus (E HTLV1, coxsackievirus, le

			Cytomegalovirus, <i>Mycobacterium tuberculosis</i> , Lyme disease
	Meningitis	Basilar meningitis especially TI	
	Tabes dorsalis (syphilis of spinal cord) Sensory ataxia, not cerebellar	Lightning pains and urinary incontinence decreased vibration proprioception Romberg	
Post-infectious	Acute cerebellar ataxia: children	VZV, JC virus, influenza, pertussis, measles (rubeola)	Days or weeks after viral illness, chicken pox; diffuse CBL abnormalities lymphocytic pleocytosis; reversible
	Acute cerebellar ataxia: adult	HIV, HSV-1, HHV-6, EBV, Lyme disease, <i>M. pneumoniae</i> , syphilis	May be associated with encephalitis; pleocytosis, high protein
	Acute disseminated encephalomyelitis (ADEM)	Acute onset encephalopathy headache, fever present with other signs of infection after infection common in children multiple gray matter enhancing lesions; lymphocytic pleocytosis	

	elevated pro	
	Whipple's disease (multi-system disease caused by gram positive acinetobacterium <i>Tropheryma whipplei</i> )	Middle-aged men, weight abdominal p steatorrhea, neuro sx may occur without ataxia in 18% loss, seizures, oculomastica, myorhythmia (20%); dx: PCR <i>whipplei</i> from intestinal biopsies
Prion	Creutzfeldt–Jakob disease (subacute)	Rapidly progr dementia over isolated cere (ataxia and c in 5%; later: “myoclonus”; ribbon-like p along cortex and hyperint caudate and FLAIR; EEG slow and shal complexes; no inflammation; protein neither nor specific; precautions i EEG
Pressure effects	High altitude cerebral edema (HACE)	Rapid expos altitudes > 3 earliest signs: unsteadiness

behavior, headache, papilledema, disorientation, vomiting, confusion

Psychiatric Pseudo-ataxia Conversion disorder (non-physiologic) Astasia-abasia often dramatic gait, typically only when seen nearby to camera. Note that patients may embellish underlying problem. MRI negative. Restricted distribution (acute infarct). Caution: (a) may be false negative stroke, (b) consider myriad causes

Inflammatory Bickerstaff's brainstem encephalitis (closely related to axonal Guillain–Barré) Ataxia and ophthalmoplegia (overlap with Fisher variant), but also disturbance of consciousness, diplegia, and tetraparesis; preceding illness Gq1b Ab in cerebrospinal fluid. MF syndrome abnormal in

Autoimmune Primary Autoimmune Cerebellar Ataxia Starts in 50s progressive, can be acute glutamic acid decarboxylase

			high prevalence other autoimmunity CBL atrophy on duration
	Hashimoto's Encephalopathy	Neuropsychiatric choreoathetosis; seizure; anti- Abs; response to steroids	
	Ataxia and nystagmus associated with antiganglioside Ab's	Anti-Gq1b, IgG4, and anti-GM1 rare; MRI, CSF conduction velocity normal; resolution months	
	Other	Sarcoid, Rosai-Dorfman (sinus histiocytosis), massive lymphadenopathy, Behcet's	
Tumor	Primary neoplasm (usually subacute)	Astrocytoma, medulloblastoma, oligodendrogloma, ependymoma, hemangioblastoma (von Hippel-Lindau syndrome), primary CNS lymphoma	Headache, painless sx and signs upon structural changes
	Cerebello-pontine masses (usually subacute)	Acoustic neuroma, meningioma, cysts	Hearing loss, paresis, hydrocephalus
	Neuroblastoma (pediatric)	With or without opsoclonus/ataxia	

		Lung and breast most common; melanoma, teratoma	Usually enhan- ce neck urinal catecholami- and VMA)
	Metastatic (usually subacute, though may present acutely if hemorrhagic metastasis)	Hydrocephalus	Usually enhan- ce MRI; may be multiple
Paraneoplastic	Paraneoplastic cerebellar degeneration (PCD). Subacute pancerebellar syndrome; antibodies can precede tumor by 2 years. Brain MRI often normal early on; later shows brainstem, CBL atrophy	Anti-Yo (PCA-1) Ab Anti-TR antibody Anti-CRMP5 (anti- CV2) or PCA-2 Ab Anti-Ma1 Ab	associated w/ breast, lung PCD; Hodgk lymphoma PCD, chorea encephalomy sensory neur SCLC and th PCD, brains encephalitis; other cancer
		Anti-metabotropic glutamate receptor R1 Ab	PCD, Hodgk lymphoma
		Anti-Ri (ANNA- 2)Ab	PCD, someti opsoclonus- breast, gynec lung, bladde
		Anti-Zic4 Ab	PCD. enceph

		SCLC
	Anti-VGCC Ab	PCD; SCLC associated w
	Anti-Hu (ANNA-1) Ab	PCD, encephalomyopathy, sensory neuropathy associated w prostate, neu
Vascular	<p>Ischemic stroke</p> <p>*MRI shows restricted diffusion – high signal on diffusion weighted imaging (DWI) and low signal on apparent diffusion coefficient (ADC) sequences in corresponding area. MRI can be false negative in up to 10% of cases, especially in posterior fossa.</p> <p>Need vascular imaging</p>	<p>Posterior inferior cerebellar artery (PICA)</p> <p>Vertigo, headache, vomiting, hemianesthesia, dysphagia, hemiparesis, Horner's syndrome, nystagmus, contralateral pain and temperature, facial, and cranial nerve palsies, body, ipsilateral mass effect (compress brainstem), 4th ventricle hydrocephalus</p>
	Vermian (medial branch of PICA)	Truncal ataxia, sometimes nystagmus, dysarthria; cerebellar peripheral vascular syndrome
	Anterior inferior cerebellar artery (AICA)	Vertigo, von Breuer's syndrome, dysarthria, ipsilateral loss; brainstem

more common  
other cerebellar  
nystagmus, i  
peripheral fa  
weakness; MI  
brachium pos  
is almost alw  
involved; if l  
more than ju  
territory, sus  
artery occlus

Superior cerebellar  
artery (SCA)

Dysarthria, i  
ataxia; vertig  
common tha  
isolated SCA  
uncommon;  
with other m  
thalamic and  
cerebral arte  
as part of “tc  
basilar” sync

Ataxic hemiparesis  
syndrome

Hemi-ataxia  
proportion to  
– both contralat  
infarct; usua  
brachium pos  
posterior lim  
internal caps  
usually due to  
penetrating t  
disease

Hemorrhagic infarct

Often larger  
infarct; as w  
hemorrhagic  
more likely to  
embolic; oft  
+ - + - + - + -

in spite of ne

	Cerebellar venous infarct	Very rare
Hemorrhage (CBL ICH = 10% of ICH)	Hypertensive	Headache, v rostral vermis truncal/gait & hemisphere: ataxia; some with ipsi 6N gaze palsy
	Arteriovenous malformation/dural AV fistula	Flow voids c listen for ma look for larg superficial v
	Cavernous hemangioma (cavernoma)	Popcorn-like heterogeneou hyperintense T2WI; look hypointensit gradient ech of MRI
	Aneurysmal subarachnoid hemorrhage	Vertebral art or PICA ane
	Superficial siderosis (usually slowly progressive)	Recurrent su bleeding; pro ataxia, sensc hearing loss, anosmia; MI echo sequenc hemosiderin in the menin of entire neu be necessary

source of bleeds

	Cerebral amyloid angiopathy (CAA)	Often associated with vascular dementia; associated with Alzheimer's disease and pathologically with cerebral microhemorrhages on gradient echo MRI
	Hemorrhagic metastasis	MRI with Gd contrast; 24 hrs may show enhancement
	Other	Bleeding diathesis (e.g., anticoagulants)
Metabolic	Endocrine (subacute)	Myxedema (severe hypothyroidism)  Hypoglycemia, hypercalcemia, hypocalcemia, hyponatremia
	Celiac disease (intolerance to gluten)	Reversible; often associated with other autoimmune diseases; rarely in isolation

Ab's; endosc  
biopsy of sm  
intestine

Acquired  
hepatocerebral  
degeneration  
(subacute–chronic)

Ataxia seen  
pts; limb > t  
opposed to a  
cerebellar de  
Cognitive de  
dysarthria,  
parkinsonism  
liver failure  
cirrhosis; hiq  
signal in bas  
and CBL

Hyperthermia  
(affects CBL  
disproportionately)

“Heat stroke”

Coma at ons  
convulsions;  
dementia, ps  
palsy; residu  
cerebellar si

Mitochondrial  
(usually slowly  
progressive, but  
can be subacute),  
and have ataxia as  
a feature

Mitochondrial  
encephalomyopathy,  
lactic acidosis, and  
stroke-like episodes  
(MELAS); primary  
CoQ10 deficiency;  
chronic progressive  
external  
ophthalmoplegia  
(CPEO);  
neuropathy, ataxia,  
and retinitis  
pigmentosa  
(NARP), and others

Common fea  
mitochondri  
maternal inh  
short stature  
intolerance,  
like headach  
seizures; pto  
sensorineura  
loss, dement  
CPK, CSF le  
cardiomyopa  
diabetes; MI  
abnormality  
to vascular t  
muscle biops  
red fibers

	<b>Leydig cell disease</b> Adult forms can be sporadic, autosomal recessive, autosomal dominant, X-linked, or mitochondrial	<b>Teti-oval disease</b> neuro sx acu subacute; nausea/vomi central respi failure, dem atrophy, int oculomotor ] deafness, dy myoclonus, sometimes ti fever or surg acidosis; MI putamen b/l; biopsy: ragg fibers
Rare inherited metabolic disorders	Wilson's disease (autosomal recessive) (subacute–chronic)	Rare disorder deposition ir brain; move disorder, dys psychiatric; Fleischer rin cornea on sli exam; high t copper excre low serum ceruloplasmi mutation ana
	Acute intermittent porphyria sensory ataxia (subacute)	Ages 18–40, rare enzyma in heme synt autosomal d with variable penetrance; ] with psychia disturbances abdominal p neripheral n

			Porphyrin increased deaminolevulinic porphobilinogen attacks
Movement disorder	Also, see Wilson's disease (above)	Opsoclonus-myoclonus syndrome	Ataxia in apoplexy (subacute) paraneoplastic (SCLC) or paraneoplastic patients, high incidence of encephalopathy Idiopathic: no better prognosis immunotherapy effective
		Oculo-palatal tremor	Oscillopsia/tilt and palatal tremor occur subacutely to months after other lesions Guillain-Barré triangle (infarct - dentate nucleus; contralateral nucleus); often include dysarthria, tremor and a cerebellar hypertrophy (Hypertrophic Degeneration)
Heredofamilial	See mitochondrial (above) and episodic ataxia table		

Trauma		Concussion, contusion, subdural hematoma	
Demyelinating	Upper motor neuron	Multiple sclerosis	May be atax tremor; may sensory atax dorsal column enhancing lesions cerebellum connections; other demyelinating lesions on MRI especially corpus callosum, periventricular sometimes subacute restricted diffusion MRI acutely
	Lower motor neuron	Miller–Fisher syndrome (acute–subacute)	(Sensory) ataxia ophthalmoparesis areflexia (Guillain– Barré variant)

---

Ab, antibody; b/l, bilateral; CBL, cerebellar; dx, diagnosis; FLAIR, Fluid attenuated inversion recovery; hx, history; ipsi, ipsilateral; MRI, magnetic resonance imaging; SCLC, small cell lung cancer; 6NP, sixth nerve palsy.

While vomiting has many causes, including raised intracranial pressure, it can be a major clue to cerebellar disease. The chemoreceptor trigger zone or vomiting center is located in the floor of the fourth ventricle. Any process which distorts the fourth ventricle – for example, a cerebellar stroke – can cause vomiting. Sometimes a patient who presents with profuse vomiting is initially misdiagnosed as having gastroenteritis or food poisoning. The patient's speech is hoarse, but this is mistakenly attributed to the vomiting. The patient is lying on a stretcher, so not even the patient is aware of being ataxic. There is no focal weakness, so stroke is not considered. Even if stroke is considered, a negative

computed tomography (CT) head scan provides false comfort, since CT is very insensitive for an acute ischemic stroke, and it is especially insensitive for a low brainstem/cerebellar infarct. Later, when the patient is unable to stand without assistance, a neurologist is called and makes the diagnosis of a Wallenberg syndrome due to a (posterior inferior cerebellar artery [PICA]) cerebellar infarction. A Horner's syndrome , which is typically seen, can be easily missed in the midst of violent vomiting. This is also a reminder that the two most important parts of the neurologic exam are the mental status and gait; *i.e.* Can the patient talk? Can the patient walk?

As with all neurologic disease, the exam localizes the lesion, but the history is the key to etiology. In taking a history, it is always important to ask what the patient was doing at the time of onset. Patients with a stroke are often embarrassed to mention that symptoms arose during sexual relations. Was there a recent fever, infection, or immunization to suggest an infectious or autoimmune process? Was there any recent chiropractic manipulation, whiplash, or other minor neck trauma? These may be associated with a cervical artery dissection and possible stroke.

It is important to keep in mind that ataxia in toddlers is most commonly due to accidental ingestions. Likewise, in adults, it is essential to take a thorough medication history and ask about potential toxins. Serum and urine toxicology is even better in many cases if substance abuse is suspected. Phenytoin toxicity is a common cause of acute ataxia in adults.

A subacute pancerebellar syndrome, including Charcot's triad of scanning speech , nystagmus , and intention tremor , should prompt investigation for a paraneoplastic cerebellar degeneration and the anti-Yo antibody . These are particularly associated with gynecologic malignancies .

Tables 7.1 and 7.2 cannot possibly include all the causes of acute and subacute ataxia, especially as ataxia may be isolated, or occur in association with other symptoms and signs. This depends, of course, upon what other parts of the neuro-axis are involved. Most of the causes of isolated ataxia are included in the tables; many but not all of those which have co-existent disease are also included. Finally, the diagnoses listed in the tables are causes of acute ataxia; however, it is indicated when the presentations are typically subacute.

## **Case vignette: when several diagnoses come together**

A 60-year-old male with a history of hypertension presented with sudden-onset

headache, vomiting, and ataxia. Past medical history was significant for hypertension and diabetes mellitus. His exam was significant for a blood pressure of 217/125 mmHg, mild dysarthria, sustained horizontal gaze-evoked nystagmus, an ataxic gait, and the absence of appendicular dysmetria. Laboratory work was significant for a macrocytic anemia and lipid profile within normal limits. Brain magnetic resonance imaging (MRI) showed an acute 2 cm left paravermian infarct. Magnetic resonance angiography (MRA) of the brain and neck showed no large vessel steno-occlusive disease. Echocardiogram and 24 hour Holter were unrevealing.

What is the main vascular supply to the cerebellar vermis? The posterior inferior cerebellar artery (PICA).

What are the possible mechanisms for this stroke? In general, the three primary mechanisms of stroke are small vessel (perforator) disease, large vessel disease, and cardio-embolism. This infarct was 2 cm, which is larger than a typical small vessel lacunar infarct (< 1.5 cm). Most cerebellar strokes, especially those in PICA distribution, are due to embolism from the heart or vertebral arteries. The MRA did not show any significant stenosis in the vertebral arteries, which are the donor arteries for the PICA. A cardiac source of emboli should be sought despite the negative echocardiogram and Holter.

What other tests might be helpful in excluding a cardiac source of emboli? Transesophageal echocardiogram (TEE) is sensitive for left atrial appendage thrombi, aortic plaques, and other sources of emboli which may not be seen on transthoracic echocardiogram. Also, mobile cardiac outpatient telemetry (MCOT) can significantly improve the yield in detection of occult paroxysmal atrial fibrillation compared with conventional arrhythmia detection (Holter or inpatient telemetry).

Transesophageal echocardiogram showed a  $2.9 \times 1.6$  cm mobile mural thrombus attached to the inferior wall of the aortic arch, just proximal to the left subclavian artery. A second mobile thrombus, 1.2 cm in length, was attached.

Is there a connection between the macrocytic anemia and this stroke? One of the most important causes of megaloblastic anemia is B12 deficiency. When B12 is deficient, homocysteine becomes elevated. Hyperhomocysteinemia increases the risk of stroke and heart disease through several purported mechanisms, including thrombosis.

The B12 level was  $<100$   $\mu\text{mol/L}$ . Homocysteine was 50  $\mu\text{mol/L}$ . Anti-parietal cell antibodies and intrinsic factor were elevated, consistent with pernicious

anemia. Ataxia improved significantly after a few days. There were no clinical signs of neuropathy or myelopathy on exam.

The patient was treated with warfarin, bridging with intravenous heparin. A subsequent TEE showed resolution of the aortic mural thrombus. Supplementation with vitamin B12 injections and folic acid led to normalization of the B12 and homocysteine. The patient had no residual deficit and no recurrence of thromboemboli.

In this case, a simple clue from the laboratory work – macrocytic anemia – led to elucidation of the pathophysiology of the stroke, and resulted in specific treatments. The symptoms of vomiting and ataxia suggested posterior fossa disease. The findings of truncal ataxia and nystagmus helped to localize the lesion to the midline cerebellum (vermis). The vermian infarct was likely due to embolization of an aortic mural thrombus. The thrombus probably resulted from a prothrombotic state due to significant homocysteinemia, which in turn, was caused by vitamin B12 deficiency from pernicious anemia . The take-home message is to pay attention to simple lab work. Also, remember to consider cardiac and aortic sources when searching for donor emboli.

## Further reading list

- Bataller L, Graus F, Saiz A *et al.* Clinical outcome in adult onset idiopathic or paraneoplastic opsoclonus-myoclonus. *Brain* 2000; 124:437–43.
- Brusse E, Maat-Kievit J, Van Swieten J. Diagnosis and management of early- and late-onset cerebellar ataxia. *Clin Genet* 2007; 71:12–14.
- Caplan L. *Posterior Circulation Disease: Clinical Findings, Diagnosis, and Management*, 1st edn. Cambridge, MA: Blackwell Scientific Publishers, 1996.
- Caplan LR. *Caplan's Stroke: A Clinical Approach*, 4th edn. Philadelphia, PA: Saunders Elsevier, 2009.
- Cooper SA, Murray KL, Heath CA, Will RG, Knight RSG. Sporadic Creutzfeldt–Jakob disease with cerebellar ataxia at onset in the UK. *J Neurol Neurosurg Psychiatry* 2006; 77:1273–5.
- Darnell R, Posner J. Paraneoplastic syndromes involving the nervous system. *NEJM* 2003; 349:1543–54.
- Gupte G, Stonehouse M, Wassmer E *et al.* Acute disseminated encephalomyelitis: a review of 18 cases in childhood. *J Pediatric Child*

*Health* 2003; 39:336–42.

Itoh Y, Yamada M, Hayakawa M, Otomo E, Miyatake T. Cerebral amyloid angiopathy: a significant cause of cerebellar as well as lobar cerebral hemorrhage in the elderly. *J Neurolog Sci* 1993; 116:135–41.

Jeong SH, Nam J, Kwon MJ, Kim JK, Kim JS. Nystagmus and ataxia associated with antiganglioside antibodies. *J Neuro-Ophthalmology* 2011; 31: 326–30.

Louis ED, Lynch T, Kaufmann P, Fahn S, Odel J. Diagnostic guidelines in central nervous system Whipple's disease. *Ann Neurol* 1996; 40:561–8.

Morris B, Partap S, Yeom K, Gibbs IC, Fisher PG, King AA. Cerebrovascular disease in childhood cancer survivors. A Children's Oncology Group Report. *Neurology* 2009; 73:1905–13.

Park SA, Heo K. Prominent cerebellar symptoms with unusual magnetic resonance imaging findings in acquired hepatocerebral degeneration. *Archiv Neurol* 2004; 61:1458–60.

Ropper A, Samuels M. *Adams and Victor's Principles of Neurology*, 9th edn. New York, NY: McGraw-Hill, 2009.

Ryan DP, Ptacek LJ. Episodic neurological channelopathies. *Neuron* 2010; 68:282–92.

Wu T, Ding S, Liu J et al. Ataxia: an early indicator in high altitude cerebral edema. *High Alt Med Biol* 2006; 7:275–80.

## **8 Ataxia, subacute or chronic**

---

Amanda J. Thompson and S. H. Subramony *Neurologic Differential Diagnosis*,  
ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge  
University Press. © Cambridge University Press 2014.

### **Introduction**

Ataxia refers to a neurologic syndrome of uncoordinated or disorganized motor activity of limbs, trunk, and cranial muscles. It is usually the result of pathology in the cerebellum or cerebellar pathways, but can also result from impaired proprioception due to sensory neuropathy. The pathology can be either acquired or genetic and generally results in atrophy of the cerebellum.

### **Clinical signs**

Patients with progressive ataxia generally experience unsteady gait and frequent falling. Their hand coordination becomes impaired and speech and swallowing function worsens. Patients also may have ocular symptoms, which are mostly related to abnormal control of eye movements. Neurologic examination is notable for dysmetria of limbs (inaccuracy of targeted movements) and tremor of the limbs on movement (kinetic tremor). There are increasing balance problems including impaired tandem stance, the need for a wider base during natural stance, and wide-based gait with body sway. Eye movements show gaze-evoked or other types of nystagmus, abnormal pursuit of visually presented objects (jerky appearance due to intrusion of saccades into pursuit), and inaccurate saccades when the person is asked to move the eyes fast towards a target (hypometric or hypermetric saccades). There is also a characteristic scanning type of dysarthria.

Limb incoordination resulting from lack of proprioception characterizes sensory ataxia. Areflexia, impaired vibration sense, along with impaired position and kinesthetic sense, are frequently seen while eye movements and speech are not affected. Both sensory and cerebellar findings can be present in some patients. Frequently, many patients exhibit other abnormalities on neurologic

examination due to extra-cerebellar involvement in the pathological process.

## Epidemiology

Precise data regarding the prevalence of all causes of ataxia is imprecise but epidemiologic studies of hereditary ataxias have found a prevalence of about 10 per 100,000 and there are likely more cases of idiopathic ataxia. Individual types of inherited and degenerative ataxias are relatively rare but there are clusters of high incidence of certain types due to founder effects and geographic variations in the prevalence of many mutations.

## Clinical approach to ataxia

The goals of the evaluation process are to identify an underlying cause if possible, offer specific therapy as needed, perform prognostic and genetic counseling, and bring diagnostic closure [1,2]. Chronic progressive ataxia can result from both acquired and genetic causes.

## Acquired causes

Most acquired ataxias evolve in an acute or subacute fashion with symptom duration measured in hours to months. Family history is negative. An acute onset of ataxia suggests a vascular, demyelinating, or infectious lesion or toxic etiology. Imaging studies are useful to sort out acquired ataxias. Imaging studies will readily detect such etiologic factors as vascular lesions (infarcts, hemorrhage, malformations), demyelinating plaques, tumors, and other compressive lesions such as Arnold–Chiari malformation and superficial siderosis. Appropriate history and laboratory tests can uncover alcohol- or drug-induced ataxia, HIV and certain immunologic diseases (Table 8.1). A chronic form of ataxia resembling some of the genetic ataxias but with no familial occurrence and of uncertain cause is common in older persons (onset > 50 years) and is labeled sporadic or idiopathic ataxia. Available gene tests are usually negative; some of these persons will develop autonomic and extrapyramidal features in addition and may be diagnosed as having multiple system atrophy (cerebellar type).

**Table 8.1 Acquired causes of ataxia.**

---

<b>Cause</b>	<b>Imaging abnormality</b>	<b>Clinical/laboratory tests</b>
Vascular lesions	Infarct, hemorrhage, malformations	Usually acute onset, contiguous signs
Demyelinating disease	White matter lesions	Multi-focal disease, CSF, VEP
Mass, compressive lesions	Tumors, crano-vertebral junction malformations, malignant meningitis	Subacute/chronic, contiguous signs, CSF studies may help
Alcohol, drugs (e.g. anticonvulsants)	Atrophy of cerebellum	History, drug levels
Immune ataxias	Atrophy of cerebellum	Other immune diseases (thyroid, diabetes) Gliadin or GAD antibodies
Infectious ataxias	Atrophy or signal density changes Cerebellar abscess	HIV testing, Whipple PCR Acute ataxia occurs with viral infections in children
Nutritional	Atrophy	Signs of poor nutrition, B1, B12 levels Megadose vitamin B6. Can be acute as in Wernicke's disease
Superficial siderosis	Hypodense MRI signal on T2 surrounding posterior fossa structures	Deafness, cognitive changes

---

CSF, cerebrospinal fluid; GAD, glutamic acid decarboxylase; PCR, polymerase chain reaction; VEP, visual evoked potential.

## Inherited causes

Inherited ataxias usually develop over many years to decades. They include autosomal recessive, autosomal dominant, and X-linked genetic defects, as well as defects involving mitochondrial genes.

## Autosomal recessive ataxias

Most of the autosomal recessive (AR) ataxias have onset in childhood but onset age can extend to adult life, even as late as the 6th decade in some [3,4]. Most cases present as “singletons” with no family history but if sibships and family sizes are large affected siblings may be found. Parental consanguinity may be seen. Symptomatic disease occurs when both alleles carry the mutation; thus the DNA test should reveal the presence of mutations in both alleles. A heterozygous mutation would indicate a carrier state. [Table 8.2](#) summarizes the well-recognized AR ataxias. Friedreich's ataxia is the most common but is confined to Indo-European populations. Ataxia with oculomotor apraxia and ataxia telangiectasia may predominate in other populations. The clinical features that may permit the identification of the underlying genotype include the presence of prominent proprioceptive sensory loss, loss of deep tendon reflexes, the presence of oculomotor apraxia, an infranuclear ophthalmoplegia, spasticity, certain systemic features such as telangiectasia, and elevation of serum alpha fetoprotein (see [Table 8.2](#)).

**Table 8.2 Autosomal recessive ataxias: clinical and genetic aspects .**

---

Disease	Gene/mutation	Clinical/laboratory features
Friedreich's ataxia	<i>FRDA/GAA</i> expansion	Onset usually < 25, but can be older Ataxia, areflexia, sensory loss. Cardiomyopathy
Ataxia, oculomotor	<i>Senataxin/Point</i> mutations	Sensory motor neuropathy, oculomotor apraxia. high

apraxia type 2		alpha fetoprotein
Ataxia, oculomotor apraxia, type 1	<i>Aprataxin/</i> Point mutations	Oculomotor apraxia, sensory motor neuropathy, low albumin
Ataxia with vitamin E deficiency	$\alpha TTP$ / Frame shift or missense mutations	Sensory ataxia, areflexia, low vitamin E levels
Ataxia telangiectasia	<i>ATM/</i> Deletions, missense mutations	Conjunctival telangiectasia, elevated alpha fetoprotein, oculomotor apraxia, hematologic malignancies
Ataxia- telangiectasia like disorder	<i>mRE 11/</i> Missense, non- sense mutations	Resembles ataxia telangiectasia
Spinocerebellar ataxia with axonal neuropathy	<i>TDP 1/</i> Missense, non- sense mutations	Axonal neuropathy
Autosomal recessive spastic ataxia of Charlevoix-- Saguenay	<i>SACS/</i> Missense, non- sense mutations	Spasticity
Marinesco-- Sjögren syndrome	<i>SIL 1/</i> Point mutations	Cataracts, myopathy
Autosomal recessive cerebellar ataxia 1	<i>SYNE 1/</i> Point mutations	Ataxia

## **Ataxia in recessively inherited (or X-linked) errors of metabolism**

Ataxia can be a feature in some well-recognized metabolic errors such as hyperammonemic syndromes, aminoacidurias, pyruvate/lactate disorders, cerebro-tendinous xanthomatosis, and hexosaminidase deficiency. Ataxia may be progressive or intermittent.

Other such diseases in which ataxia can occur include Wilson's disease, Refsum disease, and adrenomyeloneuropathy. In cases of young-onset ataxia of uncertain etiology, sophisticated laboratory studies such as enzyme measurements (hexosaminidase, pyruvate dehydrogenase complex, ceruloplasmin), metabolite studies (e.g. amino acids and organic acids, phytanic acid, long-chain fatty acids, lactate, pyruvate, cholestanol) and biopsies such as skin and nerve biopsy and muscle biopsy for measuring CoQ10 may be indicated.

## **Spinocerebellar ataxias**

The spinocerebellar ataxias (SCAs) are dominantly inherited progressive diseases with onset in young to middle adult life, though reported range of age at onset is very wide [1,2,5,6]. Common SCAs are related to unstable nucleotide repeat expansions, especially those related to CAG expansions; in these, anticipation in age at onset is prominent and onset in childhood and even neonatal period has been described. Age at onset is inversely correlated with expansion size. In the SCAs related to expanded CAG tracts in coding sequences (polyglutamine ataxias), there is often an array of additional clinical signs such as brisk tendon reflexes, spasticity, Babinski signs, akinesia, rigidity, tremor of different types, oculomotor deficits of many types, dysarthria, dysphagia, tongue and facial atrophy with fasciculations, muscle atrophy, cramps, muscle fasciculations, sensory loss, and areflexia in varying combinations. Seizures, cognitive decline, and retinopathy with visual loss occur in some SCAs. While the genotypic diagnosis of a particular type of SCA from clinical signs alone is very difficult, certain clinical features may be seen more typically in some SCAs ([Table 8.3](#)). Spinocerebellar ataxias related to “conventional mutations” often have isolated cerebellar ataxia with minor additional features and tend to be more slowly progressive ([Table 8.4](#)). While the exact prevalence of such genotypes is unclear, at this time these SCAs are uncommon and in some the experience is limited to one or a few families worldwide. The choice of the

appropriate gene test in a patient with SCA may be dictated by the relative prevalence of different SCAs in the area, clinical picture, and information regarding the phenotype in other affected family members; however, individual patients with SCA of one type may be indistinguishable from another type. The course of the SCAs is progressive with loss of ambulation 15–20 years after onset and death resulting from severe motor disability and resultant complications.

**Table 8.3 Spinocerebellar ataxias (SCAs) related to nucleotide expansions .**

Disease	Gene, repeat	Potential distinguishing clinical features
SCA 1	ATXN 1/CAG	Onset 20–30s. Spastic ataxia, with some minor EP features late. Mild sensory neuropathy
SCA 2	ATXN2/CAG	Onset 20–30s. Slow EOM early, areflexia, Parkinsonian features in some, cognitive changes in some. Sensory neuropathy
SCA 3 (MJD)	ATXN 3/CAG	Onset 20–30s. Spastic ataxia, dystonia in some, Parkinsonism in some, slow EOM late. Sensory neuropathy
SCA 6	CACNA1A/CAG	Onset in 40–50s, isolated ataxia; down beat nystagmus
SCA 7	ATXN 7/CAG	Onset from childhood to 30s; spastic ataxia, visual loss
SCA 8	ATXN8/CTG-CAG	Ataxia, UMN signs, often sporadic with no family history
SCA 10	ATXN 10/ATTCT	Associated epilepsy in some, appears confined to persons of Native American admixture

SCA 12	PP2R2B/CAG	Tremor, cognitive changes, common in India
SCA 17	TBP/CAG	Complex with dystonia, psychiatric features
DRPLA	ATN/CAG	Complex with chorea, myoclonus, cognitive decline. Common in Japan
SCA 31	TK2-BEAN/TGAA	Hearing loss; common in Japan
SCA 36	NOP 56/GGCCTG	Lower motor neuron signs; common in Japan

EOM, extraocular muscle; EP, extrapyramidal; UMN, upper motor neuron.

**Table 8.4 Spinocerebellar ataxias (SCAs) resulting from conventional mutations .**

Disease	Gene	Mutation	Clinical aspects
SCA 5	SPTBN 2	Deletions, point mutation	Pure ataxia
SCA 11	TTBK2	Insertion/deletion	Pure ataxia
SCA13	KCNC3	Point mutations	Ataxia, mental retardation in some
SCA 14	PRKCG	Deletions, point mutations	Myoclonus, dystonia
SCA 15/16	ITPR 1	Deletions, point mutations	Head and hand tremor

SCA 20	Unknown	Duplication	Palatal tremor, dentate calcification
SCA 23	PDYN	Missense	Pure ataxia
SCA 27	FGF 14	Point mutations	Hand tremor, orofacial dyskinesia
SCA 28	AFG3L2	Point mutations	Ophthalmoplegia

---

## Episodic ataxias

The episodic ataxias (EAs) usually have onset in childhood or young adult life and are characterized by episodes of ataxia often associated with dysarthria and diplopia [7]. The better-recognized EAs include EA 1 in which there are very brief episodes lasting just a few minutes; interictically one may see skeletal muscle myokymia. Episodes in EA 2 are longer, lasting hours, and may be associated with migraine; interictically these patients may have mild gait ataxia and downbeat nystagmus. EA 1 and EA 2 are neuronal channelopathies caused by mutations in the *KCNA 1* and *CACNA1A* genes coding for a potassium and calcium channel respectively. Additional EA genes are also being characterized.

## X-linked ataxias

The best-recognized X-linked ataxia is the fragile X tremor ataxia syndrome [8]. The disease has been linked to the presence of a fragile X permutation in which the CGG repeat has expanded to the 55–200 repeat range. The syndrome is characterized by tremor, ataxia, dysautonomia, parkinsonian signs, and psychiatric problems. Characteristic T2 hyperintensity in the middle cerebellar peduncles may be seen. The disease predominantly affects men.

## Mitochondrial diseases with ataxia

The association of ataxia with myopathy, external ophthalmoplegia, or other features of mitochondrialopathies such as short stature, endocrine deficiencies, cardiomyopathy, elevated CSF protein, and retinal degeneration suggests a mitochondrial disease [9]. Many well-defined mtDNA mutations such as the nt

8344 mutation related to myoclonic epilepsy with ragged red fibers (MERRF) and the nt 8993 mutation in the ATPase gene associated with neurogenic weakness, retinitis pigmentosa, and ataxia (NARP) cause ataxia. Other classic mtDNA syndromes such as progressive external ophthalmoplegia , Kearns–Sayre syndrome , and mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes (MELAS) can also be associated with ataxia [9] .

## Case vignette

A 65-year-old male was seen in 2010 for a five-year history of walking difficulties. He felt sudden freezing of the right leg from time to time. He had had a few falls and he noted that his arms would not stretch out to prevent the falls. He admitted to having hand tremors for about 10 years that interfered with writing. He had a past history of hypertension, elevated cholesterol, back pain, and reflux disease. Family history was negative for any neurologic illnesses. He had two sons who were healthy. His general physical examination was normal. On neurologic examination, he had normal mental status and language other than some difficulty with cross response inhibition. His voice was slightly hypophonic. Cranial nerves were normal with no oculomotor abnormalities. Muscle strength and tone were normal as were reflexes and sensation. He had mild dysmetria of upper limbs but no kinetic tremor. He had a low amplitude postural tremor. Rapid alternating movements were preserved. Heel to shin test was performed somewhat slowly but accurately. Gait was characterized by a non-specific shuffle, inability to do tandem and intact arm swing. Over the next two years he had progression of his neurologic deficits. In late 2012, his examination was notable for an ataxic gait that needed assistance from another individual and dysmetria in upper limbs, some disordered rapid alternating movements and dysarthric speech. An MRI of the brain, done at the outset, showed slight thinning of upper pons, prominence of the third ventricle, and FLAIR and T2 hyperintensity that occupied both middle cerebellar peduncles extending to the white matter of the cerebellum.

In summary, this man presented with a progressive neurologic syndrome that combined some features of cerebellar disease and some extrapyramidal features. There was no family history of the disease or other neurologic difficulties. A diagnosis of “olivopontocerebellar atrophy” (OPCA) had been made by another consultant. However, the MRI findings were very distinctive and typical of those seen with fragile X tremor ataxia syndrome (FXTAS). Analysis of the CGG repeat in the *FMR 1* gene revealed an expanded size of 96, in the premutation

range, thus confirming the diagnosis of FXTAS. Fragile X tremor ataxia syndrome combines features of tremor and cerebellar signs but additional features such as Parkinsonian signs and memory loss may be seen. Falls, tremor, and abnormal tandem gait are early signs. The disorder typically affects the male premutation carriers who can transmit full-blown fragile X syndrome to their grandsons through their daughters. Males with full-blown fragile X mental retardation have over 200 CGG repeats in the *FMR 1* gene. Female carriers of the premutation have less probability of having the neurologic syndrome but more often suffer from premature ovarian failure. The T2 hyperintensity in the middle cerebellar peduncle is very characteristic.

## References

1. Manto M, Marmolino D. Cerebellar ataxias. *Curr Opin Neurol* 2009; 22:419–29.
2. Schöls L, Bauer P, Schmidt T *et al*. Autosomal dominant cerebellar ataxias: clinical features, genetics and pathogenesis. *Lancet Neurol* 2004; 3:292–304.
3. Fogel BL, Perlman S. Clinical features and molecular genetics of autosomal recessive cerebellar ataxias. *Lancet Neurol* 2007; 6:245–57.
4. Anheim M, Tranchant C, Koenig M. The autosomal recessive cerebellar ataxias. *N Engl J Med* 2012; 366:636–46.
5. Durr A. Autosomal dominant cerebellar ataxias: polyglutamine expansions and beyond. *Lancet Neurol* 2010; 9:885–94.
6. Subramony SH. Overview of autosomal dominant ataxias. *Handb Clin Neurol* 2012; 103:389–98.
7. Jen JC, Graves TD, Hess EJ *et al*. Primary episodic ataxias: diagnosis, pathogenesis and treatment. *Brain* 2007; 130:2484–93.
8. Leehey MA. Fragile X-associated tremor/ataxia syndrome: clinical phenotype, diagnosis, and treatment. *J Investig Med* 2009; 57:830–6.
9. Zeviani M, Di Donato S. Mitochondrial disorders. *Brain* 2004; 127:2153–72.

## 9 Attentional problems

---

Lenard A. Adler, Thomas M. Boes, David M. Shaw and Samuel Alperin  
*Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

In 1890 , the American psychologist William James provided a definition for attention that anticipated many key issues that would be examined in subsequent years:

Everyone knows what attention is. It is the taking possession by the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought. Focalizations, concentration, of consciousness are of its essence. It implies withdrawal from some things in order to deal effectively with others, and is a condition which has a real opposite in the confused, dazed, scatter-brained state which in French is called distraction...[1]

As James noted, attention (also known as selective attention) is a state or condition of selective awareness to specific stimuli and/or information to improve perception and filter out irrelevant information or stimuli [2]. The neural basis for attention is complex, but neuroimaging research has revealed that it is controlled by two primary cortical networks working together: a bilateral dorsal frontoparietal network comprised of the intraparietal sulcus and frontal eye fields for top-down control of endogenous attention [3,4] and a right-lateralized ventral frontoparietal network comprised of the temporoparietal junction for bottom-up control of exogenous shifts of attention [5,6].

Examining the neurologic impairments and anomalies of attentional problems has provided insight into many aspects of attention. Difficulty with attention is a common neuropsychiatric condition that affects children and adults and has a diverse etiology. In this chapter, we will describe some of the most common

causes of attentional problems, such as attention-deficit/hyperactivity disorder (ADHD), mild cognitive impairment, dementia, thyroid dysfunction, sleep disorder, traumatic brain injury, seizures, and B12 deficiency (see [Table 9.1](#)).

## Case vignette

A 25-year-old male who is in his second year of law school presents for evaluation of ongoing issues with inattention, easy distraction, easy boredom, trouble listening to professors in lectures, losing track of conversations, frequent trouble remembering what he has read and needing to re-read, chronic restlessness, need for regular exercise, misplacing items needed for classes or at home (e.g. glasses, keys, etc.), and procrastination. These symptoms are affecting his performance in school (not finishing exams in allotted time, turning in writing projects late, and poor academic performance, etc.) and at home (messiness, paying bills late, not keeping appointments, etc.).

Using the World Health Organization Adult ADHD Self-Report Scale (ASRS) v1.1 Symptom Checklist [7], the patient endorsed seven of nine symptoms of inattention and three of nine hyperactive-impulsive symptoms at a level considered to be clinically significant and impairing. Furthermore, the patient reported that these symptoms began in 1st grade and that he was diagnosed with ADHD at the age of 6. Following the diagnosis of ADHD, the patient was treated with methylphenidate for several years with good efficacy and tolerability, but his parents stopped the treatment because they were concerned about the potential long-term effects of the medication. His academic performance is inconsistent, doing well in subjects in which he is interested (e.g. history), but poorly in subjects that he finds difficult (e.g. maths and sciences). The symptoms of inattention, easy distraction, procrastination, trouble finishing assignments and trouble remembering what he has read have been for the most part consistently present since the age of 6, but have become more frequent, impairing, and difficult to control since the beginning of law school when his academic workload and demands on his schedule increased.

**Table 9.1**

Differential diagnosis			
Diagnosis	Clinical features	Localization	Pathophysiology

ADHD	Inattention, impulsivity, psychomotor hyperactivity	Dorsolateral prefrontal cortex, anterior cingulate cortex, basal ganglia	Decreased dopa and norepineph effect in the DI ACC, BG
Mild cognitive impairment	Memory impairment with usual onset in middle to late age but without functional impairment, and otherwise not meeting criteria for any dementing illness. 10–15% per year progress to meet criteria for dementing illness, most typically	Neocortex, medial temporal lobe	Neurofibrillary tangle depositio medial tempora lobes, amyloid deposition throughout neocortex

Alzheimer's disease. There may or may not be symptoms in other domains, such as movement abnormalities, but these patients tend to progress at higher rates to dementing illnesses. Overall, especially those with only amnestic symptoms, may remain stable over years or even remit, the cognitive impairment does not trace back to childhood < 7yo, and by definition unlike DSM-IV criteria for ADHD which require there to be social, education, or occupational dysfunction, MCI causes no functional impairment

Dementia	Memory loss, attentional impairment, progressive deterioration in cognition in multiple domains of intellectual function leading to behavioral problems and functional impairment in complex and eventually basic activities of daily living. Although	Alzheimer's dementia: temporal and parietal lobe cortical atrophy	Alzheimer's disease neuron loss and therefore cortical atrophy best correlate with intracellular neurofibrillary tangles composed of aggregations of hyperphosphorylated tau protein disrupting the microtubules and intracellular transport. Beta amyloid plaque
----------	--	--	---

typically affecting the elderly > 65yo, there are early onset forms. Like MCI, dementia can be separated from adult ADHD by normal childhood history without evidence of attentional or executive dysfunction, but rather problems beginning in adulthood at the onset of the dementing illness and following a progressive course. Neurologic exam can help separate dementing illness from adult ADHD, as paratonia, pathologic or primitive reflexes, or gait abnormalities are all suggestive of a dementing process and inconsistent with adult ADHD

extracellularly appear to be involved in the pathophysiology

Frontotemporal dementia: frontal and temporal lobe cortical atrophy

Frontotemporal dementia: hyperphosphorylated tau protein intracellular aggregates destabilizing microtubules and leading to collapse

or neuronal intracellular transportation & neuron death is most common pathophysiology TDP-43 hyperphosphorylated ubiquitin positive, tau negative, alpha synuclein negative protein aggregates disrupting DNA/RNA expression implicated in 40% FTD especially when motor neuron involvement is present

Vascular dementia: white matter and gray matter gliosis and encephalomalacia respecting vascular territories

Vascular dementia: large cortical vessels CVA can be associated with cerebral amyloid angiopathy, or amyloid deposits in the walls of vessels leading to vessel weakening and rupture causing hemorrhagic CVA. More commonly vascular dementia associated with small vessel ischemic CVA caused by long-standing HTN.

starvation, HDL, smoking

B12 deficiency	Focus/concentrational deficits, irritability, memory loss, cognitive impairment, slowed processing speed, depression, apathy, paranoid ideation, generalized fatigue, paresthesias, gait instability, muscle weakness, decreased vibratory sense, ataxia, glossitis, angular cheilitis, pallor, petechiae	Spongiform degeneration of neural tissue, specifically edema of nerve fibers and myelin decay, sclerosis of nervous tissue especially in the posterior and anterior-lateral spinal cord causing subacute combined degeneration of the spinal cord characterized by selective degeneration of the dorsal columns and the lateral corticospinal tracts	Methylmalonyl mutase is dependent on B12 as a coenzyme in the synthesis of succinyl-CoA which is subsequently used in Krebs cycle synthesis of even chain fatty acid in the neuronal membrane. B12 deficiency results in accumulation of abnormal fatty acids in the neuronal membrane. Additionally, lack of B12 leads to deficiency of coenzyme methylcobalamin necessary for methionine synthetase to methylate homocysteine to methionine. This leads to failure of DNA synthesis which is responsible for hematologic abnormalities that ensue
Thyroid dysfunction	Clinical manifestations	Non-specific CNS localization	Hypothyroidism Hyperthyroidism

depend on whether hypo-or hyperthyroid.

Hypothyroidism can present with low energy, difficulty concentrating, rapid thoughts, short term memory impairment, depression, cold intolerance, hypersomnolence, weight gain, constipation, dry or coarse skin, thin brittle fingernails, thick tongue, facial edema, myalgia, poor muscle tone, hyporeflexia, bradycardia, menstrual irregularities, decreased libido, sensory polyneuropathy. Hyperthyroidism presents with irritability, tremulousness, fidgetiness, sweating, palpitation, heat intolerance, moist skin, scalp hair loss, ophthalmopathy, pretibial myxedema, acropachy, widened pulse pressure

can have central pituitary causes well as primary thyroid causes. Drugs such as lithium, amiodarone, aminoglutethimide, interferon alpha, thalidomide, stavudine, tyrosine kinase inhibitors name a few can cause primary hypothyroidism should be considered. Thyroid hormone acts to increase basal metabolic rate in cells throughout body, affects protein synthesis, regulates neuronal maturation increases catecholamine responsiveness in the CNS and throughout the body. In the CNS, T<sub>3</sub> increases synaptic activity of monoamines and GABA regulatory mood, attention and cognition

Seizure disorder	Observers will report episodes of staring, sudden loss of attention, motor arrest, altered consciousness,	Seizure localization can be primarily generalized or partial focal onset with or	Primary generalized seizures: Presumed genetic causes underlie abnormalities in sodium, potassium, calcium, magnesium, glucose, and other metabolites.
------------------	---	--	--

repetitive simple or complex motor activities or vocalizations, tonic-clonic motor activity. Post-ictally, observers may note disorientation, somnolence, or even motor hyperactivity or agitation, and paranoid ideation, or mood swings. Patients may report sudden loss of consciousness, olfactory disturbance, rising epigastric sensation, sudden severe anxiety or sense of doom, out-of-body experience, uncontrolled motor automatisms. Post-ictally, patients may report memory loss, inattention, cognitive slowing, period of lost time, muscle aches, lateral tongue bites, urinary incontinence, transient focal neurologic deficits without secondary generalization. Primary generalized seizures begin with synchronized diffuse neuronal activity and therefore localize to bilateral cortices, and generally present earlier in life. Partial or focal onset seizures can localize throughout the CNS, and often are caused by underlying structural abnormalities. Focal seizures most often arise from the temporal lobes, especially the medial temporal lobes as a consequence of medial temporal sclerosis. Focal seizures can be a consequence of acquired structural lesions at any point in calcium, and G receptor mediated chloride channels causing diffuse neuronal membrane hyperexcitability lead to primary generalized onset especially if triggered with sleep deprivation, drugs, toxins, alcohol consumption, hyperventilation, hypoglycemia, flashing lights. may find bilateral diffuse synchronous epileptiform activity. Focal or partial onset seizures: structural CNS lesions lead to decreased neuronal inhibition and therefore neuronal hyperexcitability. the intact neurons the border or interface with cortical gliosis structural lesions. Similar triggers as sleep deprivation, toxins, alcohol consumption, hypoglycemia can trigger a seizure. EEG may reveal

		life or due to congenital neuronal migration abnormalities	epileptiform activity localized to a region which correlate with a MRI marker of structural lesions
Sleep disorder	Obstructive sleep apnea suggested by obesity, excessive oropharyngeal tissue, snoring history disclosed by the patient or bed partners, daytime somnolence, waking up not feeling rested, complaints of	Obstructive sleep apnea: due to excessive pharyngeal tissue and decreased pharyngeal muscle tone that occurs in sleep, the airways can be closed off leading to	Apneic episodes lead to CNS oxygen deprivation and but progressive neuronal damage leading to cognitive deterioration

**complaints of**  
cognitive foginess,  
cognitive slowing,  
inattention, careless  
errors, deficits in  
executive function  
such as complex  
planning, irritability,  
depressed mood,  
multiple motor  
vehicle accidents,  
shares many  
symptoms with adult  
ADHD. Narcolepsy  
with sudden onset of  
sleep leading to loss  
of time and poor  
academic or  
occupational  
performance could  
also be confused with  
adult ADHD.  
Episodes of  
cataplexy, and  
frequent sleep  
paralysis, hypnagogic  
and hypnopompic  
hallucinations can  
help differentiate. In  
addition narcolepsy  
typically does not  
present until the  
second decade of life,  
and is rare in young  
children unlike  
ADHD. Observer  
reports of  
sleepwalking or  
complex REM sleep  
behaviors also  
**leading to**  
inability to  
ventilate. This  
leads to SpO<sub>2</sub>  
desaturation and  
triggers the brain  
to wake the pt. to  
ventilate. This  
occurs repeatedly  
all night long  
disrupting sleep.  
Central sleep  
apnea: localizes  
to medullary  
respiratory  
centers where  
genetic  
abnormalities or  
drugs such as  
narcotics and  
sedatives can  
cause disruptions  
in ventilation.  
Narcolepsy:  
localizes to  
hypothalamic  
projections  
throughout the  
CNS

**Behaviors also  
separate sleep  
disorders from  
ADHD**

Traumatic brain injury	History of severe or less severe but repetitive trauma	Frontal lobe trauma, especially dorsolateral frontal lobes and	An imbalance of cranial blood flow and metabolism inflammatory and apoptotic processes
------------------------	--	--	--

cingulate gyrus, can lead to symptoms that mimic ADHD

edema formatic and excitotoxic the CNS

Medications	Diversity of agents could cause cognitive impairments. Clues in distinction to ADHD would include relationship in time of the development of symptoms to the addition of the medication and exacerbation with medication dosage increases. Attention problems may be part	Some agents with anticholinergic or antihistaminergic properties may be especially problematic. Antiepileptic drugs such as topiramate which adversely affect memory can also interfere with attention	Diverse etiologies affecting attention in the context of complicated cognitive networks
-------------	---	--	---

## of a broader array of cognitive deficits

---

The patient reported that he drinks approximately six cups of coffee per day and has never smoked cigarettes. The patient has no history of active medical problems, no prior psychiatric history, and no history of substance use disorder, depression, or mania. The patient reported a history of one concussion at the age of 15 years of age, when he was struck in the head while playing club soccer. He denied loss of consciousness or sequelae from the concussion and an electrocardiogram performed at the time of the concussion was normal. His current blood pressure is 110/72 mmHg and his pulse is 70 beats/minute. The patient reported a significant family history of psychopathology. His younger brother was diagnosed with ADHD, which has been successfully managed with a sustained release methylphenidate compound. His mother has been diagnosed with major depressive disorder.

The patient's history is consistent with ADHD, predominantly inattentive type. He meets all DSM-IV-TR criteria [8] with sufficient and significant current symptoms, childhood onset of some significant symptoms prior to the age of 7, impairment in two domains of his life (home and school), and the symptoms and associated impairment are from ADHD and not another mental health disorder. The history of concussion was isolated and without sequelae; therefore, it is unlikely that his current symptoms are secondary to this incident. Furthermore, the symptom onset was prior to the concussion and the symptoms have been more or less present throughout his life. Therefore, his symptoms of ADHD should be treated without further evaluation for the history of concussion.

Given his prior history and family history of response to methylphenidate compounds, an appropriate course of action would be to start treatment with OROS methylphenidate (as this is a sustained-release preparation) at 18 mg PO qAM after discussion of potential risks and benefits. The dose should be titrated based upon symptom reduction, which can be evaluated by repeating the ASRS v1.1 Symptom Checklist and clinical interview, with regular monitoring for side effects, new onset of tics, and increases in blood pressure and pulse.

## References

1. James W. *The Principles of Psychology*. New York, NY: Henry Holt, 1890.

2. Breedlove SM, Watson NV, Rosenzweig MR. *Attention and Higher Cognition Biological Psychology: An Introduction to Behavioral, Cognitive, and Clinical Neuroscience*, 6th edn. Sunderland, MA: Sinauer Associates, 2010: 549–50.
3. Corbetta M, Kincade JM, Ollinger JM, McAvoy MP, Shulman GL. Voluntary orienting is dissociated from target detection in human posterior parietal cortex. *Nature Neurosci* 2000; 3:292–7.
4. Hopfinger JB, Buonocore MH, Mangun GR. The neural mechanisms of top-down attentional control. *Nature Neurosci* 2000; 3:284–91.
5. Corbetta M, Kincade MJ, Lewis C, Snyder AZ, Sapir A. Neural basis and recovery of spatial attention deficits in spatial neglect. *Nature Neurosci* 2005; 8:1603–10.
6. Vuilleumier P, Schwartz S, Verdon V *et al*. Abnormal attentional modulation of retinotopic cortex in parietal patients with spatial neglect. *Curr Biol* 2008; 18: 1525–9.
7. Adler LA, Spencer T, Faraone SV *et al*. Validity of pilot adult ADHD self-report scale (ASRS) to rate adult ADHD symptoms. *Ann Clin Psychiatry* 2006; 18:145–8.
8. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revision)* (DSM-IV-TR). Washington, DC: American Psychiatric Association, 2000.

## **10 Autonomic failure or syndromes**

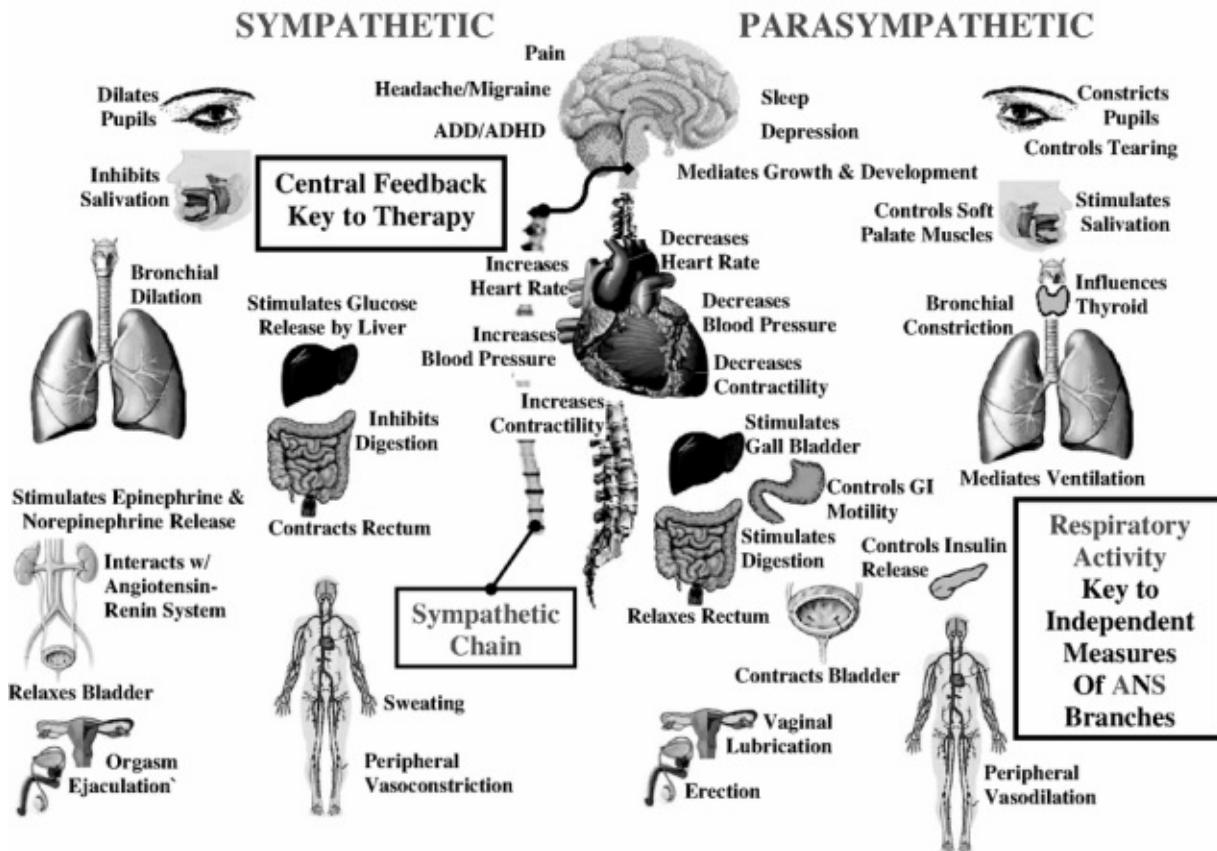
---

Rajpal Singh and Joe Colombo *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

The autonomic nervous system (ANS), including its two major branches the parasympathetic and sympathetic (P&S) nervous systems, is the third major component of the human nervous system. Historically, the P&S are the least well understood due to a lack of data ([Figure 10.1](#)). Together, P&S affect a great compromise, heart beat by heart beat and breath by breath, in order to properly mediate the needs of virtually all cells within the body [\[1–3\]](#). Convenient , clinical measures of P&S activity provide more information enabling physicians to document individual patient responses to disease and therapy, thereby reducing morbidity and mortality risk, and improving patient outcomes [\[4–11\]](#).

# The Autonomic Nervous System

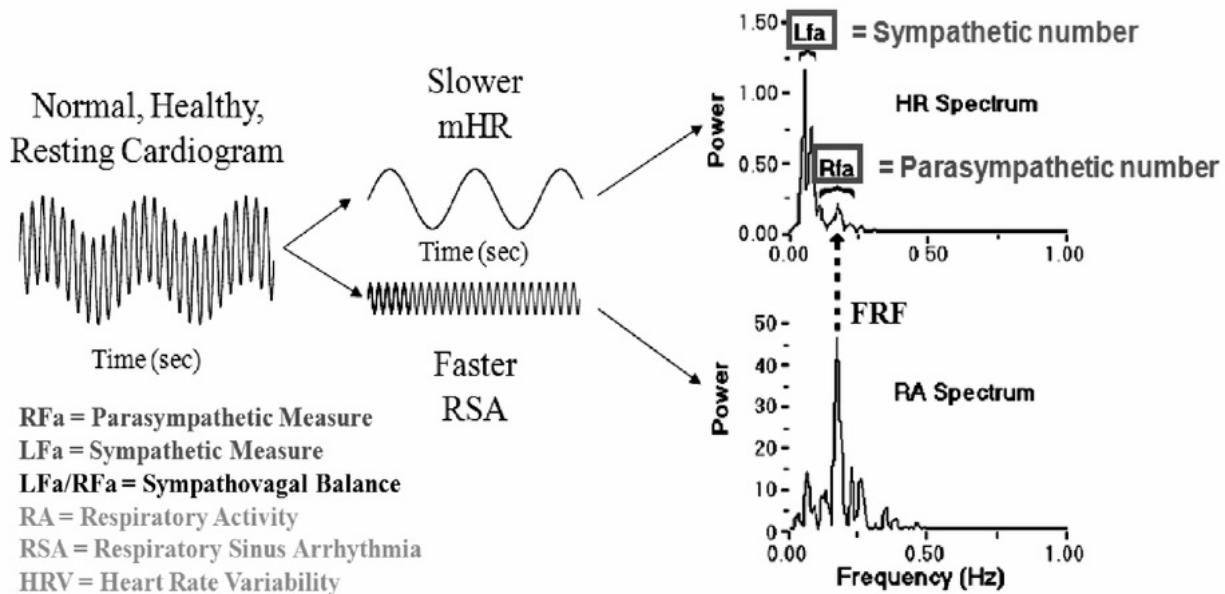


**Figure 10.1** The parasympathetic and sympathetic branches of the autonomic nervous system control or coordinate all systems of the human body. The two branches work together, even in dysfunction, to maintain homeostasis, often long before symptoms are demonstrated.

Measures of total ANS function, *e.g.* by heart rate variability (HRV) have not proven useful under clinical conditions. If the (single) measure of total ANS function changes, it is not possible to unambiguously determine which ANS branch caused the change and by how much. More information is required. The “more information” has typically been in the form of assumption and approximation which may be valid at the time of baseline assessment, but often is not valid upon follow-up, after therapy or intervention. “More information” of an independent nature is required for general clinical utility. Analysis of continuous respiratory activity (*e.g.* as measured by impedance plethysmography) satisfies the mathematical requirements to provide more information without assumption or approximation and will be labeled the P&S method for this chapter (Figure 10.2) [12–18]. The P&S method is not

contraindicated for arrhythmia [10].

## Parasympathetic and Sympathetic Measurements Model



**Figure 10.2** A pictorial representation of the P&S Monitoring method originally developed at MIT. The left panel is a stylized representation of a cardiogram from a theoretical ECG. As shown in the middle panel, the cardiogram is basically a combination of the faster respiratory sinus arrhythmia (RSA) changes in heart rate (HR) coupled with the slower mean HR changes over time. Time--frequency analysis of the respiratory activity is performed to determine the respiratory frequency (FRF). The FRF is then used in the HR spectrum to determine the parasympathetic measure (RFa). From the remainder of the low frequency range, the sympathetic measure (LFa) is determined. See text for details.

## Clinical parasympathetic and sympathetic assessment

Using the P&S method, a clinical study has been developed based on the American Diabetes Association's (ADA) recommended tests for cardiovascular autonomic neuropathy (CAN) [19]. Since CAN is the risk indicator for sudden cardiac death, regardless of disease or history, this has been adopted as the test criterion for detecting the onset of asymptomatic autonomic dysfunction prior to autonomic neuropathy (AN). The tests include the Ewing challenges: paced or deep breathing tests the parasympathetics, short Valsalva maneuvers test the sympathetics, and 5 minutes of head-up posture (e.g. stand) to assess morbidity risk and provide tilt-test information [20–23]. These results are compared with 5

minutes of rest (initial baseline) to assess mortality risk and P&S balance (sympathovagal balance, SB) [24].

Autonomic testing is recommended “at least annually” [19] (every 6 months) for patients with chronic, overt autonomic symptoms (e.g. dizziness or lightheadedness, abnormal sweating, multiple system atrophy, and primary autonomic failure) and for patients diagnosed with chronic diseases (e.g. diabetes, chronic pain, chronic inflammatory and demyelinating diseases, sleep disorders, depression and depression-related syndromes, chronic fatigue, heart diseases, arrhythmia, and hypertension) (Tables 10.1–10.3) [25–29]. The reason is to document (earlier) significant changes in P&S function that are often silent and result from hypoglycemic or ischemic attacks due to primary or secondary effects of many chronic diseases. Follow-up testing should also be considered (at 3-month intervals) to document patient responses to recorded therapy changes or intervention.

**Table 10.1 General forms of autonomic dysfunction or autonomic neuropathy.**

<b>Autonomic dysfunction (AD) Autonomic neuropathy (AN)</b>	<b>Symptoms</b>	<b>P&amp;S monitoring indications</b>
Peripheral AN	Vasomotor changes (poor peripheral circulation; poor wound healing; and pallor, rubor, cyanosis, or mottling), and sudomotor dysfunction (hyperhidrosis or anhydrosis of the extremities)	Normal resting P&S responses, with low deep breathing and Valsalva responses
Advanced AD, Diabetic AN	Resting tachycardia, exercise intolerance, orthostatic dysfunction,	Low resting P or

	constipation, gastroparesis, erectile dysfunction, sudomotor dysfunction, impaired neurovascular function, “brittle diabetes,” or hypoglycemic autonomic failure	S responses at rest
Cardiovascular AN	Persistent advanced AD symptoms, with cardiovascular risk, including: stroke, silent MI, sudden cardiac death	Resting P response very low (< 0.1 bpm <sup>2</sup> )

---

P&S, parasympathetic and sympathetic nervous systems.

## Autonomic dysfunction

Before discussing specific disease states and disorders, there are a few generalities that need to be addressed. These generalities help in understanding that: (1) treating a single autonomic dysfunction may relieve multiple conditions simultaneously; (2) treating autonomic dysfunction often relieves secondary symptoms (e.g. GI and sleep disturbance, urogenital dysfunction, dizziness, and [secondary] hypertension) and not the primary symptom, however it often stabilizes the patient so that the primary may be treated more aggressively; (3) autonomic dysfunction, prior to end-organ dysfunction, may be treated with lower-dose, shorter-term therapy to adjust the delicate balance between the P&S nervous systems and to benefit the plasticity of the nervous system.

It is known that the P&S nervous systems work synergistically to maintain homeostasis and normal end-organ function. The P&S nervous systems may maintain normal end-organ function even when they themselves are dysfunctional. In fact many P&S disorders, especially early on, are asymptomatic because symptoms are not demonstrated until the end-organ becomes dysfunctional. It is analogous to the brakes and accelerator of a car. Given that the primary purpose of the car is to transport someone from one place to another, if someone drives the car with their foot on the brakes (simulating parasympathetic excess) or over “revs” the engine (simulating sympathetic excess) the car does not fail in its primary purpose immediately. However, earlier failure and increased engine and brake repairs (i.e., doctor and hospital visits) are likely if these driving habits are not modified. These “modifications”

are possible in the form of therapy, treatment, or lifestyle interventions. In general, establishing and maintaining proper P&S balance (SB) slows the progression of autonomic dysfunction, minimizes morbidity and mortality risk, and improves outcomes.

Given that autonomic dysfunction is largely asymptomatic, the medical leadership, including the American Academy of Neurology [25], have written seminal articles that indicate chronic conditions lead to autonomic neuropathy. Since autonomic dysfunction precedes neuropathy, but is asymptomatic, the leadership and other healthcare providers agree that the chronic condition itself is the indication for P&S function testing, in addition to overt autonomic dysfunction such as dizziness and abnormal sweating. Increased P&S monitoring based on chronic disease has been shown to detect more serious conditions earlier, enabling referral to larger autonomic laboratories, and it has been shown to enable earlier intervention (including the possibility of lower-dose, shorter-term therapy) to reduce morbidity and mortality risk, reduce hospitalizations, and improve patient outcomes.

## **Cardiovascular autonomic neuropathy**

The resting results also quantitate CAN, thereby documenting mortality risk, including risk of stroke, myocardial infarct (MI), and sudden cardiac death. Cardiovascular autonomic neuropathy may be normal given the patient's age or history. Myocardial infarct and coronary artery by-pass graft (CABG) may induce CAN, as well as many chronic diseases, including advanced diabetes mellitus, advanced Parkinson's disease, multiple system atrophy (Shy–Drager syndrome ), advanced demyelinating and inflammatory neurologic diseases , primary autonomic failure , Lewy body syndromes , amyloidosis , and paraneoplastic syndromes.

**Table 10.2 Autonomic dysfunction associated with dizziness or lightheadedness disorders all associated with graded forms of brain hypoperfusion, often associated with dehydration or abnormal blood volume.**

<b>Autonomic dysfunction</b>	<b>Symptoms</b>	<b>P&amp;S monitoring indications</b>
Pre-clinical	Occasional dizziness upon	None
Grade I	Recurrent dizziness upon	None
Grade II	Recurrent dizziness upon	None

<b>Pre-clinical orthostatic dysfunction (all sub-forms)*</b>	<b>Occasional dizziness upon standing, or low energy; afternoon headache, fatigue, or cognitive difficulties; evening edema; or lower vascular abnormalities (e.g. varicose or spider veins)</b>	<b>(upon standing)</b>
<b>Orthostatic hypotension*</b>		
Pre-clinical	See pre-clinical orthostatic dysfunction	SW, ↓ BP
Clinical	Frequent dizziness upon standing	SW ≥ 20/10 mmHg ↓ BP
<b>Postural orthostatic tachycardia syndrome (POTS)*</b>		
Pre-clinical	See pre-clinical orthostatic dysfunction	SW, tachycardia or ↑↑ HR
Clinical	Frequent dizziness upon standing with heart pounding or palpitations	SW, HR > 120 bpm (adults) or ↑ HR > 30 bpm
<b>Orthostatic hypertension*</b>		
Pre-clinical	See pre-clinical orthostatic dysfunction	SW, ↑↑ BP

Clinical	Frequent dizziness upon standing	SW, > 30 mmHg ↑ BP
Orthostatic intolerance*	See pre-clinical orthostatic dysfunction	SW, normal BP response
Syncope		
Pre-clinical	Recurrent episodes; No fainting, weak and tired feeling resulting from a lack of oxygen to the brain due to a sudden drop in BP	
Clinical	Recurrent episodes; Prodrome: lightheadedness, nausea, the feeling of being extremely hot (accompanied by sweating), ringing in the ears (tinnitus), uncomfortable feeling in the heart, fuzzy thoughts, a slight inability to speak/form words (sometimes combined with mild stuttering), weakness and visual disturbances such as lights seeming too bright, fuzzy or tunnel vision, and sometimes a feeling of nervousness can occur as well; momentary LOC, collapse; immediate return of consciousness	
Vasovagal syncope**	See pre-clinical and clinical syncope above	SE, PE
Neurogenic syncope**	See pre-clinical and clinical syncope above	SE, weak HR

		response
Cardiogenic syncope**	See pre-clinical and clinical syncope above	Diagnosis by omission
Neurocardiogenic syncope**	See pre-clinical and clinical syncope above	Unbundle the two sub-forms
Dizziness due to arrhythmia	PE, SE and SW may contribute to arrhythmogenesis. Consider cardiac work-up and normalize the P or S imbalance	PE, SE, or SW coinciding with arrhythmia

\* SW is an alpha-adrenergic dysfunction, and may be masked by PE;

\*\* A beta-adrenergic dysfunction; ↓, decrease; ↓↓, excessive decrease; ↑, increase; ↑↑, excessive increase; LOC, loss of consciousness; P&S, parasympathetic and sympathetic nervous systems; PE, parasympathetic excess; SE, sympathetic excess; SW, sympathetic withdrawal.

Cardiovascular autonomic neuropathy risk is stratified by SB. With normal SB ( $0.4 < SB < 3.0$ ), CAN risk is normal. Risk of CAN may be minimized by establishing and maintaining low-normal SB ( $0.4 < SB < 1.0$ ) by titrating sympatholytics (e.g. beta-blockers and antihypertensives) if SB is high, or anticholinergics (e.g. low-dose antidepressants) if SB is low, for example. Low SB ( $SB < 0.4$ ) indicates a resting parasympathetic excess which is associated with (subclinical) depression. Depression is known to elevate CAN risk. High SB ( $SB > 3.0$ ) indicates a resting sympathetic excess. Cardiovascular autonomic neuropathy with high SB is high risk and carries the recommendation for a cardiac work-up if not recent.

**Table 10.3 Autonomic dysfunction associated with general neurology, sleep and pain management.**

<b>Autonomic dysfunction</b>	<b>Symptoms</b>	<b>P&amp;S monitoring indications</b>
General neurology Afternoon headache or fatigue	May be associated with orthostatic dysfunction, including with varicose or spider veins	SW or PE upon standing
Evening edema Restless leg syndrome		
Depression	Including subclinical depression characterized by fatigue, malaise, exercise intolerance, excessive sleepiness	PE*
Bipolar disease Manic depression ADD/ADHD PTSD	(Subclinical) depression with anxiety or hyperactivity	PE* with SE*
Anxiety	Not including depression, often involves reports of palpitations	Valsalva SE
Chronic fatigue syndrome	Persistent fatigue and excessive daytime sleepiness	Valsalva or standing PE
Chronic hypotension	Low energy, exercise intolerance	Resting PE
Brain injury, not including upper medulla, amygdala, or cingulate gyrus (if one of these structures is	Signs and symptoms of stroke	Acute phase: low, resting parasympathetic activity (associated with MI or

involved, then the acute phase persists)	pneumonia risk Chronic phase: resting parasympathetic activity rebounds (relieving MI or pneumonia risk)
Spinal cord injury , involving the sympathetic chain	Signs and symptoms depend on the level of the cord injury and associated level of the sympathetic chain
Parkinson's disease	A disease with a CNS origin. Early stages include autonomic deficits in a distal to proximal progression along autonomic pathways, including orthostatic dysfunction (associated with increased fall risk), with associated enteric nervous system disturbances. Later stages involve cardiac sympathetic denervation
Multiple system atrophy (Shy–Drager)	A disease with a CNS origin. Early stages include autonomic deficits in a distal to proximal progression along autonomic pathways, often without orthostatic

	dysfunction, with associated enteric nervous system disturbances. Later stages involve preservation of cardiac sympathetic innervation (unless treated earlier as Parkinson's)
Lewy body syndromes	A disease with a CNS origin. Includes autonomic deficits in a distal to proximal progression along autonomic pathways, including orthostatic dysfunction (associated with increased fall risk), with associated enteric nervous system disturbances, and with hallucinations and significant sleep disturbances
Primary autonomic failure (Bradbury–Eggleston syndrome , or idiopathic orthostatic hypotension )	A disease with a peripheral NS origin. Includes autonomic deficits in a distal to proximal progression along autonomic pathways, including orthostatic hypotension (associated with dizziness, fainting, and increase fall risk), urogenital dysfunction, visual disturbances, and neck pain

<b>Myasthenia gravis</b> (Eaton--Lambert syndrome )	A disease that attacks acetylcholine receptors thereby affecting both P&S branches	
Amyloidosis	Arrhythmia, heart failure, bloody sputum, enlarged spleen, GI upset with emesis and diarrhea, skin petechia, and swollen tongue	
Paraneoplastic syndrome	A cancer that may affect the ANS, in turn causing symptoms in the organ(s) associated with the portion of the ANS affected	
Pheochromocytoma	A cancer of the adrenal gland, not strictly involving the ANS, but affects the ANS, specifically the sympathetic NS by causing the adrenals to secrete excessive amounts of norepinephrine and adrenaline, leading to high HR & BP, palpitations, anxiety, excessive sweating, headaches, elevated blood glucose, and excessive weight loss	SE
Abnormal sweating: Anhidrosis	Lack of proper sweating (generalized or localized)	Sympathetic insufficiency
Abnormal sweating: Hyperhidrosis	Excessive sweating (generalized or localized)	SE

--> R -----

Sleep medicine	PE = daytime sleepiness SE = night-time sleeplessness	
Sleep apnea (obstructive or central)		SE
Insomnia	Inability to sleep at night	SE
Narcolepsy Hypersomnia	Excessive daytime sleepiness	PE
Pain management	SE with well-controlled BP indicates and quantifies pain level	
Non-physiologic pain (e.g. psychosomatic)	Reports of pain with apparently sufficient doses of pain therapy	Normal to low P&S levels throughout P&S function test
Physiologic pain		
Chronic	Reports of constant pain	High SB
Activity induced	Reports of pain during activity	Normal SB with SE upon Valsalva (upper body or lower back) or stand (lower body or lower back)
CRPS (formerly RSD)	Reports of localized pain with typically cold skin over affected area (due to poor tissue perfusion to that area)	SE* with PE*

--> R -----

Fibromyalgia	Chronic, unexplained body-wide pain and tenderness to touch, often associated with sleep difficulty, headache, depression, and anxiety	SE (rest or Valsalva) with PE (Valsalva or stand) with no significant dizziness or lightheadedness
Headache (including tension headache) or migraine	Frequently occurring and not associated with afternoon (otherwise see afternoon headache above)	PE*: (including migraine) due to brain hypoperfusion from bradycardia or hypotension, etc. SE*: (Tension headache or migraine) due to stress or high BP, includes secondary SE**

\* Anywhere during P&S function test;

\*\* Secondary SE is demonstrated during Valsalva challenge, secondary to primary (Valsalva) PE; ↓, decrease; ↓↓, excessive decrease; ↑, increase; ↑↑, excessive increase; ADD, attention deficit disorder; ADHD, attention deficit hyperactivity disorder; ANS, autonomic nervous system; CNS, central nervous system; CRPS, chronic regional pain syndrome; LOC, loss of consciousness; MI, myocardial infarction; NS, nervous system; P&S, parasympathetic and sympathetic nervous systems; PE, parasympathetic excess; PTSD, post-traumatic stress disorder; RSD, reflex sympathetic dystrophy; SB, sympathovagal balance; SE, sympathetic excess; SW, sympathetic withdrawal.

## Dizziness or lightheadedness disorders

Parasympathetic and sympathetic nervous systems monitoring may unbundle vascular from autonomic causes of orthostatic dysfunction, as well as neurogenic from cardiogenic forms of syncope. The P&S monitoring indications for

dizziness disorders are based on comparing stand responses to resting, baseline, responses, including P&S responses and BP and HR responses. P&S monitoring augments tilt-table testing, by providing more specific and sensitive P&S information. Only tilt-table testing can positively diagnose cardiogenic syncope.

## Disease-specific vignettes: signs, symptoms, therapy, and outcomes

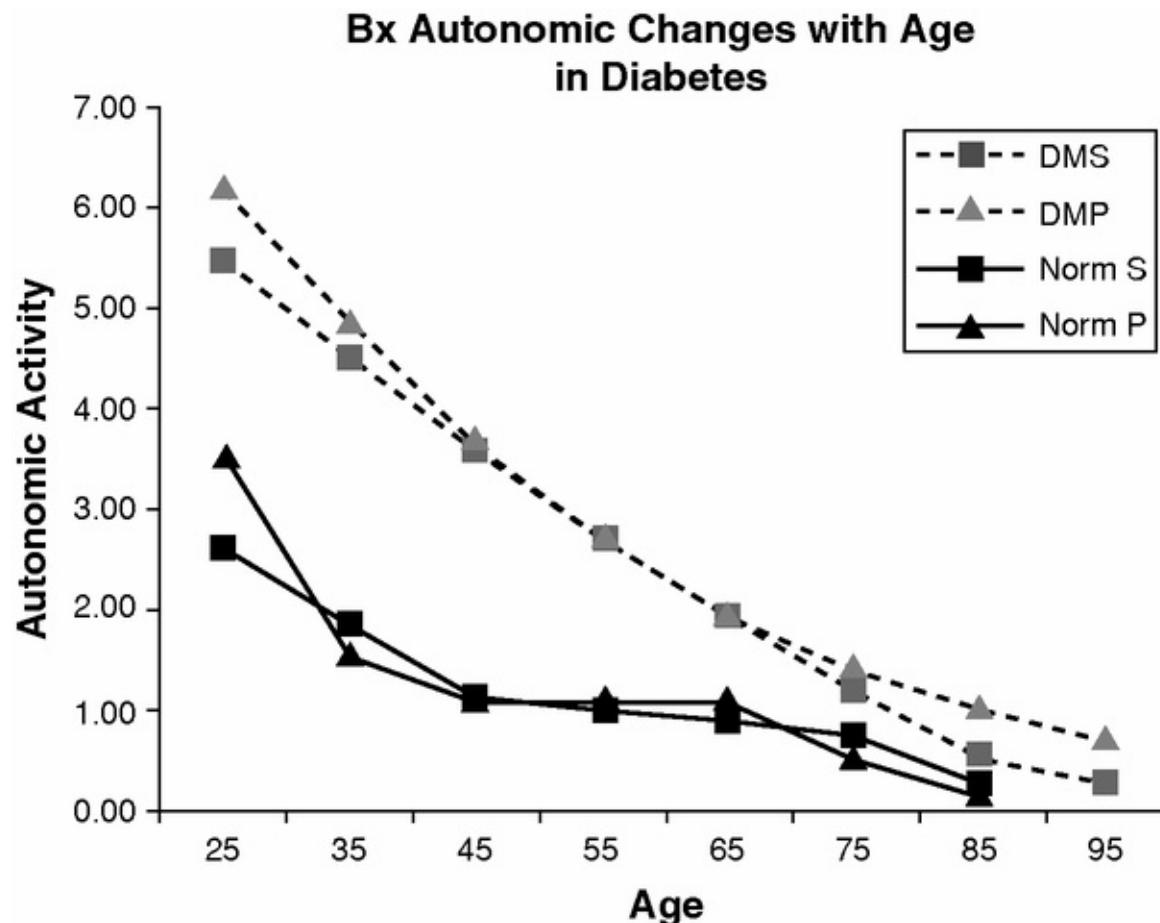
For general neurology, establishing and maintaining SB minimizes morbidity and mortality and the effects of neurologic diseases and disorders, slowing the onset of secondary symptoms. Often, once proper SB is restored, patients tend to be more stable, with fewer comorbidities, leading to reduced medication load and hospitalizations, improved outcomes, and reduced healthcare costs [4,5,8,9]. Nerve conduction velocity (NCV) studies are used to document neuropathy, and P&S monitoring is augmentative to these studies. Nerve conduction velocity studies test sensory and motor nerves (the ‘A’ and ‘B’ fibers), not the autonomic nerves (a portion of the ‘C’ fibers). True paralysis and parasthesias are morbidity (quality of life) issues resulting from deficits in the ‘A’ and ‘B’ fibers. However, given that the P&S control the organs, including the heart and vasculature, autonomic neuropathy underlies mortality risk. Therefore, for a complete assessment of the nervous system, NCV and P&S monitoring are recommended.

## Diabetes mellitus

Diabetes serves as a good model of the effects of chronic disease on the autonomic nervous system. As is well known, diabetes, like many other chronic diseases, leads to a cascade of secondary symptoms including dizziness, high blood pressure, gastrointestinal and sleep disturbance, and urogenital dysfunction. Eventually, it leads to autonomic neuropathy, which further increases morbidity risk, and then cardiovascular compromise, which increases mortality risk. The disparate nature of these disorders suggests that something else is involved, not just the disease. The suggestion that something else is involved is further highlighted when one considers the fact that many chronic diseases lead to the same cascade. The P&S nervous systems are likely candidates, given their relationship with the other systems involved in the cascade.

Diabetes, both type 1 and type 2, is well known to involve and degrade the ANS, shortening a patient's life expectancy through increased mortality risk (see

[Figure 10.3](#)). This leads to a cascade of comorbidities that can involve virtually every organ system [8, 9]. The American Diabetes Association recognizes the increased risk, even in the very early states, by stating that diabetic patients, upon first diagnosis, should have their P&S tested [30]. In fact, in age-matched studies, the average patient diagnosed with diabetes has already lost approximately 50% of their autonomic function by the time of the initial diagnosis of the diabetes itself (see [Figure 10.3](#)) [31].

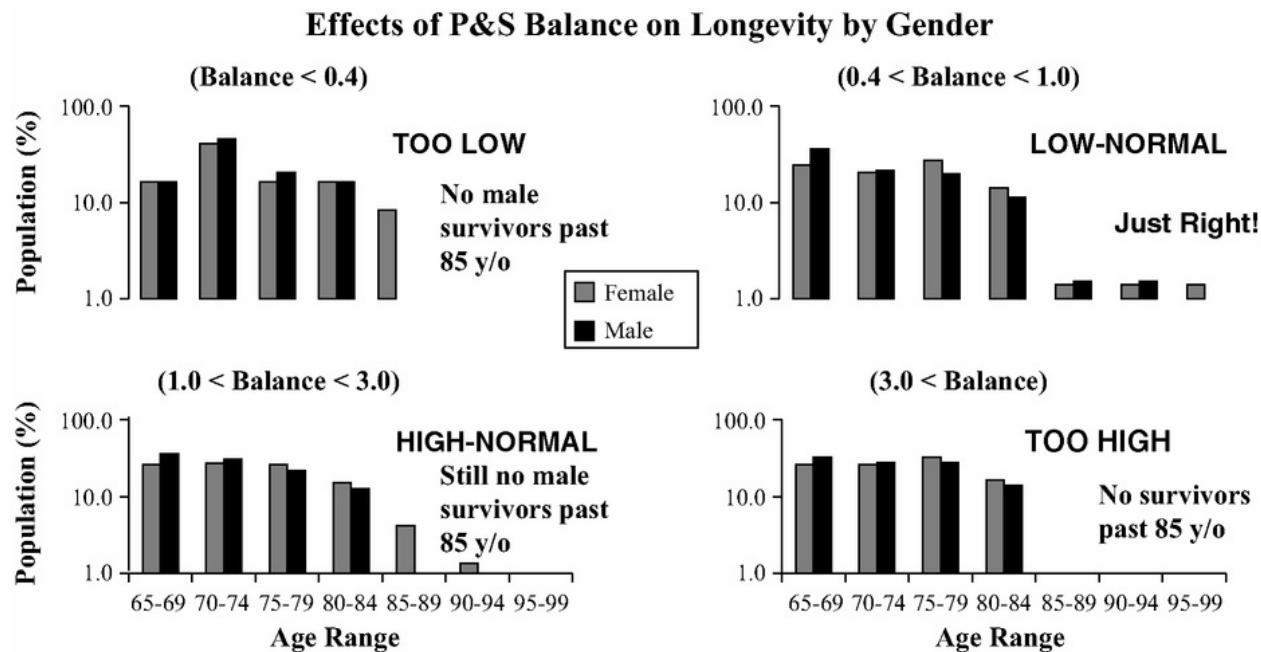


**Figure 10.3** The natural history of P&S declines with age in 511 patients diagnosed with diabetes (solid curves) as compared with 264 age-matched normals (broken curves). Normalized P&S activities are plotted on the ordinate against age on the abscissa. See text for details.

Diabetic neuropathy, starting with diabetic peripheral neuropathy, involves the sensory, motor, and autonomic nervous systems. Historically, the P&S consequences of the disease were largely assumed to co-incide with the sensory motor changes. This assumption was due to the fact that convenient, non-invasive measures of P&S were not available. Assuming autonomic neuropathy

progresses at the same rate as diabetic peripheral neuropathy may have been the best approximation available. It is now known to be largely in error. Frequent and periodic P&S assessment detects early changes in autonomic function (P&S imbalance) that leads to the involvement and degradation of the other organ systems [32]. Restoring P&S balance slows the progression of autonomic decline [5,33]. Therapy recommendations for early changes include alpha-lipoic acid (ALA, an antioxidant selective for nerves) [34,35,36], establishing and maintaining P&S balance [33] through proper diet and exercise, and proper compliance with diabetes medications.

Again, the ADA includes in its standards of care articles [19,29,32] early and frequent P&S monitoring (“at least annually”) to stay autonomic neuropathy. The ADA specifies that P&S monitoring is recommended as part of the standard of care for diabetes. Early detection and correction of P&S imbalance (dysfunction), and maintaining normal SB, reduces the risk of morbidity and mortality (see Figure 10.4) [8,9]. From an autonomic perspective, diabetes may be considered a model of chronic disease. Autonomic decline includes (in order) peripheral autonomic neuropathy (PAN), then advanced autonomic dysfunction (AAD) or diabetic autonomic neuropathy (DAN) with diabetes, and finally CAN (see Table 10.1).



**Figure 10.4** Perfect balance ( $SB = 1.0$ ) and the normal range for SB divides SB into four categories. A retrospective study of 4,911 geriatric patients shows that proper balance (low-normal SB) offers a longevity advantage over the rest of the population. Post-hoc analysis shows that low-normal SB is associated

with 21.3% fewer prescribed medications and 38.5% fewer comorbidities. See text for details. Advanced autonomic dysfunction (AAD) or diabetic autonomic neuropathy (DAN) and cardiovascular autonomic neuropathy (CAN) also place a patient at an increased risk of mortality under general anesthesia. Preoperative P&S assessment is required since AAD or DAN and CAN are often asymptomatic. If undetected or unreported, the mortality risk is exacerbated [37,38].

AAD or DAN and CAN also place a patient at an increased risk of mortality under general anesthesia. Preoperative P&S assessment is required since AAD or DAN and CAN are often asymptomatic. If undetected or unreported, the mortality risk is exacerbated [37,38].

Several studies, including the United Kingdom Prospective Diabetes Study (UKPDS) [39], the Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) study [40], the Veterans Affairs Diabetes Trial (VADT) [41], and, most recently, the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study [42], have demonstrated that intensive glycemic control is not the answer to reducing morbidity and mortality risk in diabetes. It is only part of the answer, since intensive glucose control did not reduce cardiovascular disease events. In fact, critics of the ACCORD study indicate that the lack of screening for autonomic neuropathy prior to intensive glucose control may have contributed to the increase mortality rate [43,44].

## Case vignette

A 37-year-old female known to have migraine, depression, and chronic fatigue syndrome (fibromyalgia) was referred for neurologic evaluation after complaining of palpitations, lightheadedness/dizziness, and a feeling of near-faintedness every time she stands from a seated position.

What is the most likely diagnosis?

1. Orthostatic hypotension.
2. Vasovagal response.
3. Complex partial seizures.
4. Postural orthostatic tachycardia syndrome (POTS).
5. Subclavian steal syndrome.

## **Diagnostic approach**

What questions from the history are of particular relevance to establishing a correct diagnosis?

1. Do symptoms vary depending on body positions, *i.e.* do they occur when she is lying or seated?
2. Does she have any premonitory/warning signs?
3. Is there a history of loss of consciousness/“passing out”?
4. Is the onset acute or subacute?
5. Are there any other associated symptoms?
6. What medications is she taking?
7. Are there specific situations or measures that worsen her symptoms?
8. Does she have other diseases?

## **Physical examination**

Her neurologic examination was normal. Vital signs revealed an increase in her pulse from 90 bpm while seated to 130 bpm while standing. During the exam she disclosed she had seen a cardiologist who said she had an increase in pulse from 80 bpm to 150 bpm during a tilt-table exam. However, her blood pressure was stable, and echocardiogram, blood tests, and other tests were normal. She recalled that her heart had been pounding, she felt lightheaded and weak as if she would “pass out.”

## **Work-up**

What ancillary tests would you order?

1. Non-invasive autonomic testing.
2. Plasma catecholamines.
3. Magnetic resonance imaging.
4. Electroencephalogram.
5. Chest X-ray, complete blood count, paraneoplastic antibodies.

## **Discussion**

1. This patient's history and tilt-table test results are consistent with postural orthostatic tachycardia syndrome (POTS), the most common form of dysautonomic syndrome.

Tilt-table examination is used to assess changes in heart rate and blood pressure that occur with changes in posture (as occurs in Valsalva), and sometimes in response to the administration of pharmacologic agents such as  $\beta$ -agonist isoproterenol. In POTS, the tilt-table examination reveals an elevation in heart rate by at least 30 bpm from baseline, without significant changes in blood pressure, but with symptoms of orthostasis such as lightheadedness, palpitations, generalized weakness, headache, blurry vision, etc. The etiology of POTS is unknown, but is commonly seen in females, around menses, viral infection, status post surgery, etc. POTS may be comorbid with fibromyalgia, but the significance is unclear. Treatment for POTS may include increase in fluids and salt intake, midodrine, fludrocortisone, and beta-blockers.

## 2. Differential diagnosis.

- a. Orthostatic hypotension – on standing, there would be a fall in systolic blood pressure by 20 mmHg or diastolic blood pressure by 10 mmHg.
- b. Vasovagal response – There is no tachycardia but rather transient bradycardia, and fall in blood pressure.
- c. Complex partial seizures – there would be aura, impairment in level of consciousness, and post-ictal drowsiness.
- d. Subclavian steal syndrome – results in syncope in the setting of stenosis of the subclavian artery proximal to the origin of the left vertebral artery. With exercise of the left arm blood flow steal from the vertebral arteries and basilar artery may occur, resulting in syncope and other symptoms of basilar insufficiency.

## Laboratory work/Investigations

### 1. Non-invasive autonomic testing

Non-invasive autonomic testing utilizing beat-to-beat variability and PR interval measurement can establish the diagnosis of cardiovascular autonomic failure. The most informative test is the Valsalva maneuver, whereby during the straining portion of the maneuver, there is absence of a normal recovery of blood pressure from baseline measurements, and after relaxation of the maneuver, there is absence of the expected/normal overshoot of the blood pressure to above baseline measurement.

A tilt-table test is useful when the history is suggestive of a neurally mediated (vasovagal) syncope. In such cases, a prolonged head-up tilt may produce symptoms. The baseline blood pressure and heart rate response to head-up tilt is usually normal, but after a period of 10–15 minutes typically there is a drop in blood pressure and heart rate. The combination of an acute fall in blood pressure and slowing of the heart rate is characteristic of vasovagal syncope and does not occur in autonomic failure.

2. Plasma catecholamines

Patients with pure autonomic failure (PAF) have loss of peripheral sympathetic noradrenergic fibers and therefore have low supine and standing plasma norepinephrine. In patients with multisystem atrophy (MSA), there is impairment of CNS centers but the peripheral noradrenergic fibers are intact. Therefore, supine plasma norepinephrine levels are normal but on standing may increase slightly but far less than it would be in normal subjects, to compensate for the degree of orthostatic hypotension. Plasma catecholamines measurement, however is fraught with problems. Ideally, the patient should rest quietly in the supine position, with an indwelling catheter *in situ* for at least 15 minutes, prior to sampling. The patient is then asked to stand for 5–15 minutes before sample is drawn.

3. Brain MRI

Patients with MSA have hypointensities on T2 imaging which may help differentiate it from Parkinson's disease and PAF. However, MRI is generally not very useful early in the disease process when the differential diagnosis is most difficult.

4. Chest X-ray/complete blood count (CBC), paraneoplastic antibodies

Autonomic dysfunction may be a feature of paraneoplastic disease. Some of the most commonly associated tumors are small cell lung carcinoma, ovarian carcinoma, breast carcinoma, lymphoma, and thymoma for which a variety of autoantibody markers are available for screening for these tumors (anti-Hu, anti-Yo, etc.). Chest X-ray may show lung cancer, but CT of the chest has a higher yield. Mild normochromic, normocytic anemia frequently accompanies autonomic failure. Treating the anemia with iron supplements and erythropoietin improves the orthostatic hypotension.

5. EEG

Generally not useful, unless the history is suggestive of a seizure disorder (premonitory signs, fainting, post-ictal drowsiness, etc.).

## Caveats in autonomic dysfunction

1. If the patient is having piloerection, sweating (“cold sweat”), nausea, vague abdominal discomfort, syncope → think ANS involvement.
2. If the patient is having lightheadedness, dizziness, blurry vision while seated or standing, resolves in lying → think orthostatic hypotension (but also look at medications,  $\alpha$ -adrenergic blockers, diuretics, tricyclics).
3. If the patient is having weakness, distal sensory loss, ± diabetes → think also about diabetic autonomic neuropathy, amyloidosis, exposure to neurotoxins, small fiber neuropathy with autonomic dysfunction.
4. If the patient has acute weight loss with autonomic symptoms → think paraneoplastic acute pandysautonomia.
5. If there is tremor, stiffness, slurred speech, abnormal gait → think PD, but also MSA (look for orthostatic hypotension etc.).
6. If the patient has memory loss, acting out during sleep, night-time confusion → think Lewy body dementia, Alzheimer's dementia, but also look for autonomic features.

## References

1. Guyton AC, Hall JE, Eds. The autonomic nervous system and the adrenal medulla. In *Text Book of Medical Physiology*, 11th edn. Philadelphia, PA: WB Saunders, 2006.
2. Low PA, Engstrom JW. Disorders of the autonomic nervous system. In *Harrison's Principles of Internal Medicine*, 16th edn. New York, NY: McGraw-Hill, 2003.
3. Saper CB. Autonomic disorders and their management. In *Cecil Textbook of Medicine*, 22nd edn. Philadelphia, PA: WB Saunders, 2003.
4. Umetani K, Singer DH, McCraty R, Atkinson M. Twenty-four hour time domain heart rate variability and heart rate: relations to age and gender over nine decades. *J Am Coll Cardiol* 1998; 31: 593–601.
5. Arora RR, Ghosh Dastidar S, Colombo J. Autonomic balance is associated with decreased morbidity. American Autonomic Society, 17th International Symposium, Kauai, HI, 29 Oct–1 Nov, 2008.

6. Waheed A, Ali MA, Jurivich DA *et al*. Gender differences in longevity and autonomic function. Presented at the Geriatric Medicine Society Meeting, Chicago, May 3–7, 2006.
7. Arora RR, Bulgarelli RJ, Ghosh-Dastidar S, Colombo J. Autonomic mechanisms and therapeutic implications of postural diabetic cardiovascular abnormalities. *J Diabetes Sci Technol* 2008; 2:568–71.
8. Vinik AI, Ziegler D. Diabetic cardiovascular autonomic neuropathy. *Circulation* 2007; 115:387–97.
9. Vinik AI, Maser RE, Nakave AA. Diabetic cardiovascular autonomic nerve dysfunction. *US Endocrine Dis* 2007;Dec:2–9.
10. Nanavati SH, Bulgarelli RJ, Vazquez-Tanus J *et al*. Altered autonomic activity with atrial fibrillation as demonstrated by non-invasive autonomic monitoring. *US Cardiol* 2010; 7:47–50.
11. Tobias H, Vinitsky A, Bulgarelli RJ, Ghosh-Dastidar S, Colombo J. Autonomic nervous system monitoring of patients with excess parasympathetic responses to sympathetic challenges – clinical observations. *US Neurol* 2010; 5:62–6.
12. Akselrod S, Gordon S, Ubel FA *et al*. Power spectrum analysis of heart rate fluctuations: a quantitative probe of beat-to-beat cardiovascular control. *Science* 1981; 213:213–20.
13. Akselrod S, Gordon D, Madwed JB *et al*. Hemodynamic regulation: investigation by spectral analysis. *Am J Physiol* 1985; 249:H867–75.
14. Akselrod S, Eliash S, Oz O, Cohen S. Hemodynamic regulation in SHR: investigation by spectral analysis. *Am J Physiol* 1987; 253:H176–83.
15. Akselrod S. Spectral analysis of fluctuations in cardiovascular parameters: a quantitative tool for the investigation of autonomic control. *Trends Pharmacol Sci* 1988; 9:6–9.
16. Keissar K, Davrath LR, Akselrod S. Coherence analysis between respiration and heart rate variability using continuous wavelet transform. *Phil Trans A Math Phys Eng Sci* 2009; 367:1393–406.
17. Aysin B, Aysin E. Effect of respiration in heart rate variability (HRV) analysis. IEEE Engineering in Medicine and Biology Society Conference,

New York, NY, 2006.

18. Aysin B, Aysin E, Colombo J. Comparison of HRV analysis methods during orthostatic challenge: HRV with respiration or without? IEEE Engineering in Medicine and Biology Conference, Lyons, France, 2007.
19. Boulton AJM, Vinik AI, Arrezzo JC *et al.* Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 2005; 28:956–62.
20. Ewing DJ. Cardiovascular reflexes and autonomic neuropathy. *Clin Sci Mol Med* 1978; 55:321–7.
21. Ewing DJ, Clarke BF. Diagnosis and management of diabetic autonomic neuropathy. *Br Med J* 1982; 285:916–18.
22. Ewing DJ, Martyn CN, Young RJ, Clarke BF. The value of cardiovascular autonomic function tests: 10 years experience in diabetes. *Diabetes Care* 1985; 8:491–8.
23. Bloomfield DM, Kaufman ES, Bigger JT Jr *et al.* Passive head-up tilt and actively standing up produce similar overall changes in autonomic balance. *Am Heart J* 1997; 134:316–20.
24. Low P, Ed. *Clinical Autonomic Disorders: Evaluation and Management*. Philadelphia, PA: Lippincott-Raven, 1997.
25. Low P and the Therapeutics and Technology Assessment Subcommittee. Assessment: Clinical autonomic testing report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. *Neurology* 1996; 46:873–80.
26. Joint Editorial Statement by the American Diabetes Association; the National Heart, Lung, and Blood Institute; the Juvenile Diabetes Foundation International; the National Institute of Diabetes and Digestive and Kidney Diseases; and the American Heart Association. Diabetes mellitus: a major risk factor for cardiovascular disease. *Circulation* 1999; 100:1132–3.
27. Grundy SM, Benjamin IJ, Burke GL, Chait A. AHA Scientific Statement: Diabetes and Cardiovascular Disease, a statement for healthcare professionals from the American Heart Association. *Circulation* 1999; 100:1134–46.
28. Aring AM, Jones DE, Falko JM. Evaluation and prevention of diabetic

- neuropathy. *Am Fam Physician* 2005; 71:2123–30.
29. Boulton AJM, Vinik AI, Arrezzo JC *et al.* Diabetic neuropathies: a statement by the American Diabetes Association. *Diabetes Care* 2005; 28:956–62.
  30. Vinik AI, Maser RE, Mitchell BD, Freeman R. Diabetic autonomic neuropathy. *Diabetes Care* 2003; 26:1553–79.
  31. Vinik AI, Aysin B, Colombo J. Enhanced frequency domain analysis replaces older heart rate variability methods. Fourth Annual Diabetes Technology Meeting, Philadelphia, PA, 28–30 October, 2004.
  32. American Diabetes Association. Standards of medical care in diabetes – 2008. *Diabetes Care* 2008; 31:S12–S54.
  33. Vinik AI, Murray GL. Autonomic neuropathy is treatable. *US Endocrinol* 2008; 2:82–4.
  34. Ziegler D, Ametov A, Barinov A *et al.* Oral treatment with alpha-lipoic acid improves symptomatic diabetic polyneuropathy: the SYDNEY 2 trial. *Diabetes Care* 2006; 29:2365–70.
  35. Ametov AS, Barinov A, Dyck PJ *et al.* The sensory symptoms of diabetic polyneuropathy are improved with alpha-lipoic acid. The SYDNEY trial. *Diabetes Care* 2003; 26:770–6.
  36. Ziegler D, Low PA, Litchy WJ *et al.* Efficacy and safety of antioxidant treatment with  $\alpha$ -lipoic acid over 4 years in diabetic polyneuropathy. *Diabetes Care* 2011; 34:2054–60.
  37. Boyd G, Stout D, Aultman M *et al.* Are there reliable clinical predictors of cardiac autonomic neuropathy in diabetic patients? American Society of Anesthesiologists, Annual Meeting, San Diego, 16–20 October, 2010.
  38. Boyd G, Stout D, Morris R *et al.* Prevalence and severity of autonomic dysfunction in diabetic patients presenting for retinal surgery. American Society of Anesthesiologists, Annual Meeting, San Diego, 16–20 October, 2010.
  39. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet*

1998; 352:837–53.

40. Patel A, MacMahon S, Chalmers J *et al*. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008; 358:2560–72.
41. Duckworth W, Abraira C, Moritz T *et al*. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009; 360:129–39.
42. Gerstein HC, Miller ME, Byington RP *et al*. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med* 2008; 358:2545–59.
43. Pop-Busui R, Evans G, Gerstein H *et al*. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. *Diabetes Care* 2010; 33:1578–84.
44. Calles-Escandon J, Lovato L, Simons-Morton D *et al*. Effect of intensive compared with standard glycemia treatment strategies on nortality by baseline subgroups characteristics. *Diabetes Care* 2010; 33:721–7.

## **11 Bulbar and pseudobulbar palsy**

---

Eric R. Eggenberger and David Clark *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

Pseudobulbar palsy (PBP) is weakness of oropharyngeal muscles controlling speech articulation and swallowing due to an upper motor neuron lesion resulting in dysarthria and dysphagia . Pseudobulbar palsy may be associated with pseudobulbar affect (PBA), an emotional dysregulation resulting in abnormal and inappropriate outbursts of laughter or crying.

Pseudobulbar palsy results from upper motor neuron (UMN) dysfunction of corticobulbar fibers to medullary brainstem motor nuclei ([Table 11.1](#)). Bulbar palsy refers to similar clinical features due to lesions involving the lower motor neurons (LMN) innervating oropharyngeal muscles. A brisk jaw jerk , enhanced gag reflex , and stiff/spastic tongue are signs of UMN lesions, whereas a diminished jaw jerk and gag reflex and tongue atrophy/fasciculations are signs of a LMN lesion.

### **Case vignette**

A 57-year-old female with a history of hypertension, remote 10 pack per year tobacco smoking, and depression presents with progressive dysphagia to liquids and falls over 6 months. A non-contrast computerized tomography (CT) scan of the brain prior to consultation shows mild symmetric small vessel ischemic disease. Medications include lisinopril and citalopram. Family history includes a grandfather with tremor and mother with breast cancer. Vital signs are normal. Mental status exam demonstrates normal naming, repetition, and recall, with slow nasal speech. Cranial nerve exam demonstrates normal pupillary, oculomotor, facial motor, and sensory function. Oral exam shows tongue fasciculations and a brisk jaw jerk reflex. Motor strength is 5/5 in all extremities except left ankle dorsiflexion which is 2/5. Fasciculations are noted in L

quadriceps and extensor digitorum communis. Sensation is normal. Deep tendon reflexes are 3/4 at the right patellar and Achilles tendons and 2/4 elsewhere. There is no ataxia in arms or legs and she walks with a steppage gait on the left. An ankle foot orthosis (AFO) brace is provided for her left foot drop and thickened liquids to address dysphagia. Magnetic resonance imaging (MRI) of the brain shows bilateral internal capsular T2 fluid attenuated inversion recovery (FLAIR) hyperintensities that do not enhance. Electromyogram demonstrates fasciculations with large motor units in all four extremities. The patient is diagnosed with amyotrophic lateral sclerosis, counseled regarding options and prognosis, prescribed riluzole and referred to a multidisciplinary amyotrophic lateral sclerosis (ALS) clinic.

**Table 11.1** *Differential diagnosis of pseudobulbar palsy.*

Item	Etiology	Possible clinical features
Neurodegenerative	Progressive supranuclear palsy	Supranuclear gaze palsy, bradykinesia, symmetric rigidity
	Parkinson's disease	Asymmetric resting tremor, bradykinesia, rigidity
Motor neuron disease	Amyotrophic lateral sclerosis	Muscular atrophy, fasciculations, hyperreflexia, upgoing plantar response
	Primary lateral sclerosis	Hyperreflexia, upgoing plantar response, spasticity
Vascular	CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and	Multiple subcortical infarcts, dementia, headaches

		<b>leukoencephalopathy)</b>
	Binswanger disease	Multiple subcortical infarcts
Metabolic	Osmotic demyelination (central pontine myelinolysis )	Encephalopathy, ophthalmoplegia, hyperreflexia, quadriplegia
	Leukodystrophies (metachromatic, Krabbe, Alexander)	Spasticity, hyperreflexia, decreased cognition
Trauma	Traumatic brain injury	Encephalopathy, paresis, hyperreflexia, spasticity
Inflammatory	Multiple sclerosis	Afferent pupillary defect, internuclear ophthalmoplegia, focal paresis, paresthesias, spasticity, incontinence, Uhthoff phenomenon
	Behçet disease	Recurrent uveitis, genital and oral ulcers, erythema nodosum
Neoplastic	Brainstem tumor	Headache, hyperreflexia, spasticity, ophthalmoplegia
Infectious	Creutzfeldt–Jakob disease	Stimulus sensitive myoclonus, dementia, seizure, cerebral blindness

	Herpes encephalitis	Encephalopathy, fever, seizure
	HIV/AIDS	Dementia, opportunistic infection
Congenital	Cerebral palsy	Spasticity, hyperreflexia, upgoing plantar response

---

## Further reading list

- Miller A, Pratt H, Schiffer R. Pseudobulbar affect: the spectrum of clinical presentations, etiologies and treatments. *Expert Rev Neurother* 2011; 11:1077–88.
- Miller RG, Jackson CE, Kasarskis EJ *et al*. Practice Parameter update: The care of the patient with amyotrophic lateral sclerosis: Multidisciplinary care, symptom management, and cognitive/behavioral impairment (an evidence-based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2009; 73:1227–33.
- O'Duffy JD, Goldstein NP. Neurologic involvement in seven patients with Behçet's disease. *Am J Med* 1976; 61:170–8.
- Olney NT, Goodkind MS, Lomen-Hoerth C *et al*. Behaviour, physiology and experience of pathological laughing and crying in amyotrophic lateral sclerosis. *Brain* 2011; 134:3455–66.
- Schiffer R, Pope L. Review of pseudobulbar affect including a novel and potential therapy. *J Neuropsychiatry Clin Neurosci* 2005; 17:447–54.
- Scrimjeour EM. Outbreak of methanol and isopropanol poisoning in New Britain, Paupa New Guinea. *Med J Austr* 1980; 2:36–8.
- Tan CF, Kakita A, Piao YS *et al*. Primary lateral sclerosis: a rare upper-motor-predominant form of amyotrophic lateral sclerosis often accompanied by frontotemporal lobar degeneration with ubiquitininated neuronal inclusions. Report of an autopsy case and a review of the literature. *Acta Neuropathol*

2003; 105:615–20.

## 12 Catatonic-like states

---

Edward Firouztaie *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

The term “catatonia” from the Greek word “catastinein” (to stretch tight) was first used in 1847 by Karl Kahlbaum [1] to describe a complex syndrome which presents with a combination of behavioral, motor, and vocal abnormalities [1,2]. Throughout the twentieth century, catatonia was mostly associated with schizophrenia; however, catatonia is most often produced by affective disorders and medical and neurologic illness [3].

In DSM-5, catatonia is not treated as an independent class but rather is recognized as catatonia associated with another mental disorder (i.e., neurodevelopmental, psychotic disorder, bipolar disorder, a depressive disorder, or other mental disorder), and catatonic disorder due to another medical condition [4]. In these two categories, catatonia is defined by the presence of three or more of the following 12 psychomotor features: stupor, catalepsy, waxy flexibility, mutism, negativitism (opposition or no response to instructions or external stimuli), posturing, mannerism, stereotypy, agitation which is not influenced by external stimuli, grimacing, echolalia, echopraxia [4]. DSM-5 also allows for another subtype defined as unspecified catatonia [4].

Diagnosis of catatonia, however, remains a challenge due to the complexity of presenting symptoms. Bush *et al.* [5] developed a rating scale of catatonia based on 23 signs, and others have listed over 40 signs of catatonia [6]. However, no agreement exists as to which signs, and how many, are necessary to define catatonia. The signs and symptoms of catatonia include agitation, emotional lability, hallucinations, delusions, impulsivity, automatic obedience, echolalia, echopraxia, perseveration, catalepsy, rigidity, mutism, verbigeration, gegenhalten, anxiety, staring, akathasia, posturing, grimacing, waxy flexibility, negativism, autonomic dysfunction, urinary retention or incontinence, and

dystonia, among others [5,6]. Often the motor symptoms cycle between states of agitated excitement and withdrawal .

## **Subtypes of catatonia**

A particularly dangerous form of catatonia is malignant catatonia, formerly also known as fatal catatonia due to the previously high rate of mortality. This form of catatonia is of acute onset and is associated with escalating fever and autonomic instability. Before 1960 the death rate was reported to be 75–100% and since 1986 has dropped substantially to approximately 9% [3]. Malignant catatonia “includes constellation of catatonic signs, motoric excitement, stuporous exhaustion, autonomic instability, respiratory failure, collapse, coma and ultimately death within mere days of onset.” [2] It requires intensive care unit (ICU) admission and treatment.

Neuroleptic malignant syndrome resembles malignant catatonia and is thought to be due to a systemic reaction to typical and atypical antipsychotic medications, other dopamine receptor antagonist medications, or rapid withdrawal of dopaminergic medications [2,3]. This reaction is not thought to be dose related [3]. The major presenting symptoms of neuroleptic malignant syndrome are decreased consciousness, motor rigidity, fever, and autonomic instability [2]. Neuroleptic malignant syndrome is clinically similar in adults and children [2].

Another proposed subtype of malignant catatonia is serotonin syndrome. This syndrome is dose related and is caused by serotonergic medications, as well as association of monoaminoxidase inhibitors (MAOIs) and serotonergic medications [7]. In addition to resembling malignant catatonia in its course, it also presents with gastrointestinal symptoms such as diarrhea, nausea, and vomiting. It may also present with ataxia, tremor, hyperreflexia, clonus, and muscle rigidity [7] .

## **Epidemiology of catatonia**

Due to the complexity of presenting symptoms of catatonia and lack of unifying and accepted diagnostic criteria, the prevalence of catatonia is not known. Catatonia is thought to be prevalent among psychiatric patients. In six studies conducted after 1976 with a total of 1,081 patients, the prevalence was reported as 7–31% and it was found to be more common in patients with mood disorders

[3]. Catatonia due to a medical condition is probably common, although no large-scale study is available. Based on three prospective studies in psychiatric units and with a small sample size of 65 patients, the rate of catatonia due to an underlying medical condition was reported to be 20–25% [3].

## Etiology of catatonia

The various etiologies of catatonia are discussed in prior reports [2,6,8,9]. A summary of the major etiologies associated with catatonia, as well as some early distinguishing features, is provided in [Table 12.1](#).

**Table 12.1** *Summary of the main etiologies of catatonia.*

Item	Subdivision	Specific entity	Possible clinical features
Structural		Lesions/insults in basal ganglia, thalamus, parietal lobes, cerebellum—pons, frontal lobe atrophy and lesions	Chorea, ballismus, dystonia, tics, parkinsonism, aphasia, amnesia, akinetic mutism, tremor, loss of micturition control, disinhibition, apathy, emotional lability, myoclonus, gait abnormalities, weakness, and other localized or related deficits
Drugs	Illicit Therapeutic Withdrawal	Hallucinogens, LSD, opiates, ecstasy, cocaine, stimulants Lithium, anticonvulsants,	Intracerebral or subarachnoid hemorrhage (cocaine), stereotyped movements

	baclofen, antiemetics, neuroleptics, tricyclics, monoamine oxidase inhibitors, tetrabenazines, levetiracetam, corticosteroids, azithromycin Levodopa, gabapentin, clozapine, benzodiazepine, sedative-hypnotic withdrawal	behavior, anxiety, blunting of affect, psychomotor agitation or retardation, autonomic instability, illusions, hallucinations, tremors Tremor, fasciculations, autonomic instability, impaired consciousness, ataxia, myoclonus, seizure, motor rigidity, fever, dyskinesia, delirium, hallucinations, psychosis, chorea Seizure, tremor, rigidity, illusions, hallucinations, muscle twitching, autonomic hyperactivity, psychomotor agitation
Infectious	HIV encephalitis, progressive multifocal leukoencephalopathy, herpes and viral encephalitis, viral	Fever, headache, altered mental status, early behavioral changes, personality changes, apathy, dysarthria,

	hepatitis, tuberculosis, malaria, syphilis, mononucleosis, typhoid fever, bacterial meningitis	myoclonus, tremors, seizures, stupor, coma, immobility
Pressure effects	Hydrocephalus, herniation	Headache, decreased mentation, gait disorder, urine incontinence, pupil asymmetry, ophthalmoparesis, visual disturbance, stupor, coma, seizure
Psychiatric	Schizophrenia, bipolar, major depression, obsessive- compulsive disorder, autistic disorders, mood disorders, conversion and personality disorders, childhood disintegrative disorder	Motoric immobility, stupor, excess motor activity extreme negativism, mutism, peculiarity and stereotypy, voluntary movements, echolalia, echopraxia
Inflammatory/auto- immune	Lupus	Seizures, altered mental status, depression, mania, acute confusional states, schizophreniform psychosis

		psychosis, tremor, hemiparesis, paraparesis, chorea, cerebel- ar ataxia, diplop-
Neoplastic	Glioma, pinealoma, frontal lobe tumors, paraneoplastic syndromes, angioma	Diplopia, memory impairment, lethargy, personality change, altered consciousness, rigidity, incontinence, seizure, dysarthria, focal weakness, apraxia, aphasia, opsoclonus, myoclonus, cerebellar ataxia, signs and symptoms associated with specific paraneoplastic syndromes
Degenerative	Lewy body disease, cerebellar degeneration	Cognitive deficits, parkinsonism extrapyramidal symptoms, visual hallucinations, visual change, limb ataxia
Vascular	Stroke. subarachnoid	Aphasia, limb

	hemorrhage, subdural hemorrhage, ventricular hemorrhage, venous thrombosis, anterior cerebral artery aneurysm rupture	apraxia, incontinence, headache, prominent op- disc, pupillary asymmetry, fo- deficits, altere- level of consciousness coma, ataxia, seizure, personality change
Other	Alcohol withdrawal, Wernicke's disease, parkinsonism Prader–Willi, Kleine–Levine syndrome, cerebral anoxia, N-methyl D- aspartate (NMDA)- associated encephalitis	Tremor, anxiety, lethargy, depression, autonomic instability, ap- Altered behav- hypersomnolence, stupor, mutism, rigidity, refus- eat or drink, s- cycle disturbance
Metabolic	Hepatic and renal transplantation and disease Hyperadrenalinism hyperparathyroidism, hypercalcemia porphyria diabetes, Cushing's disease, Addison's disease, vitamin B12 deficiency	Myoclonus, tremor, ataxia delirium, mar- encephalopathy coma, seizure Headache, confusion, vis- disturbance, neglect, aphasia agitation, stupor coma Muscular weakness,

		personality changes, depression, stupor, coma, tonic-clonic seizures
		Autonomic instability such as tachycardia, diarrhea, hypertension; motor and sensory deficits, altered mental state, seizure, myoclonus, tremor, irritability, apathy, emotional lability
Trauma	Closed head injury	Headache, irritability, anxiety, depression, impaired concentration, attention, fatigue, sleep disturbance, frontal lobe symptoms in case of frontal lobe injury
Ictal	Frontal lobe seizures Non-convulsive status epilepticus	Complex motor automatisms, prominent mood changes, bizarre hysterical

		appearance, vocalization Altered mentation, behavioral changes, hallucinations paranoia, mus immobility
Demyelination		
	Multiple sclerosis	Motor weakn and spasticity tremor, ataxia emotional lability, urina incontinence

## Genetics and pathophysiology of catatonia

The gene for periodic catatonia of schizophrenia is suggested to have autosomal dominant inheritance and localizes to 15q15 and in one family to 22q13 [8,10]. Prader–Willi syndrome, which is associated with catatonia, presents with hypotonia, insatiable hunger, obesity, short stature, and hypogonadism. It is a genetic syndrome linked to abnormal expression of “sex-specific” genes on 15q11–13 which contains gamma-amino butyric acid-A (GABA-A) receptor genes [9]. Given the close proximity to the genes associated with catatonia of schizophrenia on 15q15, as well as close proximity to genes associated with autism, it is suggested that there is close overlap between genes for catatonia, autism, and Prader–Willi syndrome [9].

In the malignant form of catatonia, hypothalamic necrosis is reported [6,8]. Other reported neuro-pathologic changes in catatonia include decreased cell density in the thalamus and atrophy of caudate and nucleus accumbens [8,11]. Imaging studies have pointed to mostly basal ganglia and cortical regions associated with movement, emotion, and sensory processing [8]. In functional magnetic resonance imaging (fMRI) studies of akinetic catatonic patients, abnormal activation of premotor cortex and orbital–frontal cortical areas were reported [8]. Additional fMRI studies have also implicated the supplementary

motor area, prefrontal cortex, and parietal areas [8].

The neurotransmitter model of catatonia points to GABA, glutamate, and dopamine neurotransmitters [2]. The role of GABA-A in catatonia is further validated by response of catatonia to benzodiazepines, which affect benzodiazepine/GABA-A receptors [2]. It is also suggested that GABA dysfunction in the hypothalamus is responsible for autonomic dysfunction seen in malignant catatonia [2]. The exact mechanism by which GABA plays a role in catatonia is not well understood. Motor abnormalities such as stereotypies and restlessness seen in catatonia are believed to be associated with dopaminergic dysfunction due to basal ganglia alteration [8]. Prader–Willi syndrome is associated with both GABA and hypothalamic abnormalities [2].

In the endocrine model of catatonia, hypothalamic–pituitary–adrenal dysfunction is implicated [2]. In the epilepsy model of catatonia, proposed by Fink and Taylor [12], seizure-like processes in the frontal lobes and anterior limbic system are implicated [2]. This model correlates well with the efficacy of benzodiazepines and electroconvulsive therapy (ECT), both of which raise the seizure threshold [2]. The presence of a dysrhythmic electroencephalogram (EEG) in catatonic patients, which resolves after resolution of catatonia, is postulated to correlate with non-convulsive status epilepticus [2].

## Evaluation and diagnostic work-up

Diagnosis of catatonia can be challenging, given the variety of signs and symptoms that it can present and its various etiologies. In any patient with fluctuating motor and behavioral symptoms, catatonia should be considered. In particular, malignant catatonia should always be considered, given its significant mortality rate. The evaluation should start with a complete and detailed history of the present illness and its course, which often needs to be obtained from a close relative or parent. A complete past medical history and a history of recent therapeutic medication change is imperative to rule out medication-induced or withdrawal catatonia and/or subtypes of catatonia. Infectious processes should be ruled out. Spinal tap should be considered if CNS infection or encephalitis is suspected. Laboratory studies should include complete metabolic profile (CMP), complete blood count (CBC), thyroid function tests, B12, rapid plasma reagent (RPR), folate, creatinine phosphokinase, and serum iron levels, antinuclear antibody test (ANA), and levels of medications. Urine screen should be sent to rule out illicit and recreational drug use. Computerized tomography (CT) and

MRI scans should be obtained to rule out structural abnormalities, bleed, mass, or other central nervous system (CNS) pathology or insult. An EEG should be obtained to rule out seizure activity. The EEG is also important in differentiating psychotic conditions secondary to delirium from schizophrenia.

Tardive dyskinesia, locked-in syndrome, and hypoactive delirium can resemble catatonia and should be kept in the differential [3].

## **Treatment of catatonia**

Full description of treatment of catatonia is beyond the scope of this chapter and can be found elsewhere [3,8,9,13]. In addition to identifying and treating the underlying cause, benzodiazepines and ECT are considered the initial therapy for catatonia [8]. Plasma exchange is reported to be useful in treating catatonia associated with lupus and auto-immune malignant catatonia [8,13].

## **Case vignette**

A 44-year-old male with a history of Huntington's disease, and multiple hospitalizations for impulse control disorder, depression, obsessive-compulsive disorder, panic attacks/bipolar disorder, and organic personality disorder, was transferred to the emergency room from a nursing home with a chief complaint of chest pain, dizziness, and diaphoresis. His medications upon admission were: seroquel 400 mg PO BID, Prozac 80 mg once a day, Sinemet 25/100 TID, Depakote 500 mg q 8 hours, fluphenazine 20 mg BID, Zocor 20 mg once a day, klonopin 0.5 mg TID, and Xenazine (tetrabenazine) 25 mg TID. Three weeks prior to admission the patient's Xenazine was increased from twice a day dosing to three times a day and Zyprexa was discontinued. The patient was evaluated at the emergency room and was admitted to the telemetry ward for chest pain. Telemetry revealed sinus rhythm and the patient felt better and was scheduled to be discharged.

Prior to the discharge, however, he became combative and restless with continuous abnormal movements. He was not taking his medications and had decreased PO intake. He was confused and non-verbal, and followed some one-step commands only. Psychiatry followed by a neurology consultation was called and symptoms were initially thought to be due to recurrence of his psychiatric disorder. Seroquel was changed to 300 mg BID and 200 mg qhs and Geodon PRN was added. The patient's symptoms continued and became

progressively worse. Shortly after, his creatine phosphokinase (CPK) level was found to be elevated at 6,300 and he developed a high fever of 105.5 °F. His agitation, restlessness, and abnormal movements continued. The diagnosis of neuroleptic malignant syndrome was rendered due to his medication regimen, although malignant catatonia could not be ruled out. The patient was transferred to the medical ICU. All of his neuroleptics were discontinued; however, Sinemet was continued. He was given a 2 mg dose of lorazepam, followed shortly by another dose, which resulted in reduction of his abnormal movements. Dantrium was also added at 50 mg q 8 hours with improvement of his abnormal symptoms. However, when Dantrium wore off, his abnormal movements returned and Dantrium was increased to q 6 hours together with lorazepam 2 mg IVP q 6 hours.

Shortly after, his CPK became greater than 14,000 and he developed rhabdomyolysis and acute renal failure. A nephrology consult was called and aggressive hydration was started. He became hypotensive and was started on a Levophed drip. His hospital stay was further complicated by development of methicillin-resistant *Staphylococcus aureus* (MRSA) pneumonia and he was intubated. A CT of the brain was consistent with Huntington's disease. His pneumonia was treated with antibiotics and he was weaned off the respirator. Initially he was tube fed and this was gradually advanced to regular diet by mouth. His rhabdomyolysis improved and resolved. Dantrolene and lorazepam were weaned off. His neuroleptics were gradually re-introduced and he was discharged after close to 4 weeks of stay at the hospital. Currently the patient resides in a long-term psychiatric facility. The psychiatric sequela of his Huntington's disease is controlled with medications, and intermittent ECT .

## References

1. Kahlbaum KL. *Catatonia*. Translated by Levi Y, Pridon T. Baltimore, MD: Johns Hopkins University Press, 1973.
2. Dhossche DM, Stoppelbein L, Rout UK. Etiopathogenesis of catatonia: generalizations and working hypotheses. *J ECT* 2010; 26:253–6.
3. Daniels J. Catatonia: clinical aspects and neurobiological correlates. *J Neuropsychiatry Clin Neurosci* 2009; 21:371–80.
4. American Psychiatry Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). Arlington, VA: American Psychiatric Association, 2013.

5. Bush G, Fink M, Petrides G, Dowling F, Francis A. Catatonia I: Rating scale and standardized examination. *Acta Psychiatr Scand* 1996; 93:129–36.
6. Carroll BT, Anfinson TJ, Kennedy JC *et al.* Catatonic disorders due to general medical conditions. *J Neuropsychiatry Clin Neurosci* 1994; 6:122–3.
7. Fornaro M. Catatonia: a narrative review. *CNS Agents Med Chem* 2011; 11:73–9.
8. Jakel R, Mark SA. Catatonia, a clinical summary. In Jankovic J., Ed. *Medlink Neurology*. San Diego, CA: Medlink Corporation.
9. Dhossche DM, Wachtel LE. Catatonia is hidden in plain sight among different pediatric disorders: a review article. *Pediatr Neurol* 2010; 43:307–15.
10. Stober G, Ruschendorf F, Rüschenhoff F *et al.* Splitting schizophrenia: periodic catatonia susceptibility locus on chromosome 15q15. *Am J Hum Genet* 2000; 67:1201–7.
11. Nortoff G. Brain imaging and catatonia: current findings and a pathophysiological model. *CNS Spectr* 2000; 5:34–6.
12. Fink M, Taylor M. *Catatonia: A Clinician's Guide to Diagnosis and Treatment*. Cambridge: Cambridge University Press, 2003.
13. Marra D, Amoura Z, Soussan N *et al.* Plasma exchange in patients with stuporous catatonia and systemic lupus erythematosus. *Psychother Psychosom* 2008; 77:195–6.

## 13 Chorea

---

Ruth H. Walker *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Chorea refers to involuntary movements which rapidly flit irregularly from region to region. Any part of the body can be affected. In many cases the whole body is involved, including face, arm, and leg. Unilateral involvement may be seen with a structural cause, or with diabetic non-ketotic hyperglycemia. Mild to moderate movements may not be troublesome to the patient, and may not require treatment. Sometimes patients will involuntarily disguise the movements as a purposeful gesture, such as touching the hair or clothing; this is known as “parakinesia.”

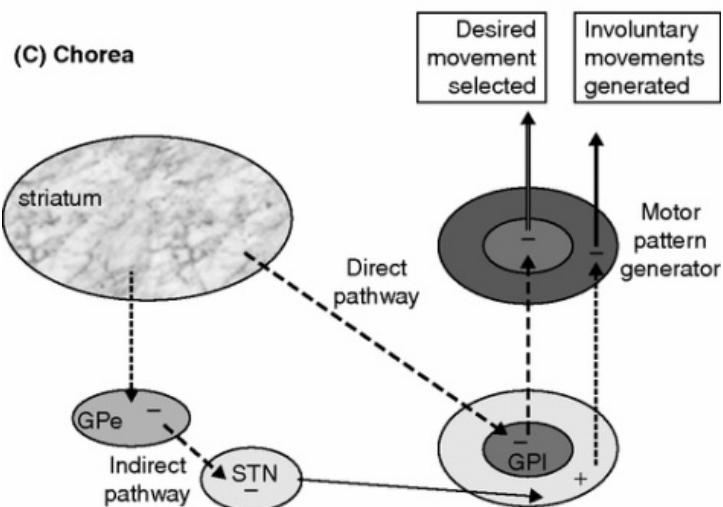
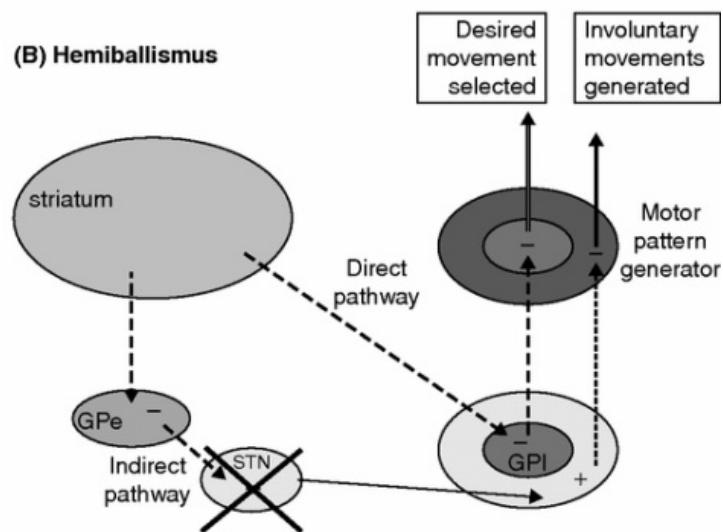
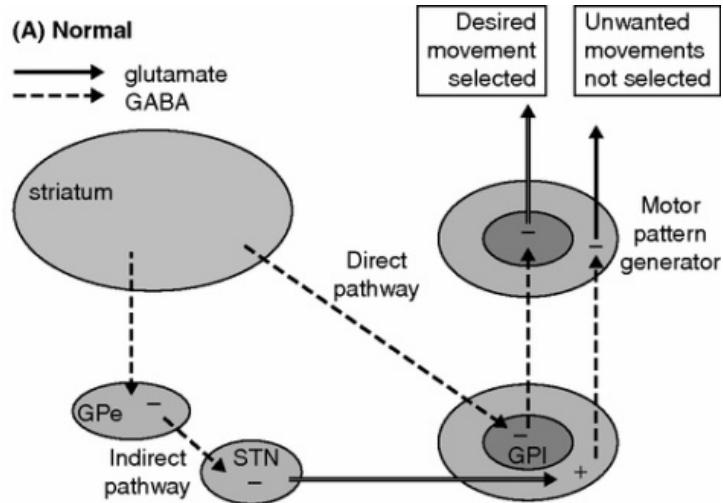
Unlike dystonia, the movements of chorea are not repetitive, and typically involve different muscle groups without a regular pattern. When the patient is mildly affected there can be an appearance of generalized restlessness, or even myoclonus with small amplitude, rapid movements of different body parts. Chorea does not usually interfere with voluntary movements unless it is severe. Rather than disrupting a voluntary task, it appears as if fragments of movements intrude; in some cases there is a loss of tone, known as “motor impersistence,” which appears to be due to lapses in the ability to perform the desired action. This phenomenon of inability to sustain a posture results in the “milkmaid’s grip” and the “trombonist’s tongue.”

The common conditions “tardive dyskinesia” and “l-dopa-induced dyskinesia” are technically choreiform in nature, although the term “dyskinesia” refers only to “abnormality of movement.”

### Pathophysiology

Many of the pathophysiologic aspects of chorea can be explained by the

traditional model of basal ganglia function developed by Albin *et al.* [1]. The direct pathway, from the D1-dopamine receptor-bearing medium spiny neurons of the caudate/putamen to the internal segment of the globus pallidus (GPi) activates a motor program in response to an input from the motor cortex. The indirect pathway, from the D2-dopamine receptor-bearing medium spiny neurons, to the globus pallidus external segment (GPe), the subthalamic nucleus (STN), and the GPi, focuses and selects the movements [2] ([Figure 13.1A](#)).



**Figure 13.1** (A) During normal function of the basal ganglia, the direct pathway from the striatum inhibits neurons of the GPi. This results in disinhibition of the motor pattern generator, consisting of the motor thalamic nuclei and their projections to the cortex, and selection of voluntary movements. The neurons of the GPi which select the motor program are represented as being surrounded by an inhibiting network, controlled by the indirect pathway, which reduces the generation of unwanted movements. (B) In hemiballismus, damage to the subthalamic nucleus results in decreased surround inhibition of the GPi. Thickness of lines indicates relative degree of activity. The decreased surround inhibition results in the generation of unselected, involuntary movements. (C) In chorea of striatal origin there is loss of striatal neurons to the indirect pathway, with decreased surround inhibition via the indirect pathway, and loss of inhibition of unselected movements.

It appears probable that an imbalance of the direct and indirect pathways can occur at a number of locations to cause chorea; within the caudate/putamen, STN (causing hemiballismus; [Figure 13.1B](#)), and the GPi. A decrease in activity of the indirect pathway from the caudate/putamen to the GPe ([Figure 13.1C](#)) [1,3] results in overactivity of this nucleus. Increased inhibition from the GPe causes decreased activity of its projection targets, the STN, the GPi, and the substantia nigra pars reticulata (SNr). This decreased activity of the indirect pathway results in a loss of selection of motor signals from the direct pathway within the GPi [2]. The consequence is disinhibition of the motor thalamus and an increase in thalamocortical, and hence cortical motor activity.

## Case vignette

A 72-year-old African–American female presents with 3 months of fidgety movements. She has no family history of a movement disorder, although she reports that her mother suffered from depression and anxiety for most of her adult life. She has two children, one of whom has two children, as well as a younger brother aged 68 who has three children and seven grandchildren. All are in good health. She suffers from rheumatoid arthritis and hypothyroidism, for which she takes medication. Six months ago she started taking sertraline for mild depression. She reported having lost a few pounds in recent months, but was unable to be more precise.

Clinical examination demonstrates mild generalized chorea affecting all four limbs and trunk. Speech was mildly dysarthric, although she attributed this to ill-fitting dentures. Eye movements were normal. She had typical hand and finger deformities consistent with rheumatoid arthritis. Deep tendon reflexes were depressed throughout. There was moderate loss of vibration sense in both ankles. She walked with an increased base, and was unable to perform tandem gait without staggering to either side.

## The approach

There are several features in this patient's history which may suggest a specific diagnosis; *i.e.* she began taking a new medication a few months before symptom onset; she has two concomitant medical conditions, either of which may be associated with chorea; the weight loss raises the concern of malignancy; she has additional neurologic findings such as peripheral neuropathy and gait impairment; and there is a family history of psychiatric illness.

The majority of patients with the new onset of any hyperkinetic movement disorder merit a brain magnetic resonance imaging (MRI) scan, unless the diagnosis is certain from clinical features, such as essential tremor , tardive dyskinesia , or Sydenham's chorea . Bloodwork should be performed to check that her levothyroxine is at the correct dose, to exclude electrolyte imbalance or hyperglycemia , to evaluate liver enzymes as a possible indicator of liver and other systemic diseases, to exclude polycythemia rubravera , and to evaluate for other autoimmune disorders such as systemic lupus erythematosus and antiphospholipid antibody syndrome [4]. Peripheral neuropathy may be caused by a number of autoimmune conditions.

Although the finding of peripheral neuropathy and dysarthria may suggest the diagnosis, her age of onset is not typical for chorea-acanthocytosis . A peripheral blood smear is not always positive for acanthocytosis in this disorder, but a normal creatine kinase, along with normal liver enzymes helps exclude this diagnosis [5].

**Table 13.1 Differential diagnosis of chorea.**

Etiology	Onset	Time course	Diagnosis

Structural	Acute/sub-acute	Stable, may slowly resolve; may have delayed onset after stroke	Ischemic stroke
	Acute	Stable, should slowly resolve	Intracerebral hemorrhage
	Sub-acute	Gradual progression	Tumour
Metabolic/endocrine	Sub-acute	Stable	Vascular malformation/moya
	Acute/sub-acute	Stable	Chorea gravidarum
	Acute	Resolves with treatment; rarely chronic or recurrent	Diabetic non-ketotic hyperglycemia
	Sub-acute	Chronic, gradually worsening	Acquired hepato-encephalopathy
	Acute/sub-acute	Chronic	Lead toxicity

Hyper/hypoparathy

Hypomagnesemia

Hypo/hyperthyroidi

Hyper/Hypoparathr  
pseudo-hypoparathr

Vitamin B12 defici

Polycythemia rubra

Autoimmune

Acute/sub-  
acute

Variable

Secondary to autoir  
disease

	Acute/sub-acute	Chronic	Systemic lupus erythematosus
	Acute/sub-acute	Chronic	Antiphospholipid antibody syndrome
			Paraneoplastic syndromes
	Acute/sub-acute	Chronic	Celiac-related chorea
	Acute/sub-acute	Stable, usually self-limiting	Sydenham's chorea
Drug-induced	Acute	Temporally related to drug/medication use	Acute toxicity
	Sub-acute	Stable	Tardive dyskinesia
Infectious/post-infectious	Sub-acute	Variable	HIV-related

## infectious

	Sub-acute	Stable	Neurosyphilis
	Acute/ sub-acute	Progressive	Creutzfeldt–Jakob disease Huntington's disease (Alzheimer's disease) autosomal dominant inherited prion disease
	Acute/ sub-acute	Stable	Post-mycoplasma
Psychogenic	Acute/ sub-acute	Unexplained fluctuations	Psychogenic
Autosomal recessive	Gradual	Progressive	Chorea–acanthocytosis
			Wilson's disease

Phospholipase A-as  
neurodegeneration/  
dystrophy

Aceruloplasminemi

Huntington's diseas

Infantile bilateral st  
necrosis

Ataxia-telangiectas

Ataxia with oculom  
apraxia I

Ataxia with oculom

apraxia 2

Friedreich's ataxia

Non-ketotic hyperglycemia

Recessive hereditary  
methemoglobinemia

Autosomal  
dominant

Gradual

Progressive

Huntington's disease

Huntington's disease

Spinocerebellar atrophy

Dentatorubropallidoluysian atrophy

Stable Benign hereditary c

Progressive *TARDBP*-related

Progressive Neuroferritinopathy

Progressive Familial amyotroph  
sclerosis

Paroxysmal Paroxysmal kinesig  
dyskinesia

Paroxysmal non-ki  
dyskinesia

Paroxysmal exertio  
dyskinesia

Paroxysmal  
choreoathetosis/epi

Paroxysmal  
choreoathetosis/spa

X-linked

Gradual

Progressive

Lesch–Nyhan synd

McLeod syndrome

Lubag

Mitochondrial

Gradual

Progressive

Leigh's syndrome

---

ASO, anti-streptolysin O; ATM, ataxia telangiectasia mutated; CK, creatine kinase; CSF, cerebrospinal fluid; CT, computerized tomography; EEG, electroencephalography; FTA, fluorescent treponemal antibody; HD, Huntington's disease; LFT, liver function tests; LP, lumbar puncture; MRI, magnetic resonance imaging; NMDA, N-methyl D-aspartate; PET, positron emission tomography; RPR, rapid plasma reagent; TSH, thyroid stimulating hormone; VDRL, Venereal Disease Research Laboratory.

At the initial visit I would recommend a trial of discontinuation of her sertraline for at least 2 months. Although chorea is an unlikely side effect of this commonly used medication, this should be excluded. If the initial laboratory and neuroimaging evaluation is unrewarding, the second line of investigation involves sending serum for paraneoplastic antibodies and consideration of testing for Huntington's disease (HD).

A paraneoplastic syndrome must be considered in a patient of this age, especially if there is evidence of weight loss or other systemic illness. It can be challenging to locate the tumor, as the antibodies generated against tumor elements which result in the neurologic syndrome may limit tumor growth. However, this is obviously a diagnosis not to be missed. Antibodies can only be screened for if their identity is known, and the list continues to grow. Antibodies which have been associated with chorea to date include anti-CRMP-5, anti-Hu, anti-Yo, anti-LGI-1, and anti-NMDA receptor antibodies [6]. Even in the absence of identified antibodies, imaging of thorax, abdomen, and pelvis with CT or MRI and PET imaging should be considered.

Genetic testing for autosomal dominant disease can have significant consequences for the patient's family. It should not be undertaken without genetic counseling which fully addresses the consequences of a positive test result, not only for the patient, but for her siblings, children, nieces, nephews, and grandchildren. The psychiatric history in her mother may or may not be related to pre-motor-symptomatic HD, but HD should certainly be considered in this patient. Late-onset chorea can be seen in patients with trinucleotide repeats of the HD gene in the intermediate range, resulting in partial penetrance of disease, but which are likely to expand into the pathogenic range in their offspring [7].

If genetic testing for HD is performed, and is negative and no other likely diagnosis is identified, testing for Huntington's disease-like 2 may be considered [8]. This autosomal dominant disease is very rare, but has been reported to date only in families of African ancestry, so is a possibility in this case .

## References

1. Albin RL, Young AB, Penney JB. The functional anatomy of basal ganglia disorders. *TINS* 1989; 12:366–75.
2. Mink JW. The basal ganglia and involuntary movements – impaired

- inhibition of competing motor patterns. *Archiv Neurol* 2003; 60:1365–8.
3. Wichmann T, DeLong MR. Models of basal ganglia function and pathophysiology of movement disorders. *Neurosurg Clin N Am* 1998; 9:223–36.
  4. Pourfar MH. Paraneoplastic and other autoimmune choreas. In Walker RH, Ed. *The Differential Diagnosis of Chorea*. New York, NY: Oxford University Press, 2011: 338–55.
  5. Jung HH, Danek A, Walker RH. Neuroacanthocytosis syndromes. *Orphanet J Rare Dis* 2011; 6:68.
  6. Panzer J, Dalmau J. Movement disorders in paraneoplastic and autoimmune disease. *Curr Opin Neurol* 2011; 24:346–53.
  7. Ha AD, Jankovic J. Exploring the correlates of intermediate CAG repeats in Huntington disease. *Postgrad Med* 2011; 123:116–21.
  8. Margolis RL, Holmes SE, Rosenblatt A *et al*. Huntington's disease-like 2 (HDL2) in North America and Japan. *Annal Neurol* 2004; 56:670–4.

# 14 Coma

---

Galen V. Henderson and Alan B. Ettinger

*Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

## Introduction

### Impaired states of consciousness

1. *Coma* implies total or near-total unresponsiveness. It is a sleep-like state of unconsciousness from which the patient cannot be aroused by external or internal stimuli. Despite vigorous stimulation, there is no purposeful movement and only posturing; brainstem reflexes may be absent or present. There are variations in the degree of coma; in its deepest stages, no reaction off any kind is obtainable; corneal, pupillary, pharyngeal, tendon, and plantar reflexes are absent and the tone in the limb muscles is diminished. With lesser degrees of coma, pupillary reactions, reflex ocular movements, and corneal and other brainstem reflexes are preserved in varying degree, and muscle tone in the limbs may be increased. Respiration may be varying. In lighter stages, sometimes referred to by the ambiguous and unhelpful terms semi-coma or obtundation, most of the above reflexes can be elicited.
2. *Stupor* refers to a state in which the patient can be roused only by vigorous and repeated stimuli but the state of arousal cannot be sustained without repeated external stimulation. Verbal output is unintelligible or nil and some purposeful movement to noxious stimulation may be noted. Restless or stereotyped motor activity is common and there is a reduction or elimination of the natural shifting of body positions.
3. *Drowsiness* denotes an inability to sustain a wakeful state without the application of external stimuli.
4. *Lethargy* (somnolence) refers to a state in which arousal, although

diminished, is maintained spontaneously or with repeated light stimulation.

5. *Confusion* refers to a state of impaired attention and implies inadequate arousal to perform a coherent thought or action.
6. *Delirium* usually refers to a state of confusion with periods of agitation and sometimes hypervigilance, active irritability, and hallucinations, typically alternating with periods during which the level of arousal is depressed.

## Pathophysiology

1. Excitatory inputs emanating from the midbrain and rostral pons ascend to the thalamus exciting thalamocortical neurons of the thalamic intralaminar and midline nuclei. The neurons project widely throughout the cerebral cortex and this reticular-activating system (RAS) supports arousal. The anatomic boundaries of the upper brainstem RAS are indistinct.
2. These ascending reticulothalamic neurons are cholinergic neurons arising from the mesopontine reticular formation.
3. Attention is thought to depend on the diffuse arousal system and cortical systems for directed attention in various spheres:
  - a. Posterior parietal lobes (sensory awareness).
  - b. The frontal association cortex (motor attention: directed movements of the eyes, limbs, and body).
  - c. Cingulate cortex (motivational aspects of attention).
  - d. Lesions that affect these areas multifocally spread down conceptual integration pathways causing global inattention or confusional states.
  - e. Acute confusional states.
    - i. Diffuse disease in the cerebral cortex.
    - ii. Focal lesions in various regions of the cortex.
    - iii. Thalamic cortical connections.
    - iv. Forebrain and subcortical structures .

## Diagnosis

# Clinical presentation

1. The goal of the examination of the unresponsive patient is to make the distinction of coma caused by destruction of brain tissue (e.g. as in cerebral hemorrhage) from metabolic coma secondary to disease extrinsic to the brain (e.g. uremic or hypoglycemic encephalopathy).
2. Neurophysiologic function is crucial in determining the level of brain involvement and disease progression.
3. The Glasgow Coma Scale (GCS; [Table 14.1](#)) is a standardized instrument designed for rapid assessment and communication about patients who have coma due to head trauma.

Table 14.1 *Glasgow Coma Scale*.

Points	Eye opening	Verbal	Motor
6	—	—	Obeys
5	—	Oriented	Localizes to pain
4	Spontaneous	Confused	Withdraws to pain
3	To speech	Inappropriate	Flexion (decorticate)
2	To pain	Unintelligible	Extensor (decerebrate)
1	None	None	None

- a. This scale attempts to quantitate the severity of trauma on the basis of the patient's best response in three areas: eye opening, motor activity, and language.
- b. The GCS scores range from 3 to 15. When the total score is 8 or

less, the patient is considered to be in coma.

## Components of the examination

1. Watching the patient yields considerable information. The predominant postures of the limbs and body; the presence or absence of spontaneous movements on one side; the position of the head and eyes; and the rate, depth, and rhythm of respirations provide substantial information.
  - a. Level of consciousness is then noted by the patient's reaction to:
    - i. Calling of his/her name.
    - ii. Simple commands.
    - iii. Noxious stimuli such as tickling the nares, supraorbital or sternal pressure, pinching the side of the neck or inner parts of the arms or thighs, or applying pressure to the knuckles.
  - b. Examination of the eyes is of great diagnostic importance.
    - i. Normal pupillary size, shape, and light reflexes indicate integrity of the midbrain structures and direct attention to a cause of coma other than a mass.
    - ii. Altered pupillary reactions with rostral midbrain lesions.
    - iii. With the presence of an overlying ipsilateral hemispherical mass lesion, a unilaterally enlarged pupil (5.5 mm) is an early indicator of stretching or compression of the third nerve.
    - iv. Loss of light reaction usually precedes enlargement of the pupil.
    - v. The pupil may become oval or pear-shaped and appear to be off-center (corectopia) because of a differential loss of innervation of a portion of the pupillary sphincter.
    - vi. As midbrain displacement continues, both pupils dilate and become unreactive to light as a result of the compression of the oculomotor nuclei in the rostral midbrain.
    - vii. In the last step in the evolution of brainstem compression, there tends to be a slight reduction in pupillary size on both sides to 5 mm or smaller.

- c. Pupillary reactions with pontine lesions.
  - i. Pontine lesions cause miotic pupils < 1 mm in diameter with barely perceptible reaction to strong light.
  - ii. The Horner's syndrome (miosis, ptosis and reduced facial sweating) may be observed ipsilateral to the lesions of the brainstem or hypothalamus or as a sign of dissection of the internal carotid artery.
- d. With coma caused by drug intoxications and intrinsic metabolic disorders, pupillary reactions are usually spared, with a few exceptions.
  - i. Serum concentrations of opiates that are high enough to cause coma have as a consistent sign pinpoint pupils, with constriction to light that may be so slight that it is detectable only with a magnifying glass.
  - ii. High-dose barbiturates may act similarly, but the pupillary diameter tends to be 1 mm or more.
  - iii. Systemic poisoning with atropine or with drugs that have atropinic qualities, *e.g.* tricyclic antidepressants, is characterized by wide dilatation and fixed pupils.
  - iv. Hippus or fluctuating pupillary size is occasionally characteristic of metabolic encephalopathy.

## 2. Movements of the eyes and eyelids and corneal response.

- a. In light coma of metabolic origin, the eyes rove conjugately from side to side in seemingly random fashion, sometimes resting briefly in an eccentric position.
- b. These movements disappear as coma deepens, and the eyes then remain motionless and slightly exotropic.
- c. Lateral and downward deviation of one eye suggests the presence of a third nerve palsy, and a medial deviation, a sixth nerve palsy.
- d. A persistent conjugate deviation of the eyes to one side – away from the side of the paralysis occurs with a large cerebral lesion (looking towards the lesion) and toward the side of the paralysis with a unilateral pontine lesion (looking away from the lesion).
- e. “Wrong-way” conjugate deviation may sometimes occur with

thalamic and upper brainstem lesions. During a focal seizure the eyes turn or jerk toward the convulsing side (opposite to the irritative focus). The globes turn down and inward (looking at the nose) with hematomas or ischemic lesions of the thalamus and upper midbrain.

- f. Retraction and convergence nystagmus and ocular bobbing occur with lesions in the tegmentum of the midbrain and pons, respectively.
- g. Ocular dipping (eyes move down slowly and return rapidly to the meridian) is observed with coma caused by anoxia and drug intoxications.
- h. Horizontal eye movements are preserved with ocular dipping but obliterated in cases of ocular bobbing as a result of destruction of pontine gaze centers.
- i. Coma producing structural lesions of the brainstem abolishes most if not all conjugate ocular movements, whereas metabolic disorders generally do not (except for instances of deep hepatic coma and anticonvulsant drug overdose).
- j. Oculocephalic reflexes (doll's eye movements) are elicited by brisk turning of the head. The response in coma of metabolic origin or that caused by bihemispheric structural lesions consists of conjugate movements of the eyes in the opposite direction.
- k. Elicitation of these ocular reflexes in a comatose patient provides two pieces of information:
  - i. Evidence of unimpeded function of the midbrain and pontine tegmental structures that integrate ocular movements and of the oculomotor nerves.
  - ii. Loss of the cortical inhibition that normally holds these movements in check.
- l. Asymmetry of the elicited eye movements remains a dependable sign of focal brainstem disease. In the instance of coma caused by a large mass in one cerebral hemisphere that secondarily compresses the upper brainstem, the oculocephalic reflexes are usually present, but the movement of the eye on the side of the mass may be impeded in adduction as a result of a compressive third nerve paresis.

- m. Irrigation of one ear with 10 ml of cold water causes slow conjugate deviation of the eyes toward the irrigated ear, followed in a few seconds by a compensatory nystagmus (fast component away from the stimulated side). This is the vestibuloocular, oculovestibular, or caloric test.
- n. The ears are irrigated separately, several minutes apart. In the comatose patient, the corrective phase of the nystagmus is lost and the eyes are tonically deflected to the side of irrigation with cold water. This position may be held for 2–3 minutes.
- o. Brainstem lesions disrupt these vestibuloocular reflexes; if one eye abducts and the other fails to abduct, one can conclude that the medial longitudinal fasciculus has been interrupted.
- p. Abducens palsy is indicated by an esotropic resting position and a lack of outward deviation of one eye with the reflex maneuvers. Complete absence of ocular movement in response to oculovestibular testing indicates a severe disruption of the brainstem tegmental system in the pons or midbrain.
- q. A reduction in the frequency and eventual loss of spontaneous blinking; then a loss of response to touching the eyelashes, and finally, a lack of response to corneal touch are signs of deepening coma. A marked asymmetry in corneal responses indicates either an acute lesion of the opposite hemisphere or less often an ipsilateral lesion in the brainstem.

### 3. Skeletal motor and reflex signs.

- a. Restless movements of both arms and both legs and grasping and picking movements signify that the corticospinal tracts are more or less intact. Oppositional resistance to passive movements (paratonic rigidity), complex avoidance movements, and discrete protective movements have the same meaning. Abduction movements (away from midline) have the same significance and differentiate a motor response from posturing. Patients who have hemispheric lesions typically lie in comfortable-appearing, relatively normal postures.
- b. Patients who have brainstem lesions often display abnormal postures. The symmetry of spontaneous movement may give a clue about the side of a focal lesion. Postures with some localizing significance are usually fragmentary and may be

- elicited by noxious stimuli.
- c. The terms *decorticate* and *decerebrate rigidity* refer to experimental studies of animals and do not accurately reflect the clinicopathologic correlations that they imply.
    - i. Decorticate posturing: lower extremity extensions and internal rotation with flexion of both upper extremities and is essentially bilateral spastic diplegia.
    - ii. Decerebrate posturing: lower and upper extremity extensions.
  - d. Upper extremity flexion reflects more superficial, less severe, and more chronic lesions at the level of the diencephalon or above. Upper and lower extremity extension will often accompany brainstem lesions; however, as mentioned, the upper extremity extension depends on the degree and acuteness of the lesion and, being reflexively driven, on the stimulus applied at the time of the examination. The responsible lesions may also be reversible, as in severe toxic and metabolic encephalopathies.
  - e. Deep tendon reflexes and plantar responses may also suggest a lateralized lesion, but they, too, are often misleading signs. Careful observation for subtle movements suggesting non-convulsive seizures should be sought in all cases of coma.

#### 4. Responses in respiratory pattern.

- a. Hyperventilation is common and has poor localizing value. Differential diagnosis includes:
  - i. Fever.
  - ii. Sepsis.
  - iii. Metabolic acidosis.
  - iv. Drug toxicity.
  - v. Cardiopulmonary disease.
- b. Cheyne–Stokes respiration refers to a periodic breathing pattern of alternating hyperpnea and apnea.
- c. Apneustic.
  - i. Characterized by a prolonged pause at the end of

inspiration and is also called “inspiratory cramp” (a pause of 2–3 seconds in full inspiration). This localizes to a lesion in the mid to caudal pons.

- d. Biot breathing (ataxia of breathing ).
  - i. Characterized by chaotic or ataxic breathing pattern with loss of regularity of alternating pace and depth of inspirations and expirations that may occur when the neurons in the respiratory center are damaged.
  - ii. This pattern progresses to one of intermittent prolonged inspiratory gasps that are recognized by all physicians as agonal in nature, and finally to apnea. In fact, respiratory arrest is the mode of death of most patients with serious central nervous system disease.
  - iii. A variety of lesions may cause this pattern .

## **Reasons for decreased level of consciousness with structural lesions**

- 1. Structural coma can result from primary cerebral hemispheric or primary brainstem involvement.
  - a. Purely unilateral cerebral lesions do not produce coma.
  - b. Loss of consciousness from unilateral cerebral lesions indicates pressure or displacement of the opposite hemisphere or brainstem as the mass effect shifts across the midline.
  - c. Persisting loss of consciousness from cerebral hemispheric disease indicates bilateral cerebral hemispheric damage.
- 2. As the mass effect builds, it causes coning through the tentorial notch and this herniation distorts the brainstem, interrupting activity ascending to the cerebral hemisphere from the reticular activating system of the rostral midbrain–thalamic area.
  - a. Secondary destruction occurs in the brainstem tegmentum. In contrast to primary brainstem hemorrhage, which is usually in the base of the pons, this damage occurs in the tegmentum.
  - b. The secondary changes lead to permanent coma and brainstem

tegmental signs involving eye movements and the pupils. The supratentorial pressure may compress the posterior cerebral arteries against the incisura of the tentorium, causing infarction of the occipital lobes. Patients may survive this compressive effect to be left with visual-field defects or blindness from damage to the striate cortex or geniculate bodies.

- c. The mass itself may be remote from the visual pathways.

## ***Locked-in syndrome***

- 1. Lesion is located in the pons.
- 2. Patient remains awake but unable to talk or move the arms or legs. The patient is “de-afferented” but remains conscious.
  - a. The only way the patient can express his or her alertness is by communication through intact voluntary eyelid and vertical eye movements.
  - b. Midbrain involvement can cause the locked-in syndrome accompanied by bilateral ptosis and third nerve palsies. The only clue that the patient is conscious is some remnant of movement such as the orbicularis oculi in response to command.
  - c. These patients require meticulous nursing and psychological care.
  - d. Survival may be prolonged and recovery is possible in patients depending on the lesion type and extent of damage .

## ***Vegetative state***

- 1. Coma seldom lasts more than 2–4 weeks and patients may improve from coma to vegetative state. This state has many eponyms – vegetative state, coma vigil, apallic syndrome, and akinetic mutism . These patients will exhibit what superficially appears to be wakefulness or preserved consciousness. Patients may open their eyes in response to painful stimuli or spontaneously and may blink to threat. Caloric and rotational nystagmus quick phases are regained if the brainstem is intact. Intermittently, the eyes may move from side to side seemingly following objects, or fixate momentarily on the physician or a family member and giving the erroneous impression of recognition.

Respirations may quicken in response to stimulation and certain automatisms such as swallowing, bruxism, grimacing, grunting, or moaning may be observed. However, the patient remains totally inattentive, does not speak, and shows no signs of awareness of the environment or inner need; responsiveness is limited to primitive postural reflex movements of the limbs. There is loss of sphincter control. There may be arousal or wakefulness in alternation cycles as reflected in partial eye opening, but the patient regains neither awareness nor purposeful behavior of any kind.

## ***Psychogenic unresponsiveness***

The eyes are particularly important in distinguishing psychogenic unresponsiveness and catatonia from coma and the vegetative state.

1. If the patient lies with the eyes closed, lifting the eyelids results in a slow closure in genuine coma but rapid closure of the eyes is non-physiologic.
2. Roving eye movements are a type of smooth eye movement and smooth eye movements cannot be produced voluntarily.
3. The patient with psychogenic unresponsiveness never has roving eye movements.
4. Caloric testing elicits nystagmus in psychogenic coma but not in coma. Fast eye movements are abolished in genuine coma. Occasional patients who feign unresponsiveness can inhibit caloric-induced nystagmus by concentrated visual fixation. However, they do not exhibit deviation of the eyes without nystagmus fast phases, as does the comatose patient. Similarly, in psychogenic coma during oculocephalic maneuvers visual fixation enhances the vestibuloocular reflex (VOR) so that the eyes move in the orbit, stabilizing the gaze in one spot. In comatose patients, the VOR may be hypoactive or lost with deep metabolic coma or with structural lesions in the pontine tegmentum.
5. Patients with psychogenic unresponsiveness often look away from the examiner, toward the mattress.

## **Case vignette**

A 50-year-old male with a history of hepatic cirrhosis related to hepatitis C and alcoholism was admitted to the hospital because of a progressive decline in

mental status and ultimately a complete state of unresponsiveness. A similar presentation had occurred 3 months earlier during which time he experienced successful reversal of altered mentation with the use of lactulose. On current presentation to the hospital, the patient exhibited fluctuating confusion and disorientation. Examination revealed no obvious focal or lateralizing abnormalities and there was no asterixis. Repeat attempts to treat hepatic encephalopathy with traditional methods, including lactulose administration, were instituted. Over the next 6 hours, the patient's mental state declined to a completely unresponsive state. An electroencephalogram (EEG) was applied, revealing a repetitive left hemispheric electrographic seizure pattern, typically lasting 1–3 minutes at a time, with the pattern repeating every approximately 20 seconds. Careful re-examination revealed very subtle nystagmoid eye movements that coincided with the time of the electrographic seizure patterns. The patient was treated emergently with intravenous levetiracetam and within 15 minutes, electrographic seizures attenuated followed by gradual and ultimate return to baseline mental status.

This case exemplifies the need to avoid assuming the most obvious reason for altered mentation and instead to cast a wide net for differential diagnosis possibilities. In cases of enduring seizure activity of complex partial or generalized absence type (neither with obvious convulsive activity), the term non-convulsive status epilepticus (NCSE) is used. Non-convulsive status epilepticus is particularly vexing to clinicians because it is so easily missed and yet can cause ongoing neuronal injury as well as persistent depressed mentation. Subtle signs such as mild clonic activity in limbs or nystagmoid movements of the eyes can occur, but are often not picked up.

Careful examination of the comatose patient ([Table 14.2](#)), and utilization of the broad list of etiologies highlighted in [Table 14.3](#), can help the clinician home in on leading causes and urgently issue appropriate testing and treatments ([Tables 14.2, 14.4, and 14.5](#)).

**Table 14.2 Approach to the assessment and management of acute coma evaluation.**

---

- Stabilization
- Airway control
- Oxygenation and ventilation
- Adequate circulation (includes avoidance of hypotension in strokes)

#### CERVICAL STABILIZATION

Immediate therapies given to all patients  
Thiamine 100 mg IV  
Dextrose 50% 50 mL IV (may be held if immediate fingerstick glucose establishes adequate serum glucose)  
Naloxone 0.4–2 mg IV (may be repeated)  
Obtain blood for CBC, PT/PTT, chemistry panel, toxic screen, blood cultures, anticonvulsant levels

Threatening conditions to be considered for possible early therapy  
Elevated ICP → head CT  
Meningitis, encephalitis or both → antibiotics, LP, blood cultures  
Myocardial infarction → ECG  
Hypertensive encephalopathy → early therapy  
Status epilepticus → EEG  
Acute stroke → consider thrombolytic therapy

---

CBC, complete blood count; CT, computed tomography; ECG, electrocardiogram; EEG, electroencephalogram; ICP, intracranial pressure; IV, intravenous; LP, lumbar puncture; PT, prothrombin time; PTT, partial thromboplastin time.

From Feske SK, Wen PY, Eds. *Neurologic Clinics: Neurologic Emergencies*, May 1998;16(2). Philadelphia, PA: London, with permission.

**Table 14.3 Selective causes of coma.**

General group	Specific disorder	Important clinical findings	Important laboratory findings
Coma with focal or lateralizing signs	Cerebral hemorrhage	Hemiplegia, hypertension, cyclic breathing, specific ocular signs	CT scan +

Basilar artery occlusion (thrombotic or embolic)	Extensor posturing and bilateral Babinski signs; early loss of oculocephalic responses; ocular bobbing	Normal early CT; MRI shows cerebellar and brainstem or thalamic infarction; normal CSF
Massive infarction and edema in carotid territory	Hemiplegia, unilateral unresponsive or enlarged pupil	CT and MRI show massive edema of hemisphere
Subdural hematoma	Slow or cyclic respiration, rising blood pressure, hemiparesis, unilateral enlarged pupil	CT scan; CSF xanthochromic with relatively low protein
Trauma	Signs of cranial and facial injury	CT and MRI show brain contusions and other injuries
Brain abscess	Neurologic signs depending on location	CT scan and MRI +
Hypertensive encephalopathy; eclampsia	Blood pressure > 210/110 mmHg (lower in eclampsia and in children).	CT ±; CSF pressure elevated

		-----, headache, seizures, hypertensive retinal changes	
	Thrombotic thrombocytopenic purpura (TTP)	Petechiae, seizures, shifting focal signs	Multiple small cortical infarctions; thrombocytopenia
Coma <i>without</i> focal or lateralizing signs, <i>with</i> signs of meningeal irritation	Meningitis and encephalitis	Stiff neck, Kernig sign, fever, headache	CT scan ±; pleocytosis, increased protein, low glucose in CSF
	Subarachnoid hemorrhage	Stertorous breathing, hypertension, stiff neck, Kernig sign	CT scan may show blood and aneurysm; bloody or xanthochromic CSF under increased pressure
Coma <i>without</i> focal neurologic signs or meningeal irritation; CT scan and CSF normal	Alcohol intoxication	Hypothermia, hypotension, flushed skin, alcohol breath	Elevated blood alcohol
	Sedative intoxication	Hypothermia, hypotension	Drug in urine and blood; EEG often

shows fast activity

Opioid intoxication	Slow respiration, cyanosis, constricted pupils	
Carbon monoxide intoxication	Cherry-red skin	Carboxyhemoglobin
Global ischemia–anoxia	Rigidity, decerebrate posture, fever, seizures, myoclonus	CSF normal; EEG may be isoelectric or show high-voltage delta
Hypoglycemia	Same as in anoxia	Low blood and CSF glucose
Diabetic coma	Signs of extracellular fluid deficit, hyperventilation with Kussmaul respiration, “fruity” breath	Glycosuria, hyperglycemia, acidosis; reduced serum bicarbonate; ketonemia and ketonuria, or hyperosmolarity
Uremia	Hypertension; sallow, dry skin	Protein and casts in urine; elevated blood urea nitrogen

	skin, uriniferous breath, twitch – convulsive syndrome	blood urea nitrogen and serum creatinine; anemia, acidosis, hypocalcemia
Hepatic coma	Jaundice, ascites, and other signs of portal hypertension; asterixis	Elevated blood NH <sub>3</sub> levels; CSF yellow (bilirubin) with normal or slightly elevated protein
Hypercapnia	Papilledema, diffuse myoclonus, asterixis	Increased CSF pressure; PCO <sub>2</sub> may exceed 75 mmHg; EEG theta and delta activity
Severe infections (septic shock); heat stroke	Extreme hyperthermia, rapid respiration	Vary according to cause
Seizures	Episodic disturbance of behavior or convulsive movements	Characteristic EEG changes

---

CSF, cerebrospinal fluid; CT, computed tomography; EEG, electroencephalogram; MRI, magnetic resonance imaging.

Reprinted with permission from Ropper AH, Samuels MA. Coma and related disorders of

consciousness. Clinical approach to the comatose patient. In *Adams and Victor's Principles of Neurology*, 9th edn. New York, NY: McGraw Hill Publishers, 2009: 301–21.

**Table 14.4 Horizontal displacement of midline structures on computed tomography scans and level of consciousness.**

Level of consciousness	True dimensions from midline (mm)	
	Pineal	Septum pellucidum
Awake	0–3	2–7
Drowsy	3–6	2–10
Stupor	6–9	7–14
Coma	9–15	12–18

From Ropper AH. Lateral displacement of the brain and level of consciousness in patients with an acute hemispherical mass. *N Engl J Med* 1986;314:953–8, with permission.

**Table 14.5 Summary of pathophysiologic disorders of consciousness and syndromes.**

Syndrome	Behavioral description	Pathophysiology
Coma	Eyes closed, no movement or reflex movement only	Global dysfunction of the corticothalamic pathways from the diffuse cellular dysfunction, disconnection, or loss of upper brainstem arousal tone. If the entire brain or brainstem is permanently non-functional, then the diagnosis is brain death rather than coma

Vegetative state	Patient may have alternating eye opening or closing, may exhibit a sleep-wake cycle and possible to have reflex movements	Same as coma, except that it implies some functioning of the upper brainstem
Locked-in state	Complete or almost complete loss of motor output resulting in the appearance of a disorder of consciousness	The loss of corticospinal tract in the ventral pons

## Further reading list

Buettner U, Zee DS. Vestibular testing in comatose patients. *Arch Neurol* 1989; 46:561–3.

Coplin WM. Intracranial pressure and surgical decompression for traumatic brain injury: biological rationale and protocol for a randomized clinical trial. *Neurol Res* 2001; 23:277–90.

Fehlings MG, Tator CH. An evidence-based review of decompressive surgery in acute spinal cord injury: rationale, indications, and timing based on experimental and clinical studies. *J Neurosurg* 1999; 91:1–18.

Fisher C. The neurological examination of the comatose patient. *Acta Neurologica* 1969; 25 (suppl 36):1–56.

Geisler FH, Dorsey FC, Coleman WP. Recovery of motor function after spinal-cord injury: a randomized placebo controlled trial with GM-1 ganglioside. *N Engl J Med* 1991; 324:1829–38.

Hadley MN. Injuries to the cervical spine. In Rengachary SS, Wilkins RH, Eds. *Principles of Neurosurgery*. London: Mosby Wolfe, 1994: 20.2–20.13.

Hanna JP, Frank JI. Automatic stepping in the pontomedullary stage of central herniation. *Neurology* 1995; 45:985–6.

Keane J. Blindness following tentorial herniation. *Ann Neurol* 1980; 8:186–90.

Lannoo E, Van Rietvelde F, Colardyn F *et al.* Early predictors of mortality and morbidity after severe closed head injury. *J Neurotrauma* 2000; 17:403–14.

Levy D, Plum F. Outcome prediction in comatose patients: significance of reflex eye movement analysis. *J Neurol Neurosurg Psychiatry* 1988; 51:318.

Lubillo S, Bolanos J, Carreira L *et al.* Prognostic value of early computerized tomography scanning following craniotomy for traumatic hematoma. *J Neurosurg* 1999; 91:581–7.

Mollaret P, Goulon M. Le coma dépassé (mémoire préliminaire). *Rev Neurol (Paris)* 1959; 101:3–5.

Pessin M, Adelman LS, Prager RJ *et al.* “Wrong-way eyes” in supratentorial hemorrhage. *Ann Neurol* 1981; 9:79–81.

Petty GW, Mohr JP, Pedley TA *et al.* The role of transcranial Doppler in confirming brain death: sensitivity, specificity, and suggestions for performance and interpretation. *Neurology* 1990; 40:300–3.

Prat R, Calatayud-Maldonado V. Prognostic factors in posttraumatic severe diffuse brain injury. *Acta Neurochir (Wien)* 1998; 140:1257–60.

President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research. *Defining Death: a Report on the Medical, Legal and Ethical Issues in the Determination of Death*. Washington, DC: Government Printing Office, 1981.

Qureshi AI, Geocadin RG, Suarez JI *et al.* Long-term outcome after medical reversal of transtentorial herniation in patients with supratentorial mass lesions. *Crit Care Med* 2000; 28:1556–64.

Ropper AH. Unusual spontaneous movements in brain-dead patients. *Neurology* 1984; 34:1089–1092.

Ropper AH, Samuels MA. Coma and related disorders of consciousness.

Clinical approach to the comatose patient. In *Adams and Victor's Principles of Neurology*, 9th edn. New York, NY: McGraw Hill, 2009:301–21.

The Brain Trauma Foundation. The American Association of Neurological Surgeons. The Joint Section on Neurotrauma and Critical Care. Guidelines for the management of severe head injury. *J Neurotrauma* 2000; 17:507–11.

The Quality Standards Subcommittee of the American Academy of Neurology. Practice parameters for determining brain death in adults (summary statement). *Neurology* 1995; 45:1012–14.

Thurman DJ, Alverson C, Dunn KA *et al.* Traumatic brain injury in the United States: a public health perspective. *J Head Trauma Rehabil* 1999; 14:602–15.

Walsh JC, Zhuang J, Shackford SR. A comparison of hypertonic to isotonic fluid in the resuscitation of brain injury and hemorrhagic shock. *J Surg Res* 1991; 50:284–94.

## 15 Dementia

---

Howard Crystal and Diana Rojas-Soto *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Dementia is defined as the development of cognitive deficits such that a patient is unable to perform his or her usual activities and the cognitive impairment is not due to an acute confusional state. Persons with life-long cognitive impairment do not meet this definition because they never were able to function at a higher level. Some, but not all, definitions of dementia require memory impairment as part of the syndrome. Because Alzheimer's disease (AD) is the most prevalent cause of dementia in the industrialized world, the notion of "gradual progression" is sometimes considered part of the definition, but clearly dementia can be sudden in onset. For example, a patient who suffers a traumatic brain contusion will at first be obtunded or in coma, but after awakening and when alert, might meet criteria for dementia.

With the increase in life expectancy over the past half century has come a huge increase in the numbers of patients with dementia. This is because in industrialized nations, greater than 90% of cases of dementia are due to AD, vascular disease, dementia with Lewy bodies/Parkinson's disease (DLB/PD), or some combination of all three, and the prevalence of these three disorders is strongly age-associated. Thus in the USA, the prevalence of all cases of dementia increases from less than 1% among those in their 60s to around 40% among patients over 90 years of age.

Often the cause of dementia is obvious – *e.g.* as an aftermath of hypoxia or head trauma. Nonetheless, scores of diseases, toxins, or deficiencies can cause dementia ([Table 15.1](#)), and many of these are fully reversible. Accordingly, each patient presenting with dementia deserves a thorough evaluation to rule out reversible etiologies. Although, in 2012, treatment options for most patients with dementia who have some combination of AD, vascular dementia, DLB/PD, or

frontotemporal dementia remained disappointing, there is good reason to be optimistic than disease-modifying or even disease-preventing treatments will become available over the next few years.

## Clinical vignette

An 81-year-old male was referred by his primary care doctor to a neurologist for visual hallucinations. His wife said that he reported seeing children without faces sitting down at the dining room table with him. The hallucinations occurred around the time the patient was eating dinner. When his wife said she didn't see them, he just got angry. The hallucinations started several months ago, each lasted several minutes, and occurred several times a week. No other alteration in consciousness was associated with these episodes.

He had been an attorney who retired 6 years earlier. He had a history of hypertension, hyper-cholesterolemia, paroxysmal atrial fibrillation, gastroesophageal reflux disease, and benign prostatic hypertrophy. His medications included aspirin, tamsulosin, irbesartan, dronaderone, pantoprazole, and rosuvastatin. He had never smoked and stopped drinking alcohol because it exacerbated his atrial fibrillation.

His wife said that at times he was as sharp as always, but at other times he was confused and out of it. He started taking a 2-hour nap every day. He had about a 20-year history of anosmia with no etiology found by an ENT.

His wife said that he occasionally lost his balance and she was afraid he would fall. His gait had slowed. The patient and his wife agreed that his memory was about as good as that of others his age.

He spent most of his day looking at TV. Occasionally he thought the people on TV were talking directly to him. He enjoyed going to Atlantic City and he reported playing poker as well as always.

**Table 15.1 *Etiologies and clinical features of dementia.***

Item	Subdivision	Specific entity	Possible clinical features
Structural	Hydrocephalus	Normal pressure hydrocephalus	Clinical triad of gait impairment, urinary

(NPH)

incontinence, and cognitive impairment

This clinical triad along with ventriculomegaly is found in virtually all patients with severe dementia and many patients with moderate dementia. When a radiologist reports "ventriculomegaly out of proportion to cortical atrophy" in such patients, NPH is raised as a possible diagnosis. Most of these patients will not improve with ventriculo-peritoneal (VP) shunting [1]. What is essential is identifying patient who might be good candidates for VP shunts. Features predictive of a sustained response to shunting include: known reason for hydrocephalus (e.g. history of meningitis or subarachnoid hemorrhage) gait impairment as the presenting symptom.

		duration less than 6 months, clinical improvement after lumbar puncture, a increased signal in periventricular region on FLAIR [
Pressure effects	Increased pressure	Cognitive impairment and cognitive slowing may be associated with increased intracranial pressure. Some patients with pseudotumor cerebri may have cognitive impairment
	Decreased pressure	In the “frontotemporal brain sagging syndrome” [3], symptoms and signs mimic behavioral variant frontotemporal dementia. MRI shows downwardly displaced brainstem herniation of the cerebellar tonsils, and midbrain swelling. CSF leak is the presumed etiology
Psychiatric	Schizophrenia	Heterogeneity in level and pattern of

cognitive deficits  
80% manifest cognitive impairment  
No single pathognomonic cognitive deficits Cognitive deficits include impairment in immediate recall on tests of auditory learning, attention, working memory, executive function and slow processing speed

#### Bipolar disease

Cognitive deficits worse during mania or depressed episodes but persist during euthymic periods. Patients with later age of onset have better overall functioning

#### Malingering

Often sudden in onset, and often secondary gain is fairly obvious. Inconsistency between apparent poor cognitive functioning when evaluated by physician or neuropsychologist and activities of

daily living. Pattern of neuropsychological strengths and weaknesses are not consistent with pattern due to “organic” illness. Some neuropsychological batteries are able to reveal patterns consistent with malingering

### “Pseudodementia”

The term “pseudodementia” used to refer to two different syndromes (a) a “conversion disorder”-like syndrome (see below), and (b) a syndrome in patients, usually at 50 and older, who present with depression (among patients without a previous history of depression) and cognitive impairment. Treatment of depression sometimes leads to marked improvement in cognitive symptoms.

However, over months to years, many go on to develop Alzheimer disease (AD). Presumably in these patients, depression is the initial manifestation of their AD

#### Conversion disorders

Relatively sudden onset of cognitive impairment, usually in patients with previous psychiatric history of depression/anxiety. Cognitive symptoms outweigh psychiatric symptoms. A history of childhood physical, sexual, or psychiatric abuse is found in up to 50% of patients with conversion disorders. It is diagnosed about 10 times as often among women than men. Long-term prognosis is guarded.

Toxic

Medication side effect

Anticholinergics

Whereas children and young adults can tolerate large doses of anticholinergics, older adults may be more sensitive and

very sensitive area  
show confusion and  
impaired memory

that persist for days  
after the medication  
is stopped. Many  
drugs have  
anticholinergic  
effects including  
oxybutynin [4],  
meclizine, tricyclics,  
some antipsychotics,  
and some anti-  
parkinsonian  
medication [5]

#### Benzodiazepines (BZD)

Their use is  
associated with  
daytime somnolence,  
confusion and  
increased risk for  
falls in the elderly.  
Impairment in  
semantic, working  
and recognition  
memory documented  
repeatedly in  
neuropsychological  
tests in normal  
subjects. These  
effects may persist  
with prolonged BZ  
use [6]

#### Other psychiatric drugs

If a drug acts on the  
brain, it may affect  
cognition. If a drug  
is designed to treat  
a brain problem, it is

more likely to be possibly associated with cognitive impairment

### Digoxin

Recognized by clinicians for decades that digoxin at toxic levels can induce disorientation, confusion, aphasia, delirium, and hallucinations [7]. Even patients with normal digoxin levels may have cognitive impairment [8]

### Statins

Although the lay press is full of reports that statins are associated with cognitive impairment, clinic studies have had mixed results; some studies claim that statins might have an important role in prevention and treatment of Alzheimer's disease while other studies have found no such benefit [8]

### Cancer

Some patients

-----  
chemotherapy

-----  
treated with system chemotherapy for

cancer unrelated to the CNS (e.g. breast cancer) probably develop cognitive impairment. When patients receive chemotherapy (including intrathecal chemotherapy) for CNS tumors, it is not clear which deleterious effects are from the tumor and which are from the chemotherapy and radiation. It is difficult to [9]

Radiation therapy

Brain dysfunction from therapeutic radiation – usually manifesting 1–10 years after the radiation – is becoming increasingly common. Patient's age at the time of radiation may be the most important factor. Cognitive impairment is reported in up to 50% of brain tumor

survivors after 6 months post-irradiation with marked decreases in verbal memory, spatial memory, attention, and novel problem-solving ability [10]

### Alcohol

Whether chronic high level of ethyl alcohol ingestion is neurotoxic remains controversial. Cognitive impairment is certainly more common in alcoholics than in moderate or alcohol abstinent control group, but poor nutrition, head trauma, and in some patients, repeated seizures are comorbid. Conversely, some studies suggest that older patients with modest alcohol intake have higher cognitive test scores than teetotalers [11]

### Cocaine

Chronic cocaine users may have deficits in executive

function. Former users may show no deficits on cognitive tests

#### Marijuana

Chronic ongoing marijuana use may be associated with impaired memory and lower IQ scores. Former users may show no deficits on cognitive test scores.

#### Heavy metals (Pb, As, Al, Sn, Fe, Mn)

Association with cognitive impairment strong for some metals than others. Consider urine collection if industrial exposure or use of well water for cooking and drinking [12]

#### CO

Unsuspected low levels of CO may be found in older homes with faulty heating systems. Symptoms may include headache, difficulty concentrating, and change in personality [13]

#### Epilepsy

The first considerations in evaluation of such patients are to look

patients are too poor for poorly controlled seizures or

medication side effects [14].

Nonetheless, several investigators believe that gradual progressive cognitive decline may occur in some patients with seizure disorders. Worse cognitive prognosis is associated with early age of onset, long duration of the disease, and poor seizure control. For some patients, cognitive dysfunction may be present at the time of diagnosis [14–17]

Seizure-type related

Complex partial seizures

A progressive amnestic disorder may occur in patients who have had focal, usually temporal lobe seizures, over decades [18]

Sleep

Lack of sleep

Behavioral symptoms are similar to those occurring with depression or

anxiety and include low mood, irritability, low energy, decreased libido, and poor judgment. Total sleep deprivation is associated with impairment in tasks that require sustained attention. Deficits in attention are often associated with memory and decision-making problems [19]. Whether cognition is affected in a global manner through decreased alertness and attention or sleep deprivation impairs specific aspects of cognition is a point of debate. Some authors suggest that sleep deprivation may particularly affect cognitive systems that rely on emotional data [19].

Infectious

Bacterial

Syphilis

Usually presents 1-25 years after infection but can present earlier depending on patient's immune

state [20].

Psychiatric and neurologic symptoms include forgetfulness, personality change, memory impairment, poor judgment, depression, mania, psychosis, dysarthria, facial and limb hypotonia, tremor and reflex abnormalities.

In countries with the ready availability of antibiotics to treat primary and secondary syphilis neurosyphilis and “general paresis of the insane” are extremely rare. Far more common are patients who have mildly positive VDRL or RPR (usually 1 : 2 or 1 : 4) either as a false positive or among patients who had been treated for primary syphilis or secondary syphilis decades earlier.

Those with false positives will have negative FTA-AB or other specific

anti-treponemal antibody test. Those previously treated usually have positive FTA-ABS, and an LP needs to be performed to rule out neurosyphilis. In such cases, CSF will be diagnostic with lymphocytosis, increased protein and a reactive VD]

#### Lyme

A post-Lyme syndrome of unknown pathogenesis has been described in patients who received proper antibiotic treatment. Symptoms such as fatigue, widespread musculoskeletal pain, memory complaints, and concentration difficulties may be present from months to years post-infection [21,22]

#### retrovirus

#### HIV

Criteria were revised in 2007 and describe three levels of impairment: asymptomatic neurocognitive

impairment, minor neurocognitive disorder, and HIV-associated dementia (HAD) .

Some investigators believe that

asymptomatic neurocognitive impairment define by impaired scores on

neuropsychological testing is more common in person with HIV than in control groups with some estimates as high as 35%. Others believe that relatively healthy persons with HIV have normal cognition.

Before highly active anti-retroviral therapy (HAART) about one third of patients with AIDS developed HAD usually followed by death within a year. With HAART, the incidence of HAD has decreased substantially.

HAART may reverse cognitive impairment in

patients with HAD whether healthy patients with CD4 levels > 350 should be treated to prevent neurocognitive impairment is controversial [23]

Fungal	Cryptococcus	<p>Presentation of symptoms can range from acute illness evolving over days to chronic illness with several months between first symptoms and diagnosis. Subacute meningoencephalitis is the most common presentation. Typically headache, lethargy, personality changes, and memory loss progress over 2–4 weeks. Fever is present in about 50% of patients. CSF examination may show markedly increased opening pressure, lymphocytosis, low glucose, and high protein. Note, however, that lymphocytosis may not be present in</p>
--------	--------------	---

patients with HIV  
India ink is positive  
in only 50–75% of  
cases.

Definitive diagnosis  
with CSF culture is  
positive in about  
90% of cases

Viral	Sequelae of herpes simplex encephalitis infection	Because herpes simplex encephalitis often affects the inferior sides of the temporal and front lobes, cognitive impairment frequently is a lasting sequela
Prion-associated	Classical CJD	Sporadic, no history of “sick contact” or exposure Median age at death 68 years Early constitutional symptoms – vertigo, fatigue, sleep disorders, headache Early presentation neurologic abnormalities – cognitive dysfunction, aphasia, apraxia, neglect, extrapyramidal symptoms, ataxia, myoclonus, visual disturbances, seizures later in

course  
Early in the course  
EEG may only show

focal slowing.  
“Typical” 1 Hz  
epileptiform  
discharges appear  
as the disease  
progresses, but are  
found in only two  
thirds of patients.  
MRI with abnormal  
hyperintensity on  
FLAIR/DWI in  
cortical gyri  
(ribboning), cauda  
putamen, and/or  
thalamus.

Sensitivity and  
specificity > 90th  
percentile.  
DWI/ADC abnormal  
signal not usually  
seen in other cause  
of rapidly  
progressive dementia  
*i.e.* auto-immune

#### Variant CJD

History of exposure  
within a country  
where the cattle  
disease bovine  
spongiform  
encephalopathy  
(BSE) was occurring.  
Predominantly  
affects younger  
people (~ 28).  
Features different

from classic,  
sporadic CJD

include longer duration of illness (13–14 months), prominent psychiatric or sensory symptoms at the time of clinical presentation, and delayed onset of neurologic abnormalities. Dementia and myoclonus may occur late in the illness  
Pulvinar sign and dorsomedial thalamus hyperintensity in MRI  
Diffusely abnormal non-diagnostic EEG

## Trauma

Chronic subdural hematoma

Presenting symptoms include cognitive decline, confusion, and psychomotor retardation [24,25]  
A history of head trauma is not always present. Headache reported in 40–80% of patients; when

reported they are described as persistent and troublesome

#### Post concussion

Data remain incomplete about the prevalence, severity and natural history of post-concussive cognitive impairment.

Although defined in part by the lack of pathology on brain imaging at the time of or post trauma, pathology may be revealed in some patients by more sensitive imaging technologies such as diffusion tensor imaging with 3T MRIs.

Neuropsychologic features include problems with concentration including impairment in working memory and other functions heavily dependent on intact frontal lobe function

#### Contusion

Anterior frontal and anterior temporal

lobes are the most frequent sites of coup and contre-coup injuries. Some patients recover completely, others are left with permanent neuropsychological impairments

## Neoplastic

### Paraneoplastic

Antibodies associated with small cell lung carcinoma, teratoma (especially ovarian thymomas, adenocarcinomas of the breast and prostate among others) may be associated with dementing syndromes. Some have relatively rapid progression over weeks and may precede other clinical manifestations of the tumor by years. Many have other associated neurologic symptoms and signs. These disorders should be especially

considered in your and middle-aged patients with subacute presentations. Athena Diagnostic has an on-line catalog where appropriate tests can be identified. When the syndrome is particularly suggestive of malignancy, abdominal or lung CT scanning may be appropriate.

Multiple brain metastases	Cognitive impairment and dementia frequently occur when multiple brain regions are affected	
Carcinomatous meningitis	Confusion and cognitive impairment are presenting signs at symptoms in 10–20% of patients with carcinomatous meningitis	
Benign tumors	Meningiomas	“Incidental” meningiomas found on brain imaging occur in 1.6% of brain MRIs and increase with aging.

~~increase with aging~~

Meningiomas that compromise function of critical brain regions may be associated with dementia, but such "significant" meningiomas are quite rare. The vast majority of the time it is judged that the meningioma is not related to the dementia, and should be watched clinically and with follow-up brain imaging.

Inflammatory/  
auto-immune

Sarcoidosis

CNS involvement occurs in 5–10% of systemic cases; isolated CNS involvement is even rarer.

Suspect if multiple neurologic deficits present at once. Cranial nerve palsies is the most frequent presenting symptom in about 50% of cases followed by headache and seizures. Diagnosis is challenging in cases without systemic involvement [26]. On MRI multiple

periventricular T2 hyperintense lesions

are frequently noted. Contrast enhancement of the pituitary infundibulum and hypothalamus, cranial nerves, leptomeninges, or large intraparenchymal lesions may be found.

Hydrocephalus may result from dysfunction of the arachnoid granulations [26,27]. Steroid response is variable. Elevated CSF angiotensin-converting enzyme (ACE) is not specific for neurosarcoidosis and is found in a variety of disorders.

#### SLE

Cognitive disorder can be seen in up to 80% of patients although development of severe cognitive impairment is reported in less than 10%. Memory and attentional deficits

are more severe than language or visuoconstructional disorders. Patients can have significant psychiatric manifestations, including major depression, anxiety, manic episodes, and psychosis. Other neurologic manifestations include peripheral neuropathy, stroke, chorea, and seizures.

#### Other auto-immune

#### Sjögren's syndrome

Associated with small-vessel arteritis which can evolve to acute meningoencephalitis. Patients with meningoencephalitis may develop dementia that is rapidly reversed with steroid therapy.

#### Cerebral vasculitis

Onset of cognitive deficits is relatively acute and associated with confusion, seizures, and cranial nerve palsies. Blood tests show increased erythrocyte sedimentation rate and C-reactive protein.

CSF has elevated protein and pleocytosis. Focal cortical and subcortical infarcts are seen on MRI. Cerebral angiography may show beading or irregular large arteries; small-vessel arteritis may not be visible on angiography. Definitive diagnosis may require a brain biopsy.

Degenerative	Without movement disorder	Alzheimer's disease (AD)	The classic syndrome is slowly progressive impairment in anterograde memory. Although patients with AD have more hippocampal atrophy on MRI scans than controls, and increasing hippocampal atrophy over a 1- or 2-year interval is a specific marker of AD pathology, as a clinical tool MRI is usually most useful for assessing the extent of white matter pathology.
--------------	---------------------------	--------------------------	--

tau pathology & previous infarcts. The combination of increased tau (or phosphorylated tau) and decreased amyloid in CSF is sensitive and specific marker of AD. PET-scans with amyloid-binding agents are sensitive markers of AD pathology, but not specific.

Many patients with clinical syndrome consistent with AI will have infarcts demonstrable on MRI scan.

Even more prevalent is increased signal on FLAIR in the periventricular and deep white matter. Autopsy studies show that mixed dementias with elements of AD, DLB, and vascular disease are the most common type of dementia in persons over age 80 at time of death.

Neuropsychologic testing is helpful in quantifying impairment in

**Impairment in various cognitive domains**

**Dementia with Lewy bodies (DLB)**

Clinical features are gradually progressive dementia with visual hallucinations (often of persons or animals and present in at least 60% of cases), fluctuations in cognition and level of alertness present in 60 to 80% and parkinsonism not sufficient to meet criteria for PD. Many patients with DLB will report increased sleepiness during the day despite having their usual sleep at night. REM behavior disorder occurs in up to 85% of patients. Patients will have especially vivid dreams that are acted out because muscular atonia does not occur during REM sleep. Other supportive features are neuroleptic sensitivity and low dopamine uptake in basal ganglia on

SPECT/PET. Common features with less specificity include repeated falls, syncope or altered consciousness, autonomic dysfunction, auditory or somatosensory hallucinations, delusions, and depression

#### Frontotemporal

Age of onset is usually in the late 50s or early 60s, but may extend through the 80s. Two major clinical presentations: behavioral variant (bvFTD) and progressive aphasia. In bvFTD initial manifestations are changes in personality and social behavior. Loss of inhibition occurs and patients may be socially inappropriate. Three phenotypes of progressive aphasia are recognized: (1) non-fluent, agrammatic, (2)

logopenic, and (3) semantic dementia. The first and third phenotype usually have pathology consistent with FT. The logopenic phenotype often has Alzheimer's disease pathology.

The gross pathologic manifestations of FTD are usually frontal and/or temporal atrophy.

Pathologic classifications refer to these disorders as frontotemporal lobar degeneration (FTLD). Cellular proteinaceous inclusions from tau, TDP-43, or fused in sarcoma protein are found in most cases of FTLD. These inclusions also occur in progressive non-fluent aphasia, some cases of motor neuron disease, and corticobasal degeneration. For this reason, these three diseases are often discussed together with the more traditional

## FTDs

### Comment about diagnosis and therapeutics in degenerative diseases

Until disease-specific course modifying therapies are available, what is the clinical benefit of a specific diagnosis of AD, DLB, or FTD?

A diagnosis of DLB might encourage the clinician to: (1) aggressively use acetylcholinesterase inhibitors, (2) avoid traditional neuroleptics, (3) monitor and manage blood pressure alterations, (4) consider a trial of dopaminergic drugs for motor symptoms and signs, and (5) limit continuing re-evaluation for syncope and possible seizure disorders.

A diagnosis of bvFTD might prompt the clinician to: (1) avoid acetylcholinesterase inhibitors or at least monitor closely for ineffectiveness or worsening of behavioral

symptoms, (2) use medications that modulate the serotonergic system such as trazodone and SSRIs more aggressively, and (possibly be more willing to use atypical neuroleptic drugs

In cases where risk of inheritance is of special concern, genetic counseling of potentially affected relatives is indicated. If the patient and family members choose to go forward with testing, specific genetic testing of the patient for known mutations in presenilin2, progranulin, or tau and other genes should be dictated by clinical syndromes. If a mutation is discovered in the patient, follow-up genetic counseling of possibly affected relatives is indicated before genetic testing of the relatives is obtained.

On the other hand, once disease-modifying therapies are available, particularly if they are disease-specific and have significant side effects, then the paradigm of diagnosis in patients and potentially affected relatives will change dramatically.

Other degenerative	With movement disorder	Huntington's disease	Executive dysfunction is prominent with diminished ability to make decisions, perform multi-tasking, or complete time-based tasks. Memory loss is usually a late finding with inefficient search of memory that improves with cuing. Aphasia or apraxia is rarely present. Patients may have lack of insight into their cognitive deficits.
		Wilson's disease	Neuropsychological impairment is present in up to 35% of patients. Frequent neurologic signs

**neurologic signs** include parkinsonian-like tremor, rigidity, clumsiness of gait, slurring of speech, uncontrollable grinning, and drooling. Only 10% of patients present with psychiatric problems that range from subtle personality change to depression, paranoia, and catatonia. CSF copper levels are increased 3-to 4-fold.

#### Parkinson's disease (PD)

Although dementia typically occurs in the last half of the clinical course of the disease, about 30% of patients without dementia meet criteria for MCI. Tests of face recognition are significantly impaired in early stages while deficits in executive function with difficulties in set shifting, attention, and planning, as well as visuospatial skills

and verbal memory are found in more advanced cases. Memory deficits related to retrieval of learned information can be improved by cuing.

#### Essential tremor

Louis *et al.* have shown that some patients with autosomal dominant forms of essential tremor have cognitive impairment. Data support strong correlation between severity of tremor, cognitive impairment, and cerebellar degeneration [28].

With other neurological manifestation

#### Striatonigral

Part of multiple system atrophy spectrum. Diminished verbal fluency, perseveration, executive dysfunction, visuospatial, and constructional function can be present.

#### Spinocerebellar

Cognitive

		ataxias	impairment may occur in patients with SCAs due to exonic CAG multiplications
Hematologic	Hyperviscosity	Polycythemia	Tissue transit time may be prolonged the deep white matter with impair oxygen exchange in patients with hyperviscosity
Cardiac		Low output	Cardiac output less than 25–30% is probably insufficient for sustained cognitive function particularly when cognitive tasks are demanding [29]
Vascular		Small vessel disease	Radiologists frequently include “small vessel disease” in the differential diagnosis of diseases that cause increased signal in the deep white matter on FLAIR brain MRI images. In patients over age 60, this may be the only abnormality specified in these reports. Nonetheless

data documenting this clinical–radiologic–pathologic relationship are sparse. There is a relationship between moderate to severe changes on FLAIR in the deep white matter and cognitive deficits as well as balance and gait impairment

#### Strategic site infarcts

A small infarct in the wrong place – for example, the dorsal medial nucleus of the thalamus, head of the caudate, the left inferior parietal lobe, at the hippocampal formation – may cause cognitive impairment and dementia

#### Multi-infarcts

The term “multi-infarct dementia” was first used by Vladimir Hachinski in 1974. Seminal studies by Blessed, Tomlinson, and Roth in the 1960s showed that when total volume of infarcts exceeded 150 mL

exceeded 100 mm,  
patients were  
invariably demented

### Post-stroke dementia

In the 1990s,  
*Tatemichi et al.*  
reported that  
dementia could be  
identified in up to  
one third of patients  
who had acute  
strokes when  
evaluated 2 months  
after the stroke

### Vascular cognitive impairment (VCI)

VCI was proposed  
by Hachinski in  
1994. Some use the  
term to describe  
patients with MCI  
likely due to  
vascular disease. The  
phenotype of MCI  
the vascular type can  
VCI differs from the  
of MCI of the  
Alzheimer's type.  
Poor balance and  
executive function  
deficits are often  
early signs and  
symptoms of VCI  
because the bulk of  
pathology is often  
deep white matter  
tracts that connect  
the frontal lobe with  
the basal ganglia,  
and the thalamus

with the frontal lobe. Longitudinal cognitive assessments in patients with VCI may show fluctuations in performance. In contrast, the phenotype of MCI, the Alzheimer type, is impaired storage of anterograde episodic memory with preserved balance and gait. Patients with this form of MCI usually progressively worsen.

### CADASIL

Hereditary disease associated with a mutation in the *Notch3* gene on chromosome 19 – angiopathy of small arteries and capillaries. Usually manifests in persons in their 40s. Suspected in patients with seizures, migraine-type headaches with aura and clinical stroke. The dementia syndrome can have a progressive course. Other symptoms may include gait

disorder,  
hemiparesis,  
spasticity, emotion  
lability, and  
depression  
MRI reveals  
significant WMLs  
with ischemic  
lesions in the  
subcortical white  
and gray matter,  
especially in the  
internal capsule and  
basal ganglia, and  
lacunar infarctions  
Diagnosed with skin  
biopsy and genetic  
testing

## Metabolic

### Hypoxic

### Chronic

Patients who  
chronically have  
decreased delivery  
of oxygenated blood  
to their brains  
whether due to  
pulmonary,  
environmental  
disease (altitudes  
greater than 10,000  
feet), anemia, or  
heart failure may  
have cognitive  
impairment.  
(Patients with low  
brain energy levels  
due to mitochondrial  
disease may have

identical syndrome

### Post-delirium

Delirium or acute confusional states occur in up to 80% of elderly patients hospitalized because of acute illness. Common clinical settings for acute confusional states include bacterial infections such as pneumonia and urinary tract infections, electrolyte imbalances, post hypoxia, and post surgical. Patients can return to normal over days to many weeks and a significant percentage never return to baseline. The delirium may mark the start of an inexorable cognitive decline leading to profound dementia. Many of these patients undoubtedly had subclinical Alzheimer's disease or other dementia at the time of their hospitalization. Whether events associated with acute

contusional states  
“trigger” a  
degenerative proce  
in susceptible  
patients is not kno

Liver dysfunction	Hepatitis C	Some, but not all studies, have suggested that patients with hepatitis C have cognitive impairment that is independent of the level of hepatic dysfunction
	Other causes	Reduced basal ganglia volumes are noted in some patients with chronic liver disease. Some studies suggest that cognitive function improves after transplantation
Hyponatremia		Chronic hyponatremia has been associated with attention deficits and falls
Uremia		Patients on hemodialysis have cognitive impairment, especially on tasks such as phonemic fluency. Some dat

**Hypothyroidism**. Some data suggest that cognitive impairment is helped by kidney transplantation

Endocrine-related	Thyroid	Hypothyroidism	Slightly elevated TSH levels are associated with cognitive impairment in the elderly, but there is no data that thyroid supplementation will help cognition in these patients
		Hyperthyroidism	Unequivocally high thyroid levels may be associated with apathetic hyperthyroidism and cognitive impairment. Low TSH levels in the elderly are associated with cognitive impairment, but there is no evidence that anti-thyroid medication improves cognitive function
	Cortisol	Cushing	In most patients hypercortisolism is drug-induced and not the result of endogenous

overproduction. Multiple neurological symptoms are associated with steroid use although cognitive impairment is rarely mentioned. Chronic excess steroids can be associated with hippocampal atrophy. In most cases, however, it may be more likely that the cognitive impairment is the result of the underlying disease that requires chronic steroid therapy (such as lupus), than of the steroids themselves.

#### Addison's

Low cortisol levels are associated with cognitive impairment

#### PTH

Cognitive impairment independent of hypercalcemia has been reported in some patients with hyperparathyroidism

#### Perimenopausal

Many women complain of

problems with concentration and memory around the time of menopause. Increased rates of anxiety and depression in the perimenopausal period may account for some of these symptoms.

Nonetheless, estrogen has multiple effects on the brain, and many experts believe that at least, in certain women, menopause and estrogen deficiency may be associated with cognitive impairment

## Other

### Chronic fatigue syndrome

Symptoms of cognitive impairment are frequent in patients with chronic fatigue syndrome. Studies report impaired alertness, impaired working memory, and impaired visual and verbal episodic memory [30]

Demyelination      multiple sclerosis      Cognitive impairment is very common in MS, reported in about 40–65% of cases. Demyelination of brain white matter tracts impairs time information transfer. Demyelination, axonal loss, and neuronal cell body loss all contribute to cognitive impairment. Complex attention, information processing speed, (episodic) memory and executive functions are usually impaired [31]

Frailty      Frailty (defined by unintentional weight loss, exhaustion, weakness, weight loss, and impaired grip strength) has been associated with cognitive decline and dementia [32,33]

Fragile X carriers      Grandfathers of children with fragile X syndrome who carry 55–200 CGG repeat in the fragile X mental

retardation gene m  
develop a syndrom  
of progressive  
tremor/ ataxia and  
cognitive  
impairment/demer  
by their 50s [34]

Mitochondrial      MELAS

A rare genetic  
disorder that is  
characterized by  
encephalopathy,  
lactic acidosis, and  
stroke-like episodes.  
Neuropsychiatric  
symptoms can  
present as a sole  
manifestation in  
early stages,  
including mood  
disorder, cognitive  
impairment,  
psychosis, and  
anxiety. Consider  
patients with an  
unexplained  
multisystem disorder  
[35]

Deficiency

B12

Cognitive  
impairment may be  
the only neurological  
manifestation of B12  
deficiency (i.e.  
evidence of spinal  
cord dysfunction or  
neuropathy may be

lacking). Some patients with B12 deficiency (usually those with B12 levels < 100 µg) may have evidence of brain demyelination with increased signal on FLAIR. Most common in the US are patients who have B12 levels measured as part of the “work-up” for dementia and then are found to have low or “lowish” (i.e. levels between 200 and 350 µg). Most of these patients' cognitive impairment will prove not to be associated with B12 deficiency and treatment with intramuscular B12 replacement will have no effect on the underlying cognitive impairment.

#### Thiamine

Vitamin B1 (thiamine) deficiency is associated with Wernicke's encephalopathy; an acute syndrome.

characterized by confusion, ophthalmoparesis, and ataxia (usually also with peripheral neuropathy). If Wernicke's encephalopathy is treated promptly enough, there may be no long-term sequelae. If not, patients may be left with Korsakoff's syndrome characterized by severe impairment of anterograde memory.

## Vitamin E

Because of the antioxidant effects of vitamin E, many studies have investigated relationships between vitamin E levels and dementia. Some clinical trials have demonstrated a modest delay in stroke or death in patients on vitamin E. Nonetheless, vitamin E may be associated with increased risk of intracerebral hemorrhage, and most experts no longer recommend it for primary prevention of cardiovascular disease.

longer recommend vitamin E supplementation [1]

## Vitamin D

The relationship between vitamin E levels and neurologic disease has become an area of intensive investigation. As of January 2014, data are lacking concerning whether to measure vitamin D levels in dementia and/or give supplemental vitamin D to patients with cognitive impairment

---

ADC, apparent diffusion coefficient; CJD, Creutzfeldt–Jakob disease; CNS, central nervous system; CO, carbon monoxide; CSF, cerebrospinal fluid; CT, computed tomography; DLB, dementia with Lewy bodies; DWI, diffusion weighted imaging; EEG, electroencephalogram; FLAIR, fluid attenuated inversion recovery; FTA-ABS, fluorescent treponemal antibody absorbed test for syphilis; FTD, frontotemporal dementia; LP, lumbar puncture; MRI, magnetic resonance imaging; PD, Parkinson's disease; PET, positron emission tomography; PTH, parathyroid hormone; REM, rapid eye movement; RPR, rapid plasma reagins; SLE, systemic lupus erythematosus; SPECT, single photon emission computed tomography; VDRL, Venereal disease research laboratory test; WMLs, white matter lesions.

His father died at age 66, his mother at age 81. There was no family history of dementia.

On general examination his blood pressure seated was 130/80; his pulse was 64. With standing his blood pressure decreased to 120/80, his pulse increased to 80.

He was oriented × 3. He could recall 2 out of 3 items on the Mini-Mental State

Exam (MMSE) memory items. On the MMSE, he lost a point for poorly drawing intersecting pentagons and two points for errors in spelling “world” backwards. His MMSE was 26. Naming appeared normal.

Cranial nerve exam showed no hypomimia or hypophonia. Upward eye movements were modestly decreased. His gait was slightly slow. He had no cog-wheeling or increase in tone. Deep tendon reflexes were 2+ except at the ankles where they were trace. Sensory exam showed modest decrease in vibratory sensation at the toes. A brain MRI without contrast showed cortical atrophy and modest increase in signal on FLAIR in the periventricular regions. Thyroid function and B12 were normal.

The neurologist made a diagnosis of “mild cognitive impairment.” Because of the fluctuations, visual hallucinations, and gait slowing, he suspected that the underlying etiology might be dementia with Lewy bodies (DLB), but did not share this with the family.

*Comment:* Whether the patient meets criteria for mild cognitive impairment or mild dementia depends mostly on whether significant impairment in activities of daily living has occurred. Functional impairment may have been more obvious if the patient was still working as an attorney.

Excessive daytime sleepiness occurring together with a patient's usual nighttime sleep, soft signs of Parkinson's disease without meeting criteria for PD, and fluctuations are all features of DLB. The systolic blood pressure drop with standing may be an early sign of postural hypotension. In the author's (HAC) experience, a form of an idea of reference – believing people on TV are actually talking to the patient – is a frequent delusion in DLB.

Gait slowing is prevalent in aging and multifactorial. When gait impairment is present from early in the course of dementia, if one disease is causing both dementia and gait impairment, then Alzheimer's disease is unlikely. Vascular dementia and dementia with Lewy bodies are the two most common disorders with both early onset of gait impairment and dementia. Although normal pressure hydrocephalus should be considered, the cortical atrophy and associated symptoms of DLB make it unlikely. Increased signal on FLAIR MRI sequences is very common in aging, and some increased signal is nearly ubiquitous among patients in their 70s and older, particularly if they have hypertension. The modest changes on FLAIR, the lack of a history of strokes, and a neurologic exam lacking signs of previous infarcts makes vascular dementia less likely.

Quetiapine was titrated to a dose of 25 mg TID; rivastigmine patch was

titrated to a dose of 13.3 mg applied daily. The hallucinations persisted but were perhaps less frequent than previously.

*Comment:* The use of neuroleptics, both typical and atypical, in older, demented patients is controversial and carries a “black box warning.” The authors frequently use atypical neuroleptics when hallucinations frighten the patient and cause agitation. We inform the patient and surrogates of the reported risks associated with their use, and explain we still believe they are the best choice. Nonetheless, clear documentation of the efficacy of neuroleptics in DLB for controlling hallucinations is lacking. Moreover, any neuroleptic, including atypical neuroleptics, has the risk of exacerbating gait impairment and other parkinsonian symptoms and signs. In this vignette, the indication for neuroleptics was borderline at best because the hallucinations were only modestly troubling to the patient.

Rivastigmine has been approved by the US FDA for use in parkinsonian dementia. The authors believe that the other available choline acetyltransferase inhibitors would be equally efficacious.

The patient and his family moved to Florida; medical records were not transferred. In Florida, his physicians all believed he had Alzheimer's disease.

Over the next 3 years he had repeated hospitalizations for evaluations of syncope and progressive dementia. No seizure activity was ever noted and repeated EEGs were either reported as normal or mild slowing; no sharp waves or spikes were ever reported. A trial of levetiracetam titrated to 750 mg BID did not influence the frequency of the syncopal episodes. Because of episodes of hypotension associated with sitting in his wheelchair, his irbesartan was held. However, another physician found his supine BP to be 170/90 and irbesartan was restarted. Two days later he collapsed getting out of bed for physical therapy. His BP standing was reported as 80/40.

*Comment:* Falls, episodes of syncope, episodes of falling asleep with difficulty being aroused, and episodes of confusion much worse than baseline cognitive impairment are all features of DLB. Postural hypotension is frequently seen together with supine systolic hypertension when supine. These facts have several implications. First, routine testing for cardiac etiologies of syncope and one or two EEGS are appropriate, but if they are negative, the clinician should accept that recurrent syncope can be part of DLB, and that repeated hospitalization and repeated testing are not fruitful. A trial of antiepileptics may be reasonable, but if they do not influence the frequency of events, there is little reason to continue

them. Part of the reason for loss of consciousness and confusion is probably decreased cerebral perfusion from low blood pressure. Elastic stockings, fludrocortisones, or midodrine may be of some help, but sometimes there is little choice but to let the systolic pressure run high if the patient is to be able to walk with adequate cerebral perfusion.

His physicians' failure to recognize that his dementia was from Lewy body disease and not Alzheimer's led to repeated evaluations and hospitalizations, as well as recurrent cycles of starting and stopping antihypertensive medications.

## References

1. Klassen BT, Ahlskog JE. Normal pressure hydrocephalus: how often does the diagnosis hold water? *Neurology* 2011; 77:1119–25.
2. Marmarou A, Black P, Bergsneider M, Klinge P, Relkin N; International NPH Consultant Group. Guidelines for management of idiopathic normal pressure hydrocephalus: progress to date. *Acta Neurochir Suppl* 2005; 95:237–40.
3. Wicklund MR, Mokri B, Drubach DA, Boeve BF, Parisi JE, Josephs KA. Frontotemporal brain sagging syndrome: an SIH-like presentation mimicking FTD. *Neurology* 2011; 76:1377–82.
4. Donnellan CA, Fook L, McDonald P, Playfer JR. Oxybutynin and cognitive dysfunction. *Br Med J* 1997; 315:1363–4.
5. Campbell N, Boustani M, Limbil T *et al.* The cognitive impact of anticholinergics: a clinical review. *Clin Interv Aging* 2009; 4:225–33.
6. Kleykamp BA, Griffiths RR, Mintzer MZ. Dose effects of triazolam and alcohol on cognitive performance in healthy volunteers. *Exp Clin Psychopharmacol* 2010; 18:1–16.
7. Anwar M. Letter: Digoxin and confusion in the elderly. *Br Med J* 1975; 3:231.
8. Huffman J, Stern TA. Neuropsychiatric consequences of cardiovascular medications. *Dialogues Clin Neurosci* 2007; 9:29–45.
9. Raffa RB, Duong PV, Finney J *et al.* Is 'chemo-fog'/'chemo-brain' caused by cancer chemotherapy? *J Clin Pharm Therapeut* 2006; 31: 129–38.

10. Greene-Schloesser D, Robbins ME, Peiffer AM *et al.* Radiation-induced brain injury: a review. *Front Oncol* 2012; 2:73.
11. Kim JW, Lee DY, Lee BC *et al.* Alcohol and cognition in the elderly: a review. *Psychiatry Invest* 2012; 9: 8–16.
12. Weiss B. Lead, manganese, and methylmercury as risk factors for neurobehavioral impairment in advanced age. *Int J Alzheimers Dis* 2011; 2011:607543.
13. Kirkpatrick JN. Occult carbon monoxide poisoning. *West J Med* 1987; 146:52–6.
14. Motamedi G, Meador K. Epilepsy and cognition. *Epilepsy Behav* 2003; 4 Suppl 2:S25–38.
15. Elger CE, Helmstaedter C, Kurthen M. Chronic epilepsy and cognition. *Lancet Neurol* 2004; 3:663–72.
16. Hermann B, Seidenberg M. Epilepsy and cognition. *Epilepsy Curr* 2007; 7:1–6.
17. Haut SR, Katz M, Masur J, Lipton R. Seizures in the elderly: impact on mental status, mood and sleep. *Epilepsy Behav* 2009; 14:540–4.
18. Helmstaedter C. Effects of chronic epilepsy on declarative memory systems. *Prog Brain Res* 2002; 135:439–53.
19. Whitney P, Hinson JM. Measurement of cognition in studies of sleep deprivation. *Prog Brain Res* 2010; 185:37–48.
20. Johns DR, Tierney M, Felsenstein D. Alteration in the natural history of neurosyphilis by concurrent infection with the human immunodeficiency virus. *N Engl J Med* 1987; 316:1569–72.
21. Cairns V, Godwin J. Post-Lyme borreliosis syndrome: a meta-analysis of reported symptoms. *Int J Epidemiol* 2005; 34:1340–5.
22. Moniuszko A, Czupryna P, Zajkowska J *et al.* Post Lyme syndrome as a clinical problem. *Pol Merkur Lekarski* 2009; 26:227–30.
23. Antinori A, Arendt G, Becker JT *et al.* Updated research nosology for HIV-associated neurocognitive disorders. *Neurology* 2007; 69:1789–99.

24. Schebesch KM, Woertgen C, Rothoerl RD, Ullrich OW, Brawanski AT. Cognitive decline as an important sign for an operable cause of dementia: chronic subdural haematoma. *Zentralbl Neurochir* 2008; 69:61–4.
25. Ishikawa E, Yanaka K, Sugimoto K, Ayuzawa S, Nose T. Reversible dementia in patients with chronic subdural hematomas. *J Neurosurg* 2002; 96:680–3.
26. Nowak DA, Widenka DC. Neurosarcoidosis: a review of its intracranial manifestation. *J Neurol* 2001; 248:363–72.
27. Elfferich MD, Nelemans PJ, Ponds RW *et al*. Everyday cognitive failure in sarcoidosis: the prevalence and the effect of anti-TNF-alpha treatment. *Respiration* 2010; 80:212–19.
28. Louis ED, Viner AS, Gillman A. Mental Status Test scores are inversely correlated with tremor severity: a study of 161 elderly essential tremor cases. *Tremor Other Hyperkinet Mov (NY)* 2012; 2:69.
29. Dardiotis E, Giamouzis G, Mastrogianis D *et al*. Cognitive impairment in heart failure. *Cardiol Res Pract* 2012; 2012:595821.
30. Constant EL, Adam S, Gillain B *et al*. Cognitive deficits in patients with chronic fatigue syndrome compared to those with major depressive disorder and healthy controls. *Clin Neurol Neurosurg* 2011; 113:295–302.
31. Jongen PJ, Ter Horst AT, Brands AM. Cognitive impairment in multiple sclerosis. *Minerva Med* 2012; 103(2):73–96.
32. Qian-Li Xue, PhD. The frailty syndrome: definition and natural history. *Clin Geriatr Med* 2011; 27:1–15.
33. Panza F, Solfrizzi V, Frisardi V *et al*. Different models of frailty in predementia and dementia syndromes. *J Nutr Health Aging* 2011; 15:711–19.
34. Olichney JM, Chan S, Wong LM *et al*. Abnormal N400 word repetition effects in fragile X-associated tremor/ataxia syndrome. *Brain* 2010; 133:1438–50.
35. Anglin RE, Garside SL, Tarnopolsky MA, Mazurek MF, Rosebush PI. The psychiatric manifestations of mitochondrial disorders: a case and review of the literature. *J Clin Psychiatry* 2012; 73:506–12.
36. Devore EE, Grodstein F, van Rooij FJ *et al*. Dietary antioxidants and long-

term risk of dementia. *Arch Neurol* 2010; 67:819–25.

# 16 Depression

---

Yelizaveta Sher and John J. Barry *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

## Introduction

The purpose of this chapter is to aid the clinician in the recognition of depressive illness as well as to provide guidance on differential diagnosis. In order to achieve this, definitions of affective illness will be provided followed by a brief discussion of pathophysiology, psychometric tests used in the diagnosis of depressive illness, review of differences in presentation of medical illness comorbid with depression (with a focus on central nervous system [CNS] disorders) and finally an extensive discussion of differential diagnosis with an illustrative case study. Treatment issues are extensive and beyond the scope of this chapter.

## Definitions

Mood disorders are common in the general population and even more frequently seen as a comorbidity associated with a medical illness. However, in almost two thirds of cases the diagnosis is missed [1–3]. This may result in a significant economic burden and may drastically affect the patient's quality of life.

In accordance with the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), mood disorders may be bifurcated into “mood episodes” and “mood disorders” [4]. It is important to remember that “depression” is a phenomenologic entity described by symptoms, not biology. Thus, many medical illnesses may manifest depressive symptoms that are not completely equivalent with the depression seen in other medical diseases or in idiopathic depressive illness [5]. There are also subtypes of depression that may be unique in and of themselves, requiring different treatment (e.g. the depression associated with bipolar illness, psychotic depression, and the mood disorders comorbid with CNS illnesses [6]).

There are two major categories of mood disorders, unipolar and bipolar affective disorder. Unipolar depression is broken down into Major Depressive Disorder (MDD), Dysthymia, and Mood Disorder NOS (not otherwise specified). Major Depressive Disorder is defined as lasting 2 weeks or longer and must include depression or anhedonia and at least five elements of the following list: loss of pleasure in normal activities, irritability, problems with weight or sleep, loss of energy and drive, difficulty with concentration, problems making decisions, hopelessness, guilt and frustration, sadness, and feeling of being better off dead. Dysthymia is often more persistent than MDD but milder in intensity [4]. This chapter is not designed to cover the features of Bipolar Affective Disorder (BAD), but it is important to recognize it since it is treated differently and may be exacerbated by antidepressant therapy. Features of the illness have been described elsewhere [7].

As time has progressed, we have become more cognizant that depression is more than a neurotransmitter dysfunction but rather involves circuits and integrated pathways in the brain that link cortical, subcortical, and limbic connections [8]. Thus it is not surprising that depression can be both a cause and a consequence of medical illnesses. Comorbidity of depression can be seen with coronary heart disease, cancer, HIV/AIDS, and in neurologic illnesses as well. In addition, the association of anxiety and depression appears to be frequent in medical illnesses and may increase morbidity [9].

The Structured Clinical Interview for DSM-IV (SCID) is still the gold standard in the diagnosis of a MDD. However, for clinicians, more user-friendly self-rating scales are available. The Beck Depression Inventory (BDI) [10] and the Center for Epidemiology Studies Depression Scale (CES-D) can be used to detect the possible presence of a depressive illness and also may be used for longitudinal assessment of treatment efficacy. Other measures include the Hospital Anxiety and Depression Scale and for the elderly patient, the Geriatric Depression Scale . Screening instruments are also available [6]. The Neurological Disorders Depression Inventory in Epilepsy (NDDI-E) was developed for epilepsy patients (Table 16.1). A score > 15 is suggestive for the presence of a MDD [11].

**Table 16.1 *Neurological Disorders Depression Inventory in Epilepsy (NDDI-E)*. For the statements below, please circle the number that best describes you over the last two weeks including today.**

---

	<b>Always or often</b>	<b>Sometimes</b>	<b>Rarely</b>	<b>Never</b>
Everything is a struggle	4	3	2	1
Frustrated	4	3	2	1
Nothing I do is right	4	3	2	1
Feel guilty	4	3	2	1
Difficulty finding pleasure	4	3	2	1
I'd be better off dead	4	3	2	1

In addition, quality of life may be severely impacted by MDD as well as in those patients with lower levels of depression, *i.e.* as seen in people with partially treated MDD and Dysthymia. This factor was reviewed by Kanner in an epilepsy population [12]. In addition, the potential for suicide is often seen more frequently in depression comorbid with a medical illness and must be searched for in every patient where depression is present. This factor is illustrated in Table 16.2 .

**Table 16.2 Summary of depression and central nervous system illnesses .**

	<b>Prevalence</b>	<b>Suicide</b>	<b>Quality of Life</b>
Epilepsy	29%	5×	
Parkinson's disease	25%	No	
Multiple Sclerosis	23%	7.5×	

Stroke	2fr-30%	2.2× greater than stroke without depression	I III
Traumatic brain injury	26.7%	3×	I III
General Population	5–17%	1–4%	

Note increased prevalence and suicide rate over that seen in the general population and diagnostic similarities (with some idiosyncratic features) along with severe impact on quality of life in this patient population [13–15].

## Differential diagnosis

After the diagnosis of depression is made, a search for a cause ensues. Other comorbidities may be a factor as well as iatrogenic causes. Table 16.3 illustrates possible associated etiologies and diagnostic signs and symptoms that will aid the physician in their treatment plan.

## Case vignette

A 25-year-old male was admitted to the emergency room with complaints of depression and suicidal ideation which was episodic in intensity. The patient had been seen by a psychiatrist in the community who had started him on a serotonin reuptake inhibitor, but it appeared to only exacerbate his depression. He was seen by the ER attending, a psychiatric consultation was called, and the patient was admitted to the psychiatric ward. Labs, including electrolytes, metabolic panel, liver function, and thyroid tests, were all normal. On the ward, the patient was noted by the nursing staff to have very brief periods of unresponsiveness that seemed to be followed by severe suicidal ideation. A video EEG was completed and the diagnosis of epilepsy was made associated with a post-ictal exacerbation of his underlying mood disorder. An MRI showed left mesial temporal sclerosis. It was felt that the SSRI had lowered the seizure threshold and increased the frequency of seizure activity. He was ultimately started on lamotrigine with good effect.

**Table 16.3** *Etiologies of depression.*

Item	Subdivision	Specific entity	Note
Toxic	Antihypertensives		Ma and Dej wit res met
	Beta-blockers		Alt blo pro met tho dep stu ana the
	Methyldopa		Use ind (H) sed dep wit dep nor dep
	Reserpine		Cai catl lead mal be dep [16]

Flunarizine  
Cal  
blo  
age  
pro  
8%  
pro  
dev  
Als  
ext  
effe

Anticonvulsants  
Epi  
dep  
son  
are  
add  
risk

Barbiturates  
Wo  
Am  
sys  
pro  
sed  
cog  
dep

Levetiracetam  
Cli  
wit  
side  
stu  
intc  
neu  
effe  
agg  
mo  
dep

Vigabatrin  
Ino

increased  
levels

12%  
pre-  
dep-  
vig-  
place-  
pati-

Topiramate  
Lin-  
dep-  
pati-  
pati-  
or f-  
wit-  
esc-

Anti-infective  
agents  
Influenza  
illness  
driving  
behavior  
psychosis  
delirium  
memory  
muscle  
[16]

Ampicillin  
Ind-  
otitis  
epiglottitis  
tracheitis  
endocarditis  
meningitis

Tetracycline  
Ind-  
infection  
chlamydia  
*Helicobacter*  
side effects

phc  
like  
(GI

Streptomycin  
Side  
oto  
dys  
opt  
and

Azithromycin  
Use  
and  
Ma  
hep  
dist  
pro

Efavirenz  
NN  
Ma  
dre  
dep  
tar  
dos

Immunomodulators    Interferon alpha  
Ma  
tre  
C v  
me]  
dep  
in t  
pati

Steroids  
Ne  
rhe  
resj  
illn  
ma  
anx  
full

and  
syn  
dep

Cyclosporine      Imi  
                    trar  
                    RA  
                    effe  
                    hyp  
                    nep

Neuropsychiatric      Levodopa      Use  
                            Ass  
                            dep  
                            per  
                            [16]

Amantadine      Ass  
                    dep  
                    per  
                    pati  
                    bee  
                    dep  
                    adj  
                    [16]

Sedative-hypnotics      Bei  
                    rep  
                    stu  
                    ass  
                    dep  
                    sui  
                    wit  
                    low  
                    Bar  
                    abc

Metaclopramide      Sor

sug  
wit  
cau  
par

Antihistaminics  
In c  
vas  
anh  
hyp  
deli  
rete

Disulfiram  
Sid  
hep  
CN  
incl  
and  
rest  
disc  
hea

Phenothiazine  
Sid  
ext  
rea  
tarc  
caro  
end  
rea

Oncologic  
Vincristine  
Ant  
effe  
sup  
neu  
(pa  
SIA  
[23

Vinblastine  
Ant  
effe

		sup
	pul	
	neu	
Oral contraceptives		Sor link but stud Ass pro
Intoxication	Cocaine	Acu par hall hyp cog suic atte
	Amphetamine	Sin CN hyp hyp tacl
	Carbon monoxide	Irr rest and amn pos con
	Thallium	Em anx hea ata sen neu

Mercury	Int hyp per men irrit acut
Insecticides	Mu nic tox arrl
Tetrodotoxin/puffer fish toxin	Aci Dia
Uremic encephalopathy	Mu dys alte seiz
Withdrawal	Cocaine
	An my flus hall anh dys pai
	Amphetamine
	Sar mar pha
	Alcohol
	Ag inst seiz trer
	Steroids
	CN ----

			em seiz
			met GI, and effe
Infective/post-infective	Viral	Hepatitis	Fev abd <a href="#">[25]</a>
		AIDS	Fat lyn pha GI
		Infectious mononucleosis (IM)	Pha cer lyn spl aty] <a href="#">[25]</a>
		Rabies	Pha hyd aere par ani
		Influenza	Sys fev mal resj pha and lyn
		Viral pneumonia	Sin 100

100.  
evid

con  
[25]

Epstein–Barr virus  
San  
ass  
lyn  
dis  
inf

Mycobacterial  
Tuberculosis  
Fev  
wei  
loss  
and

Spirochete  
Syphilis  
Pri  
Sec  
incl  
sole  
mei  
gun  
neu  
car

Lyme disease  
His  
ery  
neu  
wit  
con

Bacterial  
Brucellosis  
Un  
bac  
trar  
froi  
sep  
neu  
inv

Psychiatric	Dysthymia	At dep co-
	Premenstrual dysphoric disorder	Aff dep anx neu syn the me fin ons imp few ons res aft
	Adjustment disorder	Em a st as c div pro star of t ren of s <a href="#">[21]</a>
	Bereavement	Oc sig as c In c dep hav aro rest for

for  
Epi

Somatic symptom disorder  
Pre  
mo  
syn  
dist  
sig  
of c  
exc  
fee]  
rela  
son

Generalized anxiety disorder  
Exc  
unc  
abc  
anx  
eve

Schizoaffective disorder  
Ch:  
psy  
wel  
mai  
epis  
syn  
out  
syn  
wee

Schizophrenia  
Do:  
psy  
hall  
deli  
tho  
spe  
neg  
On:  
to e  
and

and  
[21]

Bipolar disorder	In I be a epis ther of l dep	
Cyclothymic disorder	Att dis star frec of s dep hyp med bip	
Postpartum psychosis	Ext deli slee hall deli usu pos risk inf	
Inflammatory	Rheumatoid arthritis	Syr anc my noc def vas ple pul spin con

	con	
	per	
	neu	
	dis	
Systemic lupus erythematosus	90%	
	con	
	bla	
	Phc	
	dis	
	ora	
	wei	
	artl	
	artl	
	per	
	dis	
	leu	
Fibromyalgia	Wi	
	(typ	
	boc	
	lea	
	tend	
	spe	
	boc	
Polymyalgia rheumatica	Acl	
	stif	
	hip	
	typ	
	ove	
	mal	
	wei	
Neoplastic/para- neoplastic	Brain	
	He	
	“ea	
	nau	
	seiz	
	non	

Cerebral metastases      As  
of c  
ma]

Lung      Co  
che  
hoa  
wit

Pancreatic      Ab  
wei  
pro  
deg  
psy  
syn  
ear]  
in r  
dis  
miξ  
[\[29\]](#)

Para-neoplastic/non-para-neoplastic limbic encephalitis      Ac  
mo  
cha  
me  
con  
seiz  
dys  
hyperf  
son  
end  
abn  
con  
mal  
(sm  
SC  
bre  
thy

lyn

may  
[29]

## Degenerative

## Multiple sclerosis

Mu  
acu  
mu  
mo  
ver  
dys  
inc

## Parkinson's disease

Tre  
gai  
rigi

## Frontotemporal dementia

Yon (e.g., Alzheimer's disease) [30]

## Huntington's disease

Chemo  
moto  
dys  
and  
dep  
psy

## Alzheimer's disease (AD)

Undecided visitors

Lewy body

Mil

syndrome	syn
Cortical dementia	Co ass of c aph [30]
Delirium	Acu dist fun fluc atte con cog per
Subcortical dementia	Mo slow gait
Progressive supranuclear palsy	Sup pals ver trui akin inst dys sub pse [29]
Amyotrophic lateral sclerosis	Co mo

hyf

spa  
mo  
fas  
Pre  
asy  
we  
bul  
dys  
(20  
acc  
pse  
cog  
auto  
par  
sup  
par  
[23

Vascular

Stroke

Suc  
per  
sen  
[30

Subdural hematoma

His  
uni  
and  
enl  
stu  
hen  
[23

Multi-infarct  
dementia

Phy  
imp  
stej  
hyf  
freq

Other/ Idiopathic	Terminally ill patients	Pre illn	
	Chronic daily headache	Syr pro last lon con miξ tens me hea con dai hea	
	Chronic pain syndrome	Rul	
	Reflex sympathetic dystrophy/complex regional pain ext cha syndrome	Dis reg ext cha swε of r inst cha bor Fre foll eve	
Metabolic	Endocrine	Hypothyroidism	We son intc gai loss stif bra

puf  
spe

Hyperthyroidism      Syr  
ner  
irrit  
fati  
intc  
loss  
Sig  
arrl  
fibr  
my  
[29]

Diabetes mellitus      Inc  
freq  
Co  
car  
reti  
nep  
per  
auto  
[29]

Hyperparathyroidism      And  
freq  
leth  
mu  
pai  
Mil  
cha  
spo  
init  
dys  
apa  
irrit  
con  
con

dis  
agi  
let

Adrenal  
insufficiency  
An  
nau  
dia  
pai  
mu  
Ad  
inc  
cau  
hyf  
esp  
exp  
mu  
Pos  
due  
mir  
hyf  
stre  
hyf  
hyf

Cushing's syndrome  
Tru  
stri  
hyf  
hyf  
we  
skin  
bru  
sus  
infe  
dys  
use  
exc  
sec  
pitu  
Cus

adr

Hypoparathyroidism Par  
cra spa  
gri teta  
[29]

Premenstrual Mo  
dysphoric disorder pre  
we res day  
star acc  
tend ach  
blo gai

Perimenopause Ty  
yea inc  
nig pal  
fati joir

Polycystic ovary An  
syndrome olig infi  
ovu lev inf  
obe alo aca  
hvr

-- r  
resi

Nutritional deficiency Folate deficiency Coi  
anti  
valj  
alc  
disc  
mal  
Syr  
cog  
Sig  
ane

Vitamin B12 deficiency Me  
my  
con  
deg  
den  
per  
Oce  
ane  
ulce  
gas  
byf  
dep  
bov  
disc  
mal

Pyrodoxine (B6) deficiency Per  
seiz  
chr  
dep  
Ele  
hon  
dru  
anta

Vitamin C Scu

deficiency      ecc  
gur  
hyp  
hen  
fati  
poc  
[23]

Niacin deficiency      Pel  
rasl  
are  
ton  
apa  
dis

Metabolite      Hyperventilation      Inc  
dep  
a fe  
to c  
due  
alka  
hav  
spa  
jerl

Dialysis dementia      Hig  
den  
pati  
den  
Mi  
for  
but  
wit  
Alt  
nov

Acute intermittent porphyria      Abe  
per  
and

dist  
auto  
deh  
elec  
dist  
der  
also  
Phy  
occ  
psy  
ma

Wilson's disease  
On  
ado  
occ  
dec  
inc]  
beh  
dist  
den  
dys  
cirr  
hav  
ring]

Movement disorder  
Tourette's syndrome  
Mo  
con  
tics  
wo]  
chil

Sleep disorder  
Sleep apnea  
syndrome  
Snc  
slee  
wit  
cho  
rest  
mo  
epis

-ces

[29

Genetic/heredofamilial	Narcolepsy	Chi slee epi also par and hall
	Obesity hypoxia hypocapnia syndrome	Pat mo obs (OS hav hyp rigl fail exe fro
	Restless leg syndrome	Sut of l and wo idic asse def dial dis insu
	Fragile X syndrome	Me ass neu abn

	Hexosaminidase A deficiency	Tay-Sach's disease adult form in cerebrospinal fluid protein profile liver function immunological tests <a href="#">[23]</a>
	Huntington's chorea	Ref
	Cerebrotendinous xanthomatosis	Ceroid lipofuscinosis type 2 pyruvate oxidase deficiency immune system dysfunction
Trauma associated	Post-concussion syndrome	Trauma associated headache dizziness and confusion syncope
	Post-traumatic stress disorder	Trauma related flashbacks nightmares hypervigilance sleep disturbance
Ictal	Epilepsy	Recurrent seizures with aura facial palsy focal motor seizures ictal仆倒 depression psychosis

---

## Conclusion

Depression is an unfortunately common phenomenon often presenting as a comorbidity of medical illnesses. This review has defined mood disorders especially depression and suggested psychometric evaluation techniques. Since depression appears to be a non-specific entity that can be seen in many illnesses, a comprehensive review of possible etiologic conditions presenting as a mood disorder has been performed. Treatment depends upon the presenting illness and may respond when the offending malady is treated. If depression persists, then individual treatment should be targeted for the mood disorder. Psychosocial psychotherapeutic interventions with or without antidepressant medication treatments may be needed.

## References

1. Coyle J, Schwenk T, Fechner-Bates S. Non-detection of depression by primary care physicians reconsidered. *Gen Hosp Psychiatry* 1995; 17:3–12.
2. Hirschfeld RM, Keller M, Panico S. The National Depressive and Manic-Depressive Association consensus statement on the undertreatment of depression. *JAMA* 1997; 277:333–40.
3. Hermann BP, Seidenberg M, Bell B. Psychiatric comorbidity in chronic epilepsy: identification, consequences, and treatment of major depression. *Epilepsia* 2000; 41 Suppl 2:S31–41.
4. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*. Arlington, VA: American Psychiatric Association, 2013.
5. Higgins ES, George MS. *The Neuroscience of Clinical Psychiatry*. Philadelphia, PA: Lippincott Williams & Wilkins, 2007: 227–37.
6. Barry JJ, Ettinger AB, Friel P *et al*. Consensus statement: the evaluation and treatment of people with epilepsy and affective disorders. *Epilepsy Behav* 2008; 13:S1–29.
7. Schatzberg AF. Bipolar disorder: recent issues in diagnosis and classification. *J Clin Psychiatry* 1998; 59 (Suppl 6):5–10.
8. Mayberg HS, Lozano AM, Voon V *et al*. Deep brain stimulation for treatment resistant depression. *Neuron* 2005; 45:651–60.

9. Katon WJ, Lin E, Kroenke K. The association of depression and anxiety with medical symptom burden in patients with chronic medical illness. *Gen Hosp Psychiatry* 2007; 29:147–55.
10. Beck A, Steer R. Beck Depression Inventory. In Force T, Ed. *Handbook of Psychiatric Measures*. Washington, DC: American Psychiatric Press, 2000: 519–23.
11. Gilliam F, Barry JJ, Hermann BP et al. Rapid detection of major depression in epileptics, a multicenter study. *Lancet Neurol* 2006; 5:399–405.
12. Kanner AM, Barry JJ, Gilliam F, Hermann B, Meador KJ. Anxiety disorders, sysyndromic depressive episodes, and major depressive episodes: do they differ on their impact on the quality of life of patients with epilepsy? *Epilepsia* 2010; 51:1152–67.
13. Harrison-Felix CL, Whiteneck GG, Jha A. Mortality over four decades after traumatic brain injury rehabilitation: a retrospective cohort study. *Arch Phys Med Rehabil* 2009; 90:1506–13.
14. Gilliam F, Kanner AM, Sheline YI. *Depression and Brain Dysfunction*. New York, NY: Taylor & Francis, 2006.
15. Forsstrom E, Hakko H, Nordstrom T, Rasanen P, Mainio A. Suicide in patients with stroke: a population-based study of suicide victims during the years 1988–2007 in northern Finland. *J Neuropsychiatry Clin Neurosci* 2010; 22:182–7.
16. Celano CM, Freudenreich O, Fernandez-Robels C et al. Depressogenic effects of medications: review. *Dialog Clin Neurosci* 2011; 13:109–25.
17. Stephen LI, Kelly K, Parker P, Brodie MJ. Levetiracetam monotherapy – outcomes from an epilepsy clinic. *Seizure* 2011; 20:554–7.
18. Goodman LS, Gilman A, Eds. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 6th edn. New York, NY: Macmillan, 1980.
19. Kulkarni J. Depression as a side effect of the contraception pill. *Expert Opin Drug Saf* 2007; 6:371–4.
20. Smith BD, Salzman C. Do benzodiazepines cause depression? *Hosp Community Psychiatry* 1991; 42:1101–2.

21. Sadock BJ, Sadock VA, Eds. *Comprehensive Textbook of Psychiatry*. Philadelphia, PA: Lippincott Williams & Wilkins, 2005.
22. Anfinson TJ. Akathisia, panic, agoraphobia, and major depression following brief exposure to metoclopramide. *Psychopharmacol Bull* 2002; 36:82–93.
23. Fauci AS, Braunwald E, Kasper DL. *Harrison's Principles of Internal Medicine*, 17th edn. San Francisco, CA: McGraw Hill, 2008.
24. Bezzichibnyk-Butler KZ, Jeffries JJ, Virani A, Eds. *Clinical Handbook of Psychotropic Drugs*. Boston, MA: Hogrefe & Huber, 2007.
25. Runge MS, Greganti MA. *Netter's Internal Medicine*. Philadelphia, PA: Saunders, 2009.
26. Lishman AL. *Organic Psychiatry*, 2nd edn. Palo Alto, CA: Blackwell Scientific, 1987.
27. Judofsky S, Hales RE, Eds. *Neuropsychiatry and Behavioral Neuroscience*. Arlington, VA: American Psychiatric Publishing, 2008.
28. Senanayake AU, Karalliedde L. Neurotoxic effects of organophosphorus insecticides. An intermediate syndrome. *N Engl J Med*. 1987; 316:761.
29. Levenson JL, Ed. *Textbook of Psychosomatic Medicine*. Arlington, VA: American Psychiatric Publishing, 2005.
30. Kaufman DM. *Clinical Neurology for Psychiatrists*, 7th edn. Philadelphia, PA: Saunders, 2007.
31. Bradley WG, Daroff RB, Fenichel GM, Jankovic JJ. *Neurology in Clinical Practice*, 5th edn. Philadelphia, PA: Butterworth Heinemann, 2008.
32. Barry JA, Lembke PA, Gisbert PA, Gilliam F. Affective disorders in epilepsy. In Ettinger AB, Kanner AM, Eds. *Psychiatric Issues in Epilepsy: A Practical Guide to Diagnosis and Treatment*. Philadelphia, PA: Lippincott Williams & Wilkins, 2007: 203–47.

# 17 Diplopia

---

Deborah I. Friedman *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

## Introduction

There are many causes of diplopia, and evaluating a patient with double vision can be challenging and confusing, even for an experienced clinician. As with all neurologic problems, the history helps guide the thought process and approach to the patient. The examination may be straightforward but is sometimes difficult due to limited patient cooperation, altered level of consciousness, and subtlety of the ocular motility defect.

**Table 17.1** *Localization of diplopia based on the patient's history.*

Description	Anatomy	Differential diagnosis
Horizontal	Medial rectus (median longitudinal fasciculus)	Internuclear ophthalmoplegia Orbital trauma with muscle entrapment Myasthenia gravis Thyroid eye disease
	Lateral rectus	VI nerve palsy Myasthenia gravis
	Other	Breakdown of pre-existing horizontal phoria
Vertical	Superior oblique	IV nerve palsy
	Inferior oblique	Orbital trauma with muscle

		entrapment Thyroid eye disease
Oculomotor (III) nerve		Microvascular Aneurysmal (usually at junction of internal carotid and posterior communicating artery) Myasthenia gravis (pseudo IIIrd) Brainstem disease Cavernous sinus syndrome
Central vestibular pathways		Skew deviation
Other		Breakdown of pre-existing vertical phoria
Worse in downgaze	Superior oblique	IV nerve palsy (may compensate with head tilt)
Worse in upgaze	Inferior rectus restriction	Thyroid eye disease (may compensate with a chin-up posture)

---

## History

1. Determine whether the double vision arises from either eye alone (monocular) or only when viewing with both eyes (binocular).

Rationale: Monocular diplopia is an ocular problem. Binocular diplopia is a misalignment problem that may be neurologic.

Asking the question: “Does your double vision go away when you cover *either eye*?” or, “Does your double vision go away if you cover *one eye or the other*?” If the patient isn't sure, ask them to cover each eye individually

and report the result.

Decision tree:

- Monocular diplopia – refer to ophthalmologist for ocular evaluation.

Common causes: dry eyes, corneal problem, lens opacity or irregularity, macular or retinal disorder.

- Binocular diplopia – proceed to step 2.

## 2. Ascertain whether the misalignment is horizontal or vertical.

Rationale: Because our eyes are separated in the skull, double images are not truly vertical. However, knowing whether or not there is a vertical component helps to narrow down which eye muscles are underacting or overacting and limit the differential diagnosis.

Asking the question: “Are the two images next to each other/side-by-side, or is one higher than the other?” (Use your hands to demonstrate.) Decision tree:

- Horizontal diplopia – problem with the lateral or medial rectus.
- Vertical diplopia – problem with vertically acting muscles (superior and inferior rectus, superior and inferior oblique) or central vestibular pathways [1].
- Secondary question for vertical diplopia: “Is one image slanted?”

Rationale: superior oblique (4th nerve) palsy includes a torsional component.

## 3. Establish whether the diplopia is maximal in a given direction of gaze.

Rationale: The images will be maximally separated with gaze in the direction of action of the paretic muscle.

Asking the question: “Is the double worse when you look in any particular direction?”

Note that if the misalignment is subtle, the images may not be completely separated.

Thus far, we have narrowed the anatomical localization and differential

diagnosis based on history alone ([Table 17.1](#)).

4. Other key aspects of the history that help with etiology:

*Fluctuation:* Fluctuation throughout the day or from day to day, worsening with activity and improving with rest, suggests myasthenia gravis [2].

*Eyelid ptosis:* Ask about a “droopy eyelid(s).” Oculomotor nerve palsy (microvascular, infiltrating, demyelinating, aneurysmal), brainstem disease, myasthenia gravis, Guillain–Barré syndrome, Miller–Fisher variant, chronic progressive external ophthalmoplegia, Kearns–Sayre syndrome and pituitary apoplexy are associated with ptosis.

*Proptosis:* Ask about “prominent” or “bulging” eyes. Note that eyelid retraction may produce a similar appearance when there is no exophthalmos. Consider thyroid eye disease [3], an orbital mass (tumor, infection, vascular malformation, hemorrhage), or a process just posterior to the orbit (carotid–cavernous fistula or dural shunt, pituitary apoplexy).

*History of childhood strabismus:* Ask about “lazy” or “crossed” eyes as a child, or previous eye muscle surgery. Prior surgery may complicate the exam, and previously corrected strabismus may decompensate in adulthood producing diplopia.

*Worse at distance or near:* Abducens (VI) nerve palsies, convergence spasm, and other causes of esotropia (inward turning of the eyes) produce diplopia that is worse at distance. Internuclear ophthalmoplegia (INO) and other causes of exotropia (outward turning) cause diplopia that is worse at near (e.g. reading).

*Orbital congestion:* Ask about “bloodshot” or “swollen” eye(s). Carotid–cavernous fistula, dural shunt, orbital vascular malformation, inflammatory orbital pseudotumor, and causes of eye dryness (keratitis sicca, thyroid eye disease) produce conjunctival infection. There may also be eyelid edema or erythema.

*Audible bruit:* Ask about hearing whooshing noises or hearing their own pulse. Carotid–cavernous fistula, dural shunt, and vascular malformations are often associated with a subjective bruit. Increased intracranial pressure may produce pulsatile tinnitus.

*Dissimilar images:* If the image from one eye is larger or distorted, the patient may have an undiagnosed refractive error or macular disorder.

*Head turn or head tilt:* Patients will often try to adapt to their diplopia by turning or tilting their head. Congenital disorders (Duane syndrome, congenital IV nerve palsy) that do not generally produce diplopia may

decompensate with aging and cause double vision; old photographs reveal the abnormal head position. Head tilt often accompanies an acquired IV nerve palsy; a VI nerve palsy or INO may be associated with a head turn.

*Other neurologic or systemic symptoms:* The “company it keeps” is helpful. Patients with diplopia of brainstem origin almost always have other symptoms and signs of brainstem or cerebellar dysfunction (e.g. weakness, numbness, vertigo, balance and coordination problems, tremor, dysmetria, dysarthria, dysphagia, hiccups, nystagmus [4]). Symptoms and signs of endocrine dysfunction with headache, peripheral field loss, or visual loss may accompany a pituitary tumor or pituitary apoplexy. Progressive supranuclear palsy is associated with poor balance and falls, eyelid retraction producing a wide-eyed stare, an astonished or worried facial expression, decreased blink rate, bradykinesia, and axial rigidity (there may be hyperextension of the neck). Giant cell arteritis is a diagnostic consideration in the elderly; other manifestations are often present (e.g. headache, amaurosis fugax, jaw claudication, scalp tenderness, fever, weight loss, myalgias).

## Other caveats

- Not everyone with ocular misalignment sees double (examples: bilateral INO with marked exotropia and widely separated images, poor vision in one eye, ability to alternate fixation such as in alternating exotropia).
- Diplopia always starts suddenly; don't bother asking. However, gradual worsening suggests a mass lesion .

## Examination

### 1. Observe the patient.

Look for a head turn, head tilt, ptosis, and facial asymmetry or weakness. Is there eyelid retraction (is the white sclera visible above or below the iris)?

### 2. The forest – ocular motility exam.

- A. Have the patient look straight ahead and look for a misalignment. Ptosis or proptosis can cause confusion if you use the eyelid margin for a landmark (covered in step 3).
- B. Ask the patient to slowly follow your finger (pursuit

movements) with one eye at a time (ductions) and using both eyes together (versions) to determine the extent of excursion of the eye movements. Observe horizontal and vertical eye movements.

- Most normal individuals can “bury their sclerae” in horizontal gaze. Very myopic (nearsighted) patients have large globes and a few mm of sclera may be visible in abduction and adduction.
- It is often easier to understand the ocular motility deficit testing one eye at a time (patients can change their fixating eye during testing).
- Gradual loss of upgaze is normal with aging, particularly after age 70 years. Loss of downgaze is abnormal.
- If the patient has poor vision or is blind, ask them to follow their own finger as you guide it.
- Record your findings systematically. Estimating percentage of normal excursion is easily understood and helps follow the patient's progress.
- A superior oblique palsy may not be apparent when asking the patient to look down in the oblique positions.

- C. Determine whether the pursuit movements are smooth.
- D. Test horizontal and vertical saccades by asking the patient to look back and forth between your finger and your nose. Observe the speed of the eye movements and determine whether or not both eyes refixate toward your nose simultaneously. Internuclear ophthalmoplegia produces an adductor lag that is best determined using this test.
- E. Observe for nystagmus or other abnormal eye movements (viewing the fundus using the direct ophthalmoscope is useful for observing subtle eye movements).
- F. Additional tests are needed if myasthenia gravis is suspected.
  - Fatigue with prolonged upgaze – ask the patient to look up at your finger for 1–2 minutes and observe for ptosis or downward drift of the globes.
  - Cogan lid twitch sign – have the patient look down for a minute then rapidly refixate to primary position (at the examiner's nose if standing in front of the patient). With

myasthenia, the eyelids overshoot and then drift back down to fixation.

- See--saw ptosis – if ptosis is present, manually lift the ptotic eyelid and determine whether the contralateral eyelid becomes more ptotic.
- Orbicularis oculi weakness – one should not be able to manually overcome forceful eye closure.

G. Forced duction testing if suspecting a restrictive process. After instilling topical anesthetic drops, the patient is asked to look in the direction of paresis. A cotton-tip applicator or forceps is used to push on or grasp the sclera and try to move the globe to full excursion. Resistance indicates a restrictive process.

3. The trees – determining subtle motility problems. This is the confusing part because it's all “upside down and backwards” [5].

*Corneal light reflex:* The reflection of a light shone onto the eyes should be centered on the cornea if the eyes are aligned. The “upside down and backwards” part: Inward turning of the eyes (esotropia) deflects the corneal light reflex laterally; outward turning of the eyes (exotropia) decenters the light reflex medially. Upward deviation (hypertropia) deflects the light reflex inferiorly; downward deviation (hypotropia) deflects the light superiorly.

*Cover and alternate cover testing:* Cover testing requires a cooperative patient with good fixation. These tests and the dissimilar image tests interrupt the stimulus for binocular fusion and bring out an underlying misalignment.

Ask the patient to focus on a distant target. Use your hand or an occluder to cover one eye and watch the movement of the other eye – does it move to take up fixation? The direction of movement is *opposite* the direction of the deviation (if the eye moves in, it was turned out). Also watch for movement of the occluded eye when you uncover it. Have the patient turn their head in different directions as they fixate on the same target to determine ocular misalignment in different directions of gaze. Moving the occluder back and forth between the two eyes may unmask an underlying misalignment (phoria).

*Dissimilar image testing:* This is performed with a Maddox rod or a red lens (or a small piece of colored transparent plastic, such as a report cover). Put the Maddox rod or red lens in front of the right eye. In a darkened room, stand in front of the patient and shine a light directly at their eyes; ask them to tell you

where they see the light and the colored image of the light (if using a Maddox rod, the light will appear as a single line oriented 90 degrees to the lines on the rod). The location of the colored image (viewed from the right eye) is “upside down and backwards” from the eye position. For example, if they see the colored image on their left, their right eye is turned out. Repeat in different directions of gaze, and with head tilt in both directions for a suspected superior oblique palsy. This may be quantitated using prisms or by the patient's estimation of distance between the two images.

Note that most normal people are not “perfectly aligned” with alternate cover and dissimilar image testing, and have a small misalignment that is clinically inapparent, but brought out by this type of testing (phoria). There may be a horizontal separation between the colored image and the white image but the distance between the two images will be small, and generally constant in different directions of gaze .

## **Examining comatose patients**

Rationale: Eye movements are a key component of the coma exam. They will help determine brainstem function and localize the neurologic deficit which may help determine prognosis.

1. Observe for spontaneous eye movements. If full excursion of the eyes is present, no additional ocular motor testing is needed. Also look for patterns of eye movements (ping-pong gaze, ocular bobbing, and others).
2. Oculocephalic maneuver: Often called “doll's eyes,” a confusing and misleading term, the test stimulates the vestibular system via semicircular canals in an attempt to generate eye movements. Do not perform this maneuver in patients with suspected cervical spine disease. The head is moved rapidly, but not forcefully, from one side to the other. The normal response is an eye movement in the direction opposite the head movement. Vertical and horizontal movements may be tested.
3. Oculovestibular maneuver: Referred to as “cold calorics,” this test is only necessary if there is no response to oculocephalic testing. Examine the ear canal to ensure there is no obstruction and that the tympanic membrane is patent. Elevate the head of the bed by 30 degrees and place towels around the patient's head. Attach a butterfly needle to a

large (at least 20 gauge) syringe filled with iced water, and break off the needle. Insert the butterfly tubing far enough into the ear canal so that the cold water will contact the tympanic membrane as it is injected, being careful not to rupture the tympanic membrane with the tubing. Rapidly inject 20–30 mL of iced water into the ear canal, remove the tubing, manually lift the eyelids, and observe for eye movement. The eyes should deviate towards the ear canal being injected, which may take a minute or more and may require a second bolus of iced water. Wait at least 5 minutes before testing the other side. The oculocephalic maneuver may be combined with the oculovestibular test to use the most potent stimulus to drive the eyes to full horizontal excursion. Bilateral instillation of cold water produces downward eye deviation; bilateral instillation of warm water stimulates upward deviation .

## Case vignette

*Presentation:* A 67-year-old male has experienced diplopia for 3 days with pain around the right eye.

*Key questions:*

1. Diplopia resolves if either eye is closed.
2. One image is higher than the other.
3. It is present in all directions of gaze but worst when looking to his left.

*Additional history:* Initially, the images were fairly close together and he could fuse them with effort. For the past 2 days, he has not been able to fuse the images. There is moderately severe aching pain around the right area. He noticed that his right eyelid was a bit droopy the morning of his evaluation. He has no other neurologic symptoms. There is a 10-year history of type 2 diabetes under “good control” with medications. He has no other medical problems and otherwise feels well.

*Differential diagnosis based on the history:* III and IV palsy cause vertical diplopia and may be accompanied by pain, usually ipsilateral to the side of the palsy. Ptosis makes an isolated IV nerve palsy unlikely. Myasthenia gravis causes diplopia (in any pattern) with ptosis; a 3-day history may not be long enough to establish fluctuation but myasthenia gravis is not painful. Thyroid eye disease can present without other manifestations of thyroid disease and cause diplopia in any pattern; the pain, if present, is usually bilateral and one would expect to see eyelid retraction – ptosis is not present unless there is concomitant

myasthenia gravis. Skew deviation produces vertical diplopia but other symptoms of brainstem disease would be present. Uniocular eye pain would be unusual. A decompensated phoria would not produce ptosis or pain. Giant cell arteritis is a possibility because of his age and new onset of pain.

*Examination:* The visual acuity was normal in both eyes. The pupils were equal and reactive to light, with no afferent pupillary defect. There was 4 mm of right ptosis. There was moderate (50%) limitation of upgaze, downgaze, and adduction of the right eye. Abduction was normal. Incyclotorsion was present. There was no proptosis or conjunctival injection. The fundus examination was normal. Examination of the left eye was normal. The neurologic exam was otherwise normal.

*Looking for more clues:* (Myasthenia?) There was no fatigue of the lids or globes with prolonged upgaze. Cogan's lid twitch sign was negative with no see-saw ptosis. (Giant cell arteritis?) The temporal artery pulses were strong and there was no temporal artery tenderness.

*Diagnosis:* Pupil-sparing right III nerve palsy. The most likely cause is microvascular disease, given his history of type 2 diabetes. Pain is present in about one third of cases. A mass lesion or aneurysm is less likely because the pupils are normal. Giant cell arteritis rarely causes a III nerve palsy.

*Plan:* Check hemoglobin A1c and exclude hypertension. The sedimentation rate (ESR) may be elevated because he has diabetes and clinical suspicion is low for giant cell arteritis, so may defer ESR unless other symptoms appear. The palsy is incomplete and may continue to worsen over the next several days; neuroimaging is warranted if he develops anisocoria (ipsilateral pupil larger). The natural course is one of recovery, which may take up to 4 months. Most patients have complete resolution. If there is no improvement at 4 months, or concern for an aneurysm or compressive lesion, neuroimaging may be performed .

## References

1. Wong AM. Understanding skew deviation and a new clinical test to differentiate it from trochlear nerve palsy. *J AAPOS* 2010; 14:61–7.
2. Kusner LL, Puwanant A, Kaminski HJ. Ocular myasthenia: diagnosis, treatment, and pathogenesis. *Neurologist* 2006; 12:231–9.
3. Cockerham KP, Chan SS. Thyroid eye disease. *Neurol Clin* 2010; 28:729–55.

4. Keane JR. The pretectal syndrome: 206 patients. *Neurology* 1990; 40:684–90.
5. Friedman DI. Pearls: Diplopia. *Semin Neurol*. 2010; 30:54–65.

## 18 Dissociative disorder

---

Danielle G. Koby and W. Curt LaFrance, Jr.

*Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Dissociation is understood as a deviation from the typically integrated elements of consciousness, autobiographical memory, identity, and over-arching sense of self [1] and is present as a primary symptom across a number of so-named dissociative disorders and as a component symptom in select others. Throughout the histories of neurology and psychiatry, considerable debate has taken place regarding the nature, etiology and course of dissociative phenomena. While historically regarded as pathologic, dissociation may be seen as a natural consequence of overwhelming trauma, and more recent conceptualizations maintain the necessity of some degree of individual vulnerability or predisposition toward this pattern of responding [2]. Considerable work continues toward elucidating a theoretical model of mental activities and responses to trauma [3], while neuroanatomical investigations of dissociation have begun to reveal differences in the brain function and structure [4] of individuals with histories of dissociation and trauma. As with any complex behavior, the role of cultural or religious beliefs and practices should factor prominently in any explanation of apparent dissociative phenomena.

The differential diagnosis includes: encephalopathy/delirium (e.g. Wernicke–Korsakoff's, metabolic derangement, etc.), seizure (epileptic or non-epileptic), complicated migraine, mass/ tumor, stroke, head injury, transient global amnesia, parasomnia, panic attack, psychosis, catatonia, and malingering [5]. A not uncommon occurrence with seizures are dissociative-like symptoms, including fugue states (in cursive epilepsy), déjà vu , déjà entendu , jamais vu , and jamais entendu . After work-up directed at excluding these paroxysmal possibilities, and absent a neurologic, general medical or other explanation for the presence and severity of symptoms, the following psychiatric diagnoses may appropriate for consideration.

## Dissociative amnesia

As the name suggests, the primary feature of this disorder is a substantial yet reversible loss of autobiographical memory not fully explained by another current neurologic or psychiatric disease process. Reported memory gaps often surround a recent or remote traumatic stressor and typically consist of inability to recall details immediately following the event. Alternatively, an individual may retain only partial memory for a sequence of traumatic events and their aftermath. More pervasive forms of dissociative amnesia have also been reported, including failure to recall the entirety of one's past, amnesia for all past events up to and including the present, and failure to recall events within one category or domain of functioning, *e.g.* family life, work history. Memory symptoms may co-occur with disturbances in mood, cognition, occupational and interpersonal functioning and cause clinically significant distress. Episodes of amnesia may present at any age, may be variable in duration, and may occur as an isolated incident or as a more chronic pattern of amnestic episodes. One specific type of dissociative amnesia includes fugue states, described below.

While little research has been directed toward the underlying neurobiology of memory impairment in dissociative amnesia, preliminary fMRI studies suggest increased activity in prefrontal cortex with diminished and potentially inhibited hippocampal activation during amnestic periods [6]. Considerable debate continues around the plausibility of recovered or so-called repressed memories of remote trauma and, particularly, childhood sexual abuse. While no consensus has been reached, logical alternatives and contextual models for ostensible “forgetting” of past experiences have been identified [7] and should be vetted during the process of establishing dissociative amnesia as a primary diagnosis .

## Dissociative fugue

Fugue states are now a specifier of Dissociative Amnesia and characterized by travel from one's home or habitual place of activity, *e.g.* work or school, with simultaneous partial or complete loss of autobiographical history. Correspondingly, the individual experiences confusion about his/her identity during the fugue state and may in rare cases assume elements of a new identity entirely. The duration of travel may span hours to months, during which little observable psychopathology is present, and the individual is often able to engage in complex behaviors. Resolution of fugue is frequently rapid although amnesia for those events may persist, as may amnesia for previous traumatic events. As

in the case of dissociative amnesia, traumatic stressors are believed to precipitate fugue states.

## Dissociative Identity Disorder

Individuals presenting with Dissociative Identity Disorder (DID) (formerly referred to as multiple personality disorder) report or appear to experience more than one unique identity or personality with variable amnesia for personal and historical events between those entities. Frequent gaps in recent and remote autobiographical memory are reported by what is typically one primary identity present the majority of the time. Evidence of amnesia may also come from witnesses of behavior that is seemingly out of character for and/or denied by the patient entirely. Alternate identities may emerge in the context of acute stress, and symptoms of DID are most often documented amid a history of severe childhood physical or sexual abuse. Psychiatric comorbidity, in the form of mood disturbance, post-traumatic symptoms, conversion symptoms, eating disorders, sexual disorders, and maladaptive interpersonal functioning, is common among individuals with DID across one or more alternate personalities. Prevalence data indicate symptoms are significantly more common in adult women, with a typical onset in young adulthood (ages 20–40), significant delay to diagnosis (6–7 years), and variable, often chronic, course of illness.

Increasingly rigorous research into neurobiologic underpinnings of DID has revealed unique patterns in such parameters as regional cerebral blood flow, including increased activity in frontal, orbitofrontal, and occipital cortex among patients with DID, compared with healthy controls without a history of trauma [8]. Psychophysiological investigations have also demonstrated distinct patterns of autonomic responding between alternate personality states, and studies of cognition appear to confirm differential memory for autobiographical and emotion-laden content. More research is needed to uncover the foundations of subjective alternate identities but also the more fundamental elements of consciousness, divided and selective attention, and self-awareness which may appear disrupted in this and other dissociative disorders.

## Depersonalization Derealization Disorder

Primary elements of *depersonalization* include a sense of detachment, distance, or estrangement from oneself. Additional symptoms may include feeling like an external observer of one's own mental or physical events, flat affect, perceived

lack of control over one's own body or speech, disruptions in sensory perception, and the impression that things in the external environment are not real (*derealization*). Importantly, individuals remain able to differentiate symptoms from reality, *i.e.* do not believe that others, perceptions, or sensations are actually “not real.” Perceptual abnormalities may also include increases or reductions in the size of objects or the perception that people are unfamiliar or robotic. While the discrete, occasional experience of such symptoms is generally unremarkable, recurrent or persistent symptom episodes causing significant distress may represent Depersonalization Derealization Disorder (DD). Psychiatric comorbidity is not uncommon in DD and may include depression, anxiety, personality disorders, and substance-related disorders, as well as those disorders in which depersonalization is a key symptom, such as post-traumatic stress disorder and panic attacks. In fact, symptoms of depersonalization per se may not be presenting complaints for this patient population but may rather come to light after a comprehensive psychiatric and, oftentimes, neurologic evaluation. Age at diagnosis may be earlier than in other dissociative disorders, presenting in early to mid-adolescence, with potential symptom onset in late childhood. The course of illness is variable, as is the duration of individual episodes. As with those dissociative disorders previously described, there is a subset of individuals with symptom onset following exposure to a traumatic stressor and an ensuing waxing and waning course of illness. Neuroimaging research has implicated inferior parietal cortex, angular gyrus, and insular cortex in feelings of detachment and depersonalization while decreased limbic system and increased prefrontal cortical activity may be more central to emotional numbing and flattened affective responses [ 9].

## **Conversion disorder (Functional Neurological Symptom Disorder)**

Conversion disorder (CD) is characterized by symptoms or deficits of voluntary motor or sensory functioning without clear medical evidence to explain the entirety or severity of reported symptoms. These are also referred to as *functional* symptoms, in that they do not represent observable structural abnormalities but rather aberrations in the concerted working together, or functioning, of system components. Symptoms appear to mimic a variety of neurologic impairments including tremor and gait disturbance, apparent syncopal episodes, paralysis, weakness, impaired balance, convulsions, speech arrest, visual deficits, and auditory symptoms including deafness and

hallucinations. Symptoms are non-volitional and individuals frequently perceive no control over the severity or frequency of symptom episodes. Individuals may be aloof and seemingly unconcerned by the presence and impact of symptoms or, conversely, dramatic and highly distressed. However, “*la belle indifference*” is not seen in the majority of patients with CD, and psychological factors may not be apparent upon initial examination. Non-neuroanatomic signs on exam may aid with “ruling in” conversion disorder [10], when structural and neurophysiologic causes have been adequately excluded. Common psychiatric comorbidities include dissociative disorders, depression, and personality disorders. Conversion disorders are significantly more frequent in women, tend to present between the second and fourth decades of life and may be acute or gradual in their emergence.

While the American Psychiatric Association places conversion disorders among Somatic Symptom and Related disorders, these disorders are categorized in ICD–10 as dissociative. Perhaps correspondingly, two distinct types of dissociation have been recognized in the literature, the first being psychological (or psychoform) in nature and encompassing interruptions in identity, consciousness, and memory. The second type, somatoform dissociation, involves disintegration of bodily sensations, control, and movements [11]. It has been reliably measured across several dissociative and other psychiatric populations and may be most strongly correlated with physical and sexual, *i.e.* contact, abuse, rather than emotional trauma [12]. Conversion symptoms that involve a change in consciousness are widely regarded as the product of dissociation. This view is supported by recent neuroimaging evidence of strengthened neural connectivity between brain areas responsible for emotion and motor activity in patients with non-epileptic seizures, which correlated with self-reported symptoms of dissociation, relative to healthy control participants [13].

## **Acute stress and post-traumatic stress disorders**

During or immediately following a traumatic stressor an individual may develop significant dissociative symptoms, including perceptions of numbness or detachment, diminished emotional responding, depersonalization, amnesia, derealization, and reduced awareness of the surrounding environment. When accompanied by symptoms of anxiety including re-experiencing the traumatic event, avoidance of trauma-related stimuli, persistent negative alterations in mood, or cognition and increased (anxious) arousal, a diagnosis of acute stress disorder may be made for up to 4 weeks after the traumatic event. When such

symptoms persist beyond 4 weeks, a diagnosis of Post-traumatic Stress Disorder (PTSD) may be made. The majority of individuals with Acute Stress Disorder may go on to develop PTSD. Diagnoses of PTSD continue to require the presence of “numbing of general responsiveness,” which may include dissociative symptoms of amnesia, feelings of numbness or detachment, or diminished emotional responding or interest in previously enjoyed activities.

## Case vignette

A 45-year-old married female was treated for 2 years for epilepsy, and seizures were refractory to a variety of antiepileptic drugs. She reported a remote history of closed head injury with brief loss of consciousness as a young woman, a traumatic upbringing, and recent job loss after the onset of her seizures. Prior work-up revealed slowing on routine EEG and unremarkable brain MRI performed with an epilepsy protocol. Admission for inpatient video-EEG long-term monitoring captured her typical events, which included unresponsive staring for 30 seconds to 4 minutes with right or left hand and arm shaking followed by gradual recovery of awareness, with no epileptiform activity before, during, or after the ictus. A second type of event was observed where she spoke in a childlike voice for 10–30 minutes, was frightened by males, and she was amnestic of the event afterwards. Baseline EEG revealed normal background during this event. Based upon her history, presentation and video-EEG, she was diagnosed with psychogenic non-epileptic seizures and dissociative identity disorder.

## Conclusion

The patient presenting with dissociative symptoms may have a medical, neurologic, or psychiatric cause (or a combination). Comprehensive work-up and neuropsychiatric evaluation can assist with uncovering the underlying etiology .

## References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5). Arlington, VA: American Psychiatric Publishing, 2013.
2. de Ruiter MB, Elzinga BM, Phaf RH. Dissociation: cognitive capacity or

dysfunction? *J Trauma Dissociation* 2006; 7:115–34.

3. Nijenhuis ER, van der Hart O. Dissociation in trauma: a new definition and comparison with previous formulations. *J Trauma Dissociation* 2011; 12:416–45.
4. Ehling T, Nijenhuis ER, Krikke AP. Volume of discrete brain structures in complex dissociative disorders: preliminary findings. *Prog Brain Res* 2008; 167:307–10.
5. Rugg-Gunn FJ, Sander JW. Nonepileptic paroxysmal neurological and cardiac events. In Schachter SC, LaFrance Jr WC, Eds. *Gates and Rowan's Nonepileptic Seizures*, 3rd edn. Cambridge: Cambridge University Press, 2010: 62–76.
6. Kikuchi H, Fujii T, Abe N *et al.* Memory repression: brain mechanisms underlying dissociative amnesia. *J Cogn Neurosci* 2010; 22:602–13.
7. McNally RJ. Dispelling confusion about traumatic dissociative amnesia. *Mayo Clin Proc* 2007; 82:1083–90.
8. Sar V, Unal SN, Ozturk E. Frontal and occipital perfusion changes in dissociative identity disorder. *Psychiatry Res* 2007; 156:217–23.
9. Sierra M, David AS. Depersonalization: a selective impairment of self-awareness. *Consciousness Cogn* 2011; 20:99–108.
10. Stone J, LaFrance WC Jr, Brown R, Spiegel D, Levenson JL, Sharpe M. Conversion Disorder: current problems and potential solutions for DSM–5. *J Psychosom Res* 2011; 71:369–76.
11. Nijenhuis ER, Spinhoven P, Van Dyck R, Van der Hart O, Vanderlinden J. The development and psychometric characteristics of the Somatoform Dissociation Questionnaire (SDQ-20). *J Nerv Ment Dis* 1996; 184:688–94.
12. Simeon D, Smith RJ, Knutelska M, Smith LM. Somatoform dissociation in depersonalization disorder. *J Trauma Dissociation* 2008; 9:335–48.
13. van der Kruis SJ, Bodde NM, Vaessen MJ *et al.* Functional connectivity of dissociation in patients with psychogenic non-epileptic seizures. *J Neurol Neurosurg Psychiatry* 2011: doi: 10.1136/jnnp-2011–300776.

# 19 Dizziness

---

Martin GIZZI and Manpreet Multani *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

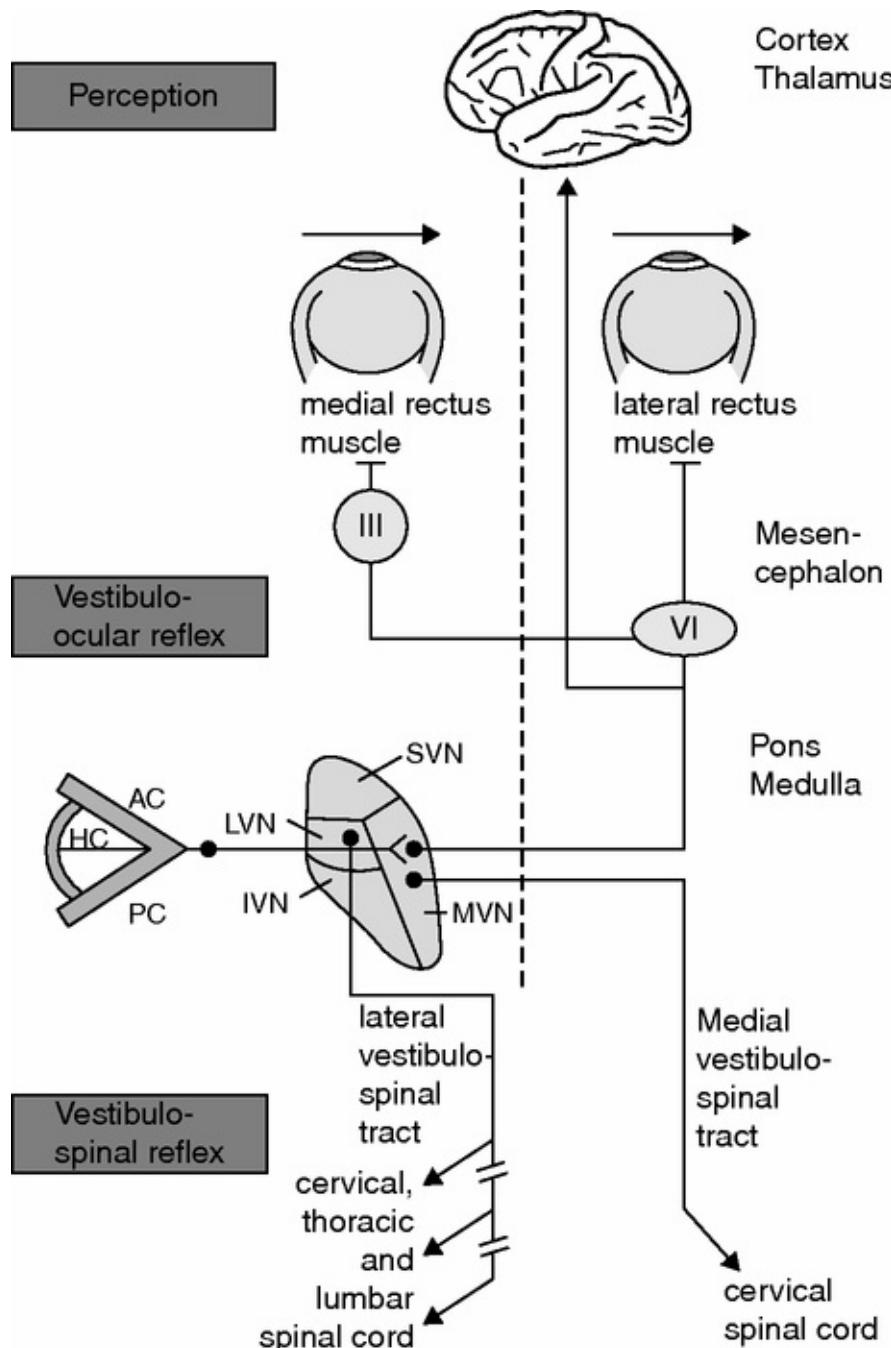
## Introduction

“Dizziness” is a non-specific term reflecting disturbance of normal balance perception and spatial orientation. Dizziness can be classified into the following categories depending upon the quality of symptoms:

1. Vertigo: An illusory perception of motion – typically spinning – of the subject or of the surroundings. This vestibular sensation does not need to be rotational as patients with otolith organ dysfunction may have a sense of rocking or tilting. (Please refer to [Chapter 76](#) on vertigo for a more detailed discussion.)
2. Lightheadedness : Usually described as an impending sensation of fainting.
3. Imbalance : A sense of unsteadiness, not necessarily associated with vertigo or lightheadedness.
4. Non-specific dizziness : Reflecting spatial disorientation and used when none of the above three match the patient's perception.

## Vestibular anatomy and physiology

The vestibular system includes the labyrinth (semicircular canals and otolith organs), the vestibular nuclei, and their brainstem and cortical connections ([Figure 19.1](#)). The vestibular, ocular, and spinal motor systems work together to maintain stability of eyes, head, and body in space. The semicircular canals and otolith organs work in opposed pairs to sense angular and linear acceleration, respectively. The afferents from these end-organs project fibers into the vestibular nuclei near the pontomedullary junction. These, in turn, synapse with the ocular motor nuclei to generate the vestibulo-ocular reflex (VOR) . Somatosensory receptors in skin, joints, and muscles provide input to the vestibular nuclei for the maintenance of posture. Visual input is integrated with vestibular and somatosensory feedback to maintain equilibrium.



**Figure 19.1** Schematic drawing of the horizontal vestibulo-ocular reflex. AC, HC, PC: anterior, horizontal, and posterior semicircular canals; SVN, LVN, IVN, MVN: superior, lateral, inferior, and medial vestibular nuclei; III, VI, oculomotor and abducens nuclei.

## Differential diagnosis of lightheadedness

Etiology	Specific type	Pathophysiology	Clinical features
Cardiovascular	Arrhythmias and other heart diseases	Decreased cardiac output leading to inadequate cerebral perfusion	Associated palpitations and diaphoresis Episodes may be unrelated to posture Pallor is commonly present during episodes
	Mixed autonomic dysfunction	Sympathetic and parasympathetic dysfunction leading to orthostatic hypotension	Dizziness upon standing and aborted with sitting or lying positions Additional features may include decreased sweating, constipation, and erectile dysfunction Associated with small fiber neuropathies, neurodegenerative and auto-immune diseases
	Sympathetic dysfunction or postural orthostatic tachycardia syndrome	Sympathetic denervation of lower extremities with relative preservation of cardiac	Dizziness and fatigue on standing Anxiety and tremor may also be present

(POTS)	sympathetic supply	Increase in heart rate by 30 bpm on standing without significant reduction in blood pressure
--------	--------------------	--

## Differential diagnosis of non-specific dizziness

Etiology	Specific type	Pathophysiology	Clinical features
Metabolic	Hypoglycemia	Inability to meet metabolic demands of the brain manifests as dizziness	Commonly associated with diabetes mellitus Diaphoresis and palpitations are usually present
	Dehydration	Orthostatic hypotension	Dry mucous membranes and decreased skin turgor may be present Tachycardia is usually present
Toxic	Medications	Antihypertensives, sedatives, and antidepressants are frequently associated with dizziness	Temporal relationship between the onset of symptoms and start of the medication is present

Some medications can present with postural hypotension

Psychiatric	Hyperventilation syndrome	Metabolic derangement associated with hypocapnea	Patients are usually young anxious women Distal paresthesias or tetany may be present Reassurance and re-breathing into a bag terminates the attack
	Panic attacks	Thought to be associated with increased autonomic outflow from the locus coeruleus	Dizziness is always associated with precipitating psychological stimuli and subjects are symptom free between the attacks Anxiety and agoraphobia are common These episodes are not related to hyperventilation syndrome

# Differential diagnosis of vertigo

Etiology	Specific type	Pathophysiology	Clinical features
Structural	Arnold Chiari malformation	Downward herniation of cerebellum and possibly the lower medulla	Oscillopsia (illusion of visual motion) Nystagmus (downbeat or gaze-evoked) Ataxia Occipital headache Myelopathic signs <i>e.g.</i> motor weakness, sensory loss, or hyperreflexia Signs of lower brainstem involvement <i>e.g.</i> dysphagia, dysarthria
	Cerebello-pontine angle mass	Destruction of the vestibular nerve Most common CP angle lesions are acoustic neuromas, meningiomas, and epidermoid tumors	Vertigo is rare and, if present, usually lasts for hours Progressive sensorineural hearing loss Tinnitus Speech perception thresholds are impaired Other cranial

			nerve deficits may be present due to compression by the tumor
	Superior semicircular canal dehiscence	Thinning or loss of bone overlying the superior semicircular canal, which creates a third mobile window into the inner ear	Vertigo and nystagmus induced by sound, Valsalva, or hyperventilation Tulio's phenomenon (vertigo induced by loud sounds) may be present Hyperacusis to bone conducted sounds Audiogram shows an air– bone gap, greatest at low frequencies
Toxic	Antibiotics	Aminoglycosides can damage cochlear and vestibular hair cells	Oscillopsia Vertigo is uncommon Bilateral high frequency SNHL Tinnitus Severe imbalance
	Alcohol	Changes in the specific gravity of endolymph leading to	Positional alcoholic nystagmus Ataxia

		positional deflection of the cupula	
Infectious	Vestibular neuritis	Inflammation of the vestibular nerve from viral infection	Severe vertigo lasting for days Nausea and vomiting are prominent Hearing is preserved Spontaneous mixed horizontal and rotary nystagmus Unilateral vestibular hypofunction on caloric portion of ENG
	Labyrinthitis	Bacterial or viral infection of the inner ear	Similar features to vestibular neuritis but with hearing loss
Degenerative	Otosclerosis	Autosomal dominant condition with bony overgrowth of the footplate of stapes	Episodic vertigo is seen in 10% of patients due to vestibular involvement Conductive hearing loss
	Spinocerebellar degeneration	Autosomal dominant disorders associated with degeneration of the cerebellum	Ataxia is the most common feature Vertigo occasionally

		cerebellum and brainstem	present in brief recurrent episodes
			Extrapyramidal signs <i>e.g.</i> tremor, chorea may also be seen
Para-neoplastic		Auto-immune process affecting the cerebellum and brainstem	Oscillopsia lasting for days Nystagmus (periodic alternating nystagmus or vertical nystagmus) is usually present Ataxia Signs of brainstem dysfunction <i>e.g.</i> diplopia, dysphagia can be seen Neuropsychiatric features may be present
Demyelinating	Multiple sclerosis	Demyelination of the vestibular nerve or vestibular nuclei	Vertigo lasting days Ataxia may be present Nystagmus Smooth pursuit is usually impaired Internuclear ophthalmoplegia (INO) may be

			present
Vascular	Infarction	Brainstem infarction Labyrinthine infarction (or AICA occlusion)	Vertigo lasting days Other neurologic signs <i>e.g.</i> ataxia, hemisensory loss, hemiparesis, cranial nerve deficits Vertigo lasting days Unilateral hearing loss
	TIA	Ischemia affecting the posterior circulation	Vertigo lasting for 2–20 minutes Other transient neurologic deficits <i>e.g.</i> diplopia, ataxia, hemisensory loss, or hemiparesis may be present Isolated vertigo is less likely to be TIA but in patients with vascular risk factors, it should be evaluated with higher suspicion
Idiopathic	Ménière's disease	Increased endolymphatic fluid in the	Vertigo lasting for hours to a day

	membranous labyrinth	Fluctuating, progressive and asymmetric SNHL Tinnitus and aural fullness that fluctuate with the episodes of vertigo Nausea, vomiting, and diaphoresis are common Audiometry classically shows low frequency hearing loss
BPPV	Displacement of otoconia from utricle into the semicircular canals. The displaced otoconia exert pressure on the cupula with position changes	Vertigo lasting seconds (< 90 s), induced by changes in head position Nystagmus (mixed vertical and rotatory) accompanies the vertigo Nausea and vomiting may be present Dix–Hallpike test is positive (vertical and torsional nystagmus seen after 3–10 s that

			tatigues after 30–60 s)
	Vestibular migraine	Believed to be related to vasodilation caused by the release of various vasoactive substances and neuropeptides	Vertigo lasting hours to days Headache may or may not be present History of motion sickness is common Nausea is common Personal or family history of migraine headaches Responds to regular anti- migraine medications
Ictal	Vestibular seizures	Ictal discharges from primary vestibular cortical zones (parieto- temporal)	Vertigo lasting a few seconds with no positional triggers Auditory or visual hallucinations accompany the episodes Altered consciousness with the episodes Family or personal history of epilepsy <small>EEG may show</small>

**EEG may show**  
parieto-temporal  
or occipital  
epileptiform  
activity

Trauma	Perilymph fistula Temporal bone fractures Brainstem concussion Post-traumatic otolith vertigo	Rupture of the oval window due to surgery or trauma Direct injury of vestibular nerve or labyrinth Thought to be caused by shearing forces on brainstem vestibular connections during trauma Caused by the displacement of otoconia	Acute fistula formation causes vertigo and hearing loss lasting days A partially healed fistula causes recurrent vertigo lasting minutes Vertigo may be precipitated by hyperventilation, Valsalva, and tragal compression Hearing loss is present Tullio's phenomenon is seen Vertigo lasting for days Hearing loss is usually present, more so with transverse fractures Mixed horizontal rotatory nystagmus beating to the unaffected side
--------	--	--	--

-----  
may be present  
Vertigo lasting  
days  
Other signs of  
brainstem  
involvement  
including cranial  
nerve deficits  
and long tract  
signs may be  
present  
Similar to  
idiopathic BPPV

### Psychiatric

Patients with  
anxiety disorder  
and obsessive  
compulsive  
disorder may  
develop phobic  
postural vertigo

Vertigo and  
subjective  
unsteadiness  
while in an  
upright position  
or walking  
Normal clinical  
balance testing  
Vertigo may be  
spontaneous or  
induced by  
exposure to  
complex visual  
stimuli  
Anxiety is a  
characteristic  
feature  
Continuous  
vertigo lasting  
more than 1  
week without  
daily variation  
also suggests  
psychogenic  
etiology

## Differential diagnosis of imbalance

Cerebellar dysfunction	Failure of integration of visual, vestibular, and somatosensory inputs	Signs of a cerebellar disorder including ataxia, scanning speech, intention tremor, or nystagmus may be present Oscillopsia Vertigo may be present Refer to <a href="#">Chapters 7</a> and <a href="#">8</a> on ataxia for further details
Peripheral neuropathy	Disruption of proprioceptive afferents	Unsteadiness of gait, more so in the dark and on uneven ground Loss of proprioception may be present on exam
Visual dysfunction	Disruption of reliable visual feedback	Low or double vision may be seen Impairment of saccades or pursuit may be seen Excessive difference in prescription between the two eyes may be seen
Bilateral vestibulopathy	Dysfunction of both labyrinths or vestibular nerves due to ototoxicity, meningitis, trauma, or Ménière's disease	Oscillopsia and blurred vision with head movements Unsteadiness of posture and gait, especially in low light Hearing loss may be

present

---

## Case vignette

A 72-year-old male with history of hypertension and diabetes presents to the ER with the acute onset of vertigo, accompanied by nausea and vomiting. He has no associated focal weakness, numbness, ataxia, diplopia, or swallowing problems. He denies tinnitus but reports hearing loss on the right side. He also gives a history of a recent upper respiratory infection. On examination, he has hearing loss, pure torsional nystagmus, and a normal VOR on head thrusts. The remainder of his neurologic examination is unremarkable.

**Comment:** Initially, one might attribute his vertigo to a peripheral lesion such as labyrinthitis but the examination is consistent with a central lesion. Pure unidirectional – in this case torsional – or direction-changing nystagmus is indicative of a central lesion. Additionally, VOR abnormalities on head thrust testing are almost always present with peripheral lesions. The acute onset of vertigo with hearing loss in older patients with multiple vascular risk factors should raise a suspicion of AICA (anterior inferior cerebellar artery) infarction. A CT angiography of the head revealed occlusion of AICA. The hearing loss was a result of impaired flow in the internal auditory artery, usually a branch of AICA.

## Further reading list

Brandt T. *Vertigo, its Multisensory Syndromes*. Berlin: Springer-Verlag, 1991.

Brandt T, Dieterich M, Strupp M. *Vertigo and Dizziness-Common Complaints*. New York, NY: Springer, 2005.

American Academy of Neurology. *Continuum on Neuro-otology*, August 2006.

Gizzi M, Rosenberg M. The diagnostic approach to the dizzy patient. *The Neurologist* 1998; 4:138–47.

## 20 Drop attacks

---

Lourdes Bello-Espinosa *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Drop attacks (DA) are defined as sudden loss of balance without loss of consciousness and unaccompanied by warning symptoms. Usually described as “the legs giving way,” they are typically followed by complete recovery in seconds or minutes. A DA is a symptom and not a diagnosis; causes are diverse [1].

### Diagnostic approach

Clinical history, especially circumstances about the attacks, provides vital information for identifying potential underlying etiologies. Table 20.1 summarizes information that can guide speculation about the diagnosis. Diagnostic work-up may include basic blood work such as CBC and chemistry metabolic panel, electroencephalography (EEG), and magnetic resonance imaging/magnetic resonance angiography (MRI/MRA) of the brain and neck. Neurologic and cardiology consultation are usually indicated. Ear, Nose and Throat specialists may be involved when a vestibular cause is a possibility. Treatment is contingent upon the specific etiology identified.

**Table 20.1 Classification of drop attacks (DA) and differential diagnosis.**

Etiology	Specific entity	Possible symptoms	Possible features
Vascular	Vertebral artery insufficiency	Vertigo, nausea, vomiting, ataxia, naresis altered	Cranial nerve involvement, visual

	<u>Movement</u>	<u>Painful, altered vision</u>	<u>Visual symptoms, orthostatic changes</u>
	Basilar artery insufficiency or stenosis	Intermittent episodes of vertigo, ataxia, diplopia, and cranial nerve involvement	Intermittent cranial nerve deficits
	Vertebral artery dissection	Headache, neck pain, focal deficits related to posterior fossa	History of trauma. Sometimes spontaneous and no apparent cause
	Transient ischemic attack usually affecting anterior cerebral arteries or posterior circulation. Stenosis or hypoplasia of major intracranial vessels	Transient neurologic deficits with complete recovery between the episodes lasting less than an hour	Transient deficits followed by full recovery
Brain	Stroke	Frequently: hemiparesis, hemisensory loss, hemifacial weakness,	Prolonged deficits

		amaurosis fugax, aphasia, neglect, or other focal deficits	
	Cataplexia	Sudden DA. Many have history of narcolepsy as well	Events triggered by laughter, startle, surprise, intense emotions
Basal ganglia	Drop attacks associated with Parkinson's or other extrapyramidal disorders such as progressive supranuclear palsy	Bradykinesia, muscle rigidity, axial spasticity, ophthalmoparesis	Worsening Parkinson features. Downgaze limitations. Dementia
Cerebellar	Degenerative cerebellar ataxias	Progressive ataxia	DA, ataxia and asterixis
Metabolic	Hepatic encephalopathy	Ataxia, asterixis, and other systemic signs of hepatic encephalopathy	Established history of hepatic failure or classic risk factors for liver disease. Progressive symptoms
Hindbrain	Chiari malformation type 1	Occipital headache, vertigo, dizziness	Neuroimaging is essential for diagnosis

	Third ventricle tumors Posterior fossa tumors	Associated with headaches Episodes triggered by abrupt neck flexion	Symptoms worsened by head position
Epileptic	Lennox–Gastaut syndrome	Severe epileptic syndrome. Most frequent type of seizure: drop attack but often in company with other seizure types such as myoclonic, tonic, tonic-clonic, and absence. Onset 3–5 years old. Often treatment-resistant. Classic EEG patterns	DA in a child with severe neurologic deficits, often with cognitive impairments. Poor response to treatment
	Myoclonic–astasic epilepsy or Doose syndrome	DA start at early age [2–5]. EEG with generalized discharges. Main differential Lennox–Gastaut but better outcome	Drop attack seizures in a neurologically intact child at onset
	Hyperekplexia	Onset in infancy. Frequent startle associated with hypertonia. Also known as stiff baby. Genetic etiology	Generalized stiffness. Exaggerated startle response

Causes			
Cardiac	Orthostatic changes	DA associated with changes of position	Orthostatic symptoms
	Arrhythmias	Irregular heart beat	Abnormal ECG
Otologic	Ménière's syndrome	Otolithic crisis also known as Tumarkin falls Characterized by a sensation of being forcefully pushed to the ground, room tilt illusion and vertigo	Associated with hearing loss and tinnitus Episodic vertigo
	Otolithic crisis <i>not</i> associated with Ménière's syndrome	Sudden falls, lack of hearing loss. Migraines are frequent	Otolithic crisis without vertigo or hearing loss.
Psychological	Anxiety, depression, panic attacks	History of specific mental health issues	Lack of neurologic abnormalities on exam
Cryptogenic	Unknown etiology	Frequent falls without other symptoms. Full recovery	Exam and work-up negative. Positive family history
Genetic	Coffin–Lowry syndrome	Attacks triggered by auditory or tactile stimuli	Intellectual disabilities Stimulus-induced drop

## Case vignette

The patient is a Caucasian 43-year-old female business executive, who presents with a history of frequent falls that began 6 months earlier. These were occurring at least once a month, at any time of day. They were described as falling forward, without warning, and with no loss of consciousness. She is alert and aware of all the details during the episode. She experienced the feeling of her legs giving way briefly, with no dizziness or focal motor activity noted. She denies headache or lightheadedness. A typical episode lasts less than a minute, and is followed by immediate recovery without further symptoms. The patient expresses fear about the episodes. They have been happening mostly during her frequent trips that her job demands and she verbalizes her anxiety of failing to be able to continue working. She describes herself as an overachiever and emphasizes the stress of her job.

*Past medical history:* She was otherwise healthy throughout childhood and adulthood. There is no history of trauma or allergies. Review of systems is non-contributory and she denies palpitations or transient neurologic deficits. She does not take any medication but does take melatonin to prevent jet lag. She reports a history of being healthy and athletic, goes to the gym three times a week, and is involved in recreational sports at least once a week. Family history reveals hypertension in both parents. There is a first-degree cousin being a "fainter." Daily habits include drinking coffee twice a day, but she denies smoking. She occasionally drinks alcohol in social settings. She denies sleep-related problems.

Bloodwork ordered by the primary care physician, 3 weeks prior, reveals normal results including blood cell count, chemistry panel, comprehensive metabolic panel, HbA1C, thyroid function tests, lipid panel, CPK, chest X-ray, and ECG.

Vital signs were B/P 117/78, HR 72, RR 12, temp 37°C. Physical examination including neurologic examination was normal. Patient was referred to Neurology. Work-up revealed normal results including EEG followed by 24 h video-EEG. Neck ultrasound and brain MRI/MRA of intracranial and neck vessels were normal. Cardiac consultation did not reveal any abnormality including echocardiogram and Holter monitoring.

## Discussion

This is the case of a healthy middle-aged female, who began experiencing drop attacks (DA) with no apparent cause. The history is striking for the lack of associated medical illnesses and the absence of abnormal findings on examination . Many conditions may cause DA, but a detailed assessment can elucidate the etiology of the symptoms. DA are more frequent in elderly patients and are responsible for occasional falls, but can be present at all ages, starting in childhood. Establishing the diagnosis is crucial to provide the appropriate therapy. The term has been used interchangeably with syncope but this is unfortunate because syncope is a different entity and is associated with loss of consciousness. Pathophysiologically, a sudden decreased brain perfusion is the suggested mechanism of symptoms in DAs [2]. In many cases, an underlying abnormality is not found and the etiology of the symptoms remains unclear.

When faced with a case of DAs, the reader may utilize [Table 20.1](#) to systematically identify or exclude specific causes. In this case, all such conditions were excluded. For example, vertebral artery (VA) insufficiency with or without stenosis is evident in some cases. MRI and MRA of the brain and neck vessels are the diagnostic tools of choice and they have shown a high sensitivity, greater than 98%, with a specificity of more than 95% in patients with vertebral artery abnormalities [3]. Angiogram has been suggested as the second diagnostic tool choice due to the risk of complications during the procedure. Basilar artery abnormalities have also been described. Transient ischemic attacks with sudden falls account for some cases, but they are most likely explained by transient neurologic deficits that involve lower extremities. Rarely, a patient presents with an association of headache and drop attacks and vertebral artery dissection has been evidenced by MRI/MRA [4]. Other DA can be the manifestation of a variety of central nervous system conditions. Drop attacks can be present in disorders of the basal ganglia, typically in patients with Parkinson's disease; such patients may fall to the ground without warning. Pathophysiology in such cases is believed to relate to decreased thalamic cholinergic activity rather than striatal dopaminergic denervation [5]. Patients with progressive supranuclear palsy also present with frequent falls. Younger patients with third ventricle tumors can experience drop attacks with changes of head position [6]. Neuromuscular disorders can predispose to DA due to either sensory impairment or muscle weakness. Guillain–Barré syndrome can present as DA as the result of acute polyneuropathy. Other rare conditions that can present with drop attacks include cerebellar degenerative ataxias . In other cases

of hemiplegic migraines recurrent DA can occur [1]. Cataplectic attacks in patients with narcolepsy consist of sudden loss of tone triggered by laughter or intense emotions [7]. Children with a rare genetic condition, Coffin–Lowry syndrome, present with DA triggered by tactile or auditory stimuli [8]. Chiari malformation 1 is rarely a cause of DA secondary to dysautonomia caused by hindbrain compression . Seizures can present as drop attacks as part of an epileptic syndrome such as Lennox–Gastaut or myoclonic astatic epilepsy (Doose syndrome) that can present with similar symptoms; usually the difference is established by clinical symptoms, EEG findings, and prognosis that tends to be more severe in Lennox–Gastaut syndrome that typically starts in a child with neurologic deficits and multiple types of seizure. Doose syndrome usually is diagnosed in patients with previously normal neurologic condition. In some cases, partial onset seizures can also present as DA. In this patient neurologic work-up was negative .

Cardiovascular causes of drop attacks or falls are responsible for a significant number of visits to the emergency room. They include several abnormalities with diverse etiologies. They can be included in two groups. In the first group, there are those patients with orthostatic changes usually seen in pure autonomic failure, drug-induced autonomic failure, and conditions where volume depletion plays an important role. A second group includes structural abnormalities that can be functional or anatomical. Functional causes include cardiac arrhythmias and anatomical causes frequently consist of cardiomyopathies or valvular diseases [2]. Cardiac work up in this patient was negative.

Vestibular causes of drop attacks are often associated with a sensation of being pushed to the ground. This feature, associated with hearing loss, dizziness, and tinnitus, is characteristic of Ménière's syndrome with DA called otolithic crisis or Tumarkin falls . Other vestibular causes without hearing loss have been also linked to otolithic crisis with DA. Symptoms were not suggestive of a vestibular cause in this patient.

Additional family history provided valuable information and this patient was diagnosed with cryptogenic drop attacks of middle-aged females. Unfortunately, treatments are limited but special ambulation precautions can be taken in individuals who are at risk for frequent attacks .

## References

1. Bradley W, Daroff R, Fenichel G, Jankovich J. *Neurology in Clinical*

*Practice*, 5th edn. New York, NY: Elsevier, 2008: 21–6.

2. Cronin H. Cardiac causes for falls and their treatment. *Clin Geriatric Med* 2010; 26:539.
3. Welsh LW, Welsh JJ, Lewin B, Dragonette JE. Vascular analysis of individuals with drop attacks. *Annals Otol Rhinol Laryngol* 2004; 113:245–51.
4. Rozen T, Gordon CD. Vertebral artery dissection in a migraine patient with recurrent drop attacks. *Headache J Head Face Pain* 2007; 47:605–6.
5. Bohnen N. History of falls in Parkinson disease is associated with reduced cholinergic activity. *Neurology* 2009; 73:1670.
6. Pollack IF, Schor NF, Martinez AJ, Towbin R. Bobble-head doll syndrome and drop attacks in a child with a cystic choroid plexus papilloma of the third ventricle. *J Neurosurg* 1995; 83:729–32.
7. Vendrame M. Narcolepsy in children: a single-center clinical experience. *Pediatr Neurol* 2008; 38:314.
8. Havaligi N, Matadeen-Ali C, Khurana DS, Marks H, Kothare SV. Treatment of drop attacks in Coffin–Lowry syndrome with the use of sodium oxybate. *Pediatr Neurol* 2007; 37:373–4.

## 21 Dysarthria

---

David B. Rosenfield *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Case vignette, part 1

A 55-year-old male complains of progressive difficulty with speech but not with swallowing. He denies weakness in his limbs and does not have any other complaints. His neurologic examination is normal, except for “slurred speech.” The examiner does not know how to differentiate elements of this slurred speech, but is able to do this after reviewing the concepts in this chapter.

### Introduction

Physicians employ many terms referring to abnormal speech. The most common term is “dysarthria,” which usually infers abnormalities with articulation, but can extend to abnormalities in “phonation” as well as “resonance.” There are basic identifying hallmarks of these three components, all of which are associated with clinically meaningful signs and symptoms.

Human speech reflects motor programming of verbal communication and should not be confused with compromise of language . Acquired compromise of language (i.e. “aphasia”) includes abnormalities in word choice (semantics), syntax (grammar), and possibly abnormal output of actual sounds. These sounds, the disruption of which can include dysarthria, are produced by coordinated interactions of the respiratory, articulatory, and laryngeal systems, all of which are controlled by cerebrally initiated neuromuscular processes. Neurologic compromise of this “speech-motor control” can affect any of these systems and produce dysarthria. Prior to discussing the signs and symptoms of these respiratory, articulatory, and phonologic (laryngeal) systems, it is necessary briefly to discuss how it is we produce human speech.

Speech almost always occurs during expiration. When we exhale and produce

sounds, muscles (e.g. interarytenoid muscles) within our vocal cords move these vocal folds (i.e. vocal cords) toward the midline, causing air pressure below the glottis (i.e. opening between the vocal folds) to increase. When the air pressure below the glottis (sub-glottic pressure) exceeds the pressure above the vocal folds (supra-glottic pressure), a vibratory system is induced and an aerodynamic effect based upon the Bernoulli principle, coupled with natural elasticity of the vocal folds, causes a to-and-fro motion of the vocal folds, producing sound. The “fundamental frequency” of this sound is the acoustic correlate of “pitch.”

**Table 21.1 Diseases associated with laryngeal (phonatory), velopharyngeal (palate), and oral examinations.**

Disease	Laryngeal	Palate	Oral
Myopathy/myositis	Hoarse, breathy low volume	Hypernasal	All vowels and consonants may be compromised
Myasthenia gravis	Similar to above; can be intermittent; can improve with rest	Similar to above; can be intermittent; can improve with rest	Similar to above; can be intermittent; can improve with rest
XII lesion	Normal	Normal	Tongue is weak, atrophy, fasciculations; imprecise vowels and lingual consonants (/l, r)

V lesion

Hoarse/breathy/low

Hypernasal

Normal

<b>A lesion</b>	<b>/uərəs/ /ʊərəmə/ /ʊəw/</b>	<b>Hypernasal</b>	<b>Tremor</b>
VII lesion	Normal	Normal	Weak orbicularis oris; imprecise vowels and consonants
V lesion	Normal	Normal	Weak mandibular muscles; imprecise vowels and consonants
Bilateral corticobulbar	Strained/harsh	Hypernasal	Imprecise consonants; slow rate
ALS	Strained/ harsh	Hypernasal	Slow articulation; imprecise consonants
Parkinson's disease	Weak; monopitch	Normal	Accelerated rate; repetitive dysfluencies; imprecise consonants
Chorea, dysarthria, or dystonia	Alterations in pitch and loudness	Normal unless involves palate	Abnormal if involved

---

The actual production of sound (phonation) requires appropriate stiffness and

slackness of the laryngeal folds, a particular dimension of the laryngeal opening and a specific volume and velocity of air moving through this opening. There is a narrow range of values necessary for these three variables to produce and maintain phonation. Neurologic compromise of any of them, whether from movement disorder, weakness, or slowed movements, will alter sound output.

The “source-filter theory of speech production” maintains that the spectrum of sound waves produced at the laryngeal sound source is modified (i.e. filtered) as sound waves traverse the cavity above the larynx (supra-laryngeal cavity), and that muscles and tissues within the cavity (e.g. palate, pharynx, mouth, tongue, lips, teeth) filter the distribution of energy within the component frequencies of the sound waves. Particular distribution of these energies can produce “vowels,” each of which has a particular set of spectral (energy) peaks and depends upon the shape of this cavity above the laryngeal muscles. Any neuromuscular disease, whether relating to the brain, brainstem, spinal cord, nerves, neuromuscular junction, or muscles, can affect any of these systems and produce particular abnormalities in speech .

## Symptoms of abnormal speech

*Onset:* Onset of abnormal speech is usually gradual, not sudden. The sudden onset of abnormal speech suggests stroke or psychogenic compromise. The fact that abnormal speech worsens in situations of stress does not imply a psychogenic cause, because all motor systems, especially those relating to the speech-motor control system, are affect sensitive.

*Pain:* Disruption of speech is seldom associated with pain, unless there is focal laryngeal pathology, which can reflect recent intubation (dislocated laryngeal arytenoid cartilage) or acid reflux (heartburn, abdominal pain, sour taste in mouth); a sensation of strain/strangle can reflect tremor or dystonia associated with spasmodic dysphonia.

*How the patient characterizes his speech:* Raspiness or hoarseness (reflects laryngeal abnormalities); particular sounds or just “slurred” (disturbance of articulators – see below); hypernasality implies weak palate.

## Examination (signs) of abnormal speech

*Motor examination:* Palate – should elevate normally and symmetrically; tongue should protrude in midline and not deviate to one side; fasciculations and

atrophy suggest lower motor neuron compromise of XII nerve; facial muscles (orbicularis oris should be strong: lips should pucker well and patient should be able to apply air pressure against pursed lips); jaw – open against resistance; look for weakness, fatigability, and tremor/dystonia in all muscles.

*Speech examination:* Ask patient to produce, hold, and then smoothly fluctuate an *eee* sound – reflects laryngeal muscles and respiratory support – listen for tremor, hoarseness, and breathiness. Ask patient to produce rapidly *papa/pa, tata/ta*, and *kakaka* each seven times. Rhythm should remain rapid and sounds remain normal (slowing reflects upper motor neuron compromise, e.g. spasticity).

Utterance of *pa, ta*, and *ka* each several times reflects not only airflow but also normal power respectively of the lips, tongue, and palate. Listen carefully for *pa* changing to *ba* and then to *ma*; *ta* > *da* > *na*; *ka* > *ga* > *nga*. These changes reflect underlying weakness in the airflow or, especially, weakness in the palate (e.g. palate is insufficiently powerful to maintain laryngeal folds closed due to weakened supra-laryngeal air pressure, thus allowing a dynamic of interplay between the vocal folds and the resonance system to make these abnormal changes).

Ask patient to say “Coca Cola” several times, and listen for increased nasality. The Coca Cola sounds require a sufficiently strong palate, disruption of which produces hypernasal speech. If the sounds are “hyponasal,” similar to the way people speak with a severe cold (/m/ becomes *b*; *n* becomes *d*; *ng* becomes *gl*), these patients seldom have disease of the central nervous system; consider enlarged adenoids, deviated nasal septum, rhinitis, and nasopharyngeal tumor .

## Case vignette, part 2

Referring to the initial case noted above, the now further experienced examiner evaluates all cranial nerves, notes the tongue is weak but protrudes in the midline, the patient has difficulty maintaining a strong *eee* sound and repetitive utterance of *pa, ta*, and *ka* respectively produce *ma, na*, and *nga*. These findings are strongly suggestive of bulbar ALS.

The above procedures for evaluating symptoms and signs of abnormal speech will prove extremely helpful in delineating the cause and disease underlying dysarthria.

## **Further reading list**

Giraud A-L, Poeppel D. Cortical oscillations and speech processing; emerging computational principles and operations. *Nat Neurosci* 2012; 15:511–17.

Raphael LJ, Borden GJ, Harris KS. *Speech Science Primer: Physiology, Acoustics and Perception of Speech*, 6th edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2011.

Rosenfield DB, Barroso AO. Difficulties with speech and swallowing. In Bradley WG, Darroff RB, Fenichel GM, Marsden CD, Eds. *Neurology in Clinical Practice: Principles of Diagnosis and Management*, 2nd edn. Boston, MA: Butterworth-Heinemann, 1996: 155–68.

Zion Golumbic EM, Poeppel D, Schroder CE. Temporal context in speech processing and attentional stream selection: a behavioral and neural perspective. *Brain and Language* 2012; doi:10.1016/j.band.2011.12.010.

## 22 Dysphagia

---

Jessica A. Shields and Anne L. Foundas *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Dysphagia is a physiologic disorder characterized by difficulty swallowing. Dysphagia is common in many neurologic conditions, and is associated with an increased risk of aspiration, and nutritional problems. An understanding of the neural mechanisms and at-risk patient populations can help the neurologist make an earlier diagnosis to develop an effective treatment plan that reduces associated complications.

### Classification of dysphagia

Dysphagia is classified into two major types: (1) *Oropharyngeal dysphagia* includes difficulty in forming the bolus, propelling the bolus or liquid to the pharyngeal vault, and in emptying the contents into the esophagus. Specific behaviors include difficulty initiating swallowing, nasal regurgitation, and coughing with ingestion (tracheal aspiration). The videofluoroscopic swallow study (VFSS) is the most comprehensive diagnostic study of oropharyngeal dysphagia and allows for the identification of oral, pharyngeal, and mixed subtypes. The oral phase, which lasts about one second, begins with mastication and ends as the bolus is propelled by the tongue to the level of the pharyngeal arch. The pharyngeal phase begins once the food bolus or liquid enters the pharyngeal cavity and ends with the opening of the upper esophageal sphincter. Causes of oropharyngeal dysphagia include a variety of neurologic conditions at the level of the brain and brainstem or affecting the skeletal muscle.

- a. Most common causes: stroke syndromes, Parkinson's disease , myasthenia gravis .
- b. Less common causes: multiple sclerosis , amyotrophic lateral sclerosis (ALS) , pseudobulbar palsy , dermatomyositis , muscular dystrophy ,

bulbar polio (developing world countries).

(2) *Esophageal dysphagia* is usually caused by a motility disorder or mechanical obstruction. The esophageal type of dysphagia is described as having a food bolus “sticking” several seconds after the onset of the oropharyngeal swallow. Patients typically localize this feeling to the suprasternal notch. Esophageal dysphagia is not as commonly found in patients with a neurologic condition, and is usually managed by a gastroenterologist or surgeon.

- a. Most common causes: achalasia, lower esophageal rings/webs, peptic stricture.
- b. Less common: diffuse esophageal spasms, systemic sclerosis, eosinophilic esophagitis, malignant or benign obstructing mass lesions.

## Differential diagnosis of dysphagia

Refer to [Table 22.1](#) for a detailed differential diagnosis of the causes of dysphagia. Clinical and laboratory tests associated with the diagnosis of dysphagia are related to dissociating structural damage from other etiologies. Diagnostic studies differ depending on the suspected localization of the dysphagia (esophageal versus oropharyngeal versus a combination). Esophageal dysphagia is evaluated with a barium swallow that may be supplemented with motility studies, and/or endoscopy with biopsies to rule out esophagitis or other lesions. A diagnosis of oropharyngeal dysphagia is based on measures of bolus flow, post-deglutitive residual, and airway invasion (i.e. tracheal aspiration) [\[1\]](#). The VFSS is used to localize, determine oropharyngeal dysphagia severity, and to develop a treatment plan [\[2\]](#).

**Table 22.1 Differential diagnosis of dysphagia.**

Item	Specific type	Etiology	Possible clinical features
Structural (congenital/acquired)	Enlarged left atrium Esophageal webs	Extrinsic compression Associated with bullous diseases	Solids more easily swallowed than liquids

	<b>causes</b>	<b>main site</b>
	(pemphigus)	
Zenker's diverticulum	Pharyngeal diverticulum	Intermittent dysphagia progresses
Peptic stricture	Gastroesophageal reflux disease	Chronic heartburn progresses
Achalasia	Loss of myenteric plexus in lower esophageal sphincter	Progressive dysphagia; dilated esophagus; distal s
Toxic (drugs, toxic substances, w/d)	Lye ingestion  Anticholinergics  Phenothiazines	Esophageal strictures
Infective	Polio  Guillain--Barré syndrome	Poliomyelitis – lower motor neuron destruction  Demyelination of motor fibers; associated with <i>Campylobacter</i> or herpes virus infections
	Diphtheria	Upper respiratory infection may lead to dysphagia

	Botulism	Paralysis of swallowing musculature	
	Lyme disease	Polyneuropathy commonly affecting the facial nerve	Chroni monoa Bell's p
	Mucositis ( <i>Candida</i> , herpes)	Inflammation of the esophageal mucosa	
Pressure	Mechanical obstruction	Esophageal web or diverticulum	Intermit dyspha progres solids > than liq
Inflammatory (auto-immune)	Sjögren's syndrome		
	Systemic sclerosis/scleroderma	Esophageal dysmotility	Raynaud syndro
	Eosinophilic esophagitis	Allergic	Chroni dyspha
Neoplastic/para-neoplastic	Esophageal cancer	Mechanical	Progres dyspha > 50
	Mass lesion	Disruption of neural pathways affecting swallowing	
	Intrathoracic tumors	Extrinsic compression	

Degenerative	Alzheimer's disease (AD)	Early-stage AD	Reduced lingual movement delayed pharyngeal swallowing
		Moderate-stage AD	Difficulty bolus preparation pharyngeal clearance increased aspiration <a href="#">[20,21]</a>
	AD vs vascular dementia (VaD)		AD difficult with oral delay; difficulty bolus formation and mastication of semisolid <a href="#">[22]</a>
	Progressive supranuclear palsy	Pseudobulbar palsy -- lesion in corticobulbar pathways in the pyramidal tract	Labile dysarthria spastic jaw jerks <a href="#">[23]</a>
Vascular	Unilateral cortical lesion (right > left)	CN VII, diparesis	Oropharyngeal dysphagia aspiration <a href="#">[7]</a>
	Cognitive effects on dysphagia outcome	Neglect	Associated persistent dysphagia

			mos pc [4]
	Insular cortex	Critical site for dysphagia	Oropharyngeal dysphagia anterior > posterior > left side [16]
	Bilateral hemisphere infarction	Pseudobulbar palsy	Dysphagia labile cough dysarthria spastic jaw jerks
	Thoracic aortic aneurysm	Extrinsic compression	
Metabolic	Plummer--Vinson syndrome	Chronic iron deficiency anemia	Glossitis postmenopausal women
Movement disorder	Amyotrophic lateral sclerosis	Degeneration of upper and lower motor neurons	25% bilateral onset – progressive symptoms include difficulty speaking, swallowing [24]
	Parkinson's disease	Motor impairment of swallowing musculature	Dysphagia present in the early stage [25]
	Huntington's disease	Hypokinetic motor signs, cognitive decline	

Demyelinating	Multiple sclerosis	including dysphagia	Demyelination of CNS leads to loss of proper control of skeletal muscle	Dysphagia in the non-disabled patient risk of aspiration pneumonia
---------------	--------------------	---------------------	---	--

A comprehensive neurologic examination is essential in many patients with dysphagia and in all acute stroke patients. The initial evaluation includes a thorough examination of the oropharynx, and a non-invasive water swallow study (refer to [Table 22.2](#)). The clinical swallowing evaluation includes an assessment of cranial nerves, oromotor strength and agility, cognition, speech, language, and voice. A water swallow test should be performed with various volumes and consistencies of material. This non-invasive bedside swallowing examination has been validated and accurately predicts which patients may have a more severe form of dysphagia that would warrant additional testing with a VFSS [3].

**Table 22.2 Clinical swallowing evaluation structure (cranial nerve – CN) examination.**

Mandible (CN V)	Symmetry on extension; strength
Lips (CN VII)	Symmetry on rest, retraction, and protrusion; strength
<ul style="list-style-type: none"> <li>– Non-speech coordination on repetitive movements and alternating movements – Speech coordination on repetitive speech (p,w) and alternating sounds (p-w)</li> </ul>	

Tongue (CN XII) Symmetry at rest, protrusion, lateralization, elevation ability, fasciculations, strength

- Non-speech coordination on repetitive movements and alternation movements – Speech coordination on repetitive (t,k) and alternating sounds (t,k) – Alternating movement (p,t,k) – Multisyllabic word repetition (tip top, baseball player, several, caterpillar, emphasize) – Conversation-speech, voice, coordination characteristics – Laryngeal function: isolated movement (i-i-i in one breath) – Alternating movement (u-i) – Buccofacial apraxia: blow out a candle, lick an ice cream cone, sip through a straw

Velum (CN IX, X, XI) Symmetry (rest, elevation)

- Coordination: repetitive movement – Appearance of hard palate – Dentition

Reflexes (CN IX, X, XI)

- Gag reflex – Swallow (cough, voice change)

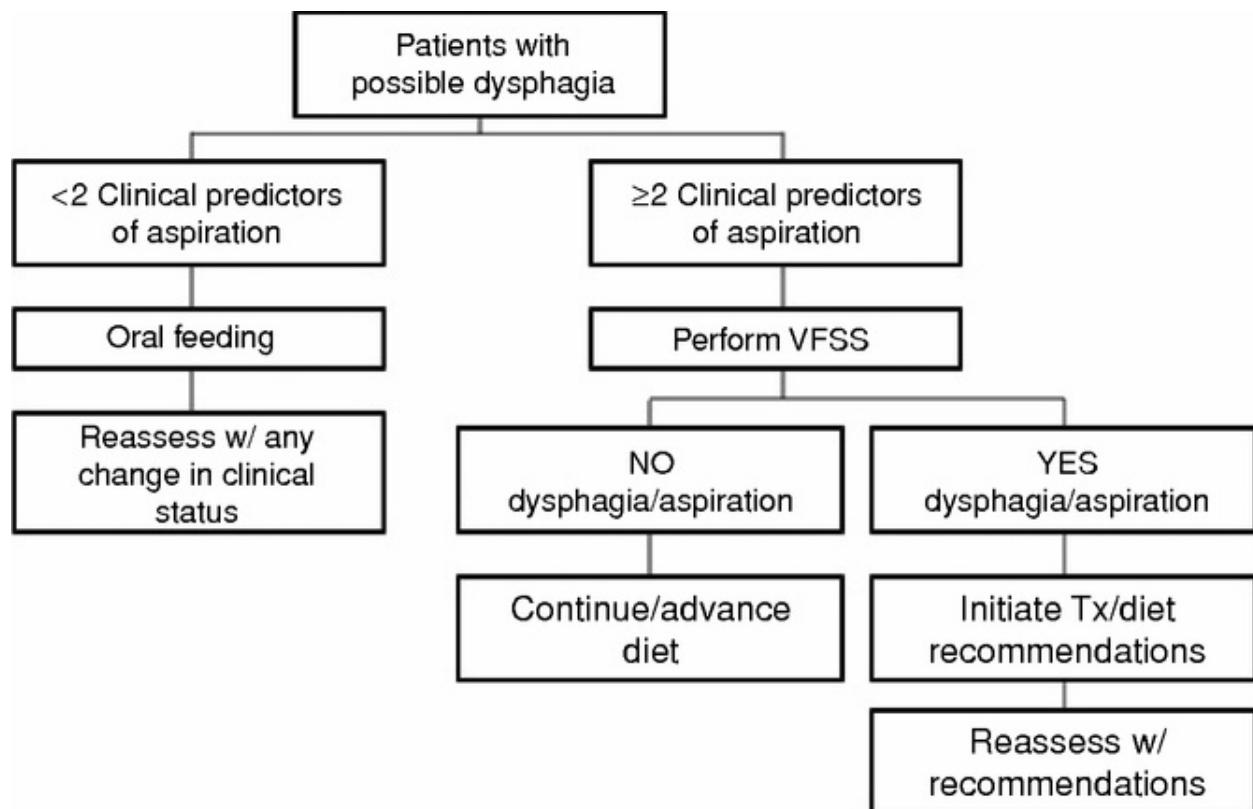
Other clinical features

- Facial numbness or tingling – Dysphonia (mild, moderate, severe) – Dysarthria (mild, moderate, severe) – Breath support – Resonance

---

Our research group identified six clinical predictors of silent aspiration in

patients with a risk of dysphagia (refer to [Table 22.3](#)). In a series of consecutive stroke patients we found that the presence of any two (or more) of these clinical features increased the risk of having silent aspiration [4]. Therefore, we validated the use of this clinical tool using an algorithm such that patients with two or more clinical predictors would be referred for VFSS. In contrast, a patient with one or without any of these clinical predictors was deemed not at increased risk of silent aspiration and was not referred for VFSS ([Figure 22.1](#)) [5]. In a follow-up study, we found that this clinical algorithm was a useful indicator of an increased risk of clinically significant dysphagia [6]. In a subsequent longitudinal study, we found that the presence of at least four of these six clinical predictors during the initial clinical swallowing evaluation was associated with poor initial (within 1 week of stroke onset) and final swallowing outcome (3 months post-stroke patients had not advanced their diets) [4].



**Figure 22.1** Clinical algorithm for dysphagia management

A clinical decision-making flow chart for dysphagia management following acute stroke. Adapted from Daniels *et al.*, 1997 [5].

**Table 22.3** *Clinical predictors of aspiration risk.*

Clinical predictor	Operational definition
1. Dysphonia	Voice disturbance of vocal quality, pitch, or intensity
2. Dysarthria	Disturbances in muscular control affecting articulation, phonation, or resonance
3. Abnormal gag reflex	Absent or reduced velar or pharyngeal wall contraction in response to posterior pharyngeal wall stimulation
4. Abnormal volitional cough	Weak, or absent, response upon command to cough
5. Cough after swallow	Cough immediately after or in 1 min of ingesting calibrated water volume of 5, 10, and 20 mL (in duplicate)
6. Voice change after swallow	Alteration in vocal quality after ingesting calibrated volumes of water

---

Dysphagia can increase the length of hospitalization [7], and increase the likelihood of discharge to a nursing-care facility rather than home [7,8]. Treatment is geared towards the identification and treatment of the swallowing disorder in order to maintain nutritional status and to reduce complications (i.e. aspiration pneumonia). Oropharyngeal dysphagia treatments include dietary restriction with swallowing therapy and retraining of swallowing muscles. Changes in diet and/or feeding techniques can improve the patient's quality of life, and can reduce caregiver burden. Esophageal dysphagia may be treated with endoscopic dilation or surgical procedures targeting the specific cause. Patients with persistent symptoms may require the placement of nasogastric feeding tubes, gastrostomy, and/or a tracheostomy.

## Post-stroke dysphagia and anatomical localization

Dysphagia following acute stroke is very common, ranging from 25–81% [9–11]. Standard practices dictate that all acute stroke patients should undergo a clinical swallowing evaluation [12]. Lesion localization studies in post-stroke patients have enhanced our understanding of the anatomical locus of dysphagia (for review, see reference [3]). We will briefly discuss post-stroke dysphagia in order to present a functional–anatomical model of swallowing.

Localization of dysphagia following stroke includes lesions of the brainstem, premotor, and primary motor cortical and somatosensory areas, the insular cortex, and periventricular white matter pathways [13–17]. Swallowing physiology is localized in a widely distributed network that requires the integration of descending motor control from both right and left cerebral hemispheres to the brainstem medullary swallowing center that in turn provides the kinesthetic representation of the motor program to the effectors (e.g. muscles of deglutition). Swallowing is mediated by top-down descending cortical (sensorimotor, insula) and subcortical (basal ganglia, thalamus) structures, with the final common pathway (the central site) at the level of the brainstem in the medullary swallowing center. Theoretically, a lesion at any one of these sites can induce dysphagia. Lesion analysis studies support this view and have demonstrated that lesions at the level of the medullary swallowing center induce chronic dysphagia; lesions to cortical sites are more likely to be associated with moderate–severe dysphagia only when the cortical lesion extends to include portions of the periventricular white matter and/or to a subcortical gray matter region (i.e. thalamus, basal ganglia). It is important to note that the insular cortex (right > left and anterior > posterior) has been identified as a critical site in the evocation of swallowing [16].

Specific functions have been attributed to specific anatomical sites. Cortical regions are involved in the initiation and modulation of swallowing with lesions interrupting voluntary control of mastication and bolus transport during the oral phase [2,18]. Brainstem structures provide the motor plan for swallowing [3] and result in the greatest swallowing compromise. Anterior cortical lesions and lesions involving larger vessels (i.e. MCA) are associated with an increased aspiration risk [17]. Discrete lesions to the periventricular white matter pathways disrupt swallowing with a longer oral transit time (as measured by VFSS) [19] providing some empiric evidence that isolated small lesions to convergence zones may disrupt swallowing behaviors. Given the prevalence of dysphagia in stroke patients and in moderate to advanced stages of dementia, neurologists can take the lead in facilitating earlier identification and treatment of dysphagia in

the aging and at-risk population.

## Clinical vignette

A 57-year-old right-handed male was admitted to the hospital with complaints of a hoarse voice, diplopia, dizziness, and a mild frontal headache. He had a history of hypertension, hyperlipidemia, and type 2 diabetes. Diffusion-weighted MRI and MRA revealed a right lateral medullary infarct with occlusion of the vertebral artery, and MRI–FLAIR showed the presence of a moderate amount of symmetric periventricular white matter hyperintensity formation consistent with chronic microvascular disease.

The following day, the patient complained that he had difficulty initiating swallowing of both solids and liquids. He also complained of coughing with swallowing. The patient was evaluated by a speech pathologist who performed a clinical swallowing examination. The patient was found to have dysarthric speech, dysphonia, a reduced gag reflex, and a weak cough. Due to an increased risk of aspiration, a VFSS was performed and showed a delay in oral and pharyngeal transit with pooling of secretions in the valleculae and penetration/aspiration with the bolus entering the trachea and not clearing despite several patient attempts. A nasogastric tube was placed. Dietary restrictions were continued and rehabilitation therapy was begun by speech pathology to treat the patient's dysphagia. Two weeks post-stroke, the patient was found to have increased oral secretions and persistent moderate–severe dysphagia on repeat VFSS. Gastroenterology was consulted for placement of a gastrostomy tube.

## References

1. Daniels SK, Schroeder MF, DeGeorge PC *et al.* Defining and measuring dysphagia following stroke. *Am J Speech-Language Pathol* 2009; 18:74–81.
2. Daniels SK, Brailey K, Foundas AL. Lingual discoordination and dysphagia following acute stroke: analyses of lesion localization. *Dysphagia* 1999; 14:85–92.
3. Daniels SK, Huckabee ML. *Dysphagia Following Stroke*. San Diego, CA: Plural Publishing, 2008.
4. Schroeder MF, Daniels SK, McClain M, Corey DM, Foundas AL. Clinical and cognitive predictors of swallowing recovery in stroke cognitive predictors

- of swallowing recovery in stroke. *J Rehabil Res Dev* 2006; 43:301–10.
5. Daniels SK, McAdam CP, Brailey K, Foundas AL. Clinical assessment of swallowing and prediction of dysphagia severity. *Am J Speech-Language Pathol* 1997; 6:17–24.
  6. Daniels SK, Ballo LA, Mahoney MC, Foundas AL. Clinical predictors of dysphagia and aspiration risk: outcome measures in acute stroke patients. *Arch Phys Med Rehabil* 2000; 81:1030–3.
  7. Smithard DG, O'Neill PA, Park CL, Morris J. Complications and outcome after acute stroke. Does dysphagia matter? *Stroke* 1996; 27:1200–4.
  8. Odderson IR, Keaton JC, McKenna BS. Swallow management in patients on an acute stroke pathway: quality is cost effective. *Arch Phys Med Rehabil* 1995; 76:1130–3.
  9. Gottlieb D, Kipnis M, Sister E, Vardi Y, Brill S. Validation of the 50 ml<sup>3</sup> drinking test for evaluation of post-stroke dysphagia. *Disabil Rehabil* 1996; 18:529–32.
  10. Meng NH, Wang TG, Lien IN. Dysphagia in patients with brainstem stroke: incidence and outcome. *Am J Phys Med Rehabil* 2000; 79:170–5.
  11. Martino R, Foley N, Bhogal S *et al*. Dysphagia after stroke: incidence, diagnosis, and pulmonary complications. *Stroke* 2005; 36:2756–63.
  12. Adams R, Acker J, Alberts M *et al*. Recommendations for improving the quality of care through stroke centers and systems: an examination of stroke center identification options: multidisciplinary consensus recommendations from the Advisory Working Group on Stroke Center Identification Options of the American Stroke Association. *Stroke* 2002; 33:e1–7.
  13. Alberts MJ, Horner J, Gray L, Brazer SR. Aspiration after stroke: lesion analysis by brain MRI. *Dysphagia* 1992; 7:170–3.
  14. Robbins J, Levine RL, Maser A, Rosenbek JC, Kempster GB. Swallowing after unilateral stroke of the cerebral cortex. *Arch Phys Med Rehabil* 1993; 74:1295–300.
  15. Daniels SK, Foundas AL, Iglesia GC, Sullivan MA. Lesion site in unilateral stroke patients with dysphagia. *J Stroke Cerebrovasc Dis* 1996; 6:30–4.
  16. Daniels SK, Foundas AL. The role of the insular cortex in dysphagia.

*Dysphagia* 1997; 12:146–56.

17. Daniels SK, Foundas AL. Lesion localization in acute stroke patients with risk of aspiration. *J Neuroimaging* 1999; 9:91–8.
18. Zald DH, Pardo JV. The functional neuroanatomy of voluntary swallowing. *Ann Neurol* 1999; 46:281–6.
19. Cola MG, Daniels SK, Corey DM *et al*. Relevance of subcortical stroke in dysphagia. *Stroke* 2010; 41:482–6.
20. Correia S de M, Morillo LS, Jacob Filho W, Mansur LL. Swallowing in moderate and severe phases of Alzheimer's disease. *Arq Neuropsiquiatr* 2009; 68:855–61.
21. Humbert IA, McLaren DG, Kosmatka K *et al*. Early deficits in cortical control of swallowing in Alzheimer's disease. *J Alzheimers Dis* 2010; 19:1185–97.
22. Suh MK, Kim H, Na DL. Dysphagia in patients with dementia: Alzheimer versus vascular. *Alzheimer Dis Assoc Disord* 2009; 23:178–84.
23. Kaat DL, Chiu WZ, Boon AJ, van Swieten JC. Recent advances in progressive supranuclear palsy: a review. *Curr Alzheimer Res* 2011; 8:295–302.
24. Watts CR, Vanryckeghem M. Laryngeal dysfunction in amyotrophic lateral sclerosis: a review and case report. *BMC ENT Disord* 2001; 1:1.
25. Lo RY, Tanner CM, Albers KB *et al*. Clinical features in early Parkinson disease and survival. *Arch Neurol* 2009; 66:1353–8.
26. Tassorelli C, Bergamaschi R, Buscone S *et al*. Dysphagia in multiple sclerosis: from pathogenesis to diagnosis. *Neurol Sci* 2008; 29 (Suppl. 4):S360–3.

## 23 Dystonia

---

Ritesh A. Ramdhani and Steven J. Frucht *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

The diagnosis and evaluation of dystonia depends critically on understanding the phenomenology and classification of the disorder. A comprehensive history and clinical examination empowers the clinician to distinguish dystonia from other hyperkinetic movement disorders, and to create an efficient and effective management strategy.

### Phenomenology

Dystonia is a syndrome of involuntary, sustained muscle contractions, frequently causing twisting and repetitive movements or abnormal postures [1]. When these sustained postures are present in the limbs or neck, a “jerky,” irregular, and often large amplitude tremor may be generated . Furthermore, dystonic movements tend to be induced with action and abate with rest or sleep. The use of sensory tricks, also referred to as *geste antagonistes*, is a pathognomonic feature of dystonia. These maneuvers temporarily alleviate the dystonia, and may even be effective if the patient only imagines the geste but does not actually perform it. Additional features supportive of this clinical diagnosis include overflow and mirror movements. Overflow refers to the spread of dystonia to unaffected, contiguous areas of the same body part [2]. Mirror dystonia refers to the phenomenon of dystonic movements triggered in an affected limb when the task triggering the dystonia is performed by the unaffected limb (for example, dystonic movements in a hand affected with writer's cramp triggered when the patient writes with the unaffected limb) . The slower pace and sustained twisting postures of dystonic movements distinguish them from other hyperkinetic movement disorders such as tremor (typically rhythmic and oscillatory), myoclonus (brief, shock-like jerks), chorea (fleeting, dancing, random, small

movements), and tics (stereotyped and usually suppressible) [3].

## Classification

Dystonia can be classified in several ways: by age of onset, body of distribution, and etiology [4].

### Age

Dystonia presenting prior to the age of 26 years is termed early onset, whereas late onset occurs after this age [5]. Early onset dystonia that manifests in the lower extremities is much more likely to generalize, while adult onset dystonia usually presents in the upper body and rarely progresses.

### Body distribution

Dystonia may be classified by distribution into focal, segmental, or generalized forms. Focal dystonia involves one body part (i.e. arm, neck, eyes). Segmental dystonia affects two or more contiguous regions (i.e. cranial–cervical, crural (one leg plus trunk or both legs), or brachial (one arm plus truck or both arms) [5]. Generalized dystonia affects at least one leg, trunk, and another body part, while multifocal involvement, though rare, affects non-contiguous body parts. Hemidystonia refers to dystonia affecting an ipsilateral arm and leg, and should prompt a search for a structural etiology.

### Etiologies

Etiologies of dystonia are subdivided into five categories: primary torsion with or without tremor, dystonia-plus, heredodegenerative, secondary, or a feature of another neurologic disease (e.g. Parkinson's disease, progressive supranuclear palsy [PSP]). Genetic studies have further enhanced the classification scheme as upwards of at least 20 dystonic syndromes, whose loci are referred to as "DYT-#", have been characterized and are responsible for many of the inherited dystonias (i.e. primary, dystonia-plus, paroxysmal dystonias).

### Primary torsion dystonia

Primary torsion dystonia (PTD) refers to a dystonic phenotype (generalized or focal) devoid of other movement disorders, muscle atrophy, spasticity,

oculomotor abnormalities, cognitive impairment, and organic brain pathology. The prevalence of generalized PTD is 3–4/100,000, and 29/100,000 for focal PTD [6]. Onset is bimodal with childhood or early onset at age 9, late or adult onset at age 45, and a nadir at 27 [5].

## Early onset

Early onset PTD is caused by DYT 1, 2, 4, 6, 7, 13, 17, and 21 genetic loci mutations. DYT 1 dystonia is inherited as an autosomal dominant disorder with a 30–40% penetrance [7]. It often begins in the legs and generalizes to the torso and upper region, sparing cranial muscles within 5 years. DYT 1 (*Tor1A* gene) is the commonest form with a prevalence in the Ashkenazi Jewish population of 1/9,000 but 1/160,000 in the general population [5]. DYT 6 PTD (*THAP* gene) begins in the upper extremities and often progresses to the cranial and neck regions, causing speech changes; the legs are usually spared. Age of onset is generally in adolescence with a mean of 16 years (range, 5–62 years), and 10% of patients have only a focal dystonia [7].

## Focal and task-specific dystonia

Late onset PTD usually begins in the upper body and is usually focal. Focal dystonias that are elicited only with certain actions (i.e. writer's cramp, musician's hand dystonia, or embouchure dystonia ) are termed focal task-specific dystonia and rarely affect the lower extremities. The genetics of late onset PTD is not as well delineated. It has a lower penetrance, more sporadic genetic mutations, and familial inheritance is rare. Currently, DYT 4 (whispering dysptonia), DYT 7 (adult onset focal limb, cervical, or blepharospasm dystonia), and DYT 13 (multifocal and segmental dystonia) are the only inherited focal dystonias discovered with an autosomal dominant inheritance pattern.

## Cervical

Cervical dystonia is the most common focal dystonia and usually occurs in the fifth decade. Symptoms manifest as involuntary pulling, twisting, and/or pain in the neck, often with an associated head tremor. The head can be flexed (anterocollis), hyperextended (retrocollis), turned (torticollis), or shifted (laterocollis) in any of the cardinal planes based on the affected musculature in the neck and shoulder. Sensory tricks, such as touching the chin with a hand or fingers, are prevalent and oftentimes helpful.

## **Blepharospasm**

Blepharospasm is an involuntary sustained contraction of the orbicularis oculi muscles. It can begin unilaterally but most often is bilateral. Stressors such as reading, watching TV, driving, and bright lights exacerbate the condition while relaxation, looking down, sleeping, and orofacial movements (i.e. talking, yawning) alleviate the symptoms [8]. Pulling on the eyelids is a common sensory trick. Oromandibular dystonia is commonly associated with blepharospasm. It affects jaw opening and closing and can involve tongue protrusion and pharyngeal muscles causing dysphagia and dysarthria [2]. Severe mutilation of the buccal membranes and lips may be present as well.

## **Writer's cramp**

Writer's cramp is the commonest task-specific dystonia with onset in the third and fourth decades. An abnormal forceful grip is created by tension on the fingers from excessive flexion of thumb and index finger, and pronation and ulnar deviation of the wrist during the act of writing [9]. Mirroring of dystonic movement with the affected hand during attempts to write with the normal contralateral hand is often observed.

## **Laryngeal dystonia**

Dystonia affecting laryngeal muscles is a rare task-specific dystonia that causes a strained, staccato voice with breaks when the adductors are affected, and a breathy sound with abductor involvement during speech.

## **Dystonia-plus syndromes**

Patients with dystonia-plus syndromes have dystonia in addition to other neurologic features which are not attributable to a neurodegenerative etiology. Dopa-responsive dystonia and rapid-onset dystonia-parkinsonism are some of the notable variants.

## **Rapid-onset dystonia-parkinsonism**

Rapid-onset dystonia-parkinsonism (RDP), DYT12, is an autosomal dominant disorder characterized as an abrupt onset of dystonia and parkinsonism that affects young adults. Mutations in the *ATP1A3* gene, which encodes a Na<sup>+</sup>/K<sup>+</sup>-

ATPase pump, underlie the disorder. The disease typically evolves over hours to weeks and is often precipitated by physical and emotional stressors. The symptoms follow a rostrocaudal pattern affecting bulbar function (i.e. dysarthria, dysphonia, and dysphagia) more than arms, which are subsequently more so affected than legs. The dystonia tends to be generalized or segmental with an overlay of parkinsonian features, primarily bradykinesia and postural instability. These patients fail to manifest other classic idiopathic Parkinson's symptoms such as a pill-rolling tremor and stooped posture. Symptoms stabilize within 1 month of the ictus, but persist with minimal improvement. Abrupt worsening occurring years later is possible but rare.

## Dopa-responsive dystonia

Dopa-responsive dystonia (DRD) is an autosomal dominant disorder, which usually presents as focal foot dystonia. It begins between the ages of 1 and 12 years, and diurnal fluctuations with worsening in the evenings are hallmark features. Genetic mutations in the tetrahydrobiopterin synthetic pathway, specifically the *GCH1* gene (DYT 5) in the autosomal dominant variant, and the *TH* gene in the autosomal recessive form, are responsible for the condition. DYT 5 patients are exquisitely responsive to L-dopa. The sustained response to levodopa underscores the importance of challenging any child with an undiagnosed dystonia or a dominant pyramidal or extrapyramidal syndrome with L-dopa.

## Secondary and neurodegenerative etiologies

Clinical signs that should prompt an investigation into secondary and degenerative causes of dystonia are: sudden onset at rest, the presence of associated neurologic symptoms (i.e. cognitive or psychiatric impairment, extrapyramidal symptoms, spasticity, ataxia, ocular and retinal abnormalities, seizures, or other constitutional symptoms), hemidystonia, cranial onset in children or lower extremity onset in adults, prominent bulbar involvement or generalization during adult onset (refer to [Table 23.1](#)).

## Secondary etiologies

Secondary dystonia results from organic conditions affecting the brain. These include cerebrovascular disease, medications (i.e. dopamine agonists and antagonists) and toxins, perinatal cerebral injury, encephalitis, CNS tumors and

paraneoplastic syndromes, trauma, and infections.

A notable dystonic emergency is oculogyric crisis, which is a tendency for the eyes to be in sustained upgaze for a duration of several seconds to possibly even hours. They occur in paroxysms, can be accompanied by rigidity and opisthotonus, and can be a part of a tardive spectrum as well. Neuroleptics are common precipitants, and intravenous diphenhydramine is the standard of treatment.

## Heredodegenerative and sporadic neurodegenerative disorders

A number of genetic diseases (i.e. Wilson's disease, iron accumulation syndromes, lysosomal storage disease, mucopolysaccharidosis, or mitochondrial diseases) are associated with dystonia – a complete discussion is beyond the scope of this chapter.

Particular attention should be paid to non-inherited or sporadic neurodegenerative diseases such as Parkinson's disease and Parkinson's-plus syndromes, as they can produce focal dystonia as part of their phenotypic spectrum.

## Paroxysmal dystonia/dyskinesia

These disorders are characterized by sudden, transient, involuntary bursts of motoric movements (combination of chorea, dystonia, athetosis) that are categorized as non-kinesigenic (DYT 8 and 20), kinesigenic (DYT 10 and 19), and exercise-induced (DYT 9/18). Symptoms usually begin in childhood and adolescence and last anywhere from seconds to minutes or even sometimes hours. Inheritance is autosomal dominant. Paroxysmal non-kinesigenic dyskinesias can be precipitated by alcohol or caffeine [7], while the paroxysmal kinesigenic form is triggered by startle or unexpected movements.

**Table 23.1 Secondary etiologies and dystonia-plus syndromes.**

Item	Specific type	Specific etiology	Clinical features
<b>Secondary etiologies</b>			

Structural	Cerebrovascular	Infarct/hemorrhage	Hemidystonia or limb dystonia is common manifestation. Usually adult, sudden onset. Hx of antecedent focal weakness
	Mass	Cerebral tumors, subdural hematomas, AVMs	Common cause of hemidystonia and/or bulbar involvement. Acute to subacute onset. Associated with headaches, seizures, cognitive impairment, visual symptoms, or gait instability
		Cervical tumor	Focal dystonia or hemidystonia with myelopathic signs (incontinence, lower extremity weakness, sensory level, brisk reflexes)
Trauma	Anoxia	Perinatal hypoxia	Hx of abnormal birth. Developmental

		delay accompanied by seizures. Can have various subtypes of dystonia
	Anoxic brain injury (cardiac arrest)	Can have any form of dystonia, but if injury is diffuse, generalized dystonia with prominent bulbar involvement is common. Encephalopathy, myoclonus, and seizures are associative sequelae
Post traumatic	Motor vehicle accident or blunt trauma	Focal dystonia, hemidystonia, or cervical dystonia. Hx of cervical spine or head injury. Lower extremity onset is not uncommon
Medications	Dopamimetics Dopamine antagonists Serotonergics	Levodopa, dopamine agonists Neuroleptics, metoclopramide Sertraline, fluoxetine, MAOIs, buspirone
		* Onset in children and young adults; tend to have dystonia in the extremities or generalized <i>when exposed to</i>

**With exposure to**

any of these medications  
A feature in Parkinson's patients  
superimposed during akinesia or dyskinésias  
Acute onset with prominent bulbar findings. Tardive dystonia commonly superimposed with tardive dyskinésia.  
Atypical neuroleptics are safer  
Acute onset. Can also manifest parkinsonism and tardive dyskinésia in addition to dystonia. Older patients are more at risk for dystonia

Infectious

Encephalitis  
Prion  
Abscess

Viral

CJD  
Immunosuppressed,  
tuberculosis

Distribution of dystonia dependent on region of brain involved.

Accompanied by cognitive changes, fevers, and systemic

			illness
Metabolic	Metal accumulation	Copper (Wilson's disease – <i>ATP7B</i> gene)	Progressive dystonia associated with liver dysfunction, neuropsychiatric symptoms, and presence of Kaiser–Fleischer rings in the cornea. MRI: T2 hyperintensities in putamen and globus pallidus. Labs: low ceruloplasmin and serum copper, elevated urine copper
		Iron (NBIA) NBIA Type 1 ( <i>PANK 1</i> gene) NBIA Type 2 ( <i>PLA2G6</i> gene)	Childhood onset. Generalized dystonia that can progress to bulbar involvement MRI – T2 image reveals “eye of the tiger sign” – iron deposit within globus pallidus (GP) interna No “eye of the tiger sign” on MRI but

		presence of iron in GP is seen
Manganese	Dystonia associated with parkinsonism. Occupation hx of steel smelting, battery manufacturing, and water purification industries. MRI – T1 hyperintensities in pallidum	
Calcium	Deposits in bilateral basal ganglia. Usually asymptomatic and incidental finding on CT. When present in setting of young adult onset dystonia, must consider hypoparathyroid, congenital infections (e.g. toxoplasmosis, CMV, herpes, HIV), Fahr's disease	
Toxins	Carbon monoxide Cyanide Methanol	Delayed onset with improvement

over 6 months.  
May have  
symmetric basal  
ganglia calcium  
deposition  
Acute dystonia  
with  
parkinsonism  
Pallidal  
hemorrhagic  
necrosis on MRI  
Acute dystonia  
with  
parkinsonism.  
Putaminal  
hemorrhagic  
necrosis on  
CT/MRI  
\*Encephalopathy  
is common  
feature with any  
of these toxins

## Dystonia-plus syndromes

Dopa-  
responsive  
dystonia

AD – *GCH1* gene  
AR – *TH* gene

Onset 1–12  
years, usually  
presents in the  
legs. Diurnal  
fluctuations are  
hallmark signs  
with worsening  
at nights  
Exquisitely  
responsive to  
levodopa  
Mimics cerebral  
palsy or early  
onset Parkinson's  
disease

## muscle

Rapid dystonia parkinsonism	DYT 12  AD – <i>ATP1A3</i> gene	Evolves over hours to days. Symptoms follow a rostrocaudal pattern affecting bulbar function (i.e. dysarthria, dysphonia, and dysphagia) more than arms, which are subsequently more affected than legs  Dystonia tends to be generalized or segmental with an overlay of parkinsonian features  Levodopa not efficacious  Stabilize in 1 month
Myoclonus dystonia syndrome (MDS)	DYT 11  AD – epsilon- sarcoglycan gene ( <i>SGCE</i> )	Onset in first two decades.  Dystonia commonly focal (cervical, limb) or task specific (writers cramp) but can also involve trunk.  Myoclonic jerks are responsive to alcohol and

AD, autosomal dominant; AR, autosomal recessive; Hx, history; NBIA, neurodegeneration with brain iron accumulation.

## Laboratory and radiographic evaluation

Primary dystonia cannot be confirmed with laboratory results, but is based on historical and clinical information. A work-up for secondary causes should include complete blood count (CBC), electrolytes, renal and liver function, erythrocyte sedimentation rate (ESR), antinuclear antibody (ANA), rapid plasma reagins (RPR), and serum ceruloplasmin. Brain MRI and a lumbar puncture to exclude infection or a cerebral inflammatory process are also necessary. Further investigations for genetic disorders should be based on clinical findings, imaging and laboratory results, and family history.

## Treatment

Prior to treating any dystonia, secondary causes should be ruled out first. If a secondary etiology is found, treatment should be tailored towards it. Treatment of dystonia is symptomatic and requires a multi-faceted approach that includes assessing the patient's underlying psychiatric comorbidities (i.e. anxiety, depression), pain, and orthopedic complications and subsequently considering physical and occupational therapy early [10]. According to the algorithm posed by Jankovic (2006) [10], for patients with segmental or generalized dystonia, a trial of levodopa as high as 1,000 mg daily for one month should be instituted. This is required in any child in whom dopa-responsive dystonia is being considered, although the dose used is more commonly 300 mg daily. Failure to respond should then lead to the addition of anticholinergic medications (i.e. trihexyphenidyl) with a slow titration to minimize adverse effects. Many patients need a combination of medications to fully optimize their treatment. These include baclofen, benzodiazepines such as clonazepam, tizanidine, and tetrabenazine. Focal dystonias usually respond to botulinum toxin injections, which can also be used in segmental or generalized dystonia to alleviate disabling symptoms. Implantation of deep brain stimulators is deferred for medical refractory cases, particularly severe generalized dystonia in children .

## Case vignette

A 34-year-old male with no past medical history presents to the emergency department with sudden onset of slurred speech, difficulty swallowing, and gait instability. Symptoms started several hours prior, with tightness of the jaw and involuntary tongue protrusion, followed by stiffness in the left arm and leg. The patient had fever and productive cough for the last 2 days. His neurologic exam revealed intact cognition, oromandibular dystonia with tongue protrusion and drooling, a flexed dystonic left arm with a large amplitude kinetic tremor, and a slight inverted left foot dystonia triggered by walking. He was also bradykinetic and demonstrated bilateral cogwheel rigidity.

Based on the phenomenologic discussion of dystonia summarized above, several conclusions can be drawn from the original patient vignette: (1) Onset is late (>26 years); (2) there is multifocal dystonia (OMD, left arm > left foot); (3) there is evidence of concomitant extrapyramidal symptoms and an abrupt onset suggesting that the etiology is either a secondary cause (stroke, encephalitis, toxin), a feature of another neurologic disease (e.g. PD), or a dystonia-plus syndrome.

This patient had normal labs, an unremarkable CSF analysis, and a normal brain MRI. Given the suspicion that this was a dystonia-plus syndrome, specifically RDP, genetic testing was undertaken, revealing a mutation in the *ATP1A3* gene consistent with the leading differential diagnosis.

## Management

The patient did not respond to levodopa and his symptoms plateaued over 4 weeks. A supportive care plan was implemented to address his swallowing (gastrostomy tube), arm dystonia (botulinum toxin), gait (physical therapy), and family planning concerns (genetic counseling).

## References

1. Fahn S. Concept and classification of dystonia. *Adv Neurol* 1988; 50:1–8.
2. Phukan J, Albanese A, Gasser T, Warner T. Primary dystonia and dystonia-plus syndromes: clinical characteristics, diagnosis, and pathogenesis. *Lancet Neurol* 2011; 10:1074–85.
3. Frucht SJ. Focal task-specific dystonia of the musicians' hand – a practical

approach for the clinician. *J Hand Therapy* 2009; 22:136–43.

4. Fahn S. Classification of movement disorders. *Mov Disord* 2011; 26:947–57.
5. de Carvalho Aguiar PM, Ozelius LJ. Classification and genetics of dystonia. *Lancet Neurol.* 2002; 1:316–25.
6. Nutt JG, Muenter MD, Melton LJ, 3rd, Aronson A, Kurland LT. Epidemiology of dystonia in Rochester, Minnesota. *Adv Neurol.* 1988; 50:361–5.
7. Fuchs T, Ozelius LJ. Genetics of dystonia. *Semin Neurol.* 2011; 31:441–8.
8. Grandas F, Elston J, Quinn N, Marsden CD. Blepharospasm: a review of 264 patients. *J Neurol Neurosurg and Psychiatry* 1988; 51:767–72.
9. Sheehy MP, Marsden CD. Writer's cramp – a focal dystonia. *Brain* 1982; 105:461–80.
10. Jankovic J. Treatment of dystonia. *Lancet Neurol.* 2006; 5:864–72.

## 24 Eating disorders

---

Nina Kirz and Vandana Aspen *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Eating disorders are classified using the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders* – fourth edition (DSM–IV). The DSM–IV recognizes two specific diagnoses: (1) bulimia nervosa which is characterized by repeated episodes of objective binge episodes followed by compensatory behaviors and (2) anorexia nervosa which is characterized by a refusal to maintain normal body weight. The DSM–IV also includes a residual diagnostic category, eating disorder not otherwise specified, for those eating disorders that are clinically significant but do not meet criteria for anorexia nervosa or bulimia nervosa. Eating disorders, especially anorexia and bulimia, are characterized by an overvaluation of shape and weight in one's self-evaluation and a fear of weight gain. The patient may have very little motivation to change his or her behavior, perceiving the eating disorder as helpful. Alternatively, especially with bulimia, the patient may be quite ashamed of his or her symptoms. Either of these factors can lead patients to try to hide their eating disorders from professionals.

### Case vignette

A 25-year-old female presenting to her primary care physician for fever was noted to have a 15 pound weight loss since her last visit 2 years prior. She reported a year history of headache, reduced appetite, nausea, and amenorrhea. Her body mass index was  $17.4 \text{ kg/m}^2$ . She endorsed a history of body dissatisfaction and frequent dieting in the past, but she denied any current intentional weight loss. However, she did not seem very concerned by her low weight, and family reported that she had been resistant to their attempts to get her to eat more. Work-up at the time was unremarkable and she was given

diagnoses of viral infection and anorexia nervosa. She followed up with a therapist specializing in eating disorders, and was temporarily able to gain some weight. Six months later the patient presented again with fever, headache, and nausea, and a body mass index of  $17.1 \text{ kg/m}^2$ . In addition, she complained of loss of vision in her right eye. Ophthalmic assessment confirmed an almost complete loss of the right temporal field of vision. Given the visual disturbance and the history of headache and nausea, an MRI scan was performed. The scan revealed a cystic calcified suprasellar mass. The tumor was surgically removed and pathology confirmed the diagnosis of craniopharyngioma. All symptoms resolved after a postoperative course of radiotherapy.

**Table 24.1 Differential diagnosis of eating disorders.**

Category	Subdivision	Specific entity	Possible clinical features
Toxic	Decreased intake/weight loss	Stimulants, either legally prescribed for ADHD or illegal	History of drug or substance abuse
	Binging	Corticosteroids, atypical antipsychotics	History of medication known to stimulate appetite
Infective/post-infective	Decreased intake/weight loss	Tuberculosis, parasites, AIDS	History of exposure, abnormal CBC/differential (not just suppression can be seen in malnutrition)
Pressure effects	Vomiting	CNS tumor	Headache, papilledema

Psychiatric	Decreased intake/weight loss	Anorexia nervosa	Distorted image, wish to lose weight, avoid high-calorie foods; involve exercise activities which emphasize body shape. Function may not improve with forthcoming treatment if brought to treatment against their will
		Depression	Depressed mood precedes weight loss, patient complains of anhedonia and lack of motivation
		Dementia	History of cognitive difficulties
		Psychosis	Psychotic symptoms such as delusions and hallucinations may be present
		Somatoform disorder	Reports of pain/nausea associated with eating without apparent neurological etiology; history of frequent somatic complaints, difficulty functioning about negative feelings

## Answers

Phobia of choking or vomiting	Has experienced witnessed episode of or vomiting to onset of symptoms; choking pt may have a time with some foods	
Contamination fears related to obsessive-compulsive disorder	Extended in around keeping hands, food dishes, and clean	
Selective eating [1]	Lifelong habit of eating very narrow range of foods	
Food avoidance emotional disorder/avoidant restrictive food intake disorder [1]	Increased restriction of stress, related to encouragement to eat more evidence of image issues	
Vomiting	Eating disorder (anorexia nervosa or bulimia nervosa)	Intentional vomiting in response to feelings of overeating
Anxiety	Vomiting in response to overwhelming	

anxiety wi  
evidence o  
image issu

Binging	Eating disorder (bulimia nervosa or binge eating disorder)	Eating a large amount and a loss of control while eating may be a response to emotional distress or previous restriction of intake causing severe hunger
Inflammatory	Decreased intake/weight loss	Inflammatory bowel disease Loose stools, bloody diarrhea, abdominal pain, anemia, arthralgias
	Celiac disease	Chronic diarrhea, abdominal distension, bloating, a positive IgA anti-endomysial antibody test. Biopsy should be done with gluten rich diet
Neoplastic/paraneoplastic	Decreased intake/weight loss	Cancer cachexia Disproportionate loss of lean body mass, especially skeletal muscle, other symptoms of malignancy such as recurrence, pallor, fatigue, pain, etc.

			easy bruising, bleeding, stiffness or persistent pain in bones or joints
		Tumor affecting hypothalamus or other structures involved in regulation of eating behavior	Diabetes insipidus, visual disturbances, hypogonadism, headache, amenorrhea
	Vomiting	Abdominal tumor causing obstruction	Worsening nausea and vomiting becomes non-focal over time
Vascular	Vomiting	Superior mesenteric artery syndrome	Syndrome usually causes rapid weight loss leading to fat pad between superior mesenteric artery and duodenum causing them to constrict duodenum symptoms consistent with proximal small bowel obstruction. May also be caused by which disrupts superior mesenteric artery such as congenital anomalies or surgery for scoliosis.

Other	Vomiting	Abdominal migraine/cyclic vomiting [2]	Episodes of recurrent vomiting which can last several days well without vomiting between episodes; may have family history of migraine
	Pregnancy		Female of childbearing age; vomiting may improve with eating, more common month since menstrual period; positive pregnancy test
Metabolic	Decreased intake/weight loss	Diabetes mellitus	Increased thirst and urine output; ketonuria
		Hyperthyroidism	Tachycardia, tremor, hyperreflexia, exophthalmos, goiter
		Adrenal insufficiency	Malaise, fatigue, weakness, hyperpigmentation, electrolyte disturbance, hypotension

Heredotamilial

Binging

Prader–Willi  
syndrome

History of  
hypotonia,  
hyperphag  
a young ag  
stature

---

## References

1. Bryant-Waugh R, Markham L, Kreipe RE, Walsh BT. Feeding and eating disorders in childhood. *Int J Eat Disord* 2010; 43:98–111.
2. Hegjazi RA, McCallum RW. Review article: cyclic vomiting syndrome in adults – rediscovering and redefining an old entity. *Aliment Pharmacol Ther*. 2011; 34:263–73.

## 25 Eye movements, abnormal

---

Heather E. Moss *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

Note: Abnormal eye movements are addressed in multiple other chapters in this volume:

- Limitations in movement and ocular misalignment
  - Diplopia ([Chapter 17](#))
  - Ophthalmoparesis ([Chapter 49](#))
  - CN III, IV, VI nerve palsies ([Chapters 103, 89, 102](#))
- Extra movements
  - Nystagmus, regular to and fro oscillations of the eyes ([Chapter 48](#))
  - Other abnormal eye movements (this chapter)

### Introduction

This section discusses extra eye movements that do not serve a visual purpose (such as following a moving object or relocating visual fixation to a new object). A person with abnormal eye movements of this type may experience shaking, translation, or blurring of the visual environment (i.e. oscillopsia). The eyes may become misaligned and an individual may experience diplopia if the abnormal eye movements are different in each eye (see [Chapter 17](#) on diplopia). Altered visual input due to abnormal eye movements may cause dizziness or disequilibrium, which should resolve when the eyes are closed. Individuals who are comatose, blind, or whose visual processing system has adapted to abnormal visual input may have abnormal eye movements without any subjective symptoms.

Exquisite coordination is required to move the extraocular muscles of both eyes in order to locate a new target (saccade), follow a moving target (smooth pursuit), or maintain visual fixation in response to head movement (vestibulo-ocular reflex). As with motor control in the rest of the body, the ocular motility system relies on cortical and vestibular inputs, and cerebellar modulation.

Brainstem pathways coordinate the motor nuclei of cranial nerves 3, 4, and 6 to signal the extraocular muscles and move the eyes. Afferent vision is important for eye movement initiation and feedback. Disruption of any component of this system can cause abnormal eye movements.

The key to identification and localization of abnormal eye movements is careful description based on systematic examination. The examiner should pay attention to any limitations in eye movements in addition to the amplitude, speed, trajectory, and regularity of extra movements.

## Case vignette

A 19-year-old male was seen in consultation for dizziness and trouble walking. This developed over one week and was preceded by 4 days of cough, sore throat, and runny nose.

On examination he was afebrile with normal vital signs. He was well nourished, alert, and oriented in no apparent distress. Visual acuity was normal with each eye, though this was limited to single character testing due to his eye movements. These were conjugate, rapid, movements in varying directions, almost as if he couldn't control them or was very nervous and looking around. On closer inspection it was determined that there was no pause between eye movements. Extraocular movements were full and the remainder of his cranial nerve examination was normal. Motor strength was full in all extremities. There were rare muscle movements consistent with myoclonus. Sensation was normal. Gait was ataxic.

**Table 25.1 Identification and localization of abnormal eye movements.**

Category	Specific type	Typical etiology	Possible clinical features
Spontaneous eye movements in coma	Ocular bobbing	Destructive pontine lesion (classic) Metabolic encephalopathies	Rapid, conjugate downgaze followed by slow return to primary gaze

		Irregular (distinguishes from downbeat nystagmus) Horizontal gaze palsy Coma
Ocular dipping (inverse bobbing)	Not localizing	Slow, conjugate downgaze followed by rapid return to primary gaze Coma
Reverse ocular bobbing	Not localizing	Rapid, conjugate upgaze followed by slow return to primary gaze Irregular (distinguishes from upbeat nystagmus)
Reverse dipping (converse bobbing)	Not localizing	Slow, conjugate upgaze followed by rapid return to primary gaze
Ping-pong gaze	Bilateral hemispheric destruction	Conjugate, horizontal eye movements oscillating between lateral

			gaze extremes every few seconds Coma
Periodic alternating gaze	Metabolic coma	Sustained conjugate lateral gaze alternating between extremes every few minutes Coma	
Roving eye movements	Bilateral hemispheric dysfunction	Slow, conjugate, horizontal eye movements moving between lateral gaze extremes Coma	
Saccadic intrusions (interrupt fixation)	Square wave jerks	Normal Psychiatric disease Hemispheric disease Parkinsonism	Small amplitude, rapid, conjugate eye movements that move the eye off the target, then back to it Brief delay between movements (distinguishes from ocular flutter )
Macro-square wave ierks	Cerebellar dysfunction	Large amplitude.	

rapid,  
conjugate eye  
movements that  
move the eye  
off the target,  
then back to it  
after a brief  
delay

Macrosaccadic  
oscillations

Cerebellar  
dysfunction

Bursts of  
crescendoing  
then  
decrescendoing  
amplitude,  
rapid,  
conjugate eye  
movements that  
move the eye  
across the point  
of fixation  
Brief delay  
between each  
movement  
Not provoked  
by change in  
fixation  
(distinguishes  
from saccadic  
dysmetria)

Ocular flutter

Paraneoplastic  
Parainfectious  
Parenchymal  
disease  
Toxic  
Idiopathic

Rapid, high  
frequency,  
small  
amplitude,  
conjugate  
horizontal eye  
movements  
No delay  
between

movements  
(distinguishes  
from square  
wave jerks)  
Occur in bursts

### Opsoclonus

Paraneoplastic  
Parainfections  
Parenchymal  
disease  
Toxic  
Idiopathic

Rapid,  
moderate  
amplitude,  
conjugate  
multidirectional  
eye movements  
No delay  
between  
movements  
Can be  
associated with  
myoclonus,  
ataxia, and  
encephalopathy

### Voluntary “nystagmus” (psychogenic flutter)

### Psychogenic

High  
frequency,  
moderate  
amplitude,  
conjugate eye  
movements  
Typically  
sustained for  
only a few  
seconds  
Often  
associated with  
some  
convergence,  
facial  
grimacing

### Saccadic

### Saccadic

### Cerebellar

Rapid,

corrections	dysmetria	dysfunction	conjugate, eye movement towards desired target following overshoot or undershoot of eye movement to a new visual target Often associated with extremity ataxia
Saccadic smooth pursuit	Various	Multiple rapid conjugate eye movements to follow a moving target	
Transient ocular deviations	Ocular neuro-myotonia	Unknown	Transient involuntary sustained deviation of one eye Often provoked by sustained voluntary gaze in that direction Ocular movements normal between episodes
Oculogyric crisis	Neuroleptic toxicity Post-encephalitic parkinsonism	Rapid, extreme conjugate deviation of the eyes (typically...	

		Parkinsonism	Eyes (typically upwards) Lasts seconds to hours Can be associated with dystonia of other muscles (e.g. face, neck)
Tics	Idiopathic		Stereotyped, brief conjugate eye deviation Associated with urge to perform the movement and ability to suppress it
Lateropulsion	Lateral medulla injury		Conjugate drift of eyes to a lateral position when fixation is removed (e.g. with eye closure) Often associated with Horner's syndrome, ataxia, dysphagia, and crossed sensory loss
Other oscillations	Convergence retraction “nystagmus”	Dorsal midbrain injury (Parinaud's)	Convergence of eyes and retraction of

	syndrome)	gloves into orbits with attempted upgaze Often associated with upgaze limitation, pupillary light-near dissociation, and eyelid retraction
Oculomasticatory myorhythmia	CNS infection with <i>Tropheryma whippelii</i>	Pendular oscillations of the eyes in a convergence, divergence pattern at approximately 1 Hz Concurrent cyclic contraction of the masticatory muscles
Oculopalatal tremor	Injury to brainstem or cerebellum (Mollaret triangle)	Pendular oscillations of the eyes at approximately 1–2 Hz Palatal tremor at the same frequency Develops months after brainstem or

		cerebellar injury
Superior oblique myokymia	Trochlear nerve injury with regeneration in some cases Typically benign	Recurrent brief episodes of monocular low amplitude, very high frequency oscillation Magnification required for examiner to visualize movement Triggered by downgaze and adduction May be associated with transient diplopia and sense of eye tremor
Nystagmus	See <a href="#">Chapter 48</a>	Regular oscillations of the eyes either with fast and slow phases (jerk nystagmus) or back to back slow phases (pendular nystagmus)

---

The eye movements were diagnosed as opsoclonus based on the

multidirectional rapid movements without slow phase or delay between movements. MRI of the brain, lumbar puncture, CT of the chest, abdomen and pelvis, and viral serologies did not provide evidence for structural brain lesion, inflammatory cerebral disease, infection, or systemic neoplasia.

A presumed diagnosis of idiopathic or post-viral opsoclonus myoclonus syndrome was made and he was treated with a course of steroids with improvement in his symptoms .

## Further reading list

Leigh JR, Rucker JC (2004). Nystagmus and related ocular motility disorders. In NR Miller & NJ Newman, Eds. *Walsh & Hoyt's Clinical Neuro-Ophthalmology*, 6th edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2004.

Liu GT, Volpe NJ, Galetta SL. Part 3: Efferent neuro-ophthalmic disorders. In *Neuro-Ophthalmology: Diagnosis and Management*, 2nd edn. Philadelphia, PA: Saunders Elsevier, 2010.

The Neuro-Ophthalmology Virtual Education Library. <http://novel.utah.edu/>  
Extensive collection of images and videos of abnormal and normal ocular motility.

## 26 Falls

---

Christyn M. Edmundson and Steven A. Sparr *Neurologic Differential Diagnosis*,  
ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge  
University Press. © Cambridge University Press 2014.

### Introduction

Falls, defined as unintentional events that result in a person coming to rest on the floor or other low-lying surface, are extremely common. This is, in part, because the erect human form is inherently unstable. The seemingly simple act of standing upright, let alone that of locomotion, involves multiple components of the nervous system, including motor, sensory, and processing elements. In order to maintain balance, each of these components must not only be individually intact, they must also interact in a complex and synchronized manner. Thus, dysfunction in any one of the systems involved in balance renders us all too easily defeated by that formidable foe: gravity.

Moreover, falls can be extremely damaging events, particularly in persons older than 65, more than one third of whom fall each year. While young children and athletes also experience a high incidence of falls, older individuals are more likely to be injured due to a variety of age-related changes.

The etiology of falls is extensive and is often multifactorial in any given individual. These etiologies can be broadly divided into several categories: (1) syncopal falls, which are caused by loss of consciousness, (2) non-syncopal falls, which are caused by a loss of balance, and (3) mechanical falls, which are caused by an alteration or obstacle in an individual's environment.

This chapter will primarily address non-syncopal falls. The reader can find an excellent review of the etiology of syncope in [Chapter 73](#). Additionally, mechanical falls will not be addressed in depth, as they do not necessarily reflect a pathologic state. However it is important that many of the diseases discussed below may increase the frequency of mechanical falls by decreasing a person's ability to successfully navigate his or her environment.

## Case vignette

An 82-year-old female with a remote history of benign paroxysmal positional vertigo (BPPV) and longstanding hypertension was brought to the emergency department after falling at home. The patient reported feeling “unsteady” while walking to the bathroom during the night and then fell to the floor. The patient sustained no head trauma or fractures. She denied loss of consciousness, vision changes, chest pain, palpitations, shaking, or jerking. She also denied prior episodes of syncope or falls. She reported that she had recently felt increasingly “unsteady” while walking, but states that this unsteadiness was markedly different than the dizziness she has experienced due to her BPPV.

On neurologic examination in the emergency department, the patient's mental status, cranial nerves, distal sensation and joint proprioception, strength, reflexes, and coordination were intact. The patient was found to have mild cog-wheeling with distraction in her right wrist, a narrow-based gait with unsteady tandem, a positive push-pull test (became unsteady when gently pushed backward), and en-bloc turning. Hallpike-Dix maneuver did not produce dizziness. In the emergency department a CBC, a basic metabolic panel, an electrocardiogram, and a head CT without contrast were all unremarkable. Given the low suspicion for acute cerebral infarct, brain MRI and angiography were not performed at that time. The patient was discharged home with outpatient neurology follow-up for her mild parkinsonism.

When seen by an outpatient neurologist, the patient's mild parkinsonism was again noted on exam. However she lacked several characteristic findings of Parkinson's disease, such as resting tremor and masked facies. An MRI of the patient's brain revealed extensive periventricular white matter disease. The patient was diagnosed with Binswanger's disease, likely secondary to her longstanding hypertension .

**Table 26.1 Differential diagnosis of falls.**

Category	Location	Signs of that location	Specific
Sensory	Proprioceptive/Somatosensory disorders (significant when affect lower limbs)	Loss of position sense on exam Unsteady, wide-based gait	Axonal   Metabol   most co- infection

**visual gait**      **mechanical**  
Imbalance      vascular  
particularly      neoplasm  
pronounced when      paraneoplastic  
visual cues are      pharmacological  
removed  
Characteristic  
exam: Testing for  
Romberg sign

Demyelinating  
polyneuropathy  
AIDP, CIDP  
See “Mc”

Herededitary  
polyneuropathy  
*i.e.* Charcot-Marie-Tooth, etc.  
Leukodystrophy

Sensory  
Paraneoplastic  
connective tissue disease,  
exposure to drugs or  
toxicity)

Dorsal c  
Multiple  
deficien  
neurosy]  
compre  
spondyl  
“Motor”

### Vestibular system disorders

Dizziness/vertigo  
Symptoms worsen  
with position  
change  
Nystagmus:  
horizontal/rotatory  
in peripheral  
vertigo, any  
direction in  
central vertigo.  
Beats away from  
side of lesion  
Characteristic  
exam: Hallpike–  
Dix testing

Ménière

Benign j  
position

## Mass eff Schwan lesions

Central

## Visual system disorders

Poor visual acuity  
Most pronounced  
in conditions that  
further decrease  
visual acuity  
Characteristic  
exam: testing for  
visual  
acuity/visual  
fields

**Extreme  
different  
etiologie  
Cataract  
macular  
among r  
etiologie**

Central

## Diffuse

Altered level of consciousness.  
Characteristic exam: Mental status exam

Syncopē

Deliriun

Cerebral cortex	See “Upper motor neuron” causes of falls	
Frontal/subcortical disequilibrium	Gait apraxia and tendency toward backward falls Preserved function of individual limbs Associated with dementia, urinary incontinence, frontal release signs, and extrapyramidal signs Characteristic exam: capable of complex limb movements while supine despite gait impairment	Normal hydroce
	Unstable in retropulsion on push--pull testing	Diffuse disease (disease)

Frontal lobe  
Tumor, bleed,  
hemorrhage

Stroke  
Lacunar  
cerebral

Dementia  
Alzheimer's  
Pick disease

### Basal ganglia

Festinating gait  
and axial rigidity  
Poor movement  
initiation  
Resting tremor  
Symptoms may be  
unilateral early in  
disease course  
Masked facies,  
slowed blink  
Characteristic  
exam:  
Cogwheeling  
induced with re-  
enforcement, pull  
test

Idiopathic  
(Parkinson's)

Parkinson's  
syndrome

	Progressive nonfluent aphasia	Progressive nonfluent aphasia
Cerebellum	Ataxic gait and truncal instability Intention tremor Impairment of fine motor skills	Acute infarct
		Toxin-induced parkinsonism
		Other movement disorders
		Parkinson's disease
		Progressive subcortical gliosis
		Corticobasal degeneration
		Multiple system atrophy (striatonigral degeneration)
		Olivoponto-rubro-pathy
		Degenerative disorders of the basal ganglia
		Drager syndrome
		Medication-induced parkinsonism

dexterous movements,  
dysarthria  
When only one hemisphere is affected, findings are ipsilateral to lesion

Nystagmus: beats towards side of lesion (vs. vestibular, which beats away from lesion)

Characteristic exam: Past-pointing, poor tandem gait

Chronic  
*e.g.* alco bismuth

Inherited syndromes

Posterior malformations

Tumors

Paraneo

Vertebral  
insuffici  
infarctio

Cerebell

Inflammr

Multiple

Metabol

Brainstem

Vertebr  
insuffici

Basilar c

Brainste  
Includes  
and Wel

Motor

Upper motor neuron

Weakness in  
variable

Cortical  
Motor c

distribution  
Spasticity and hyperreflexia in affected nervous distribution  
Interferes with gait/balance when lower extremities are involved  
Characteristic exam: Babinski sign present, marked  
fatigability in muscles with residual function

suppem cortex

Myelop  
Demyeli  
inflamm  
vascular  
vitamin  
(B12), ti  
tumors/c  
compres

Cervical myelop

Anterior horn cell  
Flaccid weakness  
and muscle  
wasting  
No sensory deficit

Amyotrophic  
lateral  
sclerosis  
Postpolio  
syndrome

Poliovirus

Lower motor neuron  
Mixed motor and  
sensory deficits  
Flaccid weakness  
Characteristic  
exam: Decreased  
tone and reflexes

See “Spinal  
cord lesions”  
Acute inflam-  
matory demyeli-  
nating polyneu-  
ropathy (Guillain-  
Barré syndrome)

Chronic  
inflammatory  
demyelin-  
ating polyneu-  
ropathy

Muscular	Neuromuscular junction	Primarily immune-mediated diseases	Myasthe
			Lambert syndrom
			Toxin m <i>e.g.</i> botu tetanus t paralysis
Muscle	Generally pure motor deficit Conditions have variable patterns of muscle involvement Characteristic exam: Proximal	Muscula <i>E.g.</i> Duc Becker c	

vs. distal muscle  
testing

Inflamm  
*e.g.* poly  
dermatomy

Hypoka  
paralysis

Other m  
Congeni  
infectiou  
HIV), to  
medicati  
myopath

Other

Drop att

---

AIDP, acute inflammatory demyelinating polyneuropathy; CIDP, chronic inflammatory demyelinating polyneuropathy; CJD, Creutzfeldt–Jakob disease; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging.

## Further reading list

- Halter JB, Ouslander JG, Tinetti ME *et al.* *Hazzard's Geriatric Medicine and Gerontology*, 6th edn. New York, NY: McGraw Hill, 2009.
- Masdeu JC, Lewis S, Wolfson L. *Gait Disorders of Aging: Falls and Therapeutic Strategies*. Philadelphia, PA: Lippincott-Raven, 1997.
- Ropper AH, Samuels MA. *Adams & Victor's Principles of Neurology*, 9th edn. New York, NY: McGraw Hill, 2009.
- Simon RP, Greenberg DA, Aminoff MJ. *Clinical Neurology*, 7th edn. New York, NY: McGraw Hill, 2009.
- Tinetti ME. Preventing falls in elderly persons. *N Engl J Med* 2003; 348:42–9.
- Verghese J, Ambrose AF, Lipton RB, Wang CL. Neurologic gait abnormalities and risk of falls in older adults. *J Neurol* 2010; 257:392–8.

## 27 Foot drop

---

Pinky Agarwal and Ryan J. Zehnder *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Foot drop is a general term for loss of voluntary ankle dorsiflexion. It is typically most apparent during gait, with a pattern of exaggerated knee flexion and hip hiking to allow toe clearance and prevent tripping during each step. There may also be a “slapping” sound after heel strike due to loss of eccentric control of forefoot contact with the ground. This pattern is classically called a steppage gait.

Foot drop is often an easily recognized sign of a more complex systemic or localized neurologic process. Most commonly it results from weakness of the dorsiflexor muscle group of the ankle, which includes the tibialis anterior, extensor hallicus longus, and extensor digitorum longus. The weakness can result from direct muscle injury, lower motor nerve dysfunction, or upper motor nerve disorders (see [Table 27.1](#)). Less commonly, mechanical ankle dysfunction such as severe arthritis or Charcot foot can lead to loss of dorsiflexion. Examination of the ankle for tenderness, swelling, and deformity, as well as passive ankle range of motion will normally reveal mechanical causes of foot drop. Plain X-rays are also helpful if there is suspicion of mechanical foot drop. One must also be aware that chronic dorsiflexion weakness often leads to secondary contracture of the Achilles tendon and loss of range of motion.

**Table 27.1** *Differential diagnosis of foot drop.*

	Specific type	Etiology	Clinical features
Neuropathy	Fibular neuropathy	Mechanical compression at	Typically unilateral

<b>peripheral neuropathy</b>	<b>compression at the fibular head (habitual leg crossing, casts, squatting, or surgical positioning), compartment syndrome, recent weight loss, total knee arthroplasty, trauma, tumor, nerve infarct secondary to vasculitis</b>	<b>weakness Weak ankle dorsiflexion and eversion strength Preserved plantar flexion and inversion strength Normal reflexes Sensory loss in lateral calf and foot</b>
<b>Sciatic neuropathy</b>	<b>Total hip arthroplasty, pelvic trauma, tumor, intramuscular injections, hip fracture, hip dislocation, herpes zoster or simplex infections, gluteal hemorrhage, cardiac surgery from lower limb ischemia</b>	<b>Weak plantar flexion, inversion, and dorsiflexion Numbness in sole, dorsal foot, and calf</b>
<b>Generalized peripheral polyneuropathy or mononeuropathy multiplex</b>	<b>Diabetes, toxins, chronic alcohol, medications, hypothyroidism, poliomyelitis, genetic</b>	<b>Often bilateral Length-dependent sensory loss Weakness plantar flexion</b>

		(Charcot–Marie–Tooth, hereditary neuropathy with liability to pressure palsies)	and dorsiflexion Claw toes, high arches Diminished ankle reflexes
Lumbar radiculopathy	L4 nerve root compression	Herniated L3-- L4 intervertebral disc, degenerative spondylosis, or spondylolisthesis	Pain in anterolateral leg Weakness in knee extensors Sensory loss in medial calf/shin Back pain Reduced knee jerk reflex
	L5 nerve root compression	Herniated L4– L5 intervertebral disc, degenerative spondylosis, or spondylolisthesis	Pain down lateral leg EHL weaker than ankle dorsiflexors Sensory loss in lateral calf and foot Back pain Reduced hamstring reflex
Lumbar plexopathy (see chapter on lumbosacral plexopathy)	Compression of lumbar plexus	Trauma, pressure during labor, diabetes, pelvic fracture, pelvic surgery, tumor, abscess, or	History of trauma Fevers, chills, weight loss, anemia, or other signs of systemic

		retroperitoneal hematoma	illness Diffuse leg weakness or numbness
Upper motor neuron disorders (central foot drop)	Stroke, spinal cord injury, traumatic brain injury, multiple sclerosis, cerebral tumor	Ischemic, hemorrhagic, trauma, or idiopathic	Upper motor signs such as cognitive changes, facial droop, hyperreflexia, spasticity, hemiplegia, etc. will usually be apparent
Motor neuron disease	Amyotrophic lateral sclerosis	Genetic, idiopathic	Normal sensory exam Fasciculations, hyperreflexia Progressive
Muscular disease	Muscular dystrophy	Genetic	Diffuse weakness, fatigue, progressive
	Myopathy	Autoimmune, toxins, medications, critical illness	Normal sensory exam Symmetric weakness Elevated muscle enzymes
Tibialis anterior muscle or tendon tear	Ankle inversion injury		History of ankle injury Associated

			ankle pain, swelling, or deformity Preserved ankle eversion strength
Non-organic		Psychiatric disorders, malingering, conversion disorder	Lack of objective abnormalities Inconsistencies between weakness observed in gait versus strength testing
Mechanical	Ankle deformity	Ankle arthritis, Charcot joint	Ankle pain, stiffness, swelling, and loss of passive ROM
	Plantar flexion contracture	Spastic, positional	Lack of ability to passively dorsiflex ankle Usually secondary to ankle dorsiflexion weakness, but can cause persistent foot drop after strength has returned

---

The fibular nerve (formerly peroneal nerve) [1] is very superficial and susceptible to direct compression in its course across the fibular head, and the most common site of focal neuropathy in the lower extremity [2]. The patient will classically present with a unilateral dropped foot and numbness and tingling in the lateral calf and dorsal foot, but rarely with pain complaints [3]. Examination will reveal weakness in ankle dorsiflexion, eversion, and weakness in the extensor hallucis longus (great toe extension), but normal strength with plantar flexion and inversion (which are controlled by tibial nerve innervated muscles). In milder cases, weakness may only be apparent when the patient is asked to walk on his or her heels. Tapping the nerve along the fibular head may also produce pain and tingling in the fibular nerve sensory distribution. Distribution of sensory loss on examination also assists in localizing the lesion. Numbness only in the lower part of the lateral distal leg suggests superficial fibular nerve involvement, whereas numbness also involving the upper third of the lateral distal leg suggests common fibular nerve involvement (see [Figure 27.1](#)). Knee and ankle jerk reflexes do not involve the fibular nerve and should be normal and symmetric. Recent significant weight loss, leg casting, habitual leg crossing, or squatting may contribute to mechanical compression of the nerve. Focal fibular neuropathy may also occur as a complication of total knee replacement, either from direct trauma, laceration, or surgical positioning [4]. Additionally, direct trauma or mass lesions such as ganglia, tumors, and Baker's cysts can cause focal fibular nerve compression.



**Figure 27.1** Sensory distributions of the fibular nerve: common fibular neuropathy will cause numbness in all shaded areas. Superficial fibular neuropathy will cause numbness in the gray area. Deep fibular neuropathy will cause numbness only in the dark gray area.

Toxin exposures or metabolic abnormalities may also cause a fibular mononeuropathy, but more commonly will cause generalized peripheral polyneuropathy, with other signs besides a foot drop [5]. Polyneuropathies often lead to bilateral foot drop with slow and chronic progression. Evidence of polyneuropathy will usually manifest with numbness also outside of fibular nerve distribution or in a stocking-glove pattern. Exam findings may include claw toe deformities and loss of ankle jerk reflexes. The most common causes of polyneuropathy are diabetes and chronic alcoholism. Various hereditary disorders such as Charcot-Marie-Tooth, infections such as leprosy, vasculitis, and toxin exposure must also be considered. Nerve conduction testing will show

diffuse abnormalities in multiple nerves. Initial laboratory work-up in suspected cases should include fasting blood sugar, hemoglobin A1C, ESR, ANA, CRP, SPEP, BMP, and B12 levels.

Direct injury to the dorsiflexor muscle group may result from trauma, such as a torn tibialis anterior muscle , or compartment syndrome . In the case of a torn tibialis anterior muscle, the patient may report acute pain after plantar flexion injury, and will still be able to evert the foot (using the fibularis longus and brevis muscles). However injury to the deep branch of the fibular nerve will also spare the everter muscles. If deep fibular neuropathy is suspected, one should examine for sensory loss in the first web space and weakness of the extensor hallucis longus (great toe extension).

Lumbar radiculopathy may result in foot drop if the L4 or L5 nerve root is compressed by a herniated disc. In addition to foot drop, patients will typically complain of pain radiating down the back of the leg or lateral calf, worsened by sitting or flexed posture. Exam findings include positive straight leg raise and loss of knee jerk reflex. Similarly, lesions of the lumbar plexus or sciatic nerve may initially present with foot drop but will also typically have weakness in non-fibular innervated muscles such as the tibialis posterior or gastrocnemius. However, sciatic nerve injuries may sometimes affect only the fibular nerve fascicles and spare tibial nerve fascicles of the sciatic nerve, making it difficult to distinguish from distal fibular nerve injury [6]. EMG testing is often essential in differentiating fibular neuropathy from sciatic neuropathy, plexopathy, or lumbar radiculopathy [7].

Central nervous system diseases such as stroke, parasagittal cortical tumors, multiple sclerosis, spinal cord injury, or traumatic brain injury may manifest with foot drop. Upper motor neuron signs including positive Babinski test, hyperreflexia, clonus, and spasticity will be important clues. Spasticity of the gastrocnemius and soleus muscles may contribute to foot drop, especially during gait. Isolated weakness of ankle dorsiflexion without other areas of weakness or clinical symptoms is extremely rare after stroke or brain injury, but has been reported [8]. Similarly, foot drop may develop with various muscular dystrophies, but is unlikely to be an isolated presenting symptom or finding. Motor neuron diseases including amyotrophic lateral sclerosis (ALS) may present with foot drop, but typically other signs are present, and there is absence of numbness. An ALS diagnosis is based on clinical signs of upper and lower motor neuron dysfunction, typically objectified with EMG studies using specific diagnostic criteria developed by the El Escorial World Federation of Neurology.

In summary, careful history and examination is typically sufficient to diagnose the cause of a foot drop. If inconsistencies are found on physical examination, then electrodiagnostics, imaging, and labs may be necessary to confirm or further isolate the etiology .

## Case vignette

A 47-year-old female with diabetes complains of repeated tripping on her right foot. In the past month she has lost 27 pounds using a fasting weight loss program. She enjoys working in her garden, but cannot squat for more than 5 minutes to pull weeds before she notices numbness in her right foot.

Results of exam are: Strength – right ankle dorsiflexion 3+/5, foot eversion 3/5, EHL 2/5, plantar flexion 5/5, inversion 5/5, knee extension 5/5. Sensation – reduced to pin-prick in dorsal and lateral foot, but normal on plantar and medial foot. Reflexes – 2+ bilateral knees, 1+ bilateral ankles. Babinski – downgoing toes bilaterally. Strait leg raise – negative. There are no other localized findings on neurologic exam and no foot deformities.

Upon review of the differential diagnosis table ([Table 27.1](#)), the clinical features of a fibular neuropathy are most consistent with the case history and examination, and this is also the most common cause of a foot drop. The typical causes of fibular neuropathy are noted in the etiology column of the table, and her history of weight loss and frequent squatting suggest mechanical compression at the fibular head. The remainder of the table should be reviewed to ensure other diagnoses can be effectively ruled out. Absent radicular pain, reflex changes, or plantar flexion weakness make lumbar radiculopathy, sciatic neuropathy, or plexopathy unlikely. Her history of diabetes does bring into question the possibility of a generalized polyneuropathy, however the clinical features as described in table are absent. Features of mechanical ankle dysfunction, upper motor neuron disorders, or myopathies described in the table are also absent.

## References

1. Federative Committee on Anatomical Pathology. *Terminologia Anatomica*. New York, NY: Thieme Stuttgart, 1998: 140.
2. Agarwal P. *Peroneal Mononeuropathy*. Medscape Reference (Online). Updated August 3, 2010.

3. Katirji MB, Wilbourn AJ. Common peroneal mononeuropathy: a clinical and electrophysiologic study of 116 lesions. *Neurology* 1988; 38:1723–8.
4. Idusuyi OB, Morrey BF. Peroneal nerve palsy after total knee arthroplasty. Assessment of predisposing and prognostic factors. *J Bone Joint Surg Am.* 1996; 78:177–84.
5. Gupta D, Bartorini TE. Clinical approach to a patient presenting with foot drop. *J Clin Neuromuscul Dis.* 2004; 5:154–65.
6. Katirji B, Wilbourn AJ. High sciatic lesion mimicking peroneal neuropathy at the fibular head. *J Neurol Sci.* 1994; 121:172–5.
7. Preston DC, Shapiro BE. *Electromyography and Neuromuscular Disorders*, 2nd edn. Philadelphia, PA: Elsevier, 2005.
8. Narendhiran G, Leach P, Holland JP. Clinical features of central isolated unilateral foot drop: a case report and review of the literature. *Surg Neurol Int.* 2011; 2:27.

## 28 Gait abnormalities

---

Michael A. Williams and Scott E. Brown *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

*Gait* is the term used to describe the pattern of a person's walking. Two functions comprise gait: balance and locomotion. *Balance* entails the postural reflexes necessary to keep the body upright and properly positioned for locomotion, and to protect against falls. *Locomotion* consists of the rhythmic, periodic movements of the limbs and trunk that move a person in a desired direction [1].

Humans normally walk on two legs (bipedal), which results in a nearly constant need to sense and correct axial posture and leg and foot position. This sensing and correcting involve neuronal circuits and pathways from the entire central and peripheral nervous system, including sensory input (visual, vestibular, proprioception) and motor coordination (premotor planning, upper and lower motor neurons, cerebellar pathways, basal ganglia, and spinal cord). Therefore, diseases or dysfunction of nearly any portion of the nervous system can result in abnormalities of gait. Conversely, careful and systematic evaluation of gait and related portions of the neurologic examination can provide clues to the location of a lesion or lesions that may be contributing to gait impairment.

The prevalence of abnormal gait in adults who are older than 70 years of age is 35.0% (95% confidence interval (CI), 28.6–42.1) [2], and patients with an abnormal gait have a higher risk of death or institutionalization (e.g. nursing home placement), with a hazard ratio (HR) of 2.2 (95% CI, 1.5–3.2). For patients with moderate or severe gait impairment, the HR is 3.2 (95% CI, 1.9–5.2) [2]. Further, the presence of gait impairment increases the risk of falling in the elderly 2.7-fold [3]. Evaluation of falling risk is recommended by The Joint Commission, and the American Academy of Neurology has published a practice parameter for assessing patients for the risk of falls [4].

Causes of gait impairment can be broadly categorized as neurologic or non-

neurologic. Neurologic causes include stroke, neuropathy, movement disorders, cerebellar disorders, spinal cord disorders, motor neuron disease, and many others. Non-neurologic etiologies include low vision; arthritis of the feet, ankles, knees, hips, or spine; and disorders that cause functional limitation, such as cardiovascular, peripheral vascular, or pulmonary disease, and morbid obesity. Of course, patients may have both neurologic and non-neurologic, or multifactorial, gait impairment.

This chapter focuses on neurologic disorders of gait impairment, with an emphasis on localization. A frequently used localization schema describes lower-level, middle-level, and higher-level gait disorders ([Table 28.1](#)) [1,5].

Lower-level gait disorders include disturbances of force production or of sensation and involve sensory neurons, lower-motor neurons, muscle weakness (e.g. myopathy), or impaired visual or vestibular sensation. If other areas of the nervous system are intact, patients generally can compensate for lower-level gait disorders.

Middle-level gait disorders are exhibited by impaired modulation of force generated by the lower-level motor system, in which postural and locomotor responses are “correct” but improperly modulated and executed. Examples include spasticity from disruption of corticospinal tracts, ataxia from disturbances of the cerebellum and its connections, hyperkinetic gait (e.g. chorea or dystonia), and hypokinetic gait such as that seen with parkinsonism.

**Table 28.1 Key features of selected gait disorders.**

Disorder or description	Descriptive features and associated findings	Portion of gait cycle affected	Localization and level of classification	Diates co
<b>Spastic gaits</b>				
Spastic gait	Typically bilateral with shortened step length and upright posture. Gait is often stiff-legged and the cadence is	Full cycle	•UMN ➢Middle level	Imbra EN CS

“choppy”  
Associated  
findings:  
Hyperreflexia,  
clonus, spastic tone,  
possible  
contractures,  
abnormal shoe  
wear. Urinary  
urgency or  
incontinence may  
be seen with spinal  
cord lesions or  
bilateral cerebral  
lesions

Scissoring gait	Severe spastic gait in which the foot strikes on the opposite side of the center of gravity, causing the legs to cross over, or “scissor”	Full cycle	See spastic gait	See spastic gait
Toe walking	Milder variant of spastic gait in which the foot strike is on the balls of the feet rather than the heels. Idiopathic toe walking can be seen in otherwise neurologically normal children, but muscular dystrophy or UMN involvement should raise suspicion of other causes.	Stance phase	•UMN ➢Lower or middle level	See spastic gait for even gait idiopathic walking

be considered if  
associated  
neurologic findings  
are present

## Hemiplegic gaits

Hemiplegic gait	Unilateral spastic gait. The paretic leg with increased tone has compensatory movements to achieve foot or toe clearance in the swing phase. Typically with upright posture Associated findings (ipsilateral to the paresis): Hyperreflexia, spastic tone, clonus, possible contractures, abnormal shoe wear, asymmetric arm swing or arm in slight flexion, shortened step length	Full cycle	•UMN ➤Middle level	Imbra
Circumducted gait	Compensatory movement in hemiplegic gait. During swing phase, the paretic leg is swung laterally and	Swing phase	See hemiplegic gait	See gait

	forward to achieve foot clearance and heel strike			
Hip hiking/pelvic lift	Compensatory movement in hemiplegic gait. Can also be seen with asymmetric limb length. During swing phase, the pelvis on side of the paretic leg is lifted vertically as the leg swings forward to achieve foot clearance	Swing phase	See hemiplegic gait	See gait

## Neuromuscular gaits

Peripheral neuropathy	Slapping or shuffling gait; typically bilateral with near-normal step length and upright or slightly bent posture. Gait may appear cautious with severe sensory loss Associated findings: weakness, distal sensory loss, Romberg sign, foot injury that the patient has not recognized due to impaired sensation	Heel strike	<ul style="list-style-type: none"> <li>•Sensory/motor peripheral nerves</li> </ul> <p>&gt;Lower level</p>	EMG apical blood urine
-----------------------	--	-------------	---	---------------------------------

Steppage gait (foot drop)	maximizes toe elevation during swing phase. Knee on the side of the foot drop is lifted high so the foot can swing forward without scuffing the toe. Often unilateral but can be bilateral; typically with normal step length and upright posture Associated findings: Abnormal shoe wear (scuffed toes), contractures, focal sensory deficits. Can be seen either with weakness of ankle dorsiflexors or increased tone of plantar flexors	swing phase	•Usualy L1-L4, can be UMN ➤Lower level	L1 if f uni inc cor im bra
Trunk propulsive/lurching gait (compensated)	Trunk lurches backward over stance leg, and hip thrusts forward to keep center of gravity behind hip joint; best evaluated from side. Typically unilateral with normal step length. Posture changes from upright to bent backward during the gait cycle Associated	Heel strike	•LMN •Myopathy ➤Lower level	

	<b>Associated findings:</b> Gluteus maximus weakness of stance leg; perform thorough hip extensor examination. Consider psychogenic gait		
Trunk propulsive/lurching gait (uncompensated)	Trunk lurches forward at heel strike; best evaluated from side. Typically unilateral with normal step length. Posture changes from upright to bent forward during the gait cycle  Associated findings: Gluteus maximus weakness of stance leg; perform thorough hip extensor examination. Consider psychogenic gait	Heel strike	•LMN •Myopathy ➤Lower level
Trendelenberg gait (compensated)	Gluteus medius weakness of the stance leg causes the trunk to lean over stance leg with little pelvic drop on swing side; best evaluated from	Swing phase	•LMN •Myopathy ➤Lower level

behind. Typically unilateral with normal step length and upright posture. If bilateral, gait has a waddling appearance Associated findings: Gluteus medius weakness of stance leg found on isolated manual muscle test

Trendelenberg gait (uncompensated)	Gluteus medius weakness of stance leg with associated pelvis drops on the contralateral swing side; trunk leans toward swing side; best evaluated from behind Associated findings: Gluteus medius weakness of stance leg	Swing phase	See compensated Trendelenberg gait
---------------------------------------	---	-------------	------------------------------------

## Ataxic gaits

Ataxic gait	Irregular and variable step lengths, often with stumbling. Typically bilateral. Posture can be upright, but also unstable with dysmetric postural	Full cycle	•Cerebellum ➤Middle level •Sensory peripheral nerves ➤Lower level	Br: im: EN ger cor cer de§
-------------	---	------------	--	--

responses

Associated findings: Cerebellar signs, such as dysarthria, dysmetria, dysdiadochokinesia, truncal ataxia, nystagmus. Distal sensory loss in feet is present with sensory ataxia

## Higher-level gait disorders

Magnetic gait	Gait initiation failure. Patient can have complete inability to initiate gait. Typically bilateral with shortened step length. Stuttering steps with frequent stops. May have stooped posture (anteropulsion) or standing retropulsion that is so severe that the patient cannot maintain stance Associated findings: Difficulty getting out of chair; falling into a chair or misaligning torso prior to sitting; inappropriate or	Toe off Full cycle	•Difficult to localize ➢Higher level	Im- bra- mic- wh- les- gar- lac- ver- enl- cor- of for par
---------------	--	--------------------	---	--

~~Inappropriate or~~  
absent postural  
responses; no  
primary motor or  
sensory deficit.  
Without side or  
back support, sitting  
retropulsion may be  
seen.  
Extrapyramidal  
signs, such as  
tremor or  
cogwheeling, and  
supranuclear gaze  
impairment.  
Dementia and  
urinary urgency or  
incontinence may  
be seen with INPH  
or bilateral  
microvascular  
white-matter lesions

Shuffling gait	Less severe variant of magnetic gait. Diminished foot clearance with audible shuffling, especially on carpeted surfaces; increased tendency to fall due to inappropriate postural reflexes	Full cycle	See magnetic gait	See gait
Festinating gait	Variant of magnetic gait associated with anteropulsion. Gait speed accelerates without control;	Full cycle	See magnetic gait	See gait

often shuffling;  
often precipitated  
by shortened step  
length that causes  
center of gravity to  
move forward of  
the base of support.  
Frequently results  
in a fall

### Non-neurologic gaits

Antalgic gait	Asymmetric gait with faster swing and shortened step length on the non-painful side (limb in swing phase) to reduce duration of weight bearing on the painful joint. Often unilateral but can be bilateral. Posture is usually upright if pain is in the limb and stooped if pain is in the spine Associated findings: Inquire about pain; observe for facial expressions of pain; palpate to provoke musculoskeletal pain (e.g. FABER test for hip-joint pathology, Ober's test for ITB,	Stance phase of the painful limb Swing phase of the non-painful limb	Hip, knee, ankle, or foot joint, or spine	Ap im ref phy rhe nei or sur ind
---------------	---	---	---	----------------------------------

straight-leg raise  
exam, anterior  
drawer, pivot-shift)

Psychogenic gait	Discrepancy between findings on formal exam and casual observation (i.e., when patient is unaware of being examined); extreme variability on formal exam (inconsistent effort, pseudo-fatiguing); give-away weakness; bizarre, non-physiologic features. Consider malingering versus conversion disorder Note that some neurologic gait disorders (such as stiff-person syndrome) can have bizarre presentations, and higher-level gait disorders are notable for the absence of primary motor or sensory deficits in the presence of significant gait impairment	Variable	Not applicable	Bre spi EN cor abs neu cat Co for eve gai
------------------	---	----------	----------------	---

CSF, cerebrospinal fluid; EMG, electromyogram; FABER, Flexion Abduction External Rotation; INPH, idiopathic normal pressure hydrocephalus; ITB, iliotibial band; LMN, lower motor neuron; NCV, nerve conduction velocity; UMN, upper motor neuron.

Higher-level gait disorders involve difficulty integrating sensory information about the position of the body in its environment, including the effect of gravity, and properly selecting and executing motor plans for gait or postural reflexes. Most notably, postural and locomotor reflexes are absent or inappropriate; however, primary deficits of motor or sensory function are also usually absent. The involved areas of the brain are basal ganglia and the frontal cortex and its connections to the basal ganglia and brainstem (e.g. white matter).

Knowledge of the normal gait cycle is helpful ([Table 28.2](#)) [6]. The gait cycle can be assessed using either the right or left foot as the reference foot. The cycle begins and ends at the same point in the cycle of one foot – for example, a complete cycle from right initial foot contact to right initial foot contact. In the gait cycle, each leg has a *stance phase* (single support, or weight bearing on one foot only) and a *swing phase* (leg and foot swung forward, with the foot normally clearing the walking surface). The transition from stance phase to swing phase is *toe off*, and the transition from swing phase to stance phase is *initial contact*. For walking, the gait cycle includes two brief periods of *double support* in which both the right and left foot are in stance phase.

Normal gait is smooth and effortless, requiring no conscious effort except for the intended direction or destination of gait. The biomechanics of a smooth gait minimize the excursions of the center of gravity through space, providing for maximal efficiency with the lowest possible energy consumption. This reduction of variation in the center of gravity is accomplished by six biomechanical “determinants of gait” [7]. Three are related to pelvic motion, two to knee motion, and one to foot motion. Thus, the most efficient gait consumes the least energy. Conversely, gait abnormalities, even if well accommodated, require increased energy consumption. Eventually, fatigue ensues, leading to further gait deterioration, pain, instability, reduced mobility, and increased fall risk. A variety of rehabilitation strategies can be employed to minimize these consequences.

Gait evaluation takes only a few minutes but is often overlooked or limited in a busy clinical setting. A systematic approach for the gait examination, as with any other part of the neurologic examination, can speed the evaluation and enhance its reliability. Several scoring systems have been validated. One of the

authors (MAW) regularly uses the Tinetti Assessment Tool [8].

Effective gait assessment requires observation. Ideally, the examination should be conducted in an area, such as a hallway, that provides the patient sufficient distance to initiate gait, maintain speed, turn around, and return. The examiner may need to observe the patient making several passes down the hall and back to view all pertinent variables from the front, back, and side. Variables to assess include the patient's ability to get in or out of a chair, stability of stance with eyes open and closed, base (distance between the heels perpendicular to the direction of gait), stride length (distance for a full gait cycle), and step length (distance for half of a gait cycle, e.g. distance between the heel-strike position of one foot and the heel-strike position of the opposite foot). Additional variables include the portion of the gait cycle affected, symmetry, foot clearance, speed, variability of gait, cadence, arm swing, fatiguing or claudication, need for assistive devices, postural reflexes, and ability to walk on toes, to walk on heels, or to tandem walk.

**Table 28.2 New and old terminology for the normal gait cycle.**

New terminology	Old terminology
Initial contact	Heel (foot strike) strike
Loading response	Foot flat
Midstance	Midstance
Terminal stance	Heel off
Preswing	Toe off
Initial swing	Acceleration
Midswing	Midswing
Terminal swing	Deceleration

Reproduced with permission from Uustal H, Baerga E. Gait analysis. In Cuccurullo S, Ed. *Physical Medicine and Rehabilitation Board Review*. New York, NY: Demos Medical Publishing, 2004.

## Case vignette

A 70-year-old male presents with complaints of leg weakness and dizziness that

have caused him to fall several times. He says that his legs get tired after he walks one block. He had a left hip replacement because of painful arthritis 5 years earlier and recovered well with physical therapy. He has mild low back pain when walking but does not consider it a limiting factor. His wife notes that he shuffles and tends to fall forward. She says that it's as if his legs don't get the message from his brain, and she is upset that he refuses to use a cane. Medical history is significant for 5 years of well-controlled diabetes, coronary artery disease with two stents but no myocardial infarction, "mild" chronic obstructive pulmonary disease, lumbar spondylosis without central canal stenosis, mild cataracts, and obesity. Notable exam findings are bruising of the left side of the face from a recent fall; normal extraocular movements, including vertical gaze; normal arm and leg strength; no tremor; mild paratonia; no cerebellar findings; diminished pinprick below the ankles; and a Montreal Cognitive Assessment Score of 24/30. Pedal pulses are strong. He struggles to rise from the chair and has to lean forward and push off with his hands. He can stand without support. He initiates gait without difficulty. Both feet intermittently shuffle, and the heel strikes even with the toe of the opposite foot. These features worsen with distance. He requires four or five steps to turn around and starts to fall sideways but corrects with a side step. No Romberg sign is present. He plops into the chair. His wife says that this is much better than his usual gait at home.

This case provides an example of a very common presentation of multifactorial gait impairment in the elderly. Such patients may have a combination of lower-level and higher-level gait disorder. Therefore, the neurologist may need to order a number of tests to help identify and treat the multiple possible diagnoses that could be contributing to the gait disorder.

## References

1. Nutt JG, Marsden CD, Thompson PD. Human walking and higher-level gait disorders, particularly in the elderly. *Neurology* 1993; 43:268.
2. Verghese J, LeValley A, Hall CB *et al.* Epidemiology of gait disorders in community-residing older adults. *J Am Geriatr Soc.* 2006; 54:255–61.
3. Tinetti ME, Kumar C. The patient who falls: "It's always a trade-off." *JAMA* 2010; 303:258–66.
4. Thurman DJ, Stevens JA, Rao JK. Practice parameter: assessing patients in a neurology practice for risk of falls (an evidence-based review): Report of the Quality Standards Subcommittee of the American Academy of Neurology.

*Neurology* 2008; 70:473–9.

5. Nutt JG, Lang AE. *Balance and Gait Disorders*. Syllabus, American Academy of Neurology Annual Meeting, 2011.
6. Uustal H, Baerga E. Gait analysis. In Cuccurullo S, Ed. *Physical Medicine and Rehabilitation Board Review*. New York, NY: Demos Medical Publishing, 2004.
7. Inman VT, Ralston HJ, Todd F. *Human Walking*. Baltimore, MD: Williams & Wilkins, 1981.
8. Tinetti ME. Performance-oriented assessment of mobility problems in elderly patients. *J Am Geriatr Soc*. 1986; 34:119–26.

## 29 Hallucinations, visual

---

Victoria S. Pelak *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Visual hallucinations (VH) are perceptions of visual images in the absence of external visual stimuli. The VH can be formed (people or recognizable objects) or unformed (lights, spots, irregular geometric shapes). They are distinct from visual illusions, which are distortions of true visual stimuli. The specific disease entities and disorders associated with VH are varied as are the regions of nervous system dysfunction that are associated with VH. Dysfunction in diffuse or specific regions of the central nervous system or retina, illicit drugs and medications, psychiatric disease, as well as vision loss from any cause, including ocular causes such as cataract or macular degeneration, have all been associated with visual hallucinations. The pathophysiology of visual hallucinations is not well-delineated, but theories include spontaneous neuronal discharge due to disinhibition or neuronal discharge due to stimulation. A careful history and the associated features can help distinguish between varied causes.

### Case vignette

A 65-year-old male presents with complaints of seeing a starburst of light that “looks like the sun.” It is round in the middle with flame-like edges with a very bright red center that throbs (i.e. moves like it is throbbing). It is the same each time and it begins in the right part of his vision, but he is not sure if it is seen out of one or both eyes. It starts on the right and traverses his vision from right to left over seconds. Followed by this visual hallucination, he feels a bit confused and disoriented for several minutes and then feels tired for several hours or the rest of the day. He also gets a headache, moderate in severity that is located throughout his head and lasts until the following day. He reports that very recently, 3–4 months prior, it happened once in a grocery store and then he

thinks that he “passed out” and awoke to find paramedics and people surrounding him and asking him if he was okay. This hallucination started 3 years ago and the frequency has increased from once every few months to once every few weeks. He takes an antihypertensive for hypertension diagnosed 10 years ago and has borderline diabetes. He has no history of migraine headaches or other medical problems. His brain MRI was normal except for evidence of small vessel ischemic disease and his complete neurologic examination was normal.

Several clues for the cause of his visual hallucinations exist in the history. The first is that his VH are stereotyped and always begins in the right area of the visual field. Next, he notes that the hallucinations are very brief and that it moves across his visual field very quickly. They are brightly colored with circular shapes. The hallucinations have also been associated with other neurologic dysfunction consisting of confusion, disorientation, and then fatigue. Recently, he had the VH prior to an episode of loss of consciousness or other dramatic change in his level of consciousness. These findings suggest a cerebral etiology involving the left hemisphere (right side of vision) and that the VH are due to seizure activity (stereotyped, move across field quickly, brightly colored, shapes involve a circle, and spread to involve other neurologic symptoms). Migraine-associated visual hallucinations are very unlikely given the following: (1) the characteristics are not typical for migraine (not geometric or predominantly black and white and do not gradually move across visual field); (2) there is no prior history of migraine headaches with similar visual symptoms; and (3) confusion, disorientation, and change in consciousness are associated with the visual hallucinations. They are also unlikely to be due to transient ischemia or stroke because VH associated with ischemia occur in association with deficits in vision or, in cases of midbrain stroke, are associated with sleep/wake anomalies. Also, when occipital ischemia occurs, for instance, the VH are most often characterized by highly patterned hallucinations that do not move from one region to another in the visual field. It is not uncommon for the older population to develop focal seizures due to underlying small vessel ischemia that does not present as a cerebral artery branch infarct. Several years of follow-up of this patient showed no other cause and there was resolution of visual hallucination with an antiepileptic medication .

**Table 29.1 Differential diagnosis of visual hallucinations (VH).**

Specific
----------

Anatomic localization or disorder	type: formed or unformed	Specific entity	Characteristics of Visual hallucinations & possible clinical features
Ocular – Retina	Unformed	Mechanical stimulation of retina from traction or detachment, inflammation, pressure, etc.	Sparkles, flashes, or light (called phosphene photopsias). Very brief or less). Visual loss rarely associated
Release hallucinations or Charles Bonnet syndrome (visual hallucinations associated with vision loss)	Formed or unformed	Occurs due to loss of vision (acuity or field) from any cause along the visual pathway (cataract, optic nerve, optic tract, optic radiations, cortical). The VH occur within the region of vision loss. If visual acuity loss, typically bilateral and 20/50 or worse	The type (formed or unformed) does not help localize constant or intermittent especially with decreased stimulation or with a background. Increases in older patients and those with cognitive impairment improve by shifting eyes and increasing visual stimulation
	Formed or unformed	Occipital ischemia or stroke	Often highly patterned like peacock feathers, chessboards, repeating stacks of red diamonds, patterned
Midbrain or	Formed	Midbrain injury	Usually temporary and

peduncular hallucinosis	more common, but can be unformed	from any cause, but particularly from stroke	Associated with disturbed sleep/wake cycle and impaired consciousness
Migraine	Unformed (rare reports of formed that are open to question)	Visual auras that are reversible, develop over 5 minutes, and resolve by 60 minutes. Gradual development or gradual change may not be noticed. Migraine headache may not occur or occurs during the VH or within 60 minutes of onset. Persistent visual aura that last weeks to months without accompanying infarction can occur	Characterized by blurred geometric lines that can scintillate. Start centrally peripherally and enlarge into other parts of the field leaving blurred vision improves. Fortification headaches have scotoma with a geometric/zigzag line in the periphery within a region if in the left hemisphere within a backward C region if in the right hemisphere
Seizure	Formed or unformed	Occipital, occipitoparietal, and occipitotemporal seizures can result in VH. Headache is frequent and associated with aura	Often has motion with moves quickly across the field and lasts for only up to 3 minutes. Most accompanied by neurological symptoms (sensory or motor dysfunction, impaired speech or change in consciousness)

		cannot be used to differentiate migraine from seizure	Occipital origin often or spherical imagery colors
Psychiatric	Formed or unformed	Psychosis (schizophrenia or other)	Auditory hallucinations associated and both can be threatening. Insight lost, delusional thinking present.
Medications	Formed or unformed	Mechanisms include retinal or cerebral dysfunction. Duration <1 second (retinal causes) or constant. Can start after prolonged symptom-free period with or without toxic levels	Non-psychotropic: Drugs (color/hue to vision changes like "snow"), erectile dysfunction drugs (color/hue to visual blockers), amantadine. Psychotropic: Levodopa, dopaminergic agents, benzodiazepines, tricyclic antidepressants, opiates
Alcohol and drugs of abuse	Formed or unformed	Can occur during or after intoxication and be associated with psychosis and poor insight	Alcohol (intoxication or withdrawal), opiates, mescaline, PCP, D-lysergic diethylamide (LSD), methylenedioxymethamphetamine (ecstasy), methamphetamine
Neurodegenerative disease	Formed or unformed	Common in dementia with Lewy bodies and Parkinson's disease ; Also in Alzheimer's disease , Creutzfeldt–	Cognitive complaints, dysfunction present. Vision or poor and VH can be frightening or non-threatening. Can be exacerbated by medications, poor sleep, medical illness.

		Jakob disease , frontotemporal dementia , posterior cortical atrophy	
Hospitalized patients – delirium	Formed or unformed	Increased susceptibility in older age, cognitive impairment, prolonged hospital stay, primary central nervous system disturbance (i.e. encephalitis), and medications	Often VH are of spid insects. Poor insight cause combativeness intermittent or persis

---

## Further reading list

- Berrios CE, Brook P. The Charles Bonnet syndrome and the problem of visual perceptual disorders in the elderly. *Age Ageing* 1982; 11:17–23.
- Cummings JL, Miller BL. Visual hallucinations – clinical occurrence and use in differential diagnosis. *West J Med.* 1987; 146:46–51.
- Teeple RC, Caplan JP, Stern TA. Visual hallucinations: differential diagnosis and treatment. *Prim Care Companion J Clin Psychiatry* 2009; 11:26–32.

# 30 Headache

---

Ira M. Turner and Richard B. Lipton *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

## Introduction

The term headache applies to pain involving the head or facial structures . The characteristics of the pain and the pattern of associated symptoms vary with the headache type and the nature of any underlying pathology. In any given year, more than 90% of the population experiences at least one headache . The causes of headache range from short-lived, monophasic conditions such as viral infections or minor head injury, to intermittent and quality-of-life-threatening disorders such as migraine, to devastating and life-threatening disorders such as subarachnoid hemorrhage headache. A simplified approach to categorizing the many causes of headache is presented in [Table 30.1](#) which follows the *International Classification of Headache Disorders*, second edition (ICHD-2) and identifies three major groups: primary and secondary headache disorders, and cranial neuralgias.

**Table 30.1   The International Classification of Headache Disorders: Overview.**

---

- A. Primary headache disorders
  - 1. Migraine
  - 2. Tension-type headache
  - 3. Cluster headache and other trigeminal autonomic cephalgias (TAC)
  - 4. Other primary headaches
- B. Secondary headache disorders
  - 5. Headache attributed to head and/or trauma
  - 6. Headache attributed to cranial or cervical vascular disorder
  - 7. Headache attributed to non-vascular intracranial disorder
  - 8. Headache

attributed to a substance or its withdrawal **9.** Headache attributed to disorder of homoeostasis **10.** Headache or facial pain attributed to disorder of cranium, neck, eyes, ears, nose, sinuses, teeth, mouth, or other facial or cranial structures **11.** Headache attributed to psychiatric disorder

### C. Cranial neuralgias and central causes of facial pain

---

The diversity of causes and the high prevalence of headaches make a systematic approach to diagnosis essential. Anatomically, head or facial pain can occur with any process that results in stimulation of the afferent branches of the trigeminal nerve and the sensory branches of other cranial or upper cervical nerves. In addition to pain of peripheral origin, headaches may arise within the central nervous system.

In this chapter, we present a three-step approach to headache diagnosis. The first step is to identify or exclude secondary headache disorders by history, physical examination and judicious use of diagnostic tests ([Table 30.2](#)). Second, we consider four syndromic groups of primary headache disorders, based on headache frequency and duration ([Table 30.3](#)). Finally, we emphasize the identification of specific disorders within syndromic groups.

**Table 30.2 “Red flags,” the secondary disorders they suggest and possible investigations.**

---

Red flag	Possible secondary causes	Possible investigations
Sudden or “thunderclap” onset	Intracranial bleed (aneurysmal subarachnoid hemorrhage, AVM, intracerebral bleed, bleed into tumor), vasospasm	CT, MRI, MRA, LP
Progressively increasing frequency, severity or duration	Space-occupying lesion (tumor, subdural hematoma) <small>Medication overuse</small>	CT, MRI

**Investigation Overview**

Focal neurologic deficits (excluding typical aura)	Ischemic disease, vasculitis, mass, vascular anomaly	Blood work CT, MRI, LP
Papilledema	Mass Venous sinus thrombosis Idiopathic intracranial hypertension Infection	CT, MRI, MRV LP (if no mass on above)
Fever or nuchal rigidity	CNS infection Systemic infection	Blood work CT, MRI, LP
Rash	Infection, vasculitis, collagen vascular disease	CT, MRI Blood work LP
Pregnancy/Postpartum	Venous sinus thrombosis Pituitary apoplexy Vessel dissection, vasospasm	CT MRI/MRA MRV
Triggered by cough, exertion, orgasm or Valsalva	Mass Intracranial hemorrhage Vasospasm Venous sinus thrombosis	CT MRI, MRA, MRV
Metabolic disorders	Thyroid disease Vitamin B12 deficiency Cushing syndrome	Blood work U/A
Acute hypertension	Renal dysfunction Pheochromocytoma Cardiac disease	CT, MRI Blood work 24-hour urine
Chronic disease (malignancy, HIV, immunosuppressives)	Metastatic disease Infection	MRI LP (if no mass)

Toxic	Carbon monoxide Medication overuse ( opiates, barbiturates, caffeine, ergots, triptans, NSAIDs, acetaminophen)	Blood work Urine Medication history
-------	--	---

AVM, arteriovenous malformation; CNS, central nervous system; CT, computerized tomography; LP, lumbar puncture; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; NSAIDs, non-steroidal anti-inflammatory drugs.

**Table 30.3 Primary headache diagnosis by syndromic group.**

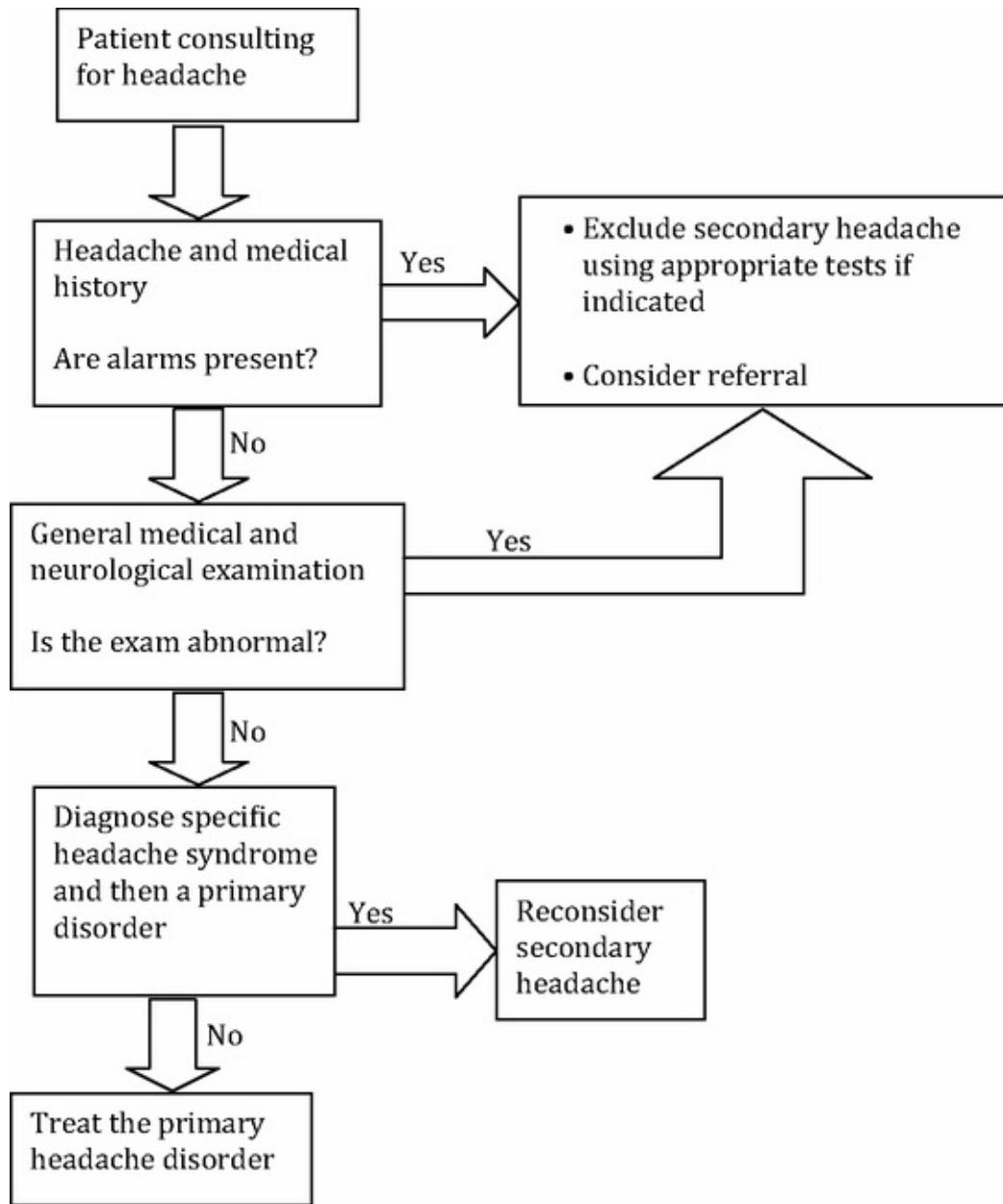
Frequency	Short duration (<4 hours)	Long duration (4 hours or more)
Low to moderate (< 15 days per month)	Low to moderate frequency, short duration Stabbing headache Thunderclap headache SUNCT syndrome Hypnic headache	Low to moderate frequency long-duration Migraine Episodic T-TH
Chronic (15 or more days per month)	Chronic short duration Cluster headache and other TACs Paroxysmal hemicrania Stabbing headache Thunderclap headache SUNCT syndrome Hypnic headache	Chronic long duration Chronic migraine Chronic T-TH Hemicrania continua New onset daily persistent headache

---

SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing; TAC, trigeminal autonomic cephalgias; T-TH, tension-type headaches.

## Identifying or excluding secondary headache

Secondary headaches are attributable to underlying organic or psychiatric disorders (see [Figure 30.1](#)). In contrast, for primary headaches the headache disorder, such as migraine or tension type headache, is the problem. Secondary headaches should be suspected if “red flags” are present. [Table 30.2](#) summarizes common red flags, the diagnoses they suggest, and a work-up to be considered. In addition to red flags, it is helpful to search for comfort signs. Comfort signs suggest that a primary headache disorder is likely. These include a long duration of similar headaches, menstrual exacerbation, a positive family history of similar headaches, and a typical response to treatment.



**Figure 30.1** Headache diagnosis.

In a patient with red flags, diagnostic tests are usually required to identify or exclude the secondary headache disorder. In the process of differential diagnosis, it is imperative to realize that one patient may have more than one headache type. It should also be remembered that a patient who has a long history of a primary headache disorder may have a significant change in frequency, severity, or associated symptoms. This and other red flags should alert the physician to the possibility of new secondary headache disorder. The first step in the differential diagnosis of headache is therefore identifying or excluding a

secondary headache disorder.

## Diagnosing a specific headache syndrome

After excluding a secondary headache disorder, the next step is to identify a primary headache syndrome. Common headache syndromes and the specific disorders to consider within each syndromic group are summarized in [Table 30.3](#). These syndromes are defined based on the number of headache days per month and on the average duration of attacks. Based on headache days, there are two broad categories: chronic daily headache with 15 or more days per month and episodic headache with fewer than 15 headache days per month. Based on duration, we consider short duration attacks to be those lasting less than 4 hours on average and long duration attacks those which last 4 hours or more.

The most common syndromic group are the episodic headaches of long duration; this group includes both episodic migraine and episodic tension type headache. The chronic daily headache of the long duration group includes four disorders: chronic migraine, chronic tension type headache, new daily persistent headache, and hemicrania continua. For the two groups characterized by headaches of short duration, the most important disorders are the trigeminal autonomic cephalgias, including cluster headache.

Many ICHD-2 defined disorders are included in more than one syndromic group. Having identified the syndrome the next task is to diagnose the specific disorder in the syndromic group. In the sections that follow, we discuss a number of specific primary headache disorders .

## Primary headache disorder: migraine

Migraine is the most disabling of the primary headache disorders, affecting about 12% of the US population. Migraine without aura is the most common form; diagnostic criteria are presented in [Table 30.4](#). In approximately 20–25% of migraine patients, however, the headache may be preceded by an aura. Auras are focal neurologic symptoms that are most commonly visual. Aura features are typically both positive (flashing lights, zig-zag lines) and negative (a graying out of vision). This differentiates aura from other causes of transient neurologic deficits including epilepsy, which is characterized by positive features, and stroke, which is characterized by negative features. Auras typically last between 5 and 60 minutes. These symptoms are fully reversible. Other common aura

symptoms could include sensory symptoms or dysphasic speech (also fully reversible). These can occur simultaneously or in succession. Headache may begin during the aura or within 60 minutes of its resolution. More common than aura are premonitory symptoms which occur in about 60% of people with migraine. Premonitory features begin hours or days prior to headache and include fatigue, neck discomfort, yawning, food cravings, irritability, restlessness, euphoria, drowsiness, fluid retention, polyuria, diarrhea, constipation, photophobia, phonophobia, and osmophobia in various combinations.

**Table 30.4 ICHD-2 diagnostic criteria for 1.1 migraine without aura.**

---

- A. At least 5 attacks fulfilling criteria B–D
  - B. Headache attacks last 4–72 hours (untreated or unsuccessfully treated)
  - C. Headache has at least two of the following characteristics:
    - 1. Unilateral location
    - 2. Pulsating quality
    - 3. Moderate or severe pain intensity
    - 4. Aggravation by, or causing avoidance of, routine physical activity (e.g. walking or climbing stairs)
  - D. During the headache attack, at least one of the following:
    - 1. Nausea and/or vomiting
    - 2. Photophobia and phonophobia
  - E. Symptoms not attributed to another disorder
- 

The headache phase of migraine with or without aura typically lasts from 4–72 hours (if untreated or not successfully treated). Migraine is a diagnosis of exclusion, in that certain patterns of pain and associated symptoms are required. The pain features include at least two of the following four characteristics: (1) unilateral location, (2) pulsatile or throbbing quality, (3) moderate–severe pain intensity, and (4) worsened by or avoidance of routine physical activity (e.g. walking, bending, lifting, or climbing stairs). The associated symptoms include either (1) nausea or vomiting or (2) both photophobia and phonophobia. Migraine is also a diagnosis of exclusion in that secondary causes of headache must be excluded based on history and physical exam or the judicious use of

diagnostic tests.

Migraine is also divided into episodic and chronic forms. Episodic migraine is defined by headache on < 15 days per month. Chronic migraine (1.5.1) is defined as migraine headaches (usually without aura) or tension-type headaches recurring more than 15 days per month for more than 3 months. There should be at least 8 days per month where the headaches are linked to migraine based either on the presence of migraine features or response to migraine-specific treatment. Chronic migraine evolves from episodic migraine. Risk factors for the development of chronic migraine include very frequent episodic headaches, high levels of disability, the presence of allodynia, depression, traumatic head injury, and overuse of drugs, most importantly opioid and barbiturate-containing analgesics.

It is difficult to diagnose chronic migraine in the setting of medication overuse. In practice, we treat medication overuse as a modifier of a headache diagnosis, *i.e.* chronic migraine with medication overuse.

## **Primary headache disorder: tension-type headache**

Tension-type headaches (T-TH) (2.0) are the most common of the primary headache disorders. The headaches are defined in opposition to migraine. While migraine is typically unilateral the pain of T-TH is usually bilateral. While migraine pain has a pulsatile quality, T-TH pain is usually a pressure pain or steady ache. Migraine pain is moderate or severe. The pain in T-TH is mild to moderate in intensity, and T-TH is not aggravated by physical activity or associated with features such as nausea, photophobia, and phonophobia. There may or may not be associated pericranial tenderness.

Tension-type headaches are classified into episodic (fewer than 15 attacks per month) and chronic (more than 15 attacks per month). The episodic T-TH are further subdivided into infrequent episodic T-TH (2:1) (less than 1 day per month) or frequent episodic (2.2) (1 to 14 days per month). Chronic T-TH (2.3) usually evolves from the episodic form and in its purest form should not be diagnosed in patients overusing acute medication. In practice, patients with medication overuse headache (a secondary headache) usually manifest the features of chronic T-TH. As with the classification of migraine, the diagnosis of probable T-TH (2.4) is warranted if all but one of the ICHD-2 criteria are met. Another headache that phenotypically resembles chronic T-TH is new daily persistent headache (see below).

## **Primary headache disorder: trigeminal autonomic cephalgias**

Cluster headache, paroxysmal hemicrania, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT), and short-lasting unilateral neuralgiform headache attacks with cranial autonomic symptoms (SUNA) are classified as trigeminal autonomic cephalgias (TACs). All are unilateral and associated with ipsilateral cranial autonomic features. Cluster headache and paroxysmal hemicrania come in both episodic and chronic forms, while SUNCT comes in only a chronic form.

## **Other primary headache disorders**

Hemicrania continua is a chronic, continuous (no pain-free intervals), side-locked headache disorder that has been present for at least 3 months. The severity is usually mild–moderate with exacerbations of severe pain. The bouts of severe pain are typically associated with ipsilateral cranial autonomic symptoms. It is responsive to therapeutic doses of indomethacin.

New daily-persistent headaches are headaches that began relatively suddenly and have never gone away. They typically have tension-type features, but migrainous features may occur. They have typically been present for at least 3 months and secondary causes have been excluded. Quite commonly, the patient can often date the exact time that the headaches began. No definite etiology has been proven to date. Should one be found, this diagnosis would then have to be considered a secondary headache disorder. For the present, it remains classified with the primary headaches.

## **Case vignette**

A 32-year-old male presents to the emergency room (ER) with a history of 2 days of recurring severe right orbital pain (“like my eye is being torn out”) lasting for 2 hours and then resolving. It is associated with ipsilateral lacrimation, conjunctival injection, and a clear nasal discharge. During this he needed to pace back and forth. This had occurred twice, each time awakening him from sleep at 3.00 a.m. On arrival in the ER he was symptom free. His wife recalled that 3 years ago he had a similar bout of nightly pain that awoke him but was not as severe. This resolved after 6 weeks.

On arrival in the ER, he seemed to no longer be in pain. He had normal vital signs. On neurologic exam there was a slight right miosis and questionable ptosis but no other focal or lateralized signs.

A non-contrast CT of the brain was normal. The patient refused a lumbar puncture. A neurologic consultation was called.

When seen by the neurologist, the patient's miosis and questionable ptosis had totally resolved. The patient had daily episodes of severe pain lasting 2 hours with ipsilateral autonomic features. The autonomic features, though typical of the trigeminal autonomic cephalgias, are also a feature of structural brain disease particularly in the region of the sella turcica, the posterior fossa, or the carotid sympathetics. Accordingly, a work-up to exclude secondary headache is generally indicated in patients with trigeminal autonomic cephalgias.

A brain MRI was totally normal. A brain MRA showed no evidence of an aneurysm or other vascular anomaly. A cervical MRA showed no evidence of a carotid dissection. Having excluded secondary headache (step 1 of Headache 1, 2, 3), the neurologist then identified a primary headache syndrome. Given the daily occurrence of short duration headache the syndromic group was primary CDH of short duration. Disorders in this group are distinguished by the pattern and location of pain and associated symptoms. This patient clearly had a trigeminal autonomic cephalgia with unilateral pain in the distribution of the first division of the trigeminal nerve and ipsilateral autonomic features. Within the TAC group, disorders are distinguished by the frequency and duration of attacks (see [Table 30.5](#)). Given the 2-hour duration of attacks that occurred daily, episodic cluster headache is the most likely diagnosis.

**Table 30.5 ICHD-2 – Diagnostic features of cluster headache and other trigeminal autonomic cephalgias.**

	<b>Cluster headache</b>	<b>Paroxysmal hemicrania</b>	<b>SUNCT</b>
Ipsilateral cranial autonomic symptoms	+	+	+
Attacks/day (untreated)	0.5–8	5+	3–200
Pain duration (untreated)	15–180	2–30 min	5–240 s

Indomethacin responsive

Indomethacin  
responsive

SUNCT, short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.

The patient was then re-evaluated by the neurologist, who told the patient that he probably had episodic cluster headache. While discussing the negative studies and potential treatments, the patient reported that his pain was recurring and became extremely severe within 5 minutes. The neurologist observed a right ptosis, miosis, conjunctival erythema, and a clear right nasal discharge. He ordered sumatriptan 6 mg sc. Within 10 minutes, the patient was totally symptom-free.

He was discharged with prescriptions for sumatriptan 6 mg sc prn, a tapering course of prednisone (starting with 60 mg per day) over 2 weeks and verapamil 240 mg per day. Follow-up with the neurologist was arranged.

When seen by the neurologist 2 weeks later, the patient reported that he had continued to have 4 more days of 1–2 headaches per day. Each attack was aborted in 5–10 minutes with sumatriptan 6 mg sc with slight neck tightness as the only side effect. He had just completed the tapering course of prednisone and was continued on verapamil for at least the next 3–4 months .

## Conclusion

In summary, the differential diagnosis of headache requires a careful history of headache onset, location, quality of pain, quantity of pain, duration, frequency, and associated symptomatology. Secondary causes need to be strongly considered and investigated when “red flags” are present. Even when a primary headache disorder has been diagnosed, possible secondary headache diagnoses should be considered when there are atypical features, a change in headache characteristics, new systemic illnesses, or even lack of response to therapy.

## Further reading list

Headache Classification Committee of the International Headache Society. The

International Classification of Headache Disorders. *Cephalalgia* 2004; 24:1–160.

Lipton RB, Silberstein SD, Dodick DW. Overview of diagnosis and classification. In Silberstein SD, Lipton RB, Dodick DW, Eds. *Wolff's Headache*, 8th edn. New York, NY: Oxford University Press, 2008: 29–43.

Olesen J, Dodick DW. The history and examination of headache patients. In Olesen J, Goadsby PJ, Ramadan NM, Tfelt-Hansen P, Welch KMA, Eds. *The Headaches*, 3rd edn. Philadelphia, PA: Lippincott Williams and Wilkins, 2006: 43–53.

## 31 Hearing deficit

---

David A. Gudis and Michael J. Ruckenstein *Neurologic Differential Diagnosis*,  
ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge  
University Press. © Cambridge University Press 2014.

### Introduction

Hearing loss is a very common complaint in both the adult and pediatric populations. In children, significant bilateral hearing loss occurs in over 3 per 1,000 newborns and over 15 per 1,000 children ages 3 through 17 years old [1,2]. Almost all children experience transient hearing loss at some point secondary to effusions and infections. In adults, prevalence increases with age, with almost half of patients over 65 years exhibiting some level of hearing loss [3]. The etiologies of hearing loss are complex and diverse, with a number of pathophysiologic mechanisms that result in impaired conduction or perception of sound.

The ear is divided into three compartments. The *external ear* consists of the pinna (or auricle) and the external auditory canal (EAC). Acoustic sound waves are captured by the pinna and channeled through the EAC to the *middle ear*, which includes the tympanic membrane (TM), the ossicular chain, and a segment of the facial nerve. These structures are contained within the middle ear cavity, aerated through the eustachian tube. The TM vibrates at the frequency of the acoustic waveform, causing vibrations of the malleus, the incus, then the stapes. The external ear confers a maximum of a 20 dB amplification to the incoming sound stimulus. The vibration of the stapes communicates with the *inner ear*, comprising the cochlea, the semicircular canals, and the internal auditory canal (IAC). The middle ear structures combine to amplify sound by a maximum of 40 dB. Inside the cochlea, the vibratory movements of fluid compartments cause depolarizations within a frequency-specific location along the basilar membrane, resulting in hair cell depolarization and cochlear nerve afferent fiber activation. The auditory signal is carried by the fibers of the VIIIth cranial nerve to the brainstem, from where it ultimately passes to the auditory cortex as complex sound.

Hearing loss is classified as *conductive hearing loss* (CHL), *sensorineural hearing loss* (SNHL), or *mixed loss*. Conductive hearing loss includes any pathophysiology that prevents the mechanical conduction of vibratory energy and therefore generally involves the external or middle ear, such as a cerumen impaction or middle ear effusion. Sensorineural hearing loss refers to any disorder of the inner ear or neural pathway resulting in impaired neural activation. Sensorineural hearing loss is seen in cases of ototoxicity, aging (presbycusis), noise-induced hearing loss, and genetic forms of hearing loss. Mixed hearing loss is any combination of conductive and sensorineural etiologies. The approach to the patient with hearing loss requires a focused history, which should elucidate the following factors: Is the hearing loss

- Acute or chronic?
- Unilateral or bilateral?
- Is there a family history of hearing loss?
- Is there a history of head trauma or barotrauma?
- Has there been exposure to ototoxins (e.g. cisplatin, aminoglycosides)?
- Is there a history of previous ear surgery or chronic infection?
- Has the patient suffered a recent upper respiratory infection?
- Is there a concomitant history of tinnitus, vertigo, otalgia, or drainage?

A physical exam must include otoscopy and the Rinne and Weber tuning fork tests. The most useful investigation is an audiogram to evaluate and classify the type and severity of hearing impairment. Based on the results of the assessment, etiologies may be delineated for the hearing loss ([Tables 31.1](#) and [31.2](#)).

**Table 31.1** *Conductive hearing loss [4–7].*

Item	Subdivision	Specific entity	Possible clinical features
Congenital	Pinna	Microtia – absence or malformation of the pinna	Usually occurs with atresia of the EAC May be part of congenital syndromes including Treacher–Collins,

		Goldenhar, or hemifacial microsomia
EAC	Aural atresia – absence or complete stenosis of EAC	Almost always occurs with microtia Usually associated with middle ear malformations
Ossicles	Congenital fusion, malformation, hypoplasia, or aplasia of ossicles	May be associated with congenital syndromes including DiGeorge, CHARGE, or Turner May result from congenital infections such as rubella or syphilis
Middle ear cavity	Congenital cholesteatoma – enlarging embryonic rest of squamous epithelium	Usually present as a small pearl behind the anterior-superior TM M > F, usually 2–4 yo
Infectious/post-infectious and inflammatory	EAC	Otitis externa – inflammation of the EAC  Otalgia, otorrhea, pruritis, aural fullness, tenderness to palpation Edema, drainage, and sloughing of EAC skin Associated with diabetes mellitus,

		water exposure
EAC	Dermatologic conditions such as psoriasis, dermatitis	Pruritis, edema, sloughing, scaling of EAC skin
TM	Tympanic membrane perforation	Associated with history of infections or trauma May actively drain
Middle ear cavity	Acute otitis media (AOM)	Otalgia, fevers, drainage Bulging hyperemic tympanic membrane (TM) Complications may be dangerous and include mastoiditis, meningitis, intracranial abscesses, and suppurative labyrinthitis
Middle ear cavity	Otitis media with effusion	Otalgia, dull aural fullness Dull grey or yellow TM
Middle ear cavity	Acquired cholesteatoma – enlarging collection of squamous epithelium cells from TM retraction or epithelium that	Associated with history of infections, TM perforations, and eustachian tube dysfunction Complications may be dangerous and include AOM.

	migrated through a perforation	mastoiditis, SNHL, facial nerve injury, and vertigo
Temporal bone	Osteomyelitis	Otalgia, drainage, aural fullness, pruritis History of immunosuppression Edema, erythema, and granulation tissue in EAC Late stage may result in cranial neuropathies, sigmoid sinus thrombosis, sepsis, death
Neoplastic	EAC	Skin cancer
		Basal cell carcinoma > squamous cell carcinoma > melanoma History of sun exposure Nodular, ulcerated, friable bleeding lesion
EAC	Exostosis, osteoma – benign bony overgrowth obstructing EAC	Stenotic EAC May be associated with otitis externa, cerumen impaction
EAC	Parotid malignancy (e.g. mucoepidermoid	Otalgia Friable lesion eroding into EAC

		carcinoma)	May have facial nerve weakness
	Middle ear cavity	Glomus tympanicum – paraganglioma of the middle ear	Pulsatile tinnitus, otalgia, cranial neuropathies Reddish mass behind TM Associated with type 1 neurofibromatosis and other neurocutaneous syndromes May produce catecholamines
Vascular	Middle ear cavity	Vascular anomalies of carotid artery, jugular vein, or branches	Pulsatile tinnitus, aural fullness
Other	EAC	Cerumen impaction	May have aural fullness, pruritis
	EAC	Foreign body	May have otalgia, pruritis, otitis externa, granulation tissue
Metabolic	Middle ear cavity	Otosclerosis – disorder of bone metabolism with progressive sclerosis and ossification of the middle ear and otic capsule	Slowly progressive hearing loss F > M, usually 20–45 yo, positive family history Physical exam usually normal May result in

			sensorineural hearing loss (SNHL)
Trauma	Middle ear cavity	Barotrauma	Otalgia, aural fullness Recent flying or diving May result in TM perforation
	Middle ear cavity	Hemotympanum	Common after head trauma, temporal bone fractures Resolves spontaneously
Ossicles	Ossicular discontinuity		Common after head trauma, temporal bone fracture

**Table 31.2 Sensorineural hearing loss (SNHL) [4–7].**

Item	Subdivision	Specific entity	Possible clinical features
Congenital	Cochlea	Hereditary hearing loss	Usually recessive, without family history Bilateral Non-syndromic > syndromic
	Cochlea	Congenital infections	Congenital rubella and

			syphilis may result in CHL and/or SNHL Congenital CMV results in SNHL
	Cochlea	Congenital hypoplasia or aplasia of cochlea	May include vertigo, vestibular pathology
Toxic	Cochlea	Antibiotics (esp. aminoglycosides), loop diuretics, salicylates, chemotherapeutics, antimalarials, cocaine, others	Usually symmetric, high-frequency loss Salicylate toxicity is reversible, other toxicities are permanent May include tinnitus and/or vertigo
	Cochlea	Radiation injury	Dose-dependent injury at doses exceeding 45 Gy May present up to 1 year after exposure
Infectious/post-infectious	Cochlea	Viral labyrinthitis	Associated with sudden-onset severe

vertigo  
Usually  
unilateral  
May follow  
simple viral  
prodrome  
(e.g. URI)  
Includes viral  
syndromes  
(mumps,  
measles,  
VZV, HSV)

Cochlea	Suppurative bacterial labyrinthitis	Usually a complication of AOM, may lead to or result from meningitis Cochlear ossification may be seen on later imaging Associated with vertigo, tinnitus, otalgia, fevers Permanent hearing loss and vestibular dysfunction
Cochlea	Other infections	Syphilis (tertiary) may be associated with vertigo Lyme disease and rocky

			mountain spotted fever associated with tick exposure in endemic areas HIV- associated neuropathy may cause SNHL
Psychiatric	None	Psychogenic, conversion disorder, or malingering	Can usually be identified by special audiology tests
Inflammatory	Cochlea	Autoimmune inner ear disease	Usually bilateral, progressing over weeks to months Responsive to steroids $F > M$ Associated with SLE, Cogan's syndrome, polyarteritis nodosa, rheumatoid arthritis, and others
Neoplastic	CN VIII, cerebellopontine angle, <del>brainstem</del>	Vestibular schwannoma (acoustic neuroma)	Unilateral progressive hearing loss <del>May include</del>

	<b>Inflammation,</b> temporal lobe	<b>Tumors,</b> meningioma, other CNS neoplasms	<b>May include</b> tinnitus, vertigo May have facial nerve weakness or other neurologic dysfunction
Degenerative	Cochlea	Presbycusis	High-frequency loss, difficulty distinguishing consonants and in noisy environments Incidence and severity increases with age
	CNS	Multiple sclerosis	Fluctuating or progressive course F > M, usually 20–30 yo
Vascular	CNS	Vertebrobasilar arterial occlusion/lateral medullary syndrome	Sudden, unilateral Often includes vertigo, facial nerve weakness, tinnitus, other cranial neuropathies

	CNS	Temporal lobe stroke	May be associated with aphasia, seizures, other stroke manifestations
	CNS	Basilar migraine/migraine aura	Fluctuating course May include vertigo, tinnitus, aural fullness
Idiopathic	Cochlea	Sudden SNHL	Rapidly progressive over hours to days Usually unilateral Often presents upon awakening
	Cochlea	Menière's disease	Fluctuating progressive course Usually unilateral, low frequency Presents with episodic spontaneous attacks that include vertigo, aural fullness, and tinnitus

Trauma	Cochlea	Head trauma/temporal bone fracture	Fracture line may extend through labyrinth or simply cause labyrinthine concussion
	Cochlea	Acoustic trauma/noise-induced hearing loss	Usually progressive, symmetric History of excessive noise exposure, usually occupational Often associated with tinnitus

---

AOM, acute otitis media; CHL, conductive hearing loss; CNS, central nervous system; HSV, herpes simplex virus; SLE, systemic lupus erythematosus; URI, upper respiratory tract infection; VZV, varicella-zoster virus.

## Case vignette

A 66-year-old veteran presents complaining of bilateral hearing loss and ringing in his ears that has progressively worsened since he retired from military service 10 years ago. Further questioning reveals an extensive history of heavy artillery use and training with firearms and explosive devices. The patient is unable to recall his medication history, but believes he was treated for malaria once while abroad.

Physical exam is remarkable for a Weber test that lateralizes to the left and a broad-based gait. The clinician then inquires more closely about any history of vertigo or dizziness, and the patient reveals, “Sometimes I get dizzy when I’m in a loud restaurant.” The clinician tests this complaint by speaking loudly into the

patient's ear, and confirms that it does in fact elicit nystagmus. The clinician obtains a head CT, an audiogram, and serologies. The CT shows thickened bone around the cochlea. The audiogram shows moderate asymmetric bilateral high-frequency SNHL, right worse than left. The serologies reveal a positive VDRL titer, confirming the diagnosis of otosyphilis.

The differential diagnosis from the patient's initial history is broad, including common pathologies such as presbycusis, noise-induced hearing loss, and pharmacologic ototoxicity from antimalarial medications. However, the patient's broad-based gait prompts concern for a vestibular or central pathology. The patient then exhibits Tullio's phenomenon, or noise-induced vertigo, a finding associated with otosyphilis. The CT shows osteitis of the labyrinth, also seen in otosyphilis. The diagnosis is confirmed with a VDRL titer, and the patient is treated with penicillin [8].

## References

1. Finitzo T, Albright K, O'Neal J. The newborn with hearing loss: detection in the nursery. *Pediatrics* 1998; 102:1452–60.
2. Gallaudet Research Institute: Demographic aspects of hearing impairment: data from the National Health Interview Survey, series. 10, no 188.
3. Nash SD, Cruickshanks KJ, Klein R et al. The prevalence of hearing impairment and associated risk factors: the Beaver Dam Offspring Study. *Arch Otolaryngol Head Neck Surg* 2011; 137:432.
4. Flint P, Haughey B, Lund V et al., Eds. *Cummings Otolaryngology: Head & Neck Surgery*, 5th edn. Philadelphia, PA: Mosby Elsevier Publishing, 2010.
5. Lalwani AK, ed. *Current Diagnosis & Treatment in Otolaryngology – Head & Neck Surgery*, 2nd edn. New York, NY: McGraw Hill Medical Publishing, 2007.
6. Wetmore R, Ed. *Pediatric Otolaryngology: Requisites in Pediatrics*. Philadelphia, PA: Mosby Elsevier Publishing, 2007.
7. Zarandy M, Rutka J. *Diseases of the Inner Ear*. New York, NY: Springer, 2010.
8. Yimtae K, Srirompotong S, Lertsukprasert K. Otosyphilis: a review of 85 cases. *Otolaryngol Head Neck Surg* 2007; 136:67–71.

## 32 Hypersomnolence

---

Jeffrey S. Durmer and Heidi D. Riney *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Sleepiness is a very common complaint and may result from a multitude of medical conditions and maladaptive behaviors. As a complaint heard in the practice of clinical sleep medicine, excessive daytime sleepiness (EDS) is second only to insomnia. Clinical estimates suggest that between 60 and 70% of children and adults complain of EDS. The inability to remain awake during the day or EDS that does not remit or that recurs over time is termed hypersomnolence . In the *International Classification of Sleep Disorders, 2nd edition* (ICSD–2, published by the American Sleep Medicine Association, 2005), hypersomnia syndromes are depicted as disorders not caused by circadian rhythm disorders, breathing disorders, other sleep medicine conditions, or known medical, psychological, or neurologic problems that may result in disturbed sleep. As a group, these disorders are termed *hypersomnias of central origin*. This category of diagnoses is noted to affect between 15–30% of people with sleep disorders [1]. Thus, while the symptom of EDS is quite routine, hypersomnolence syndromes are much less common.

Hypersomnolence and fatigue are terms often used interchangeably in the clinical arena. Although closely related these words refer to entirely different conditions. The act of falling asleep during the expected wake period on a repeated basis is not part of the defined state of fatigue. Fatigue refers to a state of *exhaustion* which may include physical, mental, emotional, or psychological components. Sleepiness implies the inability to remain awake, and when this occurs in the normal wake period the term EDS is applied. So, while on the surface this discussion appears to be a matter of semantics, it is actually a very important point to distinguish a fatigued person from a sleepy one. Fatigue, as part of the *human condition*, is expected and may lead to sleepiness, but hypersomnolence implies a cause outside of the routine human experience.

This chapter will provide a clinical framework for understanding the most common causes of hypersomnolence and an algorithm is presented to assist the busy clinician with a focused symptom-based assessment tool.

## Categorizing the causes of hypersomnolence

Sleepiness is a natural homeostatic result of prolonged wakefulness. The subcortical brain structures responsible for generating sleepiness are the subject of intense research in sleep medicine and are believed to include activation of gamma-amino butyric acid (GABA) neurons in the ventrolateral preoptic area (VLPO) of the anterior hypothalamus. Subsequent descending inhibition from the VLPO inactivates subcortical wake-promoting nuclei including hypocretin neurons in the posterior hypothalamus, histaminergic neurons in the tuberomammillary nucleus, neuroepinephrine neurons in the locus coeruleus, serotonergic neurons in the raphe nuclei, and acetylcholinergic neurons in the lateral dorsal tegmental nucleus and the pedunculopontine nucleus [2,3]. Multiple medications, neurologic disorders, medical and psychological conditions may interfere or activate these neural pathways resulting in the symptom of sleepiness, or hypersomnolence. Conditions in which sleepiness is common include obesity, diabetes, anemia, renal failure, heart failure, vitamin B12 deficiency, depression, muscular dystrophy, retinosa pigmentosa, epilepsy, traumatic brain injury, multiple sclerosis (fatigue > sleepiness), attention-deficit hyperactivity disorder (ADHD), and stroke. It is the clinician's role to first determine if a pre-existing condition or medication is responsible for EDS.

In the absence of a pre-existing cause, the following categories may be used to determine the root cause(s) of the patient's hypersomnolence.

### Quantity of sleep

A number of intrinsic and extrinsic conditions may be noted as the cause for reduced sleep quantity. These include inadequate sleep hygiene, circadian rhythm disorders, and sleep onset delays due to other primary sleep disorders or environmental factors. A simple assessment of sleep hygiene includes asking questions that follow the acronym “B-E-E-F-I”: Behaviors (are sleep/wake times and preparation routine?), Environment (are light, noise, temperature, and novelty kept low? [e.g., no TV/phones]), Exercise (is excitement reduced 2 hours before sleep?), Food (are meals limited within 2 hours before sleep?), and Interventions (are physical relaxation, cognitive restructuring, and behavioral

reinforcement strategies being used?). Sleep hygiene is especially important for children as their average sleep time requirements are between 1 and 4 hours longer depending on age than adults (who require between 7 and 9 hours of sleep per 24 hour period). Circadian rhythm disorders are another category of problems that often go undiagnosed from teenage years and run in families along with co-occurring mood disorders [4]. Typically, there is a delay in sleep onset that is either progressive (Free-Running Disorder), erratic (Irregular Sleep–Wake Rhythm) or stable (Delayed Sleep Phase Disorder) [5]. Finally, a delay in sleep onset may be caused by other sleep disorders such as insomnia (e.g., psychophysiologic insomnia), movement disorders (e.g., restless legs syndrome), or sleep-related breathing disorders (e.g., obstructive sleep apnea).

## Case vignette 1

A 28-year-old male with a past medical history of inattentive attention-deficit disorder (ADD) and seasonal allergies presents with difficulty falling asleep and daytime sleepiness. He reports being a night owl and that he has had difficulty since his job required him to wake up early.

His natural sleep time is closer to 3:00 a.m. if he is allowed to naturally fall asleep on his own schedule. If he could, he would wake up between 11:00 a.m. and 12:00 p.m. He remembers doing that during the summers after high school and he felt good when he could follow that schedule. He states that now because he has to go to bed earlier, he often has difficulty with initiating sleep.

Currently, he typically watches TV with his girlfriend in a different room until he is tired and then goes to bed. He tried reading for a period of time without the TV and he states that did not help so now he watches TV but not usually in his bedroom. He typically does not get into his bed to fall asleep until close to 2:30–3:00 a.m. He states if it is a really bad night he may not fall asleep until closer to 6:00 a.m. He denies any restless legs symptoms or rumination.

After he falls asleep, he has not been noted to snore or have any pauses in breathing. He states that he typically sleeps through the night but on occasion he may wake up one hour prior to his alarm going off. He denies any symptoms to suggest periodic limb movements, REM dysregulation, or parasomnias.

During the week he usually wakes up at around 8:15 a.m. On weekends, he sleeps in until 11:00 a.m. or 12:00 p.m. He never feels rested when he gets up in the morning. He does state that he feels more rested if he follows his naturally “late” pattern of sleep and wake. He does have some problems with

concentration, short-term memory loss, and anxiety. He states he is sleepy but he rarely naps or dozes off. His Epworth Sleepiness Scale was elevated at 13.

Following his visit, the patient was instructed to obtain a light box. He took time off of work to advance his sleep time. He began using his light box 30 minutes prior to his natural wake-up time of 11:00 a.m. and advanced it by 30 minutes every morning until he reached his goal wake-up time of 8:00 a.m. He also took Melatonin 300 mcg 5 hours prior to his natural bedtime of 3:00 a.m. and advanced it by 30 minutes every night until he reached his goal bedtime of 12:00 a.m. After doing this, he felt that he was naturally sleepy by 12:00 a.m. and was waking up without difficulty or use of an alarm by 8:00 a.m. He now feels rested during the day and no longer has problems with concentration, memory, or daytime sleepiness. His Epworth Sleepiness Scale at his return visit was normal at 4.

## Quality of sleep

Culprits that reduce sleep quality may go undetected by the sufferer for many years. A bed partner may or may not be aware of a sleep quality issue since it can be as subtle as repeated cortical arousals during sleep that can only be appreciated on electroencephalography during a polysomnographic test. Common causes for poor sleep quality include sleep-disordered breathing, periodic limb movements (either associated or not with restless legs syndrome), sleep fragmentation due to excessive brain arousal or interruptions in sleep, and medical/psychological conditions that cause light and unrefreshing sleep. One of the most common intrusive sleep-related conditions is sleep-disordered breathing. Repeated interruptions of airflow due to neuromuscular collapse of the upper airway result in multiple stimuli that arouse the sleeping brain. Oxyhemoglobin desaturation and afferent upper airway muscle sensory activation provide potent subcortical activation of not only the airway musculature but also the sympathetic nervous system which results in many of the downstream neural, cardiac, vascular, and endocrine dysfunctions associated with this group of sleep conditions [6]. Excessive movement during sleep, as noted in periodic limb movement disorder and restless legs syndrome, may also result in similar interruptions in sleep as noted with sleep-related breathing disorders; however the degree of sleepiness is notably less by comparison. Fragmentation of sleep is often noted on polysomnography as recurrent state-switching and intermittent wakefulness during sleep. The cause for this finding may be related to the sleeping environment or even stress from recent events or

physical pain. Another cause for excessive arousal is a disorder that affects sleep-wake state stability such as narcolepsy (discussed below). Other common causes for light or unrefreshing sleep include medications for conditions such as ADHD and the excessive use of caffeine or nicotine. In addition, hypomania, hypothyroidism, iron deficiency, ADHD, chronic pain, depression, anxiety, and posttraumatic stress disorder can result in fragmented sleep.

## Case vignette 2

A 51-year-old male, with a past medical history of hypertension and cerebral aneurysm, presents with daytime sleepiness, snoring with associated pauses in breathing and sleep maintenance insomnia.

Currently, he goes to bed between 10:00 and 11:00 p.m. and has no difficulty falling asleep. He denies any restless legs symptoms.

After he falls asleep, he has been noted to snore with associated pauses in breathing. He typically wakes up 3–4 times a night and occasionally has difficulty falling back asleep. He states that if he thinks of a white background he can try and get his mind from racing at night. He has been noted to mumble and sweat during sleep. He denies any symptoms to suggest periodic limb movements or REM dysregulation.

Typically, he wakes up around 7:00 a.m. He rarely feels refreshed when he wakes up. He does have some problems with dry mouth, morning headaches, short-term memory loss, difficulty focusing, depression, and anxiety. His Epworth Sleepiness Scale was 13.

The patient's polysomnogram revealed an overall AHI of 41.7 events/hour, with further elevation to 73.0 during REM sleep. His oxyhemoglobin desaturation nadir was 64%, and 3.6% of the total sleep time was spent at an oxygen saturation below 90%. His total arousal index was 34.6 arousals/hour. There were no clinically significant periodic limb movements observed. Rare PACs were noted on single-channel electrocardiogram.

Secondary to the presence of severe obstructive sleep apnea, a therapeutic polysomnogram with continuous positive airway pressure (CPAP) was performed.

His study revealed that a therapeutic pressure was achieved at 12.0 cmH<sub>2</sub>O. There were no clinically significant periodic limb movements or arrhythmias noted.

The patient returned to clinic following his study and placement on PAP therapy. His CPAP data were downloaded and show him at a pressure of 12.0 cmH<sub>2</sub>O, with an EPR of 3.0 cmH<sub>2</sub>O. He had been using it 90/90 days with 100% compliance and an average of 7.8 hours of daily use.

The patient no longer had complaints of nighttime awakenings or problems with daytime sleepiness following initiation of PAP therapy. On follow-up, his Epworth Sleepiness Scale Score was 7.

## Disorders of arousal

Disorders that affect either the stability of the sleep–wake systems or that result in deficient CNS arousal may cause the symptom of hypersomnolence. These disorders are considered rare but may begin in adolescence and take several years to diagnose. Narcolepsy is a well-known member of this category and research into this condition has led to significant developments in our understanding of sleep and wake neural systems [7]. While emotionally triggered muscle atonia, or cataplexy, and hypersomnolence noted together are considered pathognomonic for the condition, up to 40% of individuals with narcolepsy may not ever manifest cataplexy. For this reason polysomnographic testing along with multiple sleep latency testing is required to diagnose narcolepsy in most cases. When considering the diagnosis of narcolepsy the clinician should ask about REM sleep dysregulatory behaviors including sleep paralysis, hypnagogic (-pompic) hallucinations, and automatic behaviors. While only 40% of narcoleptics may demonstrate these symptoms the presence of them can be helpful, albeit non-diagnostic in and of themselves. Recurrent hypersomnolence, also referred to as Kleine–Levin syndrome, is another form of hypersomnolence that is noted in combination with bizarre drive-based behaviors (food, sex, emotion) including various levels of amnesia that may last for several days and reoccur weeks or even months later. Recent evidence suggests a genetic predilection in males of Jewish descent [8]. Another diagnostic category referred to as idiopathic hypersomnolence (IH) is often divided clinically into IH with prolonged sleep times (> 10 hours) or not. A number of potential causes are under investigation for IH including “unproclaimed” narcolepsy, excessive endogenous benzodiazepine production, and the over-activation of sleep onset pathways or the under-activation of wake promoting neural systems. Finally, emerging evidence suggests that multiple neurodegenerative disorders including Parkinson's disease, multi-system atrophy, Alzheimer's disease, and progressive supranuclear palsy demonstrate

significant clinical symptoms of hypersomnolence, often years before the traditional diagnostic features of these disorders appear [9].

**Table 32.1 Differential diagnosis of hypersomnolence.**

Item	Subdivision	Specific entity	Possible clinical features
Intake	Reduced caloric intake		Muscle wasting, impaired immune function, lack of energy or feeling tired all the time, delayed wound healing, dizziness, brittle nails, irritability, dry and flaky skin, diarrhea, irregular menses in females, and/or depression
	Caffeine overdose		Fatigue, tachycardia, palpitations, jitteriness and elevated blood pressure
	Obesity (BMI > 30)		
Toxic	Medications	Examples: anticonvulsants, antihistamines, antiemetics, antidepressants, and sedatives or tranquilizers	

## Anxiolytics

### Medication withdrawal

Depressants (including benzodiazepin and barbiturate Restlessness, anxiety, sleep problems, sweating, hallucinations whole-body tremors, seizures increased blood pressure, heart rate and body temperature Stimulants: Depression, fatigue, anxiety intense craving, suicidal ideation, paranoia, and acute psychosis Opioids: Runny nose, sweating, yawning, anxiety drug cravings, sleeplessness, depression, dilated pupils, rapid pulse, rapid breathing, high blood pressure abdominal cramps, tremor, bone and muscle pain, vomiting and diarrhea

	Medication or drug overdose	Increase or decrease in pulse, blood pressure, temperature and respiratory rate, sleepiness, confusion, constipation, vomiting, nausea, abdominal pain, diarrhea, skin changes
	Alcohol intake	Slurred speech, euphoria, sleepiness, impaired balance, flushed face, vomiting, red eyes, reduced inhibition, erratic behavior
Neurologic	Multiple sclerosis	Numbness or weakness in one or more limbs, partial or complete loss of vision usually accompanied by pain during eye movement, double or blurred vision, tingling or pain in part of body, fatigue, tremor, lack of coordination, unsteady gait,

dizziness

Infectious:  
encephalitis

Headache, fever, fatigue or weakness, altered consciousness, confusion or agitation, personality changes, seizures, loss of sensation or paralysis, muscle weakness, hallucinations, double vision, loss of consciousness, problem with speech or hearing.

Tumor

New onset or change in pattern of headaches, headaches becoming more frequent or severe, unexplained nausea or vomiting, visual problems, gradual loss of sensation in arm and/or impaired balance, impaired speech, confusion, personality or behavior changes, seizures, fatigue.

	Head trauma/concussion	Headache, temporary loss consciousness confusion, amnesia surrounding traumatic event fatigue, slurred speech, nausea vomiting, tinnitus dizziness
	Elevated intracranial pressure	Behavior problems, decreased consciousness lethargy, headaches, seizures, vomiting, focal neurologic signs
Psychiatric	Depression	Feelings of sadness, irritability, anhedonia, reduced sex drive insomnia, excessive sleeping, change in eating habit restlessness, agitation, slow thinking, distractibility, fatigue, loss of energy, feelings of worthlessness

guilt, unexplained crying spells, unexplained physical complaints

Attention deficit hyperactivity disorder (ADHD)

Inattentive, easily distractible, sleepiness, fails to finish a task, fidgets frequently, problems with organization, forgetful, talks excessively, hyperactive, impulsive, difficulty waiting one's turn, interrupts or intrudes upon others

Metabolic/vitamin deficiencies

Hypothyroidism

Fatigue, sluggishness, increased sensitivity to cold, constipation, pale and dry skin, puffy face, hoarse voice, unexplained weight gain, muscle aches, joint aches and swelling, depression, brittle fingernails, and hair loss

Hypo- or hypernatremia	Nausea and vomiting, headache, confusion, loss of energy, fatigue, irritability, restlessness, muscle weakness, seizures, loss of consciousness and coma
Vitamin deficiency anemia	Fatigue, shortness of breath, dizziness, pale yellowish skin, swollen tongue, weight loss, diarrhea, numbness/tingling in hands and feet, muscle weakness, irritability, memory confusion
Diabetes mellitus	Excessive thirst, increased urination, fatigue, weight loss, blurred vision, slow healing of sores, frequent infections
Hypoglycemia	Confusion, blurred or double vision, seizures, loss of consciousness

		lethargy, fatigue, heart palpitations, hunger, shaky, sweating, anxiety, and tingling sensation around mouth
Vascular	Congestive heart failure	Shortness of breath with exertion or lying down, fatigue, weakness, swelling in legs, ankles and feet, rapid or irregular heartbeat, reduced ability to exercise, persistent cough or wheeze, fluid retention, lack of appetite, nausea, impaired concentration, decreased alertness
	Cardiac arrhythmias	Palpitations, fast or slow heart rate, chest pain, shortness of breath, lightheadedness, fatigue, dizziness, syncope, or near-syncope
Other	Chronic fatigue syndrome	Fatigue, loss of memory, impaired

concentration,  
sore throat,  
enlarged lymph  
nodes,  
unexplained  
muscle pain,  
headache, non  
restorative sle  
extreme  
unexplained  
exhaustion

### Fibromyalgia

Pain, allodyni  
fatigue, sleep  
disturbances, l  
rates of  
psychiatric  
comorbidities

### Pregnancy

### Dehydration

Dry mouth,  
increased thirs  
sleepiness,  
decreased urir  
output, dry skin  
constipation,  
headache,  
dizziness and/  
lightheadness

### Renal failure

Widespread pa  
at tender point  
fatigue, sleep  
disturbances,  
fatigue, anxiety  
depression,  
headaches

Mixed connective

Dermatomyo

**Mixed connective  
tissue disease**

**May have**  
disease, fatigue,  
malaise, muscle  
aches, mild fever,  
joint swelling,  
swollen hands,  
puffy fingers

---

## Case vignette 3

A 26-year-old, right-handed, white female with a past medical history significant for depression, anxiety, reflux disease, and hypothyroidism, presented with a long-standing history of insomnia, sleep fragmentation, and excessive daytime sleepiness dating back to high school with recent episodes of inappropriate falling asleep during the day.

Currently, she goes to bed at 8:00 p.m. She states that she has been using Rozerem for the past 4 months and now because of it, has no difficulty in falling asleep. She does remember in the past that she had a hard time falling asleep. She denies any restless legs symptoms.

After she falls asleep, she denies any symptoms of snoring, pauses in breathing, periodic limb movements, REM behavior disorder, or parasomnias. She does state that despite the use of Rozerem, she is waking up 4–5 times a night and it often takes her at least 30 minutes to fall back asleep, causing her to walk around at night. She denies any hypnagogic or hypnopompic hallucinations. She does have rare sleep paralysis.

Typically, she wakes up at 6:00 a.m. and always feels exhausted. She has symptoms of irritability, difficulty in focusing, and depression. She denies any symptoms of dry mouth, morning headache, or short-term memory loss. Her Epworth Sleepiness Scale is 17.

The patient states that for the past 6 months, she has had episodes in which she is startled or upset, she loses muscle tone throughout her body. She states that she is conscious for the entire event, but may or may not have difficulty opening her eyes. She states that the episodes usually only last a couple of minutes with the longest lasting about 20 minutes.

A polysomnogram (PSG) and multiple sleep latency test (MSLT) revealed an overall AHI of 3.2 events/hour with oxyhemoglobin desaturation nadir of 92%.

REM sleep latency was reduced at 53 minutes. MSLT revealed a mean sleep latency of 0.5 minutes and 4 sleep-onset REM (SOREM) naps were recorded.

Serum testing for human-leukocyte antigen types (HLA-types) associated with narcolepsy were positive for HLA-DQB1–0602.

Following the patient's studies, she was started on sodium oxybate (Xyrem) therapy in conjunction with modafanil (Provigil) with resolution of her cataplexy, sleep fragmentation, and improvement of her daytime hypersomnolence .

## References

1. Leger D, Poursain B, Neubauer D, Uchiyama M. An international survey of sleeping problems in the general population. *Curr Med Res Opin* 2008; 24:307–17.
2. Espana RA, Scammell TE. Sleep neurobiology for the clinician. *Sleep* 2004; 27:811–20.
3. Mignot E, Taheri S, Nishino S. Sleeping with the hypothalamus: emerging therapeutic targets for sleep disorders. *Nature Neurosci Supp* 2002; 5:1071–5.
4. Kripke DF, Nievergelt CM, Joo EJ *et al*. Circadian polymorphisms associated with affective disorders. *J Circadian Rhythms* 2008; 7:1–10.
5. Sack RL, Auckley D, Auger RR *et al*. Circadian rhythm sleep disorders: part II, advanced sleep phase disorder, delayed sleep phase disorder, free-running disorder and irregular sleep-wake rhythm. *Sleep* 2007; 30:1484–501.
6. Zamarron C, Paz VG, Riveiro A. Obstructive sleep apnea syndrome is a systemic disease. Current evidence. *European J Int Med* 2008; 19:390–8.
7. Scammell TE. The neurobiology, diagnosis and treatment of narcolepsy. *Ann Neurol* 2003; 53:154–66.
8. Arnulf I, Lin L, Gadoth N *et al*. Kleine–Levin syndrome: a systematic study of 108 patients. *Ann Neurol* 2008; 63:482–93.
9. Abbott RD, Ross GW, White LR *et al*. Excessive daytime sleepiness and subsequent development of Parkinson disease. *Neurology* 2005; 65:1442–6.

## 33 Incontinence

---

Cara Tannenbaum and Nelly Faghani *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Incontinence is defined as any involuntary loss of urine. Many neurologic conditions such as stroke, Parkinson's disease, multiple sclerosis, and normal pressure hydrocephalus include incontinence as an early manifestation of disease. However, other disturbances of the urinary storage mechanism can also result in incontinence. The etiology of incontinence is frequently multifactorial, especially in the elderly where multiple comorbidities and the effects of polypharmacy interact. For instance, in diabetes mellitus, diabetic neuropathy (causing detrusor hyporeflexia) and hyperglycemia (causing osmotic diuresis and polyuria) may contribute. In Parkinson's disease, continence may be affected by medications, constipation, and cognitive or mobility impairment. Patients with pedal edema will likely suffer from nocturia (voiding at night), resulting in nocturnal incontinence when redistribution of fluid from the lower extremities occurs in conjunction with difficulty toileting. Medications may deleteriously affect the lower urinary tract by increasing urine production, contributing to pedal edema, or by affecting the neural mechanisms controlling bladder and sphincter function. Medications such as sedative-hypnotics and antipsychotics may also interfere with the ability to toilet successfully through independent effects on the central nervous system. It is therefore critical to review the differential diagnosis for patients presenting with urinary incontinence, and to consider more than one possible underlying etiology.

### Types of incontinence

Different types of incontinence are categorized according to distinguishing characteristics. The types include urgency, overflow, stress, mixed, and functional [1].

*Urgency incontinence* is involuntary leakage accompanied or immediately preceded by urgency, a sudden strong need to void.

*Overflow incontinence* is characterized by continuous or discrete incontinence episodes with dribbling. Overflow generally occurs as a sequela to detrusor hyporeflexia or urinary retention.

*Stress incontinence* is characterized by the involuntary leakage of small amounts of urine on effort or exertion, or on sneezing or coughing.

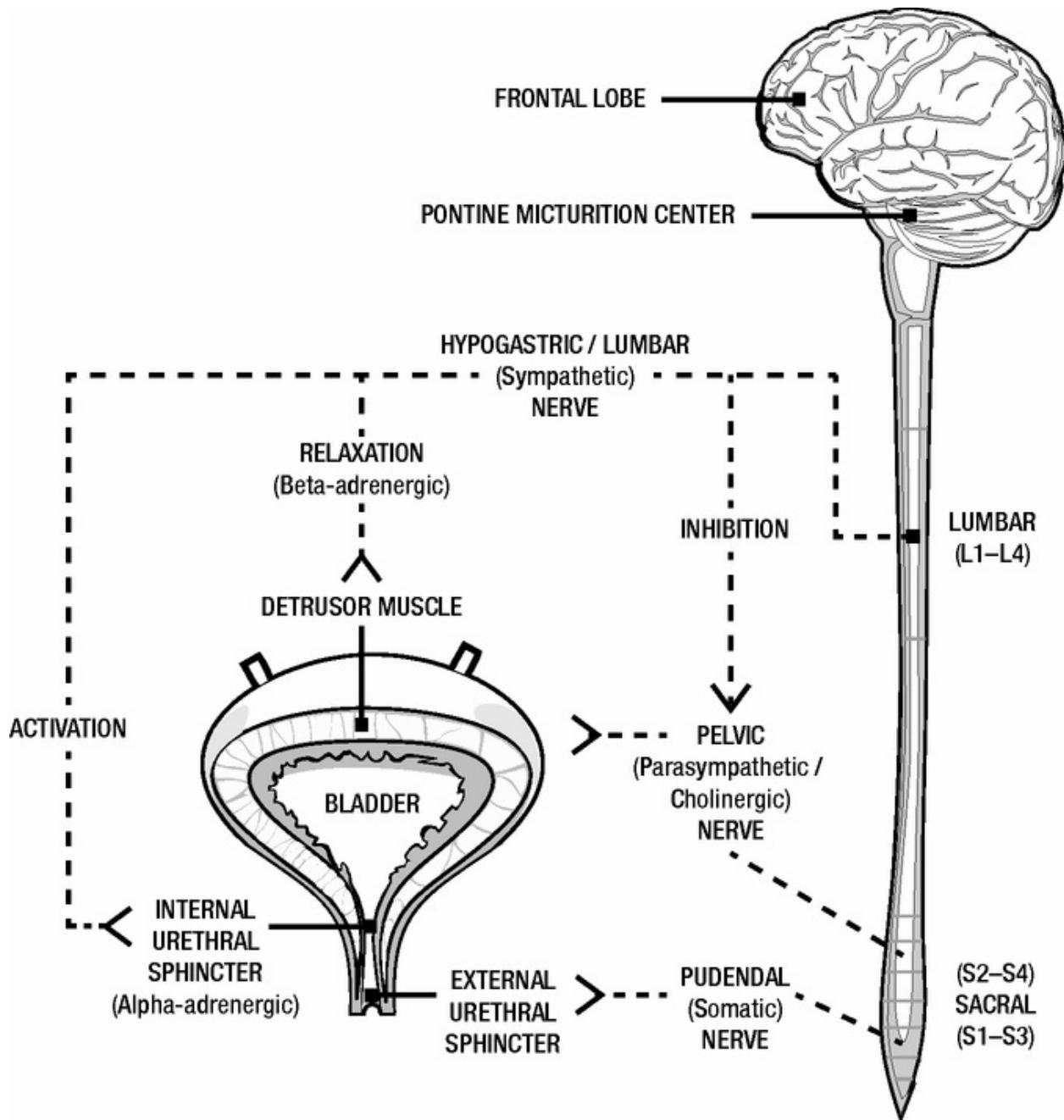
*Mixed incontinence* is the combination of stress and urgency incontinence episodes in the same individual.

*Functional incontinence* results from cognitive, functional, or mobility impairments.

Multifactorial or geriatric incontinence indicates the presence of a constellation of contributing etiologic factors, which, when they occur concomitantly, leads to a failure of the continence mechanism [2].

## **Neuroanatomy of the lower urinary tract**

Storage of urine occurs via sympathetic activity in the hypogastric nerve that mediates relaxation of the bladder detrusor muscle and a concomitant increase in tone of the internal urethral sphincter to prevent urine leakage during filling (Figure 33.1). Somatic input via pudendal nerves activates the external urethral sphincter, an integral part of the pelvic floor musculature. When the bladder is full, parasympathetic (S2–S4) activity in the pelvic nerve mediates detrusor muscle contraction, and coordinated sympathetically mediated sphincter relaxation occurs, which results in voiding. Central nervous system control of voiding acts via a tonic inhibitory influence from the frontal lobes and pontine micturition center down through the spinal cord onto the sacral nerve roots. The inhibitory influence is removed when voiding is deemed physiologically and socially acceptable .



**Figure 33.1** Neuroanatomy of the lower urinary tract.

## Differential diagnosis

Table 33.1 lists the differential diagnosis of incontinence. To determine the underlying cause, the subtype of incontinence should first be identified based on a thorough history, and then associated symptoms should be sought.

## Case vignette

A 76-year-old female presents with urinary incontinence and an unsteady gait. According to her daughter, mild symptoms of urine leakage precipitated by coughing and laughing were present since the delivery of her eighth child 40 years ago, but new and worsening episodes of urine leakage associated with urgency and frequency have developed over the past week, requiring the use of diapers day and night. The clinician suspects acute urgency incontinence on a background of chronic stress incontinence. A urinary tract infection immediately comes to mind but the patient denies fever, dysuria, or hematuria. Upon further questioning, the clinician discovers that the patient is a long-standing diabetic with renal, neurologic, and vascular complications. She also has poorly controlled hypertension for which a diuretic was recently added. The clinician wonders about polyuria, dehydration, delirium, and mobility impairment co-existing as a multifactorial etiology for the patient's symptoms. The daughter clarifies that her mother's gait unsteadiness only started 1 week ago, improving slightly with use of the cane that she bought her to prevent falls. The daughter also reports that her mother's personality has become more volatile and she now requires help to prepare meals. The clinician attempts to test the patient's orientation but she laughs inappropriately and refuses to cooperate. A wide-based ataxic gait and lack of tremor, bradykinesia, and rigidity dismiss Parkinson's disease as a diagnostic consideration. The possibilities of normal pressure hydrocephalus and Lewy body dementia cannot be ignored, however the onset seems too sudden. Neurologic exam reveals diminished strength in the left leg, a left plantar reflex, and frontal release signs. Sacral sensation, anal tone, and bulbocavernosus reflexes are intact. The clinician suspects an inferior right frontal lobe lacunar infarct and this is confirmed with brain imaging.

**Table 33.1 Differential diagnosis of incontinence.**

Type of incontinence	Etiologic category	Specific entity	Possible clinical features
Urge	Toxic	Cholinergic agents such as cholinesterase inhibitors	Incident urgency incontinence reported in 7% of patients initiating cholinesterase inhibitors for the

**causes for the  
treatment of  
dementia**

	Hormone replacement	Can precipitate or exacerbate incontinence in new or chronic post-menopausal users
	Medications causing pedal edema (NSAIDs, pregabalin, glitazone oral hypoglycemics, calcium channel blockers)	Pitting pedal edema on physical exam. Night-time urinary frequency and urgency due to redistribution of fluid in the supine position
	Caffeine, diuretics, alcohol	Polyuria, urinary frequency, and urgency
Infective	Urinary tract infection: bacterial, viral, mycobacterial or fungal cystitis	Fever, dysuria, hematuria associated with a positive urine culture
Post-infective	Guillain–Barré syndrome	Rapidly progressing limb weakness, loss of tendon reflexes, autonomic dysfunction. Urinary retention is more common.

		but urgency incontinence
		occurs in 1/4 [3]
Pressure	Normal pressure hydrocephalus	Triad of gait disorder, dementia, and urinary incontinence. Urinary urgency is present early in the course, incontinence develops later [4]
	Brain tumor, primary or metastatic	Headache, papilledema. Most common sites are frontal lobe and brainstem lesions
	Suprasacral spinal cord impingement (most commonly discs, tumors, tethered cord, or epidural abscess)	Lower extremity hyperreflexia and spasticity. Bulbocavernosus and anal sphincter tone are intact. Back or radicular pain. Detrusor-sphincter dyssynergia may be present with high post-void residuals
Psychiatric	Psychogenic	Excessive fluid

	polydipsia	consumption > 2.5 L per day associated with urinary frequency and urgency
Inflammatory	Myelopathy due to systemic lupus erythematosus	Manifestations vary but may include lower extremity weakness, sensory dysfunction, back and radicular pain. Associated with bowel incontinence
Neoplastic	Bladder tumor	Detrusor hyperreflexia associated with hematuria, weight loss. History of smoking
Degenerative	Multiple system atrophy	Incontinence precedes postural hypotension in 60% of patients. May be associated with difficulty voiding and high post-void residuals due to detrusor-sphincter dyssynergia [1]

## Symptoms

	Alzheimer's dementia	Cognitive impairment. Onset of incontinence correlates with disease progression and is probably related to functional impairment. Occurs in up to 50% [6]
	Lewy body dementia	Frontal lobe dysfunction, psychotic symptoms, mobility impairment. Urinary frequency and urgency more common than in Alzheimer's disease
Vascular	Stroke	Anterior cerebral artery strokes and lacunar infarcts are associated with lateralized lower limb weakness and frontal release signs. Parietal strokes

may be associated with loss of bladder sensation. Bilateral brainstem lesions will also lead to incontinence [7]

Venous insufficiency, congestive heart failure causing pedal edema

Pitting pedal edema. Associated with nocturia, frequency, and urinary urgency during the night

Demyelinating    Multiple sclerosis

Presenting symptom in 2%, at 5 years present in 57% and prevalence as high as 90% at 10 years. Associated with optic neuritis, paresthesias, sexual and bowel dysfunction, and detrusor-sphincter dyssynergia [8]

Metabolic disorders

Diabetes mellitus

Polyuria and polydipsia in poorly controlled diabetes. Urinary urgency and frequency

common [9]

Diabetes insipidus

Associated with polyuria, frequency, urgency, and poor renal concentrating ability in the presence of fluid restriction

Hypercalcemia

May contribute to polyuria, urinary frequency and urgency

Movement disorder

Parkinson's disease

Associated with progression of disease in 60% of patients with rigidity, mobility impairment, tremor, bradykinesia [10]

Sleep disorder

Obstructive sleep apnea

History of snoring and daytime sleepiness.  
Associated with nocturia and urinary urgency

Trauma

Spinal cord injury

History of trauma and paralysis.  
Urinary retention occurs during the

occurs during the spinal shock phase (lasting weeks), and then evolves to urgency incontinence and detrusor-sphincter dyssynergia

Overflow	Structural	Urethral stricture	Previous instrumentation of the urethra in men or women. May be congenital
		Obstructive prostatic disease in men	Enlarged firm prostate on rectal exam. Concomitant obstructive symptoms such as difficulty initiating voiding, post-void dribbling, weak urine stream
		Obstructive prolapse in women	Procidentia (uterine prolapse that cannot be reduced) visible on gynecologic examination
Toxic		Anticholinergic agents (tricyclic	Palpable and distended

	antidepressants, antihistamines, parkinsonian drugs, antipsychotics, bladder relaxants, inhalers for chronic lung disease)	bladder consistent with urinary retention. Concomitant constipation
Opioid analgesics		As per anticholinergic agents. Common post-operatively
Adrenergic		Decongestants, especially in men with a history of benign prostatic enlargement
Infective	Detrusor hyporeflexia or retention may occur post- cystitis	Occurs more commonly in bedbound patients or post- urinary catheterization. Positive urine cultures and high post-void residuals
	Herpes zoster in the lumbosacral dermatomes	Neuralgia and cutaneous vesicles in the lumbosacral dermatomes associated with urinary retention

Post-infective	Guillain–Barré syndrome	Rapidly progressing limb weakness, loss of tendon reflexes, autonomic dysfunction. Voiding difficulties and urinary retention present in 86% <a href="#">[3]</a>
Pressure	Cauda equina syndrome (disc compression), conus medullaris syndrome, tethered cord	Poor bladder sensation and saddle anesthesia. Incomplete voiding with the need for Valsalva to help expel urine. Post-void residual is high. Corresponding deficits include lower extremity hyporeflexia, sensory loss, or lower motor neuron signs. Pelvic reflexes (bulbocavernosus and anal wink) may be impaired. Anal sphincter lacks tone
Infiltrative	Amyloidosis	Autonomic dysfunction,

			paresthesias, high post-void residual volumes
	Metabolic	Diabetic cystopathy	Other diabetic peripheral neuropathies [9]
Stress	Structural	Bladder neck hypermobility	Previous pelvic surgery or obstetric history of prolonged, forceps, or multiple vaginal deliveries. Cystocele or prolapse visible on gynecologic exam
		Poor intrinsic sphincter function	History of pelvic floor radiation, familial collagen disorders
		Vesico-vaginal fistula	Primarily in young women from developing countries who received inadequate pre- natal care
		Post- prostatectomy	Transurethral resection of the prostate or complete prostatectomy for treatment of <del>benign prostatic</del>

benign prostate hypertrophy or prostate cancer. Associated with erectile dysfunction in men

Pelvic floor muscle weakness

Difficulty initiating or sustaining a pelvic floor muscle contraction. Associated with sarcopenia, deconditioning, or corticosteroid use in the elderly

Toxic

Anti-adrenergic

Use of alpha-blockers for the treatment of hypertension

Hormone replacement

Can precipitate or exacerbate incontinence in new or chronic post-menopausal users

ACE inhibitors

Due to chronic cough

Trauma (iatrogenic)

Pelvic surgery such as simple and radical hysterectomy, abdominoperineal

History of relevant surgical procedure. May be associated with sexual or

		resection	bowel dysfunction
Functional	Toxic	Sedative-hypnotics Antipsychotics	History of bed-wetting, night-time falls on the way to the toilet, associated amnestic and non-amnestic mild cognitive impairment
		Delirium	Acute confusional state associated with infection, medication ingestion, or post-operatively in older adults
Degenerative		Dementia and other central nervous system degenerative disorders	Associated with cognitive or mobility impairment, executive dysfunction
Movement disorders		Arthritis, gait disorders, chronic pain, fractures	Gait disorders, quadriceps weakness, mobility impairment
Environmental		Inaccessible toilets or unavailable caregivers for	In frail, mobility, or cognitively impaired individuals

toileting  
assistance

---

NSAIDs, non-steroidal anti-inflammatory drugs.

## References

1. Abrams P, Cardozo L, Fall M *et al*. The standardization of terminology in lower urinary tract function: report from the standardization sub-committee of the international continence society. *Neurourol Urodyn* 2002; 21:167–78.
2. DuBeau CE, Kuchel GA, Johnson T, Palmer MH, Wagg A. Incontinence in the frail elderly: report from the 4<sup>th</sup> International Consultation on Incontinence. *Neurourol Urodyn* 2010; 29:165–78.
3. Sakakibara R, Hattori T, Kuwabara S, Yamanishi T, Yasuda K. Micturitional disturbance in patients with Guillain–Barré syndrome. *J Neurol Neurosurg Psychiatry* 1997; 63:649–53.
4. Sakakibara R, Hattori T, Uchiyama T *et al*. Urinary dysfunction and orthostatic hypotension in multiple system atrophy: which is the more common and earlier manifestation? *J Neurol Neurosurg Psychiatry* 1999; 67:1–5.
5. Sakakibara R, Kanda T, Sekido T *et al*. Mechanism of bladder dysfunction in idiopathic normal pressure hydrocephalus. *Neurourol Urodyn* 2008; 27:507–10.
6. DuBeau CE, Resnick NM. Urinary incontinence and dementia: the perils of guilt by association. *J Am Geriatr Soc* 1995; 43:310–1.
7. Pettersen R, Stein R, Wyller TB. Post-stroke urinary incontinence with impaired awareness of the need to void: clinical and urodynamic features. *BJU Int* 2007; 99:1073–7.
8. Nortvedt MW, Riise T, Frugard J *et al*. Prevalence of bladder, bowel and sexual problems among multiple sclerosis patients two to five years after diagnosis. *Mult Scler* 2007; 13:106–12.
9. Brown JS, Wessells H, Chancellor MB *et al*. Urologic complications of diabetes. *Diabetes Care* 2005; 28:177–85.

10. Winge K, Fowler CJ. Bladder dysfunction in parkinsonism: mechanism, prevalence, symptoms and management. *Mov Disord* 2006; 21:737–45.

## **34 Mania and bipolar symptoms**

---

Christopher P. Kogut and James L. Levenson *Neurologic Differential Diagnosis*,  
ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge  
University Press. © Cambridge University Press 2014.

### **Introduction**

Mania is a syndrome of abnormally elevated, expansive, or irritable mood, often associated with grandiosity, a decreased need for sleep, pressured speech, racing thoughts, distractibility, an increase in goal-directed behavior or psychomotor agitation, and excessive involvement in pleasurable activities that have a high potential for negative consequences [1]. Mania is typically experienced episodically in the course of Bipolar I disorder, though discrete episodes of mania may have a number of other causes, in which case it is often referred to in the literature as “secondary mania.” Symptoms can develop in stages, and can present with a range of severity, from mild mood lability and disrupted sleep, to gross disorganization and psychosis. The course and prognosis depend in part on the underlying cause, and may be time-limited, as in intoxication with methamphetamine, or persistent or deteriorating, as after a brain injury or neurodegenerative disease [2].

### **Case vignette**

Ms. X is a 42-year-old female who was brought to the ER by her daughter for behavioral changes that began a week earlier. Initially, her daughter noticed that her mother was more irritable and argumentative, then became expansive and euphoric, talking rapidly and intensely. She had slept for periods less than an hour on 2 of the previous 4 days. She was very intent on shopping, and went to the thrift store, buying several large trash bags of clothing that she said she was coordinating into “outfits for a show.” On presentation in the ER, Ms. X was noted to be very seductively dressed, with elaborate make-up and hair. She spoke rapidly and was flirtatious with the medical student who initially interviewed her. She perseverated on multiple music projects she said she had

been asked to direct by “my managers in New York.”

Ms. X has a history of HIV infection and is well-known to the outpatient HIV clinic where she has been a patient on and off for many years. She has not been prescribed antiretroviral medication for HIV in the past 3 years due to limited adherence. She has a history of cocaine use, though denies any use in the last 6 months. She has been seen by a consulting psychiatrist in the clinic and was recently started on bupropion for depression, which she states she has been taking. She had never had symptoms of mania in the past. She was hospitalized with depression after an intentional overdose of medications after a cocaine binge 3 years ago. There is no family history of bipolar disorder, though she has several family members with histories of depression and substance use [2].

Ms. X had routine labs in the ER, which demonstrated a mild leukopenia with a WBC of  $3.5 \times 10^9 \text{ L}^{-1}$ , and normal electrolytes. Her drug screen was positive only for alcohol, with a level of 0.05%. She was admitted to psychiatry, where additional tests were ordered. Thyroid-stimulating hormone was normal, CD4 count was  $45/\text{mm}^3$ , and HIV viral load was  $58,000 \text{ m L}^{-1}$ . Brain MRI demonstrated generalized volume loss more than expected for her age, and hyperintense periventricular lesions on T2 weighted images. Cerebrospinal fluid analysis was within normal limits.

The differential diagnosis includes bipolar disorder, mania secondary to HIV infection, mania secondary to the initiation of an antidepressant, and mania secondary to stimulant use. Less likely is the possibility of mania secondary to an occult central nervous system (CNS) lesion, CNS opportunistic infection, hyperthyroidism, or other medications.

**Table 34.1 Causes and clinical features of mania.**

Category	Specific type	Specific etiology	Clinic
Toxic	Drugs of abuse	Amphetamines – methamphetamine or diverted pharmaceutical amphetamine	Abrupt positive screen limitir
		Caffeine	Histor large c

coffee  
caffein  
beverage  
coffee  
supplement

Cocaine  
Abrupt onset  
positive screen  
limits

Phencyclidine  
(PCP)  
Abrupt onset  
vertical gaze  
nystagmus  
limits

Psychiatric medications  
Antidepressants  
Use mainly for depression  
about episodes  
episodes with mood  
with episodes of mania  
bipolar disorder  
and occasionally  
in other disorders

Methylphenidate,  
amphetamines  
Used for attention deficit  
of ADHD  
and narcolepsy

Antiretrovirals  
Abacavir,  
didanosine,  
efavirenz,  
zidovudine  
Symptoms develop over weeks  
these include  
in treatment  
HIV

Antibiotics  
Clarithromycin,  
ethambutol  
Often used to treat  
prevention of  
MAC

	Isoniazid	Weak inhibit
Dopamine agonists	L-Dopa, amantadine, pramipexole, ropinirole	Used in Parkin disease leg syndrome
Endocrine agents	Corticosteroids	Probably common second Dose- Symptom development weeks treatment common in withdrawal from substances
	Thyroxine	Usually supratherapeutic doses
	Anabolic steroids	Often young men/athletes Associated with
Other agents	Baclofen	Reported dose [5]
	Cimetidine	Reported patient depression with cimetidine [4]
	Cantonril	[5, 6]

	Clonidine (withdrawal)	Assoc sudden discon [7,8]
	Procainamide	[9]
Infective/post-infective	Systemic	HIV
		Usual of hig load/a diseas structu on bra Diffici distin& bipola
	Syphillis	Mania presen symp neuro Reacti VDRI WBCs with t dorsal Rober
	Encephalitis	Viral encephalitis, infective and post- infective
	Cryptococcal meningoencephalitis	Usual HIV. I be pre sympt

		Creutzfeldt-Jakob disease (CJD)	Mania present symptoms especially variant
Psychiatric	Bipolar disorders	Bipolar I disorder	Illness manic and us episodic depression better by unc medication substances
		Bipolar II disorder	Episodic hypomanic depression
Inflammatory		Antiphospholipid antibody syndrome	Acquired hypercoagulable state, usually present in middle-aged adults
		Systemic lupus erythematosus	Unusual presentation CNS involved Must distinguish from corticosteroid-induced which common
Neoplastic/paraneoplastic	CNS tumors	Meningiomas	

	Gliomas	Right-lesions likely manic if new mania adults.
Other	Thalamic metastases	
	Carcinoid syndrome	Assoc neurofibromatosis Assoc flushir edema
Degenerative	Huntington's disease	2–12% may have mania
	Frontotemporal dementia (Pick's disease)	Mood comm Alzhei may present before memo Obsess comput comm
	Parkinson's disease	Can be the disease medic treat th Multip reports after p a deep

 stimul

Wilson's disease

Move  
disord  
liver e

Multiple sclerosis

Must l  
distin&  
cortic  
induce  
which  
comm

Fahr's syndrome

Idiopa  
gangli  
calcifi

Vascular

Cerebrovascular  
lesions

Much  
comm  
right (/  
hemis)  
lesions  
R MC  
R thal.  
infarct  
hemor  
caudat

Idiopathic/ congenital

Kleine–Levin  
syndrome

AKA :  
hibern  
syndrc

Klinefelter's  
syndrome

Males  
X chrc  
(XXY  
Assoc  
hypog  
and of  
disord

Metabolic	Electrolyte abnormalities	Hyponatremia	Case report context [13]
	Endocrine	Hyperthyroidism	Classification second as part storm
		Hypothyroidism	Less common hypertension
		Cushing's disease	Similar corticosteroid induced
	Nutrient deficiencies	Niacin deficiency	Typical elderly people anorexia Pellagra associated dermatitis cognitive dysfunction
		B12 deficiency	Typical adults, diets, bypass pernicious
Trauma associated		Traumatic brain injury	Symptoms more irritable than often disinhibited

			Depression more common than n TBI
Ictal	Complex partial seizures	Temporal lobe epilepsy (psychomotor epilepsy)	Sx may be tempo epileptic discha presence of extreme neurological halluci during [14]
	Postictal		More common with first epileptic seizure usually within hours of seizure

---

CSF, cerebrospinal fluid; HSV, herpes simplex virus; MCA, middle cerebral artery; sx, symptoms; VDRL, venereal disease research laboratory.

## References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revision) (DSM-IV-TR)*. Washington, DC: American Psychiatric Association, 2000.
2. Levenson JL, Ed. *The American Psychiatric Publishing Textbook of Psychosomatic Medicine: Psychiatric Care of the Medically Ill*, 2nd edn. Washington, DC: American Psychiatric Publishing, 2011.

3. Stewart JT. A case of mania associated with high-dose baclofen therapy. *J Clin Psychopharmacol* 1992; 12:215–17.
4. Titus JP. Cimetidine-induced mania in depressed patients. *J Clin Psychiatry* 1983; 44:267–8.
5. Gajula RP, Berlin RM. Captopril-induced mania. *Am J Psychiatry* 1993; 150:1429–30.
6. Patten SB, Brager N, Sanders S. Manic symptoms associated with the use of captopril. *Can J Psychiatry* 1991; 36:314–15.
7. Terkelsen KG. Mania after surreptitious discontinuation of clonidine. *Am J Psychiatry* 1984; 141:153.
8. Tollefson GD. Hyperadrenergic hypomania consequent to the abrupt cessation of clonidine. *J Clin Psychopharmacol* 1981; 1:93–5.
9. Rice H, Haltzman S, Tucek C. Mania associated with procainamide. *Am J Psychiatry* 1988; 145:129–30.
10. Lendvai I, Saravay SM, Steinberg MD. Creutzfeldt–Jakob disease presenting as secondary mania. *Psychosomatics* 1999; 40:524–5.
11. Raza H, Epstein SA, Pao M, Rosenstein DL. Mania: psychiatric manifestations of the antiphospholipid syndrome. *Psychosomatics* 2008; 49:438–41.
12. Alao AO, Chlebowski S, Chung C. Neuropsychiatric systemic lupus erythematosus presenting as bipolar I disorder with catatonic features. *Psychosomatics* 2009; 50:543–7.
13. McKnight RF, Hampson S. Hyponatremia-induced change in mood mimicking late-onset bipolar disorder. *Gen Hosp Psychiatry* 2011; 33:83.e5–83.e7.
14. Gillig P, Sackellares JC, Greenberg HS. Right hemisphere partial complex seizures: mania, hallucinations, and speech disturbances during ictal events. *Epilepsia* 1988; 29:26–9.
15. Nishida T, Kudo T *et al.* Postictal mania associated with frontal lobe epilepsy. *Epilepsy and Behavior* 2005; 6:102–10.

## **35 Medically unexplained symptoms**

---

Eve G. Spratt and Ryan R. Byrne

*Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

Medically unexplained symptoms are physical symptoms, signs, or complaints for which there is no clear evidence of pathophysiology to explain the diagnosis. Over 60% of all general practice patients present with at least one medically unexplained symptom. Studies have shown that physicians could not establish a psychological or physiologic basis for common acute symptoms in 74% of cases.

### **Case vignette: conversion disorder**

H is a 15-year-old female with a psychiatric history of panic disorder with agoraphobia and post-traumatic stress disorder (PTSD) who was referred to our inpatient psychiatric unit from her outpatient psychiatrist due to escalating seizure-like episodes that included reported tonic-clonic movements, hyperventilation, posturing, and frothing at the mouth. Prior to her admission, she had undergone a medical work-up including a normal brain MRI, electroencephalogram (EEG), and 24-hour video EEG monitoring. Several of her episodes were captured on video EEG monitoring and the neurology service identified no corresponding EEG changes. The neurologists determined that her episodes were not due to a seizure disorder and rendered the diagnosis of psychogenic non-epileptic events, also termed pseudoseizures and conversion disorder.

Upon initial interview with the treatment team, H endorsed a history of repeated sexual assault from an ex-boyfriend. Notably, the conversion episodes began after he resumed contact with her on a social networking website. In fact, the first conversion episode occurred the evening she told her mother about the abuse. The patient denied having any control over the conversion episodes.

There was no clear secondary gain obtained from the episodes.

H was taking numerous psychotropic medications upon admission to our inpatient unit including alprazolam extended release 2 mg BID, alprazolam 1 mg BID PRN anxiety, oxcarbazepine 150 mg BID, clonidine 0.2 mg qHS, and sertraline 150 mg daily. Upon admission, alprazolam was transitioned to clonazepam 2 mg po BID. Oxcarbazepine was tapered, as neurology had determined that the episodes were not seizure related. During admission, no other medication adjustments were made.

The majority of admission was spent upon patient education regarding conversion disorder and supportive therapy related to her abuse history. Initially, we worked to educate H and her family that these episodes were related to her psychological stress secondary to confronting the past abuse episodes. The patient was initially resistant to this explanation. Her family also hoped that further medical work-up could be performed to eliminate any medical cause for these episodes. We provided reassurance that the neurology work-up had sufficiently ruled out medical causes. We validated the patient's assertion that she was not "faking" these episodes by explaining unconscious processes. We explained that it is important to realize the mind–body connection and those symptoms can be a way of trying to resolve a conflict. Her family agreed with our assessment before H did, but, soon, she began to admit her psychological stress could play a role in her episodes. During this period, H was having 10–15 seizure-like episodes a day. She would go limp, lie on the ground, posture, and hyperventilate. When her parents would visit, they would come to her side and comfort her. When her parents were not visiting, staff and other patients in the milieu would do the same.

**Table 35.1** *Psychiatric differential diagnosis of medically unexplained symptoms.*

DSM diagnosis	Possible symptoms	DSM criteria	Possible clinical features
Conversion disorder	Non-epileptic seizures (pseudoseizures) Aphonia Aphasia Dysarthria	A. One or more symptoms or deficits affecting voluntary	Often in anxious families or patients who focus on disease Frequently precipitated by stressors

DIMINISHES		PRECIPITATED BY
Vision changes	motor or sensory function that	stressful or traumatic event
Deafness	suggest a neurologic or other general medical condition	May be a psychological problem of coping with
Anesthesia		May be a learned behavior (conditioning)
Paralysis	B.	people with sensory deficits
Parasthesia	Psychological factors are judged to be associated with the symptom or deficit because the initiation or exacerbation of the symptom or deficit is preceded by conflicts or other stressors	More common in people of low intelligence and education
	C. The symptom or deficit is not intentionally produced or feigned	More common in any condition that impairs verbal communication
	D. The symptom or deficit cannot, after appropriate investigation, be fully explained by a	Equal frequency in prepubertal boys and girls, more frequent in adult and adolescent women than men
		Often comorbid with other psychiatric diagnoses
		Symptoms are often to be non-physical (video games, electroencephalogram, deep tendon reflexes, pupillary examination)
		Some patients lack concern about the disability, known as <i>la belle indifférence</i> .
		However, presence of absence should be used to separate

general medical condition, or by the direct effects of a substance or as a culturally sanctioned behavior or experience

E. The symptom or deficit causes clinically significant distress or impairment in functioning or warrants medical evaluation

disease

These physical symptoms are unconsciously produced and generally are temporally related to conflict. They lead to attention, concern, sympathy, and nurturance.

Somatization disorder – formerly known as Briquet's syndrome [Undifferentiated somatoform disorder includes only one or more symptoms that are medically unexplained and do not fit criteria for another somatoform disorder]

Pain in multiple locations  
Gastrointestinal distress

- Nausea
- Bloating
- Vomiting
- Diarrhea
- Intolerance of foods

Sexual symptoms  
Pseudoneurologic symptoms

- Impaired coordination

A. A history of many physical complaints beginning before age 30 and resulting in treatment being sought or significant impairment in functioning

B. Each of the following criteria must have been met, with

Patients are often dramatic and seek numerous physician visits

Patients have undergone extensive diagnostic tests

Due to numerous providers, somatization can be suspected

is not often adequately diagnosed

Patients often come from chaotic families or families with

<ul style="list-style-type: none"> <li>– Impaired balance</li> <li>– Paralysis or weakness</li> <li>– Difficulty swallowing</li> <li>– Aphonia</li> <li>– Urinary retention</li> <li>– Hallucinations</li> <li>– Loss of touch or pain sensation</li> <li>– Vision changes or blindness</li> <li>– Deafness</li> <li>– Amnesia</li> <li>– Loss of consciousness</li> </ul>	<p>individual symptoms occurring at any time during the course of the disturbance:</p> <ol style="list-style-type: none"> <li>(1) four pain symptoms: a history of pain related to at least four different sites</li> <li>(2) a history of at least two gastrointestinal symptoms other than pain</li> <li>(3) a history of at least one sexual or reproductive symptom other than pain</li> <li>(4) a history of at least one symptom or deficit suggesting a neurologic condition not limited to pain</li> </ol>	<p>substance abuse</p> <p>Often use physical symptoms as a mechanism</p> <p>High comorbidity with psychiatric disorders</p> <p>Patients often with a sense of urgency</p> <p>Often present vague, non-specific complaints, for example dizzy pain</p> <p>Patients may demonstrate odd seeking behavior</p> <p>When documenting medical diagnosis present, complications are often more what would be expected</p>
--	--	---

C. Either (1) or (2):  
(1) after appropriate investigation,

each of the symptoms in Criterion B

cannot be fully explained by a known general medical condition or the direct effects of a substance

(2) when there is a related general medical condition, the physical complaints or resulting social or occupational impairment are in excess of what would be expected

D. The symptoms are not intentionally feigned or produced

Pain disorder

Chronic back pain  
Fibromyalgia  
Recurrent headaches  
Atypical facial

A. Pain in one or more sites is the predominant focus of clinical

Pain is most c presenting coi Although und disease may h been a precipi pain is judged

pain Chronic pelvic pain	presentation and is of sufficient severity to warrant clinical attention	practitioner to greater than th predicted by pathophysiol findings
	B. The pain causes clinically significant distress or impairment	Description of often dramatic Pain is often c chronic syndrom Often focus on explain all iss deny or minimiz psychological interpersonal problems
	C. Psychological factors are judged to have an important role in the onset, severity, exacerbation, or maintenance of pain	Often are depen on others and incapacitated Willing to unc surgeries or ot large procedur search of pain
	D. The symptom or deficit is not intentionally produced or feigned	Often have sev several physic same issue Patient's pain center of fami
	E. The pain is not better accounted for by a mood, anxiety, or psychotic disorder and does not meet criteria for	Are often trea and often dem large number medications Despite medic pain persists

## dyspareunia

Hypochondriasis	Fear or concern about disease Misinterpret normal bodily sensations	A. Preoccupation with fears of having, or the idea that one has, a serious disease based on the person's misinterpretation of normal symptoms B. Preoccupation persists despite appropriate medical evaluation and reassurance C. The belief is not of delusional intensity and not restricted to circumscribed concern about appearance D. Preoccupation causes clinically significant distress or impairment E. Duration is	Inappropriate processing of information Hypervigilant benign bodily sensations, for example normal pains Often overlap generalized anxiety disorder Patients often check their own medical records and print medical texts Feel transient from reassurance worries return hours or days Typically begins early adulthood continues throughout life Exacerbations often seen during times of stress an acquaintance with an illness, or after seeing information about illness in the media May impair relationships Often handles illness with a disease approach
-----------------	---	---	---

		<p>at least 6 months</p> <p>F. Not accounted for by an anxiety, depressive, or somatoform disorder</p>
Delusional disorder – somatic type – also known as monosymptomatic hypochondriacal psychosis [Differs from hypochondriasis due to fixed belief rather than general health worries]	<p>Specific, fixed belief of a physical abnormality</p>	<p>A. Non-bizarre delusions of 1 month's duration</p> <p>B. Criterion A for schizophrenia has never been met</p> <p>C. Apart from impact of delusion, functioning is not markedly impaired and behavior is not obviously odd or bizarre</p> <p>D. If mood episodes have occurred concurrently with delusions, their duration has been brief relative to the duration of the durational period</p> <p>Beliefs need relate to any specific symptom, as seen in hypochondriasis. May involve irrational unusual conditions. May involve thoughts about contamination, infestation of objects, or vermin, foul odors, and organic malfunction</p>

E. Disturbance  
is not due to  
effects of  
substance or  
general  
medical  
condition

Somatic type:  
delusions that  
the person has  
some physical  
defect or general  
medical  
condition

Body dysmorphic  
disorder – also  
known as  
dysmorphophobia

Preoccupation  
with appearance  
of specific body  
part  
Social  
withdrawal  
Seeking of  
surgical  
intervention for  
appearance

A.  
Preoccupation  
with an  
imagined  
defect in  
appearance. If  
a slight  
physical  
anomaly is  
present, the  
person's  
concern is  
markedly  
excessive

B. The  
preoccupation  
causes  
clinically  
significant  
distress or  
impairment in  
functioning

Often involve  
the shape of the  
face or perception  
of the face  
Other body parts  
include the breast,  
genitalia  
Patients often  
spend hours each day  
in a mirror or  
grooming self  
Patients have  
insight into illness  
Onset often during  
adolescence  
In severe form  
associated with  
withdrawal and  
suicide  
Often impairs  
relationships  
Low rates of . . .

		C. The preoccupation is not better accounted for by another mental disorder	remission despite treatment Can be associated with desire for multiple plastic surgeries
Factitious disorder	Various medical symptoms, notably dermatologic, infections, blood dyscrasias, and hypoglycemia	A. Intentional production or feigning of physical or psychological signs or symptoms	Main separation between factitious disorder and malingering is absence of secondary gain with factitious disorder
May include: Munchausen's syndrome (includes dissociative or wandering component)	Numerous inconsistencies between presentations	B. The motivation for the behavior is to assume the sick role	In reality, in non-presentation, may benefit from role along with secondary gain
Common factitious disorders (typically more focused on one primary symptom and do not have wandering behaviors)	No clear diagnostic pattern	C. External incentives for the behavior are absent	Patients often chaotic, stressful childhoods Often have co-diagnoses, not personality disorders Often persist in symptom production for years Munchausen's syndrome proxy has been found to have 10% rate in some studies
Munchausen's syndrome by proxy – harming a dependent (often a child) with parent having emotional gain or attention from unnecessary focus on the child's perceived medical needs			

<b>Malingering</b>	NOT a formal DSM diagnosis Definition from DSM: This term applies to individuals who intentionally pretend to have symptoms of mental or physical illness to achieve financial or other gain or to avoid criminal conviction or unwanted duty. They may also malingering to facilitate escape from captivity or incarceration	Can either pre simulated syn or exaggerated symptoms Symptom is typically disregarded when achieved May persist to face” Psychological symptoms can be detected via psychological including the Minnesota Multiphasic Personality Inventory (MMPI-2)
--------------------	--	---

---

Following education regarding conversion disorder, we began to educate H about stress management techniques and empower her that she could control the episodes through therapy and use of coping skills. We encouraged H to gradually begin to discuss her trauma. She was provided support and encouragement without pushing her to discuss more difficult parts of the trauma until she felt safe. We provided her with relaxation exercises including deep breathing and journaling that she could participate in when she felt anxious. We also educated her family and unit staff about supportive ways to intervene during the episodes while minimizing potential secondary gain with attention towards H during the episodes. We encouraged her family to empathetically tell H she was having a conversion reaction and was safe. She could overcome the episodes and would be okay without anyone running to her side, holding her, and displaying significant emotion. Staff adopted these same techniques when H's family was not visiting.

With the above interventions, H gradually became an active participant in her treatment, and her conversion episodes rapidly decreased in frequency. She worked diligently with counselors on the unit to develop numerous coping skills. Her family worked with her to develop plans for follow-up treatment including initiation of trauma-focused cognitive behavioral treatment (CBT). With these interventions in place, H continued to address her history of adversity and was much more hopeful about the future. She had no conversion episodes on the day of discharge. We explained that these episodes may recur when she left the hospital due to transition to a less supportive environment. H and her family expressed understanding and developed a plan to deal with any conversion episodes at home or school.

## Further reading list

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revision)* (DSM-IV-TR). Washington, DC: American Psychiatric Association, 2000.

Ford CV. *Somatoform Disorders. Current Diagnosis and Treatment – Psychiatry*, 2nd edn. New York, NY: McGraw-Hill, 2008: 395–410.

Ford CV. Factitious disorders and malingering. In *Current Diagnosis and Treatment – Psychiatry (Second Edition)*. New York, NY: McGraw-Hill, 2008: 411–18.

Neimark G, Caroff S, Stinnett J. Medically unexplained symptoms. *Psychiatric Ann* 2005; 35:298–305.

Shaw RJ, Spratt EG, Bernard RS, DeMaso DR. Somatoform disorders. In Shaw RJ, DeMaso DR, Eds. *Textbook of Pediatric Psychosomatic Medicine*. Washington, DC: American Psychiatric Publishing, 2010.

Spratt E, Ibeziako P, DeMaso D. Somatoform disorder. <http://emedicine.medscape.com/article/918628-overview>, 2011.

## 36 Memory loss and cognitive decline – acute and subacute amnesia

---

Max C. Rudansky, Jacques Winter, Alan Mazurek, Fawaz Al-Mufti, and and Alan B. Ettinger *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

When confronted with the problem of memory loss, the clinician is usually inclined to think of progressive neurodegenerative disease such as seen in the dementias (Alzheimer's disease being the most commonly encountered in the USA). However, there are a variety of acute and subacute amnestic syndromes and diseases, some reversible, as summarized in [Table 36.1](#). Whereas many of these conditions are part of a more generalized alteration in mental status (please refer to [Chapter 37](#) on acute mental status changes and delirium), many have memory loss as a prominent feature of their presentation. Therefore the most important tool in accurate diagnosis is a complete and detailed history from multiple sources, including the patient, family members, and friends, which can then provide the appropriate guidance through a wide diagnostic differential. As seen from [Table 36.1](#), the etiologies for acute and subacute memory loss include vascular, infectious, metabolic, toxic (including medications, illicit drugs, and alcohol), traumatic, epileptic, neurodegenerative (rapid), autoimmune, and neuropsychiatric categories. These conditions constitute a particular challenge to neurologists as the diagnosis often is different from the more typical slowly progressive dementias. Knowledge about speed of onset, duration, presence or absence of progression, and exposure to toxic substances or infection can be crucial in making a timely and potentially life-saving diagnosis.

A general rule of thumb is to remember the distinction between delirium, dementia, and amnesia.

*Delirium* is defined as “a condition of extreme mental excitement, marked by a rapid succession of confused and unconnected ideas, often with illusions and

hallucinations” [1]. As its definition implies it is an acute and sudden phenomenon.

*Dementia* is a “general mental deterioration due to organic or psychological factors” [1]. It is a gradual deterioration of mental acuity and is usually progressive.

*Amnesia* is a “disturbance in memory manifested by total or partial inability to recall past experiences” [1]. It can be acute, subacute, or chronic. It can be anterograde or retrograde, reversible or irreversible, partial or total (rare) and associated with multiple etiologic possibilities. This chapter will confine itself to the acute and subacute presentations.

Like all “rules of thumb,” these definitions are somewhat imperfect, but they do provide some guidance. It is important to remember that various combinations of these three confusional states may co-exist in the same patient.

The three interesting case vignettes that follow illustrate the commonality and variability seen in episodes of acute memory loss.

## **Case vignette 1 (modified from [2])**

A previously healthy 70-year-old right-handed female was noted to be repeatedly asking the same questions at a social gathering [2]. She was able to identify all of her acquaintances but could not remember what she had stated moments earlier. On admission to the hospital several hours later, she was alert but exhibited agitation. She repetitively asked “Where am I?” or “What happened to me?” She was able however to recall information including her address, telephone number, and the names of her son and deceased husband. On further questioning she could remember more long-term events such as notable events in history. In contrast, she exhibited difficulty assimilating new material. Formalized testing revealed verbal auditory responses including logical memory, number series, and associative word learning at a first percentile level. Other general cognitive tasks were performed adequately. Other neurologic and general examination findings were normal. Serum laboratory survey, echocardiogram (ECG), and electroencephalogram (EEG) were within normal limits.

**Table 36.1 Acute and subacute amnestic syndromes.**



Category	Possible clinical features
<b>Vascular</b>	
	Cerebrovascular risk factors Hyperacute onset
<i>Traumatic</i>	
Subarachnoid hemorrhage	Traumatic, aneurysmal, and atraumatic non-aneurysmal sulcal subarachnoid hemorrhage have been associated with amnesia (see trauma below)
<i>Occlusive disease</i>	
Bilateral median temporal branches of the posterior cerebral artery infarct	Hemianopia/quadrantanopia Pure alexia, color anomia
Paramedian/tuberothalamic artery infarct: thalamus	With bilateral thalamic lesions, consider the presence of the artery of Percheron, a rare anatomic variation in the brain vasculature in which a single arterial trunk arises from the posterior cerebral artery to supply both sides of brain structures (thalamus and midbrain)
	Somnolence Vertical gaze paresis Hemiparesis/hemiataxia
Anterior choroidal artery	Hemiparesis, hemiataxia Hemisensory parasthesia Hemianopia
<i>Vasospastic disease</i>	

Reversible cerebral vasoconstriction syndrome

Also known as Call–Fleming syndrome

Poorly understood disease in which the arteries of the brain develop vasospasm without a clear cause

May be present in varying degrees for months at a time  
Typically associated with severe thunderclap headaches which are relieved with the subsiding vasospasms

SSRIs, uncontrolled hypertension, endocrine abnormality, and neurosurgical trauma are indicated to potentially cause vasospasm [2]

Vasospasms can lead to dramatic headaches that are often of the thunderclap headache (sudden-onset) character. Ischemia is thought to cause various lesions and upper motor neuron damage in these patients which presents 3–4 days after migraine onset as focal neurologic symptoms such as dysarthria, unilateral weakness, unsteady gait, and/or hyperreflexia

Amnesia would be unlikely to be the only presentation; more likely patients may complain of global cognitive decline and forgetfulness in addition to other more prominent neurologic deficits

Cerebral venous sinus thrombosis

Presentation maybe acute or

	subacute
Multi-infarct vascular disease	<p>Females &gt; Males</p> <p>Suspect with the acute or subacute onset of altered mental status, focal neurologic deficits, headaches, or cognitive decline during pregnancy or hypercoagulable states</p> <p>MRI/MRV may reveal venous thrombosis, hyperintensities, infarctions and hemorrhages in the gray and white matter [10]</p>
Inflammatory cerebral amyloid angiopathy	<p>Individuals are usually &gt; 50 years, with risk factors for vascular disease</p> <p>Acute to subacute stepwise cognitive decline, with localizing motor, visual, or sensory signs</p> <p>MRI would be helpful in revealing multiple hyperintensities on T2 and FLAIR corresponding to vascular territories [10]</p> <p>Treatment takes the form of secondary prophylaxis, and correction of the risk factors</p>
Primary CNS angiitis	<p>40 years, Males = Females</p> <p>Subacute cognitive decline, headache, seizures</p> <p>MRI may reveal micro-hemorrhages on T2 [10]</p> <p>Check for homozygous APOE e4 genotype</p> <p>Biopsy for confirmation</p>
	Peak age 50 years

Acute cognitive decline (aphasia, hallucination), multifocal neurologic symptoms. Headache, chorea, hemiparesis, and seizures. MRI may reveal multiple T2 hyperintensities in the gray or white matter [10]  
Pleocytosis or elevated protein may be found on CSF analysis  
CNS angiogram or brain and meningeal biopsy may confirm the diagnosis  
Rx: intravenous high-dose corticosteroids;  
immunosuppression

## Migraine

Acute confusional migraine (ACM) is a rare migraine variant, affecting children and adolescents, as well as adults  
Diagnosis of exclusion with diversity of types of cortical dysfunction, such as speech difficulties, increased alertness, agitation, and amnesia  
Approximately half of the cases may be triggered by mild head trauma  
Transient global amnesia is an important differential diagnosis, possibly caused by similar pathophysiologic mechanisms – which these are remains unclear.  
The common hypothesis suggests a complex aura phenomenon, in which the cortical spreading depression wave reaches not only the occipital, but also the temporal, parietal, and frontal

cortex, as well as the brainstem and the hippocampi, leading to transient hypoperfusion and dysfunction of these brain areas

Transient global amnesia

Paroxysmal and transient loss of anterograde and retrograde memory lasting for up to 24 hours; usually less than 12 hours

Can occur after strenuous physical exertion or intense emotional arousal

Usually in the middle aged or older

Patients are usually disturbed by the deficit; tend to ask repetitive inquisitive questions of an orienting nature despite the presence of an intact sensorium  
No other neurologic or systemic symptoms or signs

Typically, permanent loss of memory for the time immediately before the episode and the entire time during the episode (no learning). Intact remote memory, immediate recall, and personality identity

## **Infectious**

Encephalitis

Often preceded by a prodrome that includes a non-specific febrile illness with headache  
Low-grade fever, chills, malaise, anorexia, vomiting that lead the way to alteration in the level of consciousness

Impaired cognitive ability and

personality change,  
hallucinations, psychosis, fever,  
agitation, irritability, and  
delirium

Suspect an infectious etiology  
with the presence of rashes or if  
there is history of animal tick  
bite: Lyme disease (tickborne;  
circular, outwardly expanding  
rash called erythema chronicum  
migrans), Rocky Mountain  
spotted fever (tickborne; red,  
spotted, petechial rash involving  
the palms or soles), typhus,  
varicella, herpes B virus, and  
herpes zoster encephalitis are  
preceded by a rash

#### Viral encephalitis

Altered mental status of varying  
severity – mild confusion or  
agitation – coma

Seizures common

Meningeal signs may be absent

Focal neurologic abnormalities  
may be present

Temporal lobe abnormalities on  
EEG and imaging studies suggest  
herpes virus infection

#### Herpes virus encephalitis

Most frequent form of viral  
encephalitis in neurologic  
practice

Herpes simplex virus-1 (HSV-1)  
is the most common source  
although 10% of cases of herpes  
encephalitis are due to HSV-2,  
which is spread through sexual  
contact. In newborns, herpes  
simplex type II transmitted from  
~~maternal genital lesions~~

~~Immunological lesions causes a~~  
diffuse necrotizing brain disease  
as well as visceral necrosis  
In immunosuppressed patients,  
both types I and II can cause a  
diffuse but less necrotizing CNS  
lesion

May follow a prodrome of 1–7  
days of upper respiratory tract  
infection with headache, fever,  
and subsequent bizarre  
psychiatric symptoms

Patients present with bizarre,  
fluctuating behavioral changes  
and a waxing and waning  
alteration of mental status.

Seizures, anosmia, olfactory, and  
gustatory hallucinations,  
personality changes, and  
psychosis

#### HIV encephalopathy

Lower CD4 counts in HIV  
patients predispose to  
encephalitis

Typical features include motor  
spasticity and subcortical  
dementia with memory  
loss/psychomotor slowing/mood  
disorder

Involvement of white matter with  
extensive neural degeneration  
presenting as multiple symmetric  
non-enhancing subcortical  
lesions on T2 MRI

#### Lyme encephalopathy

Tickborne, affects males and  
females equally  
Mostly seen in late disease  
Symptoms depend on stage of  
infection. Stage III or chronic

	<p>Lyme may be associated with subacute encephalopathy (amnesia, sleep disturbances, subtle cognitive disturbances/mood changes)</p> <p>Neuropathies ranging from distal sensory paresthesias to radicular pain (i.e. pain, numbness, and/or weakness in a dermatomal distribution)</p> <p>Leukoencephalitis is less likely to occur but results in greater neurologic impairment, such as marked cognitive deficits, bladder dysfunction, ataxia, and spastic paraparesis</p>
Cytomegalovirus encephalitis	<p>Altered mental status/confusion/agitation/focal neurologic deficits</p>
Toxoplasma encephalitis	<p>Cognitive deficits, seizures Focal neurologic deficits/fever/headache Multiple cortical/subcortical ring enhancing lesions on neuroimaging</p>
Neurosyphilis	<p>Subacute cognitive decline, psychosis, depression, pupillary abnormalities MRI may be normal but could show non-specific atrophy [10] CSF VDRL reactive and serum RPR positive Crystalline intravenous penicillin G for 10–14 days</p>
Whipple disease	Adults; rare in older adults

Subacute dementia, psychiatric symptoms, movement disorder, ophthalmoplegia, myoclonus, gastrointestinal disturbance  
MRI findings may range from being normal to demonstrating FLAIR hyperintensities in medial temporal lobe, midbrain and diencephalon with or without contrast enhancement [10]  
CSF analysis for *Tropheryma whippleii* PCR  
Jejunal biopsy (PAS with staining or PCR)

## Parainfectious encephalitis

Progressive multifocal leukoencephalopathy

JC virus infection  
Rapidly progressive neurologic changes – cognitive impairment/aphasia/focal neurologic deficits  
Almost exclusive to immunocompromised patients, such as transplant patients on immunosuppressive medications, patients on chemotherapy, or receiving natalizumab (Tysabri) for multiple sclerosis, on long-term efalizumab (Raptiva) for psoriasis, or have AIDS

Acute disseminated encephalomyelitis (ADEM)

Patients are frequently immunocompetent children and adolescents  
Typically monophasic but multiphasic cases of ADEM have been reported  
Follows viral infections but may

	<p>appear following bacterial or parasitic infection, or even appear spontaneously. There is no causal evidence linking vaccination to ADEM</p> <p>Acute onset of a flu-like prodrome, followed by encephalopathy with multifocal neurologic signs</p> <p>MRI: Multifocal T2/FLAIR hyperintensities sometimes with contrast enhancement</p> <p>MRI may reveal multifocal T2 and FLAIR hyperintensities with or without contrast enhancement.</p> <p>Multiple inflammatory demyelinating lesions in the subcortical and central white matter and cortical gray–white junction of both cerebral hemispheres, brainstem, cerebellum, and spinal cord [10]</p> <p>Mortality rate may be as high as 5%, full recovery is seen in 50–75% of cases, while up to 70–90% recover with some minor residual disability</p> <p>Average time to recover is 1–6 months</p>
Subacute sclerosing pan-encephalitis (SSPE)	<p>Rare chronic, progressive encephalitis that affects primarily children and young adults, caused by a persistent infection with measles virus (which can be a result of a mutation of the virus itself). No cure for SSPE exists, but the condition can be managed by medication if treatment is</p>

started at an early stage  
Gradual, progressive  
psychoneurologic deterioration  
consisting of personality change  
and amnesia, seizures,  
myoclonus, ataxia,  
photosensitivity, ocular  
abnormalities, spasticity, and  
coma. Death occurs within 3  
years  
It should not be confused with  
acute disseminated  
encephalomyelitis which has a  
similar etiology but very different  
timing and course. In ADEM  
onset is within 4–6 days after  
onset of rash whereas in SSPE  
the onset is gradual, on average 7  
years after measles infection,  
with slow progression

#### Prion disease

Progressive, fatal, prion-induced  
dementia. Peak age 60 years  
(range 16–82 years)  
5–10% familial, 10–15% of the  
cases of CJD are inherited  
(autosomal dominant), with the  
remaining being sporadic;  
iatrogenic (corneal transplants,  
dura mater allograft, human  
pituitary extract) very rare  
All present with cognitive deficits  
(dementing illness – memory  
loss, behavioral abnormalities,  
higher cortical function  
impairment). Most have  
myoclonus. Pyramidal tract signs  
(weakness), cerebellar signs  
(clumsiness), and extrapyramidal

signs (parkinsonian features) in > 50%

Less commonly cortical visual abnormalities, abnormal eye movements, vestibular dysfunction, sensory disturbances, autonomic dysfunction, lower motor neuron signs, and seizures

Also see entry: Variant CJD (below)

### Encephalitis lethargic

A CNS disorder presenting with pharyngitis followed by sleep disorder, basal ganglia signs (particularly parkinsonism), and neuropsychiatric sequelae

Characterized by high fever, sore throat, headache, lethargy, double vision, delayed physical and mental response, sleep inversion, and catatonia

In severe cases, patients may enter a coma-like state (akinetic mutism). Patients may also experience abnormal eye movements ("oculogyric crises"), parkinsonism, upper body weakness, muscular pains, tremors, neck rigidity, and behavioral changes including psychosis. Klazomania (a vocal tic) is sometimes present

### Toxic-metabolic/systemic

Multiple etiologies

Abnormal motor findings often present

Riluzole, acetaminophen

**Physical examination.** Tremor  
tremor  
Multifocal myoclonus

### *Sepsis*

Hepatic	Acute/chronic abnormal liver function tests Elevated ammonia level
Uremia	Elevated BUN and creatinine Symptoms may include hypertension due to volume overload, hypocalcemic tetany, and anemia due to erythropoietin deficiency, serositis, itching, and hiccups Seizures, decreased mental acuity, and coma
Hyponatremia	Serum sodium < 135 mEq/L; severe hyponatremia is defined as a serum sodium < 120 mEq/L Signs and symptoms of hyponatremia include headache, difficulty concentrating, memory impairment, confusion, weakness, and unsteadiness, which may lead to falls If the sodium concentration falls rapidly over 24–48 hours, the compensatory mechanisms of the brain are overwhelmed and severe cerebral edema occurs, leading to hallucination, syncope, seizure, brainstem herniation, respiratory arrest, and death. This can occur even with a modest fall in sodium (125–130 mEq/L) Possible causes depend on the

	<p>clinical scenario, but always suspect medication side effect,  <i>e.g.</i> antiepileptics (carbamazepine, oxcarbazepine), tricyclic antidepressants, sometimes with other psychotropic agents. Syndrome of inappropriate anti-diuretic hormone</p>
Hypernatremia	<p>Hypernatremia-induced limbic system damage: rapid correction of hyponatremia may lead to severe hypernatremia causing central pontine or extrapontine myelinolysis and neuronal damage, depending on the level and duration of hypernatremia and the rapidity of its onset</p>
Hypercalcemia/hypocalcemia	<p>Hypercalcemia (<math>&gt; 10.5 \text{ mg/dL}</math>)  Hypocalcemia (serum calcium <math>&lt; 9 \text{ mg/dL}</math> or ionized calcium level of less than <math>4.5 \text{ mg/dL}</math>)  Depending on the severity and rate of development, hypercalcemia can produce varying degrees of a generalized encephalopathy ranging from mild impairment of attention to coma  Slowly developing hypocalcemia may produce an encephalopathy, dementia, depression, or psychosis</p>
Hypoglycemia	<p>Should be suspected when patients describe episodes of</p>

adrenergic hyperactivity  
(shakiness, anxiety, nervousness, palpitations, tachycardia, sweating, coldness, clamminess), glucagon manifestations (hunger, borborygmus, nausea, vomiting, abdominal discomfort, headache), and neuroglycopenic manifestations

Neuroglycopenic manifestations include but are not limited to abnormal mentation, impaired judgment, non-specific dysphoria, moodiness, depression, negativism, irritability, combativeness, emotional lability

Confusion, amnesia, dizziness, delirium, staring, “glassy” look, blurred vision, double vision, slurred speech, stupor, coma, abnormal breathing, generalized or focal seizures

Exacerbation of baseline neurologic deficits

### Hyperglycemia

Altered mental status and acute cognitive decline is very common in patients with diabetic ketoacidosis or non-ketotic hyperglycemia

### Hypoxic–ischemic encephalopathy

Follows cardiopulmonary arrest  
Neurologic findings dependent on duration/severity of hypoxia/ischemia  
Mild confusion–delirium–coma  
Affect ranges from apathy to agitation

Hypertensive encephalopathy	Acute presentation with headaches, confusion, visual changes, seizures, and even coma Usually associated with uncontrolled hypertension, eclampsia, chemotherapy FLAIR hyperintensities in parietoccipital white matter may be found on MRI [10] Optimization of blood pressure control is the cornerstone of treatment
Posterior reversible encephalopathy syndrome (PRES)	May be associated with renal insufficiency, malignant hypertension, rheumatologic diseases, drugs like tacrolimus and cyclosporine, and hypercalcemia. Low magnesium levels can augment PRES. Patients present with acute onset of headache, seizures, loss of vision, and altered mental function MRI demonstrates that the areas of abnormality represent vasogenic edema. Lesions may be holohemispheric, superior frontal sulcal, or primary parietal–occipital [9]. Management involves promptly identifying and reversing potential offending agents; controlling hypertension, and treating active disease can lead to reversal of radiologic and neurologic findings [10]

### Wernicke–Korsakoff syndrome

Wernicke's encephalopathy, which occurs due to severe acute deficiency of thiamine (vitamin B1), is characterized by confusion, nystagmus, and ophthalmoplegia

Some patients may also have anisocoria, ataxia, sluggish pupillary reflexes, coma, and death if untreated

As Wernicke's encephalopathy resolves, Korsakoff's psychosis ensues which is characterized by memory deficits

Retrograde and anterograde amnesia/poor insight into deficits/ confabulation—fabrication of information to fill in memory gap and hallucinations

Usually follows chronic alcoholism but should also be suspected with prolonged intravenous therapy without vitamin B1 supplementation, gastric stapling, prolonged intensive care unit stays, or hunger strikes

### Marchiafava–Bignami syndrome

Corpus callosum degeneration

Gradually progressive

psychomotor

slowing/incontinence/gait ataxia

Associated with red wine intake/mechanism unclear

### Hypothyroidism–Hashimoto's encephalopathy

Acute/subacute alteration of mental status/consciousness. Two subgroups:

Central and peripheral

	<p>Gradually progressive mental status changes, hallucinations, or dementia</p> <p>Stroke-like episodes with focal neurologic deficits</p> <p>High frequency focal or generalized seizures.</p> <p>Cerebrospinal fluid pleocytosis/elevated protein</p>
Acute intermittent porphyria	<p>Acute to subacute presentation 20–30 years of age Females &gt; Males</p> <p>Presentation is usually in the form of abdominal pain, autonomic dysfunction, behavioral changes, and altered consciousness</p> <p>Elevated PBG, ALA in urine Rx: Carbohydrates, intravenous haem arginate; avoid certain medications and metabolic disturbances</p>
Acquired hepatocerebral degeneration	<p>Cirrhosis (portosystemic shunting)</p> <p>Subacute apathy, inattention, parkinsonism, cranial dyskinesia</p> <p>MRI: Pallidal T1 hyperintensities, normal T2</p> <p>Rx: Treatment of liver disease, but might be irreversible; liver transplant</p>
Carbon monoxide poisoning	<p>Neurologic deficits often restricted to changes in mental status. Mild confusion/lethargy</p> <p>Seizures/coma with more severe exposure</p> <p><i>Delayed neuropsychiatric</i></p>

~~Delayed neuropathy~~  
syndrome with cognitive  
behavioral changes usually  
within 3 weeks of exposure

## Arsenic

Acute ingestion or inhalation in workers – confusion, memory changes, headaches, gastrointestinal symptoms  
Chronic exposure – confusion, hallucinations/memory deficits  
Peripheral neuropathy with pain or sensory symptoms most common

## Medications

Special attention must be made to the temporal relationship between initiating drug use and cognitive symptoms.

### Benzodiazepine

Altered mental status/slurred speech, ataxia and anterograde amnesia  
Temazepam most sedating, while oxazepam is the least sedating  
Flunitrazepam (Rohypnol): prohibited in the USA. At low doses, flunitrazepam acts as a muscle relaxant and a sedative-hypnotic. At higher doses, it can cause lack of muscle control and loss of consciousness. Long history of abuse by heroin and cocaine addicts, and because it was specifically formulated to produce anterograde amnesia, it has been used to commit sexual assault  
Vital signs usually normal.  
Respiratory depression is

uncommon in oral overdoses

Phenylpropanolamine

Nasal decongestant  
No longer sold without a  
prescription due to a proposed  
increased risk of hemorrhagic  
stroke in younger women

## Drugs of abuse

Marijuana/THC (delta 9-tetrahydrocannabinol)

THC has low acute toxicity.  
Euphoric “high” with decreased  
anxiety  
Perceptual changes/exaggerated  
sensory phenomena/spatial  
distortion/poor  
concentration/short-term memory  
changes/motor coordination  
Psychomotor impairment lasts  
12–24 hours due to THC  
accumulation in fatty tissues with  
slow release back into circulation

MDMA (3,4-methylenedioxymethamphetamine, also called ecstasy)

Stimulation of the CNS is common and can manifest as agitation, hyperactivity, anxiety, and even delirium. Seizures and status epilepticus can occur.  
Psychomotor agitation may be associated with hyperthermia as well as rhabdomyolysis  
Persistent effects on memory function in humans have only rarely been reported so far which is unusual because of the known potential of MDMA to interfere with serotonin and dopamine brain metabolism and its established neurotoxicity in

animals  
Cases of anterograde and retrograde amnesia have been described and were associated with brain MRI showing clearly defined hyperintense signal alteration in globus pallidus bilaterally as well as in the hippocampi (causing the persistent memory problems)

## Traumatic

Post-traumatic amnesia (PTA)

Sign of trauma or foul play  
Impaired attention and retrieval  
Affective dysregulation: anxiety, PTSD  
Resolution of PTA: Initially orientation then verbal recognition then delayed verbal free recall

Subarachnoid hemorrhage (SAH)

A significant proportion of all SAH patients suffer from amnesias, most anterograde and fewer retrograde (66% of patients with SAH reported anterograde and 17% retrograde amnesias)

Superficial siderosis (SS)

SS of the CNS results from hemosiderin deposition in the subpial layers of the brain and spinal cord. Hemosiderin deposition is a consequence of recurrent and persistent bleeding into the subarachnoid space  
Classically SS presents as adult-onset slowly progressive gait (less commonly appendicular)  
*ataxia with cerebellar dysarthria*

and sensorineural hearing impairment  
Recently published cases describe cerebral amyloid angiopathy cases associated with superficial siderosis as lacking the typical clinical findings and being associated with headache, seizures, and cognitive impairment. This is most probably since SS in patients with cerebral amyloid angiopathy (CAA) have a supratentorial distribution over the cerebral convexities, while the “classic” SS mainly affects brainstem and posterior fossa

### Epidural hematoma

Males > Females; common in children and 5th/6th decade; due to trauma; lucid interval followed by severe headache, nausea, vomiting, increased intracranial pressure, altered mentation, seizures, focal neurologic deficits affecting language, motor, and sensory functions, incontinence, paresis, sensory deficits, severe back pain, cognitive decline, and amnesia

Amnesia may be for recent events (retrograde amnesia), and this may extend for some seconds or minutes prior to the injury and, rarely, with more severe impact, for days or more. A variable period of inability to learn new material (anterograde amnesia) typically follows recovery of

consciousness and may be dense enough to leave the patient with no memory of early post-injury events

Rarely, some patients tell of being “unconscious” for weeks to as long as several months following head injury. In fact, they were not unconscious but were unable to remember ongoing events

### Chronic subdural hematoma

A history of recent head injury  
Slower onset of symptoms than epidural hemorrhages because the lower pressure veins bleed more slowly than arteries  
Loss of consciousness or fluctuating levels of consciousness, disorientation, amnesia, dizziness  
Irritability, seizures  
Headache pain  
Personality changes, inability to speak or slurred speech  
Ataxia, or difficulty walking, altered breathing patterns  
Hearing loss or hearing ringing (tinnitus), blurred vision

## Epileptic phenomena

### Partial complex status epilepticus

Intermittent or continuous impairment of cognition  
May be accompanied by automatisms

### Absence status epilepticus

Altered responsiveness without loss of consciousness

	May be accompanied by eye-blinking/impaired speech/myoclonus
Transient epileptic amnesia	<p>Typically starts in late middle age</p> <p>Recurrent episodes usually on awakening</p> <p>Duration typically 20–30 minutes</p> <p>Accompanied by olfactory/gustatory hallucinations</p> <p>Automatism: Lip smacking/chewing movements</p> <p>Preserved ability to respond appropriately to conversation and act in a purposeful manner</p> <p>After resolution of event patient may have a vague recollection of not having been able to remember</p> <p>Persistent accelerated long-term forgetting, remote autobiographical memory, and topographical amnesia</p>
Post-ictal fugue	<p>Post-ictally certain individuals experience a post-ictal fugue state characterized by apparent purposeful behavior for which they are subsequently amnestic</p> <p>There is a disruption in consciousness associated with significant confusion and an abnormal EEG</p> <p>Patients display apparently purposeful behaviour despite absence of ongoing cognitive activity</p>
Aphasic seizures/aphasic status	Aphasia can be seen as an ictal or

epilepticus	<p>post-ictal phenomenon      Attempts to speak/paraphasias/comprehension deficits      Consciousness is preserved      Diagnosis by EEG monitoring/brain imaging to exclude acute stroke      Resolves with treatment by antiepileptic drugs</p>
Non-epileptic seizures (pseudoseizures)	<p>Usually non-physiologic start and stop motor activity. Transient failure to respond to others      Often difficult to diagnose/requires video EEG monitoring      Tend to be longer in duration, <i>i.e.</i> greater than 2 minutes, eyes often closed with exam finding of forced eye closure, lack of post-ictal symptoms</p>
Complex migraine phenomena	<p>Acute confusional amnesia      Headache; nausea and vomiting      Stereotypic episodes      Hypervigilance, speech difficulty, and restlessness</p>

## Psychiatry

Dissociative fugue state	<p>Triggered by stressful life event      One or more episodes of inability to recall important personal information with loss of autobiographical memories, including self-identity in the context of preserved new learning and absence of repetitive questioning (no transient alcohol)</p>
--------------------------	--

	<p>psychogenic (vs. organic causes amnesia)</p> <p>Typically too extensive to be explained by ordinary forgetfulness</p> <p>Not due to effects of medications, substances of abuse, or head trauma</p>
Malingering	<p>Deliberate and voluntary simulation of psychological or physical disorders</p> <p>May overlap with dissociative psychogenic amnesia and can be difficult to distinguish from each other</p>
Electroconvulsive therapy (ECT)	<p>Used to treat intractable depression</p> <p>Limitations of use relate to cognitive side effects</p> <p>Post ECT/post-ictal period may manifest confusion and cognitive/memory deficits followed by retrograde amnesia</p> <p>Gradually increasing disorientation may occur over the course of treatments</p> <p>However, cognition can improve in spite of problems secondary to resolution of depressive symptoms by ECT</p>

## **Autoimmune**

Demyelinating – multiple sclerosis	Memory deficit: “Impaired retrieval,” impairments in delayed free recall improved with recognition; impaired information processing; dysnomia
------------------------------------	---

	Prior history of relapsing–remitting neurologic symptoms and signs; optic neuritis, diplopia, incoordination, sensory symptoms Abnormal neurologic exam, preferentially white matter tracts; hyperreflexia, ophthalmoplegia, gait disorder
Paraneoplastic limbic encephalitis	Anterograde memory impairment with preserved awareness and attention Strong female predominance [1,2] Complex partial temporal lobe seizures
	Neuropsychiatric: depression, psychosis, or change in personality (withdrawn and apathetic) Associated neurologic findings: sensory neuropathy and gastrointestinal dysmotility Constitutional symptoms: unexplained weight loss, night sweats, and anorexia Neurologic presentation often antedates the diagnosis of cancer and an initial comprehensive search for malignancy may be unrevealing. Most commonly associated tumor: small cell lung carcinoma

### **Non-paraneoplastic limbic encephalitis**

NMDA (N-methyl D-aspartate)

NMDA receptor encephalitis is

receptor encephalitis

acute and potentially lethal but with high probability for recovery  
Autoimmune reaction against NR1-and NR2-subunits of the glutamate NMDA receptor  
Disease is associated with tumors, mostly teratomas of the ovaries (55%), and thus is considered paraneoplastic  
Prodromal flu-like illness (fever, headache, malaise, or fatigue)  
Acute to subacute development of prominent neuropsychiatric symptoms such as anxiety, mood, and affective symptoms progressing to severe behavior and personality disturbances, delusional or disorganized thinking, paranoid ideation, and hallucinations  
It is associated with seizures and decline of level of consciousness, central hypoventilation, autonomic instability, and dyskinesias  
Patients are usually first seen by psychiatrists or admitted to psychiatric wards with the diagnosis of acute psychosis or schizophrenia

Steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT)

Predominantly females  
Subacute fluctuating cognitive decline (stroke-like events), movement disorders (e.g. tremors, myoclonus, gait ataxia, and neuropsychiatric manifestations)  
Aphasias, seizures, sleep

	<p>disturbance, and headaches are common</p> <p>A corticosteroid response condition with thyroid autoimmunity (identified by serum peroxidase or thyroglobulin antibodies), often without clinical or biochemical evidence of thyroid dysfunction</p>
Encephalopathy with potassium channel antibody/VGKC antibodies (LGI1 antigen)	<p>Strong male predominance, median 60 years</p> <p>Subacute cognitive impairments with behavioral changes and hyponatremia, hyperphagia, seizures, myoclonus, ataxia, unilateral brachial–facial spasms</p> <p>Associated cranial and somatic neuropathy</p> <p>MRI may reveal medial temporal lobe hyperintensities although it might be normal</p> <p>CSF protein maybe be normal or elevated. Oligoclonal bands are infrequently seen.</p> <p>Though most cases are not paraneoplastic, occult malignancy may be present in 20%; small cell lung cancer, thymoma</p> <p>EEG slowing</p> <p>Encephalopathy with VGKC antibodies (LGI1 antigen) is a potentially immunotherapy responsive form of limbic encephalitis with infrequent relapses</p>
Systemic lupus erythematosus	<p>Neuropsychiatric lupus (NPSLE):</p> <p><u>Mood disorders, anxiety,</u></p>

#### Mood disorder, anxiety

depression  
Cognitive deficits  
Headaches  
Extrapyramidal features  
NPSLE can occur any time in the course of SLE, even during periods in which no SLE disease activity is detected

#### Antiphospholipid antibody syndrome

Female predominance  
Migraine headaches  
Livedo reticularis  
Multiple infarcts presenting with “forgetting to remember”: impaired delayed free recall improved with cueing/recognition Impaired attention, concentration, and psychomotor speed Factors significantly associated with cognitive decline are persistently positive antiphospholipid (aPL) antibodies levels, prednisone use, diabetes, higher depression scores, and less education

### **Inherited encephalopathies**

#### Mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes (MELAS)

A mitochondrial cytopathy which includes encephalomyopathy, lactic acidosis, and stroke-like episodes

Signs and symptoms of this disorder appear in childhood following a period of normal development. Initially patients develop muscle weakness, pain, recurrent headaches, vomiting, and seizures, with stroke-like

episodes of hemiparesis, seizures beginning before age 40  
Repetitive stroke-like episodes can progressively damage the brain, leading to vision loss, problems with movement, and a loss of intellectual function (dementia)

## **Malignancy/metastasis**

### **Primary CNS lymphoma**

Individuals in the fifth–seventh decades  
Subacute presentation with neuropsychiatric symptoms, focal neurologic deficits, and seizures  
Focal hypohyperintense T2 lesions with contrast enhancement. CSF may reveal lymphocytic pleocytosis. Flow cytometry reveals lymphoma cells  
Three lumbar punctures may be necessary to definitively rule out CNS lymphoma

### **Gliomatosis cerebri (infiltrative diffuse astrocytosis)**

Rare primary brain tumor found in the third and fourth decades of life.  
It may affect any part of the brain or even the spinal cord, optic nerve, and compact white matter  
Presentation is usually with the subacute onset of dementia, headaches, seizures, and alteration in mental status  
Rapidly progressive dementia and parkinsonian features have been described

MRI may reveal diffuse, poorly circumscribed, infiltrating non-enhancing lesion that is hyperintense on T2-weighted images and expands the cerebral white matter. May be difficult to differentiate from highly infiltrative anaplastic astrocytoma or GBM [10]

MR spectroscopy might be used to classify gliomatosis cerebri as a stable or a progressive disease indicating its potential therapeutic relevance

Prognosis is generally poor, with a median survival time of only 12 months

## Neurodegenerative

### Creutzfeldt–Jakob disease (CJD)

A neurodegenerative, uniformly fatal prion disease with spongiform encephalopathy Subacute cognitive decline with behavioral symptoms. Poor judgment, emotional lability, apathy, and depression Hallucinations and movement disorder in form of myoclonus and cerebellar ataxia Sleep disturbances (hypersomnia/insomnia) are often early signs Pyramidal tract signs, extrapyramidal signs, akinetic mutism, vestibular and visual dysfunction, lower motor neuron lesions, seizures, autonomic dysfunction

Rapidly progressive Alzheimer's disease can mimic CJD  
Cortical or subcortical hyperintensities may be found on diffusion-weighted MRI  
CSF may exhibit elevated total tau, elevated 14-3-3 and neuron specific enolase  
EEG exhibits characteristic changes depending on the stage of the disease, ranging from non-specific findings such as diffuse slowing and frontal rhythmic delta activity (FIRDA) in early stages to disease-typical periodic sharp wave complexes (PSWC) in middle and late stages, to areactive coma traces or even alpha coma in preterminal EEG recordings

#### Alzheimer's disease

60 years  
Subacute short-term memory impairment early in the disease  
Hippocampal atrophy may be found initially on MRI and later atrophy may spread to the temporal, parietal, and frontal regions [10]  
CSF may show decreased Ab, increased phosphotau, and increased total tau [10]  
PET with amyloid ligand

#### Lewy body dementia (LBD)

Age 50 years  
Subacute fluctuating cognitive dysfunction, development of parkinsonism, visual hallucinations, and behavioral

	<p>changes FDG-PET may be helpful in demonstrating anything specific. Usually it is normal or non-specific atrophy FDG-PET may be helpful in demonstrating occipital hypofunction [10]</p>
Behavioral variant frontotemporal dementia (bvFTD)	<p>40–70 years Subacute development of executive dysfunction and behavioral changes such as apathy, disinhibition, loss of empathy/sympathy, and repetitive behaviors MRI may reveal frontal or temporal atrophy FDG-PET may be helpful in demonstrating frontal/temporal hypofunctioning [10]</p>
Corticobasal syndrome (CBS)	<p>Age 50–70 years Subacute cognitive dysfunction, asymmetric motor abnormalities, or aphasia Cognitive impairment, especially language impairment, is prominent from onset of disease Classic features, alien limb and myoclonus, are present in a minority only, even late in disease course MRI may demonstrate asymmetric parietal or frontal atrophy [10]</p>

ALA, delta-aminolevulinic acid; BUN, blood urea–nitrogen; CNS, central nervous system; CSF, cerebrospinal fluid; EEG, electroencephalogram; FLAIR, fluid attenuated inversion recovery; FDG-PET, fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; PAS, periodic acid–Schiff; PBG, porphobilinogen; PCR, polymerase chain reaction; PET, positron emission tomography; PTSD, post-traumatic stress disorder; RPR, rapid plasma reagins; VDRL, venereal disease research laboratory.

On the following day, she could not remember having experienced memory difficulties and her short-term memory was now back to normal. Further formal neuropsychological testing a week later confirmed normal memory function.

Neuroimaging ultimately revealed an arteriovenous malformation in the left paramedial occipital region fed by the left posterior cerebral artery. There was no suggestion of stroke or hemorrhage. The patient refused any additional interventions but remained free of symptoms.

Transient global amnesia (TGA) is a syndrome characterized by a rapid onset loss of short-term memory, inability to fix new information, repetitive questioning, varying degrees of retrograde memory, and absence of lateralizing neurologic signs [3]. The recovery period, although variable, is usually within 24 hours. It has been described mostly in adults between 60 and 70 years old. It may be associated with migraine, cerebrovascular atherosclerotic disease, intracranial tumor, cardiac arrhythmia, cerebral embolism, and disorders such as diabetes, hyperlipidemia, coronary artery disease, and polycythemia vera. This case is a distinctly unusual etiology but classic presentation, possibly secondary to a steal syndrome – the posterior cerebral artery (main feeder vessel to this arteriovenous malformation) “stealing” from the anterior choroidal artery, the main vascular supply to the hippocampal formation, resulting in transient memory loss.

## Case vignette 2 (modified from [4])

A 27-year-old female drank beer during a dinner with her boyfriend and subsequently joined him in a hot tub. She woke up the following morning recalling nothing about the evening's events including having engaged in sexual intercourse. Past medical history was unremarkable and she was not on any medication. There was no history of substance abuse nor any personal or family history of neurologic disorders such as epilepsy. Examination, EEG, and neuroimaging were normal. There were no recurrences of these symptoms over the following year.

This case of TGA appeared to be precipitated by ingestion of alcohol and hot water immersion. Several cases of TGA under such circumstances have been reported [5]. TGA has also been reported following sexual intercourse [6]. Here, TGA appears to be related to possible transient decreased perfusion in the medial temporal areas.

## **Case vignette 3 (modified from [7])**

This case illustrates how two of the three confusional states mentioned above, delirium and amnesia, may co-exist in the same patient and how history was essential in making the diagnosis.

An 83-year-old female with no prior medical problems endured a tiring airplane journey characterized by prolonged waiting in the airport, flight delays, unscheduled change in planes, and missing lunch. During the flight she experienced nausea and upon disembarking appeared to be disoriented. Relatives greeting her at the baggage claim area found her repetitively asking “Where am I?” and “How did I get here?”

Examination at the hospital she was rushed to revealed an increase in blood pressure to 160/98. There were no focal abnormalities on neurologic examination but mental status testing found her inattentive and restless. Language was intact but she was disoriented to place and to recent circumstances. At times she appeared to hallucinate, attending to objects that were not there. Brain MRI revealed a few subcortical white matter hyperintensities but was otherwise normal. Basic serum including chemistries and hepatic survey was normal. An EEG performed the following day was normal. By that time, she was fully oriented and cognitive function was nearly back to normal.

The following day she seemed entirely normal to physicians and family. The discharge diagnosis was possible transient global amnesia.

At the office follow-up visit 1 week later, she had no recall of the arrival at the airport nor of the initial 18–24 hours of her hospitalization. She did remember, however, trying for the first time a patch of transdermal scopolamine in order to prevent motion sickness.

While this episode suggests the non-focal amnestic syndrome of TGA, a more appropriate label might be “acute confusional state.” Aloof restlessness and hallucinations are not features ordinarily associated with transient global

amnesia [8]. Scopolamine has a well-known potential for producing both hallucinations and amnestic states, particularly in older patients, and could certainly have been a contributory factor in this case. Thus what might have been considered purely an episode of the vascular syndrome of TGA in an 82-year-old (amnesia), could easily be now considered a case of acute and transient toxic-metabolic encephalopathy (delirium), with associated amnesia.

## References

1. *Stedman's Medical Dictionary*, 23rd edn. Baltimore, MD: Williams and Wilkins, 1976.
2. Lahoz CH, Parker SA, Alonzo A. *Clini-Pearls* 1988; 11:3.
3. Fisher CM, Adams RD. Transient global amnesia. *Acta Neurol Scand* 1964; 40 (Suppl. 9):1–18.
4. Weinstein M. *Clini-Pearls* 1985; 8:4.
5. Heathfield KWG, Croft PB, Swash M. The syndrome of transient global amnesia. *Brain* 1973; 96:729–36.
6. Mayeux R. Sexual intercourse and transient global amnesia. *N Engl J Med* 1979; 300:864.
7. Smith DB. *Clini-Pearls* 1986; 9:4.
8. Caplan LR. Transient global amnesia: criteria and classification. *Neurology* 1986; 36:441.
9. Bartynskia WS. Posterior reversible encephalopathy syndrome, Part 1: fundamental imaging and clinical features. *AJNR* 2008;29:1036–42.
10. Paterson R, Takada L, Geschwind M. Diagnosis and treatment of rapidly progressive dementias. *Neurol Clin Pract* 2012; 2:187–200.

## **37 Mental status change, acute [and delirium]**

---

G. Bryan Young, Teneille G. Gofton, and Alan B. Ettinger *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

Delirium is a clinical syndrome that is thought to be the result of a final common pathway of cerebral dysfunction that most commonly occurs in seriously ill patients or in the elderly. Many diagnostic criteria exist, with the two most widely accepted being the *International Classification of Diseases* (ICD–10) from the World Health Organization [1] and the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-IV-TR) from the American Psychiatric Association [2]. Both sets of criteria are very similar and outline that delirium is characterized by an acute change in mental status with disordered thinking and fluctuating levels of attention and arousal with altered cognition (e.g. memory, language, executive function). Patients with delirium display altered behavior, delusions, and hallucinations, changes in affect, alterations in levels of motor activity (psychomotor agitation or retardation) and disturbed sleep–wake cycles. Both criteria require evidence that the patient's state can be attributed to an identifiable source, be it a general medical condition, substance intoxication or withdrawal, or another specific etiology.

### **Clinical presentation**

The presence of delirium has serious implications for patients. There is evidence to support that delirium is associated with decreased independence, increased morbidity and mortality, and increased healthcare costs. Delirium can persist for prolonged periods of time (up to 6 months) in approximately 30% of patients, which is also associated with an increased likelihood of medical complications, re-hospitalization and death [3]. Periods of delirium are associated with post-traumatic stress disorder and cause significant distress for patients and their families [4]. Thus, appropriate detection and management of delirium is

essential.

There are three typical presentations of delirium in which patients demonstrate a hyperactive delirium, a hypoactive delirium, or a mixed delirium. Patients with hyperactive delirium often display periods of psychomotor agitation, hallucinations and delusions, and disorientation. Patients with hypoactive delirium, on the other hand, demonstrate periods of psychomotor retardation, sedation, confusion, and may also have hallucinations or delusions. Patients with a mixed delirium show features of both hyperactive and hypoactive delirium.

## Pathophysiology

Because delirium is a clinical syndrome that can result from multiple etiologies, there is a multitude of potential etiologies (Table 37.1). The leading theories regarding the pathophysiology of delirium include increases in central nervous system (CNS) inflammation, disturbances in the balance of CNS neurotransmitters (acetylcholine, dopamine, serotonin), abnormal hypothalamic–pituitary–adrenal function, and sensitivity of the CNS to systemic inflammatory mediators (IL-8) [5]. Increasing research data support these etiologic theories and a recent meta-analysis of biomarkers in the CNS of delirious individuals shows that disturbances in the levels of cerebrospinal fluid lactate (increased), serotonin (increased), dopamine (increased), acetylcholine (decreased), somatostatin (decreased), beta-endorphin (decreased), cortisol (increased), and proinflammatory chemokines (increased) exist [5]. In any one individual, one or more of these processes may be active necessitating a systematic and thorough approach to patient assessment and management .

**Table 37.1 Pathophysiologic theories for delirium.**

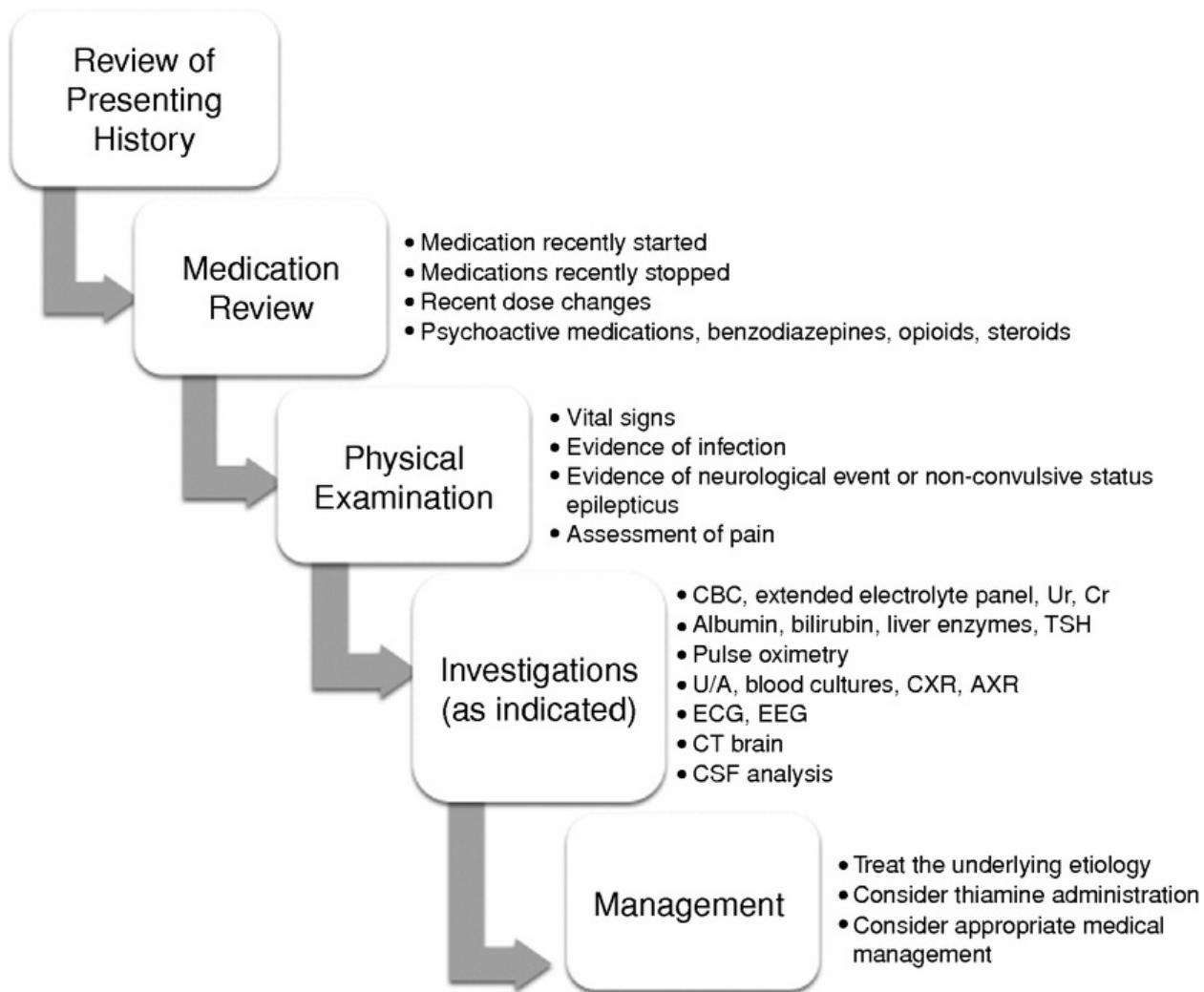
Theory	
Neurotransmitter	Dopamine excess, cholinergic deficit
Inflammatory	Proinflammatory cytokines
Physiologic stress	Hypothalamic–pituitary–adrenal axis dysfunction
Cellular	Abnormal neurotransmitter synthesis and release

## signaling

Oxygen supply	Decreased cerebral oxidative metabolism
Sleep-wake cycle	Abnormal sleep-wake cycle, altered tryptophan metabolism and melatonin levels

## Clinical approach to delirium

Delirium is commonly under-recognized, under-diagnosed, and therefore under-managed. The evidence suggests use of clinical screening tools can improve the detection and identification of delirium, thereby increasing the likelihood of intervention. Many screening tools exist, with some that were designed for screening in very general patient populations and others intended for use in a specific clinical setting such as the intensive care unit (ICU). Some of the most common screening tools include the Delirium Rating Scale-Revised-98, the Confusion Assessment Method, and the Memorial Delirium Assessment Scale [6]. A systematic approach to the evaluation of a patient with delirium is important for identification of the possible etiologies. Please see [Figure 37.1](#) for a detailed approach to the evaluation and investigations pertinent to delirium .



**Figure 37.1** An approach to the history, examination, investigations, and management of patients presenting with delirium. AXR, abdominal X-ray; CBC, complete blood count; Cr, creatinine; CSF, cerebrospinal fluid; CT, computerized tomography; CXR, chest X-ray; ECG, electrocardiogram; EEG, electroencephalogram; TSH, thyroid stimulating hormone; U/A, urinalysis; Ur, urea.

## Differential diagnosis

The differential diagnosis for a patient presenting with delirium is extensive. Selective causes are highlighted in [Table 37.2](#).

**Table 37.2** *The differential diagnosis of delirium. Adapted in part from reference [12].*

Category	Examples	Possible findings to look for
Drugs	Prescribed drugs	Pharmacy history
	Substance abuse	History, evidence of intravenous drug use on exam. Alcohol intoxication may show ataxia, dysarthria, and nystagmus
	Withdrawal	Presentation dependent on agent. Hallucinations, tremulousness, seizures, delirium tremens may occur
Toxins	Lead, arsenic, mercury, carbon monoxide, cyanide, ethylene oxide, manganese	History of work or home circumstances predisposing to exposure
Hypoxemia		Abnormal respiratory or cardiovascular examination
Hypercarbia		Neuromuscular weakness, reduced level of consciousness
Cardiac failure		History of cardiac abnormality, recent myocardial infarction
Electrolyte disturbances	Sodium, calcium, magnesium, phosphate	May be accompanied by generalized weakness Hyponatremia: history of agents that can lower sodium values Hypercalcemia: some

		neoplasms can induce Hypocalcemia: tetany, Chvostek sign, and carpopedal spasm
Endocrine abnormalities	Thyroid	Hypothyroidism: flat affect, depression, psychosis, weight gain, dry skin, hair loss, hung up reflexes Hyperthyroidism: palpitations, anxiety, weight loss, heat intolerance, psychosis, tremor, and hyperreflexia
	Pituitary	Fatigue, weakness, sexual dysfunction, hypotension, abnormal serum hormone levels
	Adrenal	Hyperadrenalinism with moon facies, hypertension, flushing, tremor, anxiety, attacks of hypertension, menstrual irregularities, truncal obesity Hypoadrenalinism: weight loss, fatigue, hypotension, generalized weakness
	Hypoglycemia	History of insulin use or malnutrition. Palpitations, diaphoresis
	Hyperglycemia	History of diabetes mellitus (DM) or classic DM symptoms such as polyuria and polydipsia
Hepatic failure		Jaundice, generalized weakness, nausea, recent gastrointestinal hemorrhage, encephalopathy

		asteregisis, ataxia, history
Renal failure		Myoclonus, fluid overload, hyperventilation, tremors
Bowel obstruction		Nausea, vomiting, reduced flatulence, abdominal pain
Infection	Systemic	Fever, hypotension, leukocytosis
	Central nervous system	Meningismus, fever, leukocytosis, focal neurologic signs, rapid clinical deterioration if bacterial
Nutritional deficiencies	Vitamin B12	Cognitive decline, macrocytic anemia, peripheral neuropathy, subacute combined degeneration with spastic paraparesis and joint position and vibration deficits, ataxic gait. History of malnutrition states or gastric surgery
	Thiamine	Eye movement abnormalities, gait change, Wernicke–Korsakoff syndrome: history of alcoholism, malnutrition states, or prior bariatric surgery. Ophthalmoparesis, ataxia, confusion, and memory loss
Dehydration		Sunken eyes, dry mucous membranes
Uncontrolled pain		Pain behaviors: facial grimacing, guarding of painful area

Constipation		Distended abdomen with or without tenderness
Trauma	Systemic inflammatory response syndrome	Multisystem organ dysfunction following history of trauma
	Traumatic brain injury	Abnormal neurologic examination and neuroimaging. Varieties of types include concussion, contusions, penetrating wounds, blast injuries, direct effects with white matter shearing, tissue destruction, or brain edema. Associated hemorrhage types include intraparenchymal, subdural, epidural, subarachnoid
Epileptic seizures	Ictal or post-ictal states	Non-convulsive status epilepticus (NCSE) is subtle and can be easily missed but picked up on electroencephalography
Cerebrovascular event	Stroke	Sudden onset focal neurologic change, differentiated by neuroimaging
	Intracranial hemorrhage	Sudden onset focal neurologic change, differentiated by neuroimaging
Neoplasms	Leptomeningeal metastases; carcinomatous meningitis	History of neoplasms notorious for metastases to brain

	Gliomatosis, invasive spread within parenchyma	History of primary tumors
	Paraneoplastic syndromes; limbic encephalitides	Wide variety of types and accompanying signs
Hypertensive encephalopathy		Severe acute exacerbation of blood pressure, vomiting, visual alterations and retinal arteriolar spasm, seizures, papilledema, retinal hemorrhages
Psychiatric disorders	Disorders associated with psychosis	Exacerbation of symptoms of disorders such as schizophrenia, bipolar disorder, major depressive disorder, catatonic states
“Pressure effects”		<i>E.g.</i> cerebral edema, hydrocephalus or early herniation
Dementing illnesses	Acute decline on top of chronic illness	<i>E.g.</i> history of Alzheimer's disease
Sensory deprivation states	Intensive care unit (ICU) psychosis	Also known as “sundowning.” Deprivation of sunlight or normal daylight cycles, sleep deprivation, continuous noises, loss of orienting stimuli

---

Drug intoxications and withdrawal syndromes vary according to the specific type of agent. Opiate intoxication is classically associated with pinpoint pupils that still react to light and respond to naloxone in contrast to lack of response with pontine hemorrhage. Anticholinergic agents may produce agitation, altered vision, papillary dilatation, flushing, and fever. Sympathomimetics like cocaine may induce hallucinations and psychosis. Among the hallucinogens, phencyclidine (PCP) may elicit paranoid behavior and hallucinations.

Among iatrogenic medication causes are cyclosporine and tacrolimus, used as immunosuppressive agents in organ transplant patients. Corticosteroids can cause mood changes or psychosis. Altered mentation associated with psychotropic agents includes neuroleptic malignant syndrome (several days of muscle rigidity, autonomic dysfunction, and fluctuating level of consciousness after exposure to dopamine antagonists) and serotonin syndrome (a few hours of myoclonus, rigidity, hyperreflexia, fever, and agitation).

Among the endocrine causes for mental status change, Hashimoto's encephalopathy is not uncommonly overlooked. Other potential endocrine abnormalities are listed [Table 37.1](#). Severe mental status aberrations have been seen with acute intermittent porphyria which may also have features of neuropathy and abdominal pain.

The features of the wide variety of infectious agents is beyond the scope of this chapter. However, it is useful to consider the wide variety of possible localizations for infection states to alter mental status. These include the meninges, intraparenchymal effects (encephalitis), local sinuses, infections of the bone, and infections outside the immediate vicinity of the CNS. A wide variety of agents should also be considered including viruses, bacteria, parasites and protozoa, mycobacteria, fungi, spirochetes, amoebae, and prions.

Post-infectious (e.g. Reye's syndrome) and other inflammatory non-infectious states such as NMDA-antibody receptor encephalitis and paraneoplastic or limbic encephalitis should also be in the differential diagnosis.

Cerebrovascular events of diverse types may cause mental status changes. Categories and specific etiologies to consider include ischemic stroke, hemorrhage (intraparenchymal, subarachnoid, subdural, epidural), thrombosis from the arterial or venous side, vascular spasm, hematologic causes, inflammatory etiologies such as vasculitis (systemic lupus erythematosus, primary angiitis of the CNS, primary and secondary vasculitis syndromes), and embolic causes. Non-dominant hemisphere strokes can sometimes confuse the

clinician if there is no associated hemiparesis. Top of the basilar syndrome can produce a behavioral syndrome such as peduncular hallucinosis in addition to other signs such as papillary, visual, and ocular movement abnormalities.

## Management of delirium

The management of delirium begins with treatment of the underlying etiology. Nonpharmacologic as well as pharmacologic treatment modalities have been shown to be effective. Nonpharmacologic interventions including frequent re-orientation, clocks, calendars, windows in the room, a quiet nocturnal environment, and maximizing hearing and vision are known to be effective. More recent research suggests that cognitive stimulation for 30 minutes per day may improve cognitive outcomes in patients with delirium [7].

When considering pharmacologic interventions, one must weigh the risks with the benefits of interventions. The main reasons to use medications in the management of delirium are to reduce potential harmful behaviors, to relieve symptoms, such as hallucinations, that are distressing to the patient and family, and to improve outcome by minimizing the duration of delirium. Administration of thiamine should always be considered in case of thiamine deficiency since it has almost no potential harmful effects with great potential benefits [8].

Low-dose regularly administered antipsychotic medications are recommended (starting dose of haloperidol 0.5–1.0 mg intravenous q12h and 0.5–2 mg q2–4h prn) [9]. The advantages of haloperidol include the possibility of intravenous administration and a relatively low anticholinergic side effect profile. However, there is little evidence for the use of antipsychotic medications and there is the potential for significant side effects including dystonic reactions, parkinsonism, and prolongation of the QT interval [9]. Intravenous haloperidol is associated with QT prolongation ( $> 450$  ms) and a subsequent risk of arrhythmia (ventricular fibrillation, torsades de pointes). More recent evidence is emerging supporting the use of atypical antipsychotics in delirium (olanzapine, quetiapine, risperidone). In general, antipsychotics should be avoided in patients with comorbidities such as Parkinson's disease and Lewy body dementia. Benzodiazepines are not helpful when used in isolation [10], but may be required in combination with antipsychotic medications in order to manage behavior.

Based on the fact that imbalances in cerebral cholinergic systems are thought to play a role in the genesis of delirium, research is ongoing to investigate the

effectiveness of cholinesterase inhibitors in the management of delirium. Prospective uncontrolled studies have been completed, but further randomized controlled trials are needed.

In the ICU, delirium is very common. It may impair weaning from the ventilator and extubation, thereby complicating patient management. There is growing evidence that alpha-2-receptor antagonists may be effective in the management of ICU-related delirium. Data support the use of dexmedetomidine to improve sleep cycles, to reduce the length of stay in an ICU, and to reduce delirium [11]. Bradycardia and unexpected death have been associated with high doses of dexmedetomidine only.

Delirium occurring in the last week of life is called terminal delirium. The medications most commonly used in this setting are haloperidol, chlorpromazine, and benzodiazepines. The latter two are used preferentially when the presence of sedation as a side effect is acceptable or even advantageous .

## Case vignette

Ten days after an uncomplicated right inguinal hernia repair, a 79-year-old male was brought in to the emergency department via ambulance after being found unconscious on the floor at home. Upon examination, he was unrousable, he did not obey commands, and he was hypotensive and hypothermic at 30 °C. There were pressure sores on the patient's face and anterior aspect of the torso. The patient's initial management required full support in the ICU including mechanical ventilation for acute respiratory distress syndrome, vasopressor support for hypotension, and broad spectrum antibiotics for sepsis. Investigations revealed a normal cerebrospinal fluid analysis, a normal CT scan and MRI of the brain, and an enterococcal bacteremia. An initial electroencephalogram (EEG) demonstrated multifocal epileptiform spikes without evidence of seizure. Despite appropriate medical management, the patient remained comatose without spontaneous movements for 2 weeks.

The patient responded well to antibiotics and a repeat EEG showed cessation of all epileptiform activity with improvement of background rhythms. All electrolyte and blood count abnormalities responded well to treatment. Late in the second week of admission the patient developed facial grimacing to painful stimulation without any limb movement. Further investigation showed evidence of critical illness neuromyopathy, which accounted for the return of facial

grimacing without limb movement to painful stimulus. Over the third week of admission the patient began to have spontaneous eye opening and some small spontaneous movements of the extremities, which was followed by return of awareness and comprehensible verbal output. He remained confused for several days after which he regained full awareness and decision-making capacity. The patient's reduced level of consciousness and slow emergence from coma is an example of a severe multifactorial delirium, principally secondary to severe sepsis. Resolution of the systemic disturbances resulted in resolution of the disturbances in awareness and consciousness.

## Conclusion

In conclusion, delirium is a complex and heterogeneous clinical syndrome for which a high degree of suspicion is necessary. Clinical screening tools may help the clinician to detect and diagnose delirium in patients with variable presentations. The detection of delirium is important in order to minimize potential deleterious outcomes and to manage potentially reversible etiologies. A complete history, medication review, physical examination, and investigations should be performed in order to formulate an effective and targeted management plan.

## References

1. World Health Organization. International Criteria for Diagnosis Version 10. 2011. Cited from: <http://apps.who.int/classifications/icd10/browse/2010/en%23;/F05> on December 18, 2011.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revision)* (DSM-IV-TR). Washington, DC: American Psychiatric Association, 2000.
3. Stagno D, Gibson C, Breitbart W. The delirium subtypes: a review of prevalence, phenomenology, pathophysiology, and treatment response. *Palliat Support Care* 2004; 2:171–9.
4. Breitbart W, Gibson C, Tremblay A. The delirium experience: delirium recall and delirium-related distress in hospitalized patients with cancer, their spouses/caregivers, and their nurses. *Psychosomatics* 2002; 43:183–94.

5. Hall RJ, Shenkin SD, MacLullich AM. A systematic literature review of cerebrospinal fluid biomarkers in delirium. *Dement Geriatr Cogn Disord* 2011; 32:79–93.
6. Adamis D, Sharma N, Whelan PJ, Macdonald AJ. Delirium scales: a review of current evidence. *Aging Mental Health* 2010; 14:543–55.
7. Kolanowski AM, Fick DM, Clare L *et al.* Pilot study of a nonpharmacological intervention for delirium superimposed on dementia. *Res Geront Nurs* 2011; 4:161–7.
8. Sechi G, Serra A. Wernicke's encephalopathy: new clinical settings and recent advances in diagnosis and management. *Lancet Neurol* 2007; 6:442–55.
9. Lonergan E, Britton AM, Luxenberg J, Wyller T. Antipsychotics for delirium. *Cochrane Database Syst Rev* 2007; 2:CD005594.
10. Lonergan E, Luxenberg J, Areosa Sastre A, Wyller TB. Benzodiazepines for delirium. *Cochrane Database Syst Rev* 2009; 1:CD006379.
11. Pandharipande PP, Pun BT, Herr DL *et al.* Effect of sedation with dexmedetomidine vs lorazepam on acute brain dysfunction in mechanically ventilated patients: the MENDS randomized controlled trial. *JAMA* 2007; 298:2644–53.
12. Greenberg D, Aminoff, Simon R, Eds. Confusional states. In *Clinical Neurology*, 8th Edn. New York, NY: McGraw Hill Publishing, 2012: 65–103.

## **38 Movement disorders in psychiatric disorders**

---

Gregory M. Pontone *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

The diagnosis of movement disorders in patients with psychiatric disorders is a common challenge for neurologists and psychiatrists. Traditionally, a common dilemma has been distinguishing between “organic” and “psychogenic” explanations when no clear anatomical cause can be identified. Today, the separation of neurologic symptoms into organic versus psychogenic categories is being challenged as many psychiatric disorders are now recognized to have a neuroanatomical basis. Even for disorders classically considered to be psychogenic there is evidence for shared brain circuitry involving sensory-motor areas, affective centers, and brain regions involved in the volitional control of movement [1]. In the future, advances in the understanding of the pathophysiologic basis of these disorders will help reconcile the broader issue of mind-brain dualism and facilitate a unified approach to treatment. The goal of this chapter is to help the clinician generate a differential diagnosis for movement disorders while considering presentations that may be specific to patients with psychiatric comorbidity.

Psychiatric disorders are common in patients with neurologic disorders, occurring in 34% of neurology inpatients and up to 40% of outpatients [2]. Movement disorders associated with psychiatric conditions can be thought of as occurring in three broad categories: (1) as a direct result of the psychiatric condition, *e.g.* conversion disorder, (2) a treatment side effect, *e.g.* drug-induced parkinsonism, or (3) “functional overlay” when psychological factors exacerbate “organic” conditions. Currently, there are no studies that estimate the collective prevalence of all movement disorders associated with psychiatric causes or treatment. However, psychogenic movement disorders represent 2–3% of new admissions to movement disorder clinics and up to 20% of patients in some specialty clinics [3,4].

What is the most common movement disorder in adults with psychiatric disorders? It is the same as in the general population, essential tremor. Although certain psychiatric disorders and psychiatric medications have unique associations with movement abnormalities, it is important to keep in mind the base rate of movement disorders to avoid committing an error in estimating their conditional probability in patients with psychiatric disorders.

## Case vignette

A 64-year-old, right-handed female complains of bilateral hand tremors for the past 3 weeks. She has been treated with sertraline 150 mg daily and risperidone 2 mg at bedtime for the past year for major depression with psychotic features. Her psychiatrist increased risperidone to 4 mg at bedtime 2 months ago after she began hearing her dead husband's voice calling to her at night. She has a history of hypertension, hypothyroidism, and cataracts. Her medications include metoprolol, levothyroxine, calcium and vitamin D supplements, and a multivitamin.

Neurologic examination reveals masked facies, a mildly kyphotic posture, decreased stride length, right greater than left resting and postural tremor, cogwheel rigidity in her upper extremities bilaterally and neck, decreased amplitude and speed of finger tapping bilaterally, and a general slowing of movement. No gaze palsy, and postural reflexes were intact. She was noted to have a constant "chewing motion" throughout the interview that she briefly suppressed when it was pointed out to her. Vital signs were sitting 135/80 P63 and 130/80 P 65 standing.

**Table 38.1 Common movement disorders in patients with psychiatric disorders [5–10].**

Movement disorder or symptom	Definition	Etiology in psychiatric disorders	Possible clinical features
Akathisia	Subjective complaints of inner tension, restlessness, anxiety, and	Most often, dopamine receptor antagonists, <i>e.g.</i>	Observable motor features are complex, semi-purposeful, and repetitive <i>e.g.</i>

	<b>anxiety, and the urge to move</b>	<b>e.g. antipsychotics; less often, antidepressants and lithium</b>	<b>repetitive, e.g. foot shuffling or tapping, shifting of weight, rocking, pacing</b>
Akinesia	Absence of physical movement	Typically seen in catatonia and may also be an adverse extrapyramidal effect of antipsychotic medications	Inability to initiate movement
Astasia abasia	Inability to walk or stand in a normal manner	Psychogenic gait disorder; seen in conversion disorder	Normal leg movements can be performed in a sitting or lying down position Gait is bizarre and does not suggest a specific organic lesion
Catalepsy	Immobile position that is constantly maintained	Typically a symptom of catatonia	Maintaining a position of the body or body part for an exaggerated amount of time; standing or lying down in the same position, holding fingers and hands in odd positions
Cataplexy	Temporary loss of muscle	Symptom of narcolepsy	Most episodes are triggered by

	tone precipitated by a variety of emotional states	thought to be related to inappropriate activation of the pathways that cause paralysis in REM sleep	strong emotions such as laughter, excitement, anger, or grief Weakness is often partial and lasts less than 2 minutes with consciousness intact
Catatonia	Behavioral syndrome in which patients are unable to move normally despite full physical capacity in the limbs and trunk	Unknown, occurs in association with schizophrenia, mood disorders, general medical conditions and antipsychotic medication use, thought to involve pathways that connect the basal ganglia with the cortex and thalamus	Common symptoms include: immobility, mutism, stupor, negativism, cerea flexibilitas, catalepsy, excessive motor activity (excitement), staring, echopraxia Symptom onset can be acute or insidious and typically occurs in patients who are severely psychiatrically ill Acute catatonia develops within hours to days after antipsychotic drug exposure “Lorazepam challenge” –

temporary relief  
of symptoms  
after treatment  
with  
benzodiazepines  
supports the  
diagnosis

Cerebral flexibilitas	“Waxy flexibility”	Symptom of catatonia	Condition in which a person can be molded into a position that is then maintained
Dyskinesia, tardive	Involuntary, non-rhythmic, repetitive, hyperkinetic movements	Associated with prolonged exposure to antipsychotic medications <i>e.g.</i> dopamine receptor blocking agents	Most often affects the orofacial and lingual musculature, <i>e.g.</i> lip smacking, chewing, protrusion, curling, or twisting of the tongue, puckering, bulging of the cheeks Choreoathetoid movements of the fingers, hands, and upper and lower extremities are also common Dyskinesias increase with emotional arousal, activation or

~~deactivation, or~~  
distraction, and  
diminish with  
sleep, relaxation,

or volitional  
effort  
Onset is typically  
after > 3 months  
of exposure and  
can be masked by  
ongoing  
antipsychotic  
treatment, re-  
emerging when  
the antipsychotic  
is reduced,  
stopped, or  
switched

Dystonia (acute)	A syndrome of sustained muscle contractions, frequently causing twisting and repetitive movements, or abnormal postures	Secondary to antipsychotic drug treatment (via dopamine blockade)	Drug-induced dystonia is typified by recent antipsychotic treatment, negative family history, focal and non-progressive course, and absence of associated neurologic signs Examples include spasmodic torticollis, grimacing, blepharospasm, oculogyric crisis, tongue protrusion or twisting,
---------------------	---	---	---

			laryngospasm, and forced jaw opening In 95% of cases, dystonia appears within 5 days of starting or increasing dose and usually resolves 24–48 h after drug discontinuation
Echopraxia	Pathologic imitation of movements of one person by another	Symptom of catatonia, sometimes seen in autism, Tourette syndrome, or schizophrenia	Movements are copied from an individual the patient is currently observing
Negativism	Motiveless resistance to all attempts to be moved or to all instructions	Symptom of catatonia	The patient resists the examiner's manipulations with strength equal to that applied, producing rigidity
Neuroleptic malignant syndrome	Life-threatening syndrome characterized by severe muscular rigidity, fever, autonomic and mental	Treatment with antipsychotic (dopamine blocking) drugs	Mental status change is first symptom in 82% of patients Two thirds of cases occur within the first 1–2 weeks after drug initiation

	status changes		
Parkinsonism, drug induced	Subacute syndrome that mimics Parkinson's disease with symptoms of bradykinesia, rest or postural tremor, rigidity	Dopamine receptor blockade in the corpus striatum, usually due to antipsychotic drug treatment	Higher doses and rapid dose escalation are risk factors Can also occur with rapid withdrawal of dopaminergic drugs (e.g. l-dopa used for Parkinson's disease) Supporting, but non-specific labs: elevated serum CK, leukocytosis, elevated LFTs, hypocalcemia, hypomagnesemia, hyperkalemia, and metabolic acidosis Myoglobinuric acute renal failure from rhabdomyolysis is possible
			Subacute bilateral onset Early presence of postural tremor Concurrent oral-- buccal dyskinesias Usually not l- dopa responsive Most cases are reversible in days <small>to weeks if drugs</small>

to weeds it may  
are stopped  
Also associated  
with lithium,  
depakote,  
tetrabenazine,  
and rarely, certain  
antidepressants

Psychogenic movement disorders	Movement disorders that cannot be attributed to any known structural or neurochemical disease, but result from an underlying psychiatric illness	Most meet criteria for a somatoform disorder, with conversion disorder being the most common	Abrupt onset and maximum disability early Convergence spasm Disability out of proportion to physical exam findings Effort testing, <i>e.g.</i> abduction test, contraction of antagonist, Hoover's sign Entrainment, <i>e.g.</i> tremor takes on the frequency of voluntary tapping Exaggerated slowness Give way weakness Movements disappear with distraction, are inconsistent over time, or precipitated by suggestion Non-neurologically
--------------------------------	--	--	---

based patterns of sensory loss  
Paralysis without

atrophy  
Self-inflicted injuries  
Spontaneous remissions  
Sudden knee buckling without falling

Punding	Constellation of complex stereotyped behaviors	Symptom of stimulant intoxication (e.g. amphetamine, cocaine) or in some cases of treatment with L-dopa and other dopaminergic drugs, certain forms seen in delirium	Intense fascination with repetitive manipulations of technical equipment, continual handling, examining, and sorting of common objects, excessive grooming, fidgeting, or picking at clothes or oneself (floccillation)
Serotonin syndrome	Potentially life-threatening adverse drug reaction resulting from excess serotonergic	Inadvertent interaction between drugs, intentional overdose, therapeutic drug use	Triad of autonomic hyperactivity, mental status change, and neuromuscular symptoms 60% of cases

	agonism	present within 6 hours of a change in dosing, initial use of medication, or an overdose Typical progression of symptoms as serotonin builds up: akathisia, tremor, altered mental status, clonus/increased reflexes, muscular rigidity, hyperthermia Other features may include: diarrhea, diaphoresis, sialorrhea, hyperactive active bowel sounds, myoclonus, mydriasis, and tachycardia
Tics	Sudden, rapid, recurrent, non-rhythmic motor movements or sounds	Typically a symptom of Tourette syndrome thought to be due to an alteration in frontal--limbic--subcortical circuits Simple motor tics involve one group of muscles, causing brief, abrupt movements, <i>e.g.</i> blinking, head jerking, blepharospasm, shoulder rotation

Complex motor tics are coordinated sequenced movements resembling normal motor acts that are inappropriately intense and timed, *e.g.* repetitive touching, hitting, or trunk bending, repetitive retching or air swallowing

Phonic tics can be simple, *e.g.* sniffing, throat-clearing, grunting, coughing, or blowing, or complex which include linguistically meaningful utterances *e.g.* shouting profanities (coprolalia), repeating after others (echolalia), repeating one's own utterances (palilalia)

Both motor and phonic tics are

often preceded by localizable sensations or discomforts in the region of the tic. The presence of these “premonitory sensations” can be helpful in differentiating tics from other hyperkinetic movement disorders.

Tremor	Unintentional, rhythmic, muscle movement involving oscillations of one or more parts of the body	In psychiatry, typically drug induced by the following agents: antidepressants, antipsychotics, lamotrigine, lithium, valproic acid	Temporal association with initiation or increase of drug, usually bilateral Typically improve with reduction of drug Action tremor: any tremor produced by voluntary contraction of muscle (1) kinetic – during any voluntary movement, (2) postural – when a particular posture is held against gravity Rest tremor: occurs in a body
--------	--	--	---

part that is not voluntarily activated and is completely supported against gravity

---

Drug-induced parkinsonism (DIP) is the second most common cause of parkinsonism after idiopathic Parkinson's disease (PD). In the vignette above there are several clues that can help make the correct diagnosis. From an epidemiologic stand point, PD occurs with an almost 2 : 1 male to female ratio, while DIP is 2 : 1 female to male. While the elderly are at greater risk for DIP, the vignette age of 64 does not help distinguish the conditions as the average age of PD onset is 62. High doses of antipsychotics are a risk factor for DIP; 4 mg of risperidone in an elderly patient is quite high. Bilateral tremor and rigidity would be most consistent with Hoehn and Yahr stage 2 if this was idiopathic PD, however progression to stage 2 in 3 weeks is highly unlikely. Resting tremor is the most common tremor in PD with postural tremor being rare early in the disease. Postural tremor is the most common drug-induced tremor [5]. The "chewing motion" described is most likely tardive dyskinesia, which is frequently associated with antipsychotic use and not a typical feature of untreated PD. The absence of gaze palsy and autonomic instability (e.g. no orthostatic blood pressure) and intact postural reflexes reduce the likelihood of PD-plus syndromes that sometimes have a bilateral onset (e.g. progressive supranuclear palsy and multisystem atrophy). Hypothyroidism can present with tremor, so checking thyroid-stimulating hormone levels is advised. Drug-induced parkinsonism typically resolves within weeks of stopping the offending agent. However, in about 15% of cases parkinsonism can persist, raising the possibility that subclinical PD was unmasked by dopamine blockade .

## References

1. Ellenstein A, Kranick SM, Hallett M. An update on psychogenic movement disorders. *Curr Neurol Neurosci Rep* 2011; 11:396–403.
2. Nicholson TR, Stone J, Kanaan RA. Conversion disorder: a problematic diagnosis. *J Neurol Neurosurg Psychiatry* 2011; 82:1267–73.

3. Hallett M, Weiner WJ, Kompoliti K. Psychogenic movement disorders. *Parkinsonism Relat Disord* 2012;18(Suppl 1):S155–7.
4. Krem MM. Motor conversion disorders reviewed from a neuropsychiatric perspective. *J Clin Psychiatry* 2004; 65:783–90.
5. Arbaizar B, Gomez-Acebo I, Llorca J. Postural induced-tremor in psychiatry. *Psychiatry Clin Neurosci* 2008; 62:638–45.
6. Caroff SN, Hurford I, Lybrand J, Campbell EC. Movement disorders induced by antipsychotic drugs: implications of the CATIE schizophrenia trial. *Neurol Clin* 2011; 29:127–48, viii.
7. Daniels J. Catatonia: clinical aspects and neurobiological correlates. *J Neuropsychiatry Clin Neurosci* 2009; 21:371–80.
8. Jankovic J, Kurlan R. Tourette syndrome: evolving concepts. *Mov Disord* 2011; 26:1149–56.
9. O'Sullivan SS, Evans AH, Lees AJ. Punding in Parkinson's disease. *Pract Neurol* 2007; 7:397–9.
10. Boyer EW, Shannon M. The serotonin syndrome. *N Engl J Med* 2005; 35:1112–20.

## **39 Movements, facial**

---

Kevin M. Biglan and Annie Killoran *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

There are a variety of abnormal movements that may occur in the face, either in isolation or as a component of a more generalized condition, as in choreiform disorders. The standard approach to such abnormalities is to first identify the movement's phenomenology, being mindful of potentially misleading clinical mimics. Secondly, one considers the movement's distribution and associated features, such as the presence of sensory tricks in dystonia, or premonitions in Tourette syndrome. Finally, in seeking to identify the movement's underlying etiology, it is crucial to ascertain the family history and exposure to medications, particularly the dopamine receptor antagonists.

### **Case vignette**

A 54-year-old female presents with a 3-year history of worsening ocular irritation and excessive involuntary blinking that interferes with her vision, particularly when driving in bright sunlight. Over the past 2 years, a tightening sensation in her lower face has progressed to activity-related difficulty in closing her mouth, and involuntary posturing including forced jaw opening, tongue protrusion, lip retraction, and platysma contraction. This improves when cupping her chin in her hand, but still interferes with speech and eating. Self-conscious, she has become socially isolated and depressed. She is otherwise healthy with no history of exposure to neuroleptics. Her examination is significant for mild dysarthria, prominent irregular brief symmetric contractions of the orbicularis oculi, and action-induced dystonic contractions of the oromandibular muscles with jaw opening. The patient is able to voluntarily close her mouth after an effortful step-wise chin retraction and neck flexion.

Diagnostically, her condition is incompatible with hemifacial spasm (see

[Chapter 69](#)), which would only involve unilateral CN VII innervated musculature. Her excessive blinking is neither suppressible nor associated with an urge or premonition, thus excluding tics. With no difficulty in eye opening to suggest eyelid apraxia, blepharospasm is most likely. The oromandibular posturing and her sensory trick typify dystonia, which in association with blepharospasm constitutes Meige's syndrome. This is likely idiopathic as there is no history of neuroleptic exposure or any suggestion of an underlying neurodegenerative disorder.

**Table 39.1 Differential diagnosis of abnormal facial movement.**

	<b>Phenomenology</b>	<b>Distribution</b>	<b>Common associations</b>	<b>Etiology</b>
Facial tics	Abrupt brief rapid stereotypical non-rhythmic simple jerks or complex movements	Often many sites involved e.g. eyelids, brows, nares, mouth, jaw, etc. ± other body parts	Premonition or urge to tic Partially suppressible ADHD, OCD	Isolated Tourette Mostly Second infectio medical
HFS	Intermittent stereotypical synchronous unilateral spasms. Persists in sleep	Periorbital twitching Spread to other ipsilateral CN VII muscles	Tinnitus, hearing loss Facial weakness if long duration	Mostly due to (compre Second brainste
BSP	Intermittent symmetric synchronous involuntary spasms	Bilateral orbicularis oculi ± frontalis, procerus, corrugators	Mildly increased blink rate, ocular irritation, photophobia	Mostly 'benign As part MSA Medica

### VIII OMD III

#### Meige syndrome

OGC	Episodic tonic muscle contraction	Bilateral superior rectus (for upward eye deviation), lids, posterior neck, back, jaw extensors	Tongue protrusion, opisthotonus Ocular pain, anxiety Dysautonomia	Medication induced Postencephalitis parkinsonism
OMD	Involuntary sustained stereotypic action-related contractions with abnormal postures	Buccal--lingual--masticatory area: nares, lips, tongue, jaw	Sensory--tricks Segmental dystonia TMJ disorders Medication-induced: opisthotonus With BSP in Meige syndrome	Mostly Medication induced heredofamilial
OFD	Irregular continuous asynchronous action-suppressed choreic-like movements	Oro--buccal--lingual, masticatory muscles	Piano-playing finger movements, akathisia, parkinsonism, tics, myoclonus	Medication induced Heredofamilial (e.g. Huntington's disease)
HMS	Painful brief involuntary paroxysmal jaw-closing muscle spasms	Masseter, temporalis, medial pterygoids	Bruxism, tongue/lip biting Facial hemiatrophy	Mostly

Jaw tremor	PD: involuntary rhythmic 4–6 Hz rest tremor ET: 5–8 Hz kinetic tremor	PD: mandible ± lips, tongue Extremities ET: mandible; more often in head, voice. Arms	PD: asymmetric rigidity + bradykinesia ET: long duration, family history	More likely (not in PSP) In elderly advance
PT	Continuous symmetric ~ 2 Hz semi-rhythmic contractions	Soft palate ± other orolingual mandibular muscles	Essential PT: “ear clicking” Symptomatic PT: ataxia, dysarthria, nystagmus	Mostly symptomatic brainstem cerebellar Primary
EPC	Persistent low-amplitude irregular variable clonic contractions ~ 2–3 Hz Persists in sleep	Typically restricted e.g. eyelid or corner of mouth	Synchronous myoclonic contractions in distal limb flexors Other seizure types Interictal weakness	Structural vascular neoplasms metabolic Rasmussen encephalitis children
Psychogenic	Non-patterned inconsistent incongruous variety of movements	Varies in the individual	Somatizations	Conversion disorder

ADHD, attention deficit hyperactivity disorder; BSP, blepharospasm; CN VII, seventh cranial nerve; EPC, epilepsia partialis continua; ET, essential tremor; HFS, hemifacial spasm; HMS, hemimasticatory spasm; Hz, hertz; MSA, multiple system atrophy; OCD, obsessive-compulsive

disorder; OFD, orofacial dyskinesia; OGC, oculogyric crisis; OMD, oromandibular dystonia; PD, Parkinson's disease; PKAN, pantothenate kinase-associated neurodegeneration; PSP, progressive supranuclear palsy; PT, palatal tremor; SCA, spinocerebellar ataxia; TMJ, temporomandibular joint.

## Further reading list

- Bien CG, Elger CE. Epilepsia partialis continua: semiology and differential diagnoses. *Epileptic Disord* 2008; 10:3–7.
- Fabbrini G, Defazio G, Colosimo C, Thompson PD, Berardelli A. Cranial movement disorders: clinical features, pathophysiology, differential diagnosis and treatment. *Nat Clin Pract Neurol* 2009; 5:93–105.
- LeDoux MS. Meige syndrome: what's in a name? *Parkinsonism Relat Disord* 2009; 15:483–9.
- Louis ED, Rios E, Applegate LM, Hernandez NC, Andrews HF. Jaw tremor: prevalence and clinical correlates in three essential tremor case samples. *Mov Disord* 2006; 21:1872–8.
- Ross AH, Elston JS, Marion MH, Malhotra R. Review and update of involuntary facial movement disorders presenting in the ophthalmological setting. *Surv Ophthalmol* 2011; 56:54–67.
- Silverdale MA, Schneider SA, Bhatia KP, Lang AE. The spectrum of orolingual tremor – a proposed classification system. *Mov Disord* 2008; 23:159–67.
- Yaltho TC, Jankovic J. The many faces of hemifacial spasm: differential diagnosis of unilateral facial spasms. *Mov Disord* 2011; 26:1582–92.

## **40 Movements, focal, clonic**

---

Daniel J. Luciano and Siddhartha Nadkarni *Neurologic Differential Diagnosis*,  
ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge  
University Press. © Cambridge University Press 2014.

### **Introduction**

Clonic motor activity is seen as an expression of epileptic activation of a restricted area of motor cortex and is repetitive and rhythmic in nature. Clonic motor activity represents simple partial motor seizures. The clonic jerks are brief and recur at a frequencies of 1–5 Hz, usually gradually slowing as the seizure terminates. The majority begin in the face or hand given their large representation in the homunculus. The corner of the mouth, thumb, or index finger are particularly involved. It is common to see spread of such activity to neighboring muscle groups, representing “Jacksonian march,” and when this occurs the homunculus is followed (e.g. spread from face to the thumb). It is important to realize that the ictal electroencephalogram (EEG) is normal in the majority of simple partial motor seizures because electrodes on the scalp are actually not very close to the vicinity of the emanation of discharges. Most disorders confused with clonic seizures represent movement disorders. Movements in such disorders are generally less regular and rhythmic, do not demonstrate a march, are often precipitated or abated by movement, and generally abate during sleep when, in contrast, seizures by contrast tend to become more prominent.

### **Case vignette**

A 27-year-old female presents with a 4-day history of twitching of her left eyelid. Twitching is almost continuous and nothing alleviates it except sleep. On examination there is a repetitive rippling movement of her left lower eyelid that does not change with stimulation and cannot be controlled by her. There is no excess blinking or involvement of the rest of the face. The remainder of her mental status and segmental neurologic examination are normal. Prolonged EEG

and magnetic resonance imaging (MRI) of her brain and brainstem are normal, as are somatosensory, brainstem, and visual evoked potentials. The symptom resolves after another 5 days.

The twitching noted by the patient involves only the eyelid without other facial involvement, as might be expected if there were Jacksonian spread of a simple partial motor seizure. There is resolution of twitching in sleep, rather than persistence or worsening, which would be expected in many movement disorders as opposed to partial seizures. Hemifacial spasm, however, would persist in sleep and would also involve other facial musculature. The clinical appearance of rippling movements along with these other considerations suggest that the patient suffered a bout of benign myokymia.

**Table 40.1** *Differential diagnosis of clonic activity.*

Item	Subdivision	Specific entity	Possible clinical features
Structural (congenital or acquired)		Spinal myoclonus	In spinal injury. Symmetric, continuous, rhythmic myoclonic activity. Persists in sleep. May be stimulus sensitive which helps establish diagnosis
		Palatal myoclonus	Continuous rhythmic jerking of palate and other cranial nerve muscles, rarely trunk or limbs. Clicking noise associated. Unaffected by

		action or sleep. Brainstem or cerebellar disease
Toxic. Med/drugs, toxic substances, withdrawal states	Tics, chorea, myoclonus (see below)	A multitude of drugs may cause various abnormal movements, including stimulants, anti- Parkinson's agents, and antiepileptics. Check medications administered
Psychiatric	Psychogenic non-epileptic seizure	Clonic activity often waxing/waning or intermittent, of fixed frequency. Flexion/extension phases of equal duration, like tremor. May abate with distraction
Degenerative	Startle myoclonus	Associated with CJD. Triggered by startle. May send protein 14– 3–3 in CSF (non- specific, but confirmatory in the right clinical setting)
Vascular	“Limb- ...	Brief coarse ...

	shaking” transient ischemic attack	trembling of arm, sometimes leg. No rhythmic clonic activity or version of head. Occurs contralateral to severe carotid disease upon standing with hypoperfusion. Resolve on sitting/lying down
Movement disorder	Paroxysmal kinesogenic choreoathetosis	Unilateral choreoathetotic (see below) rather than clonic activity. Triggered by sudden movement. Onset under age 20. Episodes less than 1 minute
	Chorea/ Choreoathetosis	Brief, semi- directed, irregular non-repetitive and non-rhythmic, sometimes flailing movements that can appear “dance-like” and appear to flow from one muscle to the next. With athetosis, <del>extending/contracting</del>

twisting/writhing movements are added

Hemiballismus      Unilateral repetitive proximal violent flinging movements of arm. More constant than seizures, which also have more distal/cortical representation. Disappear in sleep. Lesion of contralateral subthalamic nucleus. Check for history of vascular disease

Tremor      Alternating agonist/antagonist activation. Involves hands primarily. More rapid and persistent than seizure. Associated with rest (Parkinson's) or activity (benign essential tremor, cerebellar disease). Not present in sleep. Worsened by stress caffeine

Causes, current.  
Check for family history of tremor, signs of Parkinsonism, cerebellar signs. May be related to medications (stimulants, SSRI), alcohol/drug withdrawal, hypoglycemia, hyperthyroidism

Tics  
Brief repetitive involuntary movements of face or neck, can be clonic or dystonic. Can often be consciously suppressed temporarily. Often initial irresistible urge. Worsen with stress and disappear in sleep. Check for family history of tics

Tourette syndrome  
Tics with associated coprolalia, OCD

Blepharospasm  
Initially compulsory eye-

blinking and irritation around eye. Progresses to clonic and later tonic contraction of orbicularis oculi with forced eye closure. 20% start unilateral. Often develop dystonia of other facial, cervical, and perioral muscles.

Exacerbated by bright light and activity. May transiently alleviate by pulling eyelid, pinching neck, talking, yawning. Differentiate from seizures by absence of rhythmic clonic activity, disappearance in sleep, characteristic progression over time, normal EEG

Hemifacial spasm

Initially, twitches of upper face and eyelid. With characteristic progression more prolonged,

	dystonic, involves lower face. May persist in sleep. Triggered by facial movement. Muscles of pharynx, larynx, and mastication spared
Myokymia	Bundles within a muscle rhythmically contract, not enough to move a joint. Eyelid most commonly involved. Almost always benign. If involves more of face, consider MS (demyelination in brainstem), during or recovery from facial nerve inflammation (Bell's palsy), brainstem glioma
Focal myoclonus	Small group of muscles involved. May be rhythmic, but brief. No sensory symptoms. No “march”
Sleep disorder	Periodic leg
	Bouts of

	movements or sleep (PLMS)	dorsiflexion of foot and great toe and flexion at knee. Last 1–2 seconds and recur every 30 seconds over minutes to hours. Occur in light sleep, may or may not arouse. May be associated with periods of apnea. May be associated with iron deficiency. Diagnose with polysomnogram
Metabolic	“Wing-beating” proximal tremor of the arm/shoulder	Wilson's disease. Psychiatric symptoms, hepatic dysfunction. Check for Kayser–Fleischer rings in eyes. Serum copper, ceruloplasmin low; urine free copper increased
Trauma associated	Impact posturing in concussion	On impact, tonic or fencing posture and/or brief clonic activity. May indicate brainstem involvement

Ictal	Simple partial motor seizure	<p>May have a sensory aura in the region of clonic activity.</p> <p>Individual contractions are brief (&lt; 100 ms), occur 1–5/s, are rhythmic and gradually slow.</p> <p>Lasts 1–2 minutes. May demonstrate “Jacksonian” spread along homunculus.</p> <p>Possible transient post-ictal Todd's paralysis of the region involved.</p> <p>Check for co-existence of other seizure types.</p> <p>EEG slowing or epileptiform activity in appropriate region supports diagnosis, but EEG often normal even ictally</p>
Demyelinating	Multiple sclerosis	<p>Tonic/dystonic or clonic spasms.</p> <p>Last seconds to minutes. Often precipitated by movement, sensory stimuli.</p>

or  
hyperventilation.  
From brainstem  
or spinal lesions.  
Ictal crossed  
sensory  
symptoms or  
other brainstem  
symptoms (e.g.  
diplopia).  
Occurring in  
patient with  
possible or  
confirmed MS.  
Often resolve  
spontaneously  
over  
weeks/months

---

CJD, Creutzfeldt–Jakob disease; CSF, cerebrospinal fluid; EEG, electroencephalogram; OCD: obsessive-compulsive disorder; SSRI, selective serotonin reuptake inhibitors.

## Further reading list

- Ali S, Khan MA, Khealani B. Limb-shaking transient ischemic attacks: case report and review of literature. *BMC Neurol* 2006; 6:5.
- Bhatia KP. Paroxysmal dyskinesias. *Mov Disord* 2011; 26:1157–65.
- Calancie B. Spinal myoclonus after spinal cord injury. *J Spinal Cord Med* 2006; 29:413–24.
- Caviness JN, Brown P. Myoclonus: current concepts and recent advances. *Lancet Neurol* 2004; 3:598–607.
- Commission on Classification and Terminology of the International League Against Epilepsy. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. *Epilepsia* 1981; 22: 489–501.

Jankovic J, Lang AE. Movement disorders: diagnosis and assessment. In Bradley WG *et al.* *Neurology in Clinical Practice*, 5th edn. Philadelphia, PA: Butterworth-Heinemann/Elsevier, 2008: 294–323.

Waubant E, Alizé P, Tourbah A, Agid Y. Paroxysmal dystonia (tonic spasm) in multiple sclerosis. *Neurology* 2001; 57:2320–1.

## **41 Movements, complex motor activity**

---

Siddhartha Nadkarni and Daniel J. Luciano *Neurologic Differential Diagnosis*,  
ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge  
University Press. © Cambridge University Press 2014.

### **Introduction**

Complex motor phenomena can encompass many behaviors and involve both cortical and subcortical circuits, either individually or in combination. A common feature of the examples we include is that they are not fully intentional and arise unconsciously, either in a dissociative fashion (culture-bound events), a truly altered state (seizures, delirium, intoxication, etc.), or as “semivoluntary” complex movements (tics, compulsions, stereotypies).

### **Case vignette**

The patient is a 59-year-old male who originally presented with brief bouts of *jamais vu* without an alteration in awareness. Magnetic resonance imaging (MRI) showed a low-grade glioma of the right anteromesial temporal region and an electro-encephalogram (EEG) showed right anterior temporal spikes. He was placed on lamotrigine with improvement. He then underwent a total resection of the right anteromesial temporal region with resolution of the bouts of *jamais vu*. Two years later he was taken off lamotrigine and a repeat MRI did not show evidence of tumor recurrence. Three years later he presented with two new nocturnal episodes and was concerned about recurrent seizures. With the first event he recalled having a dream during which he was involved in an altercation. He was next aware of finding himself lying on the floor of his bedroom. There was no tongue-biting, incontinence, muscle soreness, or disorientation. A month later he had a second episode and recalled having a dream during which he was waiting in a physician's office, became flustered, and stormed out. As this occurred he awoke as he walked into the wall of his bedroom. Again, there was no tongue-biting, incontinence, muscle soreness, or disorientation. Both episodes had occurred late in the night after he had been asleep for several hours. A repeat

MRI showed only post-operative changes and a 24 hour ambulatory EEG was normal.

The patient's initial presentation raises concern for possible nocturnal seizures, given the patient's past history. However, the two dreams he experienced were not stereotyped, as might be expected were they seizures, and he had no other ictal or postictal signs or symptoms. In addition, an ambulatory EEG showed no sign of epileptiform activity. This raises the possibility of a sleep disorder. The fact that the events occurred late in the night, as opposed to 1–2 hours after sleep onset, would tend to speak against a non-rapid eye movement (NREM) parasomnia, such as somnambulism. In addition, the fact that the patient was able to recall a dream directly preceding his arousal, which was congruent with his behavior at the time, indicates that he mostly likely suffers from REM behavior disorder. Subsequent polysomnographic studies confirmed the diagnosis.

**Table 41.1** *Differential diagnosis of complex motor behaviors.*

Item	Subdivision	Specific entity	Possible
Structural (congenital or acquired)	Choreoathetotic CP	Chorea /athetosis	Distal flaccid dance-like camouflage
	Vascular (aneurysmal hemorrhage, hemorrhagic/ischemic CVA); anatomic hemispheric disconnection; tumors	Anarchic/Alien hand syndrome	One hand "of its own." Unintended purposeful leading to objects. The hand performs activities such as buttoning, grasping. Primary disconnection syndrome. [that it is involves frontal lobe structures]

	Synkinesia (mirror movements)	Simultaneous involuntary movements that accompany movement in Parkinson's disease or CVA, often associated with hemiparesis
Toxic. Med/drugs, toxic substances, withdrawal states	Tardive dyskinesia	Occurs very gradually over time during long-term use of drugs such as neuroleptics, buccal–limb movements, usually involving the mouth and face. Tardive dyskinesia may be reversible if discontinued.
Medications	Chorea	Flailing limb movements, particularly of the extremities, associated with anabolic steroids, lithium, phenothiazine agents, and some poisonings.
	Tics	Tics seen with cocaine, antipsychotic drugs, and poisonings. Tics may be focal or generalized.
Drug-related	Drug-induced dangerous behavior	PCP induced violent aggressive behavior, stemming from delusions of grandeur, ability to produce complex plans to commit crimes, as well as other psychiatric diagnoses.

	Alcohol-related Pathologic intoxication	Extreme amounts violent b exhaustion Usually c reactions Patient is Controver
	Withdrawal states	Delirium tremens/ formication- reaching
Infective/post-infectious	Post- Streptococcus A infection	The sens all over & hallucinat of pickin reaching Associat autonom agitation
	Sydenham's chorea	Chorea a compuls behavior gait distu fascicula months & under ag females. throat cu O (ASL)
	Pediatric autoimmune neuropsychiatric disorders associated with Streptococcus A infection (PANDAS)	Worseni disorder infection Presume phenome Presents persist ir Diagnosi culture a treated w

www.ncbi.nlm.nih.gov

IVIg

Psychiatric

Tics /Tourette 's

Tics are movement (to suppress tension), complex tics have link between them (e.g., blinking, grimacing, and hand flapping) and may occur in clusters or on an occasion of stress or fatigue. Tics may increase in frequency or intensity over time, carried out by a person with Tourette syndrome at least once a day. A vocal tic is a sound made by a person with Tourette syndrome, such as a bark, growl, or grumble. A motor tic is a movement made by a person with Tourette syndrome, such as a blink, shrug, or shrug of the shoulders. Tics can last for minutes, hours, days, weeks, months, or years.

Stereotypies

Stereotypies are coordinated, rhythmic movements seen in people with autism spectrum disorder. These movements are common in individuals with autism spectrum disorder. Stereotypies are often triggered by environmental stimuli, such as bright lights or sounds. They can also be triggered by internal stimuli, such as hunger or thirst. Stereotypies can be injurious, such as biting one's fingers or banging one's head against a wall. They can also be non-injurious, such as hand flapping or head nodding. Stereotypies can be a sign of pathology, such as autism spectrum disorder or Tourette syndrome.

hair twis  
fingers, &  
legs, cro  
tapping t

### Compulsions

Complex  
with inci  
lessened  
compuls  
checking  
symmetr  
Most fre  
intrusive  
and oftei  
expressii  
obsessio

### Command automatism

Seen in c  
hypnosis  
the instru  
to forced  
culture-t

### Intermittent explosive disorder

Aggressi  
of propo  
May hav  
behavior  
afterwar

### Culture-bound syndromes

Culturall  
complex  
Jumping  
Exagger  
Would a  
obedient  
throw or  
hand the  
pick it uj  
hyperekj  
~~~~~

associate  
related to

glycine t  
Amok: I  
following  
that lead  
homicide  
people/o  
Precipita  
Only enc  
restraine  
there is f  
amnesia.  
Malay, I  
Polynesi  
Papua N  
(*mal de I*)  
(*iich'aa*)  
*Attaque* o  
of  
palpitatio  
followed  
*e.g.* screa  
moaning  
striking  
More co  
cultures

Neoplastic/paraneoplastic

Chorea

CCRMP  
reported  
renal cel  
Can send  
antibody

Cardiac

Chorea

Chorea c  
pump im

Metabolic

Delerium  
/encephalopathy

Floccillation  
/carphology

Picking  
sheets in

Delerium  
reaching  
moveme  
illusions.  
EEG can  
pattern.

### Sleep disorder

Klein–Levin  
(Sleeping  
Beauty)  
syndrome

Mostly a  
of hyper  
to eat or  
hyperphag  
apathy, c  
cognitiv  
hallucinat  
occur. D  
be irritabl  
allowed  
to month  
months t  
between  
commen  
resolves  
initial ep  
precedin  
deprivati  
trauma. ]  
autoimm  
sleep sup  
polysom

### REM

REM behavior  
disorder

Loss of t  
seen in F  
dreams.  
amplitud  
simulatio  
Bed part  
flailing l  
awakene  
dream. N  
— — — — —

men and  
occur wi  
use/with  
ampheta  
polysom

Slow wave  
sleep

Parasomnias

Complex  
transition  
sleep. Us  
minutes  
seizures  
night. In  
sleep talk  
increasing  
dangerous  
driving).  
behavior  
medicati  
like zolp  
induce p  
triggered  
deprivati  
febrile il  
polysom  
Sleep ter  
children.  
family h  
inconsol  
moveme  
awake bi  
commun  
signs. La  
awaken &  
recall  
Sleep-wa  
can be fa  
appear a  
may perf  
(move fu  
things th

>Last less  
return to  
location.  
Confusia  
drunkeness  
Arousal  
confusec  
yelling, t  
but slow  
unreactiv

### Ictal

Temporal lobe  
complex partial  
seizure

Staring w  
responsiveness  
semipurposeful  
(automat)  
generally aware  
or aware  
rubbing,  
unilatera  
to seizure  
1–2 min  
tired, com  
about au  
seizure t  
activity o  
diagnosi

Frontal lobe  
seizures

Complex  
stereotyp  
manifest  
flailing,  
screaming  
duration  
multiple  
sleep. Ict  
Nocturnal  
(NPD): p  
moveme  
parasom

NREM s

dystonic  
semipuri  
5–50 s, c  
night. Pa  
Can be f  
dominan  
epilepsy  
Episodic  
(ENW):  
parasom  
agitated  
screamir  
complex  
automati  
Differen  
somnam  
sleep, bu  
evening  
Respond

Psychogenic  
non-epileptic  
seizure (PNES)

May hav  
generaliz  
or fronta  
Automat  
not truly  
pelvic/tr  
emotive,  
represen  
conflict.  
frontal lo  
even wit  
truly stei  
not occu  
seizures

---

AEDs, antiepileptic drugs; CP, cerebral palsy; CSF, cerebrospinal fluid; CVA, cerebrovascular accident; DTs, delirium tremens; EEG, electro-encephalogram; IVIg, intravenous immunoglobulin; OCD: obsessive-compulsive disorder; MRI, magnetic resonance imaging; NREM, non-rapid eye movement; PCP, phencyclidine; PDD, pervasive developmental disorder.

## Further reading list

- American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revision) (DSM-IV-TR)*. Washington, DC: American Psychiatric Association, 2000.
- Arnulf L, Lin N, Gadoth J et al. Kleine–Levin syndrome: a systematic study of 108 patients. *Ann Neurol* 2008; 63: 482–93.
- Bisulli F, Vignatelli L, Provini F et al. Parasomnias and nocturnal frontal lobe epilepsy (NFLE): lights and shadows – controversial points in the differential diagnosis. *Sleep Med* 2011; 12 (Suppl. 2):S27–32.
- Canavese C, Canafoglia L, Costa C et al. Paroxysmal non-epileptic motor events in childhood: a clinical and video-EEG-polysomnographic study. *Dev Med Child Neurol* 2012; 54:334–8.
- Demirkiran M, Jankovic J. Paroxysmal dyskinesias: clinical features and classification. *Ann Neurol* 1995; 38:371–9.
- Jankovic J, Gelineau-kattner R, Davidson A. Tourette's syndrome in adults. *Mov Disord* 2010; 25:2171–5.
- Muthugovindan D, Singer H. Motor stereotypy disorders. *Curr Opin Neurol* 2009; 22:131–6.
- Proserpio P, Cossu M, Francione S et al. Epileptic motor behaviors during sleep: anatomo-electro-clinical features. *Sleep Med* 2011; 12 (Suppl. 2):S33–8.
- Snider LA, Swedo SE. Post-streptococcal autoimmune disorders of the central nervous system. *Curr Opin Neurol* 2003; 16: 359–65.
- Stores G. Dramatic parasomnias. *J R Soc Med* 2001; 94:173–6.
- Wyllie E, Gupta A, Lachwani D. *The Treatment of Epilepsy: Principles and Practice*, 4<sup>th</sup> edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2006.

## **42 Movements during sleep**

---

Michael J. Thorpy *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

Abnormal movements during sleep are characterized primarily by either relatively simple, usually stereotyped movements that disturb sleep, monophasic movement disorder symptoms of sleep such as sleep-related leg cramps, or medical, neurologic, or psychiatric disorders that cause increased movements during sleep.

The types of movements that can occur include jerking movements of the muscles and most often of the limbs; restlessness of a part or the whole body during sleep; rhythmic movements of the limbs or body or specific muscle groups; suddenly sitting up in bed; and ambulation during sleep which may be quiet or abrupt.

### **Disorders that can cause jerking movements of sleep**

Involuntary, highly stereotypical, jerking or twitching of the limbs that occurs mainly during sleep. These are characteristic of periodic limb movement disorder . Sleep-related leg cramps are painful sensations caused by abrupt intense involuntary contraction of muscles. Benign sleep myoclonus of infancy is characterized by repetitive myoclonic jerks that typically involve the large muscle groups and occur during sleep in infants. Propriospinal myoclonus at sleep onset is a disorder characterized by sudden muscular jerks of the axial muscles that occur in the transition from wakefulness to sleep and they are usually absent during later stages of sleep. Sleep starts , or hypnic jerks , are sudden, brief simultaneous contractions of the body or body parts that occur at sleep onset often associated with a sensation of falling. Juvenile myoclonic epilepsy is an epileptic disorder that causes massive bilateral synchronous myoclonic jerks, most commonly upon awakening.

## **Disorders that cause restlessness during sleep**

Restless legs syndrome is characterized by a complaint of a strong, nearly irresistible, urge to move the legs that is often associated with uncomfortable paresthesias felt in the limbs that are typically relieved by movement. REM sleep behavior disorder is a disorder characterized by acting out of dreams with talking, restlessness, and sometimes violent movements during sleep. Insomnia , either primary or secondary, is characterized by concern about lack of sleep and daytime symptoms such as fatigue or cognitive difficulties.

## **Disorders that cause rhythmic movements during sleep**

Sleep-related rhythmic movement disorder is characterized by repetitive, stereotyped, and rhythmic motor behaviors that occur predominantly during drowsiness and sleep. Hypnagogic foot tremor (HFT) is a rhythmic movement of the feet or toes that occurs at the transitions between wake and sleep. Alternating leg muscle activation (ALMA) occurs with alternating muscle activation of the anterior tibialis muscles. The two disorders are connected and may be partial manifestations of each other. Sleep-related bruxism is an oral activity characterized by grinding or clenching of the teeth during sleep.

## **Disorders that cause sudden sitting up in bed**

Confusional arousals are characterized by confused mentation and movements usually with sitting up in bed and incoordinated movements. Breathing disorders during sleep that can include obstructive sleep apnea with gasping, choking, or cessation of breathing during sleep can cause the individual to abruptly sit up in bed. Laryngospasm is an acute breathing difficulty associated with laryngeal obstruction during sleep. Panic disorder is a discrete episode of intense fear or discomfort which is associated with symptoms such as palpitations, shortness of breath, sweating, or trembling.

**Table 42.1 Differential diagnosis of movements in sleep.**

| Item | Subdivision | Specific entity | Possible clinical features |
|------|-------------|-----------------|----------------------------|
|------|-------------|-----------------|----------------------------|

|                            |                                  |                                                              | features                                                                                              |
|----------------------------|----------------------------------|--------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Jerking movements of limbs | Periodic limb movements of sleep | Medication induced:<br>– Antidepressants –<br>Antihistamines | Repetitive withdrawal response of limbs (mainly legs)                                                 |
|                            | Hypnic jerks (sleep starts)      | Idiopathic                                                   | Sensation of falling that occurs at sleep onset                                                       |
|                            | Juvenile myoclonic epilepsy      | Epilepsy                                                     | Massive bilateral synchronous myoclonic jerks most commonly upon awakening                            |
|                            | Benign neonatal sleep myoclonus  | Idiopathic                                                   | Repetitive myoclonic jerks during sleep in infants                                                    |
|                            | Propriospinal myoclonus of sleep | Idiopathic                                                   | Sudden muscular jerks of the axial muscles that occur during the transition from wakefulness to sleep |
|                            | Sleep-related leg cramps         | Idiopathic                                                   | Intense painful contractions of                                                                       |

|                             |                        |                                                                                      |                                                                                        |
|-----------------------------|------------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
|                             |                        |                                                                                      | the leg muscles during sleep that are relieved by stretching                           |
| Restlessness during sleep   | Restless legs syndrome | Idiopathic                                                                           | Discomfort in the legs relieved by movement                                            |
|                             |                        | Familial                                                                             | Family history                                                                         |
|                             |                        | Medication induced:<br>– Antidepressants – Antihistamines                            | Onset associated with medication use                                                   |
|                             |                        | Secondary:<br>– Iron-deficiency anemia – Parkinson's disease – Peripheral neuropathy | Associated with a variety of medical and neurologic disorders                          |
| REM sleep behavior disorder | Idiopathic             | Medication-induced                                                                   | Sleep talking and movements during sleep in early stages, most commonly in the elderly |
|                             |                        |                                                                                      | Associated with antidepressants or antihistamines                                      |

|                                 |                            |            |                                                                                                 |
|---------------------------------|----------------------------|------------|-------------------------------------------------------------------------------------------------|
|                                 |                            | Neurologic | Associated with a degenerative neurologic disorder such as Parkinson's disease                  |
| Insomnia                        | Primary                    |            | Restlessness associated with difficulty sleeping that leads to daytime symptoms such as fatigue |
|                                 | Secondary                  |            | Sleep disturbance associated with a medical or psychiatric disorder                             |
| Rhythmic movements during sleep | Rhythmic movement disorder | Idiopathic | Recurrent rhythmical head or body movements usually persisting since infancy                    |
| Sleep-related bruxism           | Idiopathic                 |            | Grinding and clenching of teeth during sleep                                                    |
|                                 | Anxiety induced            |            | Associated with an                                                                              |



**with a history  
of GERD**

|                                 |                         |                                                                                                             |
|---------------------------------|-------------------------|-------------------------------------------------------------------------------------------------------------|
| Apnea                           | Obstructive sleep apnea | Associated with snoring and upper airway obstruction                                                        |
|                                 | Central apnea           | Not associated with snoring and usually a history of cardiovascular or central nervous system (CNS) disease |
| Confusional arousals            | Idiopathic              | Mental confusion in sleep                                                                                   |
|                                 | CNS lesion              | Rarely associated with an underlying disorder                                                               |
| Getting out of bed while asleep | Sleepwalking            | Idiopathic                                                                                                  |
|                                 | Epilepsy                | Ambulation with difficulty to arouse                                                                        |
|                                 |                         | History of epileptic seizures                                                                               |
|                                 | Neurologic              | Associated with a CNS lesion                                                                                |

|                             |                    |                                                                                                                     |
|-----------------------------|--------------------|---------------------------------------------------------------------------------------------------------------------|
| REM sleep behavior disorder | Idiopathic         | Acting out of dreams with violent behavior, most commonly in the elderly                                            |
|                             | Medication-induced | Associated with antidepressants or antihistamines                                                                   |
|                             | Neurologic         | Associated with a degenerative neurologic disorder such as Parkinsons disease                                       |
| Sleep terror                | Idiopathic         | Screaming, jumping out of bed, and difficult to arouse                                                              |
| Panic attack                | Idiopathic         | Intense fear and anxiety usually associated with other somatic symptoms such as palpitations or shortness of breath |

|          |                       |                                                                                           |
|----------|-----------------------|-------------------------------------------------------------------------------------------|
| Epilepsy | Frontal lobe epilepsy | Motoric activity with stereotypical behaviors.<br>Often with a history of daytime attacks |
|----------|-----------------------|-------------------------------------------------------------------------------------------|

---

## Disorders that cause ambulation during sleep

Sleepwalking represents complex behaviors that typically occur in children and is associated with ambulation while in an altered state of consciousness. Sleep terror is a sudden episode of terror during sleep, usually initiated with a cry or loud scream, and autonomic manifestations often with “bolting” from the bed. Nocturnal epilepsy, such as some forms of frontal lobe epilepsy, is often associated with complex behaviors that occur out of sleep.

### Case vignette

A 65-year-old male presented to his primary care physician complaining of poor quality of sleep and asking for a sleeping pill.

His physician gave him a prescription for 5 mg zolpidem and asked to see him in a month. When he returned the patient complained less about his sleep disturbance. However, his wife complained that he was very restless and often would talk in his sleep. She also noted that he moved his arms and legs a lot. His legs also twitched at night. The physician considered that the restlessness might be due to the insomnia, restless legs syndrome with periodic limb movements, or REM sleep behavior disorder. He decided to increase the dose of the zolpidem to 10 mg and asked to see the patient again in a month.

One month later the patient was sleeping better but his wife said that he still moved his arms and legs a lot, occasionally would call out at night, and even fell out of bed one night. She also was concerned that he appeared to be “slowed down” during the daytime and she wondered if the medication was sedating him in the day.

The physician examined the patient and noticed that he seemed a little apathetic and did not contribute much to the discussion. There was a very minor fine tremor of his hands at rest and there appeared to be a slight increase in muscle tone detectable in the arms.

The physician considered that the patient could have very mild Parkinson's disease and wondered if the excess motor activity could be an early manifestation of REM sleep behavior disorder. He recommended that the patient see a neurologist sleep specialist and have an overnight polysomnogram.

The sleep study confirmed disrupted sleep with a low sleep efficiency of 75% and there was an increase in muscle activity seen during REM sleep. On the basis of the clinical changes and the PSG evidence, the sleep specialist made a diagnosis of REM sleep behavior disorder most likely secondary to early Parkinson's disease .

## Further reading list

- Ahmed I, Thorpy MJ. Clinical evaluation of parasomnias. In Thorpy MJ, Plazzi G, Eds. *Parasomnias and other Sleep-related Movement Disorders*. Cambridge: Cambridge University Press, 2010: 19–33.
- American Academy of Sleep Medicine. *The International Classification of Sleep Disorders, Second Edition (ICSD-2): Diagnostic and Coding Manual*. Westchester, IL: American Academy of Sleep Medicine, 2005.
- Diederich NJ, McIntyre DJ. Sleep disorders in Parkinson's disease: many causes, few therapeutic options. *J Neurol Sci* 2012; 314:12–19.
- Seithkurippu R, Spence W, Harris S, Thorpy M, Kramer M. Parasomnias. In *Encyclopedia of Psychopharmacology*. New York, NY: Springer-Verlag, 2010.
- Thorpy MJ. Classification of sleep disorders. In Kryger M, Roth T, Dement W, Eds. *The Principles and Practice of Sleep Medicine*, 4th edn. Philadelphia, PA: Saunders, 2011.
- Thorpy M, Plazzi G. *Parasomnias and other Sleep-related Movement Disorders*. Cambridge: Cambridge University Press, 2010.

## **43 Movements, tonic-clonic type**

---

Daniel J. Luciano and Siddhartha Nadkarni *Neurologic Differential Diagnosis*,  
ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge  
University Press. © Cambridge University Press 2014.

### **Introduction**

Generalized tonic-clonic seizures are most commonly seen as an expression of partial or generalized epilepsies. Although they may appear generalized at the start, as many as 80% are an expression of partial epilepsy. They are also frequently seen as an expression of toxic and metabolic derangements, such as drug/alcohol consumption or withdrawal, or disturbances of glucose or sodium. There is an initial tonic phase followed by a clonic phase of gradually decreasing frequency. Convulsive syncope is the most common entity to be confused with a tonic-clonic seizure, but can usually be differentiated with a careful history of the event.

### **Case vignette**

The patient is a 32-year-old female with a history of seizures for the past 3 years. Events have only occurred in wakefulness. She has no aura and has a loss of consciousness during which she has been noted to have generalized shaking of her body for approximately a minute and has sometimes had associated urinary incontinence, as well as biting of the anterior tip of the tongue. There have been no associated injuries. Post-ictally, she is somewhat weak and mildly lethargic. Routine and sleep-deprived EEGs, as well as cranial MRI, were normal. She was treated with carbamazepine, phenytoin, levetiracetam, and lamotrigine with continued seizures.

The patient is admitted to the hospital for a flurry of seizures. While examining her an event occurs. It is noted that there is no initial tonic phase and clonic activity is of a fixed frequency throughout the event and occurs intermittently. During the seizure some eye blinks are noted, but there is no other suggestion of facial clonic activity. Immediately post-ictally she is somewhat

lethargic, but is not disoriented.

The initial impression is one of generalized tonic-clonic seizures, possibly as an expression of an idiopathic generalized epilepsy given occurrence only in wakefulness. However, it is noteworthy that, despite having no aura, she has never suffered associated injuries. Ictally, she has also bitten the anterior tongue as opposed to the sides. EEGs have been normal. Upon viewing the seizure there is no initial tonic phase, as might be expected, and clonic activity is intermittent and of a fixed frequency, as opposed to being persistent and gradually slowing in frequency. In addition, there is no associated facial clonic activity and she does not have post-ictal confusion. All of these factors lead one to a likely diagnosis of psychogenic non-epileptic seizures.

**Table 43.1 Differential diagnosis of tonic-clonic type movement**

| Item                                                                 | Subdivision | Specific entity                       | Possible clinical features                                                                                                                                                                        |
|----------------------------------------------------------------------|-------------|---------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Structural<br>(congenital or<br>acquired)                            |             | Brainstem or<br>spinal cord<br>lesion | Myoclonic jerks<br>can be repetitive<br>but briefer than a<br>tonic-clonic<br>seizure. No initial<br>tonic phase. Look<br>for associated<br>brainstem or cord<br>signs                            |
| Toxic.<br>Med/drugs,<br>toxic<br>substances,<br>withdrawal<br>states |             | Strychnine                            | Competes with<br>inhibitory<br>neurotransmitter<br>glycine. Initial<br>excitement,<br>irritability, then<br>generalized<br>rigidity, opisthotonic<br>posturing.<br>Muscular<br>fasciculations and |

hyperreflexia seen. Then tonic or clonic activity with clear sensorium, generated at spinal level, may be provoked by stimuli. No post-ictal state. May then have true tonic-clonic seizures

#### Tetanus

Rigidity of face, masseters, straight upper lip (risus sardonicus), then rigidity of axial muscles followed by proximal limbs. Then violent contractions repetitively in severe cases with slight stimuli or voluntary movement. Can look like GTC but retained awareness, stimulus sensitivity and normal EEG differentiate. Worsens for 10–14 days after onset

#### Neuroleptic malignant

Fever, autonomic instability, and

syndrome

diffuse rigidity.  
With tremor or  
rigors may mimic  
a GTC seizure.  
Altered mental  
status-may  
progress to coma.  
True seizures may  
occur. Markedly  
elevated CPK.  
Check medications  
list: all typical and  
atypical  
neuroleptics may  
cause. Can occur  
anytime but most  
common with  
initiation or  
increase in dose.  
More common  
with haloperidol,  
fluphenazine. Also  
associated with  
non-neuroleptic  
dopamine blockers  
(metoclopramide,  
amoxapine) and  
withdrawal of anti-  
Parkinson's  
medication.  
Similar picture  
seen in serotonin  
syndrome.  
Especially likely  
with MAOIs  
combined with  
serotonergic drugs

Malignant

Caused by

|                           |                                          |                                                                                                                                                                                                                                                                                                        |
|---------------------------|------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                           | hyperthermia                             | anesthetics and neuromuscular blocking agents. Hyperthermia and marked diffuse muscle rigidity. Associated rigors may mimic GTC. Familial: check for family history of malignant hyperthermia or death during anesthesia. May occur with muscle diseases: multiminicore myopathy, central core disease |
| Infective/post-infectious | Rigors                                   | Generalized shaking or exaggerated shivering in the setting of high fever, often bacterial infection. No tonic phase or facial clonic activity. No gradual slowing of clonic activity. May have retained awareness                                                                                     |
| Psychiatric               | Psychogenic non-epileptic seizure (PNES) | May be precipitated by stress, but patient often does not see <i>in association</i>                                                                                                                                                                                                                    |

All associations.

Possible history of sexual/physical abuse. Lacks initial tonic phase. Clonic activity often of fixed frequency, intermittent or waxing/waning. No associated facial clonic activity. If tongue bitten, often anterior. Incontinence possible. Burns not associated. May lack a post-ictal phase. Episodes lack stereotypy. EEG normal during event. Prolactin not elevated post-ictally. No elevation of WBCs. May provoke with suggestion.

Inflammatory

Stiff person syndrome

Fluctuating muscle rigidity in trunk and limbs with concurrent spasms which may be triggered by emotion and stimuli. Retained awareness speaks against GTC.

Often hunched over and stiff posture. More common in women: may be associated with breast cancer. Autoimmune: anti-GAD antibodies. Associated with other autoimmune disorders: diabetes, thyroiditis, vitilligo, pernicious anemia

Cardiovascular “Convulsive” syncope

Preceding lightheadedness, weakness, pallor, sweating, palpitations, blurring/darkening of vision. Initially limp followed by tonic posturing and myoclonic jerks. More common if upright posture maintained. Duration brief (10–20 s). Urinary incontinence can occur, tongue-biting rare. Can be tired post-ictally, but no confusion

Neurally mediated

(1)  
Neurocardiogenic

-----  
(vasovagal):  
precipitation by

pain, fright,  
prolonged  
standing (2)  
Situational:  
precipitated by  
micturition,  
cough. Consider  
tilt table test (3)  
Carotid sinus  
hypersensitivity:  
occurs with tight  
collar/pressure  
on neck. Check  
if bradycardia  
induced by  
carotid sinus  
massage

#### Orthostatic

Precipitation by  
standing. Occurs  
with dehydration,  
autonomic failure  
(e.g. diabetes,  
Parkinson's), drugs  
(e.g. diuretics,  
vasodilators, beta-  
blockers). Check  
orthostatic BPs,  
BUN/creatinine

#### Cardiac arrhythmias

Brady- (sick sinus)  
or  
tachyarrhythmias  
(V tach). Usually  
cardiac disease.  
Check pulse, ECG.

Consider Holter monitor.

Structural cardiopulmonary disease

May be triggered by exertion. Check for cardiac history. Outflow obstruction (mitral or aortic stenosis, cardiac tumors, massive PE). Check for murmurs. Cardiac rhythm, ECG. Consider blood gases, echocardiogram

Cerebrovascular

(1) Vertebrobasilar TIA: other brainstem signs/symptoms associated (e.g. vertigo, nystagmus, visual loss). Check for history and evidence of peripheral vascular disease  
(2) Subclavian steal syndrome: precipitated by use of arms. Other brainstem signs/symptoms associated. BP in

arms differs,  
often by 45  
mmHg. Consider  
MRA/angiography

|                |                 |                                                                                                                                                                                                                                                                                                   |
|----------------|-----------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Metabolic      | Tetanic attacks | Rigidity of body with carpopedal spasms. Can have associated tremulousness but not rhythmic clonic jerking. Retained awareness. Precipitated by hyperventilation, hypocalcemia, hyperthyroidism. Check calcium, vitamin D, thyroid and parathyroid function. Recreate event with hyperventilation |
| Sleep disorder | Bruxism         | Raises concern for possible unwitnessed nocturnal tonic-clonic seizure. Grinding of teeth with nocturnal biting of inner cheek. Tongue rarely bitten. No associated incontinence or muscle soreness. May have jaw pain                                                                            |

and TMJ  
syndrome. Seen  
with  
anxiety/depression

|       |                         |                                                                                                                                                                                                                                                                                                                                                                                                                             |
|-------|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ictal | Tonic-clonic<br>seizure | Generalized tonic<br>and then clonic<br>phase with gradual<br>slowing of clonic<br>activity. Version of<br>head suggests<br>seizure. Last 1–2<br>minutes. Lateral<br>tongue biting and<br>urinary/fecal<br>incontinence<br>associated.<br>Cyanotic or<br>hyperemic. Post-<br>ictal sleep or<br>lethargy/confusion.<br>Check for history<br>of other seizure<br>types. Epileptiform<br>activity on EEG<br>supports diagnosis |
|-------|-------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

---

BP, blood pressure; BUN, blood urea nitrogen; CPK, creatine phosphokinase; ECG, electrocardiogram; EEG, electroencephalography; GAD, glutamic acid decarboxylase; GTC, generalized tonic-clonic seizure; MAOIs, monoamine oxidase inhibitors; MRA, magnetic resonance angiography; PE, pulmonary embolism; TIA, transient ischemic attack; TMJ, temporomandibular joint; WBC, white blood cells.

## Further reading list

Benbadis S. The differential diagnosis of epilepsy: a critical review. *Epilepsy Behav* 2009; 15:15–21.

- Britton J, Benarroch E. Seizure and syncope: anatomic basis and diagnostic considerations. *Clin Auton Res* 2006; 16:18–28.
- Gates JR. Non-epileptic seizures: classification co-existence with epilepsy: diagnosis, therapeutic approaches and consensus. *Epilepsy Behav* 2002; 3:28–33.
- Gould P, Krahn AD, Klein GJ *et al*. Investigating syncope: a review. *Curr Opin Cardiol* 2006; 21:34–41.
- Karceski S. Seizures versus syncope. *Pract Neurol* April 2006; 3:16–18.
- McKeon A, Vaughan C, Delanty N. Seizures versus syncope. *Lancet Neurol* 2006; 5:171–80.
- Morrell MJ. Differential diagnosis of seizures. *Neurol Clin* 1993; 11:737–54.
- Schachter SC. Seizure disorders. *Med Clin North Am* 2009; 93:343–51.
- Strano S, Colosimo C, Spatanga A *et al*. Multidisciplinary approach for diagnosing syncope: a retrospective study on 521 outpatients. *J Neurol Neurosurg Psychiatry* 2005; 76:1597–600.

## 44 Mutism

---

Gaia Donata Oggioni and Alberto J. Espay *Neurologic Differential Diagnosis*,  
ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge  
University Press. © Cambridge University Press 2014.

### Introduction

This term mutism applies to the inability or unwillingness to speak, resulting in absence or marked paucity of verbal outcome. It can be isolated in children but rarely in adults, and occurs most often in association with other disturbances in behavior, thought process, or level of consciousness. The most common concurrent behavioral disorder is catatonia, which is characterized by marked psychomotor disturbances including stereotypies, posturing, catalepsy, automatic obedience, negativism, rigidity, echolalia/echopraxia, and stupor. (Please refer to [Chapter 12](#).) Mutism with catatonia is reported in adults, and rarely in children. The presence of catatonia may not suffice to distinguish between organic and psychiatric etiologies for mutism.

Mutism has been associated with lesions within the dentate–thalamo–cortical pathway (dentate nucleus, superior cerebellar peduncles, ventral lateral nucleus of the thalamus, supplementary motor area) as well as bilateral frontal lobe or cingulate lesions.

### Case vignette

A 45-year-old right-handed female presented to the emergency room with a 48-hour history of mutism and reduced motor initiative. Initially she was found mute at the kitchen table, with urinary incontinence. During the following hours she was cared for by her partner, but remained mute and with minimal interaction with others.

She had a history of bipolar disorder since age 25, with history of amphetamine and benzodiazepine drug overdoses in the past. Past medical history was non-contributory except for borderline hypertension. Family history

was positive for cardiac disease and psychiatric disorders.

Upon admission she could not communicate verbally but could answer questions through gestures. Vital signs were in the normal range. Blood work was unrevealing except for positive toxicologic screen for benzodiazepines and cannabinoids. The first neurologic examination did not reveal any other specific neurologic abnormality.

The clinical picture could at first suggest mutism secondary to depression, despite the presence of urinary incontinence and her efforts to communicate through gestures and writing. A formal neuropsychological evaluation was impossible. A more careful neurologic examination showed normal phonation, severe non-fluent aphasia with partially spared repetition and verbal perseveration, and good verbal comprehension; mild right facial paresis, right brachial dyspraxia, right hemineglect, and asymmetrical reflexes with right hyperreflexia.

A brain computerized tomography scan revealed an ischemic area in the left dorsolateral frontal cortex, overlapping with Broca's area.

After 3 days she began to spontaneously produce some words, with perseverative speech. Even if the clinical history was strongly suggestive of a mood disorder, the re-appearance of speech with perseveration is more typical of an aphasic disorder. The presence of associated right-sided neurologic signs supports the presence of an organic lesion in the central nervous system (CNS). The lack of interaction with others and reduced motor initiative are often present in psychiatric diseases, but are also features of the akinetic-mutism associated with strokes in the anterior cerebral artery (ACA) territory. Chronic amphetamine and cannabis abuse increase the risk of cerebrovascular disease.

**Table 44.1 Differential diagnosis of mutism.**

| Item               | Specific type | Specific entity | Possible clinical features                                                                             |
|--------------------|---------------|-----------------|--------------------------------------------------------------------------------------------------------|
| Psychiatric<br>[1] | Mood disorder | Depression      | Mutism with or psychomotor retardation, lack of emotional expression, apathy. History of depression or |

mood disorder  
Negativism in  
suggestive or  
psychiatric  
usually respond  
benzodiazepines

Mania  
As per above  
of mania or  
disorder

Dissociative  
disorder  
Conversion  
disorder  
Abrupt onset  
exacerbation  
stressful event  
of psychological  
stressors and  
unexplained  
symptoms, in  
absence of si-  
congruent with  
organic disorder  
substance abuse  
*belle indifférence*  
(lack of conci-  
nature or im-  
of the symptom)  
Symptoms can  
over time. With  
catatonia is a  
abrupt change  
motor behavior  
occur and pre-  
response is usually  
preserved

Brief psychotic  
disorder  
Abrupt onset  
stressful event  
present with  
and catatonia

Delusions or hallucination present. Brief (usually few self-limiting)

Schizophrenia

Catatonic schizophrenia

Suggestive history (hallucinations, delusion, impaired speech, lack of emotions, withdrawal from social function, isolation, stereotyped behavior). May be associated with catatonia: rigid position and lack of flexibility are suggestive

Anxiety disorder

Selective/elective mutism [2]

In children (2-5 years) with previously normal verbal skills. Lack of speech in setting in which speaking is usually expected (e.g. at school) but is normal in other situations (e.g. at home with parents)

Reaction to severe stress and adjustment reaction

Acute stress reaction

Abrupt onset after a “shocking” event. Initial state of daze followed by withdrawal, hypervigilance, or overarousal. Autonomic symptoms include panic and anxiety.

(tachycardia,  
sweating, flu  
can be present)

|          |                                    |                                                 |                                                                                                                                                                                                                                                                                                     |
|----------|------------------------------------|-------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Epilepsy | Frontal lobe seizure               | Partial complex seizure                         | Usually short episodes, occur in bursts. May be associated with episodic focal posturing, clonic, dystonic or tonic movements, automatisms and transient altered awareness. Auras (especially味觉) are common. Impaired sleep disturbance nocturnal seizures are common. EEG may sometimes be normal. |
|          | Partial complex status epilepticus |                                                 | Impaired consciousness for history or EEG shows continuous epileptiform activity                                                                                                                                                                                                                    |
|          | Post-ictal status                  | During the recovery after a generalized seizure | Look for signs of generalized tonic-clonic seizure, bite, incontinence, trauma), history of epilepsy or seizures, previous seizures. Possible precipitating factors post-ictal fatigue, sleepiness, confusion, memory loss.                                                                         |

|                                  |                                                                |                                                                         |                                                                                                                                                                                                                                                                                                |
|----------------------------------|----------------------------------------------------------------|-------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Vascular focal brain lesions [3] | Uni/bilateral anterior cerebral artery syndrome (frontal lobe) | Supplementary motor area<br>Cingulate gyrus<br>Dorsolateral border zone | Akinetic mutism<br>marked reduction in nearly all motor function (including facial expression, speech, and output) but variable degree of awareness. Hypokinesia and hypometria can be present. Specific action perseverations are typical. Unilateral lesions usually cause transient mutism. |
|                                  | Choroidal artery syndrome                                      | Bilateral thalamic lesion                                               | Akinetic mutism, mood changes, hemiparesis, hyperesthesia, amnesia (thalamic dementia), perseveration                                                                                                                                                                                          |
|                                  | Broca aphasia [4]                                              | Left frontal operculum lesion                                           | Non-fluent agrammatic aphasia, telegraphic speech. Comprehension preserved. Often associated with hemiparesis                                                                                                                                                                                  |
|                                  | Basilar artery, posterior cerebral artery (PCA) syndrome       | Cerebellum                                                              | Mutism is associated with other symptoms of PCA syndrome (diplopia, vertigo, cranial nerve palsies)                                                                                                                                                                                            |

|               |                       |                                                                                                          |                                                                                                                                                                                                                                          |
|---------------|-----------------------|----------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|               |                       |                                                                                                          | cranial nerve<br>ataxia)                                                                                                                                                                                                                 |
|               | Hemorrhages           | Same as above,<br>third ventricle                                                                        | Same as above<br>depending on<br>of hemorrhage<br>hemorrhage<br>third ventricle<br>meningismus<br>previous history<br>intense headache<br>be present. Critical<br>in distinguishing<br>ischemic lesions                                  |
| Neoplasia     |                       | Same as above                                                                                            | Same as above<br>depending on<br>localization,<br>symptom onset<br>progression &<br>usually progresive.<br>Seizures can<br>present                                                                                                       |
| Trauma<br>[5] | Closed head<br>injury | Posterior fossa<br>Basal ganglia<br>Diffuse brain<br>injury (w or w/o<br>left hemisphere<br>involvement) | Mutism present<br>in patients after<br>for severe closed<br>injury despite<br>recovery of<br>consciousness<br>non-verbal<br>communication<br>Recovery often<br>progressively<br>outcome in patients<br>with basal ganglia<br>hemispheric |
| Post surgical | Cerebellar            | Posterior fossa                                                                                          | 1–6 days after                                                                                                                                                                                                                           |

|                   |                       |                              |                                                                                                                                                                                                                                                                                           |
|-------------------|-----------------------|------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                   | mutism [6]            | surgery                      | surgery, more common in children with medulloblastoma. Limited duration, day to 4 months. Spontaneous resolution with or without speech. Ataxia, hypotonia, cranial nerve palsies, hemiparesis, emotional lability may be present                                                         |
| Infective disease | Temporal encephalitis | Herpes simplex virus (HSV-1) | Mutism + confusion, stupor and fever. Meningitic signs or may not be present. CSF: normal WBC 5–500/mm <sup>3</sup> , possible ↑ RBC. Diagnosis with EEG: temporal epileptiform activity. CT can show hemorrhagic infarction. MRI: T2 hyperintense temporal and/or orbitofrontal lesions. |
|                   | Cerebellitis          | Rotavirus                    | Mutism +/- altered mental status, headache, ataxia, vertigo, impaired consciousness, pathologic limb reflexes. CSF as in HSV.                                                                                                                                                             |

|                             |                                  |                            |                                                                                                                                                                                                |
|-----------------------------|----------------------------------|----------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                             |                                  |                            | encephalitis,<br>hyperintensit<br>bilateral dem<br>nucleus, ther<br>and hemisph                                                                                                                |
| Demyelinating disorders     | Disseminated encephalomyelitis   | In children                | Mutism can be presenting sign in cerebellitis                                                                                                                                                  |
| Neurodegenerative disorders | Rapidly progressive dementia     | CJD                        | History of progressive dementia, dysequilibrium, myoclonus, tonic rigidity. EEG shows classical pseudoperiodic discharges, CSF should exclude encephalitis. CSF may show increased tau protein |
|                             | Late stage dementia              | Alzheimer, other dementias | Long history of progressive dementia. Signs of frontal release (Meyerson), social environment interaction. Myoclonus and epileptic seizures may be present                                     |
| Speech development failure  | Congenital mental retardation    |                            | Children who have developed speech difficulties                                                                                                                                                |
|                             | Pervasive developmental disorder | Autism spectrum disorders  | Absence or delay in speech + difficulties in relating to people (lack of eye contact)                                                                                                          |

|                                                                |                                                              |                                                                                                                                                                                                                      |                                                                                                                                                                         |
|----------------------------------------------------------------|--------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                |                                                              |                                                                                                                                                                                                                      | contact, point behavior, lack of facial expression, limited social repetitive body movements, behavioral problems, difficulties with changes in routine<br>Onset before |
| Congenital or early onset (before age 5) deafness              | Acute infectious disease (measles, encephalitis, meningitis) |                                                                                                                                                                                                                      | Learning of language prevented by hearing before 3. Hearing loss at the age of 5 or more in loss of previously acquired language                                        |
| Toxic (thalidomide, aminoglycosides in pregnancy, kernicterus) |                                                              | No response to auditory stimuli presence of intact response to visual ones. Sensorineural deafness by audiometry. Absence of oculo-vestibular reflex in congenitally deaf children preserved in progressive deafness |                                                                                                                                                                         |
| Toxic                                                          | Hallucinogens                                                | Phencyclidine                                                                                                                                                                                                        | Drug-induced psychosis                                                                                                                                                  |
|                                                                | Alcoholism                                                   |                                                                                                                                                                                                                      | Alcohol-induced psychosis                                                                                                                                               |
| Iatrogenic                                                     |                                                              | Aspirin                                                                                                                                                                                                              | Aspirin intoxication                                                                                                                                                    |

|                 |                        |                                                                                                                                                        |
|-----------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------|
|                 | Corticosteroids        | Mutism with catatonia due to replacement for Addison's disease                                                                                         |
| Drug withdrawal | Antidepressants<br>BZD | As above, or days after abrupt withdrawal of longstanding antidepressants or BZD. Supportive treatment                                                 |
| Metabolic       | Endocrine disorders    | Diabetic ketoacidosis, hyper/hypotension, Addison's disease, Congenital hypothyroidism, cretinism, goiter, and death in addition to non-organic causes |

---

BZD, benzodiazepines; CJD, Creutzfeldt–Jakob disease; CSF, cerebrospinal fluid; CT, computerized tomography; EEG, electroencephalography; MRI, magnetic resonance imaging; RBC, red blood cells; WBC, white blood cells.

A published review and case series of 22 patients with mutism ascertained that nine had an affective disorder, seven schizophrenia, two personality disorder, and four an organic cerebral cause. Stroke was the most common organic cause in the series. In that case series, features suggesting an organic etiology included irregular respiration, abnormal pupillary responses, roving eye movements, facial weakness, and exaggerated jaw jerk. Resistance to eye opening, however, suggested a non-organic etiology [7].

## References

- Rosebush PI, Mazurek MF. Catatonia. Clinical features, differential diagnosis

- and treatment. In Jest DV, Friedman JH, Eds. *Psychiatry for Neurologists*. Totowa, NJ: Humana Press, 2006:81–92.
2. Viana AG, Beidel DC, Rabian B. Selective mutism: a review and integration of the last 15 years. *Clin Psychol Rev* 2009; 29:57–67.
  3. Nagaratnam N, Nagaratnam K, Ng K, Diu P. Akinetic mutism following stroke. *J Clin Neurosci* 2004; 11:25–30.
  4. Ropper AH, Samuels MA, Eds. Disorders of speech and language. In *Adams and Victor's Principles of Neurology*, Vol. 2, 9th edn. New York, NY: McGraw Hill, 2009.
  5. Levin HS, Madison CF, Bailey CB *et al*. Mutism after closed head injury. *Arch Neurol* 1983; 40:601–6.
  6. Gudrunardottir T, Sehested A, Juhler M, Schmiegelow K. Cerebellar mutism – review of the literature. *Childs Nerv Syst* 2011; 27:355–63.
  7. Altshuler LL, Cummings JL, Mills MJ. Mutism: review, differential diagnosis, and report of 22 cases. *Am J Psychiatry* 1986; 143:1409–14.

## 45 Myalgia, cramps

---

Gary P. Kaplan and Rina Caprarella *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Myalgia, or muscle pain, is a presenting symptom that first must be distinguished from other causes of pain involving tissues surrounding muscle. In particular, a thorough history, physical examination, and ancillary testing should separate muscle pain from the pain of joint inflammation or trauma, and from pain originating in the fascia or bone. All of us experience myalgia of a transient nature as a result of our usual activities of daily living. The most common myalgia is that associated with muscle overuse or trauma, as a result of athletic activity. The pain is typically characterized as a “soreness” or “ache.” Another commonly experienced myalgia is that associated with viral illness, especially influenza in its prodrome. These myalgias are self-limited and often do not come to clinical attention.

Common acute causes of myalgia include overuse and muscle trauma, and viral illness. Common sub-acute causes of myalgia include drug toxicity, particularly statins.

Myalgia may be a presenting symptom along with arthralgias in systemic lupus erythematosus (SLE), and an infrequent symptom in inflammatory myopathies.

The testing is targeted towards assessing for underlying myopathy or myositis. Complete blood count (CBC) and erythrocyte sedimentation rate (ESR) are useful in the assessment of inflammation/infection. Creatine phosphokinase (CPK) and aldolase along with urine myoglobin can reveal evidence of muscle breakdown. Serologic studies help to detect autoimmune disorders. Electromyography and nerve conduction studies (EMG/NCS) can be pursued to demonstrate the presence of myopathy/myositis. In addition, depending on the above results, a muscle biopsy can be helpful in cases of metabolic disorders.

## Case vignette

A 54-year-old male presented with a 6-week history of aching pain in the thighs and to a lesser extent the calves bilaterally. He remembers an upper respiratory infection just before the start of his pain, but does not recall a fever. Two months prior to the onset of his pain he had started aerobic exercises 3 days a week at a local gym. One week prior to the onset he was started on simvastatin 20 mg for persistently elevated cholesterol.

Examination revealed no evidence of muscle atrophy or rash, no tenderness to muscle palpation, and no weakness proximally or distally in either the upper or lower extremities. Deep tendon reflexes were intact at the biceps, knees, and ankles. No cramps or fasciculations were observed. Laboratory data included: ESR = 16, CPK = 145, aldolase = 4.0, and vitamin D = 11.

Although risk factors for myalgia in this case included viral illness and excessive exercise, the patient's persistent symptoms, in the face of a normal CPK, recent statin introduction, and low vitamin D level, point to statin-induced myalgia [9,10]. Simvastatin was stopped and myalgia disappeared. Consideration was given to the reintroduction of a statin after vitamin D supplementation .

**Table 45.1 Differential diagnosis of myalgias.**

| Types of myalgias                                                                                                                                       | Possible clinical features                                                                   | Etiology                                                                                                                                                        | Electrophysio findings/blood work results |
|---------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------|
| Drug-induced myalgia: statins, corticosteroids, antiarrhythmic agents, colchicine, antiviral drugs, antiretroviral medications, immunomodulatory agents | Statin medications are the most common of the toxic causes, occurring in 10% of patients [1] | Etiology is unclear: statin-induced reduction in CoQ10 may be a source of the myopathy and myalgia associated with statin therapy [2]. Vitamin D deficiency has | EMG is normal CPK is typically normal     |

deficiency has been associated and correction may

reverse or prevent symptoms [3,4]. Removal of the agent typically is accompanied by rapid resolution of muscle pain

|                               |                                                                                                                      |                                                                                                  |                                                                                                                                                                                                                                                     |
|-------------------------------|----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Rhabdomyolysis                | Acute myalgia, muscle tenderness, and generalized weakness                                                           | Drug toxicity, viral illness, direct injury, or severe potassium deficiency                      | Elevated CPK level. The extent of myofiber necrosis as evidenced by serum CPK levels can be equated with the degree of muscle pain as experienced by patient but there isn't a linear relationship. Myoglobinuria is seen. EMG is typically normal. |
| Eosinophilia–myalgia syndrome | Myalgia associated with scleroderma-like skin changes, interstitial pneumonitis, and neuropathy [5]. Currently rare, | Caused by the ingestion of a concentrated tryptophan dietary supplement produced by one company, | Eosinophil levels are elevated. Nerve conduction studies can be consistent with large fiber peripheral neuropathy. EMG is typically normal.                                                                                                         |

|                    |                                                                                                                                                                                                                                                                                 |                                                                                                                                                                                                                            |
|--------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                    | <p>but was of great concern almost two decades ago</p>                                                                                                                                                                                                                          | <p>likely related to a toxic metabolite introduced in the manufacturing process</p>                                                                                                                                        |
| Infection          | <p>Myalgia, febrile syndrome, and generalized fatigue</p>                                                                                                                                                                                                                       | <p>In the appropriate clinical setting, tick-borne illnesses, muscle abscesses, trichinosis, malaria, and dengue may be considered</p>                                                                                     |
| Metabolic myopathy | <p>Hypothyroidism can result in muscle pain, but inherited metabolic myopathies, including glycogen and lipid storage diseases, are not typically associated with muscle pain, with the exception of muscle cramping with excessive physical activity.</p> <p>Patients with</p> | <p>Results from the disruption of energy metabolism in exercising muscles</p> <p>TSH elevation hypothyroidism Muscle biopsy/EMG consistent with myopathy in inherited disorders. Elevated CPK levels are also expected</p> |

muscuar  
dystrophy  
typically do not  
experience  
muscle pain at  
rest

Autoimmune  
disorders:  
Polymyalgia  
rheumatica, SLE,  
polymyositis, and  
dermatomyositis

Polymyalgia  
rheumatica is  
typically a self-  
limited illness,  
lasting up to a  
few years. It  
occurs in  
patients over 50  
years of age, and  
is closely  
associated with  
giant cell  
arteritis.  
Myalgias are  
experienced  
primarily in  
shoulder and hip  
girdle muscles,  
and bursitis and  
synovitis are  
often present  
SLE typically  
manifests in  
abnormalities of  
the skin, joints,  
blood cells,  
kidneys, and  
nervous system,  
with evidence of  
microvascular  
inflammation.  
Patients with  
SLE may present

These  
disorders are  
characterized  
by immune  
dysregulation.  
In some cases,  
circulating  
immune  
complexes are  
found (e.g.  
antinear  
antibodies in  
SLE)

The erythrocyt  
sedimentation :  
is frequently  
elevated, and  
patients respon  
clinically to  
corticosteroid  
medication [6]  
CPK levels are  
elevated.  
EMG/muscle  
biopsy can sho  
evidence of  
myositis/myop  
Serologic testii  
often helpful

~~SLC~~ may present  
with myalgias,  
but these are  
typically

associated with  
arthralgias and  
in some cases  
frank arthritis [7]  
In polymyositis  
and  
dermatomyositis,  
less than 30% of  
patients present  
with muscle  
pain. These  
inflammatory  
myopathies  
present with  
symmetric  
proximal  
weakness,  
gradual in onset,  
and typically  
painless, even  
though CPK  
elevations may  
be striking.  
Arthralgias  
however, may be  
present [8]  
Sporadic  
inclusion body  
myositis,  
typically seen in  
older White  
males,  
progressively  
causes  
asymmetric

proximal and distal weakness. However, myalgias are uncommonly reported

|              |                                                                                                                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                              |                                                                                                   |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Fibromyalgia | A syndrome that results in widespread pain along with tenderness to touch involving the muscles, joints, and soft tissue. It is typically also accompanied by symptoms of fatigue, sleep disturbance, bowel disturbance, cognitive dysfunction, and non-dermatomal sensory complaints. Diagnostic criteria were established in 1990 by the Multicenter Criteria Committee of the American College of Rheumatology which outlined | Etiology of fibromyalgia remains unclear. There is a suggestion of genetic predisposition, as first-degree relatives of individuals with fibromyalgia have an eight-fold greater risk of development. In addition, polymorphisms that impact the metabolism or transport of monoamines have been noted. External factors including physical trauma, emotional stress, and certain infections | Work-up is done to rule out other mimicking conditions, as fibromyalgia is diagnosis of exclusion |
|--------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|

that the diagnosis is supported by at least 3 months of widespread pain, and pain and tenderness in at least 11 of 18 areas including arms, buttocks, chest, knees, lower back, rib cage, shoulders, thighs, and neck. Current FDA-approved treatment options include pregabalin (Lyrica), duloxetine (Cymbalta), and milnacipran (Savella) (hepatitis C virus, Epstein–Barr virus, parvovirus, Lyme disease) have been seen to enhance symptoms

---

CPK, creatine phosphokinase; EMG, electromyogram; ESR, erythrocyte sedimentation rate; SLE, systemic lupus erythematosus; TSH, thyroid-stimulating hormone; WBC, white blood cells.

## References

1. Harris L, Thapa R, Brown M *et al*. Clinical and laboratory phenotype of patients experiencing statin intolerance attributable to myalgia. *J Clin Lipidol* 2011; 5:299–307.
2. Mas E, Mori T. Coenzyme Q(10) and statin myalgia: what is the evidence? *Curr Atheroscler Rep* 2010; 12:407–13.
3. Linde R, Peng L, Desai M, Feldman D. The role of vitamin D and

SLCO1B1\*5 gene polymorphism in statin-associated myalgias. *Dermatoendocrinology* 2010; 2:77–84.

4. Glueck C, Abuchaibe C, Wang P. Symptomatic myositis-myalgia in hypercholesterolemic statin-treated patients with concurrent vitamin D deficiency. *Med Hypotheses* 2011; 77:658–61.
5. Medsger T. Eosinophilia-myalgia syndrome. *Medscape*. 15 October 2009.
6. Saad E. Polymyalgia rheumatica. *Medscape*. 25 August 2011.
7. Bartels C. Systemic lupus erythematosus (SLE). *Medscape*. 15 November 2011.
8. Pappu R. Polymyositis. *Medscape*. 30 September 2011.
9. Gupta A, Thompson P. The relationship of vitamin D deficiency to statin myopathy. *Atherosclerosis* 2011; 215:23–9.
10. Mor A, Wortmann R, Mitnick H, Pillinger M. Drugs causing muscle disease. *Rheum Dis Clin N Am* 2011; 37:219–31.

## 46 Myoclonus

---

Venkat Ramani, David Elliott Friedman, and Mehri Songhorian *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Myoclonus is a sudden, abrupt, involuntary jerk of a muscle or a group of muscles caused by rapid, brief bursts of muscle contraction. It can be a symptom of a diverse variety of systemic and neurologic disorders. The list of etiologic factors is extensive and includes toxins, drugs, infection, trauma, metabolic errors, degenerative disorders, genetic defects, and the epilepsies. Myoclonus is common with an estimated prevalence of 8.6 per 100,000. Early recognition of the disorder and the underlying etiology is crucial because myoclonus is often a very disabling symptom.

For the busy clinician, a systematic clinical approach will greatly facilitate the diagnostic process in suspected myoclonus ([Table 46.1](#)). Although this sequential approach is recommended for conceptual clarity, it is acknowledged that in practice clinicians will “multi-task” and use a “parallel processing” approach for establishing the diagnosis.

**Table 46.1 Clinical approach to the diagnosis of myoclonus.**

---

- A. Establish that the presenting symptom is myoclonus and rule out other abnormal movement disorders
  - B. Define the type of myoclonus in physiologic terms. Identify the probable etiology based on the clinical features of myoclonus including age and mode of onset, course of the disorder, comorbid conditions, and associated neurologic deficits
-

## Differential diagnosis of myoclonus

Myoclonus must be differentiated from a number of other abnormal paroxysmal motor phenomena such as tremor, dystonia, dyskinesia, tics, chorea, hemiballismus, and seizures. This diagnostic challenge, while not a problem for movement disorder experts, can at times be quite vexing for the non-specialist physician.

Myoclonus is an abrupt, almost shock-like muscle jerk usually involving the limbs.

Occasionally myoclonic movements may be rhythmic as in palatal myoclonus (palatal tremors). Myoclonus is most often caused by muscle contraction (positive myoclonus) but may also be on occasions secondary to inhibition of ongoing muscle activity (negative myoclonus). Asterixis is an example of negative myoclonus. Because of its unique pathophysiology, asterixis is discussed in detail later in this chapter.

Tics are quick, abnormal stereotyped movements which may be simple or complex, involving a sequence of coordinated movements such as grimacing, sniffing, or gesturing. Complex tics are encountered classically in Tourette syndrome. Simple tics can be mistaken for myoclonus. The compelling need or the “urge” felt by the patient to make motor movement distinguishes a tic from myoclonus.

Tremors usually do not present a diagnostic problem. The sustained to-and-fro rhythmic, oscillatory nature of tremors can readily be differentiated from abrupt myoclonic jerks.

Chorea can pose a diagnostic problem. Choreaform movements, while rapid and irregular, are more sustained than myoclonus and not as lightning-like.

Hemiballismus is a form of chorea in which the jerks are abrupt (flinging) and of large amplitude involving the arm and leg on one side. This symptom is usually seen in acute focal vascular lesions involving the sub-thalamic nucleus.

Dystonia is an abnormal movement characterized by sustained muscle contractions and bizarre posturing of limbs. Usually these movements are slow (athetoid) but they may be abrupt with myoclonic overtones. Dystonias can often be diminished by tactile or proprioceptive sensory input such as touching the affected limb. In action-or task-specific dystonia, the symptom may be aggravated by voluntary movements. It is important to keep in mind that such modifiability does not imply a psychogenic etiology.

Tardive dyskinesia involves persistent rapid repetitive orobuccolingual and limb dyskinetic movements and is classically encountered as an adverse side effect of dopamine receptor (D2) blocker antipsychotic drugs.

Hyperekplexia consists of dramatic complex motor (startle) response to sudden tactile or auditory stimulus. This hypermotor activity can occur in the setting of advanced neurologic disorders with myoclonus, but is most often a separate independent entity with sporadic or familial occurrence.

Focal seizures are sustained and stereotyped, with a gradual build-up and decline with possible post-ictal motor weakness. In contrast, myoclonic jerks are random, quick, and often multifocal.

Psychogenic paroxysmal movements are not uncommon and can present a difficult diagnostic challenge. Some of the features of neurologic (organic) movement disorders (NMD) can mislead the clinician to suspect a psychogenic (functional) etiology (PMD).

Neurologic movement disorders disappear in sleep and have a tendency to be exacerbated by emotional stress.

Sensory input may diminish or aggravate the abnormal movements. Psychogenic movement disorders are often bizarre and consist of an incongruous cluster of different types of abnormal movements. No single feature can reliably differentiate psychogenic from neurogenic paroxysmal movement disorder. Often careful video-analysis of the episodes and clinical follow-up are necessary to establish the correct diagnosis.

## **Pathophysiologic classification of myoclonus**

The diagnosis of myoclonus is essentially a clinical one despite the availability of electrophysiologic tests such as electromyography (EMG), electroencephalography (EEG), evoked potential (EP) testing, and computer-based EEG back averaging technology for further diagnostic refinement in selected cases. Once the diagnosis of myoclonus is established, a careful analysis of the clinical phenomenology of the symptom should be undertaken in order to define the symptom in physiologic terms.

Myoclonus may occur in random isolation or in repetitive clusters. They may be focal, segmental, or generalized. They may originate from many levels of the neuraxis and are classified accordingly as cortical, cortical–subcortical, subcortical–non-segmental, segmental, or peripheral ([Table 46.2](#)).

**Table 46.2 Clinical neurophysiologic classification of myoclonus.**

|                                      | Cortical                                                                                                 | Cortical–subcortical               | Subcortical–non-segmental | Segmentae                 | Periodic?                             |
|--------------------------------------|----------------------------------------------------------------------------------------------------------|------------------------------------|---------------------------|---------------------------|---------------------------------------|
| EEG                                  | Variable; some with grossly visible epileptiform discharges and slow waves                               | Generalized spike and wave         | No consistent findings    | Normal                    | No                                    |
| EMG                                  | Bursts typically < 75 ms                                                                                 | Bursts < 100 ms                    | Variable burst duration   | Bursts typically > 100 ms | Variable but duration of discharge is |
| Back-averaged EEG time-locked to EMG | Time-locked correlation almost always present; focal sharp wave 10–40 ms before myoclonic jerk is common | Time-locked correlation is typical | No association            | No association            | No association                        |
| SEPs                                 | Enlarged                                                                                                 | Enlarged                           | Normal                    | Normal                    | No                                    |

|                                  |                                                                                          |                                  |                                          |                                                                                |   |
|----------------------------------|------------------------------------------------------------------------------------------|----------------------------------|------------------------------------------|--------------------------------------------------------------------------------|---|
|                                  | cortical component in many cases                                                         | cortical component possible      |                                          |                                                                                |   |
| Long latency EMG reflex response | Variable; enhanced long latency reflex (C reflex) typical with cortical reflex myoclonus | Some cases have C reflex at rest | Some cases have reflex response to sound | Variable; some are very short latency and incompatible with supraspinal origin | N |

---

EEG, electroencephalography; EMG, electromyography; SEPS, somatosensory evoked potentials.

Data from Caviness H, Brown P. Myoclonus: current concepts and recent advances. *Lancet Neurol* 2004;3:598–607.

They may occur at rest or during action, spontaneously or induced by posture or sensory stimulation. Myoclonic jerks usually occur during wakefulness but sometimes they are exclusively nocturnal, occurring in sleep. Finally the symptom may be abrupt or insidious in onset.

Myoclonus may be positive or negative (sudden relaxation in tonic muscle contraction).

Asterixis exemplifies the mechanism of negative myoclonus.

In 1949 Adam and Foley described a unique type of abnormal movement, characterized by jerky “flapping” bilateral hand tremors in patients with hepatic encephalopathy, which they subsequently termed asterixis [1]. Asterixis essentially consists of arrhythmic lapses of sustained posture that allow gravity or the elasticity of muscles to produce a movement, which the patient then corrects, sometimes with overshoot. The term derives from the Greek *a*, “not” and *sterxis*, “fixed position.”

Asterixis is a disorder of motor control characterized by irregular myoclonic

lapses of posture affecting various parts of the body independently. These lapses are caused by involuntary 50-to 200-ms silent periods appearing in muscles (even antagonistic groups of muscles) which are tonically active. In 1976 Young and Shahani for the first time used the term “negative myoclonus” to label the sudden and brief jerky movements observed in patients with asterixis and post-hypoxic intention myoclonus [2]. The definition of these phenomena as “negative” was justified by the demonstration that this type of abnormal movement was due to brief inhibition of the muscular activity; and therefore was considered as the opposite, or negative, counterpart of the well-known “positive” myoclonus, caused by a sudden, shock-like enhancement of the muscular tone. Neurophysiologic evidence has shown that positive and negative myoclonus, in spite of their apparent opposite definition, may be two closely associated motor phenomena.

Negative myoclonus may occur in different conditions, physiologic as well as pathologic. Physiologic negative myoclonus can be observed in normal subjects when falling asleep, following prolonged exercise, or provoked by unexpected stimuli or by sudden fright. A combination of positive and negative myoclonus may be encountered in a variety of conditions including post-hypoxic action myoclonus, progressive myoclonus epilepsies, torsion dystonia, cerebellar ataxia, and Huntington's disease. Asterixis can occur either as a focal or a generalized condition and is usually symptomatic of toxic or metabolic encephalopathy. Unilateral asterixis is often due to focal lesions of the contralateral cerebral hemisphere.

Careful analysis of the above physiologic characteristics of myoclonic jerks usually provides a reliable diagnostic profile, and guides further clinical and laboratory assessments ([Table 46.3](#)).

**Table 46.3 Clinical classification of myoclonus syndromes.**

---

1. Physiologic (nocturnal myoclonus, hiccoughs) 2.
  - Psychogenic (pseudo-tremors/ dystonia/ myoclonus) 3.
  - Essential myoclonus 4.
  - Symptomatic (toxic, metabolic, degenerative, genetic) 5.
  - Epilepsy syndromes (primary epilepsy syndromes, progressive myoclonic epilepsies)
-

## Etiologic diagnosis of myoclonic syndromes

This is the third and final step in the comprehensive assessment of myoclonic syndromes.

As noted earlier, myoclonus is a symptom of a diverse variety of conditions caused by toxic, metabolic, infectious, and degenerative etiologies. The final etiologic diagnosis can usually be arrived at by a careful integration of the information obtained from the first two steps outlined above with an assessment of comorbid conditions and associated deficits ([Table 46.4](#)).

## An orderly approach to the clinical diagnosis of myoclonus

[Table 46.5](#) outlines the steps involved in a systematic approach to the clinical diagnosis of myoclonus.

**Table 46.5 Key clinical questions for diagnosis of myoclonus.**

---

1. Is the onset of myoclonus acute or insidious?
  2. Is the course of illness progressive or non-progressive?
  3. Are there any unique features such as triggers, specific context?
  4. Is the neurologic examination normal or are there deficits?
  5. Are there any comorbid systemic disorders?
  6. Are there significant confounding psychological factors?
- 

The following triad of clinical features (mode of onset, disease progression, and comorbidity) is especially worth emphasizing in this process.

## Age and mode of onset

Onset in infancy and childhood, especially when associated with seizures and progressive cognitive loss, indicates a severe progressive myoclonic encephalopathy. Dementia, rigidity, and ataxia are frequently associated with

adult onset neurodegenerative disorders.

**Table 46.4 Etiologic diagnosis of myoclonus.**

| Category                 | Conditions                                                                            | Key clinical features and comments                                               |
|--------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|
| 1. Physiologic           | Nocturnal myoclonus (sleep jerks)                                                     | Occurs in sleep (non-REM), benign, and non-disabling                             |
|                          | Periodic limb movements in sleep (PLMS)<br>Restless leg syndrome                      | Occurs in sleep, can be quite distressing, may be a symptom of systemic disease  |
|                          | Hiccough                                                                              | Benign, rarely intractable                                                       |
| 2. Psychogenic myoclonus |                                                                                       | Bizarre multiple types of abnormal movements, variability of clinical features   |
| 3. Essential             | Myoclonic dystonia                                                                    | Familial or sporadic, upper extremity involvement, non-progressive benign course |
| 4. Symptomatic           | Symptomatic myoclonus is the largest etiologic type of myoclonus in clinical practice |                                                                                  |
| Toxins                   | Drugs (lithium, selective serotonin reuptake inhibitors, etc.)                        | Acute, reversible                                                                |

|                             |                                                       | (serotonin reuptake<br>inhibitors,<br>levodopa)                                                                 |
|-----------------------------|-------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Metabolic encephalopathies  | Anoxic (acute or postanoxic), renal, hepatic          | Acute or subacute onset, altered level of consciousness, prognosis depends on the primary condition             |
| Immune disorders            | Celiac disease                                        | Gastrointestinal symptoms, myoclonus, ataxia                                                                    |
|                             | Opsoclonus–myoclonus syndrome                         | Post viral or as paraneoplastic syndrome (neuroblastoma) in children                                            |
| Infections                  | Viral encephalitis<br>Encephalomyelitis with rigidity | Stiffness, rigidity, startle myoclonus, abnormal cerebrospinal fluid                                            |
|                             | Subacute sclerosing panencephalitis (SSPE)            | Onset in childhood<br>Insidious onset, progressive cognitive decline, seizures, ataxia, periodic pattern in EEG |
|                             | Whipple disease                                       | Weight loss, diarrhea, arthralgia, cognitive changes, seizures, ataxia                                          |
| Trauma                      | Brain, spinal, peripheral nerve injuries              | Rare complication, rigidity, tremors, focal, rhythmic segmental, and generalized myoclonus                      |
| Inborn errors of metabolism | Lysosomal disorders (Tay–                             | Onset in infancy, progressive                                                                                   |

|                                                                 |                                                                                                                                   |                                                                                                                                                                                                   |
|-----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                                 | Sachs)                                                                                                                            | encephalopathy, seizures, startle myoclonus, macular cherry-red spots, hexosaminidase deficiency                                                                                                  |
|                                                                 | Storage disorders<br>(neuronal ceroid lipofuscinosis)<br>Four subtypes are recognized based on age of onset and clinical features | Autosomal recessive, progressive cognitive decline, myoclonus, ataxia, visual loss, photosensitivity, abnormal electroencephalogram (EEG), abnormal evoked potentials, inclusion bodies in biopsy |
| Mitochondrial disorders                                         | Mitochondrial encephalopathy with ragged red fibers (MERRF)                                                                       | Familial or sporadic, variable clinical course, progressive ataxia, myoclonus, seizures, optic atrophy, myopathy, abnormal EEG, abnormal muscle biopsy (ragged red fibers)                        |
| Neurodegenerative disorders<br>Progressive adult-onset diseases | Huntington disease<br>(autosomal dominant inheritance, short arm of chromosome 4 locus)                                           | Progressive course, positive family history, chorea, dementia, psychosis                                                                                                                          |
|                                                                 | Hereditary ataxias<br>progressive myoclonic ataxias<br>(Ramsey–Hunt syndrome)                                                     | Familial, slowly progressive, ataxia, tremor, chorea, no seizures or dementia                                                                                                                     |

|                                                     |                                                                                                                                                                                                                                                          |
|-----------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>Alzheimer's disease</b>                          | Progressive dementia, myoclonus a late feature in some                                                                                                                                                                                                   |
| <b>Prion disease (Creutzfeldt–Jakob)</b>            | Rapidly progressive dementia, rigidity, myoclonus, ataxia, amyotrophy, periodic pattern in EEG                                                                                                                                                           |
| <b>Corticobasal ganglionic degeneration</b>         | Rigidity, dementia, alien limb syndrome, cortical myoclonus                                                                                                                                                                                              |
| <b>Dentatorubral–pallidoluysian atrophy (DRPLA)</b> | Progressive dementia, seizures, myoclonus, ataxia, rigidity                                                                                                                                                                                              |
| <b>5. Epilepsy syndromes</b>                        |                                                                                                                                                                                                                                                          |
| <b>Progressive myoclonic epilepsies (PME)</b>       | <b>Lafora body epilepsy</b><br>Autosomal recessive<br><br>Onset between ages 10 and 18<br>Rapid progression, dementia, seizures, abnormal EEG, positive skin and brain biopsy                                                                            |
|                                                     | <b>Unverricht–Lundborg disease</b><br>Autosomal recessive<br><br>Onset between ages 8 and 13<br>Stimulus sensitive myoclonus, early morning occurrence, absent or mild dementia in late stages, abnormal EEG, photosensitivity, positive genetic studies |
| <b>Sialidosis type I and II</b>                     | Seizures, visual loss, ataxia, cherry red spot in                                                                                                                                                                                                        |

|                                  |                                                                                                         |                                                                                                                                                                                                                     |
|----------------------------------|---------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                  | (autosomal recessive, neuraminidase deficiency)                                                         | macula, PAS positive biopsy                                                                                                                                                                                         |
| Primary epilepsy syndromes (PES) | Early myoclonic encephalopathies (EME)<br>Neonatal epileptic encephalopathy including Ohtahara syndrome | Developmental regression, fragmentary myoclonus, seizures, burst-suppression and spike-wave pattern in EEG                                                                                                          |
|                                  | Severe myoclonic epilepsy in infancy (Dravet syndrome)                                                  | Focal and generalized febrile and afebrile seizures, myoclonus, progressive cognitive decline, and abnormal epileptiform EEG                                                                                        |
|                                  | Lennox–Gastaut syndrome (LGS)                                                                           | Mental retardation, multifocal, intractable tonic, atonic, and atypical absence seizures, slow spike-wave pattern in EEG<br>Onset within 5 years of age.<br>Differentiate classic LGS from myoclonic variant of LGS |
|                                  | Juvenile absence with myoclonus                                                                         | Atypical absence epilepsy<br>Generalized fast spike-wave pattern in EEG<br>Onset around puberty                                                                                                                     |
|                                  | Juvenile myoclonic                                                                                      | Onset between ages 12 and 18                                                                                                                                                                                        |

|                |                                                                                                                                             |
|----------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| epilepsy (JME) | Non-progressive myoclonic epilepsy, early morning myoclonus, seizures, typical fast (3.5–4 Hz) spike-wave EEG findings, treatable condition |
|----------------|---------------------------------------------------------------------------------------------------------------------------------------------|

---

Acute onset of myoclonus in an individual with no prior history of medical or neurologic disorders is usually indicative of a toxic etiology. Many drugs and toxins can lead to and precipitate acute myoclonus (case vignette 1). The condition tends to be reversible if the offending agent is quickly recognized and eliminated. Sometimes acute myoclonus is encountered in the setting of a progressive neurologic disorder such as Parkinson's (PD) or Alzheimer's (AD) disease. The etiology is again drug related as is the case with levodopa-induced myoclonus. Acute myoclonus in AD may be drug induced or may signal a rapid deterioration of the disorder. Myoclonus occurring in the context of acute anoxic encephalopathy is often associated with a burst suppression pattern in the EEG and indicates poor prognosis. Acute onset of recurrent stimulus-sensitive myoclonus may be representative of the sequelae in anoxic encephalopathy (case vignette 2).

Insidious onset of myoclonus associated with the evolution of additional subtle neurologic symptoms is an ominous sign, suggestive of a neurodegenerative disorder, as further emphasized in the next paragraph.

## Symptom progression

The second important clinical clue to the diagnosis is the rate of symptom progression. Unfortunately this variable is unknown at the onset of the disorder and the correct diagnosis eludes early recognition. In metabolic disorders (hepatic, renal) the primary diagnosis is usually well established and the cause of recurrent myoclonus is often clinically obvious. Myoclonus associated with other progressive major neurologic signs and symptoms such as dementia, seizures, and ataxia indicates a neurodegenerative disorder (case vignette 3). Juvenile myoclonic epilepsy (JME) is an example of a neurologically non-progressive disorder with episodic myoclonus and seizures (case vignette 4).

## **Comorbid conditions**

Recognition of comorbid systemic disorders along with the constellation of co-existing neurologic signs/deficits is the third major piece of the puzzle that helps establish the final diagnosis. Weight loss along with prominent gastrointestinal symptoms may suggest Whipple or celiac disease. Myoclonus may occur in patients with established systemic lupus erythematosus.

Rare co-existing signs such as opsoclonus may suggest the diagnosis of a paraneoplastic disorder due to neuroblastoma, such as infantile opsoclonus myoclonus syndrome. Episodic staring spells, convulsions, and myoclonus may indicate an epilepsy syndrome and warrant further diagnostic evaluation. In children, progressive cognitive impairment along with myoclonus and seizures indicates a primary (West syndrome) or a symptomatic epilepsy syndrome (Lafora body disease, subacute sclerosing panencephalitis), and the prognosis is inevitably poor in such cases. The presence of dementia, rigidity, and ataxia in patients with myoclonus suggests a form of neurodegenerative multisystem disorder. In infants and children with inborn errors of metabolism the clinical disorder may manifest as regression of developmental milestones, spasticity, ataxia, optic atrophy, or hearing loss.

Finally, psychogenic movement disorders are not uncommon and can be the source of considerable diagnostic uncertainty. There are no easy guidelines for confirming the diagnosis in such cases, and often an extensive and time-consuming assessment process is required. This involves a detailed psychosocial evaluation, repeated clinical and video observations of the habitual clinical events, and electrophysiologic testing.

## **Case vignette 1**

A 56-year-old female with a history of bipolar disorder controlled on lithium was hospitalized for nausea, decreased level of alertness, tremors, and myoclonus involving her limbs in an asymmetric fashion. On examination the patient was somnolent but easily arousable to verbal stimuli. There was no evidence of dysphasia and her neurologic examination was normal with the exception of tremor in both of her hands admixed with intermittent myoclonus. Neuroimaging did not reveal any abnormalities. The patient's symptoms were attributed to lithium toxicity. She was managed with observation and intravenous hydration, and serum lithium concentrations declined to normal levels on day 4. The myoclonus abated, though the tremor persisted for another 3

days.

Lithium carbonate is used as a mood stabilizer. It has a narrow therapeutic index and patients undergoing dose adjustments with impaired elimination or dehydration are at risk for toxicity. Lithium toxicity presents with gastrointestinal symptoms, as well as polyuria, somnolence, delirium, tremors, and myoclonus. Late stage symptoms include cardiac arrhythmias, seizures, and coma, with a 10% risk of permanent neurologic sequelae. Correction of dehydration, discontinuing the drug, and increasing elimination by hemodialysis are treatment options for toxicity [3].

## Case vignette 2

A 74-year-old right-handed male with a history of hypertension, diabetes, dyslipidemia, and coronary artery disease was found to be unresponsive and on the floor by family members at home. Emergency services arrived at the scene shortly thereafter and evaluation revealed cardiac arrest with pulseless electrical activity (PEA). Cardiopulmonary resuscitation was performed and a pulse was established after 6 minutes. The patient was subsequently brought to a hospital and admitted to an intensive care unit (ICU) for further evaluation and management. The patient gradually improved clinically, and his mental status evolved from coma to lethargy, to fully alert state over the course of 2 days. Other than pneumonia and acute renal failure, the patient's hospitalization was uncomplicated. Post-hospitalization neurologic deficits included dysarthria and both appendicular and axial ataxia. The patient developed positive myoclonic jerks in an asymmetric fashion predominantly involving the arms and trunk. The jerks were typically triggered by action and interfered with daily functioning.

Postanoxic (intention/action) myoclonus is commonly seen in patients recovering from hypoxic encephalopathy. The condition was first described by Lance and Adams in 1963, and they described irregular myoclonic jerks triggered by action, in particular when the patient directs fast movements towards a target [4]. The myoclonus can affect muscles of the limbs, face, pharynx, and trunk. Postanoxic myoclonus, otherwise known as Lance–Adams myoclonus, can persist for decades following the initial brain insult, and is frequently associated with cerebellar ataxia. Severity varies, but most patients experience difficulties ambulating independently.

The pathophysiology of postanoxic myoclonus is thought to be related to serotonin deficiency, as the spinal fluid level of 5-hydroxyindoleacetic acid, the

chief metabolite of serotonin, is reduced. Pathologic findings have been reported to be variable, with minor abnormalities infrequently found.

Valproic acid and benzodiazepines, such as clonazepam, are effective in some cases for symptomatic treatment. A number of other agents have also been reported to be useful, and patients often require polypharmacy in treating the myoclonus.

## Case vignette 3

A 58-year-old male with history of diabetes mellitus and alcohol dependence sought medical attention for symptoms of insomnia, subjective cognitive complaints, including difficulties with memory and concentration, and change in mood. He was experiencing stress at work, though played it down, as he thought it was no different from the stress he typically experiences at work. Physical and neurologic examination was normal with the exception of difficulties with recall. Basic laboratory evaluation was normal, and a head CT revealed moderate diffuse atrophy. It was recommended that he gradually decrease his alcohol intake.

He was brought back to the office 1 month later for worsening confusion and jerks of his limbs. His examination at this time revealed worsening attention and recall, as well as horizontal and vertical nystagmus, dysmetria, and an inability to tandem walk. Magnetic resonance imaging of the brain with gadolinium showed hyperintensities in the caudate nuclei and putamen bilaterally on diffusion weighted imaging (DWI) and T2-weighted and fluid attenuated inversion recovery (FLAIR images). An electrocardiogram (EEG) revealed diffuse background slowing with fronto-temporally predominant synchronous periodic sharp waves. Cerebrospinal fluid analysis was normal with the exception of the presence of protein 14–3–3.

Diffuse myoclonus is often an early sign of Creutzfeldt–Jakob disease (CJD) and is a prominent feature of the disorder. Creutzfeldt–Jakob disease is considered a prion disease and is characterized pathophysiologically by progressive neuronal loss, proliferation of glial cells, and absence of inflammatory response. The mean age of onset is 57–62 years. It manifests with rapidly progressive dementia and profound disturbances of gait and coordination. The myoclonus associated with CJD typically occurs in a random fashion, but may attain rhythmicity and symmetry late in the disease. One of the hallmarks of the jerks associated with advanced CJD is the exaggerated startle

response, with violent myoclonus elicited by a variety of sensory stimuli. Symptoms of ataxia, insomnia, paraplegia, paresthesia, visual disturbance, and behavioral changes are less common. The diagnosis can be confirmed by MRI findings of bilateral symmetric, high-signal intensities in the basal ganglia on T2-weighted images. These findings are 67% sensitive and 93% specific [5]. Electroencephalography findings of periodic synchronous sharp wave complexes can augment the diagnosis [6].

## Case vignette 4

A healthy 15-year-old young male began experiencing involuntary jerks of his arms in an asymmetric fashion approximately an hour after waking up in the morning. The jerks would often cause him to drop objects from his hands, and on several occasions, his toothbrush was sent flying across the bathroom when he attempted to brush his teeth. The jerks would occur roughly twice a week, and were isolated to the mornings only. He did not think much of them and did not notify his parents of these movements. Approximately 3 months later, he experienced a diffuse-onset tonic-clonic seizure upon awakening, initially preceded by a rapid series of bilateral myoclonic jerks. Neurologic examination was normal. Diagnostic evaluation included an MRI, which was normal, and an EEG, which revealed brief bursts of generalized, frontally predominant 4.5 Hz spikes admixed with polyspikes. The patient was subsequently administered valproic acid and was seizure free, with abatement of the aforementioned myoclonic jerks.

Juvenile myoclonic epilepsy (JME) is the most common form of idiopathic generalized epilepsy in older children and young adults. The disorder manifests with generalized convulsive seizures, myoclonic jerks in the mornings that often involve the limbs or entire body, and sometimes accompanied by absence seizures. The patient often seeks medical attention because of the generalized seizure. It is not uncommon for myoclonus and absence seizures to persist unnoticed for years prior to making the diagnosis. Characteristic findings on EEG include generalized 4–6 Hz spike and polyspike activity. Though the disorder is not thought to affect cognitive functioning, several recent studies have reported cognitive impairments among these patients [7,8].

Many broad spectrum antiepileptic agents have been helpful in treating the disorder, including valproic acid, levetiracetam, lamotrigine, topiramate, and zonisamide. Pharmacotherapy is often highly effective in eliminating the

myoclonic, absence, and convulsive seizures, and patients often require life-long treatment, as recurrence off medication is frequent.

## Laboratory tests in the diagnosis of myoclonus

A systematic clinical approach as detailed above is usually quite effective for establishing the correct diagnosis. In many cases additional laboratory testing is needed for final diagnostic confirmation ([Table 46.6](#)). This is the province of specialists, and the general physician should refer to standard textbooks for additional details or make appropriate patient referrals to specialized centers.

**Table 46.6** *Laboratory diagnostic tests in myoclonic syndromes.*

---

1. Complete blood count, peripheral smear (acanthocytosis) 2. Comprehensive metabolic profile (hepatic/renal diseases) 3. Blood levels and toxic screen (lithium level) 4. Blood chemistry (lactic acid), serum antibodies, CSF (infection) 5. Brain imaging MRI (atrophy, calcifications) 6. EEG (background, spike-wave, photosensitivity, back averaging) 7. EMG, EP, and ERG
  8. Biopsy (skin, bone marrow, brain) 9. Genetic studies
- 

CSF, cerebrospinal fluid; EEG, electroencephalography; EMG, electromyography; EP, evoked potential; ERG, electroretinogram; MRI, magnetic resonance imaging.

## Further reading list

Aicardi J. Overview: syndromes of infancy and early childhood. In Engel J, Pedley TA, Eds. *Epilepsy. A Comprehensive Text Book*, Vol. 2, 2nd edn. Philadelphia, PA: Lippincott Williams and Wilkins, 2008:2309–311.

Aicardi J. Overview: Syndromes of late childhood and adolescence. In Engel J, Pedley TA, eds. *Epilepsy. A Comprehensive Text Book*, Vol. 2, 2nd edn. Philadelphia, PA: Lippincott Williams and Wilkins, 2008:2365–7.

Berkovic SF. Progressive myoclonic epilepsies. In Pellock JM, Dodson WE,

Bourgeois BFD, Eds. *Pediatric Epilepsy, Diagnosis and Therapy*, 2nd edn. New York, NY: Demos, 2001:233–42.

Fahn S, Frucht S. Myoclonus. In Rowland LP, Pedley TA, Eds. *Merritt's Neurology*, 12th edn. Philadelphia, PA: Lippincott Williams and Wilkins, 2010:732–4.

Fenichel GM. Movement disorders. In *Clinical Pediatric Neurology: A Signs and Symptoms Approach*, 5th edn. Philadelphia, PA: Elsevier Saunders, 2005:281–97.

## References

1. Adams RD, Foley JM. The neurological changes in the more common types of severe liver disease. *Trans American Neurol Assoc* 1949; 74:217–19.
2. Young RR, Shahani BT. Asterixis: one type of negative myoclonus. *Adv Neurol* 1986; 43:137–56.
3. Miller MA, Olson KR. Lithium. In Dart RC, Ed. *Medical Toxicology*, 3rd edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2004:805–10.
4. Lance JW, Adams RD. The syndrome of intention or action myoclonus as a sequel to hypoxic encephalopathy. *Brain* 1963; 86:111–36.
5. Schröter A, Zerr I, Henkel K *et al*. Magnetic resonance imaging in the clinical diagnosis of Creutzfeldt–Jakob disease. *Arch Neurol* 2000; 57:1751–7.
6. Steinhoff BJ, Zerr I, Glatting M *et al*. Diagnostic value of periodic complexes in Creutzfeldt–Jakob disease. *Ann Neurol* 2004; 56:702–8.
7. Wandschneider B, Kopp UA, Kliegel M *et al*. Prospective memory in patients with juvenile myoclonic epilepsy and their healthy siblings. *Neurology* 2010; 75:2161–7.
8. Iqbal N, Caswell HL, Hare DJ *et al*. Neuropsychological profiles of patients with juvenile myoclonic epilepsy and their siblings: a preliminary controlled experimental video-EEG series. *Epilepsy Behav* 2009; 14:516–21.

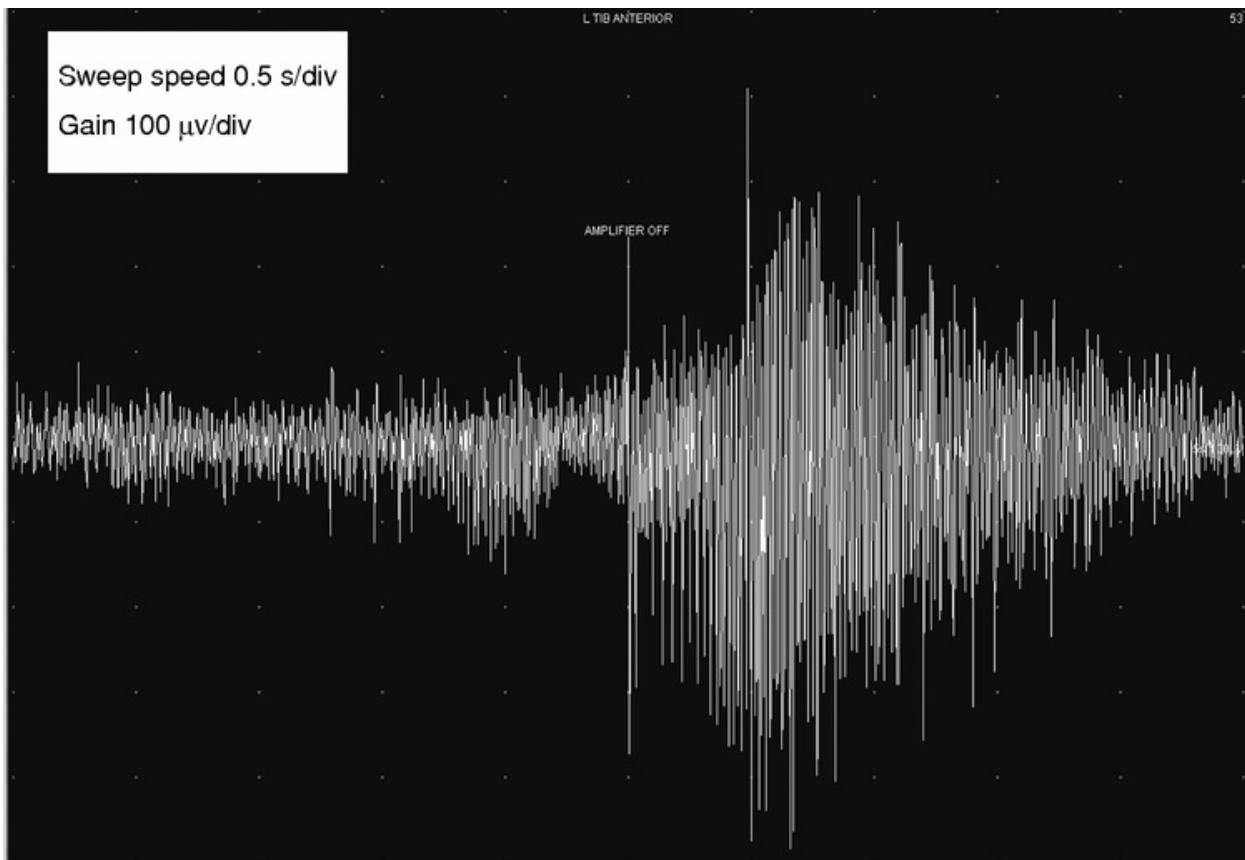
## 47 Myotonia

---

Beth Stein and Steven Herskovitz *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Myotonia is a clinical phenomenon and the cardinal feature of myotonic muscle disorders. It is the sustained involuntary contraction of a group of skeletal muscle fibers following voluntary muscle contraction (action or grip myotonia) or mechanical stimulation (percussion myotonia). The impaired relaxation of muscle from myotonia can lead to symptoms of stiffness, tightness, cramping, or pain. Clinical myotonia is the cumulative result of electrical hyperexcitability of individual muscle fiber membranes. Neurophysiologic myotonia is captured on needle electromyography (EMG) as repetitive spontaneous muscle fiber discharges with a characteristic waxing and waning frequency and amplitude ([Figure 47.1](#)).



**Figure 47.1** Myotonic discharge showing variation in amplitude and frequency. Myotonic discharges are spontaneous discharges of single muscle fibers with either a positive wave or brief spike morphology, wax and wane in frequency (20–150 Hz) and amplitude (10  $\mu$ v to 1 mv), and produce a characteristic dive-bomber sound.

Myotonia can occur in any skeletal muscle. It most commonly affects the distal hand muscles, but can also involve the eyelids, tongue, and legs. Patients often complain of symptoms immediately after initiating muscle activity. They may describe the inability to release their grip after handshake or tight grip, trouble opening their eyelids after a period of rest, and difficulty climbing stairs after sitting. While myotonia is often a presenting, non-disabling symptom, the related cramping and stiffness are major complaints throughout the course of the disease. On physical examination, action myotonia can be elicited by isotonic muscle contraction. The patient is asked to tightly grip and release the examiner's fingers. The myotonia is evident through the delayed and slow release of grip. Percussion myotonia is a prolonged muscle contraction after mechanical tap of the muscle with a reflex hammer. Percussion of the thenar eminence results in prolonged abduction of the thumb, and percussion of the

forearm extensor mass while the wrist is hanging down results in prolonged extension of the wrist/fingers. Striking the tongue may elicit contraction in the form of the napkin ring sign. The “warm-up phenomenon,” where myotonia improves with exercise or repeated efforts, can be demonstrated in involved muscles.

The myotonic muscle diseases are divided into dystrophic and non-dystrophic disorders ([Table 47.1](#)) and can be distinguished by their clinical features ([Table 47.2](#)), aided by the patterns of compound muscle action potential abnormality on the short and long exercise tests. Serum creatine kinase (CK) is usually normal or slightly elevated in these disorders. The non-dystrophic myotonias are a genetically heterogeneous group of muscle channelopathies involving the chloride (myotonia congenita) or sodium (paramyotonia congenita, hyperkalemic periodic paralysis, K<sup>+</sup>-aggravated myotonias) channels. The dystrophic myotonias, myotonic dystrophy type 1 (DM1) and type 2 (DM2), are expanded repeat disorders caused by an RNA-mediated disease mechanism with myotonia, progressive muscle atrophy, and multi-system involvement. Electrical myotonia, usually without clinical myotonia, can be seen in myotoxicity (statins, colchicine), other myopathies (acid maltase deficiency, polymyositis), or even associated with severe denervation. A number of conditions will need to be considered in the differential diagnosis of true myotonia by virtue of their association with muscle stiffness, cramping, or delayed relaxation. These include myophosphorylase deficiency (McArdle's disease; glycogenosis type V), hypothyroid myopathy (Hoffman's disease), sarcoplasmic reticulum-Ca<sup>2+</sup>ATPase deficiency (Brody's disease), acquired neuromyotonia, neuroleptic malignant syndrome, tetanus, stiff person syndrome, and dysferlinopathies. These will be distinguished by their associated clinical and electrophysiologic features ([Table 47.3](#)), and the absence of myotonia on needle EMG despite the presence of delayed muscle relaxation (pseudomyotonia) in some of these disorders.

**Table 47.1 Myotonic disorders.**

---

- Dystrophic myotonias
- Myotonic dystrophy type 1
- Congenital myotonic dystrophy
- Myotonic dystrophy type 2

Non-dystrophic myotonias  
*Chloride channelopathies*  
Myotonia congenita  
*Sodium channelopathies*  
Paramyotonia congenita  
Hyperkalemic periodic paralysis  
 $K^+$ -aggravated myotonias

---

## Dystrophic myotonias

DM1 and DM2 are autosomal dominantly inherited expanded repeat disorders with myotonia, multi-organ involvement, and progressive muscle atrophy and weakness. DM1 is the most common myotonic disorder in adults, and is caused by expansion of the CTG repeats within the 3' untranslated region in the *DMPK* gene on chromosome 9, which leads to nuclear retention of mutant RNA and subsequent RNA toxicity. In successive generations the phenomenon of genetic anticipation is often observed and is associated with instability of the repeat sequence. DM1 is a multi-system disorder that affects skeletal and smooth muscle as well as the eye, heart, endocrine, and central nervous systems. Myotonia, muscle stiffness, and muscle cramping are cardinal features. Muscle weakness and atrophy progress in a distal to proximal pattern. Respiratory muscle involvement, abnormal sleep architecture, hypercapnia, sleep apnea, and respiratory failure are late features. Cardiac conduction defects are common and contribute to patient mortality and risk for sudden death. Iridescent posterior subcapsular cataracts are often seen on slit lamp examination. Central nervous system involvement is frequent and manifests as concrete thinking, depression, low IQ, and apathy. Congenital myotonic dystrophy (CMD) affects infants born to mothers with DM1. Clinically they suffer from severe systemic involvement including hypotonia, mental retardation, cardiomyopathy, and respiratory insufficiency. The characteristic clinical myotonia is absent in infants, but may appear later on in childhood.

**Table 47.2 Clinical features of myotonic disorders.**

---

**Myotonic disorders**

|                                      | Clinical myotonia                                | Paradoxical myotonia | Cardiac conduction defects | Respiratory failure | M w |
|--------------------------------------|--------------------------------------------------|----------------------|----------------------------|---------------------|-----|
| DM1                                  | Common (percussion and grip)                     | –                    | +                          | +                   | +   |
| DM2                                  | Common (percussion and grip)                     | –                    | Variable                   | Variable            | +   |
| CMD                                  | Absent in infancy, common in child and adulthood | –                    | +                          | +                   | +   |
| Myotonia congenita – AD              | Common                                           | –                    | –                          | –                   | –   |
| Myotonia congenita – AR              | Common                                           | –                    | –                          | –                   | –   |
| Paramyotonia congenita               | Common (eyelid)                                  | +                    | –                          | –                   | –   |
| K <sup>+</sup> - aggravated myotonia | Common                                           | May be present       | –                          | –                   | –   |
| Hyperkalemic periodic paralysis      | Variable                                         | May be present       | –                          | –                   | –   |

---

AD: Autosomal dominant; AR: Autosomal recessive; CMD: Congenital

myotonic dystrophy; DM1: Myotonic dystrophy, type 1; DM2: Myotonic dystrophy, type 2; K<sup>+</sup>: Potassium.

+: Present; -: Absent

DM2, also known as proximal myotonic myopathy (PROMM), is caused by an expansion of CCTG repeats in intron 1 of the zinc finger gene ZNF9. Predominantly proximal muscles are affected, causing proximal weakness and atrophy as well as stiffness and cramping. Multi-system involvement can be seen but is less common. Myotonia may be more difficult to elicit on physical examination in patients with DM2. Electrical myotonia in DM2 may have more of a waning quality.

**Table 47.3 Differential diagnosis of myotonic disorders.**

| Potential mimickers of the myotonic disorders                        | Clinical features                                                                                                                             | Electrophysiologic features                      |
|----------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
| Myophosphorylase deficiency (McArdle's disease; glycogenosis type V) | Exercise intolerance, variably elevated CK at rest and after exercise, myoglobinuria, second-wind phenomenon                                  | Mild myopathy or normal                          |
| Hypothyroid myopathy (Hoffman's disease)                             | Muscle cramping and stiffness, fatigue, proximal weakness, muscle pseudohypertrophy, myoedema, slowed contraction and relaxation, elevated CK | Myopathy or normal, myoedema electrically silent |
| Sarcoplasmic reticulum-Ca <sup>2+</sup> ATPase                       | Muscle cramping and stiffness, exercise induced pseudomyotonia,                                                                               | Electrically silent cramps                       |

|                                              |                                                                                                                                           |                                                      |
|----------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| deficiency<br>(Brody's disease)              | may exacerbate with cold                                                                                                                  |                                                      |
| Acquired neuromyotonia<br>(Isaacs' syndrome) | Muscle cramping and stiffness,<br>pseudomyotonia,<br>pseudotetany (carpal or pedal spasms),<br>hyperhidrosis,<br>myokymia, fasciculations | Neuromyotonia,<br>myokymia                           |
| Neuroleptic malignant syndrome               | Muscle rigidity, fever, encephalopathy, autonomic instability, elevated CK                                                                | Excessive motor unit activity                        |
| Tetanus                                      | Muscle spasms and painful contractions, stimulus sensitive, trismus                                                                       | Continuous motor unit activity, absent silent period |
| Stiff person syndrome                        | Muscle stiffness and spasms, increased muscle tone, hyperreflexia and rigidity of muscles, axial predominance                             | Continuous motor unit activity                       |
| Dysferlinopathies                            | Muscle weakness and atrophy; high CK; occasionally exercise-induced stiffness                                                             | Myopathy                                             |

---

CK, creatine kinase.

Therapeutic interventions in the dystrophic myotonias are currently targeted towards symptom management. However, many advances have been made in understanding the complex pathophysiology of DM1 and will hopefully lead to novel therapeutic options for the dystrophic myotonias.

## Non-dystrophic myotonias

The non-dystrophic myotonias (myotonia congenita, paramyotonia congenita, hyperkalemic periodic paralysis, K<sup>+</sup>-aggravated myotonias), are pure skeletal muscle diseases, and do not involve the heart, brain, eye, or other organs. Muscle atrophy and weakness are not prominent features of these diseases. The major clinical complaints are muscle stiffness as a consequence of the myotonia, as well as pain and fatigue. The non-dystrophic myotonias are clinically distinguished by the presence or absence of periodic paralysis and other clinical features ([Table 47.2](#)).

Myotonia congenita is the most common inherited muscle channelopathy and is caused by mutations in the skeletal muscle chloride channel gene (*CLCN1*) on chromosome 7q. It can be inherited in either an AD (Thomsen's disease) or AR (Becker's disease) pattern; the recessively inherited disorder tends to be slightly more severe. The chloride channel myotonias are caused by a permanent reduction of the resting chloride conductance of the muscle fiber membranes. Normal chloride conductance is necessary for a fast repolarization of the muscle fiber membranes. When they are disrupted, the muscle fiber membranes stay depolarized causing myotonia, or become hyperdepolarized creating an inexcitable muscle fiber membrane leading to a transient paresis. Myotonia and its related muscle stiffness is the most characteristic clinical feature; it is most pronounced during rapid voluntary movements after a period of rest, and demonstrates the warm-up phenomenon. Severe cases may develop muscle hypertrophy. Patients with recessive myotonia congenita typically experience a transient weakness on initiating an action, which is only rarely seen in dominant myotonia congenita.

The sodium channel myotonias (paramyotonia congenita, K<sup>+</sup>-aggravated myotonia and hyperkalemic periodic paralysis) are allelic, AD disorders caused by point mutations in the skeletal muscle sodium channel gene (*SCN4A*) on chromosome 17q, resulting in a long-lasting depolarization of the muscle fiber membrane. The depolarization can initiate successive action potentials, leading to myotonia. Paramyotonia congenita is characterized by episodic muscle cramping and weakness, which are precipitated by cold and exercise. Facial, tongue, and hand muscles are most affected, and eyelid myotonia is almost always present. Paradoxical myotonia is a frequent feature of paramyotonia congenita, wherein myotonia worsens with continued exercise (opposite of the warm-up phenomenon). Hyperkalemic periodic paralysis may be accompanied by myotonia in some cases, although episodic paralysis is usually the dominant

feature. The attacks of paresis are frequent, brief, and often precipitated by rest after exercise, stress, and ingestion of certain foods. In K<sup>+</sup>-aggravated myotonia patients have myotonia that is exacerbated by potassium ingestion, without any sensitivity to cold. There is no associated weakness or attacks of paresis, and most notably patients respond to acetazolamide or mexilitine.

Many patients with non-dystrophic myotonic muscle disease who experience mild myotonia can manage their disease without medication. Severe, functionally limiting myotonia may require symptomatic treatment, usually with antiarrhythmics (mexilitene), antiepileptics (phenytoin; carbamazepine), or carbonic anhydrase inhibitors.

## Case vignette

A 41-year-old Lieutenant who was recently called back to active duty presented with progressive difficulty manipulating his gun. Over the past few months it had become increasingly difficult to release his clenched fingers from the trigger after firing. Since the age of 25 he has had mild difficulties manipulating fine objects, and hand stiffness. He had no weakness in his arms or legs, and no abnormal sensations of numbness and tingling. He stumbles frequently, but there have been no falls. He has a history of diabetes. His mother died due to sudden death at the age of 50. His 15-year-old son has difficulty texting for prolonged periods of time.

His neurologic examination revealed frontal balding, mild facial weakness, and non-fluctuating ptosis. He had mild weakness and atrophy of the intrinsic muscles of his hands and feet. He was able to toe walk, but was unable to heel walk. Percussion and grip myotonia were elicited on exam. Electromyography revealed myotonic discharges in the abductor pollicis brevis muscle (APB). Genetic analysis revealed an abnormal expansion of CTG repeats in the 19q13.3 *DMPK* gene, and he was diagnosed with myotonic dystrophy type 1. Further evaluations included a polysomnographic study which revealed the presence of sleep-disordered breathing, an electrocardiogram which revealed bundle branch block, and a slit-lamp examination which revealed posterior subcapsular cataracts.

Ankle--foot orthoses were recommended for assistance with foot weakness. Physical and occupational therapy were recommended for assistance with hand weakness and gait dysfunction. No medications were recommended for his hand stiffness due to the risk of precipitating cardiac conduction defects. He was

honorable discharged from duty.

## Further reading list

- Foff EP, Mahadevan MS. Therapeutics development in myotonic dystrophy type 1. *Muscle Nerve* 2011; 44:160–9.
- Haper PS. *Myotonic Dystrophy*. London: W.B. Saunders, 1989.
- Heatwole CR, Starland JM, Logigian EL. The diagnosis and treatment of myotonic disorders. *Muscle Nerve* 2013; 47:632–48.
- Mathews E, Fialho D, Tan SV *et al*. The non-dystrophic myotonias: molecular pathogenesis, diagnosis and treatment. *Brain* 2010; 133:9–22.
- Mexley RT. Myotonic muscular dystrophy. In Rowland LP, DiMauro S, Eds. *Handbook of Clinical Neurology*, Vol. 18. New York, NY: Elsevier, 1992: 209–59.
- Miller TM. Differential diagnosis of myotonic disorders. *Muscle Nerve* 2008; 37:293–9.
- International Myotonic Dystrophy Consortium (IDMC). New nomenclature and DNA testing guidelines for myotonic dystrophy type 1 (DM1). *Neurology* 2000; 54:1218–21.
- Saperstein DS. Muscle channelopathies. *Semin Neurol* 2008; 28:260–9.

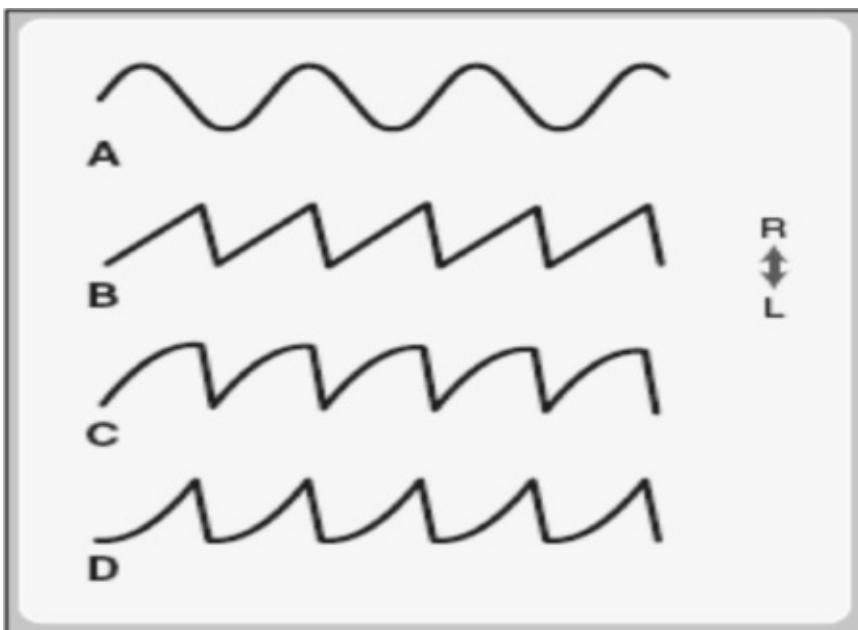
## 48 Nystagmus

---

Sarita B. Dave and Patrick J. M. Lavin *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

“Nystagmus,” from the Greek meaning “to nod off,” is an involuntary biphasic rhythmic ocular oscillation; while both phases may be slow, at least one phase always is slow. The slow phase is responsible for the initiation and generation of the nystagmus, whereas the fast phase is corrective movements bringing the fovea back on target [1–4]. Nystagmus interrupts steady fixation and may interfere with vision either by blurring the object of regard, or making the environment appear to oscillate (oscillopsia ), or both.

For clinical purposes, nystagmus is divided broadly into pendular and jerk forms. Either form may be horizontal or, less commonly, vertical. The different waveforms of nystagmus are illustrated in the oculographic diagram ([Figure 48.1](#)). Pendular nystagmus is characterized by a sinusoidal waveform with relatively equal velocities in both directions (A). Jerk nystagmus, named for the direction of the fast phase, is divided into three types on the basis of the slope of the slow phase tracing: constant linear velocity (B), exponentially decreasing velocity (C), and exponentially increasing velocity (D).



**Figure 48.1** Simulated oculographic nystagmus waveforms. A, Pendular (sinusoidal) nystagmus. B, Left-beating jerk nystagmus with a constant (linear) velocity slow phase. C, Left-beating jerk nystagmus with a decreasing (exponential) velocity slow phase. D, Left-beating jerk nystagmus with an increasing (exponential) velocity slow phase. Redrawn from Lavin [3].

Non-nystagmus ocular oscillations can mimic nystagmus and must be distinguished (see [Table 48.2](#)).

**Table 48.1 Clinical approach to diagnosis of nystagmus.**

---

Specific historical questions:

Is the nystagmus symptomatic? Congenital nystagmus, now called infantile nystagmus syndrome (INS), is usually asymptomatic

Was the nystagmus present at birth (or noted in the first few months of life) or was it acquired?

Is there a family history of nystagmus?

Is there a history of amblyopia or strabismus (lazy eye)?

Is the patient on medication known to induce nystagmus?

-----

Are there symptoms such as headache, diplopia, impaired vision, oscillopsia, vertigo, and other relevant neurologic complaints that may help focus the neurologic examination?

Focused examination:

Is the nystagmus present in primary position or only with eccentric gaze (gaze-evoked)?

Is the nystagmus monocular, binocular and conjugate, or dissociated?

Is there a latent component, *i.e.* an increase in nystagmus intensity when one eye is covered, as with INS and fusion mal-development nystagmus syndrome (FMNS)?

Is the waveform pendular or jerky?

If the nystagmus is jerky, determine the direction of the fast phase and whether it changes with the direction of gaze

Is there a torsional component?

Is there a spontaneous alteration of direction (as with periodic alternating nystagmus)?

Is there a null zone (direction of gaze where the nystagmus is minimal or absent) as with INS?

Does the nystagmus damp (suppress) or change direction with convergence (see [Table 48.2](#))?

Does the nystagmus alter (accentuate or suppress) with head positioning or posture, or with head shaking (as in spasmus nutans)?

What is the effect of optokinetic stimulation? In INS the response is suppressed or paradoxical (the fast phase is in the direction of the slow-moving target)

Are there associated rhythmic movements of other muscle groups

Are there associated myathmic movements or other muscle groups, such as the face, tongue, ears, neck, palate, or limbs, as in oculopalatal myoclonus/tremor or oculomasticatory myorhythmia (Whipple's disease)?

Is there a spontaneous head tilt or turn, titubation (as with INS)?

Are the pupil reflexes normal or paradoxical? Dilation in darkness occurs in some patients with INS and afferent visual disorders

Are there signs of ocular albinism as with INS?

Is suppression of the vestibulo-ocular reflex (VOR) impaired (as with some CNS degenerative diseases)?

---

## Mechanisms

Nystagmus results from dysfunction of the vestibular end-organ, vestibular nerve, brainstem, cerebellum, or cerebral centers for ocular pursuit. Pendular nystagmus ([Figure 48.1A](#)) is central in origin (cerebrum, brainstem, or cerebellum), whereas jerk nystagmus may be either central or peripheral (vestibular end-organ or vestibular nerve). Jerk nystagmus with a linear (constant velocity) slow phase ([Figure 48.1B](#)) is caused by peripheral vestibular dysfunction which produces an imbalance in vestibular input to the brainstem gaze centers. When the slow phase has an exponentially decreasing velocity ([Figure 48.1C](#)), the brainstem neural integrator (a network of neurons in the brainstem and cerebellum responsible for mathematically integrating neural output signals) is at fault. When the integrator is unable to maintain a constant output to the gaze centers to hold the eyes in an eccentric position, because the signal “fatigues,” the eyes drift off the target back towards primary position; then corrective saccades bring the eyes back to the target resulting in gaze-evoked (paretic) nystagmus. Exponentially increasing velocity slow phase nystagmus ([see Figure 48.1D](#)) is central in origin and is seen often with the infantile nystagmus syndrome (INS); this waveform occurs also with brainstem and cerebellar disorders that affect central vestibular function .

## Clinical evaluation

Frequently, the cause of nystagmus may be identified by the company it keeps ([Table 48.2](#)). When nystagmus is isolated, or the accompanying features are subtle, the approach outlined in [Table 48.1](#) is helpful. Associated clinical features, localization, and causes are listed in [Table 48.2](#). Examination with an ophthalmoscope, or a slit lamp, may detect subtle nystagmus not apparent to the naked eye.

## Case vignette

A 49-year-old female with a 5-month history of intermittent, then persistent, nausea and vertigo, “jumpy vision” (oscillopsia), and progressive unsteadiness, but no hearing loss or tinnitus had slow saccades, primary position downbeat nystagmus, and a wide-based ataxic gait with inability to perform tandem gait. She had no past or family history of neurologic or inner ear disorders. She did not use alcohol and was not on any medications known to cause nystagmus. The findings indicated midline-cerebellar dysfunction. Her history excluded toxic causes such as alcohol, antiepileptic drugs, lithium, and other sedatives. Her family history, and the relatively short duration of symptoms, largely ruled out familial spinocerebellar degeneration. Brain magnetic resonance imaging excluded structural disorders such as a Chiari malformation, a foramen magnum region tumor, and platybasia, and disorders such as demyelination, ischemia, inflammation, and idiopathic superficial siderosis. Her history, general exam, and tests ruled out HIV, metabolic disorders (hypothyroidism and gliadin sensitivity) and nutritional deficiencies such as vitamins E, B1 and B12. A paraneoplastic panel, including amphiphysin, was negative, and a whole body FDG-PET/CT scan was normal. Serology for GAD65 autoantibodies [[5](#)] was positive at 501 nmol/L (normal < 0.02), suggesting GAD65 positive autoimmune cerebellitis. She improved with intravenous steroids, gabapentin, and physical therapy.

**Table 48.2 Patterns, associations, and causes of different types of nystagmus and non-nystagmus oscillations.**

| Type of nystagmus | Waveform | Features | Localization |
|-------------------|----------|----------|--------------|
| Congenital forms  |          |          |              |

|                                                                                |                                                                                                                                                                                                                 |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |                |
|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Infantile nystagmus syndrome (INS)<br>(Previously called congenital nystagmus) | Pendular or jerk in primary position<br>Jerk on lateral gaze<br>If jerk then exponentially increasing velocity slow phase<br>Oscillations are usually conjugate and horizontal, and remain horizontal on upgaze | Usually asymptomatic<br>Normal vision unless associated with a condition listed under "Causes" (then a paradoxical pupil response may be present)<br>Amblyopia<br>Strabismus<br>Increases in amplitude and frequency on lateral gaze (Alexander's law)<br>Dampens with convergence<br>Null zone may be present causing a head turn<br>Increases in intensity when one eye is covered (latent superimposition)<br>Paradoxical optokinetic nystagmus (OKN) response<br>*Nystagmus blockage syndrome | Non-localizing |
|--------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|

(NBS)

|                                                                                                            |                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                  |                |
|------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------|
| Fusion mal-development nystagmus syndrome (FMNS) – Latent nystagmus (LN) – Manifest latent nystagmus (MLN) | Jerk<br>Horizontal<br>Linear<br>decreasing velocity slow phase towards the covered eye LN – with monocular fixation<br>MLN – with both eyes open but only one eye fixating  | No oscillopsia<br>Amblyopia<br>Strabismus<br>Dissociated vertical deviation<br>Some patients can suppress the oscillations at will<br><br>*NBS                                                                                                                                                                   | Non-localizing |
| Spasmus nutans syndrome (SNS)                                                                              | Pendular or jerk<br><br>May have horizontal, vertical, or torsional components<br><br>High-frequency, low-amplitude (eyes seem to shimmer), asymmetric, can be dysconjugate | Triad:<br>Torticollis,<br>Titubation (head-bobbing),<br>Asymmetric nystagmus (can appear monocular)<br><br>Onset between age 6–12 months; it resolves spontaneously in 2 years, but occasionally as long as 5 years<br>No oscillopsia<br>Esotropia<br>Vigorous head shaking to improve vision.<br>The titubation | Non-localizing |

has a lower frequency than the nystagmus and thus is not compensatory

## Acquired forms

|                                   |                                                                                       |                                                                                  |                                                                                                       |
|-----------------------------------|---------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| Gaze-evoked<br>(Gaze paretic)     | Absent in primary position                                                            | Only on eccentric gaze > 30°                                                     | Non-specific                                                                                          |
| – Physiologic<br>(Amplitude < 3°) | Jerk in direction of gaze with linear slow phase                                      | Symmetrical on right and left gaze but may be dysconjugate                       | Non-specific unless asymmetric, then structural lesion or myasthenia more likely                      |
| – Pathologic<br>(Amplitude > 4°)  | Jerk with decreasing exponential slow phase                                           | May have a torsional component                                                   |                                                                                                       |
|                                   |                                                                                       | Ataxia                                                                           |                                                                                                       |
|                                   |                                                                                       | Drowsiness                                                                       |                                                                                                       |
| Upbeat nystagmus                  | In primary position<br>Jerk<br>Increasing amplitude and velocity on increasing upgaze | Cerebellar signs<br>Brainstem signs<br>Ataxia<br>Other focal neurologic deficits | Bilateral ponto-medullary or ponto-mesencephalic junction, lower medulla, midline cerebellum (vermis) |
| Downbeat nystagmus                | In primary position<br>Amplitude increases when eyes are <del>deviated</del>          | Cerebellar signs<br>Lower brainstem signs<br>Ataxia<br>Syringobulbia             | Bilateral cranio-cervical junction, flocculus, commissural fibers in floor                            |

|                                                                |                                                                                                                                                                            |                                                                                                                                                                                                                                              |                                                                |
|----------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------|
|                                                                | deviated laterally and slightly downward<br>(Daroff's sign)                                                                                                                | syringomyelia                                                                                                                                                                                                                                | robers in floor of fourth ventricle                            |
| Periodic alternating nystagmus (PAN)<br>Congenital<br>Acquired | Horizontal jerk with fast phase in one direction, then dampens or stops for a few seconds before changing directions to the opposite side; complete cycle takes ~3 minutes | Albinism may be associated with the congenital form Cerebellar findings<br><br>Syringobulbia or syringomyelia<br>PAN rarely may be a manifestation of seizures<br><br>Hyperactive vestibular responses, poor vestibular fixation suppression | Similar to downbeat nystagmus<br>Lesions of cerebellar nodulus |
| Pendular nystagmus<br>Congenital (see above)<br>Acquired       | Sinusoidal waveform<br>Usually horizontal, may be vertical, torsional or                                                                                                   | When the oscillations are vertical they may be associated with natal tremor as                                                                                                                                                               | Paramedian pons<br>Deep cerebellar (fastigial) nuclei          |

Symptoms

elliptical  
Convergent—  
divergent  
oscillations are  
called  
“vergence  
nystagmus”  
(see  
culomasticatory  
myorhythmia  
below)

Physical examination

part of the  
“oculopalatal  
syndrome”

Mechanism

|                           |                                                                                                                                                                                                         |                                                                                                                                                                |                                                                                                                                                             |
|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Seesaw<br>nystagmus (SSN) | Pendular<br>One eye rises<br>and<br>incyclotorts<br>while the other<br>falls and<br>excyclotorts<br>Faster and<br>smaller on<br>upgaze, slower<br>and larger on<br>downgaze<br>May cease in<br>darkness | Bitemporal<br>hemianopia<br>Impaired central<br>vision<br>Congenital SSN<br>may be<br>associated with<br>a superimposed<br>horizontal<br>pendular<br>nystagmus | Lesions in the<br>region of the<br>meso-<br>diencephalic<br>junction,<br>particularly the<br>zona incerta<br>and the<br>interstitial<br>nucleus of<br>Cajal |
|---------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------|

|          |                                                                                                                                                                                                                   |                                                                                                                                                                                                                                                                                                                                                                                     |                                                                                                                                    |
|----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|
| Hemi-SSN | Jerk<br>The torsional component is conjugate<br>The direction of fast phase depends on location of lesion (see “Features”) The vertical component may be conjugate or disjunctive depending on location of lesion | With mesodiencephalic lesions, during the fast (jerk) phases, the upper poles of the eyes rotate toward the side of the lesion. The vertical component is always disjunctive (the eyes oscillate in opposite directions, with the intorting eye rising and the extorting eye falling)<br>With lateral medullary lesions, the upper poles jerk away from the side of the lesion. The | Unilateral or asymmetric mesodiencephalic lesions<br>Unilateral, or asymmetric medullary lesions (e.g. lateral medullary syndrome) |
|----------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------|

|                                                             |                                                                                                                                                                                                                                      |                                                                                                                                                                                                                                                                                                                                                                                                                   |                                                                                                                                                                           |
|-------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                                             |                                                                                                                                                                                                                                      | vertical component may be either conjugate (usually upward) or disjunctive                                                                                                                                                                                                                                                                                                                                        |                                                                                                                                                                           |
| Torsional nystagmus (TN), sometimes called rotary nystagmus | Pendular: Pure torsional oscillation in primary position or with either head positioning or gaze deviation Jerk: Fast phase toward the side of the lesion on downward pursuit and away from the side of the lesion on upward pursuit | Skew deviation With lesions in the region of the middle cerebellar peduncle, TN with a jerk waveform (similar to jerk SSN) may be evoked by vertical pursuit eye movement. The direction of the fast phase is usually is toward the side of the lesion on downward pursuit and away from the side of the lesion on upward pursuit. The same pattern of TN is seen during fixation suppression of the vertical VOR | Central vestibular pathways If purely pendular: Medulla If jerk: Middle cerebellar peduncle Mixed torsional/linear nystagmus may occur with peripheral vestibular disease |

|                      |                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                                                                             |                                                                                                     |
|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------|
| Brun's nystagmus     | Bilateral asymmetrical jerk nystagmus with decreasing exponential slow phase velocity on gaze towards the side of the lesion, and linear slow phase velocities on gaze away from the side of the lesion | Large-amplitude low-frequency oscillations on gaze toward the side of the lesion; small-amplitude, high-frequency oscillations away from the lesion<br>Other CPA findings such as:<br>– Ipsilateral deafness<br>– Facial weakness<br>– Vertigo<br>– Focal brainstem and long tract signs as result of brainstem compression or infiltration | Cerebello-pontine angle region (CPA)                                                                |
| Vestibular nystagmus | Peripheral: linear slow phase<br>Central: variable slow phase                                                                                                                                           | Peripheral: nausea, vomiting, perspiration, diarrhea, hearing loss, tinnitus<br>Central: headache, dysconjugate gaze, brainstem and pyramidal tract signs                                                                                                                                                                                   | Labyrinth, vestibular nerve, vestibular nuclei, or their connections in the brainstem or cerebellum |

|                                                                 |                                                                                   |                                                                                                                                                |                                                                            |
|-----------------------------------------------------------------|-----------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Convergence-evoked nystagmus (induced by voluntary convergence) | Usually pendular<br>Conjugate or dysjunctive<br>Upbeat more common than downbeat  | Convergence-evoked nystagmus should be distinguished from voluntary nystagmus and from convergence retraction nystagmus (see below)            |                                                                            |
| Ictal nystagmus                                                 | Usually horizontal<br>Rarely, in comatose patients, the nystagmus may be vertical | May accompany adversive seizures and beats to the side opposite the focus<br>May be associated with transient pupillary dilation of either eye | Seizure foci can occur in occipital, parietal, temporal, and frontal areas |
| Monocular nystagmus                                             | Variable                                                                          | Depends on cause                                                                                                                               | Variable                                                                   |

| <b>Non-nystagmus<br/>ocular<br/>oscillations</b> | <b>Waveform</b>                                                                                                                              | <b>Features</b>                                                                                                      | <b>Localization</b> |
|--------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------|---------------------|
| Square wave jerks (SWJs)                         | SWJs are spontaneous, small amplitude, paired saccades with an intersaccadic latency of 150–200 milliseconds that briefly interrupt fixation | May be normal or have features of cortical, basal ganglia, cerebellar, or brainstem disorders depending on the cause | Variable            |

Square-wave pulses (SWPs) were previously called macro-square wave jerks

SWPs also interrupt fixation; their amplitudes are 10–40°

Convergence-retraction “nystagmus”

Rapid dysmetric horizontal eye movement induced by attempted upgaze  
Rapid convergence, slow divergence

Dorsal midbrain (Parinaud's) syndrome:  
Paralysis of upgaze, light-near pupil dissociation, convergence-retraction nystagmus, eyelid retraction (“Collier's sign”) Impaired consciousness

Dorsal midbrain

|                                                                                                                              |                                                                                                       |                                                                                                                                           |                                                                                                                 |
|------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------|
| Ocular flutter                                                                                                               | Spontaneous horizontal conjugate back-to-back saccades                                                | Aggravated by fixation attempts<br>Triggered by a change in posture<br>Often associated with ocular dysmetria; may progress to opsoclonus | Cerebellar or brainstem disease                                                                                 |
| Voluntary flutter (voluntary “nystagmus”)                                                                                    | Induced horizontal conjugate back-to-back saccades                                                    |                                                                                                                                           |                                                                                                                 |
| Opsoclonus                                                                                                                   | Spontaneous, chaotic, multivector conjugate saccades                                                  | Aggravated by fixation attempts<br>Associated with myoclonic jerks of limbs and cerebellar ataxia                                         | Cerebellum or brainstem disease                                                                                 |
| Ocular bobbing<br>Reverse bobbing<br>Dipping (inverse bobbing)<br>Reverse dipping<br>V-pattern<br>pretectal<br>pseudobobbing | Rapid downward eye movement followed by a slow drift back to primary position (2–15 times per minute) | Coma or impaired consciousness<br>Horizontal gaze palsies<br>With atypical bobbing horizontal eye movements are                           | Central pons<br>Usually non-localizing encephalopathy<br>Usually non-localizing encephalopathy<br>Hydrocephalus |

|                              |                                                                                                                            |                                                                                               |                                       |
|------------------------------|----------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|---------------------------------------|
|                              | Rapid upward movement followed by a slow downward drift                                                                    | preserved consciousness                                                                       |                                       |
|                              | Slow downward movement, rapid return to primary position                                                                   | Coma or impaired consciousness                                                                |                                       |
|                              | Slow upward movement followed by a fast downward return to primary position                                                | Coma or impaired consciousness                                                                |                                       |
|                              | Fast downward convergent movements at higher frequency than typical bobbing; slower-than-normal return to primary position | Coma or impaired consciousness                                                                |                                       |
| Oculomasticatory myorhythmia | Continuous rhythmic jaw contractions synchronous with dissociated pendular vergence oscillations                           | Supranuclear vertical gaze palsy, altered mentation, somnolence, mild uveitis, or retinopathy | Usually non-localizing encephalopathy |

---

\* Nystagmus blockage syndrome (NBS) is a strategy used to suppress nystagmus in INS: outside the null zone the nystagmus increases in intensity (Alexander's law), so patients intentionally induce an esotropia to suppress the nystagmus in the adducting eye. This results in a head turn in the direction of the fixating (adducted) eye.

\*\* Delayed recognition and treatment can result in permanent neurologic damage.

## References

1. Classification of Eye Movement Abnormalities and Strabismus (CEMAS) Working Group. 2003. <http://www.nih.gov/news/statements/cemas>. (Accessed April 30 2007.)
2. Dell'Osso LF, Daroff RB. Nystagmus and saccadic intrusion and oscillations. In Glaser JS, Ed. *Neuro-Ophthalmology*, 3rd edn. Philadelphia, PA: Lippincott Williams & Wilkins, 1999: 369–401.
3. Lavin PJM. Neuro-ophthalmology: the ocular motor system. In Daroff RB, Fenichel GM, Jankovic J, Mazziotta JC, Eds. *Bradley's Neurology in Clinical Practice*, 6th edn. Boston, MA: Butterworth Publishing, 2012.
4. Leigh RJ, Zee DS. *The Neurology of Eye Movements*, 4th edn. New York, NY: Oxford University Press, 2006: 475–558.
5. Crino PB, Galetta SL, Sater RA *et al.* Clinicopathologic study of paraneoplastic brainstem encephalitis and ophthalmoparesis. *J Neuroophthalmol* 1996; 16:44–8.
6. Self J, Lotery A. A review of the molecular genetics of congenital idiopathic nystagmus (CIN). *Ophthalmic Genet* 2007; 28:187–91.
7. Lavin PJM. Hyperglycemic hemianopia: a reversible complication of non-ketotic hyperglycemia. *Neurology* 2005; 65:616–19.

## **49 Ophthalmoparesis, gaze conjugate lateral deficit and conjugate vertical deficit**

---

Matthew J. Thurtell *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

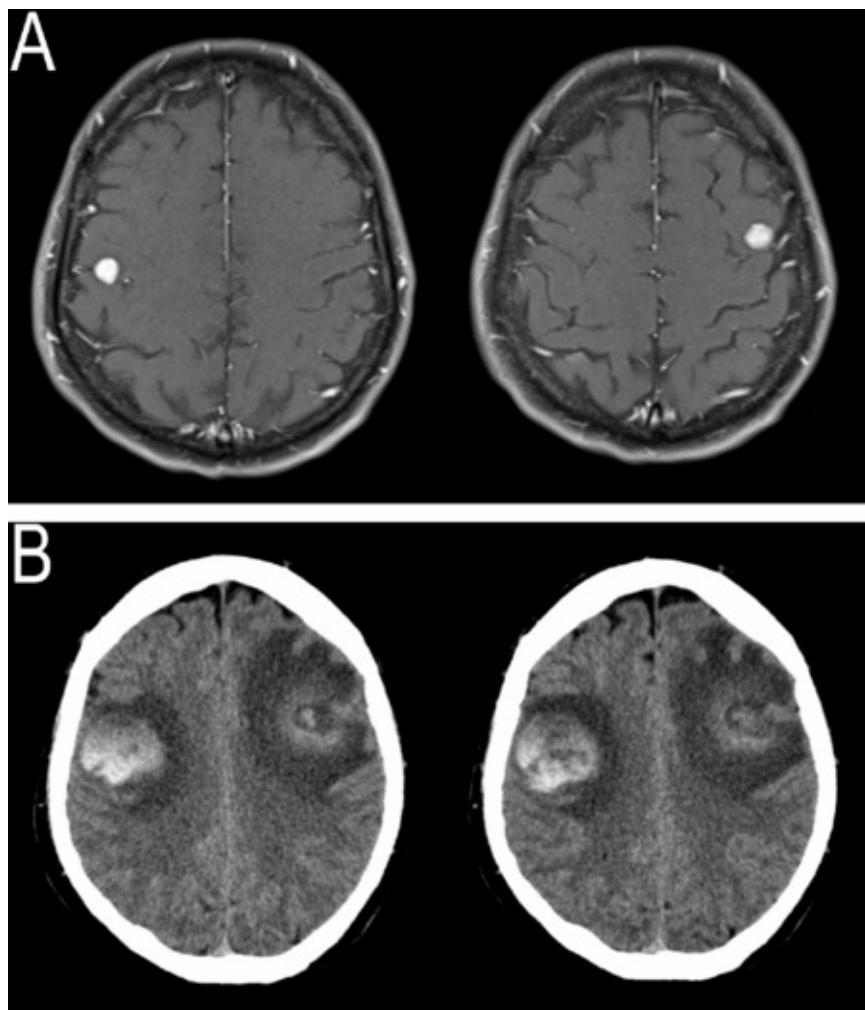
When a patient with conjugate horizontal, vertical, or complete ophthalmoparesis is encountered, it is important to determine if the lesion is *supranuclear* (upper motor neuron) or *nuclear-intranuclear* (lower motor neuron). Supranuclear lesions affect the saccadic, smooth pursuit, optokinetic, or vergence inputs to the ocular motor nuclei in the brainstem, whereas nuclear–intranuclear lesions affect the ocular motor nuclei, nerves, neuromuscular junction, or extraocular muscles themselves. The distinction can be made at the bedside by checking if the ophthalmoparesis can be overcome with the vestibulo-ocular reflex (VOR), as elicited with head movements (i.e. the “doll's eyes” or “oculocephalic” maneuver) or caloric stimulation. Provided that the labyrinth and vestibular nerve are intact, the ophthalmoparesis can be overcome using the VOR if the lesion is supranuclear, whereas it cannot be overcome if the lesion is nuclear–intranuclear.

The supranuclear commands for voluntary eye movements arise from several cortical regions. Clinically, the most important of these are the frontal eye fields (located at the caudal end of the middle frontal gyrus, just anterior to the primary motor cortex) and the parietal eye fields (located at the horizontal portion of the intraparietal sulcus, just superior to the angular gyrus). Signals from these cortical areas descend to the brainstem circuits responsible for generating conjugate eye movements. The circuits for generating conjugate horizontal eye movements are located in the pons, whereas those for generating conjugate vertical eye movements are located in the midbrain. Thus, a selective horizontal or vertical supranuclear ophthalmoparesis implies disease localized to the pons or midbrain, respectively . Clinically, it is less common to see conjugate

nuclear–intranuclear ophthalmoparesis that is selectively horizontal or vertical; the differential diagnosis for these two entities is essentially the same. See [Table 49.1](#) for a list of differential diagnoses for supranuclear and nuclear–intranuclear ophthalmoparesis. Note that many conditions causing nuclear–intranuclear ophthalmoparesis do not cause *conjugate* deficits; only those that have been reported to do so are listed.

## Case vignette

A 52-year-old male, with a history of metastatic melanoma, acutely developed headache and impaired voluntary eye movements in all directions. On examination, all voluntary eye movements (saccades, smooth pursuit, and convergence) were absent. However, a full range of horizontal and vertical eye movements could be produced with the doll's eyes maneuver, and the quick phases of vestibular nystagmus were intact, suggesting complete supranuclear ophthalmoparesis. Non-contrast computerized tomography of the brain showed intraparenchymal hemorrhages involving both frontal eye fields, at the site of known metastatic deposits (see [Figure 49.1](#)).



**Figure 49.1** (A) Post-contrast T1-weighted magnetic resonance imaging of the brain 2 months before presentation showed metastases in the right and left frontal lobes. (B) Non-contrast computerized tomography of the brain at presentation showed hemorrhage at the metastasis sites, involving both frontal eye fields.

**Table 49.1** *Differential diagnosis of conjugate horizontal and vertical ophthalmoparesis.*

| Location     | Signs of that localization                 | Etiologic category | Specific etiology                                       |
|--------------|--------------------------------------------|--------------------|---------------------------------------------------------|
| Supranuclear | Ophthalmoparesis can be overcome using the | Toxic              | Anticonvulsant (e.g. carbamazepine, phenytoin) toxicity |

vestibulo-ocular  
reflex (i.e. the  
“doll's eyes”  
maneuver or  
caloric  
stimulation)

Barbiturate toxicity

Lithium toxicity

Neuroleptic toxicity

Infective and  
post-infective

Bacterial or viral  
brainstem  
*encephalitic*

## **encephalitis**

Whipple disease

Creutzfeldt– Jakob  
disease

Pressure  
effects

Hydrocephalus

Ventriculoperitoneal  
shunt malfunction

Neoplastic and Benign or malignant  
paraneoplastic neoplasms

Paraneoplastic  
brainstem  
encephalitis

Degenerative      Spinocerebellar  
ataxia type 2

Spinocerebellar  
ataxia type 7

Ataxia with  
oculomotor apraxia

Vascular      Cortical stroke

Thalamic stroke

Brainstem stroke

Hypoxic-ischemic  
insult

Metabolic

Gaucher disease

Niemann– Pick  
disease type C

Tay–Sachs disease

Maple syrup urine  
disease

Abetalipoproteinemia

Movement  
disorder

Progressive  
supranuclear palsy

Huntington's disease

Congenital      Oculomotor apraxia

Demyelinating    Multiple sclerosis

|                          |                                                                                                                                                            |                                 |                                                                       |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|-----------------------------------------------------------------------|
| Nuclear–<br>infranuclear | Ophthalmoparesis<br>cannot be<br>overcome using<br>vestibulo-ocular<br> | Infective and<br>post-infective | Basal meningitis<br>(e.g. bacterial,<br>tuberculous,<br>cryptococcal) |
|--------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|-----------------------------------------------------------------------|

reflex (i.e. "Doll's eyes" maneuver or caloric stimulation)

Invasive fungal sinusitis

Botulism

Pressure effects

Hydrocephalus

Ventriculoperitoneal  
shunt malfunction

Pituitary apoplexy

Autoimmune      Myasthenia gravis

## Thyroid eye disease

Neoplastic and Benign or malignant  
paraneoplastic neoplasm

Metabolic Wernicke's  
encephalopathy

Chronic progressive  
external  
ophthalmoplegia

Congenital      Duane syndrome

Mobius syndrome

Horizontal gaze  
palsy with scoliosis

Heredofamilial      Oculopharyngeal  
dystrophy

Myotonic dystrophy

Trauma                  Blow-out fracture  
associated

Demyelinating      Miller Fisher  
and                    syndrome  
inflammatory

## Guillain–Barré syndrome

---

### Further reading list

- Keane JR. Acute bilateral ophthalmoplegia: 60 cases. *Neurology* 1986; 36:279–81.
- Keane JR. Bilateral ocular paralysis: analysis of 31 inpatients. *Arch Neurol* 2007; 64:178–80.
- Leigh RJ, Zee DS. *The Neurology of Eye Movements*, 4th edn. New York, NY: Oxford University Press, 2006.
- Nath U, Ben-Shlomo Y, Thomson RG, Lees AJ, Burn DJ. Clinical features and natural history of progressive supranuclear palsy: a clinical cohort study. *Neurology* 2003; 60:910–6.
- Pierrot-Deseilligny C, Gautier JC, Loron P. Acquired ocular motor apraxia due to bilateral frontoparietal infarcts. *Ann Neurol* 1988; 23:199–202.
- Rivaud S, Müri RM, Gaymard B, Vermersch AI, Pierrot-Deseilligny C. Eye movement disorders after frontal eye field lesions in humans. *Exp Brain Res*

1994; 102:110–20.

Schoser BG, Pongratz D. Extraocular mitochondrial myopathies and their differential diagnoses. *Strabismus* 2006; 14:107–13.

Thurtell MJ, Halmagyi GM. Complete ophthalmoplegia: an unusual sign of bilateral paramedian midbrain-thalamic infarction. *Stroke* 2008; 39:1355–7.

## 50 Pain, arm

---

Robert Duarte *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

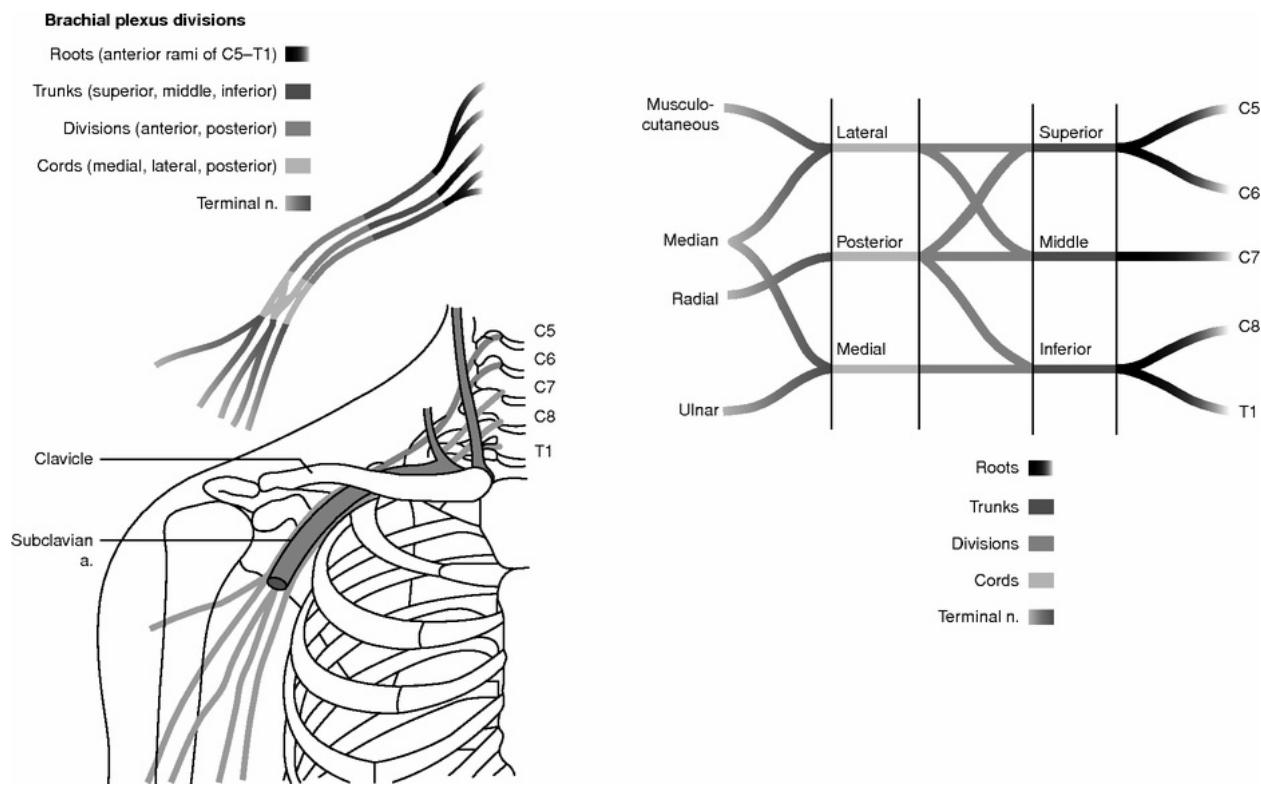
### Introduction

Understanding upper extremity pain disorders can be overwhelming for the casual observer.

When obtaining a history, the clinician must discuss with the patient, in detail, their description of the term “pain.” For example, pain that is radiating or shooting in the upper extremity is generally seen in a cervical radicular process. Complaints of a burning, numbing, unfamiliar pain are often diagnosed as a neuropathic pain condition such as painful brachial plexopathy, complex regional pain syndrome, or carpal tunnel syndrome. A localized, non-radiating, deep achy pain suggests musculoskeletal pathology.

In performing a neurologic examination, one needs to conceptualize the neuroanatomy of the cervical spine, brachial plexus, and peripheral nerve. The following is a brief overview of the upper extremity neuroanatomy and is not meant to be a detailed extensive review. (The reader may also want to refer to [Chapter 99](#) on brachial plexopathy and [Chapter 101](#) on radiculopathy.) There are eight cervical roots. However, there are only seven vertebrae; roots C1 through C7 emerge above their respective vertebrae. The C8 root exits between the seventh cervical and T1 vertebrae. The anterior rami form the brachial plexus and supply the skin to the anterolateral part of the neck and upper limb ([Figure 50.1](#)). The posterior primary rami divide into the medial branch supplying the paraspinal muscles and a lateral branch innervating the skin posteriorly. The long thoracic nerve (C5, 6, 7) arises directly from the cervical roots prior to formation of the trunks. The upper trunk of the brachial plexus gives rise to the suprascapular nerve (C5–6) innervating the supra-and infraspinatus muscles. The middle trunk is a continuation of the C7 root and problems with the middle trunk result in the same clinical deficits as seen if the C7 root were affected. Lower

trunk lesions produce clinical deficits along the medial aspects of the arm, forearm, and hand. The anterior divisions of the upper and middle trunks join to form the lateral cord of the brachial plexus. The lateral cord gives rise to the musculocutaneous nerve of the forearm (C5–7) and the lateral head of the median nerve. The medial cord gives rise to the medial pectoral nerve (C8–T1), medial cutaneous nerve of the forearm (C8–T1), and the ulnar nerve (C8–T1). The posterior cord gives rise to the subscapular nerve (C5–7), thoracodorsal nerve (C5–8), axillary nerve (C5–6), and the radial nerve (C5–8).



**Figure 50.1** Brachial plexus.

The clinician should be familiar with basic pain terminology. As part of the physical examination, the clinician needs to learn specific, clinical provocative tests related to upper extremity pain to assist in localizing the pathology.

## Pain terminology

Allodynia is a pain due to a stimulus, *i.e.* simple touch, that does not ordinarily provoke pain. Allodynia occurs in neuropathic type pain conditions such as herpetic neuralgia and complex regional pain syndromes.

Dysesthesia is an unpleasant abnormal sensation that is painful. A patient may

complain of a burning sensation.

Neuropathic pain is defined as pain caused by a lesion or disease of the somatosensory nervous system.

Paresthesia is simply an abnormal sensation, whether spontaneous or evoked, that is typically non-painful. A patient may report having numbness.

Radiculopathy is the irritation of or injury to a specific nerve root causing pain, numbness, and occasionally weakness.

Myofascial pain typically is characterized by a taut palpable band of muscle tissue that, when palpated by the examiner, reproduces the pain .

## **Provocative tests for upper extremity pain**

Adson's sign is the loss of the radial pulse in the affected arm by rotating the head to the ipsilateral side following deep inspiration.

Phalen's maneuver is performed by requesting the patient to maintain their wrists in forced flexion for 30–60 seconds. Paresthesia in the median nerve territory is considered to be a positive test.

A positive Spurling's test is defined as the reproduction of the patient's complaint into the affected extremity when the clinician laterally rotates the neck to the symptomatic side followed by axial compression of the head.

Tinel's sign is a sensation of tingling felt in the distal extremity of a limb when percussion is made over the site of an injured nerve, indicating early regeneration of the nerve.

## **Case vignette**

A 46-year-old male presented to his primary care physician with a 3-month history of non-radiating right shoulder pain. He denied any recent shoulder or neck injury. Examination revealed normal range of motion of the shoulder and a brief neurologic examination was non-focal. An X-ray of the right shoulder was unremarkable. Two months later, he presented for a follow-up visit with similar symptomatology. Physical examination was again unremarkable. He denied involvement of any other extremity. Over-the-counter analgesics and muscle relaxants provided minimal relief. A computerized tomography scan of the right shoulder was negative. Orthopedic consultation stated “no orthopedic cause for

his pain." The patient presented to his physician for a third visit describing a burning, dysesthetic sensation extending from the right shoulder to the right arm and hand. A neurologic consultation revealed a right Horner's syndrome and a sensory deficit in the C8--T1 distribution. An MRI of the chest showed evidence of a mass in the right apical portion of lung consistent with a Pancoast tumor.

**Table 50.1 Diagnosis of upper extremity pain disorders.**

| <b>Location</b>             | <b>Description of pain</b>                                                         | <b>Specific etiologies</b>                                                   | <b>Provocative signs/clinical pearls</b> |
|-----------------------------|------------------------------------------------------------------------------------|------------------------------------------------------------------------------|------------------------------------------|
| Cervical radiculopathy (C5) | Pain over shoulder radiating into lateral arm not extending beyond elbow           | Spondylosis<br>Brachial neuritis<br>Upper plexus avulsion<br>Disc herniation | Spurling's maneuver                      |
| Cervical radiculopathy (C6) | Pain at biceps muscle radiating into lateral forearm into thumb and index finger   | Spondylosis<br>Disc herniation                                               | Spurling's maneuver                      |
| Cervical radiculopathy (C7) | Deep achy pain at triceps muscle radiating into index and ring finger.<br>Possibly | Spondylosis<br>Disc herniation                                               | Spurling's maneuver                      |

|                                    |                                                                                            |                                                                   |                                                                                                   |
|------------------------------------|--------------------------------------------------------------------------------------------|-------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
|                                    | extensis into<br>medial<br>scapula<br>border                                               |                                                                   |                                                                                                   |
| Cervical<br>radiculopathy<br>(C8)  | Pain below<br>elbow<br>radiating into<br>medial<br>aspect of<br>fourth and<br>fifth digit  | Cervical rib<br>Thoracic outlet<br>Less likely disc<br>herniation | Thoracic outlet –<br>Adson's sign<br>Symptoms<br>worsen with<br>elevation and<br>abduction of arm |
| Cervical<br>radiculopathy<br>(T1)  | Deep achy<br>pain into<br>shoulder and<br>scapula                                          | Cervical rib<br>Referred pain<br>Less likely disc<br>herniation   | Thoracic outlet –<br>Adson's sign<br>Symptoms<br>worsen with<br>elevation and<br>abduction of arm |
| Levator scapula<br>myofascial pain | Reproducible<br>pain at angle<br>of neck and<br>shoulder                                   | Myofascial                                                        | Painful taut band.<br>Reproducible<br>pain upon<br>palpation of<br>levator scapula<br>muscle      |
| Trapezius<br>myofascial pain       | Reproducible<br>pain at<br>posterior<br>aspect of<br>neck                                  | Myofascial                                                        | Painful taut band.<br>Reproducible<br>upon palpation of<br>trapezius muscle                       |
| Brachial plexus<br>Upper trunk     | Abrupt onset<br>of severe<br>pain<br>followed by<br>weakness<br>and atrophy<br>of brachial | Idiopathic –<br>Parsonage<br>Turner<br>syndrome                   | Typically occurs<br>between ages 20<br>and 50                                                     |

|                                | plexus<br>innervated<br>muscles                                                                   | Affects<br>upper trunk,<br>described as<br>a dysesthetic<br>pain                                                    | Radiation<br>effects on<br>plexus                   |                                                       |
|--------------------------------|---------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------|-------------------------------------------------------|
|                                |                                                                                                   | Severe<br>dysesthetic<br>pain and<br>neurologic<br>dysfunction                                                      | Radiation<br>induced second<br>primary              | Sarcomas may<br>arise in previous<br>radiation fields |
|                                |                                                                                                   | Deep dull<br>pain along<br>the posterior<br>aspect of<br>shoulder,<br>rhomboid,<br>and dorsal<br>scapular<br>region | Compression –<br>Suprascapular<br>nerve             |                                                       |
| Brachial plexus<br>Lower trunk | Dysesthetic<br>pain in C8--<br>T1<br>distribution<br>typically<br>precedes<br>neurologic<br>signs | Pancoast tumor                                                                                                      | Up to one third<br>may have<br>Horner's<br>syndrome |                                                       |
| Median nerve                   | Parasthesias,<br>dysesthesias<br>into thumb,<br>index finger                                      | Compression                                                                                                         | Tinel's sign at<br>wrist<br>Phalen test             |                                                       |

|                                 |                                                                                               |                                                                                     |                                          |
|---------------------------------|-----------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------|------------------------------------------|
|                                 |                                                                                               | and middle finger. Can involve entire hand and may extend into shoulder             |                                          |
| Ulnar nerve                     | Dysesthetic pain along the ulnar border of forearm with weak intrinsic muscles                | Compression                                                                         | Tinel's test at elbow                    |
| Radial nerve                    | Pain at anterior aspect of forearm<br>Wrist and finger extension weakness                     | Compression – Saturday night palsy<br>Trauma                                        |                                          |
|                                 | Lateral elbow pain with weakness of wrist extensors and extensor weakness of first two digits | Idiopathic or repetitive use of forearm<br>Posterior interosseous nerve compression |                                          |
| Soft tissue or peripheral nerve | Severe dysesthetic pain                                                                       | Complex regional pain syndrome 1                                                    | Pain usually out of proportion to injury |

|                  |                                                                                           |                                                                                 | degree of injury                                                           |
|------------------|-------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------|----------------------------------------------------------------------------|
|                  | pain typically not respecting any dermatomal pattern with allodynia and autonomic changes | syndrome 1 – soft tissue injury Complex regional pain syndrome 2 – nerve injury |                                                                            |
| Peripheral nerve | Severe dysesthetic pain followed by herpetic eruptions                                    | Infectious – Herpetic neuralgia                                                 | Pain may not be associated with lesions, called herpes sine herpeticum     |
|                  | Dysesthetic pain along the medial aspect of proximal arm                                  | Post mastectomy surgery                                                         |                                                                            |
|                  | Dysesthetic pain in fingers and hand                                                      | Drug-induced neuropathies – vincristine, cisplatin                              | Symptoms may resolve over 1 year after cessation of chemotherapeutic agent |
|                  | Leg and arm pain occur within 2 days of ingestion                                         | Thallium exposure                                                               | GI, cardiovascular collapse, followed by confusion, seizures, and coma     |

|                 |                                                                                                             |                                                                                                 |                                                                                                           |
|-----------------|-------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
|                 | Gradual onset of pain and parathesias in legs and feet.<br>Fingertips and hand pain develop late in disease | Diabetes mellitus                                                                               | Compression neuropathies are more common in patients with diabetes                                        |
|                 | Painful hands or feet                                                                                       | Hypothyroidism                                                                                  | Associated weakness in limbs                                                                              |
|                 | Hand, foot pain                                                                                             | Thiamine deficiency                                                                             | Allodynia, sensory and motor impairment                                                                   |
| Musculoskeletal | Unexplained unilateral shoulder pain                                                                        | Parkinson's disease                                                                             | Diminished arm swing                                                                                      |
| Bone            | Shoulder pain                                                                                               | Metastatic from breast or prostate                                                              | Proximal third of humerus typically involved                                                              |
| Central pain    | Lesion location often dictates pain site<br>No specific pain quality<br>Variable intensity                  | Post stroke<br>Multiple sclerosis<br>Spinal cord injury<br>Syringomyelia<br>Parkinson's disease | Non-sensory neurologic symptoms may or may not be present<br>Allodynia may be present<br>Pain may involve |

|                                                                      |                         |                                                   |
|----------------------------------------------------------------------|-------------------------|---------------------------------------------------|
| Pain may occur immediately following event or be delayed up to years | Epilepsy<br>Brain tumor | large body part or be limited to one small region |
|----------------------------------------------------------------------|-------------------------|---------------------------------------------------|

---

## Further reading list

- Benzon HT, Raja SN, Molloy RE, Liu SS, Fishman SM, Eds. *Essentials of Pain Medicine and Regional Anesthesia*, 2nd edn. New York, NY: Elsevier Churchill Livingstone, 2005.
- Brazis PW, Masdeu JC, Biller J. *Localization in Clinical Neurology*, 3rd edn. Boston: Little, Brown, 1996.
- Foley KM, Woodruff JM, Ellis FT, Posner JB. Radiation-induced malignant and atypical peripheral nerve sheath tumors. *Ann Neurol* 1980; 7:311–18.
- International Association for the Study of Pain. Pain terms: a list with definitions and notes on usage. *Pain* 1979;6:249. <http://www.iasp-pain.org>
- Kanner R. *Diagnosis and Management of Pain in Patients with Cancer*. Basel: Karger AG, 1988.
- Mollman JE. Cisplatin neurotoxicity. *N Engl J Med* 1990; 322:126–127.
- Pappagallo M. *The Neurological Basis of Pain*. New York, NY: McGraw-Hill, 2005.
- Patten J. *Neurological Differential Diagnosis*, 2nd edn. Berlin: Springer-Verlag, 1996.
- Stewart JD. *Focal Peripheral Neuropathies*, 3rd edn. Philadelphia, PA: Lippincott, Williams and Wilkins, 2000.
- Wall PD, Melzack R. *Textbook of Pain*, 4th edn. Edinburgh: Churchill Livingstone, 1999.

## 51 Pain, back

---

Michael Ronthal *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

Back pain is common. It is estimated that about 90% of adults will, at one time or another, complain of back pain and/or sciatica. The vast majority of patients will have a benign cause and prognosis. A minority of patients will harbor a more serious pathology and require urgent investigation.

So as not to miss that minority we begin with a consideration of “red flag” signs or symptoms which indicate urgent imaging. The procedure of choice is magnetic resonance imaging, but if there is a contraindication (such as a pacemaker), computerized tomography (CT) scanning with or without intrathecal iodine-containing contrast medium should be done. Routine imaging of every single patient with back or root pain is discouraged.

### Red flags in low back pain

If no red flags are present, low back pain can be approached via a consideration of pain-sensitive structures in the back. These include bone, apophyseal joints, meninges, disc, nerve roots, and paraspinal muscles.

### Approach to low back pain via a consideration of pain-sensitive structures

Each nerve root supplies a specific myotome or dermatome. Careful neurologic examination will localize the root causing the symptoms.

Tables 51.1–51.3 are meant to aid diagnosis at the bedside. Most muscles have multilevel innervation, but the clinician attempts to localize one root level. The principal innervations are of diagnostic importance, not the overlap innervation.

---

**Table 51.1 Red flags.**

| <b>Sign/symptom</b>              | <b>Pathology</b>                                                                                         | <b>Comment</b>                                                                                                                                                                                                                                                                                                        |
|----------------------------------|----------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Bilateral root signs or symptoms | Disc<br>Neoplasm:<br>Solid tumor or<br>meningeal spread<br>Infection:<br>Epidural abscess,<br>meningitis | Bilateral signs or symptoms may be due to bilateral root pathology in the exit foramina, but a central cauda equina pathology with attendant risk of bladder dysfunction must be excluded                                                                                                                             |
| Bladder dysfunction              | Cauda equina compression<br>Infiltration, infection                                                      | Bladder dysfunction in this setting is an emergency and cauda equina compression must be excluded. On occasion pain or medication may trigger bladder dysfunction. If no obvious cause on imaging, cerebrospinal fluid (CSF) must be examined <i>e.g.</i> for bacterial, herpes simplex, or cytomegalovirus infection |
| Fever                            | Epidural abscess,<br>meningitis                                                                          | Bacterial infection starts in the disc and spreads to contiguous structures                                                                                                                                                                                                                                           |
| History of cancer                | Metastases to bone or meninges                                                                           | Cancer seeds to bone and pathologic fracture causes nerve signs/symptoms. Occasionally meningitis due to malignancy is the cause and if imaging is negative CSF cytology is mandatory                                                                                                                                 |

**Table 51.2 Etiologies of back pain.**

| <b>Location</b>   | <b>Signs</b>                                             | <b>Etiology</b>                                                                                  | <b>Comment</b>                                                                                                                      |
|-------------------|----------------------------------------------------------|--------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Bone              | Percussion tenderness                                    | Trauma<br>Osteoporosis<br>Fracture<br>Infection<br>Metastatic deposit                            | Percuss using a reflex hammer over the vertebral spines<br>A major bone collapse will result in a tender gibbus                     |
| Apophyseal joints | No specific sign, but adjacent root may be compressed    | Almost always degenerative<br>Occasional infection                                               | Osteoarthritis of the apophyseal joints encroaches on the exit foramina (lateral recess stenosis) and may cause spinal claudication |
| Disc              | May have no focal signs, or may have adjacent root signs | Usually spontaneous annulus rupture, sometimes traumatic<br>Bacterial infection settles in discs | The nucleus pulposus has no innervation, but the annulus has pain sensitive nerve endings sensitive to                              |

|                 |                                                               |                                                                                                                                                                                                                                                             |                                                                                                  |
|-----------------|---------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|
|                 |                                                               |                                                                                                                                                                                                                                                             | stretch or<br>frank tear                                                                         |
| Root            | Signs are related to the root which is compressed or inflamed | Usually compression by disc, but can also be compressed in the lateral recess. Spinal stenosis. Spondylolisthesis infection includes herpes simplex virus, herpes zoster, cytomegalovirus, Lyme disease. Bacterial infection usually from adjacent discitis | The commonest pain is in sciatic distribution. Trochanteric bursitis mimics sciatica             |
| Muscle          | Local tenderness to palpation paraspinally and over gluteus   | Muscle spasm is usually reactive to any of the above pathologies, but can be sui generis as in fibromyalgia                                                                                                                                                 | Muscle spasm restricts normal movement of the spine which becomes painful                        |
| Meninges        | If CSF pleocytosis, menigismus                                | Meningitis, infective, inflammatory or neoplastic Parameningeal focus of infection Spinal subarachnoid hemorrhage                                                                                                                                           | Imaging with MRI may show enhancing dura, but CSF examination is mandatory to make the diagnosis |
| Spinal stenosis | Pain in the leg(s) with exercise and with normal              | Congenital spinal stenosis implies short pedicles, a narrow canal, but, usually, a degenerative process Severe                                                                                                                                              | At time of exercise-induced sciatica, flexion of the                                             |

pedal pulses. May only have root signs after exercise, or may have signs at rest

spondylosis/spondylolisthesis will narrow even a normal neural canal

lumbar spine widens the canal and relieves the pain

CSF: cerebrospinal fluid; MRI: magnetic resonance imaging.

**Table 51.3 Nerve roots and their innervations.**

| Segmental level | Muscle innervated                        | Action                                     |
|-----------------|------------------------------------------|--------------------------------------------|
| L1, L2          | Iliopsoas                                | Hip flexion                                |
| L3              | Adductors of the thigh                   | Hip adduction                              |
| L3, L4          | Quadriceps                               | Knee extension                             |
| L4              | Tibialis anterior                        | Ankle extension                            |
| L5              | Toe extensors, hamstring, gluteus medius | Toe extension, knee flexion, hip abduction |
| Si              | Gastrocnemius and soleus, toe flexors    | Ankle flexion<br>Toe flexion               |

## Clinical vignette

A 57-year-old previously healthy male complains of pain radiating from the buttocks down the posterior aspects of both lower limbs to the big toe on each side. There is no pain at rest, but if he walks two blocks the pain is brought on. The pain persists and becomes worse if he continues to walk, but if he rests it

settles in a minute or two and he can then manage another two blocks before there is recurrence.

Twenty years previously he injured his back and had low back pain for 6 months. He denies weakness or numbness at rest, and bladder function is intact.

On examination straight leg raising is normal. There is atrophy of the extensor digitorum brevis bilaterally. There is mild weakness of toe extension, hamstring, and thigh abduction bilaterally. There is weakness of toe flexion bilaterally. There is no sensory deficit in the lower limbs. He has slightly decreased pinprick sensation paraspinally at the level of L5/S1.

The pedal pulses are present and there are no femoral bruits. There is no tenderness over the greater trochanters.

## Clinical diagnosis

### *Localization*

The signs support the diagnosis of L5 and S1 radiculopathy. Paraspinal sensory loss clinches the diagnosis of root localization because the first sensory branch to the lumbar roots is from the paraspinal skin region.

Sciatic pain can be triggered by pathology in the lumbosacral plexus or sciatic nerve, and can be mimicked by trochanteric bursitis. None of these differentials is viable on the clinical signs.

### *Pathology*

Because the pain is bilateral we should consider either lateral root pathology at L5/S1 on each side or a central pathology affecting the cauda equina at any level.

A useful way to approach the possible pathology is to divide the causes into mechanical problems as opposed to non-structural causes.

Non-structural sciatic pain could be due to a local inflammatory versus infiltrative pathology in the roots or cauda. If the imaging does not indicate structural pathology, the spinal fluid should be examined.

Structural pathology implies pressure on the roots. The differential includes disc herniation, apophyseal joint hypertrophy, primary or metastatic mass lesions either extrinsic to the roots/cauda, or mass lesions arising within the roots

themselves. Bacterial infection, subacute or chronic, must be included.

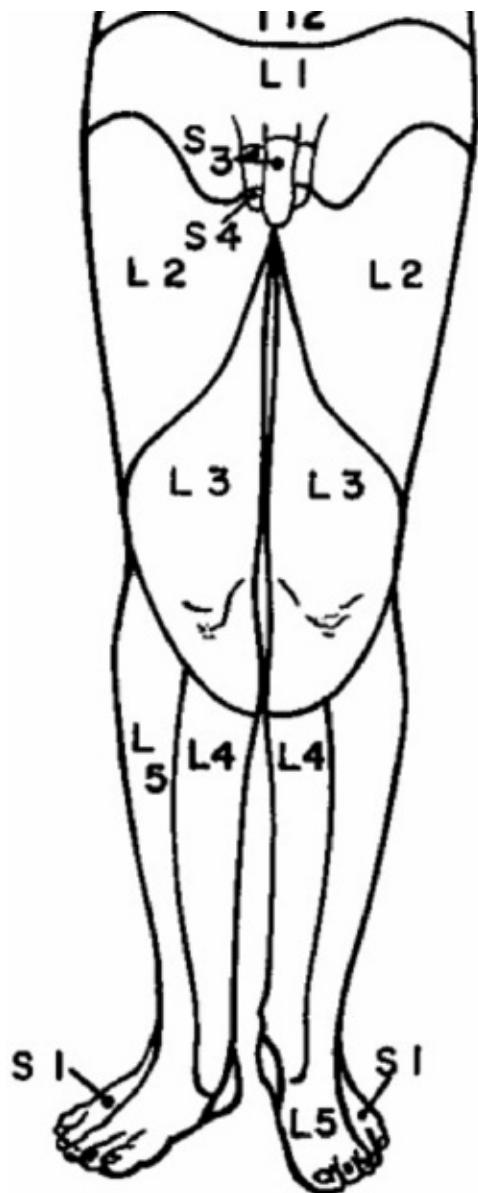
In this patient, although he has fixed signs which point to the site of pathology, his symptoms are intermittent and triggered by exercise. This suggests the diagnosis of spinal claudication. Vascular claudication is excluded because he has normal peripheral pulses. Spinal claudication is usually caused by spinal stenosis. On occasion marked osteoarthritis of the facet joints narrows the neural foramina and produces the same clinical picture. The investigation of choice is magnetic resonance imaging of the lumbar spine. The MRI confirms the diagnosis.

Spinal stenosis of this sort is usually acquired and secondary to degenerative back disease. Occasionally congenital spinal stenosis will present in the same fashion without the degenerative signs.

On rare occasions imaging will be negative and the possibility of true (vascular) claudication of the cauda equina should be entertained .



**Figure 51.1** Saggital and axial views of lumbar spine showing disc bulging and narrowed neural canal.



**Figure 51.2** Principal areas innervated by specific nerve roots.

## Further reading list

Carragee EJ. Clinical practice. Persistent low back pain. *N Engl J Med* 2005; 352:1891–8.

Chou R Huffman LH. Medications for acute and chronic low back pain: a review of the evidence for an American Pain Society/American College of Physicians clinical practice guideline. *Ann Intern Med* 2007; 147:505–14.

Cohen SP, Argoff, CE Carragee EJ. Management of low back pain. *Br Med J*

2008; 337:a2718.

Hadjipavlou AG, Tzermiadanos MN, Bogduk N, Zindrick MR. The pathophysiology of disc degeneration: a critical review. *J Bone Joint Surg Br* 2008; 90:1261–70.

Raj PP. Intervertebral disc. Anatomy-physiology-pathophysiology-treatment. *Pain Practice* 2008; 8(1):18–44.

Roudsari B, Jarvik JG. Lumbar spine MRI for low back pain: indications and yield. *AJR Am J Roentgenol* 2010; 195:550–9.

## 52 Pain, eye

---

Mark Beyer and Deepak Grover *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Pain is a common complaint that healthcare providers face every day. However, eye pain can provide diagnostic challenges to neurologists as most patients have already undoubtedly been seen by their primary healthcare provider and an ophthalmologist without any significant clinical findings. There are two main groups of patients that present to the neurologist from an ocular point of view [1]. First are those with chronic pain around the eye [1]. These pains are described as fleeting, sharp, and stabbing without significant clinical findings, with normal imaging, and unresponsive to previous treatment modalities [1,2]. An organic cause is less likely and diseases psychological in nature should be considered. The second group of patients are those with a more recent onset of pain that is physiologic in nature [1]. Though identifying causes of ocular pain is difficult, classifying pain provides helpful diagnostic cues in identifying underlying pathology. The time of onset, character, severity, and relieving factors are important in identifying anatomic location and etiology. The assessment of pain should be part of every neurologist's armamentarium and understanding the anatomy of the fifth cranial nerve is essential.

The human cornea has the highest concentration of nerve endings in the body, and is innervated by the ophthalmic division of the trigeminal nerve [2]. Within the pons, the main sensory nucleus is located lateral to the motor nucleus [3]. The fascicles travel through the subarachnoid space in close proximity to the superior cerebellar artery [3]. Microvascular compression of these fascicles results in trigeminal neuralgia [3]. The ophthalmic division arises from the trigeminal ganglia in Meckel's cave and passes through the lateral wall of the cavernous sinus [3]. As it approaches the superior orbital fissure, it sub-divides into the lacrimal, frontal, and nasociliary nerves with additional branches providing sensation to the cavernous sinus and dura of the cranial fossa [3]. The

lacrimal and frontal nerves arise above the muscle cone. The frontal nerve provides sensory information to the upper lid and forehead while the lacrimal nerve provides sensation to the lacrimal gland and temporal eyelid [2,3]. The nasociliary branch of the ophthalmic division of CN V is of significance due to its innervation to the eye, medial eyelid, and a small branch that innervates the tip of the nose [3]. This is of importance in patients with herpes zoster ophthalmicus [3]. Lesions on the tip of the nose (Hutchinson's sign), indicate a strong preponderance for ocular involvement and warrant an ophthalmic examination [3]. The infraorbital nerve is a branch of the maxillary division of the trigeminal nerve that exits inferiorly and laterally in the cavernous sinus through the foramen rotundum [3]. Cranial nerve V2 provides sensation to the temple, the area between the lower lid and lip and cranial fossa via the middle meningial nerve [3].

Ocular and orbital pain can be caused by a myriad of diseases causing irritation, inflammation, ischemia, and neoplastic involvement. Pain associated with dysesthesias can be diagnostic of adenoid cystic carcinoma of the lacrimal gland and squamous cell carcinoma due to perineural invasion [2,4,5]. However, most ocular conditions can be identified on slit lamp examination by inspection of the cornea, conjunctiva, anterior chamber, iris, lens, vitreous, and retina. The neurologic examination should include testing of visual acuity, a pupillary exam, color vision, confrontation visual fields, an assessment of the soft tissue structures of the orbit, eyelids and adnexa, palpation of the orbital rim, checking for proptosis/enophthalmos and globe retropulsion, and an evaluation of the conjunctiva, cornea, iris, and optic nerve [5].

**Table 52.1 Differential diagnosis of eye pain [6].**

| Types of eye pain | Characteristics                           | Differential diagnosis                                                                                                                                                                                                                                                                                                             |
|-------------------|-------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Ocular pain       | Foreign body sensation, photophobia, ache | Corneal related keratitis (ex: herpes simplex virus), dry eye syndrome, corneal abrasion, chemical burn, contact lens related problems, blepharitis, exposure keratitis (ex: CN VII palsy, thyroid eye disease), conjunctivitis (viral vs. allergic), episcleritis, scleritis, uveitis, ocular ischemic syndrome, endophthalmitis, |

*closure glaucoma*

|                  |                                                                                                                                                                                                        |                                                                                                                                                                                                                                                                     |
|------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Orbital pain     | Constant, deep-seated behind the eye, moderate to severe in intensity, and usually unilateral, but not migratory<br>Gaze-evoked visual obscurations are caused by tumor impingement on vascular supply | Orbital cellulitis, idiopathic orbital inflammation, orbital apex syndrome, trauma, acute orbital hemorrhage from lymphangioma, ischemic nerve palsies, adenoid cystic carcinoma of the lacrimal gland, dacroadenitis, perineural invasion, squamous cell carcinoma |
| Periorbital pain | Aching pain                                                                                                                                                                                            | Trauma, stye, herpes zoster/simplex, preseptal cellulitis, dacrocystitis, dacroadenitis                                                                                                                                                                             |

|                        |                                                                                                                                                                                                                                       |                                                                                                                                                                  |
|------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Pain with eye movement | Structures that are pain-sensitive within the orbit are the optic nerve sheath, the extraocular muscle sheaths, and the intramuscular septae. Stretching or inflammation of any of these structures produces pain on ocular movement. | Optic neuritis, myositis, idiopathic or inflammation, sinusitis, cellulitis                                                                                      |
| Pain with palpation    | Anterior orbital disease that either distends or inflames the periosteum or Tenon's capsule                                                                                                                                           | Leaking dermoid, dacryoadenitis, involving Tenor                                                                                                                 |
| Referred pain          | Most common cause of orbital pain                                                                                                                                                                                                     | Tension headache, migraines, cluster headache, occipital neuralgia, trigeminal neuralgia, Horner's syndrome, intracranial or intracavernous aneurysms, posterior |

communicating artery (PCOM) aneurysm, cavernous sinus thrombosis, cavernous arteriovenous malformation, cavernous sinus inflammation (e.g. Tolosa–Hunt syndrome), temporal arteritis, pachymeningitis, nasopharyngeal carcinoma

Painful vision loss

Symptoms

Exam

Work-up

|                          |                                                                                                                      |                                                                                          |                                                                                                        |
|--------------------------|----------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Optic neuritis           | Decreased visual acuity (VA), color desaturation, pain with motility                                                 | Mild disc edema<br>Vitreous cells if inflammatory                                        | MRI of the orbit/brain with IV contrast/FLAIR fat suppression                                          |
| Temporal arteritis       | Decreased VA, scalp tenderness, jaw claudication, fevers, weight loss, proximal muscle soreness worse in the morning | Optic disc swelling with waxy pallor, flame-shaped hemorrhage, and cotton wool spots     | CBC, CRP, and ESR (men: age/<br>female:age +10/<br>Temporal artery biopsy within 2 of starting steroid |
| Acute angle closure      | Decreased VA, red eye, pain, nausea, and vomiting                                                                    | Corneal edema, mid-dilated pupil, red eye, cell and flare                                | Elevated intraocular pressure (IOP), angle on gonioscopy                                               |
| Ocular ischemic syndrome | Decreased VA, eye pain                                                                                               | Corneal edema, neovascularization of the iris, high or low IOP, asymmetrical retinopathy | Carotid ultrasound typically > 90% stenosis                                                            |
| Uveitis                  | Decreased vision, photophobia, red eye                                                                               | Cell and flare, ciliary flush                                                            | Systemic work-up<br>autoimmune/inflammatory etiologies if bilateral or recurrent uveitis               |
| Endophthalmitis          | Decreased vision after surgery, pain, discharge                                                                      | Ciliary injection, hypopyon, vitritis                                                    | B-scan ultrasound<br>no view to posterior pole                                                         |

|               |                                                                  |                                                   |                                    |
|---------------|------------------------------------------------------------------|---------------------------------------------------|------------------------------------|
| Corneal ulcer | Foreign body sensation, photophobia, history of contact lens use | Corneal infiltrate, ciliary flush, cell and flare | Corneal cultures visual axis or 1- |
|---------------|------------------------------------------------------------------|---------------------------------------------------|------------------------------------|

---

CBC, complete blood count; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FLAIR, fluid attenuated inversion recovery; IV, intravenous; MRI, magnetic resonance imaging.

Diseases of the cornea present with predominantly severe sharp pain, foreign body sensation, tearing and photosensitivity. Inflammatory diseases of the uveal tract (i.e. uveitis) present with severe photosensitivity. Orbital involvement is characterized as a deep boring, aching pain. Orbital inflammation or infection, orbital apex syndrome, and cavernous sinus involvement typically present with diplopia, proptosis, resistance to retropulsion, and abnormal motility. Decreased vision, decreased color vision, and an afferent pupillary defect indicate optic nerve involvement. Axial and non-axial displacement of the globe localize lesions to intraconal and extraconal compartments [5]. Non-infectious diseases of the orbit may present in a more indolent course, but infections or inflammation may present rapidly with symptoms evolving over hours to days. It is important to obtain a detailed medical history as secondary orbital involvement arises from infection, thyroid disease, connective tissue diseases, and malignant metastasis [5]. Along with clinical examination and history, proper imaging provides additional information. An orbital CT scan has become the principal imaging modality in orbital diseases, particularly in evaluating the extraocular muscles, bone, and calcification [5]. Magnetic resonance imaging (MRI) is superior in viewing diseases of the orbital apex, optic nerve, and cavernous sinus, while magnetic resonance angiography (MRA) is useful in evaluating vascular lesions such as carotid cavernous fistulas [5].

## Case vignette

A 35-year-old white female presents with acute loss of vision. She states that while reading a book that morning, she had a sudden development of seeing a “gray shade” in front of her right eye. She admits to pain when she moves her eye in any direction. On exam, she is noted to have a visual acuity of 20/100 in

the right eye and 20/20 in the left eye. As well, on color vision testing, she can only see 3 out of 8 color plates in the right and sees all 8 out of 8 plates on the left. There is noted to be a relative afferent pupillary defect on the right. Her eye appears quiet without any conjunctival injection or corneal irregularities. Her anterior chamber is without any inflammatory cells. Using direct ophthalmoscopy, her right optic nerve is mildly swollen and hyperemic. After an immediate MRI that day, she was noted to have white matter lesions suggestive of demyelinating disease. She was started on methylprednisolone 250 mg QID for 3 days, and then directed for a prednisone taper over the following 11 days. She was instructed to follow with neurology and ophthalmology in the next 2 weeks for the working diagnosis of multiple sclerosis.

## References

1. Levin LA, Lessell S. Pain: a neuro-ophthalmic perspective. *Arch Ophthalmol* 2003; 121:1633.
2. Thakker MM, Orcutt JC. Neuro-ophthalmic aspects of orbital diseases. In Tassman W, Jaeger E, Eds, *Daune's Ophthalmology*. Philadelphia, PA: Lippincott Williams & Wilkins, 2006.
3. Kline LB, Bhatti MT, Chung SM, Eggenberger E, Foroozan R. Neuro-ophthalmic anatomy. In *Basic and Clinical Science Course; Neuro-Ophthalmology*. San Francisco, CA: American Academy of Ophthalmology, 2011: 57–60.
4. Kline LB, Bhatti MT, Chung SM, Eggenberger E, Foroozan R. The patient with head, ocular and facial pain. In *Basic and Clinical Science Course; Neuro-Ophthalmology*. San Francisco, CA: American Academy of Ophthalmology, 2011: 293–303.
5. Goh ES, Garrity JA. *Update on Orbital Tumors. Focal Points Clinical Modules for Ophthalmologists*. San Francisco, CA: American Academy of Ophthalmology, 2012; Module 5.
6. Friedberg MA, Rapuano CJ et al. Differential diagnosis of ocular symptoms. In Ehlers JP, Shah CP, Eds, *The Wills Eye Manual. Office and Emergency Room Diagnosis and Treatment of Eye Disease*, 5th edn. Philadelphia, PA: Lippincott Williams and Wilkins, 2008.

## 53 Pain, face

---

Egilius L. H. Spierings *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Orofacial pain is considered when the focus of the pain lies below the level of the eyebrows. Otherwise, it is considered head pain or headache, which is also the case when the focus of the pain is in or behind the eye(s). The eye(s) can be the focus of pain in the common headache condition, migraine, but more commonly in the migraine-related condition, cluster headache, and its variant, paroxysmal hemicrania. Eye pain can, of course, also be a manifestation of an ophthalmologic, as opposed to a neurologic, condition in the same manner as ear pain can be a manifestation of an otolaryngologic condition, which it often is. For eye pain in the context of headache disorders, the reader is referred to the relevant chapters of this book; for the ophthalmologic causes of eye pain and the otolaryngologic causes of ear pain, the reader is referred to textbooks related to these medical specialties.

Chronic orofacial pain refers to pain in the face and/or oral cavity that is both frequent in occurrence and long in duration. The frequency of occurrence is generally such that the pain is present daily and often also continuously. Regarding the long duration, the pain has generally been present for years at the time of consultation, if not for decades. In an epidemiologic study of chronic syndromes, orofacial pain was defined as pain in the face, mouth, or jaws, which had been present for a day or longer in the past month [1]. Chronic orofacial pain was defined as orofacial pain that had been present for 3 months or longer. In this study among adults aged 18 to 75 years, the prevalence of chronic orofacial pain was found to be 7%, with women affected twice as commonly as men. The highest prevalence of approximately 10% was found in the age group 36 to 44 years and the lowest prevalence of approximately 5% in the age groups 18 to 35 years and 64 to 75 years.

Diagnostically, a classification based on etiology is preferred but unrealistic because the cause of chronic orofacial pain is usually not known or is speculative at best. A classification based on mechanism is second best and one proposed separates chronic orofacial pain into four categories: musculoskeletal, neurovascular, neurogenic, and psychogenic. However, insight into the underlying mechanisms, of which more than one may be involved, is usually also only speculative at best, often impossible to verify in objective terms, and quickly assumed to be “psychogenic” when not understood. The latter has created the large, medically default wastebasket of “atypical facial pain,” a diagnosis better avoided in the practice of medicine or dentistry and a term that will not be used here.

A classification used in epidemiologic studies divides orofacial pain into three categories: (1) dento-alveolar; (2) musculoligamentous; and (3) idiopathic [2]. The American Academy of Orofacial Pain focuses on temporomandibular disorders, which it defines as a subgroup of craniofacial pain disorders that involve the temporomandibular joint, the masticatory muscles, and associated head and neck structures [3]. It divides these disorders into five categories: (1) masticatory muscle disorders; (2) temporomandibular joint articular disorders; (3) congenital and developmental disorders; (4) chronic mandibular hypomobility disorders; and (5) chronic mandibular hypermobility (subluxation/dislocation) disorders.

Lacking what can be considered a practical and meaningful, etiologic or mechanistic classification, chronic orofacial pain will be reviewed here under the following denominations: facial tightness or facial pressure, joint pain, jaw pain, burning face or mouth, and shooting, jabbing, or stabbing pain, with some of the categories subdivided into neuropathic and nociceptive. In addition, there is pain referred to the face, particularly from the nose and sinuses or masseter muscles. In burning mouth, the location of the pain is almost always the tongue; hence, the terms burning mouth and burning tongue are often used synonymously. The categories will be illustrated by brief case histories, based on patients personally seen and examined. The patients were seen at the Craniofacial Pain Center of Tufts University School of Dental Medicine, a medical and dental referral center, where the author is a consulting neurologist.

## **Facial tightness or pressure**

The conditions in this category generally generate low-grade face pain, one more

peripherally in the face and the other more centrally. The one more peripheral in location is mediated by tightness of the facial muscles, particularly the muscles of mastication, and is typically associated with clenching or grinding (facial variant of tension headache). The relationship between the muscle tightness and the clenching or grinding is probably circular rather than linear, with one causing the other. The facial pain more centrally located is mediated by under-pressure in the sinuses (“sinus vacuum”) through blockage of the passages, particularly the ostiomeatal complexes and nasofrontal ducts. Blockage of these passages closes off the sinuses from the outside world, resulting in the air in the sinuses being absorbed. This generates under-pressure in the sinuses, also referred to as barosinusitis, which causes a drawing feeling centrally in the face. The blockage of the sinuses is, in turn, caused by swelling of the mucosal lining, often due to allergic rhinitis, probably against the background of developmentally narrow structures.

In patients with migraine, both the muscle tightness as well as the sinus pain may trigger migraine headache, leading to what has been referred to as “tension-migraine” and “sinus-migraine.”

## **Case vignettes: examples of facial tightness**

A 32-year-old female has had bilateral jaw pain for 8 months, which came about without apparent reason. She describes the pain as tension that she cannot relieve, whatever she tries. Initially, it occurred intermittently but it has gradually become worse and for the last 3 months has been present daily and continuously. The pain is least on awakening in the morning and gradually increases in intensity as the day progresses. It is worst in the evening (7/10) when she is lying in bed and trying to fall asleep, which is difficult due to the pain. Prolonged talking makes the jaw pain somewhat worse, while chewing does not affect it. The jaw pain is not associated with tenderness and touching of the jaws provides momentary relief. Her neck and shoulder muscles are somewhat tight. Examination reveals ground-down mandibular frontal teeth and tight masseter muscles; the shoulder and upper-back muscles are tight with taut bands palpable in the upper-back muscles.

A 44-year-old female was involved in a rear-end motor-vehicle accident. Her car was stopped at a light and was hit from behind. She did not see it coming and the impact felt like an earthquake. She immediately had pain in her neck, shoulders, and upper back, left more than right. About 2 weeks later, she also

developed pain in front of the ears, left more than right, extending into the jaws. Since the accident, she has also had headaches located around the face, equal on both sides. They occur almost daily and come on early in the day when she starts talking. The headaches are not severe but when they become more intense, which happens three times per week on average, they are associated with nausea and lightheadedness. Examination reveals cross bite to the right from over-contraction of the left pterygoid muscles and her masseter muscles are tight and tender, left more than right.

A 45-year-old female has had pain in the jaws and cheeks for 7 years. The pain developed gradually after her neck and shoulder muscles became tight a year earlier. It is mild in intensity (3–4/10) and described as a dull ache or tightness. The pain is present on awakening in the morning and slightly worse at that time. It is remarkably constant during the day, aggravated by stress, jarring motions, or bouncing of the head, and stretching the neck muscles but especially hyperextending the neck. Alcohol makes it somewhat better. She has a history of anxiety and insomnia. On examination, the masseter muscles are tight and the neck and upper-back muscles tender. Pressure on the occipitocervical junction causes pain in the forehead.

## **Case vignettes: examples of facial pressure**

A 41-year-old female developed facial pain and headache 8 or 9 months ago, which was during the winter. It came about without apparent reason and has been daily and continuous since its onset. The facial pain is present on awakening in the morning, located particularly in the sides of the nose and in the cheeks. It is dull, steady in nature, and feels like a mask being pulled backwards. In the course of the day, the pain also involves the forehead, temples, top and back of the head, and neck. It is moderate in intensity (4–5/10) and does not change to any extent during the day. Bending over makes the facial pain worse; applying cold to the forehead makes the headache somewhat better. She does not have chronic nasal congestion but does have clear postnasal drip and her ears often feel plugged. Her neck and shoulder muscles are tight. Examination reveals a very nasal voice.

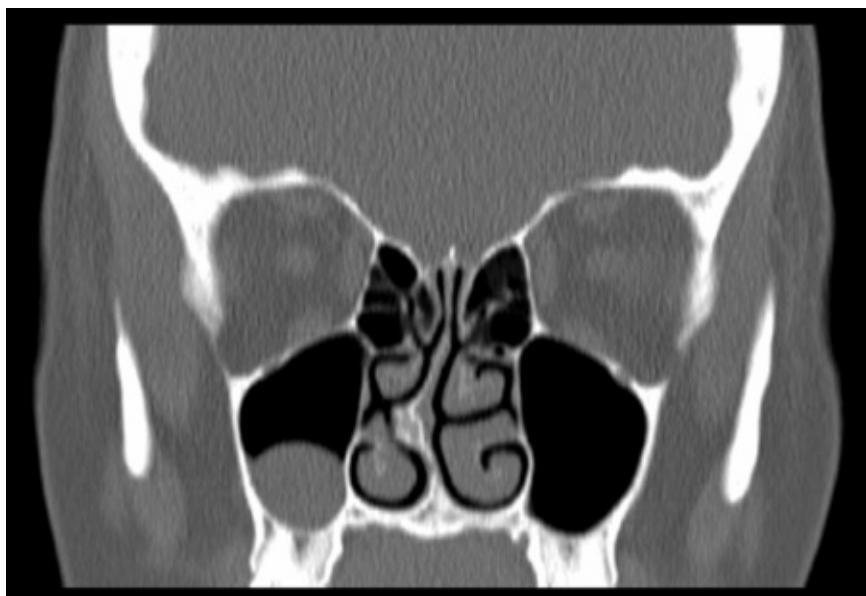
A 45-year-old female had a sinus infection 2 years ago with nasal congestion and pressure centrally in the face, described as a tight mask. She was prescribed an antibiotic and the nasal congestion improved. However, the central facial pressure continued to be present, although it has gradually improved in intensity

from severe (8–9/10) to mild (2–3/10). The facial pain occurs almost daily and is usually already present on awakening in the morning. It does not substantially change over the course of the day and nothing seems to affect it. Within months of the onset of the facial pain, her jaw and neck muscles became tight. The jaws are tight continuously as if elastic bands are present and they are also tender to touch; the neck is only tight with movement. For a year, her eyes have been itchy and she has been sneezing frequently. She was recently found to be allergic to cats, dogs, grasses, and dust mite; she has a cat and a dog. Examination reveals tight masseter muscles with taut bands.

A 50-year-old female has had pressure centrally in the face and behind the nose for 6 years, worse over time. The pressure has been daily and continuous since its onset and came about without apparent reason. It is associated with pressure in the head and ears as well as with chronic nasal congestion, right more than left, and postnasal drip. Bending over and sneezing make the facial pain and headache worse as, to a lesser extent, do coughing and straining. Also, olfactory stimuli such as perfume and smoke make the pain worse. Her neck, shoulder, and jaw muscles are tight on the right, which has been the case for 5 years. A sinus CT scan revealed clear sinuses and a straight septum but large turbinates, suggesting chronic allergic rhinitis.

Apart from diffuse pain centrally in the face when the sinuses in general are affected, localized, referred pain can occur as well when there is a particular lesion in the nose or sinuses causing pain, such as intranasal contact. The following cases are examples of referred pain unilaterally in the face as a result of intranasal contact.

A 35-year-old female developed facial pain at age 27, located in the right side of the nose and extending into the cheek and forehead. It occurs once every 1 or 2 weeks and is often present on awakening in the morning. When it comes on during the day, it is triggered by exposure to nasal irritants, such as cigarette smoke, exhaust fumes, perfume, etc. Her right nostril becomes congested and, within hours, the right-sided facial pain occurs. Her right nostril subsequently starts running and sometimes her right eye starts to tear. The pain lasts for 24 hours in an intensity that fluctuates between 5/10 and 10/10. It is not associated with nausea or vomiting. A sinus CT scan with coronal views reveals a septum that is deviated to the right with a spur, or spina, that contacts the inferior turbinate on that side ([Figure 53.1](#)). A corticosteroid nose spray, beclomethasone 50 mcg, used once per day in the right nostril, prevented the congestion from occurring and, as a result, the facial pain.



**Figure 53.1** Sinus computerized tomography scan (coronal view) showing deviated septum to the right with spur contacting the right inferior turbinate; an incidental finding is a polyp in the right maxillary sinus.

A 47-year-old male has had burning pain in the left side of the nose for 2 years, when intense extending into the left cheek, ear, maxillary teeth, and left side of the tongue. It has been present daily and continuously since its onset, gradually worse over time, and aggravated by sudden movements of the head. It is moderately severe in intensity (6–8/10) and somewhat ameliorated by applying pressure to the left side of the nose or inserting a cotton ball drenched in saline into the left nostril and positioning it in a particular spot. A sinus CT scan reveals a mildly deviated septum to the left, contacting the left middle turbinate anteriorly and, through a spina, the left inferior turbinate posteriorly.

## Joint pain

The only joint in the head is the temporomandibular joint, which is a joint like the knee joint with a meniscus and ligaments. It is a so-called sliding joint, the most complex in the body, and also the one most often used. Like the knee joint, it can be painful due to problems with the meniscus or due to “degeneration,” with loss of cartilage and osteophyte formation. Again, like the knee joint, these problems can arise from trauma or from abnormal or excessive use. Also here, the muscles around the joint, in this case the muscles of mastication, may become tight, probably a protective mechanism, and may themselves become a

source of pain and lead to clenching or grinding. The prevalence of joint and/or jaw pain in the general population is 5–10% for men and 9–15% for women, with half indicating the intensity of the pain as mild and the other half as moderate or severe [4].

## **Case vignette: example of joint pain**

A 66-year-old female had her mandibular right teeth surgically adjusted (“ground down”) and two maxillary right teeth extracted, which altered her dental occlusion. Over the subsequent months, she developed pain in front of her left ear over the temporomandibular joint. The pain is present daily and continuously and is worse on awakening in the morning, when she can barely open her mouth. She massages the left masseter muscle, resulting in improvement of the pain and jaw opening; the application of warmth is also helpful. The pain is made worse by chewing, less when eating soft food. Examination reveals tenderness of the left temporomandibular joint and tender masseter muscles bilaterally.

## **Jaw pain**

As with temporomandibular joint pain, jaw pain tends to be unilateral and is mediated by spasm of the masseter muscle: *masseter myalgia*. The pain is often described as deep in location, while the muscle is, in fact, relatively superficial and easy to examine. Palpation of the muscle will reveal one or more taut bands (localized spasms), which are tender, sometimes to the extent that the pain causes the face to twitch or the patient to jump. The localized spasms in the muscle can also be so severe that the twitching occurs spontaneously and may be associated with sharp, shooting pain.

## **Case vignettes: examples of jaw pain**

A 31-year-old male developed pain in the right jaw and tightness of his right masseter muscle 2 or 3 years ago. About 6 months later, following an airplane flight, he developed sharp, shooting pain in his right ear, associated with burning pain extending from the jaw into the temple. The shooting pain and burning were relieved by a combination of carbamazepine and gabapentin. However, the jaw pain continues to be present, associated with twitching of right masseter muscle. The pain gradually increases as the day progresses to be worst in the evening, when the right jaw throbs and the pain extends into his right ear. Stress and lack

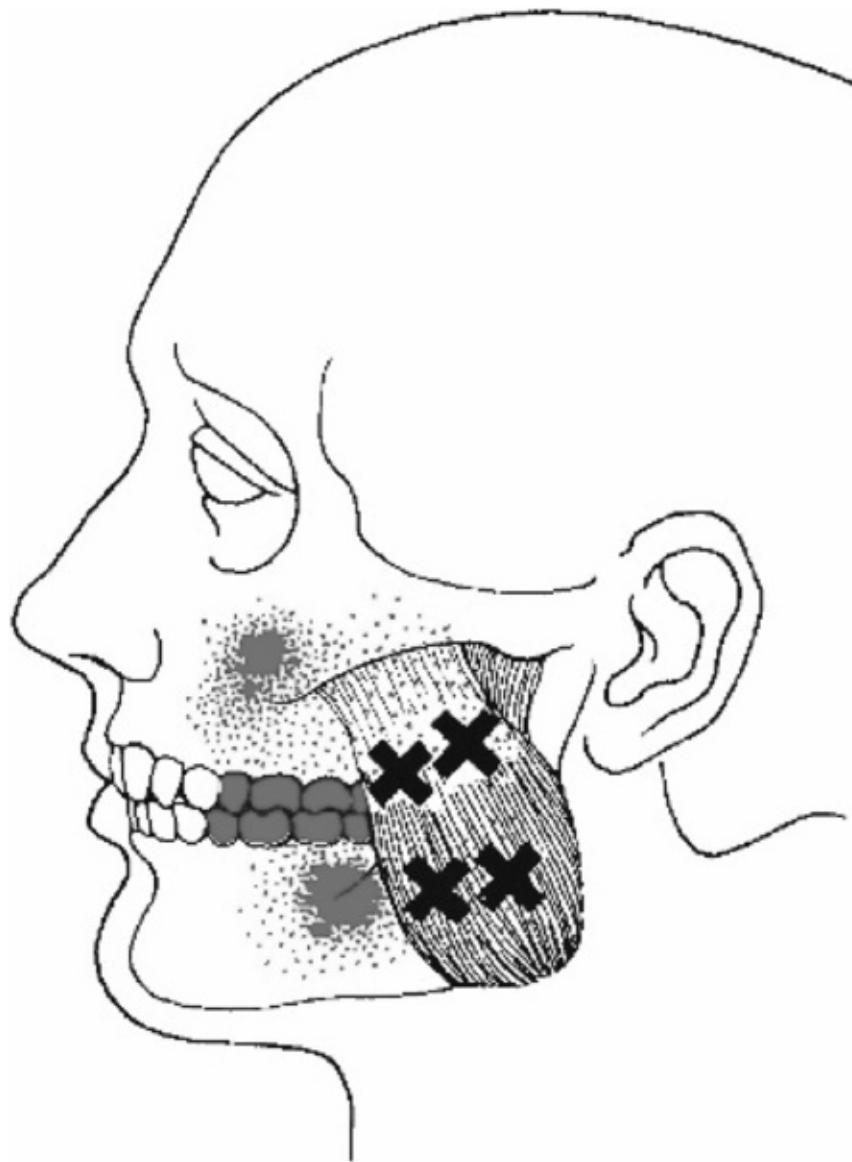
of sleep make it worse while applying heat on the muscle makes it somewhat better. Botulinum-toxin injection in both masseter muscles decreased the pain in the right lower jaw from 8/10 to 3/10. Then he was without pain for 3 weeks, after which it gradually returned. Examination reveals three taut bands in the right masseter muscle, worse going from posteriorly to anteriorly, with the most anterior one twitching unrelentingly.

A 48-year-old female has had pain in her right jaw for 10–12 years, which developed gradually. She has an overbite and on the right, in contrast to the left, her molars do not touch. She clenches at night and was given an appliance, which was not helpful in relieving her pain but physical therapy was. The pain is located deep in the right jaw and is worst on awakening in the morning. Massaging the muscle makes it somewhat better. The pain extends into the temple and causes tightness of the right neck and shoulder muscles. Treatment with botulinum toxin of the right masseter muscle rendered her free of pain for 18 months, after which the pain gradually returned. Examination reveals tender taut bands in the right masseter muscle, with palpation causing twitching of the face.

A 50-year-old female had braces until age 18. After they were removed, she noticed popping in the right temporomandibular joint when biting down on hard foods. She gradually developed pain in her right jaw, which has been present for 8–10 years. It is present daily and continuously, moderately severe in intensity (7/10), and aggravated by eating and sometimes talking. The pain is associated with tightness and soreness of the neck and shoulder muscles, right more than left, which gets worse as the day progresses. On the right side, the neck pain extends daily into the right back of the head, associated with blurred vision. On examination, she has limited mouth opening due to tightness of the right masseter muscle. The muscle is tender and has taut bands; in addition, her right posterior neck muscles are very tight and tender.

A 56-year-old female was involved in a right-sided motor-vehicle accident 18 months ago. Over the weeks following the accident, she developed pain in her right jaw and chin, present daily and almost continuously. The pain is not present on awakening in the morning but comes on immediately after she gets up. It gradually increases in intensity as the day progresses, preventing her from doing anything physically. The pain also interferes with her ability to focus, preventing her from reading. Stress makes it worse but it is not made worse by activities, such as talking or chewing. Examination reveals a tender taut band in the right masseter muscle.

Apart from causing pain in the jaw, masseter myalgia can also cause referred pain in the maxillary and/or mandibular teeth, gum, or both, as the following case illustrates ([Figure 53.2](#)).



**Figure 53.2** Areas of referred pain from the masseter muscle. Reproduced with permission from Simons DG, Travell JG, Simons LS, Cummings BD. *Travell & Simons' Myofascial Pain and Dysfunction Point Manual* [8].

A 61-year-old female had routine restorative care of the right mandibular first molar. During the drilling, she experienced a jab of pain and was referred by her dentist to an endodontist, who did a root-canal procedure on the tooth that was uneventful. However, due to prolonged wide mouth opening, her right jaw was

sore afterwards. Within 1 or 2 weeks after the procedure, she developed pain in the buccal gum of the right mandible, which gradually started to extend posteriorly into the buccal gum of the right maxilla. The pain has been present almost daily since its onset and is dull in nature. It is moderate in intensity (6–7/10) and feels like tightness. It is severe once every 2 or 3 weeks for 3 or 4 days; at one point it was severe for 6 weeks. With the severe pain, she has to lie down. Extensive talking makes the pain worse, especially when it involves a heated conversation, while chewing or applying an ice pack to the right jaw makes it somewhat better. Examination reveals the right masseter muscle to be slightly tighter than the left and the right shoulder muscle thicker than the left.

## Burning face or mouth

A burning quality of pain is often construed as an indication of the pain being neuropathic, similar to a shooting, jabbing, or stabbing quality. However, in my opinion, a particular quality, whether burning or shooting, is never enough to solely justify a diagnosis of neuropathy. Preferably, there are motor or sensory signs to establish the diagnosis and identify the nerve or nerve root involved; or there is a description of the pain that limits it to the innervation area of a particular nerve or nerve root. In the absence of both, it is suggested that an abnormal sensory response to touch should be present to indicate nerve dysfunction, that is, paresthesia, dysesthesia, or allodynia. Paresthesia refers to tingling in response to touch, dysesthesia to an unpleasant sensation to touch, and allodynia to pain resulting from a non-painful stimulus. Without such findings, burning or shooting pain should also be considered potentially nociceptive in origin. With burning mouth or tongue, there is often also decreased or altered taste, referred to as hypogeusia and dysgeusia, respectively, caused by selective, afferent C-fiber loss and, hence, a subtle sign of neuropathy.

## Case vignettes: examples of burning face

A 36-year-old female fractured a maxillary left tooth on a walnut. The tooth was subsequently extracted and, after the anesthetic wore off, she had burning pain in her left cheek and upper lip. The pain is present daily and continuously and moderately severe in intensity (7/10). It is severe (10/10) in short paroxysms that last from 30 seconds to 5 minutes. These paroxysms occur spontaneously when she lies down flat. They are triggered by touching the left upper lip or cheek, moving her left facial muscles, or exposing the face to cold (allodynia). In addition, her left upper lip and cheek feel heavy and numb and touching the area

causes an uncomfortable, vibrating sensation (dysesthesia). On examination, touch with the finger of the left cheek and upper lip is perceived as cold (dysesthesia) and causes a paroxysm of pain (allodynia).

A 56-year-old male gradually developed episodes of burning pain in the right cheek, lasting for 1–4 days and occurring every 2 days to 2 weeks. The episodes are always triggered, either by something hot or cold in the mouth, firm food, exposure of the right cheek to hot or cold (allodynia), or stress. The pain is moderately severe in intensity (7/10), building to its maximum intensity in 2 hours. An episode is generally ultimately relieved when he gets a good night's sleep. Examination reveals decreased sensation for pinprick over the innervation areas of the right ophthalmic and maxillary nerves.

## **Case vignettes: examples of burning mouth**

A 52-year-old female developed burning pain of the left side of her tongue, from front to back, and pain in her left upper jaw 2 years ago. The jaw pain is felt in the gum, bone, and teeth and is associated with pain in the left eye, temple, and back of the neck as well as with ringing in the left ear. When severe, the tongue pain is associated with sticky mucus in the back of her throat that she cannot swallow down. The pain is present on awakening in the morning (7/10) and gradually increases as the day progresses to be worst in the late afternoon (8–9/10). Bending over increases the pressure in the left eye and temple and causes it to become throbbing. Her neck and shoulder muscles are tight and sore on the left. She used to sleep on her left side with her head rotated to the side, twisting her neck. On examination, the left masseter muscle is tender with taut bands; sensation over the tongue is intact, without paresthesia, dysesthesia, or allodynia.

A 61-year-old female has had burning pain in the right lateral side of the anterior two thirds of her tongue for 19 years, stable over time. The pain has been daily and continuous since the onset and, over time, has caused anxiety and depression. On awakening in the morning, the pain is mild (2–3/10) but gradually increases in intensity as the day progresses to be worst around 6:00 p.m. (7–8/10). The pain is very severe (10/10) 2 or 3 times per week for 1 day and then extends down the right side of her throat and is associated with pain in her right eye and in the right back of her head. She sometimes feels a “lightning bolt” going through the right side of her tongue that leaves her tongue pulsating. Stress and fatigue make the pain worse, while rubbing the right side of the tongue makes it slightly better. As a result of the pain, she cannot sleep lying on her right side because of worsening of the pain. Examination reveals sensation

over the tongue to be intact, without paresthesia, dysesthesia, or allodynia.

A 75-year-old male has had a burning pain in his tongue for 3 or 4 years, worse over time. The burning involves the entire tongue, which is also sore and sensitive. The burning increases in intensity as the day progresses, sometimes to the extent of becoming unbearable. It affects his ability to eat, resulting in significant weight loss. On examination, the tongue has a smooth appearance due to loss of papillae. His hemoglobin was normal but the mean corpuscular volume was high and the serum vitamin B12 level low. Treatment with vitamin B12 rapidly improved his condition.

Due to the fact that the tongue papillae have a high turnover rate, deficiencies in micronutrients needed for energy metabolism may lead to depapillation and glossitis, particularly iron and vitamin B12. Other causes of burning mouth are allergies to food flavorings and additives, causing contact stomatitis, xerostomia, often caused by medications, candidiasis, often only detected by culture or biopsy, with risk factors including xerostomia, corticosteroid treatment, dentures, and diabetes mellitus [5].

## **Shooting, jabbing, or stabbing pain**

The best known facial pain, that is, trigeminal neuralgia, belongs to this category and because it is best known, it also tends to be over-diagnosed. Trigeminal neuralgia is often the term used, and understandably so, when shooting, jabbing, or stabbing pain occurs in the face, which is the case in 0.3% of the general population [6]. Such a shooting pain may occur by itself or on a background of burning pain; in fact, the shooting pain when triggered by touch, as it often is, should be considered an indication that the burning pain is neuropathic (allodynia). However, it is also seen and, unfortunately not that rarely, that a remote condition like cluster headache is diagnosed and treated as trigeminal neuralgia, both medically and surgically, of course to no avail and sometimes with detrimental effects, such as the development of anesthesia dolorosa.

Like burning pain, shooting pain can also be nociceptive in nature and when occurring in the head it is known as stabbing headache, also called jabs and jolts or ice-pick headache. This shooting pain in the head is quite common in patients with migraine or cluster headache, albeit generally occurring very infrequently in these patients. It can, however, also occur by itself and can occur very frequently, hundreds of times per day, in what is called jabs-and-jolts syndrome, described in an episodic and chronic form [7]. Stabbing headache can also occur

in the face and, admittedly, is difficult to differentiate from trigeminal neuralgia. It should be considered especially in the younger patient with shooting pain in the face but should be kept in mind in every patient with shooting face pain. Its treatment is with indomethacin rather than with an anticonvulsant such as carbamazepine or oxcarbazepine.

## **Case vignettes: examples of shooting, jabbing, or stabbing pain**

A 53-year-old male has had face pain since age 25, consisting of sharp jabs extending from a right-frontal mandibular tooth into the cheek and eye. The jabs last for 5–30 seconds and many of them occur during the day. They are daily for several weeks at a time, separated by remissions of 3 or 4 months without pain. The jabs occur spontaneously or are precipitated by touching or biting down on the tooth or by brushing the teeth, shaving, eating, talking, coughing, etc. A root-canal procedure performed on the involved tooth failed to provide relief, as did numbing of the right cheek with a local anesthetic. Subsequently, he was treated with carbamazepine, which provided considerable relief, however at the expense of causing significant drowsiness. At age 43, he underwent a radiofrequency procedure, which entirely eliminated the jabs for 9 years. Then, the jabs returned and on a single day, he counted as many as 370, occurring every 5–10 minutes for several hours at a time. Occasionally, when a jab hit, he would cry out or jerk his head. He had almost completely stopped eating solid foods and now also drinking triggered the jabs and, as a result, he had lost 7 or 8 pounds. He was prescribed indomethacin, 75 mg extended release twice daily, which decreased the frequency of the jabs to five or fewer per day.

A 60-year-old male had two mandibular frontal teeth extracted 5 years ago. During the anesthesia, he felt an electric shock, which he attributes to the needle hitting a nerve. Later that day, he started to experience shock-like pain lasting for 15–20 seconds in the right cheek, side of the nose, upper lip, and upper teeth. For the first 3.5 years, it occurred superimposed on a constant burning pain, which has since disappeared. He now experiences the shock-like pain two or three times per month in episodes lasting for 5–10 days. The shocks occur in bouts of 10–15, within a span of 20–30 minutes. The bouts are almost always triggered by such activities as eating, talking, touching the face, and the jolting impact on the head while walking.

A 61-year-old male had two maxillary anterior teeth extracted. During anesthetic injection in the right maxilla preceding the extraction, he felt an

electric shock. He developed pain in the cheek, side of the nose, upper lip, and maxillary teeth later that day. The pain is electric shock-like in nature and lasts for 15–20 seconds. For the first 3 or 4 years, it occurred superimposed on a constant burning pain, which has since disappeared. He is left with the electric shock-like pain occurring two or three times per month for 5–10 days. The shocks occur in bouts of 10–15, happening over a period of 20–30 minutes. The bouts are almost always triggered by activities such as eating, moving the mouth as with talking, touching the face, and the jolting impact on the head of walking.

An 88-year-old female developed sharp pain in the left lower jaw almost 20 years ago, which made her face freeze and her eyes tear. Initially, the pain occurred once every 2–3 months for 20 minutes, in jabs that lasted for 45 seconds. The episodes of jabs rapidly increased in frequency and duration and more than 15 years ago, the jabs became daily. The jabs occurred spontaneously but were also triggered by wind blowing on her face, touching the face, chewing, brushing the teeth, etc. As a result of the jabs occurring with eating, she lost significant weight. She had a radiofrequency procedure performed, which rendered the left side of her face somewhat numb and fully relieved the jabs for 3 months. They gradually returned afterwards and are currently treated with oxcarbazepine taken daily, which has greatly improved the condition.

## Conclusion

Chronic orofacial pain is a difficult medical/dental condition from a diagnostic as well as therapeutic perspective, here covered from a diagnostic perspective. As current etiologic and mechanistic classifications do not seem very useful from a practical standpoint, that is, aiding the clinician, a more descriptive approach is used, illustrated with real-life case histories. Hopefully, particularly the case histories will guide the clinician dealing with the patient with chronic orofacial pain in terms of diagnosis and, indirectly, also with treatment, whether medical, surgical, or dental.

**Table 53.1 Types of facial pain.**

| Location | Lateralization | Etiologic category | Specific etiology | Comorbidity     |
|----------|----------------|--------------------|-------------------|-----------------|
| Face     | Bilateral      |                    | Sinus vacuum      | Pain in the eye |

|            |                          |                                                 |                                          |
|------------|--------------------------|-------------------------------------------------|------------------------------------------|
|            |                          |                                                 | the<br>oft<br>ass<br>wit<br>cor          |
|            | Muscle tension           | Pain<br>per<br>in t<br>fac<br>var<br>ten<br>heε |                                          |
| Unilateral | Stabbing                 | Trigeminal<br>neuralgia                         | Pain<br>ger<br>loc<br>chε<br>or l        |
|            |                          | Facial variant of<br>stabbing headache          | Pain<br>lim<br>inn<br>are<br>trig<br>ner |
|            | Continuous               | Intranasal contact                              | Pain<br>in s<br>the<br>nos               |
|            |                          | Referred pain from<br>masseter muscle           | Pain<br>in s<br>the<br>chε               |
|            | Trigeminal<br>neuropathy | Pain<br>ger                                     |                                          |

|        |            |                  |                                                    |                                                                  |
|--------|------------|------------------|----------------------------------------------------|------------------------------------------------------------------|
|        |            |                  |                                                    | loc<br>chε<br>or l                                               |
| Jaw(s) | Bilateral  |                  | Muscle tension                                     | Pai<br>per<br>in t<br>fac<br>var<br>ten<br>heε                   |
|        | Unilateral |                  | Temporomandibular<br>joint and muscle<br>disorders | Pai<br>ove                                                       |
|        |            |                  | Masseter myalgia                                   | Pai<br>in j                                                      |
| Mouth  | Bilateral  | Micronutritional | Iron or vitamin B12<br>deficiency                  | Mi<br>ane<br>anc<br>fen<br>lev<br>ma<br>ane<br>anc<br>vit<br>lev |
|        |            | Allergy          | Flavorings or food<br>additives                    | Co<br>alle                                                       |
|        |            | Xerostomia       |                                                    | Oft<br>me<br>also<br>cor<br>Sjö<br>syr                           |

|            |                                 |                                                   |                      |
|------------|---------------------------------|---------------------------------------------------|----------------------|
|            | Candidiasis                     | Denture, diabetes, xerostomia, corticosteroid use | Oft dia by or l      |
|            | Neuropathy                      | Afferent C-fiber loss                             | Oft ass wit dec alte |
| Unilateral | Gastroesophageal reflux disease | As eso syr trea hig pro pur inh                   |                      |

---

## References

1. Aggarwal VR, McBeth J, Zakrzewska JM, Lunt M, Macfarlane GJ. The epidemiology of chronic syndromes that are frequently unexplained: do they have common associated factors? *Int J Epidemiol* 2006; 35:468–76.
2. Aggarwal VR, McBeth J, Lunt M, Zakrzewska JM, Macfarlane GJ. Development and validation of classification criteria for idiopathic orofacial pain for use in population-based studies. *J Orofacial Pain* 2007; 21:203–15.
3. De Leeuw R, Ed. The American Academy of Orofacial Pain. *Orofacial Pain: Guidelines for Assessment, Diagnosis, and Management*, 4th edn. Chicago, IL: Quintessence Publishing Company, 2008.
4. Mobilio N, Casetta I, Cesnik E, Catapano S. Prevalence of self-reported symptoms related to temporomandibular disorders in an Italian population. *J Oral Rehab* 2011; 38:884–90.
5. Drage LA, Rogers RS. Clinical assessment and outcome in 70 patients with

- complaints of burning or sore mouth symptoms. *Mayo Clinic Proc* 1999; 74:223–8.
6. Mueller D, Obermann M, Yoon MS *et al*. Prevalence of trigeminal neuralgia and persistent idiopathic facial pain: a population-based study. *Cephalalgia* 2011; 31:1542–8.
  7. Spierings ELH. Episodic and chronic jabs and jolts syndrome. *Headache Quart* 1990; 1:299–302.
  8. Simons DG, Travell JG, Simons LS, Cummings BD. *Travell & Simons' Myofascial Pain and Dysfunction Point Manual*. Baltimore, MD: Williams & Wilkins, 1998.

## 54 Pain, neck

---

Louis J. Goodrich and Ajay Berdia *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

The ancient treatment of spine injury probably aimed at causing distraction (Hippocrates 460–377 BCE). Presently, neck pain accounts for 1% of annual population visits to physicians, while 7 out of 10 people will complain of neck pain at some point in their lifetime. Indeed, at any given time, 12% of adult females and 9% of adult males suffer from neck pain. This pain most commonly arises from movement and mechanical irritation.

### Anatomy and physiology

The cervical spine is the most complex articular system in the body, with the capacity of moving approximately 600 times per hour. The cervical spine bears 8 pounds of weight in the adult, 1.3 pounds of which is contributed by the cerebrospinal fluid. The seven cervical vertebrae constitute 88% of the height of the cervical spine, while the remaining 22% is derived from the joints and discs. A fraction of a percentage of this height is due to remnants of the notochord.

The first two cervical vertebrae are often referred to as the atypical cervical vertebrae. The C1 vertebra, also known as the atlas, has no body, as it is fused to the body of C2 during embryonic development to form the dens. The atlas acts like a pedestal on which the skull rests, so movement about the atlas is questionable. The C2 vertebra, known as the axis, has the largest vertebral body of the cervical vertebrae. The presence of the dens accounts for the axis's unique identity and serves as the articulation around which the skull and atlas rotate as a unit. The remaining cervical vertebrae (C3–C7) are commonly referred to as the typical cervical vertebrae or as the subaxial cervical spine. Each of these vertebral bodies is greatest in height posteriorly. The vertebral bodies are composed of cortical and cancellous bone and are capable of withstanding a

force of approximately 1500 Newtons. Each of the typical cervical vertebrae is separated by fibrocartilagenous intervertebral discs. The cartilaginous endplates of each disc line the inferior surface of the vertebral body superior to them and the superior surface of the vertebral body inferior to them.

The five cervical intervertebral discs are composed of a central, gelatinous core (the nucleus pulposis), surrounded by the thick annulus fibrosis. In infancy, the discs are composed of 88% water, while by the 7th decade, their water content has decreased to 70%. The discs begin to desiccate in the 3rd or 4th decade, which also begins the process of spondylosis.

The nucleus pulposis, which comprises less than 50% of disc cross-sectional area, consists of loosely and obliquely arranged type II collagen fiber units and is a remnant of the embryonic notochord. Glycosaminoglycans form the structural units of the nucleus pulposis. Its central core is formed by hyaluronic acid, which binds to a protein core that ultimately binds to chondroitin sulfate and keratin sulfate. Chondroitin sulfate carries a significant negative charge, which allows it to hold proton-rich water within this disc. This water content also accounts for the efficacy of magnetic resonance imaging (MRI) in imaging the intervertebral discs. However, chondroitin sulfate is lost from the discs with age, and the consequent loss of water results in desiccation.

The annulus fibrosis consists of an outer fibrous portion, 90% of which is constituted by lamellae of type I collagen. The successive lamellae run perpendicular to one another, while the outermost lamella adheres directly to the vertebral bodies via Sharpley fibers. Fibers of ligaments and muscles directly attach to the Sharpley fibers. The innermost lamella inserts on a cartilaginous plate. The uncovertebral joints, or joints of Luschka, are situated on both sides of the cervical intervertebral discs. Osteophytes arising in these joints contribute to cervical spondylosis.

The ligaments of the cervical spine have the dual function of allowing movement within the physiologic range, while restricting motion beyond it. These include the anterior longitudinal ligament, posterior longitudinal ligament, ligamentum flavum, uncinate ligament, and the capsular ligaments of the facet joints. The ligamentum flavum decreases in length by 10% in extension, while it stretches by 30% in full flexion. A hypertrophied ligamentum flavum can cause significant cord compression during hyperextension in the elderly or following acute hyperextension injury.

The cervical segment of the spinal cord is the thickest portion of the entire

cord. The cervical cord extends from the upper level of the C1 nerve root attachment to the upper level of the T1 nerve root attachment, while the cervical enlargement extends from C3 to T2 and corresponds to the origin of the brachial plexus. The cervical cord conducts sensation from the periphery to the brain and motor signals from the brain to the body. The cord can lengthen by 10% during flexion through compensatory reduction in its cross-sectional area. Conversely, the cord expands in width to shorten during extension.

The anterior spinal artery, the right and left posterior spinal arteries, and the deep cervical arteries provide the arterial supply to the neck. The vertebral artery arises from the second part of the subclavian artery and is divided into four parts: the first portion extends from the artery's origin to the foramina transversarii of the cervical vertebrae, the second portion lies within the foramina transversarii, the third portion courses around the axis vertebra, and the fourth portion is intracranial. The bilateral vertebral arteries unite to form the basilar artery, which supplies the brainstem, cerebellum, and occipital lobe of the cerebrum. The basilar artery also communicates with the circle of Willis. The vertebral arteries are prone to traumatic dissection at their bend around the atlas; that is, at the junction of the 3rd and 4th parts. The vertebral arteries are also responsible for cervicogenic headache.

The nerve roots are formed by assimilation of dorsal (sensory) and ventral (motor) rootlets. Each spinal nerve gives rise to a sinuvertebral nerve near the rami communicantes, which innervate the posterior longitudinal ligament, epidural vasculature, dura, and spinal periosteum. The spinal nerve then splits to form anterior and posterior rami. The posterior rami supply facet joints, paracervical muscles, and dorsal nuchal skin, while the anterior rami form the cervical and brachial plexuses. The rami communicantes provide innervation to sympathetic ganglia.

The pain sensitive structures in the neck include the paracervical muscles, ligaments, bones, intervertebral discs, nerve roots, spinal dura, and vertebral arteries. Pathology of these structures, along with compression of the spinal cord or spinal nerve(s) that provide their innervation, must be considered when evaluating neck pain.

## Case vignette

A 25-year-old male presents to an office setting complaining of “pulled muscles” in his left posterior cervical and scapular regions for one month's

duration. He lifts weights as a component of regular exercise and suspects that he injured his neck and shoulder as a result of his physical activity. He denies prior history of musculoskeletal injury. He rates his level of pain as variable between 4 and 6 out of 10. He has no notable past medical history, no surgical history, and no family history of musculoskeletal or rheumatologic disease. He has no allergies to medication or food, but has environmental allergies to pollen. He takes fluticasone intranasally for his allergies and takes no over-the-counter medications.

One week prior to his visit, he sought treatment at an urgent care facility due to intractable pain in the area of his complaint. He was prescribed 10 mg cyclobenzaprine and 800 mg ibuprofen, which have not alleviated his pain. Upon further questioning, the patient admits to having been involved in an automobile accident 6 weeks prior to the onset of his present symptoms. He was impacted from behind while stopped at a traffic light. However, since he felt no pain for the first 6 weeks following the accident, he did not consider it to be relevant to his current complaint.

On physical examination, his left trapezius, sternocleidomastoid, supraspinatus, and infraspinatus muscles are hypertonic. His cervical spine is restricted in right lateral flexion and right rotation. Extension of his cervical spine elicits considerable pain and guarding. Flexion of his cervical spine slightly alleviates his pain. Immediate X-rays are performed, which rule out fracture. Loss of cervical lordosis is noted, along with moderate scoliosis that is convex to the left.

**Table 54.1** *Differential diagnosis of neck pain [1–3].*

| Item       | Subdivision      | Specific entity       | Possi                                                |
|------------|------------------|-----------------------|------------------------------------------------------|
| Congenital | Vertebral column | Spinal bifida occulta | Defect durin devel asym manif form sinus progr defor |

|              |                                         |                                                                                                                                                 |
|--------------|-----------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
|              | Myelomeningocele                        | Less<br>bifid<br>over 1<br>neurc                                                                                                                |
|              | Klippel–Feil<br>syndrome                | Triad<br>more<br>neck,<br>Three<br>Type<br>cervic<br>Type<br>level.<br>abnor<br>Type<br>thora<br>spine                                          |
|              | Soft tissue                             | Thyroglossal duct<br>cyst                                                                                                                       |
| Degenerative | Intervertebral<br>disc and<br>ligaments | Cervical<br>spondylosis                                                                                                                         |
|              |                                         | Most<br>cervic<br>and n<br>Clinic<br>pain &<br>withc<br>syndr<br>progr<br>Stage<br>hypert<br>Stage<br>facet<br>spur,<br>herni<br>Stage<br>facet |

|                          |                        |                |                                                                                                          |
|--------------------------|------------------------|----------------|----------------------------------------------------------------------------------------------------------|
|                          |                        |                | foran                                                                                                    |
|                          | Facet joint            | Osteoporosis   | A ger<br>group<br>chara<br>bone<br>result<br>outri<br>height<br>lordo                                    |
|                          |                        | Osteoarthritis | Loss<br>narro<br>form.<br>degen<br>cartil<br>weigl<br>Diagn<br>radio                                     |
| Infective/post-infective | Intervertebral<br>disc | Discitis       | Comi<br>osteo<br>post-<br>child<br>Magr<br>(MRI)                                                         |
|                          | Meninges               | Meningitis     | Acute<br>nucha<br>menin<br>Brudz<br>and c<br>sever<br>asept<br>menin<br>purpu<br>rash.<br>etiolc<br>with |

|                 |                                 |                                            |
|-----------------|---------------------------------|--------------------------------------------|
|                 | Epidural abscess                | Occu<br>chron<br>masto<br>traum            |
| Mucosal         | Pharyngitis                     | Bacte                                      |
|                 | Viral respiratory<br>infection  | May<br>bacte                               |
| Nerve           | Herpes zoster                   | May<br>affect<br>menin                     |
| Soft tissue     | Acute cervical<br>lymphadenitis | Palpa<br>cervic<br>upper<br>infect<br>Barr |
|                 | Acute suppurative<br>parotitis  | May<br>parot<br>infect<br>HIV              |
|                 | Ludwig's angina                 | Unco<br>Prese<br>of mc<br>absce            |
|                 | Bezold's abscess                | A dee<br>occur<br>of ma                    |
|                 | Mumps                           | Occu<br>child<br>parot                     |
| Retropharyngeal |                                 | Occu                                       |

|                |                  |                                                                                                         |
|----------------|------------------|---------------------------------------------------------------------------------------------------------|
|                | <u>Neck</u>      | <u>Upper</u>                                                                                            |
|                | abscess          | upper<br>Prese<br>neck,                                                                                 |
| Vertebral body | Osteomyelitis    | Espe<br>(IV) c<br>with<br>eryth<br>accor                                                                |
|                | Spondylitis      | Infla<br>body<br>tuber<br>arthri<br>sponc<br>predc<br>cranio<br>juncti<br>mobi<br>contu<br>neck<br>lymp |
| Facet joint    | Septic arthritis | Com<br>patie<br>repla<br>or im                                                                          |
| Other          | Hydatid cyst     | Due t<br>tapew<br><i>Echir</i><br>USA<br>to an<br>prim<br>invol<br>meta<br>orgar                        |
| Inflammatory   | Soft tissue      | Longus colli                                                                                            |
|                |                  | Unco                                                                                                    |

|             |                           |                                                                          |                                                                                                |
|-------------|---------------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------------------------------|
|             | tendonitis                | condi<br>pain.<br>by ca<br>C1 ar<br>May<br>retrof<br>infect<br>traum     |                                                                                                |
|             | Thyroiditis (acute)       | Histo<br>comm<br>unilate<br>radiat<br>occip<br>allevi<br>and a<br>exten  |                                                                                                |
| Facet joint | Rheumatoid<br>arthritis   | Chro<br>arthri<br>throu<br>Sero <sup>g</sup><br>rheur<br>nucle<br>sugges |                                                                                                |
|             | Ankylosing<br>spondylitis | Multi<br>disord<br>skele                                                 |                                                                                                |
| Metabolic   | Crystal<br>arthropathy    | Gout                                                                     | Preci<br>urate<br>secon<br>of uri<br>of hi <sup>g</sup><br>preci<br>first i<br>joint<br>affect |

|                           |                   |                                                                                               |
|---------------------------|-------------------|-----------------------------------------------------------------------------------------------|
|                           |                   | arthro<br>any j                                                                               |
|                           | Pseudogout        | Preci<br>pyrop<br>joints                                                                      |
| Neoplastic/paraneoplastic | Primary           | Osteosarcoma                                                                                  |
|                           |                   | Most<br>tumo<br>hallm<br>maliq<br>comm<br>espec                                               |
|                           | Spinal cord tumor | Very<br>Histo<br>major<br>epen<br>hema<br>Prese<br>due to<br>comp<br>includ<br>sensa<br>funct |
|                           | Pancoast tumor    | A lun<br>invad<br>Pain<br>8th ce<br>nerve<br>prese<br>syndr                                   |
|                           | Laryngeal tumor   | Most<br>squar<br>Histo<br>tobac<br>with<br>Symr                                               |

**Symptoms**  
may include:  
dysphagia  
odynophagia

**Esophageal tumor**  
Dysphagia is the most common symptom.  
Hoarseness and laryngeal irritation may indicate a tumor.  
not recommended for screening.  
year of diagnosis: 20–21 years old.

**Meningioma**  
Incidence: 10–15% of all brain tumors.  
meningiomas are usually benign.  
Meningiomas can occur at any age, but are most common in middle-aged women.  
cord compression, spinal cord compression, and spinal canal stenosis.  
Sequelae: progressive neurologic deficits, seizures, and cranial nerve palsies.  
definitive treatment: surgery.  
meningiomas are often slow-growing and can be present for many years before they cause symptoms.  
identification: imaging studies (CT or MRI) and biopsy.

**Neurofibroma**  
May be associated with other neurofibromatosis syndromes.  
lesions: skin, bone, and peripheral nerves.  
of neurofibromatosis: 1 and 2.  
1 and 2: type I (NF1) and type II (NF2).  
1/3,000 individuals have NF1.  
has a higher incidence of NF1 than NF2.  
1/37,000 individuals have NF2.

**Schwannoma**  
Typical symptoms: pain, numbness, and tingling.  
presence of a schwannoma: nerve compression.  
neurofibromatosis: 1 and 2.  
Patient history: family history of neurofibromatosis, schwannomatosis, or other neurofibromatosis-associated conditions.  
schwannomas: peripheral nerve compression.  
dysfunction: sensory and motor function.

nerve  
asym  
schw  
incide  
imag

Osteoblastoma  
Rare,  
bone.  
due to  
poten  
malign  
comm  
aged  
Most  
with  
frequ  
verte  
long

Metastasis  
Most  
prim  
prost  
lymph

Other, idiopathic  
Paget's disease  
Occu  
of pa  
asym  
most  
symp  
phosi  
due to  
hyper

Foreign body in  
larynx  
Most  
child

Sialolithiasis  
Can t  
prim  
oppo

|                  |                                                |                                                                                 |                                                                         |
|------------------|------------------------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------------------------------|
|                  |                                                |                                                                                 | immu<br>patie                                                           |
|                  | Diffuse idiopathic<br>skeletal<br>hyperostosis | Cause<br>prese<br>incide                                                        |                                                                         |
|                  | Hyoid bone<br>syndrome                         | Pain<br>region<br>may<br>and le<br>histoi                                       |                                                                         |
|                  | As part of<br>L'hermitte's sign                | Parox<br>sensa<br>down<br>of the<br>multi<br>sclero<br>the sp<br>sponc<br>herni |                                                                         |
| Pressure effects | Musculoskeletal                                | Thoracic outlet<br>syndrome                                                     | Neuro<br>due to<br>hyper<br>trapez<br>sterno<br>leadi<br>paras<br>upper |
|                  | Intervertebral<br>disc                         | Protrusion                                                                      | The l<br>disea                                                          |
|                  | Facet joint                                    | Herniation                                                                      | depe                                                                    |
|                  |                                                | Osteophytes                                                                     | verte                                                                   |
|                  |                                                | Osteophytes                                                                     | radiat                                                                  |
|                  |                                                | Ganglion                                                                        | Pain                                                                    |
|                  |                                                | Tumor                                                                           | the p                                                                   |
|                  |                                                |                                                                                 | C6-7                                                                    |

the sc  
is cor  
distract  
by inc  
spina  
Valsalva  
the be  
determ  
prese  
to dis

|                                        |                                                      |                                                               |                                                                                                                                      |
|----------------------------------------|------------------------------------------------------|---------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
| Psychiatric                            | Psychogenic pain                                     |                                                               |                                                                                                                                      |
|                                        | Fibromyalgia                                         | Systemic<br>syndrome<br>characteristic<br>in neck<br>the back |                                                                                                                                      |
| Structural (congenital or<br>acquired) | Congenital<br><br>Musculoskeletal<br><br>Soft tissue | Cervical rib<br><br>Postural disorder<br><br>Torticollis      | Associated<br>outlet<br><br>Neck<br>compression<br>to keep<br><br>Due to<br>sternocleidomastoid<br>Head<br>flexed<br>away<br>muscles |
|                                        |                                                      | Esophageal<br>diverticulum,<br>Zenker<br>diverticulum         | Dysphagia<br>fetid                                                                                                                   |
|                                        | Subluxation                                          | Down's syndrome                                               | Atlantoaxial<br>subluxation                                                                                                          |

|                   |                         |                                                                                                          |
|-------------------|-------------------------|----------------------------------------------------------------------------------------------------------|
|                   | (Atlanto-axial)         | occur<br>with<br>(triso                                                                                  |
|                   | Rheumatoid<br>arthritis | See “                                                                                                    |
|                   | Morquio syndrome        | Auto:<br>muco<br>IV).<br>coars<br>and li                                                                 |
| Trauma-associated | Musculoskeletal         | Strain cervinalgia                                                                                       |
|                   |                         | Comi<br>accel<br>(whip<br>be ati<br>of pa<br>ligam<br>facet<br>isolat<br>sever<br>range<br>neurc<br>more |
|                   |                         | Fracture                                                                                                 |
|                   |                         | Perfo<br>rule c<br>with                                                                                  |
|                   | Neurologic              | Nerve injury                                                                                             |
|                   |                         | Loca<br>affect<br>“Pres<br>descr<br>from<br>nerve                                                        |
|                   |                         | Myelopathy                                                                                               |
|                   |                         | Neck<br>range<br>deform                                                                                  |

|          |            |                                         |                                                          |
|----------|------------|-----------------------------------------|----------------------------------------------------------|
|          |            | Myelomalacia                            | Loss<br>subst<br>previ<br>lesio<br>chan<br>comp<br>ische |
| Vascular | Dissection | Internal carotid<br>dissection          | Neck<br>prese<br>of ca<br>neck                           |
|          |            | Vertebral artery<br>dissection          | Neck<br>of ca                                            |
|          |            | Dissecting aortic<br>aneurysm           | 6% e<br>prese<br>with<br>symp<br>distre                  |
|          | Thrombosis | Carotid thrombosis                      | May<br>cereb<br>amau                                     |
| Other    |            | Carotid<br>hypersensitivity or<br>tumor | Cause<br>and s<br>may l<br>turnir<br>garm                |
|          |            | Cardiac disease                         | Rule<br>myoc<br>ische                                    |

Based upon the distribution of his pain, pain with cervical extension, and his history of whiplash, injury to his lower cervical discs is suspected. An MRI is ordered to confirm the presumptive diagnosis, and the patient is prescribed 2 mg tizanadine PRN for his muscle spasms until follow-up.

At follow-up, the patient states that the tizanadine has provided him little relief. His MRI demonstrates anterior, midline protrusion of the C5/6 and C6/7 intervertebral discs. No other abnormalities are noted. An epidural injection of corticosteroid through the right 6th/7th cervical intravertebral foramen leads to complete resolution of symptoms within 48 hours. Follow-up MRI demonstrates resolution of the disc protrusion.

## References

1. Bogduk N. The anatomy and pathophysiology of neck pain. *Phys Med Rehabil Clin N Am* 2003; 14:455–72, v.
2. Watson JE Jr, Thorn SW. Differential diagnosis of neck pain. *J Am Med Assoc* 1951; 148:11–16.
3. Levy HI. Cervical pain syndromes: primary care diagnosis and management. *Compr Ther* 2000; 26: 82–8.

## 55 Papilledema

---

Don C. Bienfang *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

The term papilledema should be reserved for optic disc swelling that is due to raised intracranial pressure (ICP). This principle applies with rare exception and guides the descriptions in this chapter.

### Physiology

Papilledema occurs when raised intracranial pressure is transmitted to the optic nerve sheath. The raised pressure mechanically disrupts axoplasmic flow within the nerve. The swelling one sees is blocked axoplasmic flow. Venous obstruction and dilation, hemorrhages, nerve fiber ischemia, and vascular telangiectasias are secondary phenomena.

### Neurologic causes

- Intracranial mass lesions that obstruct cerebrospinal fluid absorption and drainage (e.g. tumor, hematoma).
- Cerebral edema (such as in acute hypoxic ischemic encephalopathy, large cerebral infarction, severe traumatic brain injury).
- Increased cerebrospinal fluid (CSF) production, e.g. choroid plexus papilloma.
- Decreased CSF absorption, e.g. arachnoid granulation adhesions after bacterial meningitis.
- Obstructive hydrocephalus.
- Obstruction of venous outflow, e.g. venous sinus thrombosis, jugular vein compression, neck surgery.

- Idiopathic intracranial hypertension (pseudotumor cerebri).

## Clinical manifestations

Papilledema is usually discovered when a patient is evaluated for other symptoms of increased intracranial pressure, rather than for symptoms directly resulting from optic nerve pathology. On the other hand, it is not uncommon for asymptomatic patients who are suspected of having papilledema due to raised ICP to turn out to have normal ICP. In other words papilledema is often over-diagnosed.

Because the causes of intracranial hypertension are generalized phenomena, papilledema is almost universally bilateral though asymmetric. Truly unilateral disc swelling, confirmed by extensive testing and examination of the eyes, is unlikely to be due to raised ICP. However, if there is underlying optic nerve injury or disease, then the appearance of papilledema may be unilateral, since the damaged nerve does not swell. The classic example is the Foster-Kennedy syndrome in which a frontal lobe tumor compresses and destroys the optic nerve on one side before causing increased intracranial pressure. This gives rise to optic atrophy in one eye and disc edema in the other.

## Head symptoms

Headache is a cardinal symptom of increased intracranial pressure. Headache worse when the patient is horizontal and relieved by an erect posture is suggestive.

A pulsatile machinery-like sound in the ear probably due to venous sinus obstruction is common and often persistent even after the raised intracranial pressure is relieved.

Another classic symptom of increased intracranial pressure is binocular horizontal diplopia resulting from unilateral or bilateral lateral rectus paresis. Cranial nerve six, the abducens nerve, is believed to be peculiarly vulnerable to the effects of increased intracranial pressure because of its long course in the subarachnoid space and its bend to enter the cavernous sinus.

## Visual symptoms

One visual symptom is common in patients with papilledema: visual alterations that occur unilaterally and for only a few seconds. They may occur

spontaneously or with changes in position, and they are believed to represent transient fluctuations in nerve head perfusion. Their presence correlates with the degree of intracranial pressure elevation. Increasing intensity, frequency, and duration of these symptoms can be a prognostic sign for sustained visual loss, but this symptom is not reliably predictive.

It is unusual for patients to have persistent deficits of visual acuity, field loss, or a relative afferent pupillary light defect until quite late in the course. Untreated, chronic papilledema can lead to progressive visual field loss in the form of peripheral field contraction, nerve fiber bundle defects, and even blindness. The pattern of field loss is like that of glaucoma .

## **Appearance with an ophthalmoscope**

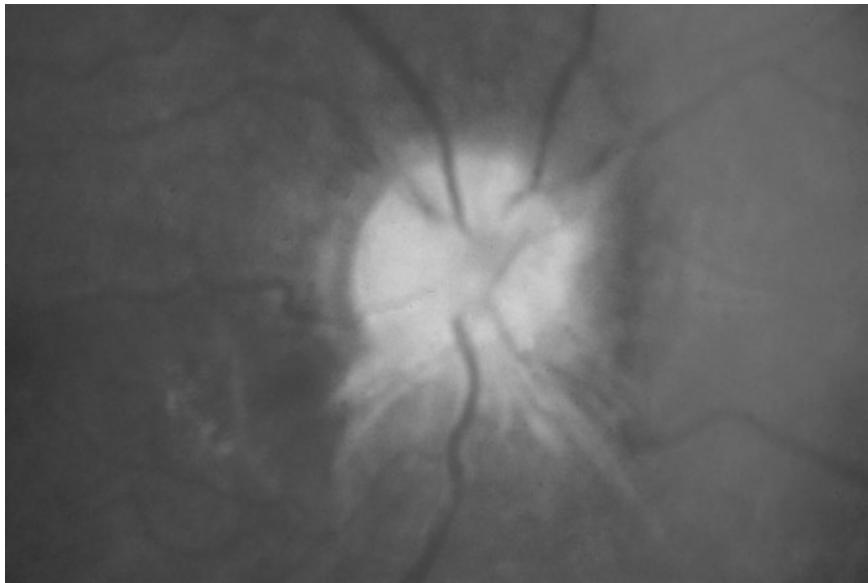
### **Early**

One of the earliest findings in papilledema is loss of spontaneous venous pulsations, occurring with pressure elevations of only 200 mm. However, 20% of normal individuals do not have detectable venous pulsations. These pulsations are best seen in the section of the central retinal vein that is diving into the optic nerve cup.

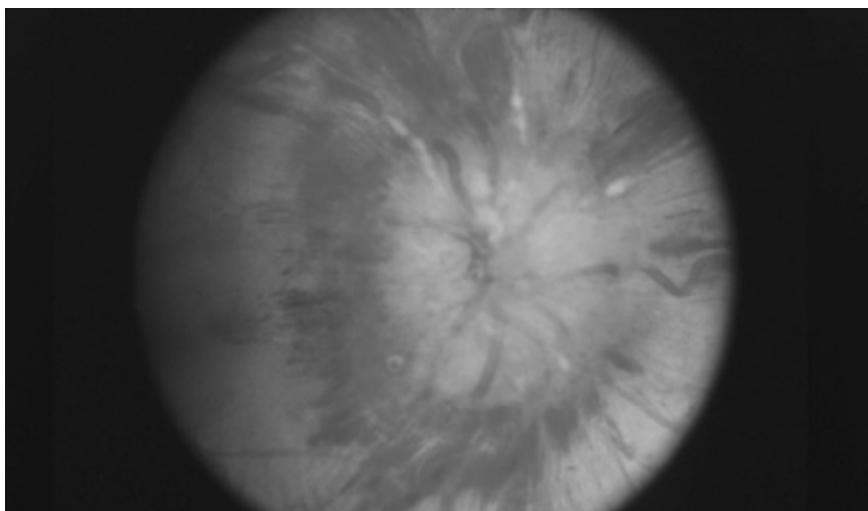
The optic cup is retained early on. However, hemorrhages in the retinal surface, at or beyond the disc margin, *but not to the extreme retinal periphery*, may be seen early. This is also not a specific sign, especially in the elderly.

### **Fully developed**

As the edema progress (this can occur in a few days), the optic disc becomes elevated, the cup is obliterated, and the disc margins become obscured. Blood vessels are buried as they course through the disc. Serpentine engorgement of retinal veins is evident, and the disc appears hyperemic. The edema extends into the retina, giving the appearance of an enlarged optic nerve head. Multiple flame hemorrhages and cotton wool spots, resulting from nerve fiber infarction, appear. Retinal folds form concentrically around the swollen disc. At this stage, the blind spot size on visual field examination will be increased.



**Figure 55.1** Chronic papilledema.



**Figure 55.2** Fully developed papilledema. Photo courtesy of W. F. Hoyt, MD.

## Chronic

The central cup remains obliterated. Hemorrhagic and exudative components resolve. The appearance of so-called “gliosis,” a white veil covering the peripheral portion of the optic nerve, indicates a process of some months’ duration. The nerve now appears flat with irregular margins; nerve fiber attrition leads to disc pallor. One usually can detect some loss of visual field at this stage.

## Differential diagnosis

There are many causes of an elevated optic nerve head. While the term papilledema is sometimes used to describe the findings in these conditions, it should be reserved for patients who have elevated disc heads as a consequence of increased intracranial pressure. The causes of papilledema (i.e. increased intracranial pressure) are listed above.

Since most of the time there is additional information from the history and physical exam, this may be a useful differential diagnosis.

## Bilateral disc abnormalities

Below is a list of conditions that can cause bilateral disc swelling but perfectly normal visual function. Funduscopic findings, the clinical setting, and the presence of associated visual loss usually help distinguish the following entities from each other.

- Disk swelling from raised intracranial pressure (as per above).
- Pseudopapilledema – congenital anomalies of the disc, including drusen and myelinated nerve fibers, and even farsightedness or hyperopia may cause the appearance of disc swelling or pseudopapilledema. This term is reserved for conditions that are not due to disease states.
- Drusen – hyaline bodies thought to be remnants of calcific axonal degeneration. Drusen tend to be buried in children (sometimes raising concern for increased intracranial pressure) and become more exposed in adults. Most are bilateral. Disc drusen appear as a lumpy mass with refractile bodies within.
- Malignant hypertension – check the blood pressure. These patients are almost always encephalopathic.
- Diabetic papillopathy – the blood sugar is usually out of control.
- Graves' disease – the orbital problem will be obvious.

Unilateral disc abnormalities that mimic raised ICP, with normal visual function, are so rare as to be beyond the scope of this chapter.

## Diagnostic testing

Diagnostic testing can help differentiate papilledema from other causes of disc edema, follow the course of papilledema, and determine the underlying etiology.

## **Neuroimaging**

When a patient presents with findings suggestive of papilledema, diagnostic evaluation should proceed expeditiously. A computerized tomography (CT) scan can be ordered initially if access to magnetic resonance imaging (MRI) is delayed because a mass lesion causing raised ICP will usually be large. MRI will detect meningeal abnormalities not detectable by CT. Additional sequences, magnetic resonance venography (MRV), can be used to detect venous obstruction in the dural sinuses and in the neck. Rarely, increased intracranial pressure may arise from spinal lesions; therefore, if this diagnosis is suggested by clinical signs or symptoms (back or neck pain, myelopathic signs, abnormal spinal fluid) an MRI of the spine may be necessary as well.

## **Lumbar puncture**

If neuroimaging is normal and one is suspicious of raised ICP, lumbar puncture (LP) should be done for opening pressure and analysis: 200 and lower is normal, 200–250 is equivocal and above 250 is abnormal. The standard for children is probably the same as adults. Beware, however, even in the best of circumstances (LP with fluoroscopy) positioning is important and may be difficult with obese patients. Many patients with normal neuroimaging and raised ICP will be young, obese females that have pseudotumor cerebri.

## **Visual field testing**

Formal visual field testing with perimetry is very useful in the detection of subclinical visual field abnormalities and quantifying changes over time but it is not usually a diagnostic test to detect papilledema. It is helpful in following the progress of the visual sequelae of papilledema and monitoring response to treatment. The size of the blind spot is an indirect measure of the degree of disc edema and very sensitive to the patient's glasses prescription. Constrictions in field perimetry and development of sector field defects especially infero-nasally are signs of impending serious visual loss. This finding is more valuable for prognosis than either symptoms or fundus appearance.

## **Fluorescein angiography**

Fluorescein angiography of the retina may be helpful in the detection of early papilledema, showing dye leakage, disc vascularity, and excess early and late disc fluorescence. Ophthalmologists, however, find it incompletely reliable,

especially in equivocal situations, and usually unnecessary in this clinical setting.

## **Optical coherence tomography**

When available, optical coherence tomography may be useful to monitor the swelling of the nerve and also to clarify the effect upon and changes within the surrounding retina. This technique is very dependent upon the skills of the person performing the test and thus is prone to error. Modern technology (spectral rather than time based) has improved reliability .

## **Visual prognosis**

Permanent loss of vision can be a consequence of papilledema that is untreated or unresponsive to treatment. Clinical findings predictive of central visual loss are high-grade disc edema, peripapillary subretinal hemorrhages, opticociliary shunt vessels, abnormal vision at presentation, and the development of visual field loss. Treatment depends on etiology.

## **Summary and recommendations**

The term papilledema is most properly applied to optic disc edema occurring as a consequence of intracranial hypertension.

- The causes of papilledema often have serious consequences for impending morbidity and mortality; hence, diagnostic evaluation is urgent.
- Truly unilateral disc swelling and abnormal visual function at presentation almost always mean alternative diagnoses.
- The first step in the evaluation for the cause of papilledema should be a neuroimaging study; a brain MRI is preferred, but a CT scan should be done if an MRI is not immediately available.
- Lumbar puncture with measurement of opening pressure and analysis of cerebrospinal fluid should follow any normal neuroimaging study if one is certain the patient has raised ICP.
- Serial clinical evaluations including measurements of visual acuity, funduscopic examination, and visual field testing with perimetry are invaluable in following the course of papilledema and response to treatment.

## Case vignette

A patient sees an optometrist for the first time. The optometrist examines the fundi and is concerned that the patient may have increased intracranial pressure. After reviewing this chapter, one can apply a few questions to the situation to avoid getting an MRI and a lumbar puncture on everyone. While not foolproof, the following questions will help guide the decision.

- Does the patient have a headache?
- Does the patient hear a machinery type noise in the ear?
- Does the patient lose vision briefly if he/she stands up after bending over?
- Does the patient have any localizing neurologic signs or symptoms?
- Is the patient an obese, young female?
- Is the patient farsighted (hyperopic)?
- Is the alleged disc swelling bilateral?
- On funduscopy are there spontaneous venous pulsations at the optic nervehead cup?
- Are there supporting findings on the fundus exam that the nerve is abnormal, such as hemorrhages around the nervehead, wrinkles in the retina, and grossly enlarged veins?

An MRI scan is expensive and often discovers entities that are unrelated and trivial; CT scans have the same issues and expose the patients to radiation.

## Further reading list

Burde RM, Savino PJ, Trobe JD Eds. *Clinical Decisions in Neuro-Ophthalmology*, 2nd edn. St Louis, MO: Mosby Year Book, 1992.

Digre KB, Corbett JJ. Idiopathic intracranial hypertension (pseudotumor cerebri): a reappraisal. *The Neurologist* 2001; 7:2–67.

Hayreh SS. Optic disk edema in raised intracranial pressure VI. Associated visual disturbances and their pathogenesis. *Arch Ophthalmol* 1977; 95:1566–79.

Orcutt JC, Page NGR, Sanders MD. Factors affecting visual loss in benign intracranial hypertension. *Ophthalmology* 1984; 91:1303–12.

Pavan PR, Aiello LM, Wafai MZ *et al.* Optic disk edema in juvenile onset

- diabetes. *Arch Ophthalmol* 1980; 98:2185–92.
- Rosenberg MA, Savino PJ, Glaser JS. A clinical analysis of pseudopapilledema I. *Arch Ophthalmol* 1979; 97:65–70.
- Sadun AA, Currie JN, Lessell S. Transient visual obscurations with elevated optic disks. *Ann Neurol* 1984; 16:489–94.
- Sedwick LA, Burder RM. Unilateral and assymetric optic disk swelling with intracranial abnormalities. *Am J Ophthalmol* 1983; 96:484–7.
- Wall M, Hart WM, Burde RM. Visual field defects in idiopathic intracranial hypertension (pseudotumor cerebri). *Am J Ophthalmol* 1983; 96:654–69.

## 56 Paresthesias

---

George D. Baquis and Anant M. Shenoy *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Paresthesias are abnormal sensations that are described as prickling, tingling, burning, or pins and needles [1–3]. The causes of paresthesias are numerous and include neurologic and non-neurologic etiologies (see [Table 56.1](#)). Clinicians rely on the clinical history and physical examination when considering various possibilities. This directs the evaluation and prevents unnecessary testing which can delay appropriate diagnosis and treatment.

Paresthesias have diverse potential causes and can arise from multiple peripheral and central nervous system (CNS) anatomic locations. They can be a symptom of benign or more serious disease, and the etiology is determined by the mode of onset and temporal course, anatomic distribution, associated symptoms and neurologic examination findings, and results of diagnostic tests. [Table 56.1](#) provides many common causes of paresthesias but is not exhaustive [2–8].

### Case vignette

A 43-year-old female with a 15-year history of diabetes mellitus and panic attacks complains of episodic right hand numbness and wrist pain, bilateral foot numbness, and perioral tingling. Right hand numbness involves her thumb, index, and middle fingers and awakens her from sleep causing her to panic; she breathes rapidly, anxiously shakes out her hand for relief, and denies neck or shoulder pain.

Differential diagnosis: Sensation is altered in the median nerve territory which is commonly affected in carpal tunnel syndrome. A cervical radiculopathy or brachial plexopathy could cause similar sensory symptoms. Spinal cord and

cerebral disease would not typically cause this pattern of paresthesias. Bilateral foot numbness could be due to a polyneuropathy, and transient perioral numbness could be due to hyperventilation during panic attacks.

Examination: She has right hand finger 1, 2, 3 and the median half of 4 reduced pinprick sensation, reduced distal lower extremity pinprick, and absent ankle tendon reflexes. She has a positive Tinel sign at the right carpal tunnel.

Our assessment: Her history and examination support the diagnosis of right carpal tunnel syndrome. A cervical radiculopathy or brachial plexopathy is unlikely because she lacks radiating neck pain, muscular weakness, or tendon reflex asymmetry. Distal foot sensory loss with absent tendon distal reflexes is probably caused by a distal diabetic polyneuropathy but other etiologies should also be considered. Perioral numbness occurs only during panic attacks and is probably due to hyperventilation.

Plan and treatment: She is referred for electromyography and nerve conduction electrodiagnostic testing which confirm the diagnosis of carpal tunnel syndrome and a distal polyneuropathy. She is treated with wrist splints and corticosteroid injections but these only provide temporary relief. Therefore, she is referred for a carpal tunnel release surgery. Other causes of polyneuropathy are excluded by laboratory testing. With improved diabetic control and treatment of panic attacks, her foot numbness stabilizes and episodic perioral numbness resolves.

**Table 56.1 Differential diagnosis of paresthesia etiologies.**

| Anatomic localization                        | Specific entities                          | Possible clinical features                                                                                                                            |
|----------------------------------------------|--------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cerebral cortex and subcortical white matter | Stroke and transient ischemic attack (TIA) | Parietal lobe lesions can cause contralateral face, arm or leg numbness but are usually accompanied by other symptoms of neurologic dysfunction [2,3] |
|                                              | Migraine                                   | Paresthesias start in a localized limb area and can migrate over minutes to                                                                           |

|             |                                                                                   |                                                                                                                                                   |
|-------------|-----------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------|
|             |                                                                                   | contiguous limb locations often followed by severe headache, nausea, and photophobia [2,3]                                                        |
|             | Seizure                                                                           | Intermittent paresthesias in isolation rarely represent an ictal symptom [2,3]                                                                    |
|             | Multiple sclerosis (MS)                                                           | Tingling or numbness can last days to months and arise from central nervous system (CNS) demyelinating plaques [2,3]                              |
|             | Neoplasm, arteriovenous vascular malformation, cyst, and other structural disease | Focal structural lesions should be considered when paresthesias persist and are accompanied by focal examination abnormalities [2,3]              |
| Thalamus    | Stroke and TIA                                                                    | Contralateral numbness and sensory loss can be patchy, split the body midline, and cause Dejerine–Roussy pain syndrome [2,3]                      |
| Brainstem   | Stroke, TIA, MS, and other structural disease                                     | Consider brainstem lesions when there are crossed examination abnormalities such as ipsilateral cranial nerve with contralateral body signs [2,3] |
| Spinal cord | Spinal cord neoplasm or disc compression,                                         | Girdling thoracic or abdominal tightness may be accompanied by a truncal                                                                          |

|            |                                                                                                               |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------|---------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|            | infarction,<br>infection,<br>trauma, cyst,<br>inflammation,<br>vitamin or<br>mineral<br>deficiency, and<br>MS | sensory level, paresthesias,<br>ataxia, weakness, back pain,<br>or bladder symptoms [2,3].<br>Spinal cord compression can<br>be caused by spondylosis and<br>spinal stenosis, malignancy,<br>hematoma, and abscess.<br>Other causes include MS,<br>viral infection <i>e.g.</i> HIV,<br>human T-cell leukemia virus<br>(HTLV), trauma, radiation,<br>and ischemic infarction [2–4].<br>Cervical syringomyelia can<br>cause a shoulder “shawl-like”<br>distribution of pain and<br>temperature loss with<br>associated limb paresthesias<br>[2,3]                                       |
| Nerve root | Degenerative<br>spinal arthritis,<br>infection,<br>inflammation,<br>and neoplasm                              | Cervical, thoracic, and<br>lumbosacral spinal<br>radiculopathies can arise from<br>nerve root compression<br>caused by degenerative<br>arthritis and disc herniation.<br>Dermatomal paresthesias and<br>sensory loss may accompany<br>radiating pain. Muscle<br>weakness and tendon reflex<br>loss correspond to the nerve<br>root distribution. If<br>degenerative changes are<br>extensive, multiple nerve<br>roots can be affected [2,3,5].<br>Other causes include spinal<br>epidural abscess,<br>cytomegalovirus, herpes<br>zoster, syphilis, Lyme<br>disease, sarcoidosis, bone |

|                                 |                                                       |                                                                                                                                                                                                                                                                                                                     |
|---------------------------------|-------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                 |                                                       | metastasis, carcinomatous meningitis, radiation therapy, and intrathecal chemotherapy [3,5]                                                                                                                                                                                                                         |
| Brachial and lumbosacral plexus | Neoplasm and hemorrhage                               | Tingling and numbness accompany severe pain and weakness involving multiple nerve territories and can mimic a radiculopathy. Lumbosacral retroperitoneal hemorrhage can be caused by anticoagulation treatment, thrombocytopenia, or hemophilia [3,5,7]                                                             |
|                                 | Parsonage–Turner syndrome (brachial neuritis)         | Acute onset severe shoulder pain followed several weeks later by sensory loss, paresthesias, and peripheral nerve weakness [3,5,7]                                                                                                                                                                                  |
|                                 | “Burners and Stingers”                                | Severe arm pain and tingling after contact sport and direct shoulder trauma. Symptoms are usually short lived [5,7]                                                                                                                                                                                                 |
| Peripheral nerves               | Distal symmetrical sensorimotor peripheral neuropathy | Distal foot and leg tingling, which can be painful, slowly progresses in a “stocking” and “glove” distribution accompanied by mild distal weakness and distal tendon reflex loss [2,3,5]. Diabetes mellitus is a common cause but other etiologies include vitamin deficiency, vasculitis, infection, rheumatologic |

|                                               |  |                                                                                                                                                                                                                                                                    |
|-----------------------------------------------|--|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                               |  | disease, metabolic, endocrinopathy, malignancy, circulating paraprotein, and toxins [3,5]                                                                                                                                                                          |
| Sensory ganglionopathy                        |  | Generalized pain and non-length dependent sensory loss are accompanied by severe extremity ataxia. Etiologies include Sjögren's syndrome and paraneoplastic [5]                                                                                                    |
| Mononeuropathy multiplex                      |  | Multifocal tingling and numbness due to multiple mononeuropathies can be caused by diabetes mellitus, rheumatologic, vasculitic, and infectious diseases. Hereditary neuropathy with predisposition to pressure palsies (HNPP) can appear clinically similar [5,7] |
| Acute and chronic inflammatory polyneuropathy |  | Rare variants of Guillain–Barré syndrome and chronic inflammatory demyelinating polyneuropathy (CIDP) can cause a primarily sensory polyneuropathy [3,5]                                                                                                           |
| Mononeuropathy Median                         |  | Median mononeuropathy at the wrist causes carpal tunnel syndrome. Numbness and tingling typically affects the first three fingers and frequently causes nocturnal awakening with relief by hand shaking and repositioning. Examination                             |

findings often include a positive Phalen maneuver and Tinel sign [7]

#### Ulnar

Cubital tunnel syndrome or tardy ulnar palsy due to nerve compression at the elbow causes fourth and fifth finger numbness or tingling. Tinel sign may be positive over the ulnar nerve at the medial elbow, and sensory loss splits the fourth finger [7]

#### Radial

Superficial radial sensory neuropathy at the dorsal wrist causes numbness, tingling and dysesthesias between the dorsal thumb and index finger and can arise from handcuff or wristwatch injury [7]

#### Lateral femoral cutaneous

Compression at the inguinal ligament causes meralgia paresthetica, a syndrome of lateral thigh pain, numbness and tingling that is associated with obesity, pregnancy, and diabetes mellitus [7]

#### Peroneal

Nerve entrapment at the upper fibula near the knee causes anterior lower leg and dorsal foot numbness that overlaps the L5 dermatome and can be accompanied by ankle dorsiflexion and eversion weakness. Traction, compression, or habitual leg

|                        |                                          |                                                                                                                                                                                                                                                                                               |
|------------------------|------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                        |                                          | crossing are common causes [7]                                                                                                                                                                                                                                                                |
| Neuromuscular junction | Lambert–Eaton myasthenic syndrome (LEMS) | This autoimmune disorder with antibodies directed at presynaptic voltage-gated calcium channels can be paraneoplastic [2,3,5]. Sensory paresthesias can accompany muscular weakness, autonomic symptoms, and oculobulbar dysfunction [8]                                                      |
| Other                  | Psychiatric                              | Patients with panic attacks, somatization disorder, and anxiety can have paresthesias [2,3]. These paresthesias may not conform to anatomical patterns and can be discordant with other examination findings. Hyperventilation can also lead to paresthesias of the face, hands, and feet [2] |
|                        | Metabolic                                | Hypophosphatemia can cause facial paresthesias [2]                                                                                                                                                                                                                                            |
|                        | Medications                              | Carbonic anhydrase inhibitors, such as acetazolamide and topiramate, can cause perioral and hand paresthesias [6,7]                                                                                                                                                                           |
| Unusual                | Mental mononeuropathy                    | Often called “numb chin” syndrome, this condition is often due to metastatic cancer                                                                                                                                                                                                           |

[2]

|                          |                                                                                                       |
|--------------------------|-------------------------------------------------------------------------------------------------------|
| Notalgia<br>paresthetica | This dorsal spinal neuropathy causes a syndrome of back pruritus, paresthesias, and hyperesthesia [7] |
|--------------------------|-------------------------------------------------------------------------------------------------------|

---

## References

1. Dirckx JH. *Stedman's Concise Medical Dictionary for Health Professions*. Baltimore, MD: Lippincott Williams & Wilkins, 1997.
2. Evans RW. *Saunders Manual of Neurologic Practice*. Philadelphia, PA: Elsevier Science, 2003.
3. Rowland LP, Pedley TA. *Merritt's Neurology*. Philadelphia, PA: Lippincott Williams & Wilkins, 2010.
4. de Seze J, Stojkovic T, Breteau G *et al*. Acute myelopathies: clinical, laboratory and outcome profiles in 79 cases. *Brain* 2001; 124:1509–21.
5. Amato AA, Russell JA. *Neuromuscular Disorders*. New York, NY: McGraw-Hill, 2008.
6. Engel J Jr, Pedley TA. *Epilepsy. A Comprehensive Textbook*. Philadelphia, PA: Lippincott Williams and Wilkins, 2008.
7. Stewart JD. *Focal Peripheral Neuropathies*. West Vancouver: JBJ Publishing, 2010.
8. O'Neill JH, Murray NMF, Newsom-Davis J. The Lambert-Eaton myasthenic syndrome. A review of 50 cases. *Brain* 1988; 11:577–96.

## **57 Parkinson's disease and related extrapyramidal syndromes**

---

Oded Gerber, Fawaz Al-Mufti, and Alan B. Ettinger *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

The disorders discussed in this chapter are those that have symptoms (e.g. hypokinetic states), that overlap with classic Parkinsonian manifestations. This differential diagnosis is important since such conditions can be easily misdiagnosed as Parkinson's disease, when in fact the underlying etiology is quite different and the symptoms are potentially reversible. This chapter also describes syndromes that fall into a category called "Parkinson-Plus syndromes" (e.g. multiple system atrophy disorders; MSA) which have many of the classic Parkinsonian symptoms but also feature other symptoms and signs that distinguish these disorders from the classic idiopathic Parkinson's disease.

Parkinson's disease is one of many types of extrapyramidal syndromes. The extrapyramidal tract modulates activity of the pyramidal tract and is an integral part of voluntary movement control. Anatomical structures involved include the basal ganglia which consist of the caudate, putamen, globus pallidus, substantia nigra, and subthalamic nucleus.

Parkinson's disease is usually idiopathic; genetic underpinnings may be identified in a minority of cases. Classically cited manifestations include masked facies, poverty and slowness of movement. There is difficulty initiating repetitive (ramp) motions although surprisingly fast reactive (ballistic) motions may be executed. Typical features include flexion posture at the neck, elbows, wrist, waist, knees, and ankles, a stooped posture as a result of the flexion, festinating shuffling gait (marche à petit pas) with reduced armswing that is more pronounced on one side, retropulsion or propulsion, cogwheel rigidity which is virtually always asymmetric and which increases with contralateral fist opening and closing (reinforcement), pill-rolling or flexion – extension resting

tremor, preserved sensory function, and positive glabellar and palmomental reflexes. Deep tendon reflexes are generally normal. Speech is sometimes hypophonic and monotonous sounding. Mental status assessment may reveal signs of dementia in later stages and depression, due to involvement of the locus coeruleus, and sleep disturbance are common. Dysautonomia may be present with sialorrhea, urinary symptoms, or orthostatic hypotension, which correlate with involvement of the dorsal motor nucleus of the vagus. Patients receiving treatment may have dyskinesia, on-off periods, and mental status aberrations including hallucinations or delusions.

Beyond the conditions listed below which include movement disorders, other conditions can cause hypokinetic presentations such as rheumatologic conditions with limitations of motion (e.g. ankylosing spondylitis) or other conditions that induce mechanical limitations of motion. The rigidity of stiff person syndrome can also be confused with extrapyramidal disorders but hyperreflexia is usually apparent.

## Case vignette: Parkinson's disease

A 62-year-old male with no prior medical problems had been noticing occasional tremor at rest in his left middle three fingers. He also had REM sleep disorder behavior for the past 10 years intermittently (talking and fighting in his sleep). After 6 months the tremor was frequently present, especially with stress. He also noted at times the entire hand was tremulous at 4/second. His wife noticed he was stone faced with infrequent blinking and had developed very small handwriting and was not moving his right hand/arm while walking. He was diagnosed with Parkinson's disease. A year later he noted difficulty with turning in bed and getting up quickly. He saw a neurologist who started pramipexole and rasagiline. He improved somewhat. Two years later he noted difficulty with gait. He turned with extra steps, his steps were smaller, his tremor now affected the other hand, and he was somewhat stooped. On starting levodopa he improved significantly.

**Table 57.1 Differential diagnosis of Parkinsonian presentations [1–3].**

| Item      | Specific type              | Further subdivision | Comments                          |
|-----------|----------------------------|---------------------|-----------------------------------|
| Metabolic | Enzyme deficit/denervation | Wilson's disease    | Onset may be a<br>early as age 16 |

### ceruloplasmin

early to 10 years. Autosomal recessive, hepatolenticular degeneration, abnormal accumulation of copper in liver, brain, kidneys, eyes; liver disease.

Parkinsonian symptoms with resting/action tremor, spasticity, rigidity, chorea, dystonic posture, unsteady gait, Kayser-Fleisch ring, sunflower cataracts, optic neuritis, night blindness, strabismus, abnormal eye movements, arthropathy, dystonia, incoordination, dysadiadokines, personality changes, psychosis, depression, anxiety, mania, irritability, osteoarthritis, osteoporosis and osteomalacia, chondrocalcinosis.

joint  
hypermobility,  
dysarthria,  
scanning speech  
azure lunulae on  
the fingernails

Pantothenate kinase-  
associated  
neurodegeneration  
(PKAN)

Formerly known  
as Hallervorden-  
Spatz syndrome  
rare autosomal  
recessive (AR)  
disorder

pathologically  
associated with  
iron deposition  
in the basal ganglia  
due to a mutation  
in the gene for  
pantothenate  
kinase (*PANK2*)

Three  
presentations:  
Early onset (<10  
years), late onset  
(10–18 years),  
and adult variant  
characterized by  
progressive  
personality  
changes, cognitive  
decline,  
dysarthria, motor  
difficulties,  
spasticity.

Dystonia is  
common but  
choreoathetosis  
tremor may be

|              |                         |                     |                                                                                                                                                                                                                                                                                 |
|--------------|-------------------------|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|              |                         |                     | present; retinitis pigmentosa, optic atrophy, and seizures may also occur; MRI: decreased T2-weighted signal in the globus pallidus and substantia nigra; some have a hyperintense area within the hypodense area producing the “eye of the tiger” sign                         |
| Degenerative | Heredofamilial, genetic | Huntington's chorea | Autosomal dominant, polymorphic trinucleotide repeat sequence Symptom onset usually 35–42 years but can be earlier. Symptom progress over several decades Involuntary movements – chorea, explosive speech, fidgetiness, clumsiness, restlessness Can present earlier with poor |

emotional continuity  
psychiatric problems,  
personality disorders

Chorea phase – multiple movements of face, arms, and legs with progressive deterioration mentally and physically.

Progressive dementia

Westphal variant – onset as child rigidity, mimics Parkinson's Can initially present with psychological changes dementia symptoms

Progressive loss of intellect and psychiatric problems

Difficulty initiating saccades eye movements common early Juvenile-onset tends to present with parkinsonism and dystonia

Machado–Joseph's

Rare autosomal

disease (MJD; spinocerebellar degeneration type-3 )

dominantly inherited neurodegenerative disease. This spinocerebellar degeneration syndrome causes progressive cerebellar ataxia with loss of muscle control and coordination. Genetic mutation with expansion of abnormal “CAC” trinucleotide repeats in the *ATXN3* gene. Some symptoms such as clumsiness and rigidity, make MJD commonly mistaken for drunkenness and/or Parkinson's disease. May see ophthalmoplegia and mixed sensory and cerebellar ataxia. Symptoms of MJD are memory deficits, upper motor neuron signs of spasticity, difficulty with speech and

swallowing,  
quadripareis,  
clumsiness,  
frequent urinati  
and involuntary  
eye movements  
parkinsonism, &  
late chorea  
Symptoms can  
begin in early  
adolescence and  
they progress.  
Eventually, MJ  
leads to paralys  
however,  
intellectual  
functions usual  
remain unchang

Familial idiopathic  
basal ganglia  
calcification  
(FIBGC)

Parkinsonian  
symptoms with  
behavioral  
changes and  
seizures. Onset  
often in 3rd to 5  
decade.  
Autosomal  
dominant

Fragile X tremor  
ataxia syndrome  
(FXTAS)

Not to be  
confused with  
FragileX  
syndrome in the  
differential  
diagnosis of  
intellectual  
disabilities.  
Presents similar  
MSA with

parkinsonian features, autonomic dysfunction and dementia. More often in men

Neuronal ceroid lipofuscinosis

Rigidity and choreoathetosis may occur. Often salient behavioral changes, psychosis, dementia

Mitochondrial cytopathies with striatal necrosis

Dystonia often prominent

Lubag syndrome :  
Filipino X-linked dystonia  
parkinsonism, DYT3

X-linked recessive transmission.  
Only in those of Filipino descent.  
Presents with parkinsonian features but ultimately dystonia becomes prominent

Dystonia-plus syndromes

Example is dopamine responsive dystonia which usually pediatric onset and has significant and enduring responses to levodopa

|          |                                                          |                                                                                                                                                                                                                 |
|----------|----------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|          | Neuroacanthocytosis                                      | Oral and lingua<br>dystonia, tics,<br>chorea, seizures,<br>parkinsonism.<br>Behavioral<br>changes,<br>dysarthria, axon<br>neuropathy                                                                            |
| Acquired | Idiopathic adult<br>onset Parkinson's                    | As per the<br>description in tl<br>chapter<br>introduction                                                                                                                                                      |
|          | Hemiparkinsonism--<br>hemiatrophy<br>(HPPA) syndrome     | Rare variant.<br>Usual onset in 3rd<br>or 4th decade.<br>Unilateral<br>hemiatrophy<br>accompanies<br>parkinsonian<br>features                                                                                   |
|          | Lewy body disease<br>(dementia with<br>Lewy bodies; DLB) | Onset around age<br>50 years<br>Subacute<br>fluctuating<br>cognitive<br>dysfunction,<br>parkinsonism,<br>visual<br>hallucinations,<br>and behavioral<br>changes.<br>Levodopa may<br>produce florid<br>psychosis |
|          | Striato-nigral                                           | Consider in a                                                                                                                                                                                                   |

degeneration (type of multiple systems atrophy; MSA)

Parkinson's-like syndrome that does not respond to levodopa. Akinetic rigidity is most prominent. Tremor is absent or atypical. Cogwheel rigidity is symmetric unlike the situation in idiopathic Parkinson's disease

Shy–Drager syndrome (type of MSA)

Parkinsonism with major autonomic dysfunction. Disabling orthostatic hypotension. May see urinary retention or incontinence, and/or impotence in males. Anhydrosis, constipation, are reduced/absent pupillary reactivity

Olivopontocerebellar atrophy (OPCA) (type of MSA)

Cerebellar type MSA with prominent ataxia and dysarthria. Onset in mid-

adult life with  
gradual  
progression

Progressive  
supranuclear palsy  
(PSP) (Steele—  
Richardson—  
Olszewski  
syndrome)

Type of tauopathy  
that is frequently  
mistaken for  
Parkinson's  
disease because  
of rigidity and  
bradykinesia.  
However,  
disproportionate  
limitation of  
downward gaze  
is relatively specific  
to PSP and  
subsequent  
limitations of  
other eye  
movement  
in directions  
occurred.  
Postural  
instability is  
common early on  
and tremor is infrequent  
in only one third.  
Rigidity is  
primarily axial  
and may be  
severe, especially  
at the neck.  
Ultimately  
progresses to  
dementia,  
pseudobulbar  
state, and  
depression.  
Horizontal

saccadic intrusions while staring at an object, called square-wave jerks, are a consistent and often early finding. Eye movements show characteristic supranuclear findings of increasing fluid progressing from voluntary gaze, following an object, to oculocephalic maneuver. Frontal lobe symptoms, such as apathy, decreased verbal fluency, and frontal release signs, may occur early in PSP. Death in approximately 10 years after onset.

Juvenile Parkinson's disease  
10% of Parkinson's cases are estimated to occur before age 50. Tends to have more rigidity and akinesia.

presentations.  
Tremor is less prominent. May have dystonia. Cases induced by recreational drugs have been recognized

Corticobasal  
ganglionic  
degeneration  
(CBGD)

A tauopathy.  
Asymmetric progressive parkinsonism initially, but minimal response to levodopa. Asymmetric progressive rigidity and limb apraxia, often with limb dystonia, bradykinesia, and stimulus-sensitivity. May have alien limb and limb apraxia. May see intellectual decline, frontal release signs, supranuclear gaze problems, dysphagia, or dysarthria. Patients with CBGD often have slow initiation of saccades but normal saccade speed and usually normal

usually normal.  
PSP, patients  
often have  
slowing of  
saccade speed,  
which can occur  
prior to the  
supranuclear gaze  
palsy

#### Dementias

Dementing  
illnesses such as  
Alzheimer's  
disease may have  
features that may  
look parkinsonian  
typically in late  
stages of the  
disease. Some  
individuals with  
idiopathic  
Parkinson's  
disease may  
progress to  
include dementia

#### Hydrocephalus

Structural lesions causing  
obstructive  
hydrocephalus may cause rapid  
progressive  
parkinsonism.  
Obstructive  
hydrocephalus secondary to  
meningitis and  
subarachnoid  
hemorrhage may  
mimic

parkinsonism

Vascular

Lacunar infarctions in the basal ganglia, insidious and slowly progressive, however acute worsening may occur with new strokes; infarctions in the frontal gyri and supplementary motor areas may also lead to acute parkinsonism. Vasculitis or arteriovenous malformation of the putamen are uncommon vascular etiologies.

Dementia– parkinsonism– amyotrophic lateral sclerosis complex of Guam

Exhibits gross atrophy of the frontotemporal regions, depigmentation of the substantia nigra, and loss of anterior roots; histologically, there are neurofibrillary tangles in the cortical neurons; loss of pigment

neurons in the substantia nigra without Lewy bodies, and loss of anterior horn cells with neurofibrillary tangles

|       |             |                                                                |                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|-------|-------------|----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Toxic | Medications | Phenothiazines, butyrophenones, and some atypical neuroleptics | Extrapyramidal effects associated with these agents include acute dystonia, a parkinsonism-like syndrome and akathisia (motor restlessness), tardive syndromes, and dyskinesias. Neuroleptic malignant syndrome is another potential complication. Parkinsonism may persist for weeks to months after discontinuation of the offending agent. Quetiapine and clozapine are unlikely to induce this syndrome. Drug-induced parkinsonism is virtually always symmetric, |
|-------|-------------|----------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

providing an important differentiating sign from idiopathic Parkinson's disease

#### Metoclopramide

Used to treat gastroparesis or nausea, may produce dyskinesia, parkinsonism, neuroleptic malignant syndrome, especially in patients taking high doses. Symptoms usually resolve within several months but may persist indefinitely

#### Valproic acid

Easily mistaken for Parkinson's disease. Reverses with withdrawal of agent

#### Lithium

Used to treat bipolar disorder  
Notable tremor

#### Toxic substances

N-methyl-4-phenyl-  
1,2,3,6-tetrahydropyridine  
(NMDP)

May cause severe acute parkinsonism if introduced abruptly

(IVR 11)

intravenous drug abusers after the first few doses. Crosses blood-brain barrier and then is converted to toxic compound MPP by MAO-B in astrocytes

Carbon monoxide

Symptoms usually gradual onset after exposure with poor response to levodopa

Manganese

Exposure in workplace such as with welding. Psychiatric symptoms in addition to extrapyramidal symptoms

Mercury

Resting tremor, choreoathetosis parkinsonian facies, abnormal gait, visual and hearing impairments, anxiety, and excitability

Methanol

Leading to hemorrhagic necrosis of basal ganglia. May also

cause vision loss and high risk of mortality. Methanol or methyl alcohol also known as wood alcohol and is found in many household or automobile-related liquids and industrial solvents. It may be a contaminant in some alcohol drinks. May occur in suicide attempts, in alcoholics, or in accidental ingestions.

|        |                                                                                                                    |
|--------|--------------------------------------------------------------------------------------------------------------------|
| Trauma | Controversial association                                                                                          |
| Other  | Post-hypoxic<br>Usually symmetric and mostly with an akinetic--rigid state. Tremor is not a prominent feature      |
|        | Hypothyroidism<br>May produce a hypokinetic state along with other classic symptoms including such as weight gain, |

fatigue, cold intolerance, constipation

---

## **Case vignette: corticobasal ganglionic degeneration**

A 53-year-old right-handed male complained of difficulty using his right hand. He had difficulty writing and dressing with his right hand, slowly beginning 4 months ago. He saw a neurologist who diagnosed Parkinson's disease on the basis of bradykinesia and increased tone particularly on the right side. None of the medications including high doses of carbidopa/levodopa were of any help. He stated to his neurologist that at times his right limbs moved on their own. In addition, the neurologist found astereognosis in the right hand. At that point, the neurologist reviewed the patient's previous MRI and noted focal atrophy in the left hemisphere as compared with the right. A diagnosis of corticobasal ganglionic degeneration was made. The patient subsequently developed dysphasia and ultimately aphasia. He became stiffer and unable to walk and swallow, and succumbed 6 years later in a nursing home.

## **Case vignette: progressive supranuclear palsy**

A 55-year-old male had been diagnosed with Parkinson's disease 2 years earlier. He had bilateral stiffness, significant bradykinesia, and frequent falls. He had dysarthria and was difficult to understand. Swallowing was a problem. He did not respond to pramipexol, ropinirol, or large doses of carbidopa/levodopa. He switched neurologists. On the first visit he was found to have no downward gaze. He continued to deteriorate, becoming stiffer, unable to walk and swallow. He developed retrocollis. He further deteriorated and died approximately 6 years after the diagnosis.

## **Case vignette: dystonia**

A 7-year-old male was noted to have the beginning of an unusual gait over several months. His feet were turning in. This occurred one after the other. This proceeded to the point that he had difficulty walking. After several consultations he was diagnosed with dystonia. He had an uncle with dystonia. He was found to have DYT1 dystonia. His symptoms improved somewhat with high-dose

cholinergic medications. However, the dystonia was spreading to his arms and torso. It was decided to perform deep brain surgery to the globus pallidus interna bilaterally, before his dystonia resulted in fixed postures. Over the first 2 years he improved remarkably, walking with a limp but using his hands well.

## **Case vignette: Huntington's disease**

A 37-year-old female was seen in the hospital with fidgety movements of her face, hands, and shoulders. Her father, whom she had never known, had died at age 60 in a mental institution. Her mother had died 10 years earlier at 61. She was sent to a movement disorder clinic. Testing for Huntington's disease demonstrated 45 trinucleotide repeats. She was diagnosed with Huntington's disease. When she looked into her father's medical documents she found documents stating that he was hospitalized and died with Huntington's disease. Over the next 10 years her chorea increased and she ultimately had to be hospitalized. She became confused and disinhibited.

## **References**

1. Paterson RW, Takada LT, Geschwind, MD. Diagnosis and treatment of rapidly progressive dementias. *Neurol Clin Pract* 2012; 2:187–200.
2. Jankovic J, Shannon KM. Movement disorders. In: Bradley WG, Daroff RB, Fenichel GM, Jankovic J, Eds. *Bradley: Neurology in Clinical Practice*, 5th edn. Philadelphia, PA: Butterworth Heinemann Elsevier, 2008; Ch. 75.
3. Molloy FM, Healy DG. Parkinsonism plus syndromes. In Hardiman O, Doherty CP, Eds. *Neurodegenerative Disorders*. London: Springer, 2011: 181–96.

## **58 Proptosis [exophthalmos]**

---

Luis J. Mejico and Laryssa A. Huryn *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

Proptosis is an axial protrusion of the globe. It may be unilateral or bilateral. The term proptosis is often used interchangeably with exophthalmos. Often exophthalmos is used to describe bilateral proptosis and suggests an endocrine-related etiology.

Pseudoproptosis presents with relative asymmetry as compared with the contralateral eye, retraction of the upper eyelid of the ipsilateral eye, and enophthalmos of the opposite eye .

### **Key elements of history and examination**

#### **History**

- Onset rapid or slowly progressive?
- Local pain?
- Systemic symptoms?
- Trauma?
- History of malignancy?

#### **Examination**

- Pupillary size and reactivity to light.
- Vision/color vision.
- Confrontational visual fields.
- Extraocular movements.
- Palpation of orbital rim feeling for a mass.

## ***Measuring proptosis***

Inspection from inferior view.

Hertel exophthalmometer – a difference of more than 2 mm between sides is abnormal.

## **Case vignette**

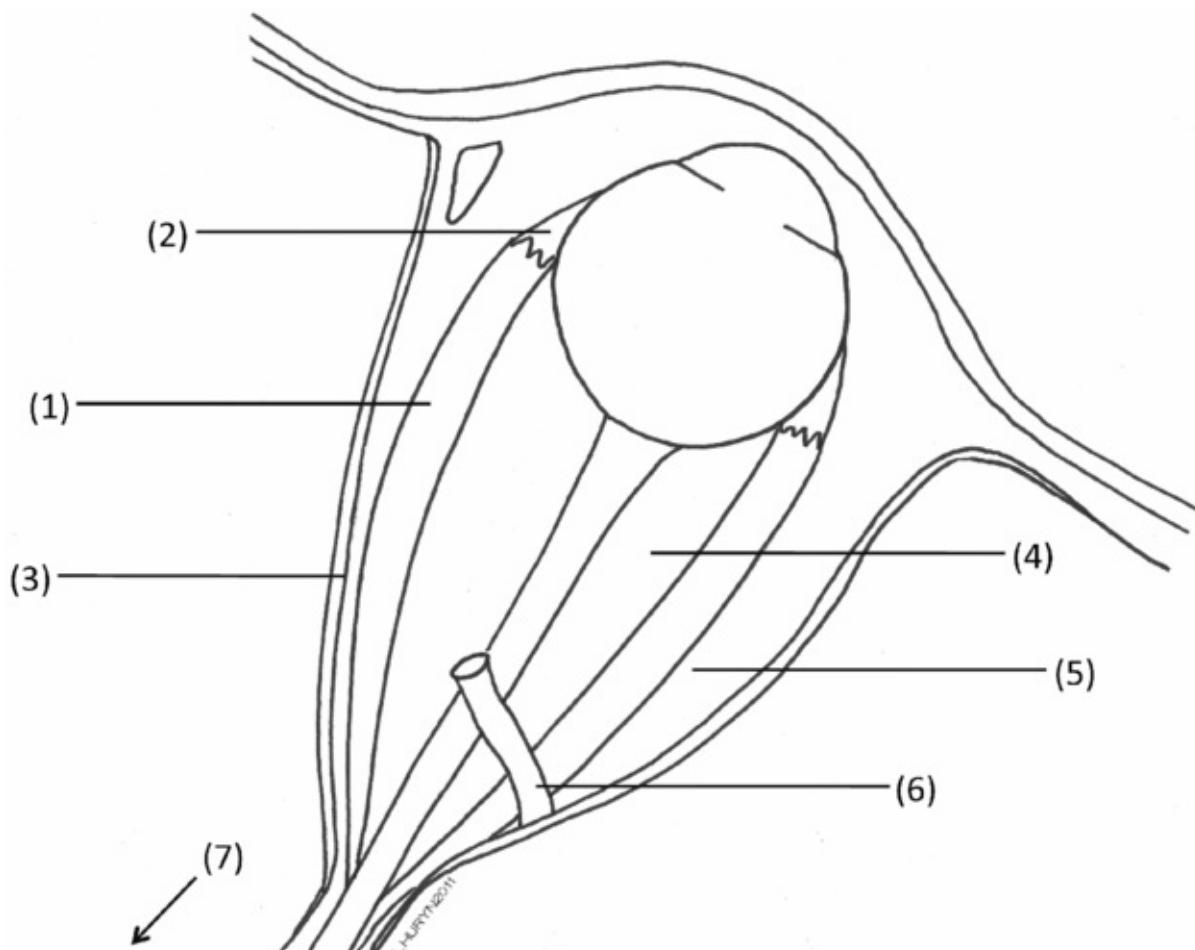
A 47-year-old female with a history of sinusitis presented with acute swelling around her right eye and vision loss. The night prior to presentation, she began having a right-sided headache. She awoke from sleep at 3:30 a.m. because of her intense headache, took Tylenol and went back to sleep. When she woke up in the morning, the patient thought she had a migraine and called in sick to work. She napped throughout the morning because of headache, nausea, and vomiting. When she woke from her nap in the afternoon, she noted a swollen eyelid and no vision in the right eye. She had no recent trauma, no fever or chills, and her last episode of sinusitis was 3 months prior.

She presented to the local university hospital. On examination she had significant redness, edema of the right upper and lower eyelids, chemosis and injection of the right conjunctiva, and pulsatile proptosis. Vision in the right eye was no light perception and the pupil was fixed at 6 mm. She had no sensation on the right forehead. Ophthalmic examination of the left eye was within normal limits.

A differential diagnosis for acute, unilateral, seemingly spontaneous proptosis was formulated based on [Table 58.1](#). By history and physical examination, orbital cellulitis, arteriovenous (AV) fistula, cavernous sinus thrombosis, orbital pseudotumor, and spontaneous hemorrhage of an orbital vascular lesion were all possible. Given the patient's unilateral loss of vision, ophthalmoplegia, and loss of facial sensation, the lesion could be further localized to the ipsilateral cavernous sinus. The presence of pulsatile proptosis made AV fistula the most likely diagnosis.

The patient underwent a computerized tomography scan with contrast which showed no distinct fluid collection, no abscess, no muscle enlargement, no sphenoid sinus disease nor enlarged superior ophthalmic vein, and no evidence of cavernous sinus thrombosis. However, it was positive for an internal carotid artery aneurysm with a possible fistula. She subsequently underwent a conventional angiogram which showed an  $8.5 \times 9.0 \times 7.5\text{mm}$  cavernous internal

carotid artery aneurysm with a carotid–cavernous fistula. She underwent coil embolization of her carotid–cavernous fistula. Her vision remained with no light perception, but she regained ocular motility and facial sensation.



**Figure 58.1** Proptosis: axial view. (1) extraocular muscle; (2) extraocular muscle tendon; (3) subperiosteal space; (4) intraconal space; (5) extraconal space; (6) orbital veins; (7) cavernous sinus. See [Table 58.1](#) for clinical correlation.

**Table 58.1 Differential diagnosis of proptosis. The numbers in parentheses refer to the anatomical locations of involved pathology shown in [Figure 58.1](#).**

| Mechanism  | Disease process    | Etiology/pathophysiology | Clinic featur |
|------------|--------------------|--------------------------|---------------|
| Infectious | Orbital cellulitis | Direct extension from    | Acute         |

|              |                                  |                                                                                                                         |                                                                                        |
|--------------|----------------------------------|-------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------|
|              | (4, 5)                           | sinus or dental infection;<br>orbital trauma;<br>complication of orbital<br>surgery; seeding from<br>systemic infection | present<br>eyelid<br>and er<br>chemc<br>injecti<br>conjur<br>limitat<br>pain w<br>EOMs |
|              | Subperiosteal<br>abscess<br>(3)  | See orbital cellulitis                                                                                                  | Same<br>celluli<br>consid<br>diagn<br>absces<br>patien<br>not res<br>IV ant<br>treatm  |
| Inflammatory | Orbital<br>pseudotumor<br>(4, 5) | Non-granulomatous<br>inflammatory condition                                                                             | Acute<br>unilate<br>lid ede<br>chemc<br>injecti<br>limitat<br>proptc<br>afebril        |
|              | Orbital myositis<br>(1, 2)       | Idiopathic inflammation of<br>EOMs                                                                                      | Acute<br>unilate<br>painfu<br>enlarg<br>EOM<br>restrict<br>motili                      |
|              | Thyroid orbitopathy              | Proliferation of orbital fat                                                                                            | Evolvi                                                                                 |

|            |                                                 |                                                                                                                                              |                                                                                      |
|------------|-------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------|
|            | <b>Tumoral exophthalmos</b><br>(1, 4, 5)        | Proptosis or orbital fat<br>and enlargement of the<br>EOMs secondary to<br>increase in hydrophilic<br>mucopolysaccharide<br>leading to edema | Eyes<br>retract<br>lag on<br>downs<br>diplop<br>symp<br>be acu<br>subaci<br>chroni   |
| Vascular   | <b>Varix</b><br>(6)                             | Large vein that produces<br>proptosis when it dilates<br>and fills with blood                                                                | Intern<br>proptc<br>pulsat<br>audibl<br>worse<br>proptc<br>precip<br>Valsal          |
|            | <b>Cavernous sinus<br/>thrombosis</b><br>(6, 7) | May result from spread of<br>infection, trauma, or<br>surgery                                                                                | Acute<br>subaci<br>proptc<br>chemc<br>edemæ<br>alterec<br>consic<br>possib           |
|            | <b>AV fistula</b><br>(6, 7)                     | Spontaneous or traumatic<br>communication between<br>arterial and venous<br>systems such as aneurysm<br>rupture                              | Acute<br>subaci<br>pulsat<br>proptc<br>chemc<br>corksce<br>episcl<br>vessel<br>bruit |
| Neoplastic | <b>Lymphangioma</b>                             | Vascular hamartoma of                                                                                                                        | First d                                                                              |

(4, 5) lymphatic channels life; slow progression; intermittent proptosis; worse in upper respiratory infections; may present with ecchymosis

Cavernous hemangioma (4) Most common benign orbital mass in adults Younger patients; middle-aged; slow course; proptosis; diplopia

Rhabdomyosarcoma (1, 4, 5) Tumor arises from mesenchymal precursors that usually differentiate into muscle cells Average age at presentation: 4 years; malignant; rapid progression

Metastases (4, 5) Most common orbital mass in adults; most common breast cancer, lung, prostate Middle-aged; elderly; onset

Dermoid (5) Choristoma of keratinized material Birth-adult; cystic growth; usually located superciliary area

rare rt  
causin  
inflamm

|                                      |                                     |                         |
|--------------------------------------|-------------------------------------|-------------------------|
| Malignant orbital lymphoma<br>(4, 5) | Proliferation of monoclonal B cells | Unilateral edema diplop |
|--------------------------------------|-------------------------------------|-------------------------|

|        |                                  |                           |                                                |
|--------|----------------------------------|---------------------------|------------------------------------------------|
| Trauma | Retrobulbar hemorrhage<br>(4, 5) | Trauma or orbital surgery | Acute resistance retrop. tight eye vision RAPD |
|--------|----------------------------------|---------------------------|------------------------------------------------|

---

CT, computerized tomography; EOM, extraocular muscle; IV, intravenous; MRI, magnetic resonance imaging; RAPD, relative afferent pupillary defect.

## Further reading list

Baharestani S, Zoumalan CI, Lisman RD, Scott IU, Fekrat S, Eds. Evaluation and management of orbital subperiosteal abscess. American Academy of Ophthalmology. EyeNet. July/August 2009.

<http://www.aao.org/publications/eyenet/200907/pearls.cfm>.

Ehlers JP, Shah CP, Fenton GL, Hoskins EN, Shelsta HN, Eds. *The Wills Eye Manual: Office and Emergency Room Diagnosis and Treatment of Eye Disease*, 5th edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2008.

Yanoff M, Duker JS, Duker JS, Eds. *Ophthalmology*. St Louis, MO: Mosby, 2004.

## **59 Psychosis, thought disorder**

---

Ramses Ribot and Andres M. Kanner *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

Psychosis is defined as a loss of reality testing such that affected individuals cannot evaluate the accuracy of their perceptions or thoughts and draw incorrect inferences about external reality [1]. This is evidenced by hallucinations, delusions, or thought disorganization.

**Delusions** – Delusions are false beliefs that are firmly held despite obvious evidence to the contrary, and not typical of the patient's culture, faith, or family [1].

**Hallucinations** – Hallucinations are false sensory perceptions occurring in any of the five sensory modalities. They have a delusional aspect if patients endorse them as reality [1].

**Thought disorganization** – Disruption of the logical process of thought may be represented by loose associations, nonsensical speech, or bizarre behavior. These symptoms are typically accompanied by a high level of functional impairment and high risk for agitated and aggressive behavior [1].

The most common symptoms of psychosis include paranoid delusions, ideas of reference, and persecutory thoughts. However, some delusions can have a specific or single theme. Some of these content-specific delusions are listed below:

**Capgras syndrome:** the patient is convinced that some important person (usually the spouse) has been replaced by an identical-appearing impostor. Sometimes there is associated violence towards the presumed impostor.

**Fregoli syndrome:** the patient believes that a persecutor is able to take on the appearance of others in the patient's environment.

**De Clerambault syndrome (erotomania):** delusional belief, more common in women, that an older, more influential male is in love with her despite outward

evidence to the contrary.

Incubus syndrome (Othello syndrome): delusional jealousy manifested by unjustified conviction of the spouse's infidelity.

Cotard's syndrome: delusional belief that one is dead.

Ekbom syndrome (acrophobia , parasitophobia ): belief that one's body is inhabited by worms or insects.

Heutoscropy : delusion that one has an exact double that can be visible or invisible.

## Prevalence

Lifetime prevalence estimates of psychosis in community samples are strongly influenced by methods of assessment and diagnosis with evident discrepancy among different epidemiologic studies. Most investigations report the lifetime prevalence of all psychotic disorders to be approximately 2–3% [2,3].

Psychosis is more common in primary psychiatric disorders, followed by substance-induced disorders, and psychotic disorders due to a general medical condition. Perala *et al.* reported the overall lifetime prevalence to be 3.06% with lifetime prevalence of 0.87% for schizophrenia, 0.32% for schizoaffective disorder, 0.35% for major depressive disorder with psychotic features, 0.42% for substance-induced psychotic disorders, and 0.21% for psychotic disorders due to a general medical condition [3].

## Pathophysiology

There is evidence suggesting psychosis is associated with abnormalities in the network of the limbic system including structures of the temporal lobes, frontal lobes, basal ganglia, thalamus, and connecting tracts [4,5]. However, the presence of psychosis does not predict an exact location as many diseases affecting the limbic system are not accompanied by psychosis. Bilateral brain involvement is a risk factor in developing psychosis [5,6].

**Table 59.1** *Differential diagnosis of psychosis.*

| Item | Subdivision | Specific entity | Additional c<br>features may<br>include |
|------|-------------|-----------------|-----------------------------------------|
|------|-------------|-----------------|-----------------------------------------|

---

|               |                        |                                                                                                                                            |                                                                                                                                       |
|---------------|------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------|
| Toxic – drugs | Anticholinergics       | Antipsychotics,<br>benztropine,<br>biperiden,<br>diphenhydramine,<br>procyclidine,<br>tricyclic<br>antidepressants                         | Anxiety, agit<br>aggression, c<br>hypertension<br>hyperthermia<br>tachycardia, ↓<br>dry mouth, se<br>coma                             |
|               | Dopaminergics          | Amantadine,<br>pergolide,<br>apomorphine,<br>lisuride,<br>bromocriptine,<br>ropinirole,<br>cabergoline,<br>pramipexole                     | Anxiety, irrit<br>depression, fa<br>visual halluc<br>psychomotor<br>akathisia, cog<br>impairment                                      |
|               | Antidepressants        | Fluoxetine,<br>paroxetine,<br>citalopram,<br>escitalopram,<br>sertraline,<br>fluvoxamine,<br>venlafaxine,<br>duloxetine,<br>desvenlafaxine | Anxiety, agit<br>sexual dysfun<br>sleep disturba<br>weight gain,<br>diaphoresis, ↓<br>and paranoid<br>auditory hallu<br>serotonin syn |
|               | Antiepileptic<br>drugs | Ethosuximide,<br>felbamate,<br>levetiracetam,<br>vigabatrin,<br>topiramate,<br>zonisamide,<br>ezogabine                                    | Anxiety, dep<br>irritability, ei<br>lability                                                                                          |
|               | Antimalarials          | Chloroquine,<br>mefloquine, quinine                                                                                                        | Anxiety, pan<br>confusion, de<br>hallucination<br>delirium, alte                                                                      |

~~depression, and~~  
perception, v

|                             |                                                        |                                                                                                                     |
|-----------------------------|--------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------|
| Endocrine agents            | Prednisone,<br>methylprednisolone                      | Depression, elation, mania, confusion, paranoid delusions, hallucination, suicidality, aggression                   |
| Antihypertensives           | Clonidine, thiazides, sulfonamides, nitrates/nitrites  | Anxiety, delusions, hypomania, confusion                                                                            |
| Toxic – withdrawal syndrome | Alcohol                                                | Tremors, anxiety, panic, diaphoresis, palpitations, tachycardia, hallucination, delirium, seizures, death           |
|                             | Sedative--hypnotics<br>(benzodiazepines, barbiturates) | Anxiety, panic, paranoia, hallucination, insomnia, irritability, confusion, hypertension, tachycardia, constipation |
|                             | Psychostimulants<br>(amphetamines, methylphenidate)    | Anxiety, agitation, depression, fatigue, hypersomnolence, hyperphagia, tachycardia                                  |
| Toxic – Metals              | Mercury                                                | Excitability, tremors, nephrotoxicity, peripheral neuropathy                                                        |
|                             | Arsenic                                                | Hallucinations, delusions, agitation, encephalopathy, peripheral neuropathy, rashes                                 |

|           |                           |                                                                                                                                      |
|-----------|---------------------------|--------------------------------------------------------------------------------------------------------------------------------------|
|           |                           | vomiting, dia<br>rrhythmias                                                                                                          |
|           | Manganese                 | Irritability, m<br>changes, con<br>behavior, rigi<br>tremors                                                                         |
| Metabolic | Systemic                  | Uremia and dialysis<br>dementia                                                                                                      |
|           |                           | Depression, c<br>delirium, anx<br>bipolar disease<br>hemiparesis                                                                     |
|           | Hepatic<br>encephalopathy | Delirium, co<br>sleep disturba<br>bradykinesia,<br>muscle wasti<br>jaundice, asc<br>palmar erythe<br>telangiectasia<br>hepaticus, ed |
|           | Hyponatremia              | Confusion, le<br>irritability, w<br>nausea, vomi<br>seizures, deli<br>coma                                                           |
|           | Hypercalcemia             | Depression, c<br>cognitive imp<br>lethargy, con<br>coma, diabet<br>insipidus,<br>nephrolithias<br>failure, arrhy<br>weakness         |
|           | Hypoglycemia              | Cognitive im<br>tremors, palp<br>anxiety, para                                                                                       |

anxiety, pare  
seizures, con

Porphyria

Anxiety, dep  
hallucination  
disorientation  
apathy, tachy  
restlessness,  
neuropathy

Post-operative and  
intensive care unit  
psychosis

Anxiety, dep  
hallucination  
delusions,  
disorientation  
agitation, par  
delirium

Endocrine

Hypothyroidism

Depression, &  
paranoid deli  
hallucination  
delirium, neu  
alopecia, cold  
intolerance, w  
gain, somnol  
constipation,  
menorrhagia,

Hyperthyroidism

Depression, &  
hallucination  
delusions, ma  
tremors, hypo  
heat intoleranc  
loss, tachycard  
diaphoresis

Hypoparathyroidism

Depression, &  
irritability, ag  
mania, cognit  
impairment

|                   |                                  |                                                                                                                        |
|-------------------|----------------------------------|------------------------------------------------------------------------------------------------------------------------|
|                   | Hyperparathyroidism              | Depression, e<br>irritability, pe<br>changes, hall<br>paranoid deli<br>delirium, we<br>fatigue                         |
|                   | Addison's disease                | Depression, e<br>irritability,<br>hallucination<br>delusions, ca<br>posturing,<br>hyperpigmen<br>sexual dysfun         |
|                   | Cushing's disease                | Depression, e<br>emotional lat<br>paranoia, obe<br>menstrual irr<br>weakness                                           |
|                   | Recurrent menstrual<br>psychosis | Sudden onset<br>duration, con<br>remission, de<br>mania, stupor<br>delusions,<br>hallucination<br>to menstruation      |
|                   | Post-partum<br>psychosis         | Within 2 wee<br>childbirth, ma<br>depression,<br>hallucination<br>delusions, ins<br>anxiety, irrita<br>suicide, infant |
| Deficiency states | Thiamine<br>(Wernicke–           | Chronic alco<br>anorexia nerv                                                                                          |

|                      |                              |                                                                                                                                                                    |
|----------------------|------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                      | Korsakoff syndrome)          | hyperemesis pregnancy, encephalopathy, oculomotor dysfunction, delirium, cognitive memory impairment, coma, death                                                  |
| Vitamin B12 / Folate |                              | Depression, anxiety, irritability, paresthesias, delusions, cognitive impairment, macrocytosis, pancytopenia, dementia, progressive weakness, ataxia, paresthesias |
| Niacin (pellagra)    |                              | Aggression, irritability, anxiety, depression, delusions, photosensitivity, diarrhea, dermatitis (hyperpigmentation), dementia, depression                         |
| Inflammatory         | Systemic lupus erythematosus | Depression, anxiety, hallucinations, delusions, cognitive impairment, delirium, seizures, headache, neuropathies                                                   |
| Sarcoidosis          |                              | Depression, anxiety, encephalopathy, hydrocephalus, neuropathies, myelopathy, neuroendocrinopathies, cognitive impairment, dysfunction                             |



|           |                                       |                                                                                                                                                 |
|-----------|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------|
|           |                                       | mania, cognitive impairment, dementia, hallucination, delusions, cataplexy, sleep disturbance                                                   |
| Non-viral | Creutzfeldt–Jakob disease             | Personality change, cognitive decline, anxiety, emotional lability, euphoria, insomnia, delusions, myoclonus, ataxia                            |
|           | Cerebral malaria                      | Paranoid delusions, manic syndrome, altered consciousness, delirium, seizures, dementia, coagulopathy, failure, circulatory collapse            |
|           | Central nervous system (CNS) syphilis | Delusions, hallucination, depression, amnesia, irritability, emotional lability, delirium, confusion, catatonia, delusions, seizures, paroxysms |
|           | Cysticercosis                         | Seizures, headache, nausea, altered status, hydrocephalus, depression, amnesia, cyclosporine, schizoaffective disorder                          |

|                              |                              |                                                                                                                                                                              |
|------------------------------|------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                              |                              | psychosis                                                                                                                                                                    |
| Degenerative                 | Trypanosomiasis              | Encephalitis,<br>chancre, lym                                                                                                                                                |
|                              | Alzheimer's disease          | Psychosis, de<br>memory imp,<br>verbal dysflu<br>of visuo-spat<br>and executiv<br>apraxia                                                                                    |
|                              | Dementia with Lewy<br>bodies | Delusions, vi<br>hallucination<br>parkinsonism                                                                                                                               |
|                              | Fronto-temporal<br>dementia  | Delusions, pe<br>lethargy, disi<br>aphasia                                                                                                                                   |
| Acquired CNS<br>disturbances | Vascular<br>disturbances     | Infarctions,<br>aneurysms,<br>arteriovenous<br>malformations, post-<br>anoxic encephalitis                                                                                   |
| Epilepsy                     | Ictal psychosis              | Bilateral lesio<br>affecting lim<br>structures and<br>parietal areas<br>hemispheric<br>manifest as ic<br>reference and<br>persecution; i<br>lesions as del<br>visual halluci |
|                              |                              | Can be presen<br>(highest asso<br>with tempora<br>epilepsy, and<br>common with<br>originating fr<br>left-sided epi<br>or generaliz<br>Electroenceph                          |

**Electroencephalogram (EEG)** is essential to differentiate between convulsive status epilepticus and certain psychoses. Psychotic processes such as catatonia and stupor which can be associated with unresponsive and manneristic behavior may mimic complex partial seizures with automatisms.

#### Interictal psychosis of epilepsy

Similar symptoms to schizophrenia and other psychiatric disorders include hallucinations, delusions, disorganized speech, and behavior. There are also remarkable affective changes (e.g. affective flattening, alexithymia, avolition), behavioral changes, premorbid data, function, and deterioration in the patient's personality.

#### Alternative psychosis (forced normalization phenomenon)

EEG normalizes during the psychotic episode. These changes are present in both primary and generalized epilepsies, particularly in psychoses, after seizures, and after changes in anticonvulsant therapy.

#### Post-ictal psychosis

Auditory and visual hallucinations are common.

|                    |                      |                                                                                                                                                                     |
|--------------------|----------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                    |                      | paranoia, aggression, affective changes included features of depression or increase in the frequency of secondarily generalized tonic-clonic seizures preceding the |
| Neoplasms          | Brain tumors         | Masses affecting brainstem or cerebral lobes. Alternating paraneoplastic encephalitis                                                                               |
| Sleep disorders    | Narcolepsy           | Psychosis, delusions, hypnagogic hallucination, cataplexy, sleep paralysis                                                                                          |
| Demyelinating      | Multiple sclerosis   | Psychosis, depression, euphoria, fatigue, neuritis, paraesthesia, ataxia                                                                                            |
|                    | Marchiafava–Bignami  | Psychosis, alcohol abuse, malnutrition, spasticity, cognitive impairment                                                                                            |
| Movement disorders | Parkinsonism         | Von Economo's encephalitis /post-encephalitic Parkinson's disease                                                                                                   |
|                    | Choreiform disorders | Huntington's disease                                                                                                                                                |
|                    |                      | Anxiety, depression, mania, paranoid/granulomatous disease                                                                                                          |

|             |                                             |                                                                                                                                                      |                                                                                                 |
|-------------|---------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
|             |                                             | dementia, delusion, hallucination, dystonia, bradykinesia, rigidity, ataxia                                                                          |                                                                                                 |
|             | Sydenham's chorea                           | Emotional lability, irritability, obsession, compulsive behavior, muscle weakness, hypotonia, cognitive impairment                                   |                                                                                                 |
|             | Wilson's disease                            | Personality changes, disinhibition, delusions, hallucination, depression, dementia, rigidity, tremor, chorea, dystonia, parkinsonism, Fleisher rings |                                                                                                 |
|             | Idiopathic basal ganglia calcification      | Personality changes, agitation, paranoid thoughts, chorea, dystonia, dysarthria, dysphagia, ataxia, seizures                                         |                                                                                                 |
|             | Spinocerebellar degeneration                | Friedreich's ataxia                                                                                                                                  | Psychosis, atrophy, weakness, cardiomyopathy, diabetes                                          |
| Traumatic   |                                             | Traumatic brain injuries                                                                                                                             | Schizophrenia, psychosis, left hemisphere damage                                                |
| Psychiatric | Schizophrenia and other psychotic disorders | Schizophrenia                                                                                                                                        | Hallucinations, delusions, disorganized thinking and behavior, impairment in social functioning |

## DISORDERS

|                           |                                                                                                                                                    |                                                                                                                        |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------|
|                           |                                                                                                                                                    | <p><b>Impairment</b>: occupational, academic fun always present. Symptoms must be present for a period of 6 months</p> |
| Schizophreniform disorder | Same as above<br>Impairment in occupational, academic fun may or may not be present. Symptoms must last at least 1 month but no more than 6 months |                                                                                                                        |
| Brief psychotic disorder  | Same as above<br>symptoms present for less than 1 month non-recurring                                                                              |                                                                                                                        |
| Schizoaffective disorder  | Same as above<br>combination of depressive, manic episodes                                                                                         |                                                                                                                        |
| Delusional disorder       | Presence of delusions logically connected and internally consistent typical with no general disturbance                                            |                                                                                                                        |
| Mood disorders            | Psychotic major depression                                                                                                                         | Depressed mood associated with delusions or hallucinations sometimes in                                                |

|               |                                  |                                                                                                                                                                                                                       |
|---------------|----------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|               |                                  | daydreaming                                                                                                                                                                                                           |
|               | Bipolar disorder—manic psychosis | Manic episodes associated with hallucinations and delusions. If psychotic symptoms are present for a significantly longer period than the mood episodes, a diagnosis of schizoaffective disorder is more appropriate. |
| Miscellaneous | Leber's hereditary optic atrophy | Psychosis, decreased visual acuity, optic nerve defect, dystonia, tremors, cardiac arrhythmias                                                                                                                        |
|               | Niemann–Pick disease             | Paranoid delusions, sleep disturbances, depression, ataxia, dysarthria, cerebellar dystonia, dementia, seizures, upper limb palsies, hepatosplenomegaly, thrombocytopenia                                             |
|               | Agenesis of corpus callosum      | Psychosis, cognitive dysfunction, Aicardi's, Anand, and Apert's syndrome                                                                                                                                              |

---

In primary psychiatric disorders with psychosis as the main symptom, neuropathologic investigations have shown reduced volume indicating neuronal

loss with gamma-amino butyric acid (GABA) interneurons being more selectively affected [ 4,7].

## Differential diagnosis

In addition to primary psychiatric disorders, psychosis is a manifesting symptom of a wide variety of neurologic and medical illnesses. The differential diagnosis of psychosis in neurologic disorders and other medical conditions is summarized in Table 59.1.

## Case vignette

A 48-year-old male with a history of partial epilepsy presented with increased seizure frequency and personality changes. He started having partial complex seizures aged 23. Initial work-up with brain neuroimaging and video-electroencephalography revealed a focal epilepsy of left temporal lobe origin and of unknown etiology. His seizures remained well controlled with valproic acid in a monotherapy regimen for the last 10 years. His past medical history was also pertinent for hypertension and hyper-cholesterolemia. His family history was significant for depression and anxiety disorders in his mother and sister.

One month before admission he had four complex partial seizures and levetiracetam was added to his antiepileptic regimen. In the past 2 weeks he started having personality changes including insomnia, increased irritability, and paranoid delusions described per wife as ideas of being spied on initially, and later thinking his food was being poisoned. In the previous week, he started having intermittent worsening confusion and worsening of his delusions. A repeat brain MRI revealed an enhancing lesion in the right temporal lobe. Based on the imaging reading a differential diagnosis of herpes simplex encephalitis or infiltrative glioma was entertained.

This case addresses the broad differential diagnosis of psychosis in a patient with a neurologic disorder including (1) ictal psychosis (new enhancing right temporal lesion with psychotic symptoms being a manifestation of his partial seizures), (2) post-ictal psychosis (since he had a cluster of his seizures related to the psychotic episode), (3) neoplasm or infection-induced psychosis (right temporal lesion, possibly glioma vs. herpes encephalitis), (4) iatrogenic (introduction of new antiepileptic drug: levetiracetam). The patient already had pathology in the left temporal lobe given his seizure onset on that side. The

development of new pathology in the other side increases the risk of psychosis due to bilateral involvement of his temporal lobes.

The patient was admitted to the neurology ward. Continuous video EEG monitoring revealed no subclinical seizures but epileptiform activity arising from both the right and left temporal regions. Serum and CSF analysis including cytologic evaluation did not reveal any infectious or neoplastic etiology. A repeated MRI 4 weeks after the original one showed marked reduction of the right temporal lesion suggesting the lesion most likely represented post-ictal changes. Levetiracetam was discontinued and the patient was started on antipsychotic medications with marked improvement in his symptoms.

## References

1. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (Text Revision)* (DSM-IV-TR). Washington, DC: American Psychiatric Association, 2000.
2. Van Os J, Hanssen M, Bijl RV, Vollebergh W. Prevalence of psychotic disorder and community level of psychotic symptoms: an urban–rural comparison. *Arch Gen Psychiatry* 2001; 58:663.
3. Perala J, Suvisaari J, Saarni SI *et al*. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry* 2007; 64:19.
4. Fornito A, Yucel M, Pantelis C. Reconciling neuroimaging and neuropathological findings in schizophrenia and bipolar disorder. *Curr Opin Psychiatry* 2009; 22:312–19.
5. Keller J, Shen L, Gomez RG *et al*. Hippocampal and amygdalar volumes in psychotic and nonpsychotic unipolar depression. *Am J Psychiatry* 2008; 165:872–80.
6. Rabins PV, Starkstein Se, Robinson RG. Risk factors for developing atypical (schizophreniform) psychoses following stroke. *J Neuropsychiatry Clin Neurosci* 1991; 3:6–9.
7. Harrison PJ. The neuropathology of schizophrenia. A critical review of the data and their interpretation. *Brain* 1999; 122:593–624.

# 60 Ptosis

---

Andrew R. Harrison, Ali Mokhtarzadeh and Juwan Park *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

## Introduction

A myriad of neurologic and structural disorders can result in abnormal positioning of the eyelid with one of the most common in a neurologic setting being blepharoptosis or downward displacement of the upper eyelid. Depending on the etiology, blepharoptosis can be only of cosmetic concern or may be a diagnostic clue to a more sinister underlying pathology.

## Anatomy

Elevation of the upper eyelid is achieved by the combined actions of levator palpebrae superioris, Müller's, and frontalis muscles. Each derives separate sources of innervation – from the oculomotor nerve, sympathetic innervation, and fibers from the facial nerve respectively. The etiology of ptosis can typically be clarified with a simplified understanding of each of these components. Measurement of the palpebral fissure – the distance between the upper eyelid and lower eyelid in primary position, and levator function – the distance between the position of the upper lid from maximum downgaze to upgaze while blocking the effect of frontalis muscle using a finger – are useful in the identification of the etiology.

## Differential diagnosis

An outline of differential diagnosis of ptosis is given in [Table 60.1](#).

## Case vignette

A 29-year-old otherwise healthy female presents for evaluation of a droopy right upper eyelid. She states she has noticed this for several years but never had a droopy lid until her mid-20s. On review of old pictures she notes she previously had a droopy left upper eyelid. She adds that her drooping right upper eyelid is present in the morning but it gets worse as she gets tired. She denies any history of trauma, periocular injury, infection, or inflammation and is a contact lens wearer. She describes blurry overlapping images on occasion. She denies any dysphagia or other weakness.

Several diagnoses among the acquired ptosis category need to be considered. Contact lens wear can be associated with an aponeurotic ptosis secondary to presumed mechanical irritation and ultimate dehiscence or disinsertion of the levator aponeurosis. With aponeurotic ptosis one would not expect the symptoms to worsen with fatigue, though this can be a misleading aspect of the history as many people relate worsening with fatigue. Mechanical causes could be considered if any responsible lesions or masses are noted on examination. Myasthenia gravis would be high on the differential and appropriate clinical examination and tests need to be performed. She can be questioned about botulinum toxin injections. Myogenic causes are less likely due to her age and unilateral symptoms. Certainly Horner's syndrome and an oculomotor nerve palsy needs to be ruled out.

On examination her palpebral fissure is 4 mm on the right and 9 mm on the left and there is notable decreased levator function on the right. Extraocular motility is limited on upgaze in the right eye but otherwise it is normal. Visual acuity is 20/20 in each eye and pupils are symmetric and briskly reactive without an afferent papillary defect. Facial sensation is normal as is masseter tone. Orbicularis strength is reduced bilaterally. On sustained upgaze her ptosis worsens. After looking down when she looks into primary gaze her eyelids elevate higher than expected and then fall back into position – Cogan's lid twitch. Elevation of her ptotic right eyelid caused her other eyelid to droop – this indicates the left is also ptotic but due to exaggerated effort to elevate her right eyelid her palpebral fissure appears normal on the left.

**Table 60.1** *Differential diagnosis of ptosis.*

| Category | Examples | Etiology | Comments features |
|----------|----------|----------|-------------------|
|----------|----------|----------|-------------------|

## Congenital

|                              |                                                                   |                                                                                     |                                                                                              |
|------------------------------|-------------------------------------------------------------------|-------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------|
| Myogenic ptosis              | Isolated congenital ptosis                                        | Levator palpebrae or tendon dysgenesis.<br>Usually sporadic, few autosomal dominant | Present at birth<br>Lid lag on downgaze vs.<br>weak levator function.<br>Minimal to moderate |
|                              | Blepharophimosis                                                  | Autosomal dominant                                                                  | Severe bilateral ptosis, phin epicanthus inversus, ar telecanthus                            |
|                              | Double elevator palsy                                             | Associated superior rectus dysfunction                                              | Common embryological origin of superior rectus and levator palpebrae muscles                 |
|                              | Congenital ptosis associated with fibrosis of extraocular muscles | Maldevelopment of III, IV, and VI nuclei                                            | Severe bilateral restriction of ocular motility typically frank in downgaze                  |
| Synkinetic neurogenic ptosis | Marcus Gunn jaw-winking syndrome                                  | Sporadic. Anomalous innervation of levator by cranial nerve V                       | Unilateral ptosis which elevates with particular jaw movement                                |
|                              | Horner's syndrome                                                 | See below                                                                           |                                                                                              |
|                              | Cranial nerve III palsy                                           | Compressive mass, birth trauma – see below                                          |                                                                                              |

|                    |                         |                                                                                                                                                                                                                                                                                                                         |
|--------------------|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Mechanical ptosis  | Eyelid or orbital tumor | Neurofibroma, lymphoma, hemangioma                                                                                                                                                                                                                                                                                      |
|                    | Eyelid swelling         | Trauma, infection, inflammation, hematoma                                                                                                                                                                                                                                                                               |
| <b>Acquired</b>    |                         |                                                                                                                                                                                                                                                                                                                         |
| Aponeurotic ptosis | Aponeurotic ptosis      | Dehiscence or disinsertion of levator aponeurosis. The muscle itself is normal                                                                                                                                                                                                                                          |
| Myogenic ptosis    | Myotonic dystrophy      | Autosomal dominant – unstable triplet repeat on chromosome 19q13.3.<br>Defect in phosphorylation of skeletal muscle ion channels<br><br>Progressive atrophy of face and extremities. Ptosis and rarely diplopia. Christmas tree cataract, pigmentary retinal changes. Myotonia. Cognitive difficulties and arrhythmias. |

heart failure  
in males  
associated w/  
temporal b&  
testicular at

|            |                                                     |                                              |                                                                                                                            |
|------------|-----------------------------------------------------|----------------------------------------------|----------------------------------------------------------------------------------------------------------------------------|
|            | Chronic progressive external ophthalmoplegia (CPEO) | Mitochondrial DNA deletion. Usually sporadic | Symmetric bilateral ptosis and ophthalmoplegia since young adulthood. poor Bell's phenomenon Orbicularis weakness. I pupil |
|            | Kearns–Sayre syndrome                               | Mitochondrial DNA deletion. Usually sporadic | CPEO + on before 20, pigmentary retinal chan and either h block, ataxia elevated cerebrospinal fluid (CSF) protein         |
|            | Oculopharyngeal dystrophy                           | Autosomal dominant 14q11.2–13                | French Canadian ancestry. May be bilateral gradual ptosis and dysphagia. Often some degree of ophthalmoplegia              |
| Neurogenic | Horner's                                            | Disruption of                                | Unilateral ptosis                                                                                                          |

|        |                         |                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                                                                                     |
|--------|-------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| ptosis | syndrome                | <p>sympathetic innervation – central, preganglionic, or postganglionic.</p> <p>Innocuous appearing signs need to be explored to detect often ominous underlying etiology</p>                                                                                                  | <p>ptosis (less 2 mm), mio and anhidrc the face – tl latter in postganglio Anisocoria in the dark. Dilation lag Lighter colo iris on affec side in cong cases and occasionally acquired</p>                                                                                         |
|        | Cranial nerve III palsy | <p>Compressive (aneurysm, pituitary tumor, cavernous sinus or sphenoid wing meningioma) or ischemic (giant cell arteritis, diabetes, hypertension, atherosclerosis), inflammatory/infiltrative (sarcoid), meningitis, trauma.</p> <p>Ophthalmoplegic migraine in children</p> | <p>Unilateral c bilateral mi severe ptosi strabismus - exotropia, hypertropia hypotropia oblique deviation, mydriasis. Aberrant regeneration seen in microvascu third nerve Primary regeneration (eyelid retr during adduct or depression likely paras lesion. Susp ischemic ca</p> |

with a complete third nerve palsy that is pupil sparing

### Myasthenia gravis (MG)

Antibodies against acetylcholine receptors prevent neurotransmission

Diurnal variation.  
Fatigable (sustained upgaze), visual disturbances, strabismus, variable unilateral or bilateral asymmetric ptosis, orbicularis oculi weakness, can be associated with diplopia, dysarthria, dysphagia, systemic weakness. Can be isolated symptom of myasthenia gravis.  
Fluctuating symptoms - caution mainly people with myasthenia who endorse worsening of symptoms with fatigue. Cogan's lid twitch. Improved with ice or rest. Can be in association with other diseases.

**ASSOCIATION**  
Grave's  
syndrome or  
thymoma

|                                         |                                                                                                                                                                                        |                                                                                                                                                         |
|-----------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------|
| Lambert–Eaton<br>myasthenic<br>syndrome | Two major forms;<br>paraneoplastic and<br>primary autoimmune.<br>Anti-voltage gated<br>calcium channel<br>antibodies on the<br>presynaptic segment of<br>the neuromuscular<br>junction | Neuroophthalmic<br>features are<br>less prominent<br>than autonomic<br>and fatigable<br>proximal<br>weakness. Some<br>symptoms improve with<br>exercise |
| Botulinum toxin                         | Blocks release of<br>acetylcholine from<br>presynaptic terminal                                                                                                                        | Iatrogenic if<br>In infants<br>ingestion of<br>honey, home<br>canned or bought<br>goods                                                                 |
| Apraxia of eyelid<br>opening            |                                                                                                                                                                                        | Often<br>accompanied by<br>blepharospasm.<br>Can be<br>associated with<br>conditions including<br>Parkinson's disease specifically                      |
| Mechanical<br>ptosis                    | Eyelid or orbital<br>tumor                                                                                                                                                             | Neurofibroma,<br>lymphoma,<br>hemangioma                                                                                                                |
|                                         | Eyelid swelling                                                                                                                                                                        | Trauma, infection,<br>inflammation,<br>hematoma                                                                                                         |

|                       |                                                                                      |                                                   |
|-----------------------|--------------------------------------------------------------------------------------|---------------------------------------------------|
|                       | Dermatochalasis                                                                      | Redundant skin                                    |
|                       | Brow ptosis                                                                          |                                                   |
|                       | Cicatricial<br>conjunctival<br>scarring                                              |                                                   |
| <b>Other</b>          |                                                                                      |                                                   |
| Other<br>pseudoptosis | Contralateral<br>eyelid retraction                                                   | Thyroid eye disease                               |
|                       | Hypotropia, globe<br>ptosis                                                          |                                                   |
|                       | Enophthalmos,<br>microphthalmos,<br>phthisis bulbi<br>/contralateral<br>exophthalmos | A sunken g<br>or shrunken<br>globe/protr<br>globe |
|                       | Guarding                                                                             | Ocular pain, discomfort                           |

---

These features certainly make myasthenia gravis the most likely culprit. Specific tests can be performed in clinic. Ice placed over the right (affected) eye could result in improvement in ptosis; pre-and post-ice photos are helpful. Allowing the patient to rest in a dark room for 30 minutes is also likely to result in improvement in ptosis. A dramatic but short-lived response can also be noted with edrophonium though results are neither sensitive nor specific, require monitoring, and can have undesired effects. The diagnosis of myasthenia gravis can then be confirmed with antibody testing and/or single fiber electromyography. It is worth noting that 25–50% of patients with myasthenia with purely ocular features will have negative antibodies.

## Further reading list

Ahmad K, Wright M, Lueck CJ. Ptosis. *Pract Neurol* 2011; 11:332–40.

Cohen AJ, Weinberg DA, Eds. *Evaluation and Management of Blepharoptosis*. New York, NY: Springer-Verlag, 2010.

Collin JRO. Ptosis. In *Manual of Systematic Eyelid Surgery*. Oxford: Butterworth-Heinemann, 1999: 41–72.

# **61 Pupil constriction and Horner's syndrome**

---

Robert C. Sergott and Scott Uretsky *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

## **Introduction**

Anisocoria, the asymmetric appearance of the pupils, can be fundamentally divided into two categories: pupillary dilation or enlargement and smaller, miotic, or constricted pupils. This chapter will describe the differential diagnosis and management approach to the topic of smaller, miotic pupils. An anatomic approach will be taken to this subject beginning with intraocular disorders involving the iris and then moving posteriorly through the orbit to the cavernous sinus, ultimately reaching the midbrain and brainstem.

[Table 61.1](#) lists the most common etiologies of miotic pupils, their anatomic localization, and clinical findings.

## **Anatomic pathway**

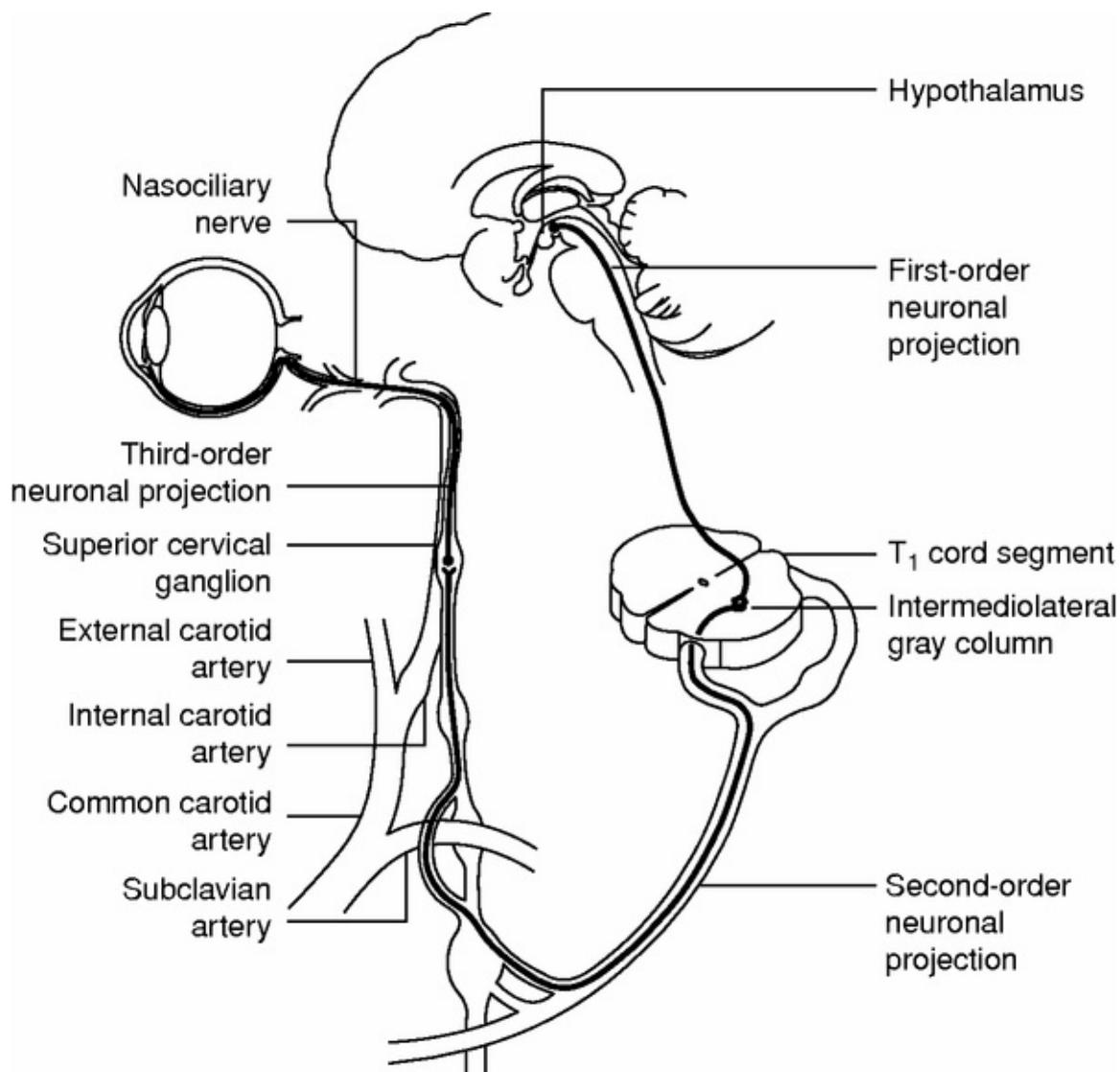
Upon entering the eye, light interacts with two classes of cells, photoreceptors (rods and cones) and photosensitive ganglion cells. Through a series of biochemical actions, these cells propagate electrical signals that are conducted to nerve fibers controlling pupillary size as well as fibers responsible for central and peripheral visual function.

The retino-tectal fibers transmit the neural input from the retina to the pretectal nucleus in the upper midbrain. The retino-geniculate fibers remain in the tract of the afferent visual system before synapsing in the lateral geniculate body. The retino-tectal fibers have a primary impact upon pupillary size.

Axons emerge from neurons within the pre-tectal area to travel to the Edinger-Westphal nucleus from which the oculomotor, third cranial nerves exit. The axons from the Edinger-Westphal nucleus reach the ciliary ganglion, synapse, and then send parasympathetic fibers for innervation of the sphincter

muscle of the iris.

The size of the pupil is then determined by a balance between the parasympathetic innervation described above and the sympathetic innervation from the oculo-sympathetic pathway. [Figure 61.1](#) provides details of the oculo-sympathetic nerve pathways for innervation of the dilator muscles of the iris.



**Figure 61.1** Sympathetic innervation of the dilator muscle of the iris. Cell bodies of the first-order sympathetic neurons in the hypothalamus project axons through the brainstem to the interomedial gray column of the lower cervical and upper thoracic spinal cord. Second-order neurons project via white rami communicantes through the paravertebral sympathetic chain to the superior cervical ganglion. On the left side, the chain splits in its course around the subclavian artery. Third-order neurons travel within the pericarotid plexus to the cavernous sinus, where they join the sixth cranial nerve briefly before entering

the orbit on the first division of the trigeminal nerve. These axons enter the globe to innervate the iris dilator muscle. (Reprinted with permission from Burde RM, Savino PJ, Trobe JD, Eds. *Clinical Decisions in Neuro-Ophthalmology*, 2nd edn. St Louis, MO: Mosby Year Book, 1992.)

## Physiologic anisocoria

An estimated 20% of the population have unequal sizes of their pupils, so-called physiologic anisocoria. Therefore, this harmless syndrome represents the most common cause of anisocoria. Recording the size of the pupils in a well-lit and then darkened room is the first step in evaluating anisocoria. If the inequality in the size of the pupils remains the same in a light and dark environment then no pathologic process is present.

## Iris lesions causing a small pupil

### Pharmacologic effects upon the iris sphincter

For many years, the most common cause of small, miotic pupils was the treatment of primary open-angle glaucoma with pilocarpine. In solutions with a concentration of pilocarpine equal to or greater than 0.25%, the pupil will become smaller due to stimulation of a subtype of muscarinic receptor within the iris sphincter muscle. Pilocarpine is effective in glaucoma because it also produces contraction of the ciliary muscle. Ciliary muscle contraction opens the trabecular meshwork permitting improved drainage of aqueous humor from the eye. Miotic pupils secondary to pilocarpine are quite small, in the range of 2–4 mm in diameter, are round, and do not react to direct light stimulation or to a near target.

**Table 61.1 Common etiologies of miotic pupils, their anatomic localization, and clinical findings.**

| Etiologies and anatomic localization | Clinical signs and symptoms               | Clinical pearls                           |
|--------------------------------------|-------------------------------------------|-------------------------------------------|
| Congenital miosis                    | Typically bilateral. Extrinsically small. | Caused by congenital absence of the iris. |

|                               |                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                                                              |
|-------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                               | <b>Exremely small pupil size that is only slightly reactive to light</b><br><b>Poor dilation after instillation of topical sympathomimetic agents</b>                                                     | <b>Absence of the iris dilator muscle</b><br>Most cases caused by transmission of an autosomal dominant trait<br>Can be associated with systemic disorders: albinism, congenital rubella syndrome, oculocerebrorenal syndrome of Lowe, Marfan syndrome, and skeletal anomalies                                                                                               |
| <b>Physiologic anisocoria</b> | The amount of anisocoria is equal in the light <i>and</i> the dark<br>Example:<br>Exam in light → OD = 4mm<br>OS = 3mm<br>(anisocoria = 1mm)<br>Exam in dark → OD = 6mm<br>OS = 5mm<br>(anisocoria = 1mm) | The most common cause of anisocoria in the general population<br>No underlying pathology is suspected and no evaluation is necessary if the remainder of the exam (e.g. eyelids, motility, and orbit) is normal<br>The pupils must be examined in well-lit and dark environments for assessment of an abnormal pupil size (i.e. sympathetic and parasympathetic dysfunction) |
| <b>Iris sphincter:</b>        | <b>Small irregularly</b>                                                                                                                                                                                  | <b>A sign of active or</b>                                                                                                                                                                                                                                                                                                                                                   |

|                                                                                                                                                                                                           |                                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                     |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <b>uveitis</b>                                                                                                                                                                                            | <b>Constricted, irregularly shaped pupil</b><br>Acute and active stages: edema of the iris, miosis, and erythema of circum-corneal tissue<br>Posterior synechiae<br>→ May develop chronically and are found on slit lamp exam. They are adhesions between the posterior surface of the iris and the anterior capsule of the lens | <b>sequela of active or prior anterior ocular inflammation</b>                                                                                                                                                                      |
| <b>Chronic adie tonic pupil</b>                                                                                                                                                                           | Miosis, along with other features of the tonic pupil, may be seen several years after onset as opposed to the mydriasis seen in the acute, sub-acute, and early chronic phase                                                                                                                                                    | Proposed causes for this finding include “denser” re-innervation compared with normal pupils, with re-innervation increasing over time                                                                                              |
| <b>Horner's syndrome:</b><br><b>Oculo-sympathetic dysfunction</b><br><b>Differential diagnosis:</b><br><b>Hypothalamic tumor</b><br><b>Wallenberg syndrome</b><br><b>Demyelination</b><br><b>Cervical</b> | <b>Classic triad of ipsilateral ptosis, miosis, and anhidrosis</b><br>Practically the anhidrosis is typically not reported or seen. Upper lid ptosis may even be absent in ~10%. The affected eye may                                                                                                                            | <b>Major anatomic locations of pathology</b> include the cavernous sinus, internal carotid artery, hypothalamus, lung apices, and lesions of the neck<br><b>Differentiation</b> between first-and second-order neuronal involvement |

|                                                                                      |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |
|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| spondylosis                                                                          | appear smaller or sunken. “Reverse ptosis” of the ipsilateral lower lid<br>→ the lower lid may be slightly elevated                                                                                                                                     | compared with third-order neuron involvement is no longer clinically useful. Widespread use of magnetic resonance imaging (MRI) allows detection of lesion pathology throughout the course of the sympathetic pathways Evaluation with neuroimaging should be guided by other clinical signs. |
| Brain stem syrinx                                                                    | Pupil size measurements: extent of anisocoria is greater in dark versus light. There will also be a dilation lag of the affected pupil upon extinguishing the lights and as time passes in dark conditions the anisocoria will lessen but not normalize | Contrast MRI is the preferred modality. When refined localization is not possible imaging should include:                                                                                                                                                                                     |
| Spinal cord, head, or neck trauma                                                    | Congenital Horner's syndrome: ipsilateral iris hypopigmentation (lighter colored iris)                                                                                                                                                                  | MRI brain                                                                                                                                                                                                                                                                                     |
| Brachial plexus trauma                                                               | Clinical testing: Topical cocaine → Normally causes pupil dilation by blocking reuptake of norepinephrine. In Horner's syndrome the involved pupil remains miotic while the uninvolved pupil dilates                                                    | MRI skull base to T1/T2 (soft tissues, fat suppressed)                                                                                                                                                                                                                                        |
| Carotid artery dissection                                                            | Topical apraclonidine → An alpha-adrenergic                                                                                                                                                                                                             | MRA neck                                                                                                                                                                                                                                                                                      |
| Apical lung lesions                                                                  |                                                                                                                                                                                                                                                         | Examine carefully for orbital signs, motility defects, cranial neuropathies, hypervascularity of the globe, increased intraocular pressure, and focal neurologic signs to localize the pathology                                                                                              |
| Sympathetic chain or intercostal nerve schwannoma                                    |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |
| Superior cervical ganglion tumor (e.g. paraganglioma)                                |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |
| Thyroid carcinoma                                                                    |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |
| Iatrogenic (surgery)                                                                 |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |
| Cavernous sinus meningioma                                                           |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |
| Carotid–cavernous fistula                                                            |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |
| Paravertebral neuroectoderm tumor                                                    |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |
| Mediastinal tumors                                                                   |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |
| Cluster headache                                                                     |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |
| Raeder paratrigeminal neuralgia (associated with trigeminal neuralgia or neuropathy) |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |
| Horner's syndrome in children (<18 years):                                           |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |
| Congenital ~42%                                                                      |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |
| Post-operative ~42%                                                                  |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |
| Acquired ~15%                                                                        |                                                                                                                                                                                                                                                         |                                                                                                                                                                                                                                                                                               |

|                                                                                                                                             |                                                                                                                                                           |
|---------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------|
| Acquired Horner's syndrome in children (<18 years):                                                                                         | agonist that has minimal effect on the normal pupil but                                                                                                   |
| Neoplasm, especially neuroblastoma                                                                                                          | dilates the pupil in Horner's syndrome due to denervation supersensitivity.                                                                               |
| Spinal cord tumors                                                                                                                          | Thus it causes reversal of the anisocoria → the affected pupil dilates and the unaffected pupil does not                                                  |
| Brachial plexus trauma                                                                                                                      |                                                                                                                                                           |
| Intra-thoracic aneurysm                                                                                                                     |                                                                                                                                                           |
| Embryonal cell carcinoma                                                                                                                    |                                                                                                                                                           |
| Rhabdomyosarcoma                                                                                                                            |                                                                                                                                                           |
| Internal carotid artery thrombosis                                                                                                          |                                                                                                                                                           |
| Vascular malformation of the brainstem                                                                                                      |                                                                                                                                                           |
| Pharmacologic Note: most cases of pharmacologic anisocoria are due to parasympathetic blockade causing a dilated pupil on the affected side | Poor reactivity to direct light stimulation and for the near reaction Brimonidine tartrate, a common topical glaucoma medication, causes pupillary miosis |
| Agents that constrict the pupil:                                                                                                            | In pharmacologic parasympathetic stimulation causing miosis 1% topical                                                                                    |
| Pilocarpine                                                                                                                                 |                                                                                                                                                           |
| Methacholine                                                                                                                                |                                                                                                                                                           |
| Arecoline                                                                                                                                   |                                                                                                                                                           |
|                                                                                                                                             | These effects can be exerted upon the iris sphincter (e.g. pilocarpine) or upon the central nervous system (CNS)                                          |
|                                                                                                                                             | Common classes of medication causing miosis:                                                                                                              |
|                                                                                                                                             | Benzodiazepines                                                                                                                                           |
|                                                                                                                                             | Barbiturates                                                                                                                                              |
|                                                                                                                                             | Opiates (but not meperidine)                                                                                                                              |

|                                                                                                                                                                                                                                                                                               |                                                                                                                                                                                                                             |                                                                                                                                                                                                                                                                                                                                                                                                                                        |
|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Carbachol<br>Anticholinesterase drugs (e.g. physostigmine)<br>Brimonidine<br>Thymoxamine HCl<br>Dapiprazole HCl<br>Reserpine<br>Guanethidine                                                                                                                                                  | tropicamide will not dilate the pupil                                                                                                                                                                                       | Environmental exposures, potentially routine in patients who garden or who are active in nature, can cause abnormal pupillary size. Such history should be excluded                                                                                                                                                                                                                                                                    |
| Argyll Robertson pupils:<br>Neurosypilis<br>Other entities that produce Argyll Robertson pupils:<br>Diabetes mellitus<br>Chronic alcoholism<br>Encephalitis<br>Multiple sclerosis<br>CNS neurodegenerative disease<br>Midbrain tumors (rare)<br>Sarcoidosis (rare)<br>Neuroborreliosis (rare) | Extremely small pupils, typically 1–2mm, that are irregularly round<br>Light–near dissociation → Pupil reactivity to a near target is greater than reactivity to direct light stimulation (in the setting of normal vision) | Potentially lesions in the rostral midbrain can produce such pupil findings by affecting efferent fibers from the Edinger–Westphal nucleus responsible for response to light and sparing fibers responsible for the near reaction<br>Small, chronically tonic pupils can be distinguished from Argyll Robertson pupils by noting brisk re-dilation after a strong accommodative effort in the latter, that is not seen in tonic pupils |
| Brainstem                                                                                                                                                                                                                                                                                     | Variable neurologic signs depending on location of lesion:<br>Dorsal mesencephalon → unilateral Horner's                                                                                                                    | Wallenberg syndrome is most commonly caused by occlusion of the ipsilateral vertebral artery and less commonly by                                                                                                                                                                                                                                                                                                                      |

syndrome + contralateral trochlear nerve palsy  
Pons → uncommon cause of Horner's syndrome + abducens palsy (most commonly these signs localize to the cavernous sinus)  
Pontine hemorrhage → pinpoint pupils that under magnification are reactive to light  
Lateral medullary syndrome of Wallenberg → ipsilateral loss of facial pain/temperature, Horner's syndrome, limb ataxia, and dysarthria or dysphagia with contralateral loss of limb pain/temperature sensation. Patients complain of vertigo and lateral pulsion

occlusion of the posterior inferior cerebellar artery  
Major considerations of etiologic pathophysiology at any location include: ischemia, hemorrhage, tumor/neoplasia, demyelination, and vascular malformation  
Metabolic derangements causing coma typically do not affect neuronal pupillary pathways.  
Thus intact pupil responses in the setting of otherwise abnormal brainstem reflexes strongly suggest coma of a metabolic and not structural origin

## Trauma

Variable findings of the globe and orbit depending on type and severity of injury  
In the acute phase, blunt or penetrating injuries to the globe

Following the acute period of miosis examination will reveal a variable extent of iridoplegia or mydriasis  
Note: Iris atrophy

|                                |                                                                                                                               |                                                                                                                                                                                                                                                                     |
|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                                | cause several hours of miosis                                                                                                 | secondary to trauma, ischemia, or inflammation may preferentially affect the dilator muscles of the iris causing ipsilateral miosis                                                                                                                                 |
| Neoplastic disease of the iris | Iris border irregularity with or without visualized mass, anisocoria, abnormal pupil reactivity                               | Very few mass lesions involve the iris. Consider leiomyoma, malignant melanoma, and lymphoma                                                                                                                                                                        |
| Migraine and cluster headache  | Cluster headache: ipsilateral tearing, nasal stuffiness, conjunctival injection, and ptosis with or without Horner's syndrome | Anisocoria can be seen, episodically, in classic or common migraine as well. Most commonly pupillary mydriasis of the affected side is considered abnormal. Hypothetical mechanisms include hyper- or hypofunctioning of the parasympathetic or sympathetic systems |

---

The miosis produced by pilocarpine was often a rate-limiting step in treating glaucoma patients who also had cataracts because the size of the pupil in these patients further impaired their vision. Because of this side effect, as well as the need for four times a day dosing, pilocarpine has been replaced by other topical medications. Its most common, current use is now the treatment of dry mouth syndrome as part of Sjögren's syndrome or sequelae of radiation therapy to the

area of the salivary glands.

In comparison to enlarged pupils which are usually produced by central nervous system (CNS) stimulants, small pupils are produced by medications that exert a depressant effect upon CNS activity. The most common medications that produce small pupils include benzodiazepines such as diazepam, as well as barbiturates and opiates including heroin, morphine, and fentanyl, but not meperidine.

## **Uveitis**

A small pupil may be associated with the sequelae of acute uveitis due to the inflammatory process producing adhesions between the posterior surface of the iris and anterior capsule of the lens. These adhesions are referred to as posterior synechiae and produce a small pupil that is irregular (that is, not round) in shape in the region of the synechiae. On rare occasions, the synechiae may encompass the entire posterior surface of the iris producing what is called an iris bombe, which may result in a secondary glaucoma since the scar formation prevents circulation of aqueous humor from the anterior to the posterior chamber.

## **Horner's syndrome – lesions in the cavernous sinus and oculo-sympathetic pathway**

Horner's syndrome refers to any lesion that interrupts the oculo-sympathetic pathway from its origin in the hypothalamus through its course in the brainstem, spinal cord, and along the internal carotid artery into the cavernous sinus. The classic triad of clinical findings consists of ipsilateral miosis, ptosis, and anhidrosis ([Figure 61.1](#)). Clinically the anhidrosis is rarely seen. Patients may paradoxically report that the normal eye has an enlarged pupil; therefore, clinicians must always look for the associated finding of ipsilateral ptosis of the upper lid produced by a lack of sympathetic innervation to the superior tarsal muscle of Müller. The lower lid will also often be slightly elevated, so-called “reverse ptosis.” In congenital Horner's syndrome, the involved eye will often demonstrate lighter color of the iris because sympathetic stimulation is required for melanocytes to produce melanin in the stroma of the iris.

Diagnostic verification of Horner's syndrome depends upon the lack of dilation of the involved pupil following the instillation of topical cocaine. In the normal pupil, cocaine blocks the reuptake of norepinephrine, producing a dilated

pupil. In Horner's syndrome, norepinephrine is absent and the pupil affected by Horner's syndrome remains miotic. Since cocaine is a controlled substance and even topical instillation can result in a positive drug-screening test for 48 hours, the testing is not usually a simple matter. Using the alpha-agonist apraclonidine will produce reversal of the anisocoria, that is, the affected miotic pupil will dilate due to denervation hypersensitivity and the contralateral side will constrict.

The oculo-sympathetic pathway is a three-neuron system and lesions are often classified according to which neuron is affected. First-order neuron lesions involve the central pathway from the hypothalamus to the spinal tract. Second-order neuron lesions involve pre-ganglionic pathology and third-order lesions are termed post-ganglionic.

Hydroxyamphetamine has been used in the past to differentiate a first- or second-order Horner's syndrome from a third-order lesion. Until the advent of magnetic resonance imaging (MRI), the accepted thinking was that third-order Horner's syndromes were produced by benign lesions. In truth, however, serious pathology may present with third-order lesions and we no longer find hydroxyamphetamine testing clinically useful now that MRI can detect lesions that previously escaped detection.

## **Argyll Robertson pupils**

Argyll Robertson (AR) pupils are the classic neuro-ophthalmologic finding for neurosyphilis. These pupils are always extremely small, measuring 1–2 mm, and they are always irregularly round. There is always light–near dissociation which means that the pupil reacts more briskly to stimulation to a near target compared with direct light stimulation. When Douglas Argyll Robertson first described the pupils that bear his name, he astutely specified that the vision in both eyes had to be normal, realizing that the most common cause of light–near dissociation was poor vision due to an optic neuropathy.

In his first description in 1863, Robertson reported the pupillary findings in a patient with spinal disease and referred to it as “spinal miosis.” Approximately 30 years later, CNS syphilis, tabes dorsalis, and general paresis were ultimately linked and the single unifying diagnosis of neurosyphilis was accepted, with the AR pupils emerging as a classic finding in this syndrome.

Although not completely proven, the rostral midbrain in the area of the third ventricle and cerebral aqueduct appears to be the most accepted area of

pathophysiologic damage. A lesion in this territory would affect the efferent fibers in the Edinger-Westphal nucleus (responsible for light response) but spare the fibers associated with the near response. The near-response fibers are separated anatomically from those governing the light response.

## Pontine hemorrhage

Patients with large pontine hemorrhages will present with decline in consciousness leading to coma in association with very miotic pupils, bulbar muscle weakness, hyperventilation, and hyperthermia. The very small pupils develop because of bilateral interruption of the central hypothalamic spinal pathway permitting unopposed parasympathetic stimulation of the iris sphincter.

## Case vignette

A 27-year-old female with no significant past medical history presented with drooping of the right eyelid (see [Figure 61.2](#)) noted one day after being involved in a motor vehicle accident. She reported being “rear-ended.” The patient denied head and neck pain and other focal or transient neurologic symptoms. Examination revealed mild right-sided ptosis and anisocoria. The right pupil was smaller than the left and the anisocoria was greater in dim light compared with a well-lit environment. The remainder of the neurologic exam was normal.



**Figure 61.2** Right Horner's syndrome with ptosis and miosis. This 27-year-old female presented with drooping of the right upper lid with an ipsilateral miotic pupil. Anisocoria was greater in dark compared with light. Axial T1-weighted, fat-suppressed contrast-enhanced MRI confirmed ipsilateral carotid arterial dissection. (Courtesy of Scott Uretsky MD.) Magnetic resonance imaging of the

brain was normal as was magnetic resonance angiography (MRA) of the extra- and intracranial vessels. Additional imaging with axial T1-weighted, fat-suppressed images of the neck revealed right-sided carotid dissection. The patient was managed conservatively with anti-platelet therapy (aspirin) and otherwise remained neurologically asymptomatic.

This case illustrates the most common findings of a Horner's syndrome: ipsilateral ptosis and miosis with anisocoria greater in dark than light and pupillary dilation lag. Additionally it illustrates the limitation of MRA, which is based on blood flow. In the absence of a flow-limiting narrowing of the artery the dissection may not be apparent on MRA. Thus axial T1-weighted, fat-suppressed, contrast-enhanced images are needed to confirm the diagnosis.

## Further reading list

Al-Moosa A, Eggenberger E. Neuroimaging yield in isolated Horner syndrome. *Curr Opin Ophthalmol* 2011; 22:468–71.

Miller NR, Newman NJ, Biouss V. *Walsh & Hoyt's Clinical Neuro-Ophthalmology*, 6th edn. Philadelphia, PA: Lippincott, Williams & Wilkins, 2005.

Patel RR, Adam R, Maldjian C *et al*. Cervical carotid artery dissection: current review of diagnosis and treatment. *Cardiol Rev* 2012; 20:145–52.

## 62 Pupil dilation

---

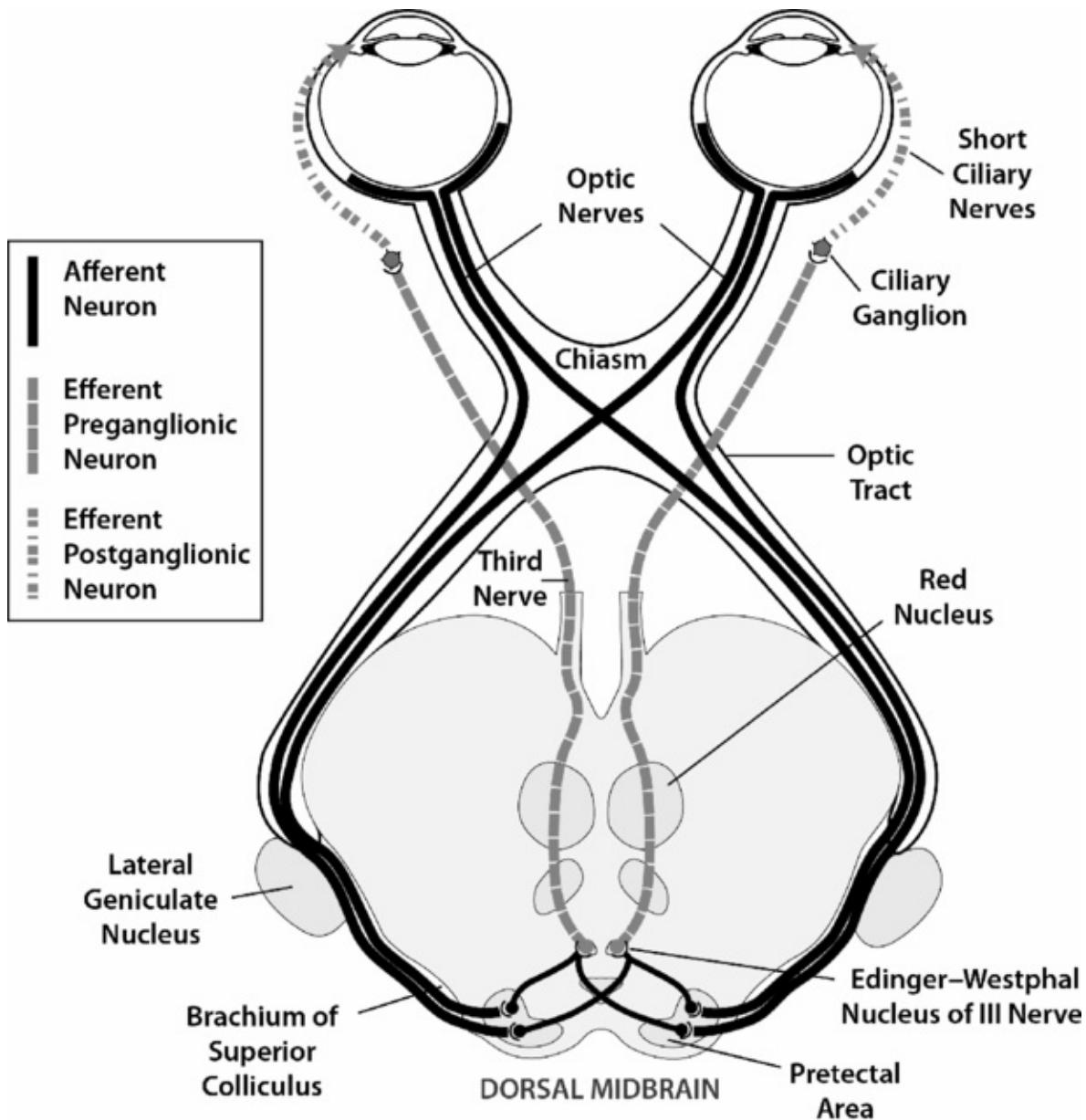
Jade S. Schiffman, Rosa Ana Tang, Anastas F. Pass, and and L. Anne Hayman  
*Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

In most normal people, the pupils are of equal size or there is a minimal size asymmetry. A dilated pupil could signify a serious life-threatening problem and therefore requires a rapid assessment. An organized clinical exam will uncover whether the dilated pupil is isolated or if other signs accompany it. This information can help determine what the problem is and its potential localization. Key signs include the reactivity of the pupil to light and the involvement of the fellow travelers: lid (ptosis) and motility (ophthalmoplegia) [1,2].

### Pathway of parasympathetic fibers: relevant anatomy

In general, the evaluation of the pupil provides significant clinical information regarding the integrity of the afferent and efferent light-visual pathway (see [Figure 62.1](#)). Light entering the eye is transmitted along the optic nerve and ultimately to the visual cortex for processing. Along the way, approximately 20% of these fibers branch off the visual pathway prior to or at the lateral geniculate ganglion (LGN). It is not known if these are specific pupil fibers encoded from the retina or collateral fibers. These fibers synapse in the pretectal nucleus, forming two fiber tracts from the synapse; some decussate, becoming the crossed fibers, and some of them do not decussate, being the uncrossed intercalated neurons. The crossed intercalated neurons travel through the posterior commissure, pairing with the uncrossed intercalated neurons from the contralateral side, forming the pretecho-oculomotor tract to the right and left aspect of the paired Edinger-Westphal subnuclei of the oculomotor nucleus (CN III).



**Figure 62.1** Diagram shows the “afferent visual pathway” and the genesis of the parasympathetic fibers to the pupil (efferent motor pathway).

The parasympathetic fibers to the eye begin in the Edinger-Westphal subnucleus of CN III from where the parasympathetic fibers travel in close association with the fibers from the inferior oblique subnucleus of CN III passing through the midbrain, subarachnoid space, cavernous sinus then into the orbit. The parasympathetic fibers ultimately synapse in the ciliary ganglion, located in the posterior aspect of the orbit lateral to the optic nerve and medial to the lateral rectus muscle. The parasympathetic fibers to the pupil constrictor muscle synapse in the ciliary ganglion while the sympathetic fibers, nasociliary

nerve, and motor fibers from CN III pass through without synapsing in this structure. The postganglionic parasympathetic pupillary constrictor fibers then enter the 30 µm thick space between the sclera and choroid (suprachoroidal space) and travel as the short posterior ciliary nerves, which then innervate the ciliary body and the iris sphincter in a 30 : 1 ratio [3].

## Pupil examination

The pupil examination is essential for determination of the afferent input into both eyes and if there is an inequality of this input between the eyes from dysfunction of the retina, optic nerve, optic chiasm, optic tract, or pretectal region. Additionally the pupil exam can determine if there is a problem with the autonomic nervous system supply to the pupil (parasympathetic or sympathetic). In a patient presenting with a dilated pupil, the pupillary evaluation combined with a careful lid and ocular motility exam often distinguishes between benign causes of parasympathetic dysfunction (e.g. pharmacologic blockade or Adie's tonic pupil) versus a life-threatening cause of parasympathetic dysfunction (e.g. CN III compression by an aneurysm of the posterior communicating artery). A "Blown Pupil" usually refers to a very large pupil that is fixed to light, but there may be variations on this definition. There are a number of causes of a blown pupil; of great concern regarding the "Blown Pupil" is a posterior communicating artery (PCoA) aneurysm compressing CN III. A "Tonic Pupil" implies a parasympathetic denervated pupil. The tonic pupil is reserved for pupils that are fixed to light (no response to light or do so sectorially) and usually have a better reaction to accommodation and a slow "tonic" period of redilation. However, a recently denervated pupil will not immediately react to accommodation, so a pupil that has been immediately denervated does not have the time to develop this response feature. [Table 62.1](#) provides an overview of neurologic versus non-neurologic causes of a dilated pupil.

**Table 62.1 Neurologic and non-neurologic causes of the dilated pupil.**

| Neurologic causes of the dilated pupil |                        |            |                        |
|----------------------------------------|------------------------|------------|------------------------|
|                                        | Site                   | Presents   | Comment                |
| "Blown pupil" associated               | Subarachnoid<br>CN III | Unilateral | Must exclude posterior |

|                   |                                                                                                                                                    |                                                                                                                                                                                                                                       |
|-------------------|----------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| with CN III palsy | pathway                                                                                                                                            | communicating artery (PCoA) aneurysm. Look for other signs of CN III involvement (ptosis, ocular motility) Can be early sign of temporal lobe herniation also usually associated with other CN III signs                              |
| Tonic pupil       | P-sympathetic pathway, ciliary ganglion or postganglionic fibers<br><br>(Note: there are non-neurologic causes of tonic pupils – see next section) | Unilateral Often benign Adie's syndrome and may be precursor to Holmes–Adie's syndrome (see below) May be seen as a transient phenomenon in migraine Rarely seen with giant cell arteritis (GCA)<br>Rarely seen in Sjögren's disease. |
|                   | Bilateral                                                                                                                                          | Consider syphilis Other autonomic testing may be abnormal including blood pressure (BP) (orthostatic hypotension), sweating disorders, etc.<br>Holmes–Adie's                                                                          |

syndrome is associated with deep tendon reflexes (DTR) areflexia and may start unilaterally Ross syndrome is associated with anhidrosis Peripheral neuropathy as diabetes, amyloid, paraneoplastic syndrome (autoimmune autonomic ganglionopathy with positive ganglionic AChR antibody) Exclude Sjögren's disease

|                                                  |                      |            |                                                                                                                                                                                                                        |
|--------------------------------------------------|----------------------|------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Cavernous sinus pupil:<br>alternating anisocoria | Cavernous sinus      | Unilateral | Cavernous sinus lesion affecting both parasympathetic and sympathetic pathways. Mid-dilated and relatively fixed pupil “Alternating” anisocoria, in the light the pupil is larger and in the dark the pupil is smaller |
| Midbrain lesions:                                | Midbrain From pineal | Bilateral  | Pupils mid-dilated and constricted                                                                                                                                                                                     |

| <b>causes</b>               | <b>from pupil</b>                                   | <b>and can be</b>                                                                                                                                                                                                                                                                                                            |
|-----------------------------|-----------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Usually extra-axial lesions | gland or thalamic                                   | associated with central herniation as well as intrinsic midbrain lesions                                                                                                                                                                                                                                                     |
| Usually intra-axial lesions | lesions extrinsic<br>From intrinsic midbrain lesion | Parinaud's syndrome complex; pupil size may be mid-dilated or larger but is not reactive to light, pupils constrict to near stimulus (light–near dissociation), convergence retraction nystagmus, skew deviation as well as other features                                                                                   |
| Unilateral                  |                                                     | Weber's syndrome (affecting the substantia nigra, corticospinal tract, corticobulbar tract, and the oculomotor nerve fibers resulting in a dilated pupil)<br>Claude's syndrome (affecting the cerebellar fibers, corticospinal tract, the corticobulbar tract, and the oculomotor nerve fibers resulting in a dilated pupil) |

|                                              |                                      |                         |                                                                                                                                                            |
|----------------------------------------------|--------------------------------------|-------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Death                                        |                                      | Bilateral               | Mid-fixed position of pupils that are unreactive due to damage of both the parasympathetic and sympathetic system Diffuse hypoxic-ischemic cerebral injury |
| “Tadpole” pupil                              | Iris dilator muscle                  | Unilateral              | Rare and benign transient pupillary distortion associated with segmental iris dilator spasm [4]                                                            |
| Trauma to the short posterior ciliary nerves | Suprachoroidal space                 | Unilateral or bilateral | A very tight scleral buckle for repair of retinal detachment, very heavy pan-retinal photocoagulation (PRP) used for diabetes retinopathy                  |
| Blunt globe trauma                           | Iris sphincter tear                  | Unilateral              | Generally a mid-dilated misshapen pupil presentation                                                                                                       |
| Pharmacologic pupil                          | Blocked iris P-sympathetic receptors | Unilateral or bilateral | P-sympatholytic agents (e.g. atropine, scopolamine, which may be used behind the ear, or similar)                                                          |

exposure) Can be caused by contact with alkaloid-containing plants from the *Solanaceae* family e.g. Jimson weed

|                                                     |                |            |                                                                                                                                                                           |
|-----------------------------------------------------|----------------|------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Congenital myopathy of iris sphincter               | Iris sphincter | Bilateral  | Associated with gastrointestinal dysfunction in a baby                                                                                                                    |
| Irido-corneal angle closure (“narrow angle attack”) | Iris sphincter | Unilateral | Ischemic paresis of the iris sphincter.<br>Look for other signs of angle closure (increased ocular pressure $> 50$ mmHg, hyperemia, cloudy cornea, reported pain, nausea) |

---

It is important to measure the pupil's diameter in the light and in the dark. Measuring the pupils in the light is best performed by having the room lights turned up the highest and using a bright light source, such as a transilluminator, at its highest intensity and directed from below onto both pupils. In the dark, it is best performed utilizing the transilluminator set at the lowest intensity also directed from below that allows the clinician to see the pupils. This will give the clinician a good approximation of the pupillary diameter in the dark. The pupil size can be measured by placing a near card above the pupils with pupil “half-moon” diameters on it so that the pupil size can be accurately measured. Up to 20% of normal healthy infants were found to have benign pupillary asymmetry of 0.5 mm or more [5]. Lam *et al.* found the prevalence of this so-called simple, central, or essential anisocoria to be  $\sim 41\%$  for 0.4 mm difference [6]. Essential

anisocoria subjects have normal pupil reactions and no abnormalities of lid and eye movements.

Conditions that create a dilated pupil will have a greater diameter difference (anisocoria) in the lighted assessment condition. In the dark conditions, the pupil sizes between the two eyes become more symmetric. Testing the pupillary light reflex is critical as this response is normal in essential anisocoria but reduced or absent in pathological dilated pupils. Pupils either may show pathologically better constriction to near response than to light [light–near dissociation] or show lack of both the direct and near responses as seen with a relatively new CN III paresis (which will show motility abnormality) or pharmacologic pupillary dilation (no ocular motility abnormality).

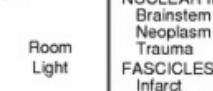
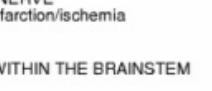
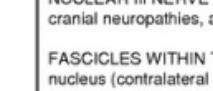
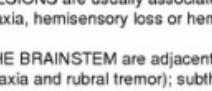
Midbrain pupils are mid-dilated bilateral pupils that have poor light reaction. These pupils may occur as a result of an intrinsic midbrain process or while a patient is undergoing central herniation. These pupils tend to be smaller than the pupils are when the midbrain process is concentrated more dorsally. This is because when the midbrain is affected more ventrally, the sympathetic pathway is affected, thus causing both parasympathetic and sympathetic denervation resulting in a mid-dilated pupil (which is also the pupil seen at death). When the midbrain process is localized more dorsally, sparing the sympathetic fibers, the pupils tend to be larger and often sparing the accommodative/convergence pathway, thus leading to light–near dissociation. These are the pupils seen with the dorsal midbrain syndrome (also known as Parinaud's syndrome or periaqueductal syndrome) where often there is the presence of concomitant vertical gaze paresis (upgaze more than downgaze) and convergence retraction nystagmus. Lesions that result in a “midbrain” pupil are pineal region tumors, thalamic tumors that grow into this area as well as other pathologies including vascular lesions, demyelination, traumatic injuries, and others.

Absolute paralysis of pupillary constriction includes both iridoplegia and cycloplegia representing internal ophthalmoplegia as seen with compressive lesions of CN III (due to transmission blockade) and with pharmacologic dilation of the pupil (due to end-organ iris receptor blockade).

Patients with a large pupil that does not react to light, must have a careful ocular motility exam to determine if there are any signs of a third nerve palsy. A CN III palsy may show only subtle motility signs. Some patients could be orthotropic in primary position and only if you examine them in the nine cardinal positions will you find abnormalities consistent with a CN III nerve paresis. For example, if a patient with a right dilated and fixed pupil shows a

right hypotropia in upgaze, a right hypertropia in downgaze, and a right exotropia in left gaze, this can be due to a partial CN III palsy.

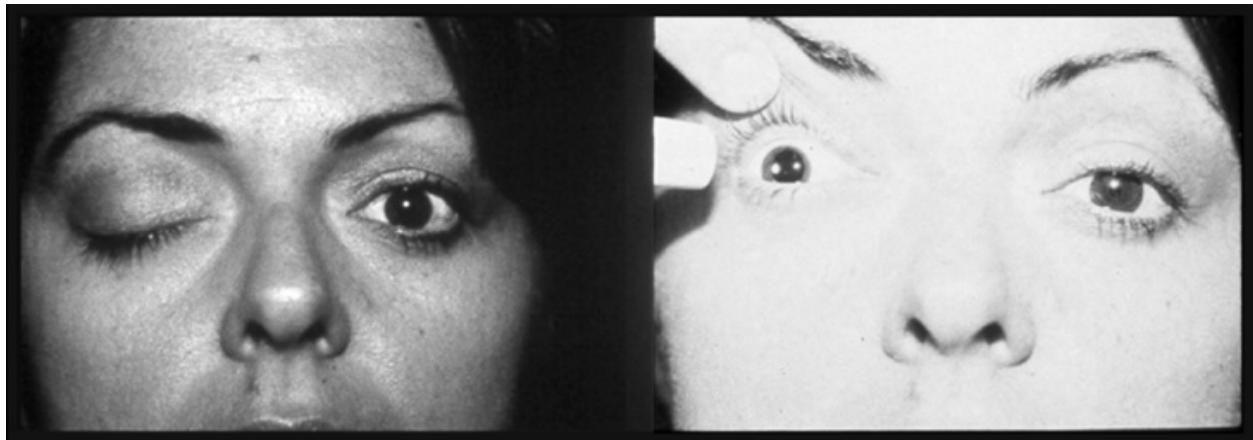
Once a CN III palsy is detected, a careful neurologic exam is necessary to determine where the CN III palsy is coming from (e.g.) midbrain, subarachnoid space, cavernous sinus, and superior orbital fissure. Lesion of the fascicular portion of CN III may manifest other neurologic company that may assist the clinician in determining where along the course of the CN III the lesion is (see [Figure 62.2](#), second and third columns).

| PREGANGLIONIC NEURON IN THE EFFERENT PATHWAY [III Nerve Palsy with a Poorly Reactive Dilated Pupil] |                           |                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                          |
|-----------------------------------------------------------------------------------------------------|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| III Nerve Lesion (Ptosis & Exotropia) with Fixed and Dilated Pupil                                  |                           | Common Etiologies                                                                                                                                                                                                                                                                                                | Clinical Clues                                                                                                                                                                                                                                                                                                                                                                           |
|                    | Lesion Normal             | NUCLEAR III NERVE<br>Brainstem infarction/ischemia<br>Neoplasm<br>Trauma                                                                                                                                                                                                                                         | NUCLEAR III NERVE LESIONS are usually associated with other cranial neuropathies, ataxia, hemisensory loss or hemiparesis                                                                                                                                                                                                                                                                |
|                    | Room Light                | FASCICLES WITHIN THE BRAINSTEM<br>Infarct<br>Hemorrhage<br>Neoplasm                                                                                                                                                                                                                                              | FASCICLES WITHIN THE BRAINSTEM are adjacent to the red nucleus (contralateral ataxia and rubral tremor); subthalamic region (contralateral hemichorea or hemitremor); brachium conjunctivum (cerebellar ataxia) or cerebral peduncle (contralateral hemiparesis)                                                                                                                         |
|                    | Flashlight                | SUBARACHNOID SPACE<br>Posterior communicating aneurysm<br>Uncal herniation<br>Basilic meningitis (Infection, Tumor)                                                                                                                                                                                              | SUBARACHNOID SPACE bleeding causes headache and stiff neck. It strongly suggests a cerebral aneurysm. This is a neurosurgical emergency.                                                                                                                                                                                                                                                 |
|                   | 1/16% Topical Pilocarpine | CAVERNOUS SINUS AND SUPERIOR ORBITAL FISSURE<br>Neoplastic pituitary tumor, meningioma, metastasis, sphenoid sinus neoplasm, lymphoma, craniopharyngioma<br>Infection: Mucormycosis, Aspergillosis<br>Vascular: aneurysm of Internal Carotid Artery, carotid-cavernous fistula<br>Inflammatory lesions<br>Trauma | CAVERNOUS SINUS & SUPERIOR ORBITAL FISSURE lesions produce third, fourth or sixth cranial nerve palsies and/or trigeminal dysfunction or pain. Proptosis usually indicates superior orbital fissure involvement. Imaging of the orbit is needed.                                                                                                                                         |
|                  | 1% Topical Pilocarpine    | ORBIT (Fibers to the Oiliary Ganglion) - Rare<br>Inflammatory<br>Ischemic<br>Traumatic<br>Neoplasm                                                                                                                                                                                                               | ORBIT (Fibers to the Ciliary Ganglion) lesions produce the following signs: proptosis, chemosis & conjunctival injection, enophthalmos, or concomitant optic neuropathy. The latter produces progressive unilateral visual loss, disc swelling (followed by atrophy) and optociliary shunt vessels (retinal - orbital venous collaterals). Imaging of the orbit establishes an etiology. |
|                  | Convergence               |                                                                                                                                                                                                                                                                                                                  |                                                                                                                                                                                                                                                                                                                                                                                          |

**Figure 62.2** Pupil responses to light, pilocarpine drops, and convergence with lesions of the third nerve pathway presenting with dilated pupil with the related anatomy, common etiologies, and clinical clues from adjacent structures [7].

## Differentiating a vasculopathic CN III palsy from a compressive CN III palsy

Pupillary dilation secondary to a compressive CN III involvement will typically show little to no constriction to a light stimulus or near convergence response and there will typically be some degree of oculomotor paresis, with partial to complete involvement of the CN III innervated muscles (see [Figures 62.3](#) and [62.4](#)). In some cases of CN III palsy, the pupil may be normal.



**Figure 62.3** A patient presenting with a right-sided compressive CN III palsy manifests a complete ptosis of that eye (left image). With the superior lid held and light directed to both eyes, the right eye presents with a “blown” pupil.



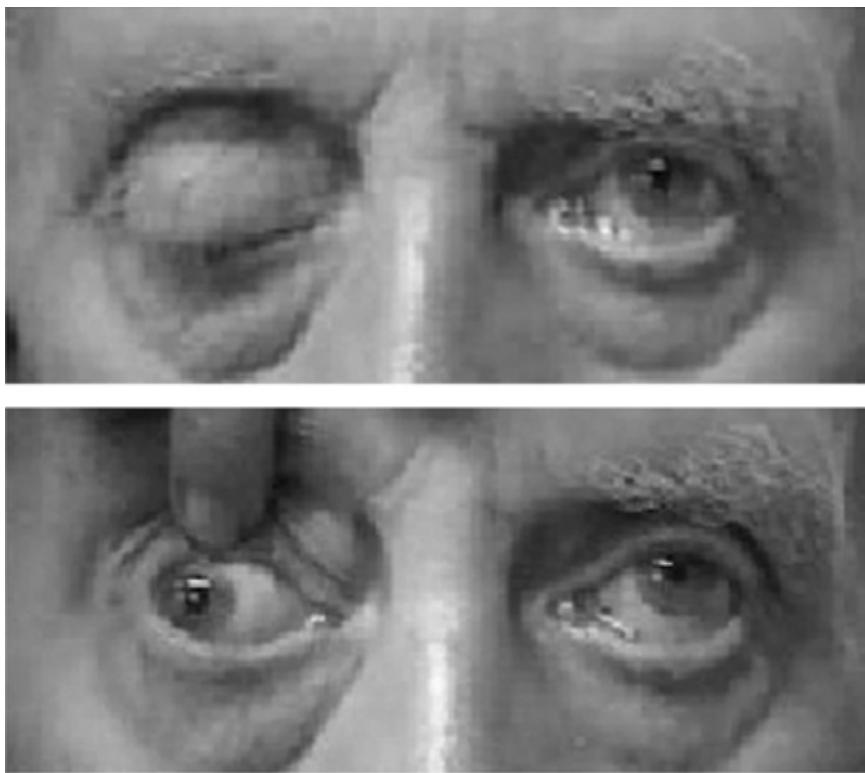
**Figure 62.4** The same patient as seen in [Figure 62.3](#) demonstrating the lack of motility associated with the CN III palsy.

Some patients present with a CN III palsy that is not due to a compressive lesion but is related to vasculopathic factors, the most common being diabetes. A diabetic CN III is far more common in a diabetic than an aneurysm; however,

how can we be sure? Traditionally diabetic CN III palsies are painless and have pupil sparing as opposed to the PCoA aneurysm, which is typically associated with pain and is associated with a dilated pupil.

In a paper by Kupersmith *et al.*, no patients with a posterior communicating artery aneurysm and a complete oculomotor palsy had true “pupil sparing.” Therefore, in complete pupil-sparing oculomotor palsy, it may be possible to exclude a compressive lesion on clinical grounds. If the pupil is not sparing, magnetic resonance angiography (MRA) demonstrates sensitivity in detecting all aneurysms larger than 2 mm in patients with third nerve palsy. Kupersmith *et al.* also note that the source images are much more sensitive than the three-dimensional reconstructions [8].

For the purpose of this paper we advise work-up for aneurysm unless the patient demonstrates a total external ophthalmoplegia in the distribution of CN III and a totally normal ipsilateral pupil in size and reaction. This is the only condition in which we can apply the term of “pupil sparing” ([Figure 62.5](#)) and this is how many of the so-called “microvascular” or diabetic CN III palsies present [9]. Unfortunately many CN III palsies show partial weakness of the extraocular muscles innervated by CN III with no “blown pupil” in which case we advise the patient be worked-up for an aneurysm.



**Figure 62.5** Pupillary sparing right CN III paresis in a diabetic patient. This

patient cannot elevate, depress, or adduct his right eye, but the pupil responds normally to light.

In a recent study of 234 patients with diabetes, microvascular ischemia was the cause of CN III palsy in approximately 66% of the patients. Of those patients that presented with aneurysms as the cause of the CN III palsy, only 2% of aneurysms spared the pupil. Eye pain experienced at the onset was seen in 94% of aneurysm patients and in 69% of diabetic cases, so it is not a particularly helpful symptom [10].

If the lesion is in the cavernous sinus, we could see anisocoria that alternates. That is, in the brightly lit room, the larger diameter pupil will be noted in the eye with the cavernous sinus lesion due to parasympathetic dysfunction, and in the dark the same eye will demonstrate a smaller size due to sympathetic dysfunction.

Parasympathetic denervation to the pupil due to a postganglionic lesion will typically demonstrate changes that are best seen under the slit lamp. One can see uneven constriction of sectors of the iris, which may be reflected in a vermiform movement noted of the iris frill. The iris surface will show areas of iris stromal tissue spreading smooth (“stromal spread” over areas of iris sphincter paralysis) and areas of iris stromal tissue streaming to the iris border (“stromal streaming” over areas of still viable but reduced capability of the iris sphincter).

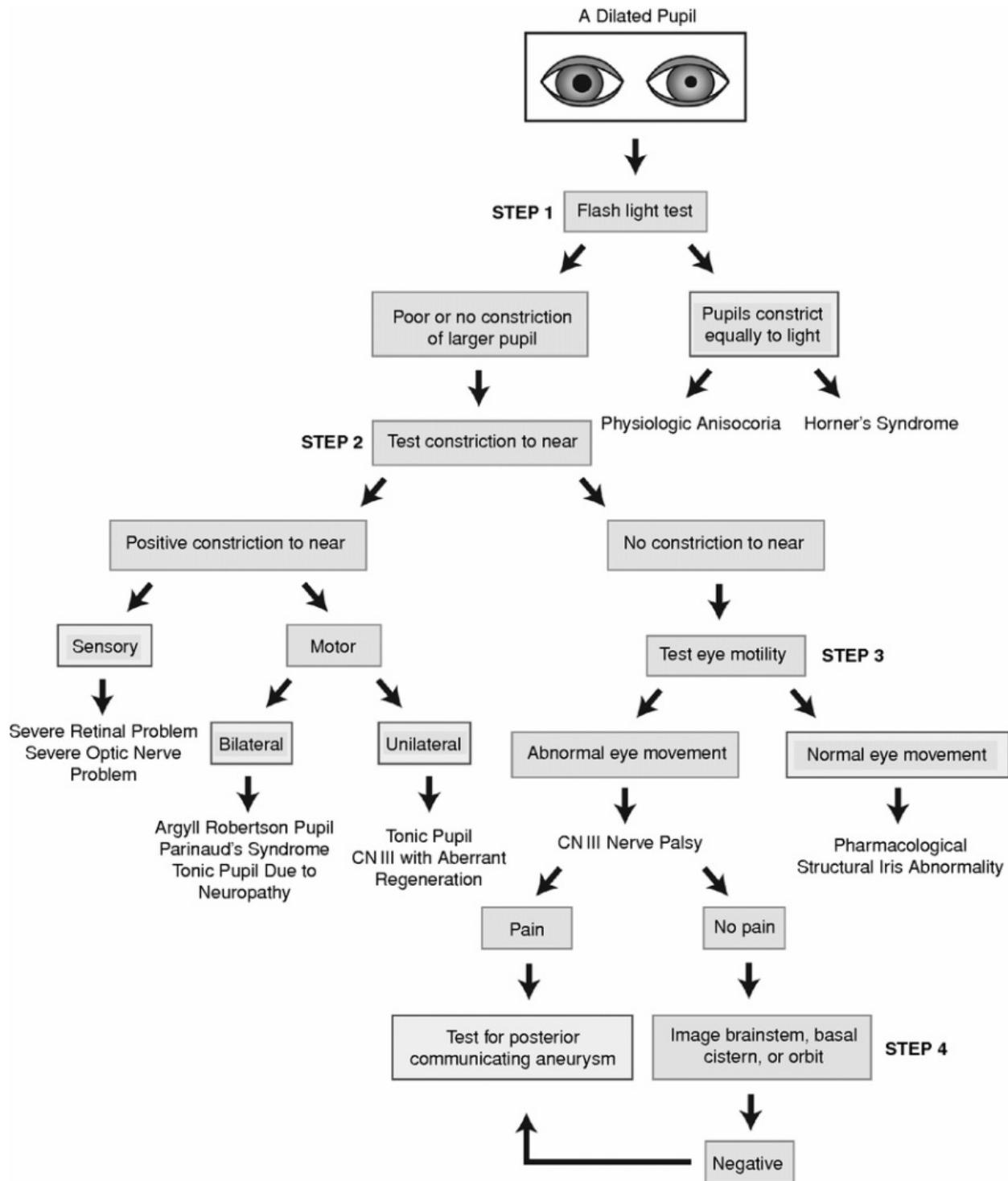
## **Pharmacologic assessment of the dilated pupil**

Absolute paralysis of pupillary constriction includes both iridoplegia and cycloplegia representing internal ophthalmoplegia as seen with compressive lesions of CN III. The internal ophthalmoplegia is due to transmission blockade and pharmacologic dilation of the pupil is due to end-organ iris receptor blockade.

Pharmacologic assessment of the dilated pupil may help to differentiate the lesion site. It is critical in verifying the presence of the CN III dilated pupil due to the urgency of management of the PCoA aneurysm that may be present. Of the intracranial aneurysms, the PCoA aneurysm makes up about 30–35% of the total [11].

Pharmacologic assessment is limited to using varying concentrations of pilocarpine. If one suspects parasympathetic denervation, it is best to instill 1

drop of 0.0625% (1/16%) pilocarpine to each eye and observe in about 45 minutes. Due to hypersensitivity of the cholinergic receptors in the iris sphincter muscle of the tonic pupil patient, only the involved eye with the dilated pupil will constrict (see [Figure 62.6](#)).



**Figure 62.6** Stepwise approach to the patient with an isolated dilated pupil.

When the pupil does not constrict to the dilute solution of pilocarpine (0.0625%), then 1% pilocarpine is instilled in each eye. In patients with a dilated

pupil from a compressive lesion of CN III, the dilated pupil will constrict, as the iris receptors are intact. This alerts the physician to take appropriate action to exclude the presence of a PCoA aneurysm.

Those patients whose pupils do not constrict even to the 1% pilocarpine are deemed to have a pharmacologically dilated pupil (the pupil is dilated and does not constrict to either light or to near reflex), besides the exposure to *Datura* species (such as Jimson weed) used as a hallucinogen and causing bilateral dilated pupils not constricting to 1% pilocarpine. Most other exposures occur with prescribed medications.

With the increasing medical use of botulinum toxin for treating various neurologic processes one needs to be aware that in nearly 50% of cases of systemic botulism there is impairment of the release of Ach from the distal short ciliary nerve terminals, resulting in a bilateral dilated pupil [2]. Because the botulinum toxin acts presynaptically, the pupil will constrict to 1% pilocarpine differently from most other toxic dilated pupils.

Healthcare workers with access to parasympatholytic agents or the traveler who utilizes transdermal scopolamine patches to combat nausea can present with a pharmacologically dilated pupil. Also, contamination while using topical glycopyrrolate cream for treating axillary hyperhidrosis can dilate the affected pupil [2]. In the hospital setting direct exposure to nebulized anticholinergic agents such as ipatropium used in the intensive care unit (ICU) when treating patients with bronchodilators can also produce a dilated pupil that will not constrict to 1% pilocarpine testing [2]. The appropriate management in these cases is observation.

[Figure 62.6](#) shows the stepwise assessment of the dilated pupil, while [Table 62.2](#) shows the testing characteristic of patients that present with a dilated pupil secondary to CN III palsy, tonic pupil, and pharmacologic dilation.

**Table 62.2 Testing characteristics of the dilated pupil.**

|            | <b>CN III palsy</b>   | <b>Parasympathetic denervation:<br/>tonic pupil</b> | <b>Pharmacologic pupil</b> |
|------------|-----------------------|-----------------------------------------------------|----------------------------|
| Anisocoria | Greatest in the light | Greatest in the light                               | Greatest in the light      |

|                                                 |                                                                                                                                 |                                                                       |      |
|-------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------|------|
| Response to light                               | Minimal to none (internal ophthalmoplegia)                                                                                      | Minimal to tonic constriction<br>Vermiform movement at the iris frill | None |
| Response to near convergence                    | None                                                                                                                            | Tonic constriction (with tonic recovery)                              | None |
| Motility restriction                            | Associated with underaction of the medial, superior, inferior, inferior oblique, and levator muscles (external ophthalmoplegia) | None                                                                  | None |
| Response to pharmacologic (pilocarpine) testing | Constricts to 1% pilocarpine but not to 0.0625% (1/16%) unless very longstanding                                                | Hypersensitive; constricts to diluted 0.0625% (1/16%) pilocarpine     | None |

---

## Case vignette

A 20-year-old female with a 2-day history of throbbing headaches states that she has noted her right pupil to be dilated for several hours with no other symptoms reported.

The patient states that she recalls this pupil change sometimes, and usually when she has a bad headache, for the past 3 years. Exam showed right pupil larger than left by 1 mm in light and dark with normal pupillary reactions and no ptosis or motility disorder. The eye exam was otherwise unremarkable.

This case represents the syndrome of episodic unilateral mydriasis

characterized as:

- Brief episodic unilateral mydriasis seen in otherwise young healthy females.
- Periorbital discomfort/headache.
- Sometimes there is impaired accommodation, but this is rare.
- Sometimes associated with migraine [12].
- Probably comprises a heterogeneous group of conditions that result in:
  - Parasympathetic insufficiency of the iris sphincter [13] in which case the pupil may be larger in the light and more equal in the dark. This is unlikely in migraine.
  - Sympathetic hyperactivity and discharge affecting the iris dilator [14].

The differential diagnosis includes simple anisocoria [6] and tadpole pupil [4] in which there is transient pupillary distortion coupled with segmental iris dilator spasm, which is benign.

## References

1. Lee AG, Taber KH, Hayman A *et al.* A guide to the isolated dilated pupil. *Arch Fam Med* 1997; 6:385–8.
2. Moeller JJ, Maxner CE. The dilated pupil: an update. *Curr Neurol Neurosci Rep* 2007; 7:417–22.
3. Weinstein JM. The pupil. In Slamovits TL, Burde R, Eds. *Volume 6: Neuro-Ophthalmology. Textbook of Ophthalmology*. St Louis, MO: Mosby Year Book, 1994.
4. Thompson HS, Zackon DH, Czarnecki JSC. Tadpole-shaped pupils caused by segmental spasm of the iris dilator muscle. *Am J Ophthalmol* 1983; 96:467.
5. Roarty JD, Keltner JL. Normal pupil size and anisocoria in newborn infants. *Arch Ophthalmol* 1996; 108:94.
6. Lam BL, Thompson HS, Corbett JJ. The prevalence of simple anisocoria. *Am J Ophthalmol* 1987; 104:69.
7. Lee A, Tang R, Schiffman JS, Hayman LA. *Parasympathetic Supply to Iris*. Smart Charts LLC, 1995.
8. Kupersmith MJ, Heller G, Cox TA. Magnetic resonance angiography and

- clinical evaluation of third nerve palsies and posterior communicating artery aneurysms. *J Neurosurg* 2006; 105:228–34.
9. Bioussé V, Newman, NJ. Third nerve palsies. *Semin Neurol* 2000; 20:55–74.
  10. Keane JR. Third nerve palsy: analysis of 1400 personally-examined inpatients. *Can J Neurol Sci* 2010; 37:662–70.
  11. Beck J, Rohde S, Berkefeld J, Seifert V, Raabe A. Size and location of ruptured and unruptured intracranial aneurysms measured by 3-dimensional rotational angiography. *Surg Neurol* 2006; 65:18–25.
  12. Woods D, O'Connor PS, Fleming R. Episodic unilateral midriasis and migraine. *Am J Ophthalmol* 1984; 98:229.
  13. Edelson RN, Levy DE. Transient benign unilateral pupillary dilation in young adults. *Arch Neurol* 1974; 31:12.
  14. Jacobson DM. Benign episodic unilateral midriasis – clinical characteristics. *Ophthalmology* 1995; 102:1623.

# **Chapter 63 Respiratory difficulties, neurologic causes**

---

Wan-Tsu W. Chang and Paul A. Nyquist *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

## **Introduction**

Respiratory failure is a syndrome in which the respiratory system fails in one or both of its gas exchange functions: oxygenation and carbon dioxide elimination. The respiratory system consists of the lungs and the pump that ventilates the lungs. Failure of the lungs results in failure in gas exchange, manifested by hypoxemia. Failure of the pump results in failure in ventilation, manifested by hypercapnea. Ventilation involves the respiratory muscles moving the chest wall, the respiratory drive of the central nervous system, and the pathways of spinal and peripheral nerves that connect the respiratory control centers with the respiratory muscles.

Respirations require a pressure gradient to generate flow. Spontaneous respirations are achieved by a negative intrathoracic pressure created by the actions of the respiratory muscles for inspiration, followed by their elastic recoil for passive expiration. The main muscle that generates this inspiratory pressure is the diaphragm, innervated by the phrenic nerves. The external intercostal muscles and the accessory muscles sternocleidomastoids and scalenes provide additional inspiratory effort especially during respiratory distress. Active expiration, such as with exercise, is achieved by contraction of the abdominal wall muscles and the internal intercostal muscles.

Neural control of respiration involves both conscious and automatic components. Automatic respiration is controlled by respiratory centers located in the medulla and pons. The main respiratory center is in the floor of the fourth ventricle, with the dorsal respiratory group controlling inspiration and the ventral respiratory group controlling expiration. The pontine respiratory group is also comprised of inspiratory and expiratory neurons, however, with reciprocal connections with the medulla, allowing for smooth transitions between

inspiration and expiration. Lumsden performed a series of transection experiments in 1923 where he showed that removal of the upper pons resulted in a slower breathing rate and an increase in tidal volume, whereas removal of the lower pons resulted in a variable, gasping breathing pattern. Breathing is also under voluntary control from the cerebral cortex by direct fibers in the corticospinal tract.

While the basic rhythm of breathing is established by the respiratory control centers, it is regulated by input from central and peripheral chemoreceptors. Central chemoreceptors in the medulla monitor the pH associated with CO<sub>2</sub> levels within the cerebrospinal fluid in the fourth ventricle. These chemoreceptors synapse directly with the respiratory centers. Peripheral chemoreceptors are located in the carotid bodies at the bifurcation of the common carotid arteries and the aortic bodies within the aortic arch. These chemoreceptors monitor the pCO<sub>2</sub>, pH, and pO<sub>2</sub> of arterial blood while relaying the information to the respiratory centers via the vagus and glossopharyngeal nerves. An increase in the pCO<sub>2</sub> in the blood leads to an increase in hydrogen ions in the cerebrospinal fluid, thereby decreasing the pH. This stimulates the central chemoreceptors which in turn send more nerve impulses to the respiratory centers, resulting in an increased respiratory rate and depth, increasing the amount of CO<sub>2</sub> elimination. A similar response is seen by the peripheral chemoreceptors. The peripheral chemoreceptors also respond to a drop in arterial pO<sub>2</sub> below 60 mmHg, stimulating the respiratory centers to increase ventilation in an attempt to improve oxygenation. Hypercapnia is a more sensitive respiratory stimulus than hypoxemia in most people, except those who have compensated for chronic CO<sub>2</sub> retention such as in chronic obstructive pulmonary disease (COPD) .

**Table 63.1 Differential diagnosis of neurologic causes of respiratory failure.**

| Location of neurologic disease | Respiratory signs and symptoms                           | Etiology of disease                        |
|--------------------------------|----------------------------------------------------------|--------------------------------------------|
| Bilateral hemispheres          | Cheyne–Stokes respiration (cyclic crescendo–decrescendo) | Stroke<br>Trauma<br>Infection/inflammation |

|                                  |                                                                                         |                                                                                           |
|----------------------------------|-----------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------|
|                                  | pattern of respiratory frequency and tidal volume with periods of apnea)                | Toxic/metabolic                                                                           |
| Lower tegmentum of pons          | Apneustic breathing (prolonged inspiratory pause)                                       | Stroke<br>Trauma<br>Infection/inflammation<br>Neoplasm<br>Increased intracranial pressure |
| Lower pons or upper medulla      | Cluster breathing (irregular quick breaths regularly separated by long pauses)          | Stroke<br>Trauma<br>Infection/inflammation<br>Neoplasm<br>Increased intracranial pressure |
| Medulla                          | Ataxic breathing (irregularly timed breaths with variable tidal volumes)                | Stroke<br>Trauma<br>Infection/inflammation<br>Neoplasm<br>Increased intracranial pressure |
| Ventrolateral high cervical cord | Ondine's curse (impaired autonomic control of ventilation but intact voluntary control) | Congenital<br>Stroke<br>Trauma<br>Infection/inflammation<br>Neoplasm                      |
| C3–C5 myelopathy                 | Diaphragmatic weakness (paradoxical abdominal breathing)                                | Stroke<br>Trauma<br>Infection/inflammation<br>Neoplasm                                    |
| T1–T12 myelopathy                | Intercostal muscle weakness (limited chest                                              | Stroke<br>Trauma                                                                          |

|                           |                                                                               |                                                        |
|---------------------------|-------------------------------------------------------------------------------|--------------------------------------------------------|
|                           | excursion)                                                                    | Infection/inflammation<br>Neoplasm                     |
| L1–L5 myelopathy          | Abdominal wall muscle weakness (limited forced expiration)                    | Stroke<br>Trauma<br>Infection/inflammation<br>Neoplasm |
| Motor neurons             | Disordered breathing<br>Respiratory muscle weakness<br>Oropharyngeal weakness | Degeneration                                           |
| Peripheral polyneuropathy | Respiratory muscle weakness<br>Oropharyngeal weakness                         | Infection/inflammation<br>Neoplasm<br>Toxic            |
| Neuromuscular junction    | Respiratory muscle weakness<br>Oropharyngeal weakness                         | Autoimmune<br>Infection<br>Toxic                       |
| Myopathy                  | Respiratory muscle weakness<br>Oropharyngeal weakness                         | Infection/inflammation<br>Toxic/metabolic              |

---

Neurologic causes of respiratory failure are often due to dysregulation of the respiratory drive or consequences of neurologic injury on the respiratory muscles. Cortical and subcortical injuries result in alterations of breathing pattern such as in Cheyne–Stokes respiration. Brainstem injuries with damage to the respiratory centers result in apneustic, cluster, or ataxic breathing. Sedatives, hypnotics, and opiates depress the respiratory drive. Peripheral nerve disorders such as Guillain–Barré syndrome and myasthenia gravis cause respiratory muscle weakness while high cervical cord injuries lead to respiratory muscle paralysis. Acute neurologic injuries can also be associated with myocardial stunning resulting in acute cardiogenic shock and acute pulmonary edema leading to hypoxemic respiratory failure.

**Table 63.2 Examples of neurologic causes and clinical features of**

**respiratory failure.**

---

| Etiology of disease   | Examples of disease                                                   | Clinical features                                                                                                                                                            |
|-----------------------|-----------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Structural/congenital | Congenital central hypoventilation syndrome ( <i>PHOX2B</i> mutation) | Neonatal onset<br>Hypoventilation with nearly absent respiratory response to hypoxemia and hypercapnea during sleep<br>Can be associated with global autonomic dysregulation |
| Toxic                 | Opioid toxicity                                                       | Central nervous system (CNS) depression, respiratory depression, pupillary miosis<br>May respond to naloxone                                                                 |
|                       | Sedative-hypnotic toxicity                                            | CNS depression, respiratory depression<br>May respond to flumazenil if solely benzodiazepine toxicity                                                                        |
|                       | Alcohol intoxication                                                  | CNS depression, respiratory depression                                                                                                                                       |

Hyperventilation with metabolic acidosis can be seen with ethylene glycol toxicity

#### Anesthetics

CNS depression, respiratory depression

#### Carbon monoxide toxicity

Malaise, headache, confusion, stupor, coma  
Symptoms may not correlate with HbCO levels

#### Organophosphates

Nicotinic effects: weakness, fasciculations, paralysis  
CNS effects: seizures, CNS depression  
Muscarinic effects: diarrhea, diaphoresis, urination, miosis, bronchorrhea, bronchospasm, bradycardia, emesis, lacrimation, salivation

#### Infectious/post-infectious

#### Meningitis /encephalitis

CNS depression, respiratory depression from increased intracranial pressure

|                  |                |                                                                                                                                          |
|------------------|----------------|------------------------------------------------------------------------------------------------------------------------------------------|
|                  |                | pressure,<br>hydrocephalus, or<br>seizures<br>Oropharyngeal<br>muscle weakness<br>from cranial<br>neuropathies                           |
|                  | Tick paralysis | Ascending<br>weakness<br>Neurotoxin from<br>tick saliva                                                                                  |
|                  | Botulism       | Descending<br>weakness<br>Associated with<br>autonomic<br>dysregulation<br>Neurotoxin from<br><i>Clostridium</i><br>botulinum            |
|                  | Tetanus        | Periods of apnea<br>from spasms and<br>rigidity of<br>respiratory muscles<br>Wound infection<br>from <i>Clostridium</i><br><i>tetani</i> |
| Pressure effects | Herniation     | Progression from<br>apneustic to ataxic<br>breathing due to<br>brainstem<br>compression                                                  |
| Psychiatric      | Breath holding | Episodic apnea in<br>children<br>precipitated by fear,<br>anger, frustration,                                                            |

|                           |                                   |                                                                                                                                                                               |
|---------------------------|-----------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|                           |                                   | or pain                                                                                                                                                                       |
| Inflammatory              | Myasthenia gravis                 | Respiratory muscle weakness,<br>oropharyngeal muscle weakness<br>Often associated with ocular muscle weakness<br>Symptoms increase with exertion, progress throughout the day |
|                           | Transverse myelitis               | Respiratory muscle weakness from myelopathy                                                                                                                                   |
| Neoplastic/paraneoplastic | Lambert–Eaton myasthenic syndrome | Proximal muscle weakness which may improve after exercise then weaken with sustained activity<br>Most frequently associated with small cell lung cancer                       |
| Degenerative              | Amyotrophic lateral sclerosis     | Upper and lower motor neuron findings<br>Respiratory and oropharyngeal muscle weakness<br>Sleep disturbances                                                                  |
| Vascular                  | Ischemic stroke                   | CNS depression, respiratory                                                                                                                                                   |

|                      |                                     |                                                                                                                                              |
|----------------------|-------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------|
|                      |                                     | depression from<br>brainstem infarct                                                                                                         |
|                      | Hemorrhagic<br>stroke               | CNS depression,<br>respiratory<br>depression from<br>mass effect                                                                             |
|                      | Cerebral venous<br>sinus thrombosis | CNS depression,<br>respiratory<br>depression from<br>increased<br>intracranial<br>pressure                                                   |
| Metabolic /endocrine | Hypokalemia                         | Muscle weakness,<br>hyporeflexia<br>Can present with<br>periodic paralysis                                                                   |
|                      | Hyperkalemia                        | Muscle weakness<br>Cardiac<br>arrhythmias                                                                                                    |
|                      | Hypomagnesemia                      | Muscle weakness,<br>tremors,<br>hyperreflexia,<br>tetany<br>Often associated<br>with hypokalemia,<br>hypocalcemia, and<br>metabolic acidosis |
|                      | Hypermagnesemia                     | Muscle weakness,<br>hyporeflexia, CNS<br>depression,<br>respiratory<br>depression<br>Most cases<br><i>iatrogenic</i>                         |

.....

|                |                                                                                                                                       |            |
|----------------|---------------------------------------------------------------------------------------------------------------------------------------|------------|
| Hypocalcemia   | Paresthesias,<br>muscle spasms,<br>seizures<br>Bronchospasms<br>Can be associated<br>with severe<br>hypomagnesemia                    |            |
| Hypercalcemia  | Muscle weakness,<br>hyperreflexia,<br>altered mental<br>status<br>Associated with<br>phosphate and<br>sodium<br>disturbances          |            |
| Uremia         | Malaise, headache,<br>confusion, stupor,<br>coma<br>Associated with<br>edema, electrolyte<br>abnormalities, and<br>metabolic acidosis |            |
| Hyperammonemia | Confusion, stupor,<br>coma<br>Associated with<br>asterixis                                                                            |            |
| Myxedema       | CNS depression,<br>respiratory<br>depression, reflexes<br>with slow<br>relaxation phase<br>Hypothermia                                |            |
| Sleep disorder | Central sleep                                                                                                                         | Night-time |

|               |                            |                                                                                                                                                                                                        |
|---------------|----------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|               | apnea                      | awakenings,<br>nocturnal hypoxia,<br>excessive daytime<br>sleepiness<br>Apneic episodes for<br>10 seconds or<br>longer by<br>polysomnography<br>Can have<br>component of<br>obstructive sleep<br>apnea |
| Trauma        | Traumatic brain<br>injury  | CNS depression,<br>respiratory<br>depression from<br>mass effect,<br>hydrocephalus, or<br>seizures                                                                                                     |
|               | Spinal cord injury         | Respiratory muscle<br>weakness from<br>myelopathy                                                                                                                                                      |
| Demyelinating | Guillain–Barré<br>syndrome | Ascending<br>weakness,<br>hyporeflexia<br>Paresthesias,<br>numbness,<br>dysesthesias<br>Can be associated<br>with autonomic<br>dysregulation                                                           |

---

## Case vignette

A 70-year-old male with poorly controlled hypertension collapses in public. He

is unresponsive, with irregular respirations, pinpoint pupils, and BP 250/110 mmHg. The emergency services administer naloxone without improvement of the patient's mental or respiratory status. The patient is intubated for airway protection and brought to the hospital. On admission, the patient is GCS 4T with extensor posturing, pinpoint pupils, and absent oculocephalic reflex. Non-contrast head computerized tomography (CT) shows a pontine hemorrhage with effacement of the fourth ventricle and associated hydrocephalus. Extraventricular drainage is performed for his hydrocephalus. His hypertension is aggressively treated to maintain a SBP < 160 mmHg. Care is taken to avoid hypercapnea or hypoxia to prevent secondary insults. Despite this management, the patient continues to have a poor neurologic exam. Given his poor prognosis due to the location of his intra-cerebral hemorrhage, his family decides to withdraw care.

In this scenario, the patient was found unresponsive with irregular respirations, pinpoint pupils, and hypertension. Often, patients who are unresponsive with irregular respirations and pinpoint pupils are presumed to have an opioid overdose, thus treated with naloxone. However, this patient did not have any improvement of his mental or respiratory status with naloxone. His hypertension along with his decreased mental status may suggest a hypertensive encephalopathy. However, he had an abrupt onset of symptoms that led to his collapse in public rather than a progression of symptoms over 24–48 hours typically seen with hypertensive encephalopathy. When considering an acute neurologic change associated with abnormal respirations and pupillary findings, this localizes the pathology to the brainstem due to involvement of both the reticular activating system as well as the respiratory centers. In this scenario, the patient sustained a pontine hemorrhage likely due to his poorly controlled hypertension, though other etiologies including vascular malformations and tumors cannot be excluded. Due to his decreased mental status as well as respiratory compromise, this patient required intubation for airway protection and ineffective ventilation. Even with treatment of his hydrocephalus with extraventricular drainage, thereby relieving associated intracranial hypertension, the patient may be ventilator dependent due to a predisposition for hypercapneic respiratory failure resulting from damage to the respiratory centers and central chemoreceptors.

## Further reading list

Cherniack NS, Longobardo G, Evangelista CJ. Causes of Cheyne-Stokes

- respiration. *Neurocrit Care* 2005; 3:271–9.
- Laghl F, Tobin MJ. Disorders of the respiratory muscles. *Am J Respir Crit Care Med* 2003; 168:10–48.
- Lumsden T. The regulation of respiration. *J Physiol* 1923; 58:81–91.
- Nyquist P, Mirski MA. Neurologic injury and mechanical ventilation. *Contemporary Critical Care* 2007; 5:1–11.
- Polkey MI, Lyall RA, Moxham J, Leigh PN. Respiratory aspects of neurological disease. *J Neurol Neurosurg Psychiatry* 1999; 66:5–15.
- Roussos C, Koutsoukou A. Respiratory failure. *Eur Respir J* 2003;Suppl. 47:3s–14s.
- Wijdicks EF. Short of breath, short of air, short of mechanics. *Pract Neurol* 2002; 2:208–13.

## 64 Retardation, mental

---

Tal Gilboa, Varda Gross-Tsur, Rolla Nuoman, and Alan B. Ettinger  
*Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Mental retardation (MR) is a disorder appearing in childhood (< 18 years), characterized by impaired cognitive function (measured by Intelligence Quotient (IQ) – [Table 64.1](#)) and deficits in two or more adaptive behaviors (communication, self-help skills, interpersonal skill, etc.). Due to improper non-professional use of the term MR, the term intellectual disability (ID) is gradually replacing it. The current definition of ID by the World Health Organization is “... a significantly reduced ability to understand new or complex information and to learn and apply new skills (impaired intelligence). This results in a reduced ability to cope independently (impaired social functioning), and begins before adulthood, with a lasting effect on development.”

**Table 64.1 IQ, academic and functioning potential in mental retardation/intellectual disability (MR/ID).**

| MR class | IQ        | Academic potential                     | Functioning level                                 |
|----------|-----------|----------------------------------------|---------------------------------------------------|
| Profound | <<br>20   | None                                   | Completely dependent                              |
| Severe   | 20–<br>34 | Little or no<br>communication<br>skill | May learn some self-help but<br>needs supervision |
| Moderate | 35–       | Minimal,                               | Learn self-hygiene, simple                        |

|            |       |                                                    |                                                                                    |
|------------|-------|----------------------------------------------------|------------------------------------------------------------------------------------|
|            | 49    | speech difficulty                                  | safety skill<br>Live in protected environment, may travel alone to familiar places |
| Mild       | 50–69 | Read, write, calculations as a 9–12-year-old child | Independently cook, use transportation, simple work                                |
| Borderline | 70–84 | Read, write, calculations                          | Independent in society                                                             |

---

MR affects 2–3% of the population, of which 75% have mild forms. Mild and borderline MR is often missed in early life and may become apparent only during the first years of school. Etiology may be determined in 30–50% of children with MR. For most individuals with mild–moderate MR, despite extensive work-up, the etiology often remains unknown. Multiple chromosomal abnormalities and dozens (and possibly hundreds) of single genes are associated with MR; some carry a high mortality rate in the first year of life (and are therefore not mentioned here). MR may be a result of congenital insult or of an acquired one in early life. [Table 64.2](#) lists some of the known etiologies of MR.

## Case vignette

Dan, a 6-year-old male, was born after a spontaneous pregnancy to healthy non-consanguineous parents; birth weight was 3.2 kg, Apgar scores were 9 and 10 in the first and fifth minute respectively. Dan has three older brothers with no developmental disorders and there is no familial history of neurologic problems.

Since birth Dan has had recurrent pyelonephritis, feeding problems, and poor growth. On examination, there was hypotonia, global developmental delay with no communication problem, and although he developed slowly, he continued to gain developmental milestones. A neurologic evaluation at the age of 3 years revealed the following: with the exception of general hypotonia, there were no other motor or cerebellar neurologic findings and head circumference was in the 25th percentile. Electroencephalography (EEG) and brain imaging were normal. A psychological testing at the same age demonstrated an IQ of 55; he attended a rehabilitation kindergarten.

**Table 64.2 Etiologies of mental retardation/intellectual disability (MR/ID).**

| <b>Category</b> | <b>Division</b>                   | <b>Subdivision</b> | <b>Specific entity</b> |
|-----------------|-----------------------------------|--------------------|------------------------|
| Genetic         | Visible chromosomal abnormalities | Trisomy 21         | Down's syndrome        |
|                 |                                   | 47,XXY             | Klinefelter syndrome   |

|                                       |                                                                                                                                                                                                 |                         |
|---------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------|
|                                       | Unbalanced translocations<br>An unbalanced translocation occurs when a child inherits a chromosome with extra or missing genetic material from a parent with a balanced translocation           | Translocation Disorders |
| Microscopic chromosomal abnormalities | Copy number variants<br><br>Copy number variation has also associated with autism, schizophrenia, and idiopathic learning disability – clinical phenotype varies depending on the specific CNVs |                         |
| Microdeletions                        | Di-George syndrome                                                                                                                                                                              |                         |
|                                       | Prader–Willi syndrome                                                                                                                                                                           |                         |
|                                       | Angelman syndrome                                                                                                                                                                               |                         |

William's syndrome

|                       |                            |                          |
|-----------------------|----------------------------|--------------------------|
|                       |                            | Wolf–Hirschhorn syndrome |
| Single gene disorders | Tuberous sclerosis complex |                          |
|                       | Fragile X – FMR            |                          |
|                       |                            | Rett syndrome – MECP2    |
|                       |                            | CDKL5                    |
| Toxic/drug exposure   | Congenital                 | Fetal alcohol syndrome   |

Drugs exposure i  
utero

Acquired

Lead poisoning

Brain radiation

Infection

Congenital

Cytomegalovirus

Rubella

Toxoplasmosis

|                                   |                            |                      |                                |
|-----------------------------------|----------------------------|----------------------|--------------------------------|
|                                   | Acquired                   | Encephalitis         | Multiple viruses               |
|                                   |                            | Meningitis           | Multiple bacteria              |
| Inborn<br>errors of<br>metabolism | Organic<br>acidemia        |                      | Phenylketonuria -<br>PKU       |
|                                   | Aminoaciduria              |                      | Non-ketotic<br>hyperglycinemia |
|                                   | Mitochondrial<br>disorders | Maternally inherited | Leigh syndrome                 |

MELAS syndrom  
(mitochondrial  
encephalomyopathy,  
lactic acidosis, ar-  
stroke-like episoc

Other respiratory  
chain complex  
disorders

Autosomal inheritance

Leigh syndrome

MELAS

Other respiratory  
chain complex  
disorders

X-linked

Pyruvate  
dehydrogenase  
complex deficien

Peroxisomal  
disorders

Adrenoleukodyst  
(ALD)

Lysosomal

Sphingolipids

Gaucher type II

storage

Niemann--Pick type C

Metachromatic  
leukodystrophy –  
Juvenile form

Krabbe – late onset

Gangliosides

Tay Sachs/GM2  
gangliosidosis –  
Juvenile form

|                                |            |                        |                              |
|--------------------------------|------------|------------------------|------------------------------|
|                                |            | Other leukodystrophies | Alexander                    |
|                                |            | Mucopolysaccharidosis  | Hunter                       |
|                                |            |                        | Hurler                       |
|                                | Urea cycle |                        | Citrullinemia                |
| Metabolic<br>– non-<br>genetic | Hormonal   | Congenital             | Congenital<br>hypothyroidism |
|                                |            |                        | Menke's disease              |
|                                |            |                        | Pyridoxine<br>dependency     |

Ischemia

Hypoxic ischemic  
encephalopathy (

Nutritional

Deficiency

Thiamine

Epileptic

0–2 years

Ohtahara syndrome

Iodine (previously  
known as cretinism)

Early myoclonic  
epilepsy

West syndrome

2–6 years

Lennox–Gestaut  
syndrome

Electrical status  
epilepticus in sleep

> 6 years

Progressive myoclonic  
epilepsies

Psychiatric

Childhood  
disintegrative dis

Brain  
tumor

Neurofibromatos  
(NF)

Vascular

Multiple ischemic

Sturge–Weber  
syndrome

At 4 years a comprehensive metabolic work-up and muscle biopsy revealed that Dan suffers from complex 4 mitochondrial respiratory chain deficiency. At the age of 5 years, on a routine neurologic outpatient clinic, the mother reported that during the last 2 years Dan hadn't progressed as expected. She noted that even when he slept well, he was very tired, less responsive, and didn't concentrate. The physician attributed the symptoms to the mitochondrial disorder. A month later, the mother reported further deterioration manifested by communication regression. At that point the neurologist recommended performing an overnight EEG. The sleep recording showed an epileptic encephalopathy characterized by continuous spike waves, or electrical status epilepticus in sleep, and spike and waves were seen during 20–30% of his wakefulness. Treatment with steroids was started; 3 months later there were signs of developmental progress and resolution of the abnormal communication.

## Further reading list

- Abrams L, Cronister A, Brown WT *et al.* Newborn, carrier, and early childhood screening recommendations for fragile X. *Pediatrics* 2012; 130:1126–35.
- Aggarwal S, Bogula VR, Mandal K, Kumar R, Phadke SR. Aetiologic spectrum of mental retardation & developmental delay in India. *Indian J Med Res* 2012; 136:436–44.
- Daily DK, Ardinger HH, Holmes GE. Identification and evaluation of mental retardation. *Am Fam Physician* 2000; 61:1059–67, 1070.
- Donaldson M, Jones J. Optimising outcome in congenital hypothyroidism; current opinions on best practice in initial assessment and subsequent management. *J Clin Res Pediatr Endocrinol* 2013; 5 Suppl. 1:13–22.
- Ellison JW, Rosenfeld JA, Shaffer LG. Genetic basis of intellectual disability. *Annu Rev Med* 2013; 64:441–50.
- Kenneth F, Ashwal S, Swaiman KF, Ferriero DM, Schor NF. *Swaiman's Pediatric Neurology: Principles & Practice*, 5th edn. Philadelphia, PA: Elsevier.
- Khan S, Al Baradie R. Epileptic encephalopathies: an overview. *Epilepsy Res*

*Treat* 2012; 2012:403592.

Kohlschütter A, Eichler F. Childhood leukodystrophies: a clinical perspective. *Expert Rev Neurother* 2011; 11:1485–96.

Patel KP, O'Brien TW, Subramony SH, Shuster J, Stacpoole PW. The spectrum of pyruvate dehydrogenase complex deficiency: clinical, biochemical and genetic features in 371 patients. *Mol Genet Metab* 2012; 105:34–43.

Shevell M, Ashwal S, Donley D *et al.* Quality Standards Subcommittee of the American Academy of Neurology; Practice Committee of the Child Neurology Society. Practice parameter: evaluation of the child with global developmental delay: report of the Quality Standards Subcommittee of the American Academy of Neurology and The Practice Committee of the Child Neurology Society. *Neurology* 2003; 60:367–80.

Toriello HV. Approach to the genetic evaluation of the child with autism. *Pediatr Clin North Am* 2012; 59:113–28.

van Karnebeek CD, Houben RF, Lafek M, Giannasi W, Stockler S. The treatable intellectual disability APP: [www.treatable-id.org](http://www.treatable-id.org): a digital tool to enhance diagnosis and care for rare diseases. *Orphanet J Rare Dis* 2012; 23:7–47.

van Karnebeek CD, Stockler S. Treatable inborn errors of metabolism causing intellectual disability: a systematic literature review. *Mol Genet Metab* 2012; 105:368–81.

World Health Organization: Regional Office for Europe. 2010. Definition: intellectual disability. <http://www.euro.who.int/en/what-we-do/health-topics/noncommunicable-diseases/mental-health/news/news/2010/15/childrens-right-to-family-life/definition-intellectual-disability>

## 65 Seizure

---

David J. Anschel *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

A seizure relates to an abnormal electrical discharge in the brain with resultant clinical findings. The vast majority of seizures are self-limited with a full recovery. When a patient presents with a seizure, the evaluation should be focused on finding the underlying cause for the seizure and assessing the risk for a recurrent seizure or other sequelae from the underlying cause.

Many seizures will be found to be provoked by circumstances generally external to the central nervous system (CNS) or only transiently acting upon the CNS. Every effort must be made to determine if any of these factors exist and a plan made to address any potential etiology. Other seizures will be caused by an apparent brain lesion or be idiopathic in nature. The repetitive recurrence of these “unprovoked” seizures is known as epilepsy.

### Case vignette

A 38-year-old female was sitting at the dinner table with her husband and two young children. She recalls eating a dinner roll when she had a strange sensation followed by an involuntary contraction of her left hand. The sensation rapidly went up her arm and then she lost consciousness. The next thing she recalls is being on the ground with the emergency medical personnel around her. Her husband says that the stiffening spread from her left arm to her face, then her legs extended, she let out a scream and her whole body was shaking. The shaking subsided over approximately 2 minutes and she gradually became more alert over the next 20 minutes.

The history is very typical for a partial onset seizure with secondary generalization. When evaluating a patient with the history of a paroxysm with neurologic manifestations the majority will fall into one of three diagnostic

categories: stroke (transient ischemic attack – TIA), seizure, or migraine. A common distinguishing feature of symptoms between these diagnoses is the time course of symptom evolution. A stroke/TIA will typically have an instantaneous onset of symptoms, *e.g.* a patient may say, “my left body suddenly became heavy.” A focal onset seizure will usually have an evolution of symptoms over a period of between one and several seconds. A migraine aura will evolve over minutes to tens of minutes and is usually followed by a throbbing headache. Other features which commonly distinguish these diagnoses are that stroke/TIA symptoms tend to be negative (*e.g.* loss of vision, loss of strength/sensation); while migraine and seizures are initially positive symptoms (*e.g.* visual hallucination, abnormal sensation, motor seizure), rarely followed by negative symptoms (*i.e.* Todd's paralysis or complicated migraine).

Unrelated to this case but worthwhile noting in the differential diagnosis of non-epileptic events resembling seizures are psychogenic causes. Any features atypical for a neurologic pattern should arouse the suspicion of a psychological cause. In such cases, there may be evidence of primary or secondary gain along with psychological risk factors such as a history of physical or sexual abuse.

The other mimickers of seizures described in [Table 65.1](#) are unlikely to be playing a role in this case.

**Table 65.1 Etiologies and differential diagnosis of seizures.**

| Classification | Type                                              | Subtype | Sp |
|----------------|---------------------------------------------------|---------|----|
| Provoked       | Toxic (drugs,<br>toxins,<br>withdrawal<br>states) |         |    |
|                | Prescribed<br>medications                         |         |    |

## Metabolic

Non-ketotic  
hyperglycemia

Infective/post-  
infective

Viral (HSV, HIV  
insect/tickborne  
viruses, others)

Bacterial  
meningitis/Ence

Fungal/parasitic/

Inflammatory Behçet's disease

Celiac disease

Infantile spasms  
(West syndrome)

Landau–Kleffner  
~~~~~

synrome/continuous  
spike waves during  
sleep

Limbic encephalitis

Paraneoplastic

Non-paraneoplas

Systemic lupus  
erythematosus

Hashimoto's  
encephalopathy

Posterior  
leukoencephalopathy

Rasmussen  
encephalitis

Sarcoidosis

Neoplastic

Brain hypoxia

Brain  
hemorrhage

Febrile

Trauma

Unprovoked  
and repetitive  
(epilepsy)

Focal onset

Infective/post-  
infective

Neoplastic

Heredofamilial

Autosomal domi  
frontal lobe epile

Autosomal domi  
temporal lobe ep

## **temporal zone ep**

Benign epilepsy  
childhood with c  
temporal spikes

Benign familial  
infantile seizures

Benign familial  
neonatal infantile  
seizures

Familial partial  
epilepsy with vari  
foci

Familial tempora  
epilepsy with feb  
seizures with dig  
inheritance

Malformations o  
cortical developr

Neurofibromatos

Partial epilepsy v  
pericentral spike

Rolandic epileps  
paroxysmal exerc  
induced dystonia  
writer's cramp

Rolandic epileps  
oral and speech  
dyspraxia

Tuberous scleros  
complex

Mesial temporal  
sclerosis

Trauma

Vascular

Stroke

Vascular malform

Generalized  
onset

Secondary  
symptomatic  
generalized

Primary generalized

Absence epilepsy

Adenyl succinate  
deficiency

Alpers' disease

Angelman syndrome

Benign febrile nocturnal convulsions

Benign familial infantile convulsions and choreoathetosis

Biotinidase deficiency

Deficiency of sepiapterin biosynthesis

Folinic acid-responsive seizures

GABA transaminase deficiency

GAMT deficiency

Generalized epilepsy with febrile seizures +/autosomal dominant epilepsy with fetal seizures/Dravet syndrome

GLUT1 deficiency

Juvenile myoclonic epilepsy

Late infantile neurodegeneration ceroid lipofuscinosis

Menke's disease

Molybdenum cofactor deficiency and/or sulfite oxidase deficiency

Non-ketotic hyperglycinemia

Progressive myoclonic epilepsy

epilepsies

Pyridoxal 5'-  
phosphate-depen  
epilepsy

Pyridoxine-depe  
seizures

Ring chromosom  
syndrome

Neurologic

Ischemic  
stroke/TIA

Migraine

Movement disorder

Sleep disorder

Transient global amnesia

Vertigo

Non-epileptic and potentially mistaken for seizures      Psychological      Factitious disorder

Malingering

Conversion disorder

Panic attacks

Hyperventilation spells

Night terrors

Somatization

disorder

Cardiac

Syncope

Cardiac arrhythmias

Hypoglycemia

Hypoxia

---

ACE, angiotensin-converting enzyme; ACTH, adrenocorticotrophic hormone; AMPA,  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CSF, cerebrospinal fluid; CT, computerized tomography; EEG, electroencephalography; GABA, gamma-amino butyric acid; GAD, glutamic acid decarboxylase; GLUT1, glucose transporter deficiency syndrome; HSV, herpes simplex virus; MRI, magnetic resonance imaging; SLE, systemic lupus erythematosus; TB, tuberculosis; TIA, transient ischemic attack.

## Further reading list

Bhalla D, Godet B, Druet-Cabanac M, Preux PM. Etiologies of epilepsy: a comprehensive review. *Expert Rev Neurother* 2011; 11: 861–76.

Engel J, Pedley TA, Aicardi J *et al.*, Eds. *Epilepsy: A Comprehensive Textbook*, 2nd edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2007.

## 66 Sensory deficits and abnormal sensations

---

Paul W. Brazis *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### Anatomy of the sensory system

The peripheral sensory unit consists of the sensory receptor (each with a characteristic modality and receptive field), its contiguous axon, the cell body in the dorsal root ganglion, the dorsal root, and the axonal terminus in the dorsal horn or dorsal column nuclei (depending on the specific sensory system) [1]. Cutaneous sensory afferent fibers are histologically divided into C-type (small unmyelinated), A-d (small, thinly myelinated), and A-a (myelinated).

The central somatosensory pathways conveying pain, temperature, and soft touch enter the spinal cord via small lateral group fibers which dichotomize into collaterals that ascend and descend one or two levels before synapsing in the dorsal horn. The secondary sensory neurons decussate in the anterior commissure of the spinal cord and then ascend in the contralateral anterolateral funiculi as the *spinothalamic tracts*. Within the spinothalamic tract, the fibers mediating sensation of pain and temperature appear to occupy the dorsolateral part of the anterolateral funiculus and those conveying the sensation of touch are found in the ventromedial part. The fibers in the spinothalamic tract are somatotopically arranged. For example, at the cervical levels, fibers from sacral segments are found most superficially followed by fibers originating at successively more rostral levels. Intraparenchymal lesions of the cord may therefore cause a loss of sensation of pain, temperature, and soft touch below the level of cord damage but with sparing of sacral sensation (i.e. “*sacral sparing*”). The somatotopic arrangement is maintained during the further course of the spinothalamic tract in the medulla, pons, and midbrain, with the tract ending in the thalamus, predominantly in the ventral–posterior–lateral (VPL) nucleus, the posterior complex, and parts of the intralaminar nucleus.

The sensory pathways mediating proprioception, vibratory sensation, deep

pressure, and soft touch enter the white matter of the spinal cord medial to the dorsal horn via a large medial group of sensory fibers that then ascend in the *posterior column* of the spinal cord ipsilateral to their corresponding nerve root and ganglion cells. These fibers give off few collaterals and terminate in the nuclei gracilis and cuneatus in the caudal medulla oblongata. The ascending fibers of the dorsal columns are somatotopically organized. During their ascending course, nerve fibers in the dorsal columns are steadily pushed more medially because fibers entering at succeeding rostral levels intrude between the ascending fibers and the dorsal horn. Therefore, fibers occupying the most medial part of the medial funiculus gracilis in the upper cervical region will belong to the sacral dorsal roots, and then follow the fibers from the lumbar dorsal roots (i.e. the fibers from the lower extremity are found more medially in the dorsal columns). Fibers belonging to the upper extremity are found more laterally in the funiculus cuneatus, close to the dorsal horn, with fibers from the upper cervical roots found more laterally than those from lower cervical roots of the thoracic fibers. Approximately the lower six occupy the lateral part of the funiculus gracilis; the upper six occupy the medial part of the funiculus cuneatus.

The axons of the cells of the nuclei gracilis and cuneatus form the medial lemniscus, which crosses the midline in the medulla. The segmental somatotopic organization present in the dorsal columns and their nuclei is maintained in the medial lemniscus. In the medulla, the fibers of the medial lemniscus, after crossing, occupy a triangular area dorsal to the pyramidal tract. Here, fibers from the gracile nucleus are situated ventrolaterally and those from the cuneate nucleus dorsomedially. This same arrangement is maintained in the pons. Further along the tract, a certain rotation takes place, so that fibers that were originally ventrolateral occupy the lateral position, whereas the originally dorsomedial fibers from the cuneate nucleus are found medially. In this order, the fibers enter the VPL nucleus of the thalamus.

From the thalamus, the sensory impulses are conveyed mainly to the somatosensory areas of the cerebral cortex (e.g. the *postcentral gyrus*). Within the somatosensory cortex, there is a somatotopic organization. For example, in the postcentral gyrus, the calf and foot are represented on the medial surface of the hemisphere, followed by the thigh, abdomen, thorax, shoulder, arm, forearm, hand, digits, and face. Therefore, a parasagittal lesion may cause sensory changes confined to the lower limb.

## **Sensory signs and symptoms**

Sensory symptoms and signs may be positive or negative. Positive symptoms/signs include:

1. Paresthesias – spontaneous sensations occurring without stimulation.
2. Hyperesthesia – exaggerated sensation.
3. Dysesthesia – altered sensation.
4. Allodynia – a painful response to non-noxious stimulation.
5. Hyperpathia – an exaggerated sensation to a painful stimulus.
6. Neuropathic pain – often increased during periods of rest, especially at night.

Hypesthesia is decrease in sensation, whereas anesthesia is complete loss of sensation; both may occasionally be associated with pain (*anesthesia dolorosa* or “sorrowful anesthesia”).

## **Sensory disturbances with peripheral nerve lesions and polyneuropathies**

With the division of a peripheral sensory nerve, all modalities of cutaneous sensibility are lost only over the area exclusively supplied by that nerve (the autonomous zone). For example, with a median nerve impingement at the wrist (carpal tunnel syndrome), a sensory loss will occur on the radial palm, the palmar aspect of the first three-and-a-half fingers, and the dorsal aspect of the terminal phalanges of the second, third, and half of the fourth fingers. This sensory loss is usually most prominent in the appropriate fingertips. The autonomous zone is surrounded by an intermediate zone, which is the area of the nerve's territory overlapped by the sensory supply areas of the adjacent nerves. The full extent (autonomous plus intermediate) of the nerve's distribution constitutes the maximal zone. In general, with peripheral nerve lesions, the area of light touch sensory loss is greater than the area of pinprick sensory loss. Pain and paresthesias may also help in localizing a peripheral nerve lesion, but these subjective sensations frequently radiate beyond the distribution of the damaged nerve (e.g. proximal arm pain may occur with carpal tunnel syndrome). Some patients describe pain that is evoked by non-noxious stimulation of the skin innervated by a damaged nerve (*allodynia*).

*Mononeuropathy multiplex (multifocal mononeuropathy)* refers to the involvement of several isolated nerves. The nerves involved are often widely separated (e.g. right median and left femoral nerve). These multiple neuropathies

result in sensory and motor disturbances that are confined to the affected individual nerves. Mononeuropathy multiplex is usually due to a disseminated vasculitis that affects individual nerves although multiple compressive neuropathies may, for example in a patient with diabetes mellitus or hereditary neuropathy with liability to pressure palsies, have a similar presentation ([Table 66.1](#)).

**Table 66.1 Differential diagnosis of mononeuropathy multiplex.**

---

Vasculitis (e.g. polyarteritis nodosa)

Diabetes mellitus

Sarcoidosis

Infectious

Leprosy

CMV infection

Lyme disease

Human immunodeficiency virus 1 (HIV1) infection

Hepatitis C infection

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)

Multiple compressive neuropathies (e.g. predisposed to by hypothyroidism, diabetes mellitus)

Hereditary neuropathy with liability to pressure palsies

Lymphoma

Sickle cell disease

Severe burns

In *polyneuropathy*, the essential feature is the impairment of function of many peripheral nerves simultaneously, resulting in a symmetric, usually distal, loss of

function. In general, the legs are affected before the arms. Polyneuropathy may be caused by different processes and may be mainly sensory (e.g. amyloidosis, paraneoplastic, leprosy), motor (e.g. Guillain–Barré syndrome, porphyria, lead intoxication), or both sensory and motor. The presence of spontaneous paresthesias is helpful in distinguishing acquired polyneuropathies (occurring in more than 80% of these patients) from inherited polyneuropathies (reported in only 17% of this group). Negative sensory symptoms are more common in inherited than in acquired polyneuropathies.

The loss of sensation in peripheral polyneuropathies may involve all modalities of sensation, but because nerve fibers of a specific caliber may be preferentially involved in the pathologic process, sensory impairment may be restricted to a certain form of sensation (*dissociation of sensory loss*). For example, preferential loss of pain and temperature perception may be seen in polyneuropathies preferentially involving small-diameter nerve fibers conveying pain and temperature sensation (Table 66.2). Conversely, a selective loss of touch pressure, two-point discrimination, and joint position sense (conveyed by larger myelinated fibers) with spared pain and temperature sensibility may occur with predominantly large fiber peripheral polyneuropathies. Proprioceptive impairment may cause ataxia and pseudoathetosis (involuntary movements of the fingers when the hands are outstretched and the eyes are closed). Asymmetric sensory loss involving the limbs, trunk, or face accompanied by disabling sensory ataxia combined with inability to localize the limbs in space should raise the likelihood of a primary disorder of sensory neurons or *sensory polyganglionopathy* (Table 66.3).

**Table 66.2 Differential diagnosis of small fiber sensory neuropathies.**

---

Idiopathic small fiber sensory neuropathy (most common cause)

Amyloidosis (familial or primary)

Diabetes mellitus

Tangier disease

Fabry disease

Leprosy

Hereditary sensory and autonomic neuropathies

Ciguatera intoxication

---

**Table 66.3 *Sensory ataxic neuropathies and neuronopathies.***

---

**Sensory polyganglionopathies (sensory neuronopathies)**

Paraneoplastic  
Sjögren syndrome  
Idiopathic

Inflammatory  
demyelinating

Guillain–Barré syndrome  
Monoclonal gammopathy  
GALOP syndrome (Gait disorder,  
Autoantibody, Late-age, Onset,  
Polyneuropathy)

Infectious/toxic

Tabes dorsalis  
Cisplatin  
Taxol  
Bortezomib  
Vitamin B6 excess

Hereditary  
disorders

Biemond ataxia  
Friedreich ataxia  
Spinocerebellar ataxia (SC4)  
Hereditary sensory ataxia (*SNAX1*)  
Sensory neuropathy with scoliosis

The pattern of sensory and motor deficits in many polyneuropathies (e.g. diabetic polyneuropathy) develops according to axonal length, with sensory changes initially occurring at sites most distal from dorsal root ganglia cells [2]. When the sensory abnormality in the limbs extends proximally to 35–50 cm from the dorsal root ganglia, a region of sensory loss over the anterior torso also develops in accordance with the length of axons traversing the body wall. This sensory abnormality is wider in the lower abdomen and tends to be narrower in the thoracic region because of the longer, more oblique course of the sensory fibers to the lower abdomen and the shorter course of the nerves traveling along the ribs. When nerves 20 to 24 cm in length become involved, a “beanie cap” of sensory change over the scalp vertex occurs owing to the distal involvement of the ophthalmic branches of the trigeminal nerves. In extreme sensory neuropathies, only the shortest (12 cm) nerve fibers are spared, so that there is sensory loss over the entire body except for a band of intact sensation over the posterior midline from the occiput to the sacral region [2].

In some neuropathies (e.g. Tangier disease), the *short* axons are preferentially involved, and hence the sensory loss starts proximally and progresses distally, sometimes to the point where the entire body, except for the hands and regions below the knees, shows sensory impairment.

In other neuropathies, the initial involvement and subsequent progression of clinical deficits may not be determined by the axonal length. For example, in lepromatous leprosy neuropathy, sensory loss occurs initially over the areas of the body having cooler surface temperatures (e.g. the tip of the nose, the malar areas of the cheeks) [3] because the proliferation of *Mycobacterium leprae* is greater in cooler tissues.

## Sensory disturbances with dorsal nerve root lesions

Irritative lesions of a *dorsal root* result in *radicular or root pain*. This pain has three characteristic features:

1. An abrupt, sharp, lancinating, shooting, electric, or burning quality to the pain.
2. Pain well localized and referred to a specific dermatome or myotome.
3. Pain characteristically accentuated or precipitated by maneuvers that cause increased intra-spinal pressure or stretching of the dorsal nerve root, such as

coughing, straining, sneezing, Valsalva maneuver, or spine movements.

Pain is often the first manifestation of a sensory radiculopathy and may be associated with paresthesias or dysesthesias in the area involved. Destructive dorsal root lesions result in hypesthesia or anesthesia that is confined to the specific dermatome involved. Because of the overlap of cutaneous supply by adjacent nerve roots, especially in thoracoabdominal regions, sectioning of a single dorsal root may result in little or no sensory loss. Therefore, the absence of sensory loss does not exclude the possibility of a lesion affecting a single dorsal root. When multiple dorsal root lesions are present, sensory loss is evident with the area of analgesia being larger than the area of anesthesia to light touch.

The spinal roots may be injured by direct (e.g. missile or penetrating wounds) or indirect (e.g. spinal traction) trauma and are frequently compressed by lesions in and about the intervertebral foramina (e.g. disc disease, spondylosis, a hypertrophied ligamentum flavum, or primary or metastatic tumors of the vertebrae or spinal nerves). The most common disc prolapse in the cervical region is at the C6–C7 interspace, resulting in signs and symptoms of C7 root involvement. In the lumbar region, the most common disc prolapse is at the L4–L5 or L5–S1 level, resulting in signs and symptoms referable to the L5 or S1 roots, respectively.

Certain generalized peripheral nervous system diseases have a predilection for the spinal roots (e.g. Guillain–Barré syndrome ). Herpes zoster typically occurs in the distribution of sensory dermatomes, most often at a thoracic level. Unilateral or bilateral radiculopathies may occur with Lyme disease , especially affecting the fifth cervical dermatome or lower thoracic levels. Diabetes may cause thoracic root pain or *thoracoabdominal neuropathy* [4], presenting with severe abdominal or chest pain, often not radicular in character. The presence of dysesthesias and abnormal findings on sensory examination of the trunk aid in the diagnosis of these diabetic neuropathies. Diabetic truncal neuropathy may result in sensory changes in a complete dermatomal band, in multiple dermatomal levels, in the distribution of the ventral or dorsal rami of the spinal nerves or branches of these rami, or in varying combinations of these distributions.

## Sensory abnormalities with spinal cord lesions

With *transverse myelopathies*, all sensory modalities (soft touch, position sense, vibration, temperature, and pain) are impaired below the level of the lesion [5].

Transverse myelopathy of acute onset is often due to traumatic spine injuries, tumor (e.g. metastatic carcinoma, lymphoma), multiple sclerosis, neuromyelitis optica, or vascular disorders. Other causes include spinal epidural hematoma or abscess, paraneoplastic myelopathy, autoimmune disorders, herniated intervertebral disc, and parainfectious or postvaccinal syndromes. In complete lesions, particularly with extramedullary pathology, the sensory level may be many segments below the level of the lesion. The somatotopic distribution of fibers in the lateral spinothalamic tract, with the lowest segments represented more superficially, has been invoked to explain this apparent discrepancy. More reliable band-like radicular pain or segmental paresthesias may occur at the level of the lesion and may be of localizing value for the appropriate spinal level. If the pain is cervical, it radiates to the arms; if thoracic in origin, it is circumferential to the chest or abdomen; and if lumbar or sacral, it radiates to the legs. Localized vertebral pain (over the vertebral spinous process), which is accentuated by palpation or vertebral percussion, may occur with destructive lesions (especially infections and tumors) and may also be of localizing value. Pain that is worse when recumbent and better when sitting or standing is common with malignancy. Defects in pain and temperature sensation below a certain level in the trunk are almost always a sign of spinal cord disease. However, because of the somatotopic organization of sensory fibers in the spinothalamic tract at higher levels, rarely a lateral medullary or lateral pontine lesion may cause a sensory deficit in the contralateral leg, trunk, or both to a specific level. For example, a very laterally placed medullary lesion may damage the sacral and lumbar afferent fibers of the lateral spinothalamic tract but spare the more medial thoracic and cervical afferent fibers, resulting in a sensory loss below a specific lumbar level.

Functional hemisection of the spinal cord results in a characteristic syndrome (the Brown–Séquard syndrome), which consists of the following signs and symptoms:

1. Loss of pain and temperature sensation contralateral to the hemisection due to interruption of the crossed spinothalamic tract. This sensory level is usually one or two segments below the level of the lesion.
2. Ipsilateral loss of proprioceptive function below the level of the lesion due to interruption of the ascending fibers in the posterior columns (dorsal funiculi). Tactile sensation may be normal or minimally decreased.
3. Ipsilateral spastic weakness with hyperreflexia and Babinski sign caudal to the level of the lesion due to interruption of the descending corticospinal tract.
4. Segmental lower motor neuron (segmental weakness and atrophy) and

sensory signs (segmental anesthesia) at the level of the lesion due to damage of the anterior horn cells and dorsal rootlets at this level.

5. Ipsilateral loss of sweating caudal to the level of the lesion due to interruption of descending autonomic fibers in the ventral funiculus, and an ipsilateral Horner's syndrome, if the lesion is cervical, and ipsilateral hemidiaphragmatic paralysis due to damage of the upper motor neuron pathways for breathing, if the lesion is high cervical.

A *central spinal cord syndrome* may occur with syringomyelia, hydromyelia, hematomyelia, and intramedullary cord tumors. Spinal cord damage starts centrally and spreads centrifugally to involve other spinal cord structures. Characteristically, the decussating fibers of the spinothalamic tract conveying pain and temperature sensation are compromised initially. This results in thermoanesthesia and analgesia in a "vest-like" or "suspended" bilateral distribution with the preservation of soft touch sensation and proprioception (dissociation of sensory loss). With forward extension of the disease process, the anterior horn cells become involved at the level of the lesion, resulting in segmental neurogenic atrophy, paresis, and areflexia. Lateral extension results in an ipsilateral Horner's syndrome (due to involvement of the ciliospinal center of Budge with C8-T2 lesions), kyphoscoliosis (due to involvement of the dorsomedian and ventromedian motor nuclei supplying the paraspinal muscles), and, eventually, spastic paralysis below the level of the lesion (owing to the corticospinal tract involvement). Dorsal extension disrupts dorsal column function (ipsilateral position sense and vibratory loss), and with extreme ventrolateral extension, the spinothalamic tract is affected, producing thermoanesthesia and analgesia below the spinal level of the lesion. Because of the lamination of the spinothalamic tract (dorsomedial cervical sensation and ventrolateral sacral sensation), sacral sensation is spared (sacral sparing) by intraparenchymal lesions.

The posterior and lateral columns in the upper spinal cord may be selectively damaged in *subacute combined degeneration of the spinal cord* due to vitamin B12 (cobalamin) deficiency and other conditions. Pathologic changes in cases of subacute combined degeneration predominantly involve the cervical cord, although changes may extend to the thoracic and lumbar cord regions. Pathologically, the spinal cord shows multifocal vacuolated and demyelinating lesions in the posterior and lateral columns. The lesions spread laterally and longitudinally. The fibers with the largest diameters are preferentially affected. Most patients with subacute combined degeneration complain of paresthesias in the feet and, less often, in the hands, difficulties with gait and balance, and have

signs of dorsal column dysfunction, including loss of proprioception and vibration sense in the legs as well as sensory ataxia with a positive Romberg sign and bladder atony. Pain and temperature sensations remain intact because of the preservation of the spinothalamic tracts. Bilateral corticospinal tract dysfunction results in spasticity, hyperreflexia, and bilateral Babinski signs. However, the ankle reflexes may be lost or become hypoactive early in the process because of superimposed peripheral neuropathy. Myelopathic signs tend to be symmetric. Posterior and lateral spinal cord involvement is also seen in cases of vacuolar myelopathy associated with acquired immunodeficiency syndrome (AIDS), human T-lymphotropic virus type 1 (HTLV-1)-associated myelopathy (tropical spastic paraparesis ), extrinsic cord compression (e.g. cervical spondylosis), copper deficiency myelopathy, and a variety of spinocerebellar ataxias.

The *posterior columns* are selectively damaged by tabes dorsalis (tabetic neurosyphilis, progressive locomotor ataxia). Inflammation and degeneration of the dorsal roots cause secondary destruction of the posterior columns of the spinal cord. Tabes dorsalis usually develops 10–20 years after onset of leutic infection and results in impaired vibration and position sense and decreased tactile localization. The lower extremities are more affected than the upper. Patients often complain of increased unsteadiness in darkness. There is sensory ataxia, noted first at night or in the dark, and a positive Romberg sign due to proprioceptive interruption; the swaying begins as soon as the eyes are closed and occurs in all directions. The gait is ataxic, and “stomping” or “double tapping.” The gait disorder is much more pronounced in darkness or with eye closure because visual cues can no longer be incorporated in maintaining balance. Often patients fall forward immediately following eye closure (wash-basin sign or positive “sink” sign). Lightning pains are the hallmark of tabes dorsalis and occur most frequently in the legs. Trophic disturbances result in neurogenic arthropathies (Charcot joints), which are analgesic joints that disintegrate and become deformed as a result of chronic trauma. Many patients have diminished pain sensation demonstrated by insensitivity to pressure of the Achilles tendon (*Abadie sign* ). Often, there is impaired light touch perception in the *Hitzig zones* (e.g. the central area of the face, the nipple area, the ulnar borders of the arms, the peroneal borders of the legs, and the perianal area). With dysfunction of the posterior columns in the cervical region, neck flexion may elicit a sudden “electric-like” sensation down the back or into the arms (*Lhermitte's sign* or “barber's chair syndrome”). Lhermitte's sign may occur with any process affecting the posterior columns in the neck (e.g. multiple sclerosis, cervical spondylosis causing cord compression, previous radiation therapy, etc.).

*Spinal cord infarctions* most often result from involvement of the *territory of the anterior spinal artery*. The lower thoracic segment of the spinal cord and conus medullaris are most frequently involved. Patients with anterior spinal artery syndrome have an abrupt onset of neurologic deficits, often associated with radicular or “girdle” pain. Loss of motor function (e.g. flaccid quadriplegia or paraplegia) occurs within minutes or hours below the level of the lesion (bilateral corticospinal tract damage). There is impaired bowel and bladder control, and thermoanesthesia and analgesia below the level of the lesion (compromise of the spinothalamic tracts bilaterally). Position sense, vibration, and light touch remain intact because of the preservation of the dorsal columns (supplied by the posterior spinal arteries). Patients may develop painful burning dysesthesias below the level of cord injury, likely related in part to selective neospinothalamic deafferentation and preservation of the posterior columns. Spinal cord infarction often occurs in “watersheds” or boundary zones where the major arterial systems supplying the spinal cord anastomose at their most distal branches. These boundary zones include the T1 to T4 and the L1 segments.

*Infarction in the territorial supply of the posterior (posterolateral) spinal arteries* is uncommon. Manifestations include loss of proprioception and vibration sense below the level of the lesion and loss of segmental reflexes.

## Sensory abnormalities with brainstem lesions

The *medial medullary syndrome (Dejerine anterior bulbar syndrome)* [6] may result from atherosclerotic occlusion of the vertebral artery, anterior spinal artery, or the lower segment of the basilar artery. Vertebrobasilar dissection, dolichoectasia of the vertebrobasilar system, embolism, and meningovascular syphilis are less common causes of the medial medullary infarction. The anterior spinal artery supplies the paramedian region of the medulla oblongata, which includes the ipsilateral pyramid, medial lemniscus, and hypoglossal nerve and nucleus. Occlusion results in the following signs:

1. Ipsilateral paresis, atrophy, and fibrillation of the tongue (due to cranial nerve XII affection).
2. Contralateral hemiplegia (due to involvement of the pyramid) with sparing of the face.
3. Contralateral loss of position and vibratory sensation (due to involvement of the medial lemniscus). The dorsolateral spinothalamic tract is unaffected so pain and temperature sensation are spared.

The *lateral medullary syndrome* (*Wallenberg syndrome*) [6] is most often secondary to intracranial vertebral artery or posterior inferior cerebellar artery occlusion. Spontaneous dissections of the vertebral arteries are a common cause. The syndrome has also been described with cocaine abuse, medullary neoplasms (usually metastases), abscess, demyelinating disease, radionecrosis, hematoma (secondary to rupture of a vascular malformation), neck manipulation, trauma, bullet injury to the vertebral artery, and posterior spinal fusion surgery with instrumentation in a patient with a previously undiagnosed Chiari type I malformation. The characteristic clinical picture results from damage to a wedge-shaped area of the lateral medulla and inferior cerebellum and consists of several signs:

1. Ipsilateral facial hypalgesia and thermoanesthesia (due to trigeminal spinal nucleus and tract involvement).
2. Contralateral trunk and extremity hypalgesia and thermoanesthesia (due to damage to the spinothalamic tract).
3. Ipsilateral palatal, pharyngeal, and vocal cord paralysis with dysphagia and dysarthria (due to involvement of the nucleus ambiguus).
4. Ipsilateral Horner's syndrome (due to affection of the descending sympathetic fibers).
5. Vertigo, nausea, and vomiting (due to involvement of the vestibular nuclei).
6. Ipsilateral cerebellar signs and symptoms (due to involvement of the inferior cerebellar peduncle and cerebellum).

The sensory defect in the lateral medullary syndrome usually affects the ipsilateral face and the contralateral leg, arm, and trunk. However, several patients with lateral brainstem lesions developed a sensory defect involving the ipsilateral face and the contralateral foot, with the latter defect extending upward to end in a sensory level [7]. These patients with a *crossed pattern* of sensory defect had far lateral lesions of the lateral medulla and pons, with the leg and lower torso involvement due to selective partial disruption of the somatotopically organized sacral and lumbar afferent fibers of the lateral spinothalamic tract (located far laterally in the brainstem), with sparing of the more medial thoracic and cervical fibers [7]. Several patients have also been described with a continuous hemisensory defect of the face, arm, and trunk (*unilateral pattern*), with the lower border demarcated at a sensory level [7]. These patients were thought to have medio-lateral medullary and pontine lesions contralateral to the side of the sensory defect, which affected the medial cervical and thoracic afferents of the lateral spinothalamic tract (i.e. spared the lateral sacral and lumbar afferents) and the ventral trigeminothalamic tract (accounting

for contralateral facial sensory loss), but spared the spinal nucleus and tract of the trigeminal nerve. In rare instances of infarcts involving the pontomedullary sulcus, sensory symptoms electively involve the contralateral upper limb and base of the neck resulting in loss of pain and temperature, and reinforcing the notion of a somatotopic arrangement of the spinothalamic tract in its medullary course.

*Lesions affecting the pons or midbrain* may cause similar symptoms to the sensory changes outlined under medullary lesion but associated with pontine cranial nerve signs and symptoms (e.g. horizontal gaze palsies ) or midbrain cranial nerve signs and symptoms (e.g. vertical gaze palsies ), respectively.

## **Sensory abnormalities with lesions of the thalamus and cerebrum**

*Thalamic lesions* may cause sensory loss, often accompanied by paresthesias and pain. Clinically, small lesions in the *ventral posterior lateral nucleus of the thalamus* may yield only contralateral paresthesias that lack “objective” sensory loss when tested at the bedside. Such paresthesias tend to occur on one side of the face, particularly around the mouth, and in the distal portion of the limbs. Occasionally, this cheiro-oral or distal distribution of the paresthesias may suggest a more distal lesion (e.g. radiculopathy). These areas of the body have the largest representation in the thalamic sensory nuclei. When the trunk is also numb, the subjective feeling of numbness may stop abruptly in the midline, although on objective testing the sensory loss often fades toward the midline. Such a “thalamic midline split,” which is absent with parietal lesions, has been thought to have some clinical value in identifying the site of the lesion.

Pain referred to as *thalamic pain* is perhaps the best known component of Dejerine–Roussy thalamic syndrome . The unpleasant or excruciatingly painful sensation on the side of the body contralateral to a thalamic lesion (an infarct is most common) may appear at the time of the injury or when the sensory loss begins to improve. Cutaneous stimuli trigger paroxysmal exacerbations of the pain, which persist after the stimulus has been removed. The latency between the stimulus and pain perception is prolonged, suggesting that the pathways conveying it are polysynaptic. Because the perception of epicritic pain, such as that induced with a pinprick, is reduced on the painful areas, this symptom has been termed anesthesia dolorosa , or painful anesthesia. Ventral-posterior thalamic nuclear lesions are more likely to produce half-body pain than lesions

elsewhere in the sensory pathways. The lesion may be restricted to the ventral-posterior nucleus and it is generally accompanied by hypesthesia to cold but not to heat. Thalamic pain has been described most often with vascular lesions, some of which involve not only the thalamus but also the deep parietal white matter. Delayed pain may also follow cortical parietal infarcts, particularly those in the bank of the Sylvian fissure, affecting the second somatosensory area (*pseudothalamic syndrome*).

All somatosensory modalities are processed in the ventral posterior nucleus of the thalamus contralateral to the side of the body where they are perceived. Within the nucleus there is a definite topographic distribution: the head is represented anteroinfero-medially, whereas the leg is represented posterosuperolaterally; the arm is represented in an intermediate position. A larger volume of the nucleus is dedicated to the mouth, tongue, and distal portion of the extremities; their thalamic representation is almost completely crossed. The face, proximal portion of the limbs, and trunk are represented in a smaller volume of thalamic tissue, mainly contralateral but partially ipsilateral. Thalamic sensory loss tends to occur maximally in the distal portion of the limbs and often spares the face. Such sparing may be related to the different vascular supply of this portion of the ventroposterior region (paramedian territory) or to the bilateral thalamic representation of the face.

Because the perception of pinprick, temperature, touch, or vibration is altered more often after thalamic than after cortical lesions, these sensory modalities have been termed *primary* or *thalamic*. By contrast, conscious joint position identification, two-point discrimination, stereognosis, and graphesthesia tend to be more impaired after cortical parietal lesions, and are thus termed *secondary* or *cortical* sensory modalities. Nevertheless, parietal lesions often cause some impairment of thalamic modalities and vice versa. Occasionally, a lesion in the thalamus may disturb mainly the so-called cortical sensory modalities.

*Lesions of the postcentral gyrus* cause contralateral impairment in the perception of size and shape by palpation. As a result, the identity of the palpated object remains unknown (*astereognosis*). Such impairment, which is greatest in the limb represented in the lesioned area, also affects *two-point discrimination* and *graphesthesia* (the ability to recognize a letter or digit traced on the patient's skin). Pinprick is also perceived as less sharp on the side contralateral to an acute parietal lobe lesion. Sensory loss with parietal lesions tends to be localized to the distal portions of the limbs, which have the largest cortical representation and are almost exclusively innervated by the contralateral

hemisphere. Paresthesias, usually of a tingling quality, may occur in the limb represented in an area of the postcentral gyrus affected by ischemia or epileptic activity (sensory seizure). It has been postulated that lesions of the parietal operculum (superior lip of the Sylvian fissure corresponding to the secondary somatosensory area) may cause a pseudothalamic syndrome, with pronounced impairment in the perception of pain and temperature in the acute stage and a delayed “thalamic” type of pain. However, delayed pain and paresthesia frequently occur after deep or large parietal lesions. Persistent impairment of tactile object recognition (*tactile agnosia*) can also follow lesions of the secondary sensory area, in the inferior extent of the somatosensory cortex, abutting the Sylvian fissure, whereas lesions of the supplementary motor cortex, in the medial aspect of the parietal lobe (precuneus), generally cause more severe but transient disruption of somesthetic processing.

Parietal stroke can cause different sensory syndromes depending on the topography of the underlying lesion [8]. Although sensory loss may be the only finding, they never present as a “pure sensory stroke” involving face, arm, leg, and trunk together. In a study of patients with acute parietal stroke with hemisensory disturbances (but no visual field deficit and no or only slight motor weakness), without thalamic involvement on CT or MRI, three main sensory syndromes were found:

1. The *pseudothalamic sensory syndrome* consists of a faciobrachiorcral impairment of elementary sensation (touch, pain, temperature, and vibration). All patients have an inferior-anterior parietal stroke involving the parietal operculum, posterior insula, and, in most patients, underlying white matter.
2. The *cortical sensory syndrome* consists of an isolated loss of discriminative sensation (stereognosis, graphesthesia, position sense) involving one or two parts of the body. These patients show a superior-posterior parietal stroke.
3. The *atypical sensory syndrome* consists of a sensory loss involving all modalities of sensation in a partial distribution. Parietal lesions of varied topography are responsible for this clinical picture, which probably represents a minor variant of the two previous sensory syndromes.

The localization of lesions affecting somatosensory pathways is summarized in [Table 66.4](#).

**Table 66.4 The localization of lesions affecting the somatosensory pathways.**

Location of lesion	Clinical findings
Peripheral nerve (mononeuropathy)	<p>Sensory symptoms mainly in the distribution of sensory supply of nerve, but may radiate beyond the distribution of the damaged nerve</p> <p>Sensory loss generally confined to the area supplied by the nerve. In general, the area of light touch loss is greater than the area of pain loss</p>
Polyneuropathy	<p>Usually distal symmetric sensory loss (e.g. feet)</p> <p>Rare proximal sensory loss (e.g. proximal sensory neuropathy with porphyria or Tangier disease)</p> <p>Rare temperature-related sensory loss (e.g. leprosy)</p> <p>Sensory loss progresses according to axonal length</p> <p>Sensory loss may preferentially affect certain modalities depending on the etiology (e.g. small fiber sensory loss with primary amyloidosis)</p>
Dorsal root ganglion	<p>Similar to dorsal root lesion</p> <p>Diffuse involvement with dorsal root ganglionopathy (e.g. due to remote effect of cancer or Sjögren syndrome) – diffuse pansensory loss with sensory ataxia</p>
Dorsal root	<p>Irritative symptoms (e.g. radicular pain or paresthesias) and sensory loss in dermatomal (i.e. segmental) distribution</p> <p>Because of overlap of innervation, interruption of one thoracic or upper lumbar dorsal root may give rise to sensory symptoms without definite sensory loss</p> <p>Sensory loss to touch may extend over larger territory than pain and temperature loss</p>
Spinal cord	Dorsal horn or central gray matter lesion

	<p>produces the same ipsilateral segmental sensory disturbance as dorsal root lesion; segmental sensory loss “marks” the level of cord involvement</p> <p>Lesion of anterolateral funiculus causes loss of pain and temperature sense on the contralateral side of the body at all levels caudal to the site of lesion; upper border of the sensory loss approximately corresponds to the lower border of the dermatome belonging to lowest preserved cord segment</p> <p>If the lesion is limited to more superficial parts of tract, a more restricted sensory loss occurs, with upper segment of sensory loss found several segments farther caudally; the more so, the more superficial the lesion</p> <p>If the lesion is deep and spares superficial fibers, sensory loss may “spare” the distal segments (e.g. “sacral sparing”)</p> <p>Lesion of the dorsal funiculus causes loss of vibratory and position sense and sensory ataxia below the involved segment ipsilateral to the lesion</p> <p>Brown–Séquard (hemicord) syndrome</p> <p>Central cord lesion (e.g. syringomyelia) – dissociation of sensory loss</p>
Medulla oblongata	<p>Association of sensory abnormalities with other medullary signs and symptoms (e.g. cranial nerve [CN] XII paresis) – often “crossed” findings (CN palsy on one side of the face and sensory or motor loss on the opposite side of the body)</p> <p>Lateral medulla</p> <p>Loss of pain and temperature on the contralateral side of the body, may spare medial lemniscus functions</p> <p>Frequently associated with involvement of the spinal tract and nucleus of CN V – decreased</p>

	<p>pain and temperature on the ipsilateral face and contralateral body (hemianesthesia alternans)</p> <p><b>Medial medulla</b></p> <p>Impairment of vibratory and position sense on opposite side of the body, may spare the spinothalamic tract</p> <p>Often associated with ipsilateral CN XII paresis</p> <p>Because of somatotopic organization, there may be sensory changes “below a level” or “to a level” mimicking spinal cord involvement</p>
Pons	<p>Similar to the sensory changes outlined under medullary lesion but associated with pontine CN signs and symptoms (e.g. horizontal gaze palsies)</p>
Midbrain	<p>Similar to the sensory changes outlined under medullary lesions but associated with midbrain CN signs and symptoms (e.g. vertical gaze palsies)</p>
Thalamus	<p>Lesion of ventral–posterior–lateral (VPL) nucleus results in sensory loss to all modalities on the opposite side of the face and body</p> <p>Somatotopic localization exists in the thalamus</p>
Cerebrum	<p>Circumscribed lesion of the postcentral gyrus causes localized sensory loss in part of the opposite half of the body (e.g. lesion of parasagittal postcentral gyrus causes sensory changes in opposite leg)</p>

---

From: Brazis PW, Masdeu JC, Biller J. *Localization in Clinical Neurology*, 6th edn. Philadelphia, PA: Lippincott Williams and Wilkins, 2011. With permission.

## Case vignette

A 65-year-old male relates the acute onset of slurred speech, right hemiplegia, and gait instability. Examination reveals that his protruded tongue deviates to the left and he has a right hemiplegia. Sensation to pin, temperature, and soft touch are preserved in all four extremities but vibratory and position sensation are impaired in the right arm and leg. Where is the lesion?

## Discussion

The patient has suffered a left medial medullary syndrome which often results from atherosclerotic occlusion of the vertebral artery, anterior spinal artery, or the lower segment of the basilar artery. The anterior spinal artery supplies the paramedian region of the medulla oblongata, which includes the ipsilateral pyramid, medial meniscus, and hypoglossal nerve and nucleus. Therefore, occlusion resulted in ipsilateral paresis, atrophy, and fibrillations of the tongue; contralateral hemiplegia sparing the face from pyramidal tract involvement; and contralateral loss of position and vibratory sensation from involvement of the medial meniscus.

## References

1. Brodal A. The somatic afferent pathways. In *Neurological Anatomy in Relation To Clinical Medicine*, 3rd edn. New York, NY: Oxford University Press, 1981: 46–147.
2. Sabin TD. Classification of peripheral neuropathy: the long and the short of it. *Muscle Nerve* 1986; 9:711–19.
3. Sabin TD. Temperature-linked sensory loss: a unique pattern in leprosy. *Arch Neurol* 1969; 20:257–62.
4. Stewart JD. Diabetic truncal neuropathy: topography of the sensory deficit. *Ann Neurol* 1989; 25:233–8.
5. Brazis PW, Masdeu JC, Biller J. Spinal cord. In *Localization in Clinical Neurology*, 6th edn. Philadelphia, PA: Lippincott Williams and Wilkins, 2011: 99–126.
6. Brazis PW, Masdeu JC, Biller J. Brainstem. In *Localization in Clinical Neurology*, 6th edn. Philadelphia, PA: Lippincott Williams and Wilkins, 2011: 385–402.

7. Matsumoto S, Okuda B, Imai T *et al*. A sensory level on the trunk in lower lateral brainstem lesions. *Neurology* 1988; 38:1515.
8. Bassetti C, Bogousslavsky J, Regli F. Sensory syndromes in parietal stroke. *Neurology* 1993; 43:1942–9.

## 67 Sensory deficits in the face

---

Jeffrey A. Brown and Alan B. Ettinger *Neurologic Differential Diagnosis*,  
ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge  
University Press. © Cambridge University Press 2014.

### Introduction

Facial sensory deficits are intertwined with the subject of neuropathic facial pain and the reader may also want to refer to [Chapter 53](#) on facial pain for a discussion of relevant diagnoses. The most common form of intertwined facial numbness and pain syndrome is trigeminal neuralgia (TN1). TN1 is characterized by episodic, single side, stabbing pain often with a sensory trigger. There is usually only minor sensory loss. TN2 is characterized by an underlying constant, usually burning electrical quality to the pain. Facial numbness may more often be detected. Both are forms of neuropathic pain caused by injury to the trigeminal sensory pathway. TN1 is usually a consequence of a vascular compressive neuropathy at the root entry zone of the trigeminal nerve, but it can also be a result of a multiple sclerosis plaque. Peripheral trigeminal injury causing numbness is usually not a cause of persistent neuropathic pain, but may be, especially if there is an underlying vascular compression of the trigeminal nerve root.

The etiologies of facial numbness summarized in [Table 67.1](#) can alternatively be considered according to anatomic location. Clues to lesion localization are based upon the distribution of the sensory deficit. Readers are referred to standard anatomic texts to review the specific distribution of the trigeminal nerve branches and the specific demarcations of the upper, middle, and lower face sensory deficits associated with V1 (ophthalmic division), V2 (maxillary division), and V3 (mandibular division) lesions respectively. Notably, the angle of the jaw, the posterior head and post-auricular areas descending to the neck (all supplied by C2 and C3) are typically spared with lesions of cranial nerve V.

**Table 67.1** *Differential diagnosis of facial numbness and pain syndromes.*

---

Anatomic site	Common causes	Symptoms	
Root entry zone	SCA compression SCA + venous compression	Episodic stabbing (early) Constant burning+episodic stabbing (late) Constant burning+episodic stabbing	N F N N
Mid-cisternal/distal root	Venous compression SCA + venous compression Trigeminal schwannoma	Constant burning Facial numbness	N S J €
Meckel's cave	Tumor – meningioma/schwannoma	Facial numbness	J €
Peripheral trigeminal nerve	Surgical injury Facial trauma Parotid tumor	Divisional facial numbness Constant burning	F S N J
Brainstem	Lateral medullary infarct glioma	Facial numbness Constant burning	N
Thalamus	Thalamic infarct	Facial numbness Constant burning	N
Odontogenic	Teeth	Aching	C

Major categories of disease

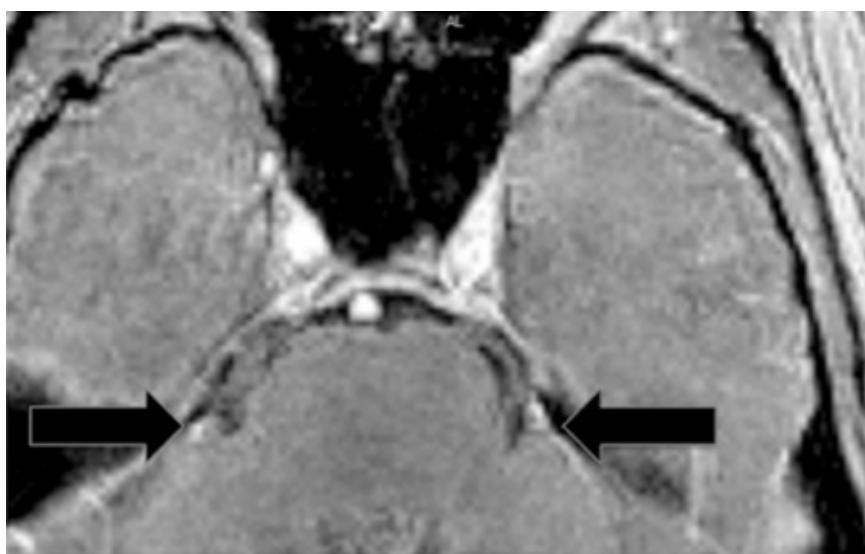
Tumor	Schwannoma  Meningioma	Facial numbness/burning	F T
	Parotid carcinoma/adenocarcinoma	Facial numbness/burning	T
Infection	Post-herpetic neuralgia Cavernous sinus thrombosis	Facial numbness/burning Facial numbness/burning/other cranial nerve findings	F S
Trauma	Consider associated root vascular compression	Facial numbness/burning	F S
Vascular	Compressive neuropathy Thalamic/brainstem infarct AVM		F N S N
Demyelinating	Brainstem MS plaque	Stabbing – constant burning	F
Congenital	Chiari malformation	Constant burning/headache	C C
Odontogenic	Periodontal or tooth procedure	Aching	C
Psychiatric	Associated fibromyalgia/depression		F

---

ACDs, anticonvulsant drugs; AVM, arterial venous malformation; MS, multiple sclerosis; MVD, microvascular decompression; SCA, superior cerebellar artery.

Lesions proximal to the Gasserian ganglion are associated with hemifacial deficits, while lesions of the brainstem may produce the classic “onionskin” sensory deficit. Thalamic lesions often produce more widespread hemibody sensory deficits, while lesions of the internal capsule may also have accompanying hemiparesis. Numbness associated with parietal lobe deficits is often associated with other higher cortical function deficits such as neglect.

Lesions of the trigeminal branches include trauma (such as invasive dental procedures, surgery, injuries especially with facial bone fractures) (Figure 67.1). Reactivation of the herpes zoster virus within the trigeminal ganglion usually affects V1 and is associated with a peri-ocular vesicular rash and rarely is associated with a dreaded middle cerebral artery stroke. Another infectious cause usually outside the USA is leprosy, which affects the tip of the nose or ears. Other causes are neoplasms from local or metastatic spread such as nasopharyngeal tumors, sinusitis-associated inflammatory processes, as part of a systemic neuropathy, and drug effects such as with cocaine affect V2. Vascular etiologies such as carotid dissection have produced facial numbness. Idiopathic trigeminal sensory neuropathy is a diagnosis of exclusion after other causes for neuropathy such as connective tissue diseases have been ruled out. Numb chin and numb cheek syndromes need to be investigated thoroughly as they may be signs of a virulent neoplastic process.



**Figure 67.1** Magnetic resonance imaging of the brain with contrast. Arrows point to sites of trigeminal vascular compression thought to be the cause of neuropathic facial pain.

Similar categories of disease may affect the Gasserian ganglion or root

including neoplasms arising within the ganglion (usually painful) or root (with less pain). Many other types of tumors may invade the ganglion including neuromas, neural sheath tumors, chordomas, nasopharyngeal tumors, and metastases. Accompanying symptoms and signs such as other associated cranial neuropathies often give a clue to the localization of the lesion. Other etiologies include infectious processes, inflammatory diseases such as sarcoidosis, and toxic solvents. Classic sites for potential affection of cranial nerve V or its branches include the cerebellopontine angle, the skull base, the petrous temporal bone, or the cavernous sinus.

Central pathway-associated deficits may be produced by a neoplasm, syrinx, demyelination, blood vessel abnormality (e.g. arteriovenous malformation), or stroke. For example, the lateral medullary syndrome (Wallenberg's syndrome) produces ipsilateral facial numbness, but affection of the spinothalamic tract causes contralateral body pain and temperature sensory deficits.

## **Case vignette**

A 40-year-old male developed constant, burning, itchy pain around both of his eyes. Examination showed bilateral periorbital hyperesthesia. Lyme studies and herpes simplex DNA were negative. Magnetic resonance imaging (MRI) of the brain did not show a lesion and the cerebrospinal fluid (CSF) profile was normal. His diagnosis was neuropathic facial pain. He was treated with carbamazepine and multiple other anticonvulsant medications. These failed to effectively relieve the pain and he underwent surgical insertion of bilateral supraorbital and infraorbital subcutaneous peripheral stimulating electrodes. These provided 2 years of pain relief. He then progressed to intermittent bilateral, stabbing periorbital pain worse on the left in addition to the itchy pain. Review of the previous MRI suggested that there was underlying bilateral vascular compression at the trigeminal root entry zone. Because of this and the onset of stabbing pain, he underwent a left microvascular decompression. A distal vein was mobilized off from the nerve. The stabbing pain on the left resolved. The peripheral electrodes on the left were removed 6 months later. Pain on the right continued to be controlled by the peripheral electrodes and he discontinued oral medication.

## **Further reading list**

Barker FG, 2nd, Jannetta PJ, Bissonette DJ, Larkins MV, Jho HD. The long-term

outcome of microvascular decompression for trigeminal neuralgia. *N Engl J Med* 1996; 334:1077–83.

Brown JA. The trigeminal complex. Anatomy and physiology. *Neurosurg Clin N Am* 1997; 8:1–10.

Brown JA, Pilitsis JG. Percutaneous balloon compression for the treatment of trigeminal neuralgia: results in 56 patients based on balloon compression pressure monitoring. *Neurosurg Focus* 2005; 18:E10.

Burchiel KJ. A new classification for facial pain. *Neurosurgery* 2003; 53:1164–6; discussion 6–7.

Fontaine D, Hamani C, Lozano A. Efficacy and safety of motor cortex stimulation for chronic neuropathic pain: critical review of the literature. *J Neurosurg* 2009; 110:251–6.

Leal PR, Hermier M, Souza MA *et al.* Visualization of vascular compression of the trigeminal nerve with high-resolution 3T MRI: a prospective study comparing preoperative imaging analysis to surgical findings in 40 consecutive patients who underwent microvascular decompression for trigeminal neuralgia. *Neurosurgery* 2011; 69:15–25; discussion 6.

Linskey ME, Ratanatharathorn V, Penagaricano J. A prospective cohort study of microvascular decompression and Gamma Knife surgery in patients with trigeminal neuralgia. *J Neurosurg* 2008; 109 Suppl:160–72.

Love BB, Beattie MR. Approach to the patient with facial numbness. In Biller J, Ed. *Practical Neurology*, 4th edn. New York, NY: Wolters Kluwer, 2012.

Zacest AC, Magill ST, Miller J, Burchiel KJ. Preoperative magnetic resonance imaging in type 2 trigeminal neuralgia. *J Neurosurg* 2010; 113:511–15.

Zakrzewska JM, Lopez BC, Kim SE, Coakham HB. Patient reports of satisfaction after microvascular decompression and partial sensory rhizotomy for trigeminal neuralgia. *Neurosurgery* 2005; 56:1304–11; discussion 11–2.

## 68 Smell deficit

---

Richard L. Doty and Hakan Tekeli *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Smell dysfunction is not uncommon, occurring in over 3 million adults in the USA alone. Chronic loss occurs in about half of those between 65 and 80 years of age and in about three quarters of those 80 years of age or older [1]. Although rarely appreciated, smell disorders have significant consequences for the patient, including (i) impaired quality of life; (ii) increased health or safety risks from spoiled foods and dangerous vapors, including leaking natural gas; (iii) compromised vocational abilities; and (iv) altered food choices and consumption patterns that can adversely impact health or worsen underlying illnesses (e.g. decreased body weight, impaired immunity, overuse of salt in hypertension or sugar in diabetes mellitus). The etiology of most olfactory deficits can be obtained from the medical history where coincident events determine probable cause (e.g. upper respiratory infection, head trauma, toxic exposures) [2].

### Definitions

*Anosmia* – inability to detect odors; *Hyposmia/microsmia* – decreased ability to detect odors; *Dysosmia* – altered perception of smell in the presence of an odorant, usually unpleasant; *Phantosmia* – perception of smell without an odorant present; *Agnosia* – inability to perceive odors, although able to detect them.

### Etiology

Numerous diseases, disorders, drugs, and interventions can adversely influence smell function. However, nearly two thirds of chronic anosmia or hyposmia cases are due to prior upper respiratory infections, head trauma, and nasosinus

disease. Common colds or influenzas are the most frequent causes of *permanent* smell loss in the adult human [2]. Rhinosinusitis and head trauma are the next most common disorders associated with such loss. In the case of head trauma, blows to the back of the head are more likely to cause greater olfactory loss than blows to the front of the head, although both can produce dysfunction [3]. Common etiologies and their physiologic bases are noted in [Table 68.1](#).

**Table 68.1 Overview of anatomy and etiology of olfactory disorders.**

Anatomic site of damage	Typical CN I finding	Other neurologic and medical findings	Common etiologies
Intranasal airflow blockage	Hyposmia or anosmia; can be unilateral	Rhinorrhea; difficulty nose breathing; pale nasal epithelium	Allergies; polyposis; nasal malformations; infections; trauma; iatrogenesis
Sensory receptors and primary neurons	Hyposmia or anosmia; dysosmia; phantosmia; can be unilateral	With trauma, rare nasal leaks of CSF; if viral upper respiratory infections (URI), hypogeusia	Head trauma; URI; nasosinus disease; toxic exposures; intranasal neoplasms; iatrogenesis
Secondary neurons; olfactory bulb cells; anterior olfactory nuclus; olfactory tract	Hyposmia or anosmia; dysosmia; phantosmia; can be unilateral	Foster Kennedy syndrome; gait dyspraxia; disinhibition; change in personality	Meningiomas; neurodegenerative diseases (e.g. Alzheimer's, Parkinson's Huntington's)

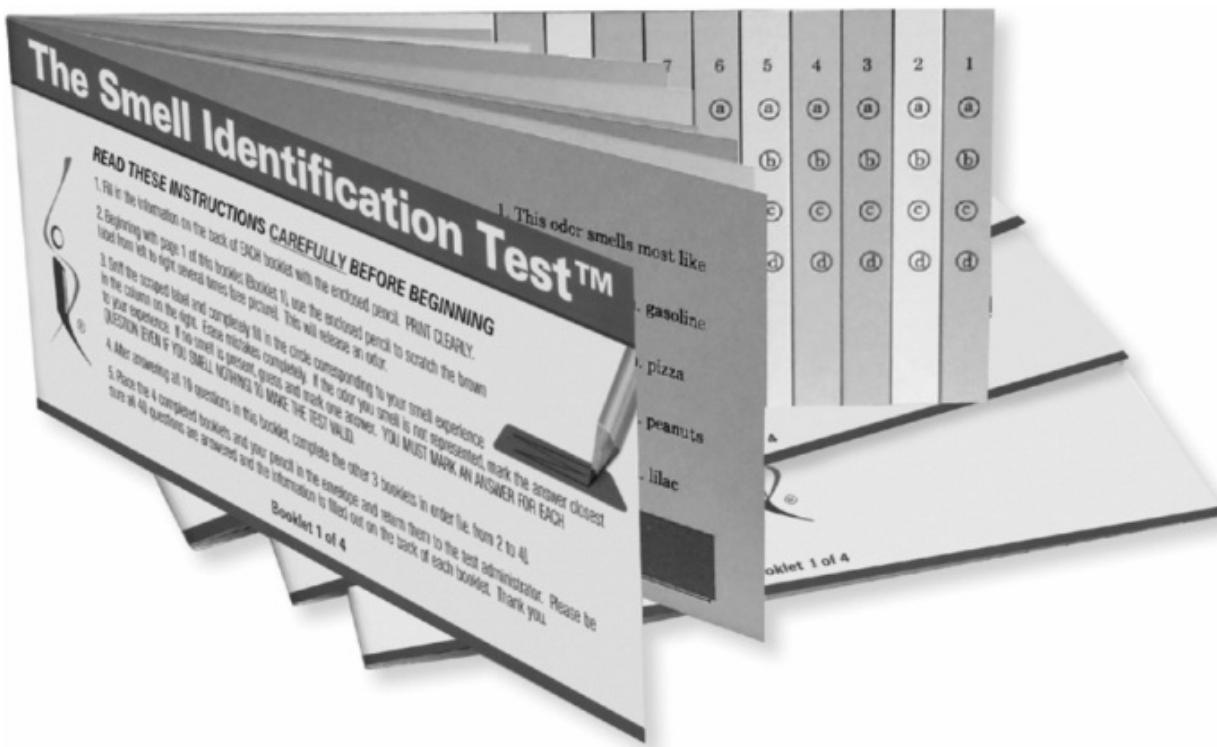
<b>anatomical</b>	<b>decreased</b>	<b>signs of</b>	<b>Wernicke—</b>
dorsal nucleus of thalamus*	odor identification; normal or increased detection thresholds; odor memory deficits	Wernicke— Korsakoff syndrome; ataxia, extraocular paresis, nystagmus, memory problems; confabulations	Korsakoff syndrome; infarctions
Primary and secondary olfactory cortices*	Decreased odor identification; normal or increased odor thresholds; odor memory deficits	Lip smacking, automatisms during seizures; dementia, memory loss; tremor, bradykinesia; chorea, contralateral weakness, aphasia, homonymous quadrant visual field deficits	Epilepsy; neurodegenerative disorders (e.g. Alzheimer's, Parkinson's, Huntington's) Tremors or infarcts

---

\* Because of bilateral cortical and subcortical representation of olfactory function, unilateral lesions at these levels generally do not cause meaningful olfactory dysfunction.

Since most patients are not cognizant of less-than-total smell loss [4], empirical assessment of their function should be performed in addition to obtaining a thorough history and appropriate magnetic resonance imaging (MRI) and computerized tomography (CT) scans to identify rhinosinusitis, brain lesions, and other factors that may relate to the problem. There are now numerous commercially available tests for assessing olfactory function, the most widely used being tests of odor identification [5]. In general, tests of odor identification, detection, and discrimination are correlated with one another. The most widely used clinical olfactory test is the University of Pennsylvania Smell

Identification Test (UPSIT) , which involves smelling 40 microencapsulated odors in a scratch-and-sniff format, with four response alternatives accompanying each odor (Figure 68.1) [6]. This test can be self-administered. The examinee is required to guess if no odor is perceived or if they are not certain about the correct answer (i.e. provide a forced-choice response). Normative data are available to establish absolute dysfunction (i.e. normosmia, mild microsmia, moderate microsmia, severe microsmia, anosmia), as well as relative dysfunction (age-and sex-adjusted percentile ranks relative to normal subjects). Anosmic patients tend to score at or near chance (10/40 correct). Malingeringers avoid the correct responses and can be captured in the test score.



**Figure 68.1** The University of Pennsylvania Smell Identification Test (known commercially as the Smell Identification Test) [6]. This test, developed in the early 1980s, comprises 40 microencapsulated odorants located next to forced-choice questions on each page of 10-page booklets. Copyright © 2004, Sensonics, Inc., Haddon Heights, New Jersey.

## Patient management

Allergy management, antibiotic therapy, topical and systemic corticosteroid therapies, and various surgical interventions can restore, in some cases, olfactory dysfunction secondary to airway blockage or inflammation. Once inflammation

is controlled using a systemic steroid, steroid nasal sprays or drops can be made more efficient by administering them in the Moffett position. When tumors are involved, judicious removal with the goal in mind of maintaining the integrity of the olfactory pathways can often restore olfactory function.

Only rarely does cessation of medications reverse dysosmia. Adverse effects of medications usually are confined to the taste system, influencing sweet, sour, bitter, or salty perception or producing dysgeusias attributable to taste-bud mediated sensations. Dysosmias are common in patients with hypothyroidism and readjustment of their medication dose may relieve their symptoms [2]. Use of bovine rather than synthetic thyroxin has been reported efficacious, although reports on this point are anecdotal. Dialysis sometimes reverses dysosmias associated with kidney disease. In rare cases of long-term chronic dysosmia not attributable to central lesions – particularly cases associated with significant depression, weight loss, or nausea because of the perversion of food flavor – surgical approaches may be considered. If the dysosmia is unilateral (detected by blocking the flow of air to one side of the nose or by anesthetizing the olfactory epithelium unilaterally), unilateral ablation of sectors of the olfactory epithelium may correct the problem while sparing contralateral function. Should the dysosmia reappear, additional intranasal ablations may be performed. Surgery should only be considered in cases where the disability has lasted for years, significantly alters health, and has proved intractable to other approaches, including the use of antiseizure medications. Usually dysosmias spontaneously remit over time.

Treatment of patients with anosmia due to neural damage is challenging. Although there are a few advocates of zinc and vitamin therapies, including the use of alpha-lipoic acid, sound empirical evidence of efficacy is lacking. Although spontaneous improvement occurs to some degree over time in about half of those with olfactory loss, those with complete anosmia have less than a 10% chance of regaining smell function normal for their age. This percentage is closer to 20% for those with less-than-total smell loss [7]. It should be noted that simply providing patients with accurate information about their disorder, establishing objectively the degree of the deficit, and ruling out the possibility of a serious disorder as the cause of the problem can diminish anxiety and is usually very therapeutic. Because half of elderly persons with permanent olfactory loss are at or above the 50th percentile of their norm group, these individuals can be informed that while their olfactory function is below what it used to be, they still are outperforming most of their peers. This knowledge is extremely therapeutic and helps to place the natural age-related loss of olfactory

function into a broader perspective. Importantly, it is incumbent upon the practitioner to point out to the patient the hazards associated with the inability to smell odors, such as being less able to detect smoke, natural gas leaks, and spoiled food. Smoke detectors, as well as natural gas and propane gas detectors, are commercially available to minimize such risks.

## Case vignette

A 56-year-old female fell on ice in her driveway, striking the back of her head on the ground and suffering brief disorientation but no loss of consciousness or amnesia. A few days later she discovered that she had difficulty smelling. Soon thereafter she experienced distortions of smell, which she interpreted as taste problems. Routine CT and MRI assessments proved negative. A course of systemic steroids was without benefit. The UPSIT score was 17/40; bilateral, left, and right detection threshold scores on the phenyl ethyl alcohol detection threshold test were indicative of anosmia, as was the chance performance on the 12-item Odor Memory Test . Nasal airway airflow and patency assessed by anterior rhinomanometry and acoustic rhinometry were normal. Scores on a series of taste tests were normal, as were scores on the Mini-Mental State Examination and the Beck Depression Inventory II.

## Discussion

This is a classical case of trauma-induced bilateral anosmia, unaccompanied by true taste loss. The dysfunction likely reflects contrecoup movement of the brain and the resulting shearing or stretching of the olfactory filaments at the level of the cribriform plate. The smell and taste “distortions” most likely are due to decreased flavor sensations secondary to lack of retronasal olfactory stimulation and the possible presence of a few aberrant olfactory nerve fibers that are still active.

## References

1. Doty RL, Shaman P, Applebaum SL *et al*. Smell identification ability: changes with age. *Science* 1984; 226:1441–3.
2. Deems DA, Doty RL, Settle RG *et al*. Smell and taste disorders: a study of 750 patients from the University of Pennsylvania Smell and Taste Center (1981–1986). *Arch Otolaryngol Head Neck Surg* 1991; 117:519–28.

3. Doty RL, Yousem DM, Pham LT, Kreshak AA, Lee WW. Olfactory dysfunction in patients with head trauma. *Arch Neurol* 1997; 54:1131–40.
4. Wehling E, Nordin S, Espeseth T, Reinvang I, Lundervold AJ. Unawareness of olfactory dysfunction and its association with cognitive functioning in middle aged and old adults. *Arch Clin Neuropsychol* 2011; 26:260–9.
5. Doty RL. Office procedures for quantitative assessment of olfactory function. *Am J Rhinol* 2007; 21:460–73.
6. Doty RL, Shaman P, Dann M. Development of the University of Pennsylvania Smell Identification Test: a standardized microencapsulated test of olfactory function. *Physiol Behav* 1984; 32:489–502.
7. London B, Nabet B, Fisher AR *et al*. Predictors of prognosis in patients with olfactory disturbance. *Ann Neurol* 2008; 63:159–66.

## 69 Spasm, hemifacial

---

Jagga Rao Alluri *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Hemifacial spasm is a segmental myoclonus of muscles innervated by the facial nerve. Typical characteristics include:

- Almost always unilateral.
- 5th or 6th decade.
- Brief clonic movements of the orbicularis oculi which then spread to other facial muscles.
- Clonic movements progress to sustained clonic contractions of involved musculature.

### Causes

- Idiopathic, vascular compression such as arteriovenous malformation (AVM), facial nerve compression by mass, Paget's disease, stroke, multiple sclerosis, basilar meningitis, fungal tuberculosis, trauma, or Bell's palsy.
- Most instances of hemifacial spasm thought to be idiopathic or probably caused by aberrant blood vessels, e.g. distal branch of anterior inferior cerebellar artery or vertebral artery compressing the facial nerve within the cerebellopontine angle.

### Epidemiology

All races are affected equally; occurrence is slightly higher in females. Most likely to present in the 5th or 6th decades (idiopathic). If patient is younger than 40 consider multiple sclerosis.

## Case vignette

For further details on disorders that can mimic hemifacial spasm and for a case vignette, please refer to [Chapter 39](#) on movement abnormalities in the face.

**Table 69.1 Selected facial movements that should be distinguished from hemifacial spasm.**

Facial movements	Possible features
Facial myokymia	Vermicular twitching under the skin often in a wave-like spread. Most are idiopathic but brainstem pathology also may underlie symptoms. May occur after Bell's palsy. Electromyography helpful in diagnosis
Craniofacial tremor	May occur in association with essential tremor, thyroid dysfunction, electrolyte disturbance, Parkinson's disease. Rarely in isolation; more commonly with tremor in other parts of the body
Oromandibular dystonia	Dystonia affecting the lower facial musculature, jaw, pharynx, tongue. Two types: jaw opening and jaw closing. Jaw deviation implies involvement of lateral pterygoid muscle. Low response to medications. Jaw closure type more responsive to botulinum toxin
Focal motor seizure	Clues include other ictal symptoms, post-ictal paresis
Facial chorea	Chorea is a random flowing non-patterned set of movements. Occurs with systemic movement disorder (Huntington's disease, Sydenham's chorea)
Orofacial dyskinesia of the	Primarily in the edentulous. Treated with properly fitted dentures

## Symptoms of the proprioceptive system elderly

### **Myoclonic movements**

Myoclonic movements affecting facial muscles may arise from the brainstem or cerebral hemispheres (see [Chapter 46](#) on myoclonus) These are generalized, bilateral. May respond to antiepileptic drugs

### **Hemimasticatory spasm**

Analogous to hemifacial spasm. Irritation to the motor trigeminal nerve. Rare condition. Segmental myoclonus presents with unilateral involuntary contractions of the trigeminally innervated muscles of mastication (usually the masseter). Response to treatment with medication and botulinum toxin. Less evidence for surgical benefits

### **Meige's syndrome**

Oromandibular dystonia + blepharospasm

### **Tics**

Brief, repetitive, coordinated semi-purposeful movements of grouped facial and neck muscles. Examples of etiologies include idiopathic, as part of a diffuse encephalopathy, and medication effects such as caffeine, stimulant, or antiparkinsonian medications. Simple tics are repetitive stereotyped movements such as repetitive grimacing, throat clearing, vocalizations

---

## **Further reading list**

Adler CH, Zimmerman RA, Savino PJ *et al.* Hemifacial spasm: evaluation by magnetic resonance imaging and magnetic resonance tomographic angiography. *Ann Neurol* 1992; 32:502–6.

Campos-Benitez M, Kaufmann AM. Neurovascular compression findings in

hemifacial spasm. *J Neurosurg* 2008; 109:416–20.

Colosimo C, Chianese M, Giovannelli M *et al.* Botulinum toxin type B in blepharospasm and hemifacial spasm. *J Neurol Neurosurg Psychiatry* 2003; 74:687.

Jankovic J, Schwartz K, Donovan DT. Botulinum toxin treatment of cranial-cervical dystonia, spasmodic dysphonia, other focal dystonias and hemifacial spasm. *J Neurol Neurosurg Psychiatry* 1990; 53:633–9.

Mauriello JA, Leone T, Dhillon S *et al.* Treatment choices of 119 patients with hemifacial spasm over 11 years. *Clin Neurol Neurosurg* 1996; 98:213–16.

## **70 Stroke and hemorrhage syndromes**

---

George C. Newman and Aparna M. Prabhu *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

The focus of this chapter is on hemorrhagic stroke. However, there are also tables related to the differential diagnosis of acute ischemic stroke and ischemic stroke syndromes.

### **Intracranial hemorrhage**

Intracranial hemorrhage (ICH) describes extravasation of blood into the brain or surrounding compartments.

Intracranial hemorrhage can be classified by the anatomic spaces containing the hemorrhage:

- Extradural (epidural) hematoma .
- Subdural hematoma .
- Subarachnoid hemorrhage .
- Parenchymal (encephalic or brain) hemorrhage .
  - Cerebral (lobar or basal ganglia).
  - Cerebellar.
  - Brainstem.
- Intraventricular hemorrhage .

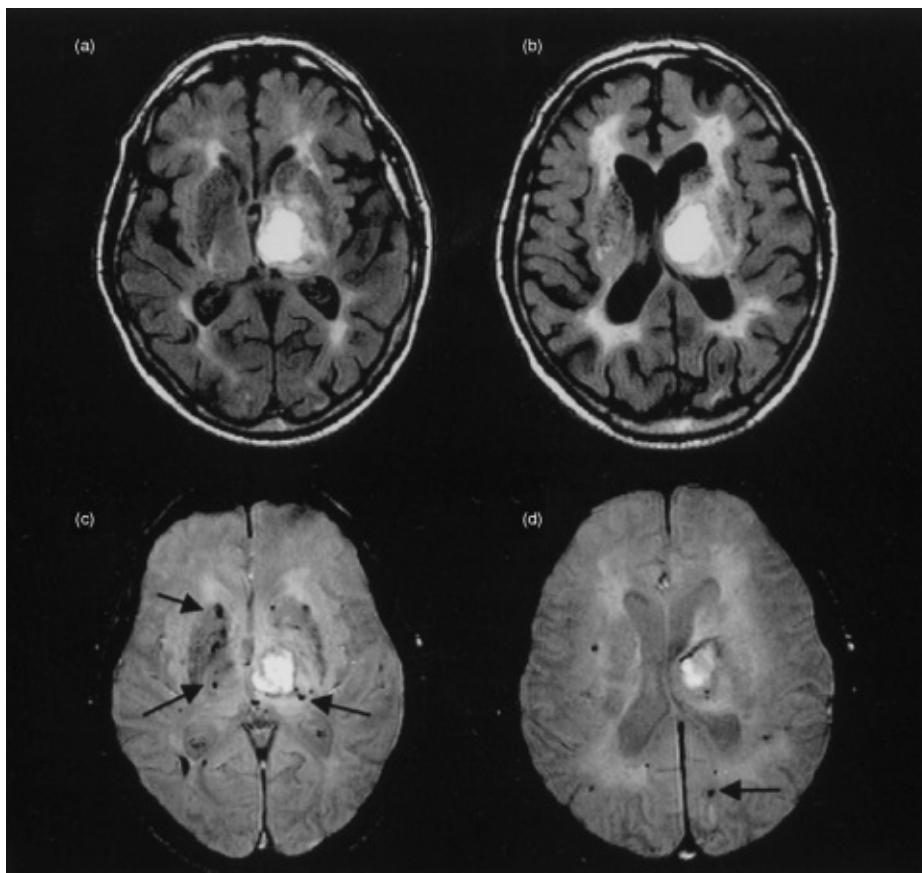
The term “intracerebral hemorrhage”, strictly applied, refers to bleeding into the parenchyma of the cerebral hemisphere, though it often is applied loosely to bleeding into any part of the brain, including the brainstem and cerebellum. This term may also be applied together with subarachnoid hemorrhage as the two often occur together. Similarly, intraventricular hemorrhage is almost always

seen with a parenchymal hemorrhage and/or a subarachnoid hemorrhage.

Intracranial hemorrhage is the third most common cause of stroke following atherosclerosis and embolism. The majority of non-traumatic hemorrhages are associated with hypertension or conditions that produce an acute increase in blood pressure, with ruptured vascular malformations or the use of anticoagulants. Intraparenchymal hemorrhage (IPH) represents nearly 15% of all strokes. Its clinical importance derives from its frequency and accompanying high mortality and morbidity. The overall mortality exceeds 25%, largely determined by the location and size of the hemorrhage, and the age of the patient. Age-adjusted annual incidence ranges from 11–31/100,000. The risk of IPH in African Americans is 1.4 times that of the white population.

## Imaging

Computerized tomography (CT) of the head remains the standard imaging modality for detecting an intracranial hemorrhage. Its high sensitivity and straightforward interpretation are particularly valuable. Advances in magnetic resonance imaging (MRI) have improved the sensitivity to the point that it is at least as good as CT acutely and superior for small hemorrhages after 12 hours, but rapid changes in the chemical composition of extravascular blood make interpretation more complex than CT. While MRI is the preferred test for excluding underlying causes of the hemorrhage, CT angiography may substitute for this purpose if the patient cannot have an MRI.



**Figure 70.1** Case vignette. a, b. MRI revealed no local lesion associated with the hemorrhage. c, d. Gradient echo T2-weighted imaging demonstrated innumerable microhemorrhages consistent with amyloid angiopathy.

## Can we differentiate hemorrhage from ischemic stroke clinically?

The typical hemorrhagic stroke occurs when the patient is awake and involved in some activity, including Valsalva maneuver or stress, which can elevate blood pressure. Severe headache is a reliable indicator of the presence of an intracranial hemorrhage, although it may not be present in small parenchymal hemorrhages. Hemorrhages are usually accompanied by acute anxiety, tachycardia, and significantly elevated blood pressure.

## Case vignette

The patient is a 66-year-old right-handed white male with a past history of mild, controlled hypertension. His wife had noted minimal cognitive disturbances in

the last couple of years. He was driving to his office one evening when he “heard” his car hit a car parked on the right side of the road. He got out to see what had happened and realized he had had an accident. He didn’t think that he had hit his head but felt somewhat confused and so he simply sat in his car. When the police arrived they found him confused and ataxic. He was arrested for drunk driving. After an hour in the police station a breathalyzer test was performed. When the blood alcohol level was found to be zero, he was transported to the nearest hospital where a CT scan revealed an intracerebral hemorrhage. He was transferred to Einstein Medical Center where an MRI revealed no local lesion associated with the hemorrhage ([Figure 70.1a, b](#)) but gradient echo T2-weighted (GRE T2) imaging ([Figure 70.1c, d](#)) demonstrated innumerable microhemorrhages consistent with amyloid angiopathy.

**Table 70.1 Differential diagnosis of acute ischemic stroke: characteristics of major stroke types.**

---

### Predominant risk factors

General comments: There is considerable overlap among the risk factors and certain factors, such as systemic inflammation, dehydration, and polycythemia, can increase the risk of any stroke mechanism

#### Atherosclerotic    Cardioembolic    Lacunar

Age > 45 years	Rheumatic	Hypertension
History of	valvular disease	Sleep apnea
MI/angina	Prosthetic	Cocaine abuse
Peripheral	valves	also
vascular disease	Atrial	Cigarette smoking
Family history	fibrillation,	Diabetes mellitus
of	with left	
atherosclerosis	ventricular	
Dyslipidemia	dysfunction or	
Cigarette	in patients > 65	
smoking	years old	
High or low	Recent anterior	
alcohol intake	wall MI	
Diabetes	Patent foramen	

menitus	ovale with
Sedentary	secondary
lifestyle	features such as
Type A	atrial septal
personality	aneurysm or
	leg DVT
	Aortic arch
	atheromas > 4
	mm thick or
	mobile

### **Useful signs on general physical exam**

General comments: The findings on general physical examination mirror the risk factors

<b>Atherosclerotic</b>	<b>Cardioembolic</b>	<b>Lacunar</b>
------------------------	----------------------	----------------

Carotid bruit	Murmurs	Elevated BP
Fundic emboli (platelet or cholesterol)	Irregularly irregular heart beat	Fundus changes of HTN
Decreased peripheral pulses	Splinter hemorrhages	Accentuated and tympanitic S <sub>2</sub>
Skin changes of vascular insufficiency in distal legs/feet		
Arcus senilis		
Ear lobe creases		
Tar stains on fingers		
Xanthelasma		

### **Common neurologic syndromes**

General comments: Strokes due to atherosclerosis and cardioembolus usually occur in the distribution of the bifurcating vessels of the circle of Willis or on the surface of the brain, that is, the leptomeningeal vessels. Strokes related to occlusion of the extracranial vasculature

are usually atherosclerotic (or dissections). Atherosclerosis tends to produce occlusions of the proximal portions of the intracranial vessels while cardioemboli tend to involve more distal branches. As a result, the complete cerebral artery syndromes are seen more often in atherosclerotic strokes and partial syndromes are more common in cardioembolic strokes. The hallmark of cardioemboli is multiple strokes in multiple territories. Lacunar strokes are in the distribution of the penetrating blood vessels, particularly the lenticulostriates, thalamostriates, and brainstem penetrators. The syndromes listed in this table are the most common, classical syndromes. [Table 70.2](#) and other chapters provide greater detail

<b>Atherosclerotic</b>	<b>Cardioembolic</b>	<b>Lacunar</b>
Ophthalmic artery: Transient monocular blindness MCA: Sensorimotor syndrome involving face $\geq$ arm > leg, may be accompanied by aphasia or other cognitive disturbances ACA: Sensorimotor syndrome involving leg > arm $\geq$ face. Both legs may be affected PCA: Homonymous hemianopia	Same syndromes as atherosclerosis, but may see: MCA: Motor > sensory, sensory > motor isolated aphasia or cognitive syndromes PCA: Isolated hemianopsia due to isolated involvement of the calcarine artery alone In addition, cardioembolic strokes are more likely to present with a seizure	Pure motor Pure sensory Cranial neuropathies involving any of the cranial nerves Strokes of the caudal medulla may be particularly difficult to localize due to crossing pathways at that level. Beware of bilateral leg weakness or quadriplegia with dysarthria, as medullary strokes are hard to recognize and produce significant disability if they progress

with significant  
memory,  
behavioral  
and/or language  
disturbance

Basilar:

Locked-in  
syndrome

Vertebral:

Wallenberg  
syndrome

## **Imaging**

The non-contrast head CT has a relatively low sensitivity for acute ischemic stroke. It is useful, however, to exclude intracranial hemorrhage and it may show prior strokes that give clues about the impact of the patient's risk factors. The typical acute stroke findings of loss of gray--white margins, hypodensity, and edema are subtle and often misleading. Occasionally, a dense MCA sign or hyperdensity in other vessels may be recognized. Diffusion weighted imaging (DWI) is exquisitely sensitive to acute ischemic stroke. T2-weighted FLAIR is useful for detecting prior strokes and T2-weighted sequences, such as GRE and SWAN, are useful for identifying prior microhemorrhages. Older fast spin echo T2 sequences remain useful for detecting brainstem ischemia and the major arteries. Computerized tomography angiography (CTA) and MRA are invaluable for demonstrating acute occlusion of the extracranial and cerebral vessels. Perfusion MRI and CT provide valuable physiologic information for guiding management decisions but are rarely required for diagnosis. Carotid duplex correlates well with stenosis but is only modestly sensitive to carotid ulcerations. Transthoracic echocardiography (TTE) is a valuable first test to identify low ejection fraction, ventricular wall abnormalities, valvular heart disease, patent foramen ovale (when combined with bubble contrast) and other less common conditions, including cardiac tumors. When suspicion of cardioembolus or endocarditis is high and transthoracic imaging is negative, transesophageal echocardiography (TEE) provides greater sensitivity

Atherosclerotic	Cardioembolic	Lacunar
CT or DWI demonstrate territorial infarction of the MCA, ACA, or PCA territories. Calcifications of vertebral and other arteries may be apparent on CT CTA and MRA show multiple regions of stenosis Carotid duplex will often show plaque at the carotid bifurcations TTE may show ventricular wall motion abnormalities	CT or DWI show acute infarcts in branches of the major cerebral vessels CT and T2-FLAIR show chronic infarcts near the cortical surfaces (gray--white junctions) in multiple distributions Extracranial and intracranial stenoses are absent or mild TTE and TEE demonstrate the risk factors for cardioembolism discussed above	DWI demonstrates infarcts that are typically < 2 cm in the distribution of a penetrating artery CT and T2-FLAIR often show prior lacunar strokes and evidence of ischemic small vessel disease in the deep hemispheric white matter. While there may be rare intracranial stenoses on CTA or MRA, and diastolic dysfunction or LVH on TTE, the typical findings of atherosclerosis and cardioembolism are lacking

ACA, anterior cerebral artery; BP, blood pressure; CT, computerized tomography; DVT, deep vein thrombosis; DWI, diffusion weighted imaging; FLAIR, fluid attenuated inversion recovery; GRE, gradient recalled echo; HTN, hypertension; LVH, left ventricular hypertrophy; MCA, middle cerebral artery; MI, myocardial infarct; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PCA, posterior cerebral artery; SWAN, susceptibility weighted angiography sequences.

**Table 70.2 Ischemic stroke territories.**

## Carotid distribution

Internal carotid artery territory. The middle cerebral artery (MCA) syndrome may be indistinguishable from occlusion of the complete internal carotid artery (ICA). When the circle of Willis (CoW) is complete, the anterior cerebral artery (ACA) territory will be spared by diversion of blood from the contralateral ICA but if the CoW is incomplete, the patient may experience a combination of MCA and ACA injury. In some cases of distal ICA, the ophthalmic artery may be occluded and the patient will have symptoms from that vessel along with the MCA. There is also considerable variability in the distal branching of the MCA. Because all regions of cortex are activated by the thalamus, thalamic lesions may mimic any syndrome of the cerebral arteries but, in thalamic lesions, true corticospinal tract signs are absent.

Occluded artery	Structures involved	Symptoms	Differential
MCA, complete	Most of the cerebral hemisphere, including frontal, temporal, parietal, and insular cortex as well as the basal ganglia and internal capsule. The territory is variable but usually extends from Broca's area and lateral frontal lobe to the posterior	Overwhelming contralateral deficits of hemiparesis and hemisensory loss to all modalities with face and arm worse than leg; gaze paresis; hemineglect; often hemianopia and global aphasia if the dominant hemisphere is involved	Complete ICA occlusion; may be difficult to distinguish from distal MCA occlusion clinically. Rarely, severe thalamic lesions may produce a similar syndrome

	parietal lobe where the optic radiations or upper half of optic radiations may be involved		
MCA, distal	Most of the cerebral hemisphere, including frontal, temporal, and parietal cortex (often including the optic radiations). Insular involvement is variable and often partial; basal ganglia and internal capsule are spared	Severe contralateral deficits of hemiparesis and hemisensory loss to all modalities with face and arm worse than leg; gaze paresis, hemineglect; often hemianopia and global aphasia if the dominant hemisphere is involved. May find unusual posturing and tone of arm or leg due to sparing but denervation of the basal ganglia	Proximal MCA or distal ICA may be difficult to distinguish. Branch occlusions of the MCA rarely produce this full syndrome and can be distinguished on careful examination. Severe lesions of the thalamus may mimic this syndrome

MCA, superior branch	One artery supplies the orbital frontal lobe, including Broca's area, and dorsolateral frontal lobe, including the frontal eye fields; a second artery supplies the pre-central and post-central gyri	Non-fluent expressive aphasia and gaze paresis from the orbito-frontal artery; hemiparesis--hemisensory disturbance of face and arm greater than leg from pre-Rolandic and Rolandic branches	Basal ganglia infarcts may produce similar motor features but aphasia and gaze paresis are infrequent; thalamic infarcts can mimic nearly any cortical lesion but do not produce Babinski and rarely produce a gaze paresis
MCA, inferior branch	There are three temporal branches, one branch to the angular gyrus and two parietal branches	Aphasia, amnesia, and behavioral changes result from temporal branch insults; the angular branch produces Gerstmann's syndrome in the dominant hemisphere and spatial confusion in the non-dominant hemisphere; parietal branch occlusions produce	This is may be very difficult to distinguish from thalamic or posterior cerebral artery syndromes, especially if the lateral geniculate is involved. Often the stroke risk factors are as helpful as the neurologic syndrome since thalamic strokes are often lacunar while PCA strokes are often cardioembolic or atherosclerotic

		symptoms of agnosia, neglect, transcortical sensory aphasia, and occasionally hemi- or quadrantanopia	
Anterior cerebral artery	Medial surface of the frontal and parietal lobe, including the orbito-frontal cortex, supplementary motor cortex, primary motor and sensory cortex for the leg (paracentral lobule), corpus callosum, cingulate gyrus, and the head of the caudate (via the recurrent artery of Heubner)	Paralysis and sensory loss in the contralateral leg and foot; urinary incontinence; impairment of gait and stance (gait “apraxia”); abulia; reduced emotional range; perseveration; aphasia; dysexecutive syndrome; frontal lobe release signs	The same structures may be affected by midline tumors such as a falk meningioma and by hydrocephalus. Parkinson's disease and other Parkinsonian syndromes, including frontotemporal dementias, may produce similar symptoms and signs. Metabolic or immune-mediated encephalitides may also resemble this stroke
Ophthalmic artery	The retina, extraocular muscles, levator palpebrae	Transient or permanent monocular blindness is the hallmark of	Central retinal artery occlusion produces similar visual loss but when the deficit is

**purple** superioris, the lacrimal gland, the conjunctiva, the muscles and skin of the forehead, the posterior ethmoidal sinuses, and the frontal meninges

**the hallmark of** ischemia in this distribution and overwhelms the presence of other symptoms or signs. Aching pain above the orbit is common in the acute syndrome. Conjunctival injection may occur in chronic ischemia

**when the defect is** fixed, it is usually possible to identify a peripheral rim of light perception due to blood flow through ciliary arteries. The actual site of occlusion may reside in the distal ICA rather than the ophthalmic itself, in which case symptoms of MCA ischemia may also be present. Retinal detachment is usually heralded by floaters and blindness progresses over days rather than minutes. While atherosclerotic cerebrovascular disease is the most common cause, temporal arteritis, arteritic, and non-arteritic ischemic optic neuropathy may also cause this syndrome. Transient monocular blindness (“amaurosis fugax”) is usually caused by an ulcerated plaque at

## the carotid bifurcation

### Vertebro-basilar distribution

All of the causes of stroke that affect the carotid distribution also affect the vertebro-basilar distribution. Atherosclerosis still occurs at bifurcations, such as the take-off of the posterior inferior cerebellar artery (PICA) from the vertebral or the bifurcation of the basilar into the posterior cerebral arteries. Cardioembolic strokes which enter the posterior circulation are likely to continue straight up the basilar and either lodge at the top of the basilar or head out one of the posterior cerebral arteries. Lacunar strokes arise frequently in the midline penetrators, short circumflex, or long circumflex arteries that arise from the basilar, the vertebrals, or the proximal portions of the posterior cerebral arteries.

Occluded artery	Structures involved	Symptoms	Differential
Posterior cerebral artery (PCA), complete from origin of the basilar	Thalamus, occipital lobe, medial surface of the temporal lobe	Hemiplegia, hemianesthesia, hemianopia, and aphasia or severe disorientation and behavioral changes with confusion. There may be visual hallucinations or other disturbing visual changes	Complete MCA occlusion. Distinguishing features include more prominent hemianopia, greater behavioral disturbances, and the absence of a Babinski in PCA strokes because the weakness is

due to thalamic involvement and the corticospinal tract is often spared

PCA, calcarine branch	Occipital lobe	Hemianopia or quadrantanopia; less commonly color blindness or dyslexia without agraphia	Patient may complain of monocular blindness. Confirm monocular by history of cover-uncover testing. Bilateral calcarine lesions produce “cortical blindness”
PCA, temporal branch	Medial and inferior surfaces of temporal lobe, including hippocampus and amygdala	Amnesia and behavioral changes, visual neglect, visual hallucinations	This is very difficult to distinguish from drug intoxication, psychotic illness, partial complex seizures, limbic encephalitis, etc.
Thalamostriate perforators	Thalamus, occasionally the third nerve complex or supranuclear	Contralateral hemisensory loss or dysesthesias, hemiparesis,	Because the thalamus projects and activates virtually all

	oculomotor pathways, the dentatothalamic tract, rarely the subthalamic nucleus	choreoathetosis, tremors, limb ataxia, spasms of hands, memory loss, aphasia, complex visual disturbances. Bilateral lesions reduce the level of consciousness. Occasionally a top of the midbrain syndrome may occur with third nerve palsies. Hemiballismus occurs if the subthalamic nucleus is involved	areas of cerebral cortex, lesions of the thalamus can mimic virtually any syndrome that can occur with cortical lesions. Bilateral thalamic lesions do occur (artery of Percheron) and can be confused with encephalopathy or upper midbrain syndromes. Pupillary and ocular motility involvement helps to distinguish from encephalopathy
Anterior choroidal artery	Posterior limb of internal capsule inferiorly, medial pallidum, cerebral peduncle, thalamus	Contralateral hemiparesis, hemianesthesia, and hemianopia	MCA syndrome
Basilar artery	Most of pons	Quadriplegia, sensory loss, and autonomic dysfunction	Neuromuscular dysfunction

(or single vertebral artery)	and midbrain. Bilateral thalamus, occipital and medial temporal cortices also may be affected, depending on CoW collaterals	quadraparesis, ophthalmoplegia sparing upgaze. May also have cortical blindness, coma or severe alteration of consciousness. Cerebellar signs may be difficult to detect. Sensation may be normal	paralysis of any cause when consciousness is preserved; encephalopathy or encephalitis when consciousness is lost (skew eye deviation and abnormal doll's eyes are key elements for recognizing basilar)
Vertebral artery	Medial medulla, including CN XII on exiting medulla as well as the pyramidal tract and the medial lemniscus	Ipsilateral paralysis with atrophy of the tongue. Contralateral hemiparesis sparing the face and loss of touch and proprioception	Internal capsule strokes may spare the face and do not involve the tongue
Posterior inferior cerebellar artery (PICA)	Lateral medulla, including descending tract or nucleus of V, vestibular nuclei, sympathetics, emerging CN IX and X, nucleus solitarius	Ipsilateral loss of pain sensation on face, ataxia of gait and limbs, nystagmus, Horner's syndrome, paralysis of vocal cord, diminished gag, <b>hemianesthesia</b>	May be impossible to distinguish from occlusion of vertebral artery or a major branch. Basilar meningitis would rarely present in similar manner

	Somatosensory	Hemianesthesia	Other findings
	cuneate and gracile nuclei, and spinothalamic tract	to touch and proprioception. Contralateral hemianesthesia to pain and temperature. Also may have nausea, vertigo, vomiting, hiccups, dysphagia, and hoarseness	
Paramedian branches of the basilar artery	Corticospinal and corticobulbar tracts, middle cerebellar peduncle, medial longitudinal fasciculus. Inferiorly also the pontine gaze center, abducens nerve, and vestibular nuclei	Ipsilateral gaze paresis, horizontal diplopia (CN VI palsy inferiorly), nystagmus, limb and gait ataxia. Contralateral hemiparesis that may spare the face. May have contralateral hemisensory disturbance inferiorly	This midline, or paramidline, syndrome can present an extreme diagnostic challenge because it may present with bilateral leg or simply generalized weakness, with or without dysarthria. In the absence of sensory or oculomotor disturbance it can be confused with metabolic or syncopal syndromes. Note, however, that

consciousness  
is not routinely  
affected

Anterior inferior cerebellar artery	CN VI, VII, VIII nerves or nuclei; pontine gaze center, middle cerebellar peduncle and cerebellar hemisphere, spinothalamic tract, and descending tract of CN V	Ipsilateral nystagmus, facial paresis, lateral gaze palsy, deafness or tinnitus, ataxia, facial sensory disturbance. Nausea, vomiting, and oscillopsia are common. Contralateral anesthesia for pain and temperature	When vestibular symptoms predominate, a labyrinthitis or vestibular neuronitis is suspected, especially when the severity of symptoms makes detailed neurologic exam difficult so that central signs are less apparent
Short circumflex branch of the basilar artery	Middle cerebellar peduncle, nucleus of CN V (motor and sensory)	Ipsilateral limb ataxia, paralysis, and abnormal sensation on the face	When facial paresis dominates, a Bell's palsy is suspected, especially since patients with Bell's palsy routinely complain of “numbness” on their face. Limb ataxia or actual sensory disturbance on exam

			distinguishes the two
Superior cerebellar artery	Middle and superior cerebellar peduncles, superior cerebellum and dentate nucleus; sympathetic fibers, spinothalamic tract, and lateral medial lemniscus	Ipsilateral limb and gait ataxia, falling toward lesion, horizontal nystagmus, gaze paresis, skew deviation, Horner's syndrome. Often with vertigo, nausea, and vomiting. Contralateral sensory disturbance to all modalities	This syndrome is relatively distinctive and the primary differential is to distinguish lesions that are slightly rostral in the midbrain or caudal in the pons. The absence of contralateral hemiparesis is against midbrain

**Table 70.3 Classification of intracranial hemorrhages.**

Location	Pathophysiology	Clinical features	Radiology
<b>Epidural (extradural) hematoma</b>			
Between the dura and the skull, typically over the lateral cerebral convexities	Trauma; associated skull fracture tearing the dural arteries (middle meningeal artery in 90%), rarely venous or dural sinus. 100 mL of	Classic presentation is concussion followed by lucid interval and then rapidly progressive hemiparesis	CT shows biconvex hyperdense clot outside the lateral cerebral convexities. Plain films show skull fracture crossing groove of middle

blood can be fatal

with loss of consciousness. Lucid interval may be absent in more severe injuries.

Progresses to asymmetric herniation syndrome.

Hemiparesis may be false localizing but pupil dilatation is always ipsilateral to lesion

## **Subdural hematoma (SDH)**

Within a potential space between the lamina of the dura mater

Chronic SDH are usually due to minor trauma injuring the bridging veins. Associated with atrophy, anticoagulation, severe cerebral atrophy, or intracranial hypotension. Acute SDH are traumatic and associated with laceration of the parenchyma

Gradual increase in headache and altered mentation over weeks or months. May present with hemiparesis, seizures, or ataxia. Acute SDH resemble epidural hematomas clinically

CT shows crescentic shaped blood extra-axially. Appears hyperdense < 1 week, hypodense after ~3 weeks and isodense in between. When isodense, may be suspected by loss of underlying sulcal markings. MRI or contrast CT will reveal the hematoma

## **Subarachnoid hemorrhage (SAH)**

Within the subarachnoid space over the convexities or in the basilar cisterns (see below)	Usually arterial bleeding due to trauma, or a ruptured aneurysm or other vascular malformation	Typically a dramatic onset of the “worst headache ever,” frequently with altered consciousness and focal deficits that depend on location. Meningismus is common	CT scan reveals blood over convexity or in the cisterns with about 90% sensitivity. MRI may be slightly more sensitive. LP reveals blood or xanthochromia. Caution that blood may not be present during the “sentinel syndrome of SAH” when the wall of the aneurysm has infarcted but not yet ruptured. CT, MR or conventional angiography is required to detect the aneurysm in those cases
---	--	--	---

### Intraparenchymal (intracerebral) hemorrhage (ICH or IPH)

Within the actual brain tissue, most commonly the basal ganglia, cerebellum, or pons	Usually arterial bleeding from hypertensive vasculopathy or amyloid angiopathy. Also may result from small intraparenchymal vascular	Sudden onset of severe headache, accompanied by focal neurologic deficits that vary with location. Headache may	CT is over 95% sensitive to clinically relevant hemorrhages. MRI (GRE or SWAN) will detect microhemorrhages associated with amyloid
--	--	---	---

malformations (see below)	be absent in smaller hemorrhages. Altered consciousness accompanies brainstem, thalamic, or large hemorrhages. Anticoagulation or intensive antiplatelet therapy increase risk	angiopathy or multiple cavernous malformations. LP is not indicated
------------------------------	--	---

### Intraventricular hemorrhage (IVH)

Within the ventricles	Usually associated with ICH or SAH. Primary IVH is rare except in germinal matrix hemorrhages of prematurity	Presentation is of ICH or SAH. The primary complication of IVH per se is hydrocephalus	CT is diagnostic. Watch for casting of the aqueduct of Sylvius or fourth ventricle which is associated with rapid deterioration
-----------------------	--	--	---

CT, computerized tomography; GRE, gradient recalled echo; LP, lumbar puncture; MRI, magnetic resonance imaging; SWAN, susceptibility weighted angiography sequences.

**Table 70.4 Intracranial hemorrhage.**

Pathophysiology	Clinical	Diagnostic testing
-----------------	----------	--------------------

STRUCTURAL

### Arteriovenous malformations (AVM)

A tangled collection of vessels between arteries and veins lacking the normal microvascular architecture. There is surrounding disturbance of blood flow and autoregulation (cerebral steal)	Up to 50% present with SAH, typically less severe than from an aneurysm. One tenth as common as saccular aneurysms, no gender preference, often in 2nd or 3rd decade. May present with seizure (20%), headaches (20%), or focal or cognitive deficit. Auscultation may detect a bruit. Suspect AVM when migraines are STRICTLY unilateral	CT reveals lobar or deep SAH. Large veins or displaced parenchymal architecture may be apparent. MRI is usually diagnostic with ICHSA surrounded by prior old hemorrhages and serpentine flow voids on GRE and MRA usually reveals the extent of the lesion but conventional angiogram required for accurate therapeutic decisions. It can miss significant AVMs, however, especially at the surface
--	---	--

## Pial AVM

A nidus of abnormal vessels with arteriovenous shunting entirely within the dural leaflets. May have extracranial or intracranial feeders

Typically present with SAH before the age of 40

Imaging reveals a superimposed lobar hematoma, usually adjacent to the AVM

## Dural AVM

Most are idiopathic but may arise from prior venous sinus thrombosis, associated vascular atresia, severe head injury, or Osler-Weber-Rendu syndrome

Usually present with headache in association with findings of increased ICP. Less commonly with SAH, ICH, or SDH

Mostly at the cerebral convexity of anterior fossa. MRI/MRV may suggest a fistula. Conventional angiogram with venous phase confirms diagnosis

## Weber–Rendu syndrome

### Venous angioma

Most common entirely venous AVM

Most are clinically silent with small bleeding risk. Often found “incidentally” during evaluation of headache or seizures. Relationship then difficult to ascertain

Contrast CT reveals dilated veins extending in radiating pattern on the cortical and ependymal surface

### Cavernous angioma or malformation

Low flow vascular anomaly with sinusoidal endothelial channels without muscle or elastica. No arterial feeders. Often thrombose, hyalinize, or calcify as a cyst. Familial cases, especially in Mexicans, linked to chromosome 7q

Commonly present with seizure (30–70%), focal neurologic deficits, or intraparenchymal hemorrhage (up to 30%). May be found on evaluation of headaches but relationship is unclear. May produce progressive disability from recurrent hemorrhages, suggesting other diagnoses

CT may show an intraparenchymal hemorrhage in subcortical white matter, especially temporal lobe and pons. CT may also show adjacent calcification suggesting correct diagnosis. MRI shows irregular lesion bright on T2 with surrounding hemosiderin ring. GRE sequence SWAN often reveals numerous similar lesions, especially in familial cases, which should be distinguished from amyloid angiopathy (AA). AA differ because of more numerous, smaller sizes, some being large and confluent. Conventional angiogram may be normal or show “avascular” capillary beds.

### Intracranial aneurysm (saccular or “berry”)

Etiology not fully understood. Arise at branch points of

Aneurysms are the most common cause of nontraumatic SAH (80%)

CT reveals SAH in most cases. LP will reveal blood or xanthochromia in some cases.

**Causes:** Branch points of hemodynamic stress. Thought to involve intracranial vessels because of limited wall thickness with thinner muscular, elastica, and adventitial layers. Up to 85% are in the anterior circulation, most commonly anterior communicating (A comm), posterior communicating (P comm), or middle cerebral artery (MCA) origin or MCA trifurcation. Posterior circulation aneurysms are usually at basilar tip or origin of PICA. Risk of rupture low when less than 7 mm. Moderate size and asymmetric aspect ratio increase risk of SAH. Up to 15% of SAH may be non-aneurysmal “perimesencephalic” hemorrhages. Venous etiology has been proposed for these

**Symptoms:** Frequently associated with adjacent intraparenchymal hemorrhage. Between 1 and 6% of adults harbor aneurysms. Mean age of SAH is 50 years. Trigger is usually an event which elevates blood pressure. Risk factors for aneurysm include cigarette smoking, hypertension, polycystic kidney disease, Ehler–Danlos syndrome (IV), Marfan syndrome, and neurofibromatosis Type I. Cigarette smoking increases risk of rupture. Presentation is typically “worst headache ever,” often with loss of consciousness, nausea, and vomiting, with or without focal neurologic deficits. Up to one third of all patients with SAH have visited their family doctor or an emergency department within 2 weeks of the SAH with the sentinel syndrome of SAH which resembles SAH but with less severe headache

**Diagnosis:** Additional imaging studies should be considered whenever aneurysm is suspected because of a typical headache with associated symptoms. (may approach 99% sensitivity). Conventional angiography is confirmatory and provides evidence of other aneurysms and details necessary for therapeutic planning. Transcranial Doppler and perfusion imaging are useful for following patients with SAH for vasospasm. Perimesencephalic SAH tends to be relatively symmetric and may extend part of the Sylvian fissure

The origin of this syndrome is not clear but may not involve a

“leak” but rather infarction or inflammation of the aneurysm wall. P comm aneurysms frequently present with local headache and an isolated CN III palsy. It is distinguished from the “diabetic third” which spares the pupil, because the aneurysm nearly always compresses pupillary fibers. Vasospasm following SAH is responsible for much of the disability among those who survive the initial SAH. Perimesencephalic SAH carries a more benign prognosis with most making good recoveries although cognitive deficits may be detectable

## Moya Moya

Idiopathic progressive stenosis of the distal internal carotid artery branches at the circle of Willis with extensive collateralization in the region of the basal ganglia giving

Presents with ischemic symptoms in children but increased relative risk of hemorrhage when presenting in adults (up to 20%). Peak incidence is 5 years of age, but adults tend to present about age 40. May present with focal

Parenchymal hemorrhage to occur periventricularly. SAH may be present. CTA demonstrates the vascular stenoses or occlusions often suggests the extensive collateral pattern. FLAIR sequences may show hyperintense signal “ivy sign” of collateral vessels. Conventional

rise to a characteristic name – “puff of smoke.” Strong predilection for Asian population but seen in all races. May be associated with aneurysms, microaneurysms, and pseudoaneurysms

deficits. Seizures, headaches, choreiform movement disorders, and cognitive deficits are less common presentations

angiography is diagnostic required for planning interventions

## Sickle cell disease (SCD)

Strokes in SCD present as ischemia in children but more commonly as intracranial hemorrhage in adults. Bleeding may be subarachnoid, parenchymal or a combination of the two. A “pseudo-Moya Moya” pattern may result. Multiple aneurysms may be present and lead to SAH

Hemorrhages account for one third of strokes in SCD. The peak incidence of intracranial hemorrhage is between ages 20 and 29. Two independent risk factors include chronic low steady state hemoglobin and increased steady state leukocyte count. IPH is more common and differs somewhat from those seen in chronic hypertension because of a higher incidence of seizures at onset and lower incidence of severe hemiplegia. After SAH, associated IVH may lead to obstructive hydrocephalus

CT and MRI retain the value. Angiography is important to identify st collaterals, and aneurysms. Family history and race identify people at risk. Hemoglobin electrophoresis diagnostic

## DRUGS, TOXINS, AND SYSTEMIC DISEASES AFFECTING COAGULATION



## **Anticoagulation (warfarin, direct thrombin or Xa inhibitors, red clover heparin and heparinoids)**

Up to 15% of intracranial hemorrhages may be related to anticoagulant exposure. Risk increases with age (> 75), falls, hypertension, and the intensity of anticoagulation. Newer agents appear to have a lower, but non-vanishing, risk. Duration of exposure also likely to correlate with risk

Onset with IPH or SAH is usually rapid and dramatic but SDH may be indolent. Hematoma expansion until reversal of the anticoagulation is the rule. Additional challenge without strong evidence-based guidance is whether and when to re-start anticoagulation based on the risk of recurrence of the original disease indication

CT demonstrates the hemorrhage, often after prior cardioembolic stroke. Multiple hemorrhages are present. Contrast enhancement on CTA may predict continuing expansion ("sign"). GRE and SWI sequences can identify microhemorrhages from amyloid angiopathy or multiple cavernous malformations, in which further anticoagulation contraindicated

## **Antiplatelet agents and non-steroidal anti-inflammatory agents (NSAII)**

All antiplatelet agents are associated with an increased risk of intracranial hemorrhage, especially when used in combination or with concomitant anticoagulation. Predilection for lobar hemorrhages suggest that many may be related to simultaneous ischemic microvascular disease and amyloid

Risk increases with hypertension, non-white race, renal failure, trauma, age > 75, excessive bruising or bleeding, associated intracranial vascular or neoplastic lesions, and, possibly, in diabetics

CT demonstrates lobar hemorrhage in most cases. MRI is useful to identify underlying lesions and MRI sequences can reveal prior microhemorrhage

## **and amyloid**

angiopathy

### **Thrombolytic therapy for ischemic stroke**

Risk of a symptomatic intracranial hemorrhage after intravenous tPA is between 2 and 6%. Typically IPH but may also have SAH.

Hemorrhage following intravenous thrombolysis usually occurs between 12 and 36 hours post treatment. There is usually a dramatic change in vital signs and obvious worsening of the neurologic deficit. Risk of hemorrhage increases with increasing age, NIH stroke scale, uncontrolled hypertension, and uncontrolled blood sugars

Hemorrhages are typical within the basal ganglia, lobar. Radiologic predictors of hemorrhage include involvement of more than one third of the MCA territory on CT, an ADC value below  $550 \times 10(-06) \text{ mm}^2/\text{s}$  on diffusion MRI and absence of perfusion in the core of the ischemic territory on CTP MRI perfusion imaging. Amyloid angiopathy does appear to be a major risk factor.

### **Alcohol**

Alcohol increases the risk of hemorrhage by elevating blood pressure, leading to falls, motor vehicle accidents, or altercations, and by altering both the clotting cascade and platelet function. Other predisposing medical complications may arise with chronic alcoholism

SDH and IPH are the most common types of hemorrhage although SAH may also occur. Trauma is often apparent or suspect. History or physical findings often suggest chronic alcoholism. Alteration of consciousness may occur because of the hemorrhage, intoxication, withdrawal, seizures, hepatic encephalopathy, or a

SDH often reveal mixed findings with acute and chronic hemorrhage as well as hygroma. Parenchymal hemorrhage tends to be large. Evidence of past or remote trauma may be apparent

combination

## Hemophilia

Hemophilia A, an inherited, X-linked, recessive disorder caused by deficiency of functional plasma clotting factor VIII (FVIII), presents in adults when the deficiency is mild (levels > 5% but < 40%). Disruption of the normal intrinsic coagulation cascade results in spontaneous hemorrhage or excessive hemorrhage in response to trauma. Low levels of FVIII may arise from a defect in von Willebrand factor (vWF) which is an autosomal dominant condition. Acquired hemophilia, from development of autoantibodies to FVIII, can be idiopathic (age > 50 years), related to connective tissue disorders, or drugs (penicillin)

More common in males as it is X-linked recessive, often with a family history of bleeding disorder. Intracranial hemorrhage and hemorrhage involving the airway are the most important life-threatening complications. Other neurologic complications include bleeding into the spinal canal, and peripheral nerve compression resulting from expanding hematomas. The lifetime risk of intracranial bleeding is 2–8% in hemophilia A despite the current use of factor VIII replacement. Co-existent parvovirus B infection (with resultant bone marrow suppression), hepatitis B, and hepatitis C (with resultant liver failure) can occur as a complication of factor replacement and increase the risk for hemorrhage. The clinical features are dependent on the

CT of the head is the imaging of choice. The location of the hemorrhage. There may be epidural/subdural/subarachnoid hemorrhage if the bleed is secondary to trauma. MRI helps characterize of the bleed and identify hemorrhages. MRA rules out other causes of lobar hemorrhage *i.e.* vascular malformations. Blood tests should include aPTT, PT, INR and platelet count. A prolonged aPTT and a normal PT may indicate an abnormality in the early part of the intrinsic coagulation pathway. However, if the FVIII deficit is mild the aPTT may be normal. FVIII and FV assays are important to the diagnosis. In von Willebrand disease bleeding time is prolonged and vWF levels are low.

Hemophilia B, due to deficiency of factor IX (FIX), is an inherited X-linked disorder

location of the ICH but may include headache, stiff neck, vomiting, lethargy, irritability, and focal signs

## Platelet disorders

Idiopathic thrombocytopenic purpura (ITP) is a benign self-limiting disorder which occurs in young adults, and results from autoantibodies to platelets causing platelet dysfunction. Thrombocytopenia occurs in association with drugs such as cytotoxic agents, furosemide, antiepileptic agents, thienopyridines, and antimalarial agents. It could also be a consequence of severe sepsis, disseminated intravascular coagulation, uremia, liver failure, or alcohol.

Thrombotic thrombocytopenic purpura (TTP) patients have large multimers of von

In ITP, TTP, or drug-induced thrombocytopenia, the risk of ICH is surprisingly low until platelet counts fall below 20,000. However, the risk increases substantially with trauma. In TTP, neurologic symptoms are often accompanied by fever and renal dysfunction. Evidence of DIC is lacking. The mortality rate associated with ICH in ITP is similar to that of spontaneous ICH.

CT demonstrates lobar hemorrhage in most cases occasionally with SAH. Microscopic slit hemorrhages that are seen pathologically often invisible on CT, but MRI is useful to identify underlying lesions and MRI sequences can reveal prior microhemorrhage.

Willebrand's factor in their plasma due to a deficiency of the protease ADAMTS13

## INFECTIVE/POST-INFECTIVE

### Infective endocarditis

Endocarditis may be caused by Gram+ or Gram- cocci, or fungi. Particularly common are *Staphylococcus aureus*, *viridans streptococci* and *enterococci*, *Aspergillus*, and *Candida* species. Up to one third of infection-related intracranial hemorrhages occur due to transformation of ischemic infarcts caused by septic emboli. Mitral valve involvement carries a higher risk of emboli than aortic valve. Mycotic aneurysms are also a risk due to infection of the vasa vasorum, and typically involving the distal or pial vessels of the cerebral arteries.

Intracerebral hemorrhages account for up to 30% of neurologic complications of infective endocarditis. The combination of stroke with encephalopathy should always raise suspicion of infective endocarditis and lead to blood cultures, echocardiography, and expectant therapy. Risk factors include chronic otitis media (temporal lobe), sinusitus (frontal lobe), valvular heart disease, including prosthetic valves, intravenous drug abuse, and possibly dental procedures without antimicrobial prophylaxis. Antibiotic treatment reduces long-term but not short-term risk of hemorrhage. Anticoagulation is contraindicated, even in

Superficial parenchymal hemorrhages and infarcts local subarachnoid hemorrhages are suggestive of infective endocarditis with mycotic aneurysms. Conventional angiography is usually required to demonstrate aneurysms themselves. Blood cultures are the mainstay of diagnosis. Echocardiography is extremely helpful. Transthoracic ECHO is diagnostic but transesophageal ECHO is more sensitive and may provide more definitive visualization of certain

the presence of septic emboli

## Infectious vasculitis

The classical pattern is of a vasculitis of the vessels at the base of the brain (meningovasculitis) due to tuberculosis or fungi (including coccidioides, cryptococcus, histoplasma). More distal and/or anterior circulation involvement suggests a bacterial or viral agent.

Pathophysiologic mechanisms may include direct infection or immunologic mechanisms (antibody, immune complex, or cell mediated)

Intraparenchymal or subarachnoid hemorrhages are actually uncommon in these conditions which are dominated by patterns of ischemic stroke and encephalopathy in the setting of fever and systemic illness, often with meningismus

CT or MRI shows small parenchymal or subarachnoid hemorrhages in the setting of ischemic stroke, often with basilar meningitis. CT/MRA, or conventional angiography demonstrate luminal irregularities. Cerebral examination is usually diagnostic with positive microscopy, PCR or culture

## CHRONIC AND ACUTE HYPERTENSION

### Chronic hypertension

Hypertension plays a role in up to 80% of intraparenchymal hemorrhages. The vascular changes of chronic hypertension

These hemorrhages are proportionately more common in African Americans and Asians than in whites. Onset usually involves sudden

Globular or irregular hemorrhages in the deep cerebral hemispheres are typical. ICH less than 30ml calculated by the abc/2 rule usually have a favorable

**Chronic hypertension** include arteriolar fibrinoid necrosis, lipohyalinosis, and media degeneration with Charcot–Bouchard aneurysms. These changes occur much more frequently in the penetrating arteries and arterioles serving the basal ganglia, including the thalamus, and the basis pontis

**usually involves sudden onset of a neurologic deficit with headache and dramatic elevation of blood pressure and heart rate.** There is frequently reduced level of consciousness. Bringing the systolic blood pressure close to 140 mmHg is of critical importance in preventing expansion of the hemorrhage in the first 6 hours. However, it is also important to avoid lowering blood pressure by more than 25% of the estimated chronic mean arterial pressure to avoid ischemic complications

**usually have a favorable prognosis.** Hemorrhages mL that involve the deep hemispheres virtually universally lead to death permanent total care. M shift > 4 mm and IVH the risk of severely negative outcome. Repeat imaging hours is recommended to ensure cessation of bleeding and beyond 24 hours to establish the absence of hydrocephalus, especially the presence of intraventricular extension. MRI, and especially GRE type sequences, is useful for excluding underlying lesions or demonstrating hemorrhages

## Acute changes in blood pressure

IPH can be caused by sudden, acute changes in blood pressure independent of the changes of chronic hypertension. These may be related to sudden isolated changes in blood pressure due to sympathomimetic stimulation or more complex patterns in which the sudden changes in blood pressure occur in

Clinical pattern of the acute hemorrhage is similar to that of chronic hypertension. However, the stimulus is often distinctive and may include: sleep apnea, cold-related ICH, stimulations of the trigeminal nerve as in dental procedures, cardiac surgery, break dancing, ECT, with migraines, activities associated with Valsalva maneuver such as

Imaging patterns and usefulness are similar to those of chronic hypertension

relationship to more complex physiologic changes such as found in sleep apnea and pregnancy. ECT, for example, may simultaneously increase arterial, venous, and intracranial pressures

vomiting and coughing, sexual climax, strenuous physical activity such as weight lifting, and emotional or stressful situations

### **Hyperperfusion syndrome after carotid endarterectomy or stent**

The exact etiology and pathogenesis of this condition which follows carotid revascularization are not well established. In fact, there is evidence that this is really a hyperdynamic condition with reduced perfusion of the parenchyma at the microvascular level

The “hyperperfusion” syndrome occurs hours to weeks after a carotid procedure, virtually always accompanied by absolute or relative hypertension. Bilateral critical stenoses appear to increase the risk. Close observation and management of blood pressure after the procedure is the best means of avoiding this complication

CT may demonstrate either basal ganglia or lobar hemorrhages

### **Pregnancy-related hemorrhage**

Pregnancy is accompanied by complex physiologic changes which increase the risk of intracranial hemorrhage including systemic

The clinical presentations of IPH or SAH related to pregnancy are the same as in chronic hypertension or in the presence of a saccular aneurysm, respectively.

During gestation, it is preferable to avoid the radiation and contrast associated with CT so that MRI is considered a safe and sensitive method. In general, it is reasonable to include an MRV as part

hypertension, increased vascular resistance, increased intravascular volume, and hypercoagulability. It is important to recognize that eclampsia may occur postpartum as well as pre-partum. In addition, hypercoagulable states are common causes of dural sinus thrombosis postpartum (see below)

Diagnosis is more difficult when headache is the dominant syndrome. Independent risk factors for pregnancy-related arterial hemorrhages include advanced maternal age, black race, gestational hypertension or pre-eclampsia, known coagulopathy, and cigarette smoking

MRI studies of women suspected stroke or intri hemorrhage because of prevalence of cerebral dural sinus thrombosis below)

## Sympathomimetic drugs

Risk of ICH appears to be increased with exposure to sympathomimetic agents, at least in part due to the abrupt increase in BP that is produced. Surprisingly, though, 80% of strokes related to base cocaine are hemorrhagic while only 50% of strokes related to alkaloidal cocaine ("crack") are hemorrhagic and BP elevation is greater

Women appear to be more sensitive to the effects of sympathomimetic agents, probably because their basal BP regulation is more likely to depend on parasympathetic tone while men have a relatively greater contribution from sympathetic tone for their basal regulation. "First exposures" to drugs may carry higher risk

CT appearance is similar to other causes of ICH. It is important to exclude an underlying lesion, such as AVM, for which the drug may have served as a "trigger"

with the latter.  
Chronic drug use may also alter platelet aggregation and lead to cardiomyopathy.  
The literature documenting vasculitis from sympathomimetics is conclusive only for amphetamines

## NEOPLASTIC/PARANEOPLASTIC

### Primary brain tumors

2–7% of intracerebral hemorrhages are secondary to a bleed into a tumor. Brain tumors may be associated with significant neovascularity with dilated, thin walled vessels, breakdown of the blood–brain barrier, tumor necrosis, and an increased risk for hemorrhage  
Though glioblastomas are the most common primary brain tumors in adults and are the most likely to bleed overall, oligodendrogiomas have a predilection

Bleeding into a tumor may cause an acute change in the neurologic status, with headache, signs of increased intracranial pressure such as vision disturbance, seizures, vomiting, and focal neurologic deficits  
Leptomeningeal infiltration may present with dysfunction of multiple cranial nerves but the course is subacute

Glioblastoma multifiori (GBM) is often located subcortical white matter frontotemporal lobes  
On CT a GBM appears heterogeneous mass lesion with intralesional hemorrhage and surrounding edema  
Lobar hemorrhage has a hemorrhage which appears out of proportion to the underlying hemorrhage size, suspect tumor. Tumor edema is likely to spare the cortex  
MRI appearances are often atypical because blood differing ages may be present and admixed with abnormal neoplastic tissue. Vasoconstriction is greater with glioblastomas than with primary tumors and it persists even into the chronic phase of hemorrhage

have a predilection toward bleeding and represent a disproportionate share. Sarcomas, intravascular lymphomas, hemangiopericytomas are rare

**CHIARI PHASE OF MENINGOMYELOMALACIA**  
When a tumor in the frontal cortex spreads across the corpus callosum into the contralateral hemisphere it appears bilaterally symmetrical, hence the term butterfly glioma. MRI with gadolinium based contrast medium will reveal tumor enhancement.

## Pituitary tumors

Among the “benign” tumors, pituitary adenoma that has outgrown its blood supply results in infarction with hemorrhage – causing pituitary apoplexy

Female predominant, these present with sudden onset of headache, visual disturbances, vomiting, and endocrine abnormalities, predominantly adrenal insufficiency. Blindness is a dreaded complication. Risk factors include radiation, anticoagulation, head trauma, hypertension, and pregnancy (Sheehan's syndrome)

CT or MRI may show subarachnoid hemorrhage in the setting of pituitary expansion or infarction above an enlarged sella turcica.

## Secondary or metastatic brain tumors

Approximately 40% of intracranial neoplasms are metastatic. Neovascularity, friable vessel wall, tumor necrosis as growth exceeds blood

The relative frequency of lung cancer makes it the most common metastatic tumor to bleed even though only a small proportion do so. Brain metastases from melanoma,

On MRI melaninogenic metastases are distinctive because they contain melanin or due to hemorrhage. Solitary metastatic disease must be distinguished from primary brain tumor. Screening for primary cancer should include CT scan.

supply or following radiation, coagulopathy from underlying malignancy or chemotherapy, all contribute to hemorrhage risk

choriocarcinoma, thyroid carcinoma, and renal cell carcinoma have a high propensity to cause spontaneous intracerebral bleeding. Clinical features include but are not limited to headache, seizures, and focal neurologic deficits

thorax, abdomen, and pelvis. A thorough skin examination, mammography, and tumor markers. If search for a malignancy fails, tumor resection with biopsy may be helpful. Abscess is difficult to detect radiographically.

## DEGENERATIVE

### Cerebral amyloid angiopathy (CAA)

Most common cause of intracranial hemorrhage after hypertension and aneurysm especially in ages more than 60 years. Amyloid deposits on the small- and medium-sized arteries of the cortex and leptomeninges make it susceptible to fibrinoid necrosis, replacing its contractile elements. Within the elastic lamina it fragments, making it susceptible to rupture in response to minor trauma or hypertension. Amyloid protein may inhibit serine proteases including

CAA is age dependent like Alzheimer's disease and should be suspected in ages 60 years or more with one or more lobar hemorrhages and no obvious cause. The prevalence is above 40% in those > 60 years of age. Multiple and recurrent hemorrhages are common. Can occur as a sporadic disorder with or without associated Alzheimer's dementia. Risk factors for hemorrhage include: trauma, iatrogenic (ventriculostomy/cortical biopsy), anticoagulation, thrombolysis, and uncontrolled

Characteristically lobar (occipital/temporal) – cortical cortex and sometimes leptomeninges, it may extend to the subarachnoid space. Finger-like extension appearance and rupture of ventricles on CT is common. Cluster in posterior brain regions and tend to occur in the same location in an individual. Gradient echo MRI shows signal drop out caused by deposits containing hemosiderin in old hemorrhages especially at gray--white junction. Some may have CSF abnormalities: increased protein, decreased solute amyloid or ApoE.

coagulation factors XIa and IXa. The deposits occur in the cerebral vessels only without affecting other body areas. CAA increases steadily with age

hypertension  
Large lobar hemorrhages may cause hemiplegia or depressed consciousness. Smaller hemorrhages may cause headache or seizure or limited focal deficits

### Familial cerebral amyloid angiopathy

These are described in forms such as Flemish, Iowa, and Dutch types based on the populations in which they are seen to occur. Hereditary cerebral hemorrhage with amyloidosis-Dutch type is an autosomal dominant disorder with complete penetrance. The most likely genetic defect is in the amyloid protein precursor protein (APP) gene on chromosome 21. Hereditary cerebral hemorrhage with amyloidosis-Icelandic type is also autosomal dominant. The amyloid protein is a mutant of the cysteine protease inhibitor cystatin C

In the Dutch type, 87% have ICH and 13% have infarcts (deep). The age of onset of ICH is in the 6th decade like the non-hereditary variant. ICH in the Icelandic variant presents in the 3rd or 4th decade. Amyloid angiopathy is more widely distributed in the Icelandic type, involving the cerebellum and the brainstem in addition to the cerebral hemispheres

Imaging characteristics as above  
Genetic evaluation can be considered, especially with a family history of

## OTHER VASCULAR

### Hemorrhage into a cerebral infarct/hemorrhage secondary to cerebral

Hemorrhagic transformation of acute ischemic stroke is an undesirable complication that occurs in 2.2%–44.0% of clinical cases. Infarcted brain tissue has a propensity to bleed, particularly when reperfused in the acute phase. The risk of bleeding is higher with venous infarction than with arterial infarction. Hemorrhage results from diapedesis of red blood cells through ischemic capillary endothelium or rupture of the underlying ischemic artery or arteriole may occur

Factors that have been associated with an increased risk of bleeding in stroke patients treated with thrombolytic agents include the baseline stroke severity, dose of thrombolytic, delay in treatment, an initial diastolic blood pressure of 100 mmHg or greater, white matter disease burden, aspirin use, and very low levels of residual cerebral blood flow in the region of ischemia

CT may not be able to differentiate an intra-in hematoma, but presence edema that conforms to arterial territory may be MRI brain with diffusion weighted sequences showing restricted diffusion with matched apparent diffusion coefficients suggesting ischemic area underlying hematoma  
Silent microhemorrhage GRE sequence on MRI risk factor for future hemorrhagic transformation

### Cortical vein or dural sinus thrombosis

Thrombosis may occur either in the dural venous sinuses or the cortical veins. Secondary to thrombotic impedance

Presenting symptoms include headache and emesis. Signs include papilledema, proptosis, chemosis, and gaze palsies. Hemiparesis

CT with contrast has the classic ‘empty delta sign’ (hyperdense thrombus) opacification of the sagittal sinus in sagittal sinus thrombotic infarction

**Cavernous sinus syndrome**

venous drainage, there is ischemia and hemorrhage which do not conform to a usual arterial territory

Cerebral venous thrombosis may develop in relation to infections of the adjacent ear, paranasal sinuses, or to bacterial meningitis. Septic thrombosis usually occurs at the cavernous sinus as a complication of facial or nasopharyngeal infection

Aseptic thromboses are seen disproportionately in women during pregnancy or postpartum periods, or while taking oral contraceptives

In the elderly, a malignant or paraneoplastic process predisposing to a hypercoagulable state is a possibility.

If there are no obvious risk factors or an underlying inherited hypercoagulable state, the possibility

**Local signs and symptoms**

Local signs and symptoms of ear or nose infections may be present

Cavernous sinus thrombosis causes chemosis and proptosis with dysfunction of cranial nerves III, IV, and VI and possibly ophthalmic division of V

The slower evolution of clinical stroke syndrome, the presence of multiple cerebral lesions in non-arterial territories, seizures, and presence of hemorrhage favour venous over arterial thrombosis

**Non-arterial distribution**

non-arterial distribution white matter and/or cortex white matter junction, associated with hemorrhage should suggest the possibility diagnosis of venous thrombosis. Bilateral cortical involvement can occur including the superior colliculus white matter of the cerebellum from superior sagittal sinus thrombosis, or the basal ganglia and thalamus from internal cerebral vein thrombosis in which the internal cerebral veins appear hyperdense in the non-contrast scan

MRI with MRV is preferred for diagnosis of cerebrovascular venous thrombosis as it is sensitive and specific. Less sensitive imaging techniques can be used (i.e. 2-dimensional time-of-flight [2D TOF] phase-contrast MRV) to accurately assess the veins of the sinuses

Angiography in the venous phase shows thrombus within the cortical veins or the sinuses. Classic findings include filling defects or thrombus within the vein of Galen sinus or occlusion of a sinus

of malignancy should be considered

## TRAUMA

### Closed head trauma

The most common closed injuries are contusions, diffuse axonal injury, subarachnoid, epidural (see [Table 70.1](#)), and subdural hematomas (see [Table 70.1](#)).

Coup contusions are caused by direct transmission of impact energy through the skull into the underlying brain and occur directly below the site of injury. Contrecoup injuries are caused primarily when the brain rebounds after the direct impact to strike the opposing inner table of the skull. Rotational shear force causes the basal frontal and temporal cortices to impact or sweep across rigid aspects of the skull, including the sphenoid wing

Traumatic injuries remain the leading cause of death in children and in adults aged 45 years or younger. Death occurs in 15% of patients with severe head injury

Closed head injuries have better outcomes than penetrating head injuries

Motor vehicle collisions are the most common cause for head injuries in teenagers and young adults, followed by alcohol and use of abusive drugs. In the elderly, use of antiplatelet agents and anticoagulants is a risk factor. The most important prognostic factor for a contusion is the presence of a subarachnoid hemorrhage

Secondary consequences of closed injury with intracranial hemorrhage include vasospasm with

CT of the head is the technique of choice for demonstrating hemorrhage, cranial fracture, soft tissue injury, intracranial air, and foreign bodies. invaluable for understanding the physical forces of traumatic injury

CT is relatively insensitive to shearing white matter injury, although small hemorrhages in the corpus callosum and cerebral peduncles may be seen. MRI is more sensitive for detecting brainstem injury and brain edema as well as evaluating the posterior fossa. Diffusion tensor imaging has recently been used to evaluate white matter integrity secondary to blunt head injury

and petrous ridges, as well as disruption of axons in the upper brainstem and lower cerebral hemispheres. These same forces act on the cerebral circulation, causing disruption of vessels with various forms of microhemorrhages and macro-intracerebral hemorrhages, including Duret hemorrhages, which may be lethal when they occur in the brainstem.

ischemia, edema, raised intracranial pressure, infection, epilepsy, and hydrocephalus

## Open head trauma

A “penetrating” wound is one in which a projectile breaches the cranium but does not exit it. In a “perforating” injury, the projectile passes entirely through the head, leaving both entrance and exit wounds. The pathologic consequences of penetrating head wounds depend on the properties of the

Management of open head injuries is neurosurgical. Initial medical management should be directed toward maintenance of airway, breathing, and systemic circulation, as well as addressing increased intracranial pressure if present with mannitol or hypertonic saline and hyperventilation. Emergency labs should be directed at assessing

CT of the head demonstrates the extent of intracranial damage, bleeding and the presence of foreign bodies. Bone windows should be evaluated for cranial fractures including the orbits. Angiography or CTA can be used to diagnose vascular injuries such as carotid and vertebral artery dissection, traumatic pseudoaneurysms, arteriovenous fistulas. MRI is contraindicated in patients with intracranial metallic fragments. On

weapon or missile, the energy of the impact, and the location and characteristics of the intracranial trajectory. There are usually severe mechanical, vascular, and biochemical consequences, including epidural hematomas, intracranial hematomas, subarachnoid hemorrhage, and diffuse axonal injury

electrolyte and hematologic status, particularly coagulation

intracranial metallic fragments have been ruled out, an MRI scan of the brain provides valuable information on the posterior fossa structures, the extent of shearing injuries as well as on the contusion and hemorrhages

## IDIOPATHIC

### Cerebral endometriosis

Endometriosis is defined as the presence of functional endometrial tissue located in extrauterine sites. Cerebral endometriosis likely results from hematogenous spread from the uterine cavity although lymphatogenous spread also has been implicated

This is very rare but may be suspected when there are recurrent cyclical SAH, severe headaches, or seizures associated with menstrual bleeding

CT shows ring enhancing lesions at the gray-white matter margins with surrounding edema  
MRI shows T1 hyperintense rounded lesions with T2 hypointensity and surrounding edema suggesting tumor  
Biopsy shows endometrial glands and stroma

## Silastic dural substitute

Large hematomas formed around pieces of dural substitute used to repair defects in the dura over the cerebral hemispheres. It was suggested that bleeding resulted from rupture of fragile capillaries formed in the neomembrane enveloping the graft

Should be suspected in the clinical setting of prior placement of silastic dural substitute post craniotomy

CT demonstrates subdural hematoma with blood of varying ages  
MRI confirms the presence of the silastic dural substitute

## Idiopathic hypereosinophilic syndrome (HES)

HES is unexplained eosinophilia of greater than 1500/ $\mu$ L present for longer than 6 months with evidence of organ injury related to the hypereosinophilia, such as cardiomyopathy, peripheral neuropathy, and encephalopathy

Neurologic manifestations include multiple recurrent emboli of cardiac or local origin. Arterial and venous thromboses may occur. Hemorrhagic transformation occurs frequently

CTA with late venous phase may be preferable to MRI for evaluating dural sinuses and cerebral veins  
Digital subtraction angiography may be necessary for demonstrating thromboses in smaller vessels

---

ADC, apparent diffusion coefficient; aPTT, activated partial thromboplastin time; CSF, cerebrospinal fluid; CT, computerized tomography; CTA, computerized tomography angiography; ECT, electroconvulsive therapy; GRE, gradient recalled echo; ICH, intracranial hemorrhage; ICP, intracranial pressure; INR, international normalized ratio; IPH, intraparenchymal hemorrhage; IVH, intraventricular hemorrhage; LP, lumbar puncture; MRI, magnetic resonance imaging; NEX, number of excitations; PCT, partial thromboplastin time; T1, T2, proton density, spin echo times; TEE, transesophageal echocardiogram.

lumbar puncture; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; NIH, National Institutes of Health; PICA, posterior inferior cerebellar artery; PT, prothrombin time; SAH, subarachnoid hemorrhage; SDH, subdural hematoma; tPA, tissue plasminogen activator.

## Further reading list

- Batjer H, Caplan L, Friberg L. *Cerebrovascular Disease*. New York, NY: Lippincott-Raven, 1997.
- Bradley W, Daroff R, Fenichel G, Jankovic J. *Neurology in Clinical Practice*, 5th edn. Waltham, MA: Butterworth-Heinemann, 2008.
- El-Mitwalli A, Malkoff MD. Intracerebral hemorrhage. *Internet J Emerg Intens Care Med* 2000; 5:No. 1.
- Ropper A, Samuels M. *Adam's and Victor's Principles of Neurology*, 9th edn. New York, NY: McGraw-Hill, 2009.

## **71 Stroke in adults, etiologies**

---

Susan W. Law and Daniel M. Rosenbaum *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

Strokes are defined as a sudden, non-convulsive, focal neurologic deficit that continues for more than 24 hours. Strokes are the third most common cause of death and one of the leading causes of serious, long-term disability in the USA. Over a year, about 795,000 people suffer from strokes, and more than 140,000 people die in the USA.

Risk factors for stroke include hypertension, hypercholesterolemia, intracranial disease, atrial fibrillation, and tobacco usage. This chapter focuses upon ischemic stroke.

The following are the objectives of this chapter:

- Systematically approach acute focal neurologic deficits.
- Approach common etiologies of stroke, particularly ischemic etiology.
- Emphasize basic stroke work-up.
- Discuss evaluation of acute stroke management.
- Discuss overall secondary prevention options for ischemic strokes.

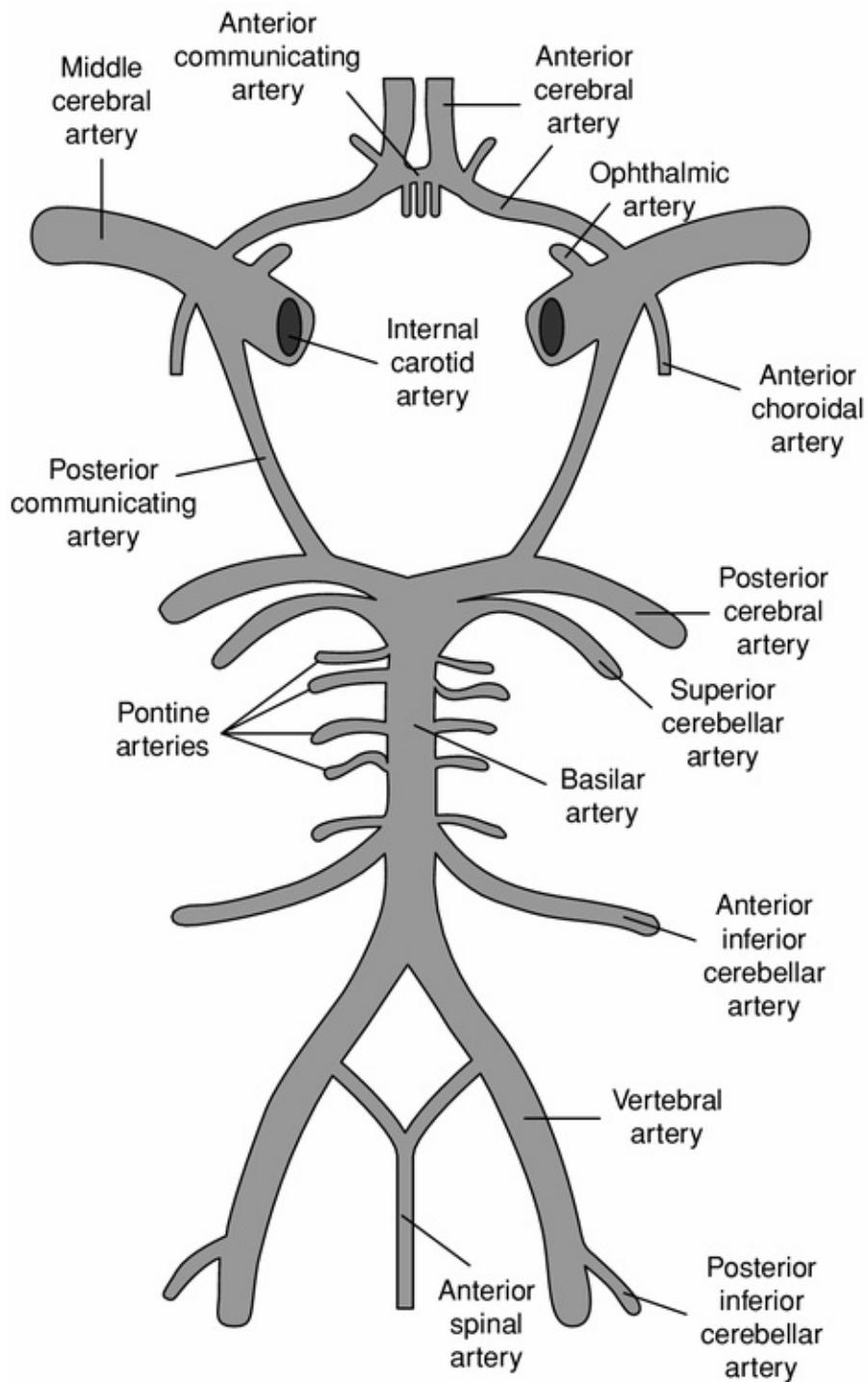
### **Types of stroke**

Strokes are classified as cardioembolic, artery to artery, and lacunar. A basic stroke work-up includes brain imaging, transthoracic echocardiogram, investigation of intra-and extracranial arteries, and risk stratifications (hgbA1C, lipid panel). Other work-up to consider ordering depending on clinical circumstances includes investigation of prothrombic state – protein C, protein S, antithrombin III, factor V Leiden, and homocysteine.

## Anatomy

A solid understanding of cerebral arterial architecture is needed for localizing lesions. There are two categories of findings when investigating the location of a stroke lesion – cortical deficits and brainstem deficits. Cortically based deficits involve functions such as language, attention, visual field deficits, and apraxia. Brainstem-based deficits involve oculomotor dysfunction, swallowing, and forehead-involved facial paresis and may be associated with ataxia, discoordination speech, nystagmus, and vertigo. Cerebellar lesions may be associated with ataxia, discoordination speech, nystagmus, and vertigo.

[Figure 71.1](#) shows the anatomic structures of the cerebrovascular system. Cerebral arterial anatomy is divided into anterior and posterior circulations. The anterior circulation involves intracranial carotid, anterior, and middle arteries. Posterior circulation includes posterior cerebral artery, basilar arteries, cerebellar arteries (anterior inferior cerebellar, posterior inferior cerebellar, superior cerebellar), anterior spinal, and vertebral. Both anterior and posterior circulatory systems combine to form the circle of Willis which sits near the sella turcica.



**Figure 71.1** Circle of Willis. From *Neuroanatomy through Clinical Cases*, 2nd edn. Sunderland, MA: Sinauer Associates, 2002.

## Major cerebral artery syndromes

## **Anterior cerebral artery (ACA)**

The ACA supplies the medial portion of the frontal and parietal lobes. The leg is more affected than arm or face. Damage to the dominant dorsolateral frontal region causes decline in verbal intellect and perseverations while damage to the ventromedial area leads to speech and gait apraxia. Bilateral infarcts, which are caused by occlusion of the parent vessel that supplies both ACAs' orozygous variant, can lead to dementia, environmental dependency, Bruns' frontal lobe ataxia or marche à petits pas , and akinetic mutism .

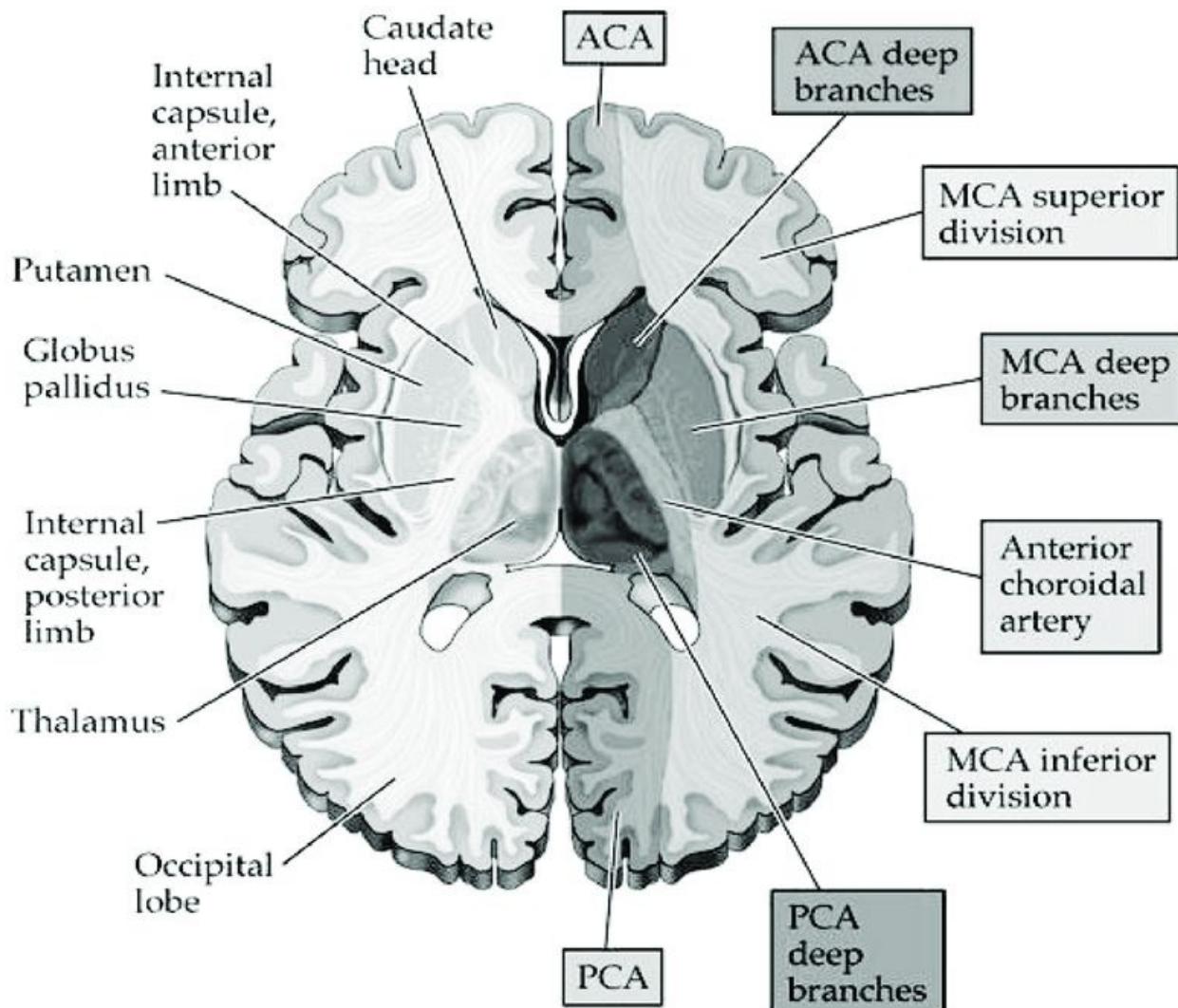
## **Middle cerebral artery (MCA)**

The MCA supplies the majority of the frontal, temporal, and parietal lobes of the brain. Damage to either side of the MCA (dominant or non-dominant) leads to hemiparesis , hemianesthesia , and hemianopsia . Non-dominant MCA infarctions cause inattentiveness while dominant MCA infarctions cause language impairment or aphasia . Complete MCA infarctions lead to contralateral hemiparesis, hemianesthesia, and hemianopsia with contralateral gaze deviation or preference. Superior division infarcts involve frontal or executive functions such as Broca's area (dominant) and prosity (non dominant), and gaze preference (frontal eye fields). Weakness pattern is face and arm greater than leg with a motor predilection of extensors in the upper extremity and flexors in lower extremity. The inferior division involves parietal and superior temporal lobes which house Wernicke's area (dominant) and visual pathways. The inferior MCA infarctions can lead to hemianopsia and receptive language deficits. Gerstmann syndrome, which involves the dominant angular gyrus, leads to agraphia , acalculia , right–left confusion , and finger agnosia .

## **Posterior cerebral artery (PCA)**

The PCA supplies the occipital, inferior, and mesial temporal lobes ([Figure 71.2](#)). Infarctions of the PCA lead to hemianopia. Rare syndromes include alexia without agraphia which occurs when the lesion is located at the splenium of corpus callosum. Alexia occurs when there is an impairment of reading function due to defective connection between the unilateral visual field (non-dominant) and the contralateral visual field and language area (dominant hemisphere). Anton's syndrome or bilateral occipital lobe infarction leads to cortical blindness with confabulation of deficits. Balint's syndrome , caused by bilateral parieto-occipital infarctions, is characterized by ocular apraxia or inability to visually

guide limb movement as well as simultagnosia , the inability to recognize objects as a whole . A summary of classic symptoms with large artery occlusion can be found in [Table 71.2](#).



**Figure 71.2** Brain structure. From *Neuroanatomy through Clinical Cases*, 2nd edn. Sunderland, MA: Sinauer Associates, 2002.

**Table 71.1 Pathophysiology of stroke.**

Ischemic	Artery to artery	Dissection	Common of neck Horner location /ICA <sup>2</sup>
----------	------------------	------------	--

Risk fa  
trauma  
vasculæ  
(see dis  
section  
Diagn  
cerebra  
CT ang  
with cc  
neck

Aortic thrombosis  
Mostly  
cholest  
plaque  
Risk fa  
ascendi  
atheror  
mobile  
Diagn  
TEE

Cardioembolic      Cardiac thrombus  
Locatio  
append  
Low ej  
fractio  
second  
cardior  
to ische  
conges  
failure,  
syndro  
PFO w  
septal c  
Risk fa  
fibrillat  
hyperco  
disorde  
ejectio  
Diagn

TEE, T  
Dopple  
study

Endocarditis

Bacteri  
*Staphylo-*  
*aureus*,  
*Streptococcus*  
*viridans*  
Non-bacterial  
(maran)  
Cardiac  
Risk factors  
of intraoperative  
abuse,  
particularly  
Hodgkin's  
lymphoma  
Diagnosed  
TEE

Right to left  
shunts

Air  
Cholesterol

Intracardiac  
ASD  
Extracardiac  
Pulmonary  
Risk factors  
history of  
diving,  
history of  
bone fracture  
Diagnosed  
TEE with  
saline transesophageal

Thrombosis

Small vessel  
lipohyalinosis

See section  
lacunar

Hypoperfusion

MI  
Shock

**SHOCK**

Prothrombotic	Drug induced	Estrogen related	Risk factors of receiving contraceptives
	Pregnancy related	Cerebral venous thrombosis	Thromboembolic major complications Risk factors include age and blushing during pregnancy and postpartum in women. Diagnosis by MRV of the head.
Hereditary	Sickle cell disease Antiphospholipid antibody Protein C/S deficiency Premature atherosclerosis (homocysteine) Thrombotic thrombocytopenia (TTP)	Risk factors history of venous thromboembolism at young age with stroke years old minimum vascular Diagnosed in lupus antiphospholipid antibodies cardiolipin antibodies glycoprotein	

phosph  
factor  
protein  
homoc  
blood s  
antithr  
hemogl  
electro]

Inflammatory	Arteritis (primary)	Primary angiitis of the CNS Behçet's Susac's Sjögren's syndrome	Autoin disorde certain causing Risk fa of othe autoim disorde polymy rheumā Diagno autoim (ANCA rheumā antinuc VDRL, angiog leptom artery t
	Arteritis (secondary)	Large arteries Takayasu disease <sup>5</sup> Granulomatous giant cell arteritis of aorta Medium arteries Polyarteritis nodosa Kawasaki disease Small to medium:	

Wegener's  
granulomatosis<sup>6</sup>

Churg–Strauss  
syndrome

Sneddon's  
syndrome<sup>7</sup>

Small arteries  
Henoch–Schönlein

purpura

Lupus

erythematosus

### Infectious

#### Virus:

CMV

HIV

VZV

HSV

Risk fa  
of  
immun  
includi  
HIV, H  
prolong  
usage  
Diagno  
lumbar

#### Bacteria:

*Rickettsia*  
*Treponema pallidum*  
*Haemophilus influenzae*  
*Streptococcus pneumoniae*  
*Neisseria meningitidis*

#### Fungi:

*Aspergillus*  
*Coccidioides*  
*Histoplasma*

#### Protozoa:

*Plasmodium*  
*Toxoplasma*

Degenerative/Metabolic	MELAS (mitochondrial encephalopathy, lactic acidosis, stroke-like episodes)	Equally distributed in sex. Symptoms include recurrent migrainous headaches, ischemic stroke at < 40 years old, seizures (myoclonic, focal and generalized) Diagnostic test: Muscle biopsy: red ragged fibers CSF lactate elevated
Fabry's		Lipid storage disorder, ceramide trihexosidase (alpha-galactosidase A) enzyme deficiency, autosomal dominant X linked Symptoms include acroparesthesia, renal failure, cardiomyopathy, angiokeratomas (papules along trunk and legs), ocular involvement Diagnosis: serum test for level of alpha-

galactosidase  
activity  
Treatment:  
enzyme  
replacement  
therapy

Homocysteinuria      Autosomal  
recessive,  
deficiency of  
cystathione-  
beta-synthase  
Family history of  
homocystinuria,  
Marfanoid habitus,  
seizures, ocular  
abnormalities  
(downward  
dislocation of  
lens), stroke  
usually in third or  
fourth decade,  
history of  
coronary artery  
disease  
Diagnosis:  
Sodium cyanide  
test in urine –  
urine turns red  
Treatment:  
supplementation  
of pyridoxine and  
folate, methionine  
restriction

---

ANCA, antineutrophil cytoplasmic antibodies; ASD, atrial septal defect; AVM, arteriovenous malformation; CMV, cytomegalovirus; CNS, central nervous system; CSF, cerebrospinal fluid; CTV, computerized tomography venography; HIV, human immunodeficiency virus; HSV, herpes simplex

virus; HTLV, human T-lymphotropic virus; MI, myocardial infarct; MRV, magnetic resonance venography; PFO, patent foramen ovale; TEE, transesophageal echocardiogram; VDRL, venereal disease research laboratory; VZV, varicella zoster virus.

1. Horner's syndrome: sympathetic dysfunction involving the face and eye. Common triad – ptosis, miosis, anhydrosis.
2. See section on cervical and vertebral dissections below.
3. Takasubo syndrome: stress induced cardiomyopathy; sympathetic overdrive causes apical sparing hypokinesis of myocardium, usually seen in TTE.
4. Osler Weber Rendu or hereditary hemorrhagic telangiectasia syndrome: autosomal dominant, endoglin gene on chromosome 19.
5. Takayasu syndrome: arteritis causing stenosis of the large vessels – aorta, common carotid, and subclavian arteries. Associated with Crohn's disease and other autoimmune disorders.
6. Wegener's granulomatosis: associated with lung and kidney dysfunction.
7. Sneddon's syndrome: arteriopathy of small to medium sized vessels. Clinically suspected if patient suffers from libido reticularis and cerebrovascular episodes.

**Table 71.2 Classic symptoms with large artery occlusion.**

---

Anterior cerebral artery (ACA)	Contralateral anesthesia, hemiparesis (leg > arm), abulia Dominant – mutism Non-dominant – confusion Bilateral – gait apraxia, urinary incontinence, akinetic mutism
Middle cerebral artery (MCA) Entire	Contralateral hemiparesis/hemianesthesia/ hemiopnia with gaze preference Dominant – aphasia Non-dominant: aposodia, inattention
Superior	Contralateral hemiparesis, (dominant) expressive aphasia. sometimes gaze preference

	<b>aphasia, sometimes gaze preference (contralateral)</b>
Inferior division	Contralateral hemianopia, receptive aphasia *Gerstmann (dominant angular gyrus) – agraphia, acalculia, right–left confusion, finger agnosia
Posterior cerebral artery (PCA)	Hemianopia Alexia without agraphia (splenium of corpus callosum) Anton (bilateral occipital) cortical blindness Balint (bilateral parieto-occipital): ocular apraxia, simultagnosia

---

## Lacunar syndrome

Lacunar strokes were first described by C. Miller Fisher as small infarcts (3–20 mm) in non-cortical regions of the cerebrum and brainstem which result from occlusion of penetrating branches of the larger cerebral arteries. Common places for lacunar strokes are putamen, caudate, thalamus, pons, and internal capsule. Though Fisher described more than 20 lacunar strokes in his review article in 1971, there are five most established lacunar syndromes – pure sensory, pure motor hemiparesis, ataxic hemiparesis, dysarthria (clumsy hand syndrome), and motor–sensory. A summary of classic locations of lacunar strokes can be found in [Table 71.3](#).

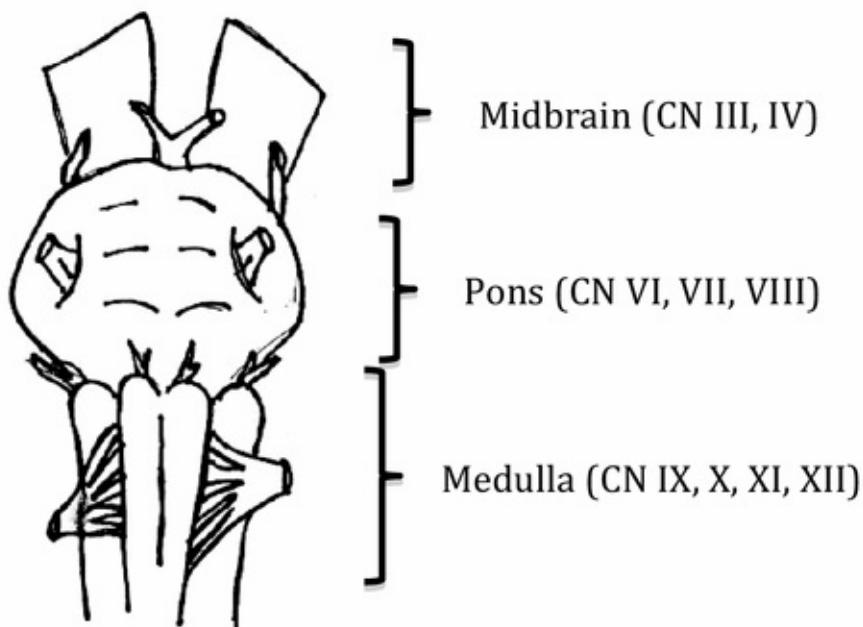
**Table 71.3 Lacunar syndromes**

Pure motor	Internal capsule, corona radiata, thalamus
Motor–sensory	Internal capsule, thalamus
Ataxic hemiparesis	Corona radiata, internal capsule, basal ganglia, pons
Dysarthria (“Clumsy hand”)	Corona radiata, internal capsule, basal ganglia, pons

## Brainstem strokes

A review of brainstem anatomy is important in localizing lesions. Three main rules apply to localization of brain anatomy:

1. Midbrain contains CN III–IV, pons VI–VIII, medulla IX–XII as shown in [Figure 71.3](#)
  - a Exception: Trigeminal nerve (CN V) is distributed throughout the brainstem.
2. Motor nuclei are located *medially* in the brainstem whereas the special and sensory nuclei are predominantly lateral in the brainstem.
3. All nuclei except CN IV subserve ipsilateral structures whereas the tracts affect contralateral structures . A summary of classic locations and symptoms of brainstem strokes can be found in [Table 71.4](#).



**Figure 71.3** Brainstem diagram.

**Table 71.4** *Brainstem vascular syndromes.*

PCA

Weber's

Cerebral  
peduncle, ventral

Ipsilateral  
oculomotor palsv.

		midbrain (sparing red nucleus, cerebellothalamic tract)	contralateral hemiparesis
Benedict's	Cerebral peduncle, ventral midbrain	Weber + Claude	
Claude	Cerebral peduncle, ventral midbrain (with red nucleus)	Ipsilateral oculomotor palsy, contralateral tremor	
Basilar	Lock-in syndrome	Bilateral median pontine	Quadriplegia with sparing of upgaze ocular movements
	Tip of basilar syndrome	Bilateral medial thalamus, occipital, pons, midbrain	Aneurysmal
	Millard–Gubler syndrome	Mid pons	Ipsilateral facial weakness, contralateral hemiparesis
Superior cerebellar artery			Ipsilateral ataxia, vertigo, pseudobulbar speech, contralateral hemiesthesia
Anterior spinal artery	Dejerine–Roussy	Medial medulla	Ipsilateral tongue weakness, contralateral hemiparesis/vibration and proprioception

Anterior inferior cerebellar artery			Bilateral deafness, ipsilateral ataxia, facial paresis
Posterior inferior cerebellar artery	Wallenberg	Lateral medulla	Ipsilateral Horner's syndrome, dysphagia, ataxia; contralateral hemianesthesia

---

## Facial weakness (palsy of facial nerve CN VII)

A 58-year-old right-handed male with past medical history of hypertension and diabetes presents with 2-hour onset of right facial weakness and slurred speech.

Facial weakness is a common neurologic symptom that promotes clinical suspicion of stroke. Facial motor fibers descend from the motor cortex (homunculus) into the internal capsule where the fibers are predominantly located at the genu of the internal capsule and descend into the facial nucleus at the pons via cortical and corticobulbar tracts.

At the pons, the facial nerve leaves the pons ventrolaterally at the base of the pons (or the pontomedullary junction) and enters the inner ear (auditory canal). There in the internal auditory meatus, the nerve passes the geniculate ganglion (which provides taste in the anterior two thirds of tongue) and travels with the vestibulocochlear nerve via the auditory canal and out of the stylomastoid foramen.

After the stylomastoid foramen, the facial nerve divides into five branchial motor branches (temporal, zygomatic, buccal, mandibular, and cervical branches) which provide motor facial function. Other important muscles that are innervated by the branchial nerves (as the facial nerve *exits* the stylomastoid foramen) are stapedius, posterior belly of the digastric, and stylohyoid muscles.

As a rule of thumb, lesions of the cortex and along the corticobulbar tract cause *contralateral* facial weakness that *spares* the forehead. Lesions that affect the facial nucleus and along the nerve tract as it leaves the brainstem and skull cause an *ipsilateral* weakness of the *entire face*. For further details, please refer

to Chapter 88 on facial nerve palsy, and Table 71.5.

**Table 71.5 Etiologies of facial palsy with emphasis on vascular etiologies.**

Forehead-sparing facial (upper motor neuron facial)	Cortex	Ipsilateral arm weakness If on dominant hemisphere may involve language function (unable to name)	Vascular (CVA, ICH, SDH) Trauma Mass lesion (adult – GBM, astrocytoma; child – ganglio- astrocytoma, xanthro - astrocytoma) Infectious (bacterial abscess – <i>Staphylococcus</i> <i>aureus</i> , fungal abscess, PML) Inflammatory (vasculitis, sarcoidosis, multiple sclerosis)
Brainstem down to ventrolateral pons (facial nucleus)	Midbrain: oculomotor deficits, ptosis, vertical eye movement Pons: severe dysarthria > facial weakness Horizontal gaze palsy (involvement of CN VI and PPRF)	Midbrain: oculomotor deficits, ptosis, vertical eye movement Pons: severe dysarthria > facial weakness Horizontal gaze palsy (involvement of CN VI and PPRF)	Vascular (CVA, ICH) Mass lesion (schwannoma, meningioma, epidermoid, metastasis; adult – pontine glioma, child – PNET) Inflammatory (vasculitis, sarcoidosis, multiple sclerosis)
Forehead .....	Meningeal	Altered	Infectious (bacterial – .....

involving facial weakness (lower motor neuron facial)	mental status	abscess, otitis, tetanus, tuberculosis, fungal abscess viral – CMV, HSV, cryptococcal, Lyme, West Nile) Inflammatory (Guillain–Barré, Miller–Fisher variant, vasculitis, sarcoidosis, multiple sclerosis) Developmental: Mobius syndrome
Within auditory meatus (temporal bone)	Loss of taste sensation anterior 2/3 tongue May be associated with facial pain	Inflammatory: Gradenigo's syndrome, Bell's palsy, sarcoidosis Infectious (HIV, HSV, Lyme)
Stylo mastoid foramen	May affect chorda tympani nerve (innervates stapedius) – hyperacusis	Neoplastic: squamous cell, parotid tumor Trauma – surgery, blunt Inflammatory: Bell's palsy, sarcoidosis Infectious (HIV, HSV, Lyme)

---

CMV, cytomegalovirus; CVA, cerebrovascular accident; GBM, glioblastoma multiforme; HIV, human immunodeficiency virus; HSV, herpes simplex virus; ICH, intracerebral hemorrhage; PML, progressive multifocal leukoencephalopathy; PNET, primitive neuroectodermal tumor; PPRF, pontine paramedian reticular formation; SDH, subdural hematoma.

Work-up includes:

- Imaging (MRI brain with or without contrast).
- If clinically suspicious of infectious or inflammatory causes (i.e. Guillain–Barré syndrome, vasculitis), lumbar puncture would be recommended. Tests should include cell count, glucose, protein, viral culture, Lyme titer, angiotensin-converting enzyme (ACE) level.
- If patient has repeat episodes of facial weakness, would consider vasculitis and HIV testing .

## Vertigo

Vertigo is a symptom that is frequently seen in the emergency room but not easy to localize. Symptoms of vertigo can be localized anywhere in the vestibular pathway. Please see [Chapter 76](#) on vertigo for more details.

In patients with stroke, vertebrobasilar ischemia and cerebellar hemorrhage can initially present innocuously. It is importantly to quickly diagnose when possible so as not to delay treatment. Usually in patients with a solitary vertiginous complaint without other “posterior circulation symptoms” (i.e. diplopia, vision loss, slurred speech, hemiparesis, or ataxia), peripheral causes of vertigo are suspected. For more details on vertigo, see [Chapter 76](#) or [Table 71.6](#).

**Table 71.6 Differential diagnosis of vertigo with emphasis on vascular disease.**

Disorder	Onset	Frequency	Triggers	Associating symptoms
Benign paroxysmal positional vertigo	Acute	Seconds	Positional	Positive Dix Hallpike with torsional upbeatning nystagmus, nystagmus does not change .. ..

				direction
Posterior circulation transient ischemic attack	Acute	Seconds	None	Vision loss, slurred speech In young patients, consider vertebral dissection
Stroke, cerebellar and vertebrobasilar ischemia	Acute	Hours to days	None	Diplopia, vision loss, unsteady gait. May see vertical gaze nystagmus
Ménière's disease	Subacute	Hours	Unknown, sodium intake?	Fluctuating hearing loss
Migraine-associated dizziness	Subacute	Minutes to days	Stress, fatigue	Headache
		Central vertigo		Peripheral vertigo
Nystagmus		Immediate		Delayed
Characteristics of nystagmus		May have vertical gaze nystagmus		No vertical nystagmus

## Cervicocerebral arterial dissection

Two percent of ischemic strokes are accounted for by cervicocerebral arterial

dissections. Vertebral artery dissections are more common in men than in women. Dissections are caused by an intima tear and consequently a development of hematoma. Common causes of dissection can range from iatrogenic to severe trauma. There has been reported triggers from sudden head movement, chiropractic manipulation, and various sports activities. Dissections can be divided into two regions – internal carotid and vertebral arterial regions (see [Table 71.7](#)).

**Table 71.7 Dissection syndromes.**

	<b>Internal carotid artery</b>	<b>Vertebral</b>
Location	Extracranial: 2 cm distal to bifurcation (C2–3)	C1–2
Age group	Children	Adults
Symptoms	Ipsilateral head, face, neck pain Headache Focal symptoms (cerebral, retinal) Horner's syndrome CN palsies: CN XII > CN IX, X, XI, and V Pulsatile tinnitus	Unilateral or bilateral head, neck pain Headache Lateral medullary signs
Associated diseases	Arteriopathies Ehler–Danlos syndrome type IV Marfan syndrome Type I collagen point mutation Alpha1-antitrypsin deficiency Osteogenesis imperfecta type I Autosomal dominant polycystic kidney disease	Subarachnoid hemorrhage Trauma

polycystic kidney disease  
Moya-moya disease  
Fibromuscular dysplasia

---

Work-up includes:

- Vascular imaging – cerebral angiogram, magnetic resonance angiography (MRA) of the neck without contrast (conventional T1 and T2 weighted and fluid attenuation inversion recovery [FLAIR] with time of flight [ToF]), multimodal extracranial ultrasonography.

## Treatment

Treatment of extracranial cerebrovascular dissection is controversial. Anticoagulation with intravenous heparin with subsequent therapy of warfarin for 3–6 months is a common treatment in prevention of artery-to-artery embolism. Reassessment of dissection is usually performed after warfarin therapy. Continuation of medical therapy (antiplatelet versus anticoagulation) remains debatable. Neurovascular therapy (stent or coil) is reserved for patients who despite medical therapy continue to have ischemic symptoms, enlargement of dissection, or have contraindications for anticoagulation.

## Intracerebral hemorrhage

Intracerebral hemorrhage (ICH) is the result of arterial or venous bleeding into brain parenchyma. Incidence of ICH is 5–10% of strokes. The most common risk factors include hypertension, advanced age, tobacco/alcohol use, and low serum cholesterol. The causes of hemorrhagic stroke are included in [Table 71.8](#).

**Table 71.8** *Intracerebral hemorrhage.*

---

Hemorrhagic	Intraparenchymal	Hypertension
		Putamen, basal ganglia, cerebellum, thalamus, pons, white matter
		Trauma

Бүрдэл	Ашигчийн аягуудадаа, hemorrhagic transformation
	Tumors Breast cancer, medullar thyroid, choroid carcinoma, clear cell renal carcinoma, lung cancer (small cell)
Intraventricular	Germinal cell matrix (intrauterine) Choroid plexus (newborn)
Subarachnoid	Aneurysm Congenital (fibromuscular dysplasia, adult polycystic kidney disease, sickle cell, hereditary hemorrhagic telangiectasia) Trauma/Injury Vascular Arteriovenous malformations Arteritis Moya-moya disease Pituitary apoplexy Drug induced: selective serotonin reuptake inhibitors (Prozac), cocaine, amphetamines

Prognostication of ICH includes volume of ICH (>60 cc, poor prognosis), intraventricular hemorrhage involvement, advanced age, initial pulse pressure, and adverse Glasgow Coma Scale score. Indications of neurosurgical consultation include: posterior fossa involvement of >3 cm diameter, worsening mental status, and compression of the fourth ventricle .

## Cerebral venous thrombosis

Cerebral venous thrombosis (CVT) is an uncommon but fatal cause of stroke.

The venous system is comprised of superficial, deep, and posterior fossa venous structures. The superficial veins are found along the cerebral cortex except the temporal and occipital lobes which drain into Trolard and Labbe's veins. These veins drain into the superior sagittal and cavernous sinuses.

The more common risk factors for cerebral venous thrombosis are prothrombotic states. Diagnostic imaging includes CT head of brain without contrast, CT venography with contrast, MRI combined with magnetic resonance venography (MRV).

Treatment of CVT includes antithrombotic treatment and concurrent therapies of associated conditions – seizures, headache, vision loss, and increased intracranial pressure. Antithrombotic therapy is debatable but there is consensus that full-dose anticoagulation using heparin with possible mechanical thrombectomy should be initiated in acute to subacute CVT. Duration of anticoagulation is unknown but usually performed up to 12 months after acute CVT.

## Conditions easily confused with stroke

Symptoms suggestive of stroke may be due to alternative etiologies as described in [Table 71.9](#).

**Table 71.9** *Conditions that may mimic stroke.*

Neurologic	Epilepsy – Todd's paralysis Demyelinating – multiple sclerosis, Devic's disease, transverse myelitis Usually accompanied with history of prior weakness or numbness, or optic neuritis Patients usually do not have other vascular risk factors (hypertension, hypercholesterolemia, diabetes, etc.) Neuromuscular – myasthenia gravis
Metabolic	Hyperglycemia Infectious Hyperosmotic syndrome – iatrogenic correction of hyponatremia, bariatric surgery, NO <sub>2</sub> toxicity, B12 deficiency

Neoplasm	Space-occupying lesion Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis Lambert Eaton
Psychogenic	

**Table 71.10 Differential diagnoses of lesions.**

Location of lesion	Symptoms	Differential diagnoses
Brainstem/CPA	Midbrain: – Oculomotor deficits – Ptosis – Vertical eye movement Pons: – Severe dysarthria > facial weakness Horizontal gaze palsy (involvement of CN VI and PPRF) CPA: hearing loss Vertical nystagmus	Vascular (CVA – AICA labrythine artery, ICH) Mass lesion (schwannoma, meningioma, epidermoid, metastasis; adult – pontine glioma, child – PNET) Inflammatory (vasculitis, sarcoidosis, multiple sclerosis) Infectious (bacterial – abscess)
Meningeal	Altered mental status	Vascular (dolichoectasia of vertebrobasilar artery, SAH) Infectious (bacterial – abscess, tuberculosis, fungal abscess –

viral – CMV, HSV,  
cryptococcal, Lyme, West Nile)  
Inflammatory (arthritis,  
sarcoidosis, multiple sclerosis)  
Drugs, toxic/metabolic

Vestibular organs	Unilateral hearing loss Dix Hallpike maneuver Fatigable rotatory nystagmus	Benign positional vertigo Ménière's disease Vestibulitis
-------------------	--	--

---

AICA, anterior inferior cerebellar artery; CMV, cytomegalovirus; CPA, cerebellopontine angle; HSV, herpes simplex virus; ICH, intracerebral hemorrhage; PNET, primitive neuroectodermal tumor; SAH, subarachnoid hemorrhage.

## Case vignette

A 52-year-old right-handed male with a medical history of alcohol abuse came to the ER with onset of left-sided weakness. He stated that he was at home at around 3:00 a.m. when he started to have left-sided weakness. He came to the ER at 4:56 a.m. with his wife and EMS when his symptoms did not improve. His initial blood pressure was 185/116.

Neurologic examination revealed the following:

Mentation: Lethargic, oriented to person/place but not time.

Language: He was able to follow simple one step commands. He was able to name simple objects only. Repetition and reading sentences were intact.

Cranial nerves: Pupils 3–2 mm to light and accommodation. Extraocular muscles were intact. There was no gaze deviation or visual field deficit. He had a mild left upper motor neuron facial paresis but no facial sensory deficits elicited. He had clear dysarthria when saying

“R” and “L.” His tongue was midline.

Motor:

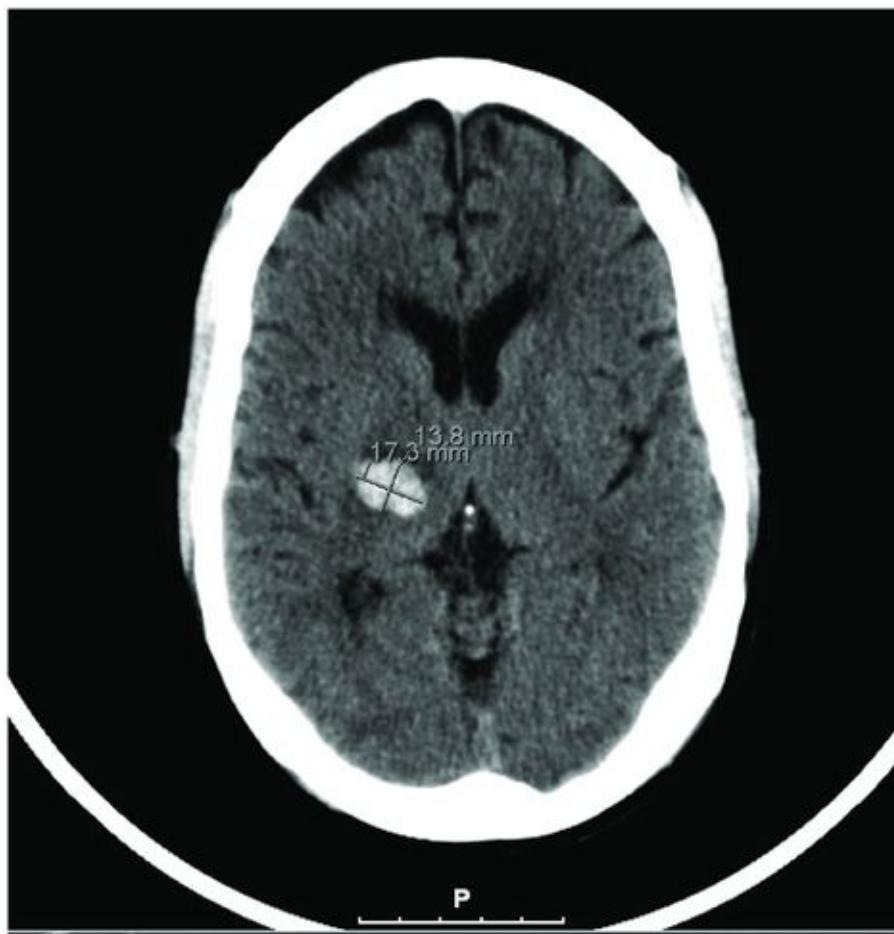
Both his left arm and leg had decreased tone with normal bulk. On the right side, he had full strength upon confrontation. The left arm motor examination as follows: deltoid 2/5, biceps 3/5, triceps 2/5, wrist extension 3/5, finger extension 3/5. His left leg revealed hip flexion 2/5, knee extension 3/5, knee flexion 2/5, dorsiflexion 3/5, plantar flexion 4/5.

Coordination:

Left finger to nose and heel to shin were normal.  
Patient deferred right arm testing.

Gait:

Patient was unable to stand or ambulate.



**Figure 71.4** CAT scan of head without contrast shows a right thalamocapsular intraparenchymal bleed of 3.6 cubic centimeter volume with no subarachnoid or intraventricular extension.

In light of an acute neurologic deficit, the clinician must rule out intracranial hemorrhage with neuroimaging. A CAT scan of head without contrast ([Figure 71.4](#)) is the diagnostic test of choice to rule out intracranial hemorrhage. The etiology of an intraparenchymal hemorrhage is uncontrolled hypertension and trauma. The clinician should ask the patient if he has a history of hypertension and recent head trauma (possibly secondary to alcohol intoxication).

The patient revealed that he had been diagnosed with “a pressure problem” 8 years ago but does not take his medication due to side effects. He does not recall a history of recent head trauma.

By examination of the CT of head, the location of the intraparenchymal hemorrhage is commonly seen in hypertensive intracranial hemorrhages. With the patient's history of uncontrolled hypertension and alcohol abuse, the clinician has a diagnosis of an intraparenchymal hemorrhage secondary to uncontrolled hypertension .

## Further reading list

Blumenfeld H. Neuroanatomy overview and basic definitions. In *Neuroanatomy through Clinical Cases*, 2nd edn. Sunderland, MA: Sinauer Associates, 2002: 14–44.

Caplan, L. Basic pathology, anatomy, and pathophysiology of stroke. In *Caplan's Stroke: A Clinical Approach*. Philadelphia, PA: Saunders Elsevier, 2009.

Mohr JP, Wolf PA, Grotta JC *et al*. In *Stroke: Pathophysiology, Diagnosis, and Management*, 5th edn. Philadelphia, PA: Elsevier Saunders, 2011: 661–80.

Ropper AH, Samuels MA, Eds. Cerebrovascular diseases. In *Adams and Victor's Principles of Neurology*, 9th edn. New York, NY: McGraw-Hill, 2009.

## **72 Stroke in the young, etiologies**

---

Walter J. Molofsky *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

Neonates, infants, and children can suffer strokes. Neonates and infants also may present with strokes that were prenatal in origin. A stroke is a prolonged or permanent dysfunction of brain activity due to interruption of normal vascular flow or due to hemorrhage within the brain. Stroke symptoms that last less than 24 hours are called transient ischemic attacks (TIAs).

Strokes can be divided into two types: ischemic and hemorrhagic.

*Ischemic strokes* are cerebrovascular insults that occur as a result of obstruction of cerebral blood flow.

*Hemorrhagic strokes* are lesions resulting from extravasation of blood from normal, congenitally abnormal, or damaged blood vessels.

Ischemic strokes can be associated with hemorrhagic infarction and hemorrhagic strokes can have areas of surrounding ischemia, called penumbra. This can lead to clinical findings that initially exceed the area of primary hemorrhage or ischemia and offers an explanation for why improvement can occur following a stroke as the area of hemorrhage or transient ischemic impairment subsides.

The incidence rates of ischemic and hemorrhagic strokes in pediatric patients are approximately the same (1 to 2/100,000), leading to a combined incidence of about 3/100,000. This is in contrast to the adult population, where ischemic strokes predominate by about 3–4 : 1.

### **Risk factors for stroke in children**

## **Ischemic stroke**

Major risk factors for ischemic pediatric stroke include cardiac disease, hematologic disorders, primary vasculitis, drug reactions, abuse, metabolic abnormalities (homocystinuria), lipid abnormalities, migraine, and states of decreased perfusion, such as dehydration or shock ([Table 72.1](#)). The most common clinical presentations of ischemic stroke in children include sensory motor deficit, aphasia, dystonia, isolated motor hemiplegia, headache, and seizures.

Cardiac abnormalities account for almost one third of the ischemic strokes seen in children. These anomalies may be either congenital or acquired. Between 1.5% and 4% of children with uncorrected cyanotic heart disease, which may be complicated by hypoxia, polycythemia, or cyanosis, can suffer strokes. These patients also are at high risk because of right to left shunting. Tetralogy of Fallot, transposition of the great vessels, tricuspid atresia, and pulmonary atresia are common cyanotic congenital cardiac anomalies that may lead to ischemic stroke. Thrombosis may develop in the atria in patients with mitral valve prolapse, rheumatic heart disease, cardiomyopathy, and endocarditis. Ischemic stroke also may result as a complication of extracorporeal membrane oxygenation procedures (ECMO). Coagulation abnormalities account for about 14% of ischemic strokes.

## **Hemorrhagic stroke**

Primary hemorrhagic strokes account for approximately 40–50% of pediatric strokes. The major etiologies of non-traumatic brain hemorrhage in children include vascular malformation (33%), cavernous malformation (2%), aneurysm (6%), brain tumor (13%), hemorrhagic disorders (17%), coagulopathies (16%), hemorrhagic infarction (8%), and spontaneous dissection (2.9%).

The clinical presentation of hemorrhagic infarction includes headache, hemiplegia (60%), aphasia (30%), motor seizures (39%), and lethargy and coma (21%). Seizures occur frequently, usually within 48 hours of the hemorrhage. The areas most frequently affected by intracerebral hemorrhage (ICH) are the putamen (35%), cerebellum (15%), thalamus (10%), caudate (5%), and pons (5%).

**Table 72.1 Etiologies of stroke in children.**

Etiology	Ischemic	Hemorrhagic	Comments
Congenital heart disease			<a href="#">1</a>
Ventricular septal defect	x		
Atrial septal defect	x		
Patent ductus arteriosus	x		
Aortic stenosis	x		
Mitral stenosis	x		
Coarctation	x		
Cardiac rhabdomyoma	x		
Complex congenital heart defects	x		
Acquired heart disease			<a href="#">2,3</a>
Rheumatic heart disease	x		
Prosthetic heart valve	x		
Libman–Sacks endocarditis	x		
Bacterial endocarditis	x		
Cardiomyopathy	x		
Myocarditis	x		
Atrial myxoma	x		
Arrhythmia	x		
Systemic vascular disease			<a href="#">4,5,6</a>

Systemic hypertension	x	
Volume depletion or systemic hypotension	x	
Hypernatremia	x	
Superior vena cava syndrome	x	
Diabetes	x	
Vasculitis		7,8,9,10,11,12
Meningitis	x	x
Systemic infection	x	
Systemic lupus erythematosus	x	x
Polyarteritis nodosa	x	
Granulomatous angiitis	x	
Takayasu's arteritis/rheumatoid arthritis	x	
Dermatomyositis/inflammatory bowel disease	x	
Drug abuse (cocaine, amphetamines)	x	
Hemolytic–uremic syndrome	x	x
Vasculopathies		13,14
Ehlers–Danlos syndrome IV	x	AD
MELAS × M homocystinuria	x	AR

Moya-moya syndrome	x		AR,/AD, M
Fabry's disease	x		AR
Malignant atrophic papulosis	x		
NADH-CoQ reductase deficiency	x		AR
Vasospastic disorders			15,16
Migraine	x		
Ergot poisoning	x		
Vasospasm with subarachnoid hemorrhage	x		
Hematologic disorders and coagulopathies			17,18
Hemophilia A/B		x	X
Hemoglobinopathies	x	x	AR
Sickle cell anemia	x	x	AR
Sickle cell hemoglobin	x		AR
Immune thrombocytopenic purpura	x	x	
Thrombotic thrombocytopenic purpura	x	x	
Thrombocytosis	x		
Daltonism	v		

<b>Risk factor</b>	<b>Incidence</b>	<b>Associated conditions</b>	<b>References</b>
Disseminated intravascular coagulation	x		
Leukemia or other neoplasm	x		
Congenital coagulation defects	x		
Oral contraceptive use	x		
Pregnancy and the postpartum period	x	x	
Antithrombin deficiency	x		AD
Protein S deficiency	x		AR
Protein C deficiency	x		AR
Congenital serum C2 deficiency	x		
Liver dysfunction with coagulation defect	x		
Vitamin K deficiency	x		
Lupus anticoagulant	x		
Anticardiolipin antibodies	x	x	
Cerebrovascular structural anomalies			19,20,21,22
Arteriovenous malformation	x		
Intracranial aneurysm		x	
Arterial fibromuscular disease	x	x	

## **causipasia**

Hypoplasia of the internal carotid or vertebral arteries	x		
Hereditary hemorrhagic telangiectasia	x		
Sturge–Weber syndrome	x	x	
Trauma	x		<a href="#">23,24</a>
Child abuse	x		
Fat or air embolism	x		
Foreign body embolism	x		
Carotid ligation (e.g. ECMO)	x	x	
Vertebral occlusion following abrupt cervical rotation	x	x	
Post-traumatic arterial dissection	x	x	
Blunt cervical arterial trauma	x	x	
Arteriography	x	x	
Post-traumatic carotid cavernous fistula	x	x	
Coagulation defect with minor trauma	x		
Amniotic fluid/placental embolism	x	x	
Penetrating intracranial trauma	x		

---

ECMO, extracorporeal membrane oxygenation procedures; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes.

Congenital heart disease

**1** Heart murmurs

Acquired heart disease

**2** Heart murmurs

**3** Congestive heart failure

Systemic vascular disease

**4** Blood pressure

**5** Electrolyte abnormalities

**6** Glucose

Vasculitis

**7** Systemic illness

**8** Rash

**9** Muscle weakness

**10** Gastrointestinal complaints

**11** History of drug use

**12** Renal failure

Vasculopathies

**13** Skin tone abnormalities

**14** Recurrent episodes

Vasospastic disorders

**15** Recurrent headache

**16** Severe headache

Hematologic disorders

**17** Bleeding disorders

**18** Anemia

Cerebrovascular structural anomalies

**19** Bruits

**20** Macrocephaly

**21** Prominent facial veins

**22** Hemangiomas

Trauma

**23** Bruising

## **24** Retinal hemorrhages

Genetic disorders: AD, autosomal dominant; AR, autosomal recessive; M, mitochondrial; X, Sex-linked recessive

## **Clinical presentations**

Pediatric cerebrovascular disorders may present with a variety of clinical scenarios. The classical presentation is rapid onset of clinical signs and symptoms related to an acute abnormality of brain function. The symptoms may include acute onset of mental status change, ataxia, language problems, motor impairment, or focal weakness in a previously normal child.

A second presentation is slowly progressive or recurrent neurologic dysfunction. Examples of this include patients who have recurrent strokes or transient neurologic dysfunction due to ischemic or microhemorrhagic events, underlying disorders such as arteriovenous malformations (AVMs), metabolic encephalopathy and lactic acidosis and stroke syndrome (MELAS), and sickle cell disease.

A third presentation is that of evolving recognition of focal neurologic impairment related to a prenatal or perinatal stroke. This is especially common in the first year of life, presenting as the result of a fetus or neonate having sustained a cerebrovascular insult that was not recognized previously. During the first year of life as the infant develops, it may become apparent that there is an asymmetry of motor function. Imaging to evaluate this problem may reveal prior infarcts or strokes.

## **Differential diagnosis of presenting symptoms**

It is important to determine the nature of the presenting clinical disorder before proceeding with further work-up ([Table 72.2](#)). The differential diagnosis of acute neurologic events includes stroke, seizure, trauma, migraine, intracranial obstruction, abscess, metabolic disorder, toxic ingestion, drug reaction, meningitis, tumors, and syncope. Tumors classically present as slowly progressive disorders. Inflammatory and infectious disorders usually present with fever and other systemic findings. The focal impairment resulting from a seizure usually is transient. The differential diagnosis of acute neurologic impairments and the associated diagnostic tests are included in [Table 72.2](#).

**Table 72.2 Causes of acute neurologic impairment.**

Cause	Diagnostic evaluation
Stroke	CT/MRI
Seizure	EEG
Trauma	CT/Skull X-ray
Migraine	MRI
Ventricular obstruction	CT
Abscess	MRI
Metabolic disorder	Comprehensive metabolic screen
Toxic ingestion	Urine/serum toxicology screen
Drug reaction	Urine/serum toxicology screen
Meningitis	CBC, ESR, LP

CT, computerized tomography; EEG, electroencephalography; ESR, erythrocyte sedimentation rate; LP, lumbar puncture; MRI, magnetic resonance imaging.

## Evaluation of stroke syndromes

Once it has been confirmed that a cerebrovascular insult has occurred, the work-up should focus on the specific disorder and risk factor responsible for the stroke ([Tables 72.3, 72.4](#)). The clinical evaluation of a child with recognized evolving or acutely acquired cerebrovascular events begins with stabilization of the patient's airway, breathing, and cardiovascular system (ABCs). A complete medical history and physical examination must then be performed. The history serves to determine if there are any underlying disorders that would predispose

to the neurovascular event. The physical examination documents the presence of the neurologic impairments and any associated systemic disease which may predispose to the stroke. For example, a child with a heart murmur, sickle cell disease, or evidence of infection may have a cardiovascular, hematologic, or inflammatory process responsible for the stroke.

**Table 72.3 Stroke evaluation in the first 24 hours.**

---

Computerized tomography of the head

Magnetic resonance imaging

Electrocardiogram

Chest X-ray

Echocardiogram

Urine toxicity screen

Complete blood count

Electrolytes, Ca, Mg, phos

Blood urea nitrogen/creatinine

Liver function tests

Prothrombin time *partial thromboplastin time* international normalized ratio

Erythrocyte sedimentation rate /ANA test for presence of abnormal antibodies

Lumbar puncture – infection, inflammation, or neoplasm suspected

Transcranial and carotid ultrasound

---

The initial investigation recommended for patients with a suspected cerebrovascular disorder is summarized in [Table 72.3](#). In the stable patient, the imaging technique of choice is magnetic resonance imaging (MRI). A computed tomography (CT) scan may not identify an area of ischemia or infarction within the first 24 hours. However, in unstable patients, a non-contrast CT scan of the head should be obtained, and if a vascular lesion is suspected, follow-up evaluation with an MRI and magnetic resonance angiography (MRA) should be undertaken.

Following stabilization of the patient and the initial evaluation, a more detailed work-up may be pursued ([Table 72.4](#)). This includes a comprehensive list of hematologic, cardiac, laboratory tests, and imaging that may be included in the stroke evaluation. Selection of additional tests should be guided by the clinical history, exam, and the initial laboratory and imaging assessments.

**Table 72.4 Stroke evaluation after 24 hours.**

---

Cerebral angiogram

HIV testing

Hemoglobin electrophoresis

Factor VII, VIII

Plasminogen level

Fibrinogen level

Antiphospholipid antibody panel

Arterial lactate and pyruvate

Cerebrospinal fluid lactate, pyruvate

Plasma ammonia and amino acids

Urine and serum homocysteine

Lipid profile

Serum protein electrophoresis

MELAS/MERF profile

*MTHFR* polymorphism

Folate level

Vitamin B12

Hypercoagulability studies

Protein C, protein S

Antithrombin III

Lupus anticoagulant

Anticardiolipin antibody

Factor V (Leiden) mutation

---

MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MERF, myoclonus epilepsy with ragged-red fibers.

## Case vignette

An 8-year-old female presents with a history of acute onset of right hemiparesis, lethargy, and decreased level of consciousness.

She has been noted in the past to have macrocephaly. She has a history of intermittent headaches beginning about a year ago. The headaches have been described as diffuse and throbbing in nature, lasting anywhere from 1–2 hours, and associated nausea or vomiting. They have increased in frequency. She has been complaining of some mild right-sided weakness. A week before admission, she had an episode of clonic-tonic movements of her right arm and leg. On the day of admission, she presented with an acute deterioration in her mental status,

and lethargy.

Past medical history is significant for the fact that she was the product of a normal pregnancy, labor, and delivery. Growth and development were normal.

On exam, she had a head circumference of 56 cm (> 98%). She had prominent veins on her forehead and face. There was an evident bruit. She had evidence of right-sided weakness and upgoing toe.

A CT showed a left frontotemporal hemorrhage compressing the lateral ventricle. Angiographic studies revealed a hemorrhagic lesion in the left temporoparietal area with some enhancing draining veins. Diagnosis was AVM that bled acutely.

The salient features of this vignette are the chronic macrocephaly, chronic prominent draining veins on her face, the bruit, and the recent increase in her headaches. These features should prompt an imaging work-up in children when they present with headaches. She then had a partial seizure, probably from a small sentinel bleed, and then an acute bleed leading to her presenting symptoms. She was treated with anticonvulsants, and then had a series of embolization procedures that began after the blood reabsorbed. She has a residual mild right hemiparesis.

## Further reading list

Carlin T, Chanmugam A. Stroke in children. *Emerg Med Clin North Am* 2002; 20:671–85.

Carvalho K, Garg B. Arterial strokes in children. *Neurol Clin* 2002; 20:1079–100.

deVeber G. Cerebrovascular disease in children. In Swaiman K, Ashwal S, Eds. *Pediatric Neurology, Principles and Practice*. St. Louis, MI: CV Mosby, 2011: 1437–62.

Giroud M, Lemesle M, Madinier G et al. Stroke in children under 16 years of age. Clinical and etiologic differences with adults. *Acta Neurol Scand* 1997; 96:401–6.

Kirkham F. Stroke in childhood. *Arch Dis Child* 1999; 81:85–9.

Lanksa MJ, Lanska DJ, Horowitz SJ, Aram DM. Presentation, clinical course and outcome of childhood stroke. *Pediatr Neurol* 1991; 7:333–6.

Lanthier S, Carmant L, David M *et al.* Stroke in children: the coexistence of multiple risk factors predict poor outcome. *Neurology* 2000; 54:371–7.

Nass R, Trauner D. Social and affective impairments and important recovery after acquired stroke in childhood. *CNS Spect* 2004; 9:420–34.

Roche E. Etiology of stroke in children. *Semin Pediatr Neurol* 2000; 7:244–50.

## 73 Syncope

---

Todd J. Cohen *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Syncope is one of most common causes of emergency room visits, making up approximately 3–6% of all visits. Syncope may be defined as a complete loss of consciousness. A near or presyncope definition will include lightheadedness and dizziness or symptoms short of complete loss of consciousness. A misnomer is that syncope is often a neurologic problem. This occurs in a minority of cases.

The causes of syncope or presyncope can be divided into two categories, cardiac and non-cardiac. Cardiac syncope has a worse prognosis and is often related to arrhythmias. Other causes include outflow tract obstruction (aortic stenosis, pulmonic stenosis, and that which occurs during hypertrophic cardiomyopathy). In addition, the most frequent cardiac arrhythmia resulting in syncope or loss of consciousness is in the category of tachyarrhythmias and includes ventricular tachycardia, ventricular fibrillation as well as supraventricular tachycardia, and has a variety of etiologies. The bradycardias (sinus node dysfunction), atrioventricular block, and complete heart block are less common causes of syncope or presyncope. Almost half of the non-cardiac causes of syncope are due to neurocardiogenic and/or vasovagal variants. These are principally due to a vasodilation or drop in blood pressure. Some cardiac and even vasovagal type syncopes may look neurologic in nature. Cerebral hypoperfusion can result in tonic-clonic activity, which is very similar to that which occurs during a grand mal seizure.

The minority of syncopal and/or presyncopal episodes are due to neurologic events. These are principally focal and well described. It is unusual for a stroke and/or seizure to result in syncope, but it does occur.

The best approach for diagnosing and treating syncope or presyncope is based on a thorough and complete history and physical examination and an

electrocardiogram (ECG). If the history, physical examination, and/or electrocardiogram points to a cardiac etiology, it is important to proceed with a cardiac work-up as the history dictates. For example, if the patient comes in with a history of a prior myocardial infarction and is having runs of non-sustained ventricular tachycardia and has a left bundle-branch block pattern, a cardiac work-up to rule out ischemia and define the cardiac substrate, followed by an electrophysiology study to define inducibility of a cardiac arrhythmia, is important. If the patient has inducible sustained ventricular tachycardia, an implantable defibrillator would be warranted. If however, the history, physical examination, and ECG are essentially normal from a cardiac standpoint and point to a neurologic etiology (i.e. aura, some focality such as weakness, numbness, loss of function with laterality), a neurologic etiology should be pursued including a complete neurologic consultation and evaluation. If the history, physical examination, and ECG are entirely negative, it may be prudent to proceed with a head-up tilt-table test, a test designed to assess changes in blood pressure and heart rate over time. Typically, the patient is strapped to a table and placed erect between 60 degrees and 80 degrees. Occasionally, a pharmacologic agent such as isoproterenol is used to provoke a neurocardiogenic response. Carotid massage may also be performed while the patient is upright, which increases the yield for diagnosing carotid sinus hypersensitivity. The latter condition may occur in patients who have syncope related to turning their neck and/or tight collar. The tilt-table test may be useful in diagnosing orthostatic hypotension , autonomic dysfunction , Shy--Drager syndrome , vasopressor, and/or cardio-inhibitory syncope, and/or mixed neurocardiogenic syncope.

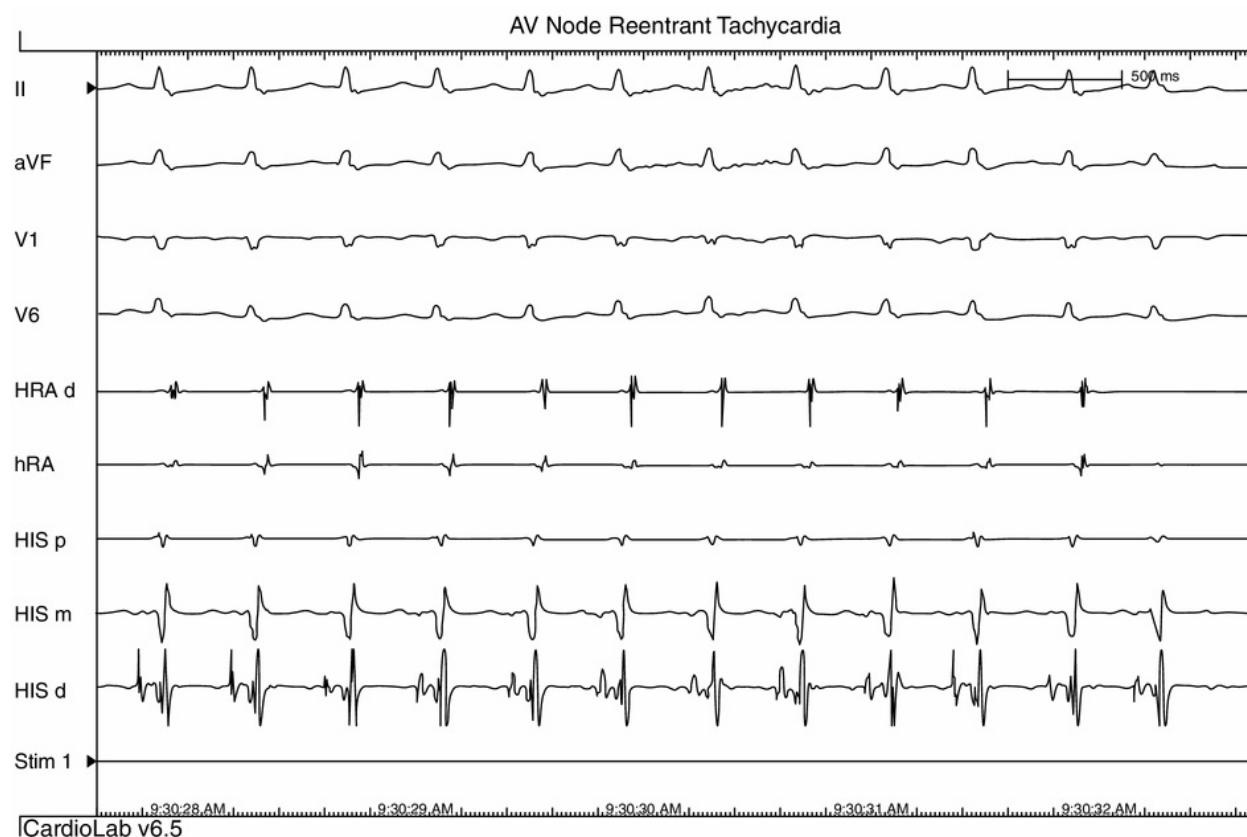
The implantation of a cardiac monitor (implantable loop recorder or implantable cardiac monitor) is often useful in patients who have a complete work-up and still remain with the diagnosis of syncope of unknown etiology. This small device can be placed subcutaneously and kept in place for up to 3 years. It can record information automatically and will be triggered by an external device. This device has been very useful in diagnosing syncope of unknown etiology and can not only show arrhythmias and/or rule out cardiac arrhythmias as a cause of syncope, but may be useful in showing a high-frequency activity consistent with the muscle twitching and movement motion characteristic of an epileptiform behavior.

In summary, syncope is very common. Neurologic etiologies are often sought first but should be sought last unless laterality or common neurologic sequelae are identified. It is important to rule out cardiac syncope since it is associated with the highest mortality and can be easily treated. The history, physical

examination, and ECG are the first steps in a complete diagnosis and an implantable loop recorder may be useful when all else fails to identify an appropriate etiology to the syncope.

## Case vignette

A 59-year-old female was referred to an epileptologist for multiple collapses preceded by dizziness. The episodes were described as a sudden loss of consciousness followed by headache and fatigue, with confusion upon awakening. The patient underwent a full neurologic work-up including electroencephalogram (EEG), computerized tomography (CT), and magnetic resonance imaging (MRI) with no significant findings. The patient was sent to the cardiologist who performed a head-up tilt-table test which was positive but of unclear clinical significance. The patient was referred for electrophysiology study and possible implantable loop recorder. The electrophysiology study revealed an atrioventricular nodal reentrant tachycardia ([Figure 73.1](#)). This is a specific form of supraventricular tachycardia in which there are two AV node pathways (a fast one and a slow one). In this patient's case, the slow pathway was successfully ablated with a very low chance for recurrence.



### **Figure 73.1 Atrioventricular node reentrant tachycardia.**

This case illustrates the typical confusion between syncope and seizure that is discussed in this chapter. It is important to rule out the condition with the highest mortality (cardiac syncope). Syncope accounts for 3–6% of all emergency room visits. Most causes of syncope are not neurologic in nature. It is common to confuse syncope with seizure disorder. One study demonstrated stereotypical tonic-clonic movements in 45% of those with induced ventricular tachycardia or fibrillation. This could also occur with supraventricular tachycardia. The driving force behind these movements is cerebral hypoperfusion which triggers the medullary reticular formation and results in characteristic myotonic activity. Some characteristics to keep in mind when differentiating syncope from a seizure is the presence of a prodrome associated with syncope. This consists of nausea, vomiting, dizziness, and/or blurred vision, however these may be absent in syncope that is due to arrhythmia. Additionally, the typical loss of consciousness in syncope is often brief, lasting mostly 1–2 minutes, with rare episodes lasting 5 minutes or longer. Moreover, post-episode confusion is almost never seen and brief when present (less than 5 minutes).

The work-up for patients suspected of having cardiac syncope should begin with a thorough history, physical examination, and an ECG. If this is negative for cardiac disease a head-up tilt-table test may be useful for evaluating neurocardiogenic syncope. If the history is positive for cardiac disease or the head-up tilt-table test is negative, an electrophysiology study can be useful to determine the presence or absence of an arrhythmia. When head-up tilt-table testing and an electrophysiology study are inconclusive, consideration should be given to the use of an implantable loop recorder which can determine the presence of an underlying infrequent arrhythmia. In the majority of these patients the underlying cause is most often a transient bradycardia that is undetectable by conventional methods. Many times, a pacemaker is then implanted .

**Table 73.1 Causes of syncope.**

Classification	Specific type	Specific etiology	P f
Cardiac	Arrhythmias	Abnormal cardiac	P ..

syncope	Tachycardia (supraventricular tachycardia) Ventricular tachycardia/ventricular fibrillation	substrate	II (I d fi C te S
	Bradycardias Sinus node dysfunction AV block/heart block	Conduction disease	L (I S fi C d
	Outflow tract obstruction Hypertrophic cardiomyopathy Aortic stenosis Pulmonic stenosis	Abnormal cardiac substrate possibly inherited or acquired	F li (I S e d e
	Pacemaker failure/malfunction	Lead-related failures, generator malfunction, insertion site issues	L (I S d a ir al
Non-cardiac syncope	Neurocardiogenic syncope Cardioinhibitory syncope Vasodepressor syncope Mixed cardioinhibitor/vasodepressor syncope	Over-exaggerated response often induced by catecholamine trigger causing an overactive vagal response	L (I S f p n si te h

Orthostatic hypotension	Volume depletion/dehydration	L (I S b c p u ir a h
Autonomic dysfunction	Decreased vascular tone which occurs in diabetes and Parkinson's disease	L (I S d p si ir
Neurologic seizure	Sudden paroxysmal episodes of involuntary muscle contractions with changes in consciousness, behavior, sensations, and autonomic function	N b n c f fl p s u je si o w st
CVA/TIA	Central nervous system abnormality or hemorrhagic and/or embolic event	S v d w

C  
ir  
c  
d  
b  
f  
w  
C  
S

Vertigo	Vertebrovascular insufficiency, disruption receiving sensory system signals	F o s n t r s n fi
---------	---	--

---

AV, atrioventricular; CVA, cerebrovascular accident; ECG, electrocardiogram; TIA, transient ischemic attack.

## Further reading list

Boersma L, Mont L, Sionis A *et al*. Value of the implantable loop recorder for the management of patients with unexplained syncope. *Europace* 2004; 6:70–6.

Hess DS, Morady F, Scheinman MM. Electrophysiologic testing in the evaluation of patients with syncope of undetermined origin. *Am J Cardiol* 1982; 50:1309–15.

Kapoor WN, Smith MA, Miller NL. Upright tilt testing in evaluating syncope: a comprehensive literature review. *Am J Med* 1994; 97:78–88.

Ozkara C, Metin B, Kucukoglu S. Convulsive syncope: a condition to be differentiated from epilepsy. *Epileptic Disord* 2009; 11:315–19.

Paisey JR, Yue AM, Treacher K *et al.* Implantable loop recorders detect tachyarrhythmias in symptomatic patients with negative electrophysiological studies. *Int J Cardiol* 2005; 98:35–8.

Sheldon R, Rose S, Ritchie D *et al.* Historical criteria that distinguish syncope from seizures. *J Am Coll Cardiol* 2002; 40:142.

Soteriades E, Evans J, Larson M *et al.* Incidence and prognosis of syncope. *N Engl J Med* 2002; 347:878–85.

Task Force for the Diagnosis and Management of Syncope of the European Society of Cardiology (ESC). Guidelines for the diagnosis and management of syncope (version 2009). *Eur Heart J* 2009; 30:2631–71.

Zaidi A, Clough P, Cooper P *et al.* Misdiagnosis of epilepsy: many seizure-like attacks have a cardiovascular cause. *J Am Coll Cardiol* 2000; 36:181–4.

## 74 Tinnitus

---

Eric E. Smouha and Grace M. Charles *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Tinnitus is defined as a sound perceived by the patient that cannot be attributed to an external acoustic stimulus. Patients may perceive it as a ringing, buzzing, whistling, or humming sound. It can be transient or persistent, continuous or intermittent, sudden-or gradual-onset, pulsatile or non-pulsatile, and can vary in pitch and loudness. Tinnitus may be classified as *objective*, in which patients are hearing real somatic sounds that are audible to an outside listener, or as *subjective*, in which patients falsely perceive sound in the absence of any acoustic stimulus.

Tinnitus is a prevalent disorder, affecting about 15% of the population, and in about 10% of these cases, tinnitus may be *disabling*, with impairment of quality of life.

In the majority of cases, tinnitus is subjective, continuous, and results from sensorineural hearing loss. However, tinnitus can be a symptom of a broad range of disorders and thus requires a comprehensive multidisciplinary diagnostic work-up. For example, pulsatile tinnitus can be caused by a glomus jugulare tumor, and unilateral tinnitus can be a sign of acoustic neuroma.

### Related anatomy

Tinnitus is generated in the auditory system and related neural pathways. The ear is the peripheral organ of hearing, and consists of an outer ear (*pinna* and *ear canal*) that gathers sound, a middle ear (*tympanic membrane* and *ossicles* – malleus, incus, and stapes – vibrating in an air-containing space) that acts as an impedance-matching transformer, and inner ear (*cochlea*) that transduces the mechanical energy of sound into electrical impulses encoded for frequency and

intensity. The cochlea is an elaborate organ that contains the *organ of Corti*, wherein specialized neuro-receptor cells called *hair cells* are arranged in an orderly tonotopic array on a basilar membrane and transduce the mechanical deflections of sound into electrical membrane depolarizations. Each hair cell is “tuned” to respond to a specific frequency, and the magnitude of its membrane depolarization is proportional to the intensity of the incoming sound. Each hair cell is coupled to an auditory nerve fiber that is similarly “tuned” to respond to a certain frequency. The *auditory nerve* (cranial nerve VIII) enters the brainstem (pons) and forms a synapse within the cochlear nucleus. The ascending neural pathways are crossed (80% of the fibers decussate in the pons) and form connections in the superior olive, lateral lemniscus, inferior colliculus, and medial geniculate body to end in the *auditory cortex* in the temporal lobe where the conscious awareness of sound occurs.

The exact pathophysiology of tinnitus has yet to be delineated. Current theories regarding subjective tinnitus suggest that a decrease in cochlear input to the auditory cortex results in the disinhibition of cortical auditory neurons and possibly the creation of new synaptic pathways. This may trigger an increase in spontaneous activity of the central auditory system, generating the perceived sound. Non-auditory brain areas, in particular the dorsolateral prefrontal cortex, may also be involved in tinnitus by failing to produce cortical inhibition of auditory signals. The limbic and autonomic systems may also produce secondary psychological and physiologic reactions to the tinnitus.

Objective tinnitus results from the real sounds of physiologic and pathophysiologic processes, such as vascular pulsations, occurring in the vicinity of the cochlea.

## Differential diagnosis

The evaluation of tinnitus always begins with the history and physical examination. Important elements in the history are whether the tinnitus is pulsatile or non-pulsatile, and whether it is acute, paroxysmal, or constant. Pulsatile tinnitus should initiate the search for a vascular cause (see [Table 74.1](#)). If constant, it should be determined whether there is hearing loss, vertigo, headache, history of trauma, neck or musculoskeletal disorders, and whether there is associated anxiety or depression. Grading the severity of the tinnitus may be done using a standardized questionnaire such as the Tinnitus Handicap Inventory (THI). A complete examination of the ears, nose, throat, and neck

should be performed, and the neck and ears should be auscultated if the tinnitus is pulsatile. Referral to an otolaryngologist or neurotologist is often advisable.

The need for ancillary tests is guided by the initial findings. For pulsatile tinnitus, a CT scan of the temporal bones will reveal a middle ear tumor, aberrant carotid artery, high jugular bulb, or other vascular abnormality. Doppler studies, MRI, MRA, or standard angiography can be performed when indicated. For non-pulsatile tinnitus, standard audiology (pure tone, speech, impedance testing, acoustic reflexes) is the first step in diagnosis. Patients with conductive hearing loss should be worked up for middle ear pathology, usually with CT scanning of the temporal bone. Patients with unilateral tinnitus, or with “retrocochlear” signs (asymmetric sensorineural hearing loss, poor speech discrimination, absent acoustic reflexes) should have auditory brainstem response testing (ABR, equivalent to brainstem auditory evoked response [BAER] or brainstem auditory evoked potential [BAEP]) to look for a lesion of the eighth cranial nerve. If ABR test is positive, they should have MRI of the internal auditory canals and posterior cranial fossa with and without gadolinium enhancement.

## **Case vignette**

A 46-year-old male complained of tinnitus of 2 years’ duration that he claimed was “affecting the quality of his life.” This he described as a constant ringing, that was high pitched, varying in intensity throughout the day, non-pulsatile, heard in both ears and in the center of his head. It was made louder by loud noises, so that he no longer enjoyed going to restaurants and movies. It was less noticeable in the daytime while working, but more noticeable at night and he frequently had trouble sleeping. He tried using gingko biloba and a “homeopathic” tinnitus remedy without benefit. He was not aware of any hearing loss. His only medical problem was hypertension that was well controlled on a beta-blocker. He denied any current noise exposure but he had worked with printing presses in his 20s. Examination revealed an anxious gentleman, BP 135/85, HR 80 and regular, normal otoscopic findings, no findings in the nose, throat, and neck, no audible bruits, no gross neurologic deficits. Audiometry revealed normal hearing at the low and middle frequencies, but there was bilateral, symmetric high frequency sensorineural hearing loss, severe at 4 kHz, moderate at 6–8 kHz (“notch type”), with speech discrimination score of 92% in both ears, type A tympanometry (normal) bilaterally, and absent acoustic reflexes at 4 kHz bilaterally. ABR revealed normal morphology and

normal interpeak and interaural latencies bilaterally. MRI of the brain and internal auditory canals, ordered by another physician, was negative. His THI score was 84 out of a possible 100 points.

This patient has tinnitus and hyperacusis, moderately disabling, which is secondary to high frequency sensorineural hearing loss that is noise-induced. Sensorineural hearing loss (of any cause) is the most common etiology of tinnitus. The presence and severity of the tinnitus is impossible to predict from the audiogram or by any means – the majority of patients with high frequency sensorineural hearing loss will not have tinnitus, and the majority of those with tinnitus will not find the tinnitus disabling.

The treatment of tinnitus is elusive, and should be directed at the cause, if one can be identified. For this patient (and as is most commonly the case), no structural lesion was identified, and the sensorineural hearing loss that caused his tinnitus has no direct treatment.

First, the patient was counseled as to the nature of his problem. He was told that, although the problem is distressing, it is not life threatening and does not signify something dire. He was further advised that while no available treatment could make the tinnitus disappear, remedies exist that can lessen the symptom. He was told to avoid silence, and to use ambient masking when in quiet environments in the daytime and especially at night. He was advised to place a tabletop radio on his nightstand and play static noise (with the FM radio tuned between two stations) at the lowest audible volume when trying to sleep. He was also given noise-attenuating ear inserts to wear in loud settings. Because he admitted to feelings of anxiety and occasional depression, he was advised to consult with a psychiatrist, but he declined, saying that he did not find the problem to be that severe. The patient had previously been given zolpidem (Ambien) and later alprazolam (Xanax) by his primary care physician but neither was helpful. After discontinuing these drugs, he was prescribed nortriptyline 25 mg qhs. After 4 weeks, he reported that he had better patterns of sleep, and his THI score decreased to 74. Because of continued symptoms in the daytime, he consulted with an audiologist who recommended a wearable sound generator (“tinnitus masker”), a small device the size and shape of a hearing aid that produces a masking sound to block the tinnitus. He found this to be of modest benefit however, and returned it after a one-month trial. Eventually, he opted for tinnitus retraining therapy, administered at a local center with expertise in this area. Tinnitus retraining therapy utilizes sound therapy using an ear-level sound-producing device, along with intensive counseling. After 6 months, the patient

reported significant improvement and his THI score decreased to 32. Although he is still aware of the tinnitus, he reported better coping skills, more regular patterns of sleep, and little impact on his activities of daily living .

**Table 74.1 Diagnosis of tinnitus.**

Quality	Subdivision	Specific entity	Clinical features may include
Pulsatile (structural, vascular)	Arterial	Glomus jugulotympanicum tumor	Red mass in middle ear, tumor on CT/MRI, erosion of jugular bulb
		Carotid artery stenosis	Bruit over neck, abnormal Doppler sonography
		Arteriovenous malformation	Bruit over mastoid or ear, abn MRI and angio
		Aberrant carotid artery	Bruit, red “mass” in middle ear; aberrant vessel on CT
		Carotid–cavernous fistula	History of trauma; proptosis with orbital bruit
Venous	Benign intracranial hypertension	Obesity, papilledema, relief from LP, acetazolamide	

**acutazumatum**

	Sigmoid sinus diverticulum	Detected on CT
	“Venous hum”	Relief of tinnitus with gentle compression of neck
	Sigmoid thrombosis	Venography
Paroxysmal	“Aural flutter”	Myoclonus Intermittent clicking, tympanic membrane (TM) contraction seen on otoscopy
	Microvascular compression of VIII	Abnormal vascular loop on MRI
	Epilepsy	Detected on EEG
Constant, Unilateral	Acute tinnitus with sudden hearing loss	Sudden SNHL Sudden hearing loss, +/- tinnitus, +/- vertigo
	Acoustic trauma	After blast, temporary threshold shift for < 3 days
	Unilateral progressive SNHL	Acoustic neuroma + ABR, + MRI; Rx by surgery or stereo RT

	SNHL with vertigo	Ménière's disease	Fluctuant hearing loss, vertigo, ear fullness
		Labyrinthitis	Acute or chronic, with vertigo, history of viral or bacterial ear infection
Post traumatic		Temporal bone fracture	Hemotympanum, +/- CSF leak, +/- facial paralysis; + CT
		Carotid cavernous fistula	See above
		Carotid artery dissection	Detected by CT angiography, surgical emergency
		Otitic barotrauma	+/- hemotympanum, CHL or SNHL
		Ossicular discontinuity	TM perforation, CHL
Constant, Bilateral	Conductive hearing loss	Chronic otitis media	TM perforation, sclerosis
		Otosclerosis	Normal TM, + family history
		Cerumen impaction	Obvious on otoscopy

	Eustachian tube dysfunction	Ear fullness, following URI or allergy
	Superior semicircular canal dehiscence	Noise-induced vertigo, detected on CT scan
Sensorineural hearing loss	Presbycusis	Progressive bilateral symmetric SNHL
	Noise-induced hearing loss	Industrial noise exposure, HF notch type SNHL
	Genetic hearing impairment	+ family history, CT may reveal cochlear dysplasia
Ototoxicity	Aminoglycosides – imbalance, HF SNHL	Cisplatin SNHL
	Salicylates, quinine derivatives – dose-dependent tinnitus, reversible	
Headache	Chiari	Detected by MRI, consult neurosurgery

	Space-occupying lesion	Detected by MRI, consult neurosurgery
	Benign intracranial hypertension	see above
	Migraine	Paroxysmal headache, +/- aura
Psychiatric	Anxiety	Apprehension, motor tension, autonomic hyperactivity
	Depression	Depressed mood, loss of interest, poss suicidality
	Somatization	Somatic symptoms w/o physical basis, other psychiatric comorbidity

---

ABR, auditory brainstem response testing; CHL, conductive hearing loss; CSF, cerebrospinal fluid; CT, computerized tomography; MRI, magnetic resonance imaging; SNHL, sensorineural hearing loss.

## Further reading list

Biesinger E, Del Bo L, De Ridder D *et al.* Algorithm for the diagnostic and therapeutic management of tinnitus. [[http://www.tinnitusresearch.org/en/documents/downloads/TRI\\_Tinnitus\\_Flowchart.pdf](http://www.tinnitusresearch.org/en/documents/downloads/TRI_Tinnitus_Flowchart.pdf)]

- De Ridder D, Vanneste S, Kovacs S *et al*. Transcranial magnetic stimulation and extradural electrodes implanted on secondary auditory cortex for tinnitus suppression. *J Neurosurg* 2011; 114:903–11.
- Hoare DJ, Kang S, Hall DA. Systematic review and meta-analyses of RCTs examining tinnitus management. *The Laryngoscope* 2011; 121:1555–64.
- Jastreboff PJ. Tinnitus retraining therapy. *Prog Brain Res* 2007; 166:415–23.
- Langguth B, Salvi R, Elgoyen AB. Emerging pharmacotherapy of tinnitus. *Expert Opin Emerg Drugs* 2009; 14:687–702.
- Lockwood AH, Salvi RJ, Burkard RF. Tinnitus. *N Engl J Med* 2002; 347:904–10.
- Newman CW, Jacobson GP, Spitzer JB. Development of the Tinnitus Handicap Inventory. *Arch Otolaryngol Head Neck Surg* 1996; 122:143–8.
- Pirodda A, Claudio B, Ferri GG. Drugs and tinnitus: a review of a controversial matter. *Audiologic Med* 2010; 8:1–4.
- Roberts LE, Eggermont JJ, Caspary DM *et al*. Ringing ears: the neuroscience of tinnitus. *J Neurosci* 2010; 30:14972–9.
- Sismanis A. Pulsatile tinnitus. *Otolaryngol Clin North Am* 2003; 36:389–402, viii.
- Tyler RS, Ed. *Tinnitus Handbook*. San Diego, CA: Singular, 2000: 149–79.

## 75 Tremor

---

Odi Oguh, Esther Baldinger, and and Tanya Simuni *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Tremor is defined as a rhythmic oscillatory movement of a body part produced by alternating or synchronous contractions of antagonist muscles. Tremor is the most common type of all movement disorders, incidence of which increases with age.

Tremor can be classified according to the behavioral circumstance in which it occurs, distribution, frequency, or etiology.

1. Rest tremors : occur in a body part that is fully supported against gravity and that is not voluntarily activated.
2. Action tremors: occur with voluntary activation of a muscle. This includes postural tremor and kinetic tremors.
  - A. Postural tremors present during an antigravity posture such as holding a body part motionless against gravity (e.g. an outstretched arm).
  - B. Kinetic tremors : occur during a voluntary movement such as while performing a finger to nose or heel to shin maneuver. Kinetic tremors can be of three types:
    - I. Task-specific tremors which become evident during specific tasks (e.g. primary writing tremor or occupational tremors).
    - II. Intention tremors : appear when tremor amplitude increases as a body part approaches a visually guided target such as during a finger to nose test.
    - III. Isometric tremors : occur during a voluntary contraction of muscle against a rigid object (e.g. orthostatic tremor).

## Syndromatic classification of tremors

Table 75.1 summarizes the syndromic classification of tremors as it is beyond the scope of this chapter to discuss each of them. Etiologies are discussed in Table 75.2. From the clinical standpoint, it is useful to define the tremor syndrome which will guide the choice of therapeutic intervention.

**Table 75.1** *Syndromatic classification of tremor.*

Diagnosis	Frequency	Activation by		
		Rest	Posture	Goal-directed movement
Enhanced physiologic tremor	8–12 Hz		Necessary	Possible
Essential tremor	4–12 Hz	Possible	Necessary	Possible
Primary orthostatic tremor	13–18 Hz		Necessary	Possible
Task-specific tremor	5–10 Hz		Possible	Necessary
Dystonic tremor	< 7 Hz		Possible	Necessary
Parkinsonian tremor	4–6 Hz	Necessary	Possible	Possible
Cerebellar tremor	< 5 Hz		Possible	Necessary
Holmes'	< 4.5 Hz	Necessary	Possible	Necessary

tremor				
Palatal tremor				
Neuropathic tremor	3–10 Hz		Necessary	Possible
Toxic and drug induced tremor	Depends on type of medication	Possible	Possible	Possible
Psychogenic tremor	Inconsistent pattern variable frequencies		Necessary	Possible

---

'Necessary' means necessary for diagnosis; 'Possible' means may be present.

Adapted from Deuschl G, Bain P, Brin M, Adhoc Scientific Committee. Consensus statement of the Movement Disorder Society on Tremor. *Mov Disord* 1998;13:2–23.

## Physiologic tremor

Physiologic tremor is present in every healthy subject, in the joint or muscle that is free to oscillate with a frequency of 6–12 Hz. In the majority of cases it is not visible.

## Enhanced physiologic tremor

Enhanced physiologic tremor (EPT) is defined as a high frequency easily visible tremor (8–12 Hz), predominately postural in character with no evidence of underlying neurologic disease. Enhanced physiologic tremor should be differentiated from similar tremors with *defined* etiologies including other neurologic diseases, and often overlaps with toxic/drug-induced tremors. These etiologies are often reversible hence respond to identification and withdrawal of the offending agent. Screening for potential metabolic derangements associated

with tremor is pertinent to the diagnostic work-up of EPT.

## **Essential tremor**

A diagnosis of essential tremor (ET) is established based on the presence of a bilateral predominately symmetric 4–12 Hz postural or kinetic tremor, that involves hands and forearms, which is visible and persistent. Tremor may involve the head or voice, while chin or leg tremor is atypical and if present an alternative etiology such as Parkinson's disease should be considered. An isolated head tremor can be a manifestation of ET though in the majority of cases it is a manifestation of an underlying cervical dystonia. Essential tremor is classified into the definite, probable, and possible based on the degree of diagnostic certainty. Definite ET is a monosymptomatic, predominately postural and action tremor that is slowly progressive over time and has a strong familial predisposition, pointing to a likely autosomal dominant inheritance and is also referred to as benign familial essential tremor. However, lack of family history does not preclude the diagnosis of ET .

## **Primary orthostatic tremor**

This is a syndrome characterized by a subjective feeling of unsteadiness while standing, mainly involving the legs and trunk, which improves with ambulation. It is associated with the presence of high-frequency subtle 13–18 Hz tremor of the lower limbs. Tremor might persist during ambulation in severe cases.

On clinical exam findings may be limited to minimally visible and sometimes only palpable fine amplitude rippling of the legs. The diagnosis can be confirmed by electromyography (EMG) recordings from the quadriceps femoris muscle with a typical 13–18 Hz tremor frequency.

## **Task-and position-specific tremor**

These are tremors that occur during specific tasks such as writing or other specific limb positions without other neurologic manifestations. The most common is the primary writing tremor.

Other examples include task-specific tremors of musicians, athletes, or golfers as well as isolated voice tremors. Often these tremors can occur in conjunction with focal dystonic posturing and hence classified as focal dystonia with

dystonic tremor.

## Dystonic tremor syndromes

These are tremors that occur in a body part that is affected by dystonia. They tend to have an irregular pattern with variable frequency and usually resolve with complete rest. Patients may describe a sensory trick (*gestes antagoniste*) to overcome the dystonic movement. An ET type tremor can be present in a body part not affected by dystonia and is likely a manifestation of an ET–dystonia overlap syndrome.

**Table 75.2 Etiologic classification and differential diagnosis of tremors.**

Tremor type	Disease categories	Selected disease entities	Additional clinical features may include
Rest	Hereditary degenerative diseases	Parkinson's disease (PD)	Asymmetric bradykinesia, cogwheel rigidity, ± postural instability
		Parkinsonism-plus syndrome	Typically presents with symmetric parkinsonian features; specific clinical entities are outlined below
		Multiple systemic atrophy	+ Early autonomic features ± Cerebellar ataxia
	Progressive supranuclear palsy		Vertical gaze palsy Predominant axial rigidity: neck rigidity greater than limb rigidity

## Dysarthria

Corticobasal syndrome

Asymmetric pyramidal findings  
Spectrum of cortical abnormalities:  
Alien limb phenomenon  
Focal or asymmetric myoclonus  
Cortical sensory loss  
Visual or sensory hemineglect  
Apraxia of speech  
Focal or asymmetric ideomotor apraxia  
Other signs of extrapyramidal dysfunction:  
dystonia

## Wilson's disease

Presents with a spectrum of different movement disorder phenomenologies including dystonia, tremor, and chorea  
Kayser–Fleisher rings are usually present on ophthalmologic exam

## Fragile X tremor ataxia syndrome (FXTAS)

Predilection for older males  
In addition to tremor, presents

with cerebellar ataxia; may be accompanied with cognitive decline, parkinsonism, neuropathy, and autonomic failure  
Positive family history of mental retardation in male grandchildren  
Magnetic resonance imaging (MRI) reveals hyperintense signal changes in the middle cerebellar peduncle

#### Spinocerebellar ataxia (SCA-3)

Positive family history  
Ataxia, dystonia, levodopa-responsive restless leg syndrome, pyramidal signs, and neuropathy are additional findings that can be seen

#### Cerebral diseases of various etiologies

#### Secondary parkinsonism

Drug induced (most common): neuroleptics, reserpine, tetrabenazine, metoclopramide

Causal relationship of drug initiation and onset of symptoms should be sought. Presents with symmetric

~~metoclopramide,~~  
lithium

~~metoclopramide~~  
signs of  
parkinsonism. On  
exam may also have  
signs of tardive  
syndrome such as  
orobuccolingual  
dyskinesia

Infectious diseases:  
post-encephalitic  
parkinsonism, *etc.*

Present with  
symptoms of acute  
onset parkinsonism  
within the  
convalescent phase  
of a febrile illness  
May be associated  
with neuro-  
behavioral changes  
such as obsessive  
compulsive disorder

Vascular: multi-  
infarct (rarely  
associated with  
tremor)

Lower body  
parkinsonism  
describes its  
predilection for  
affecting the lower  
extremities. Gait  
and balance  
disturbances such as  
freezing of gait and  
falls are the most  
frequent presenting  
features  
Tremor is rarely  
present  
Neurologic exam  
demonstrates  
findings of other  
parts of CNS  
involvement

Space-occupying lesions Normal pressure hydrocephalus	Classic triad of cognitive decline, urinary incontinence, and gait disturbance commonly described as magnetic gait
Trauma: pugilistic encephalopathy, midbrain injury	Pugilistic encephalopathy has been classically described in retired boxers but can be seen in other athletes who participate in contact sports  This occurs several years or decades after recovery from an acute or post-concussive trauma  Early symptoms of cognitive impairment, later parkinsonism, speech and ocular abnormalities are usually seen in the context of cognitive impairment
Toxins: MPTP, carbon monoxide (CO), manganese, cyanide	Causal relationship to toxin exposure should be sought <i>e.g.</i> miners, drug addicts

Often indistinguishable from classic PD except for its acute onset  
Classically symmetric onset of gait, tremor and associated dystonia has been described in cases of manganese exposure  
History of CO exposure is demonstrated on MRI by the presence of confluent symmetric white matter abnormalities involving the semiovale and corpus callosum and low intensity lesions in the pallidum

Action	Enhanced physiologic tremor	Stress induced: emotion, exercise, fatigue, anxiety, etc.	Tremors are usually intermittent and exacerbated by these stressful situations
		Endocrine:	Other systemic symptoms should be checked The most common signs and symptoms are described below

Hypo-and hyperglycemia	Acute onset usually in the context of hypoglycemia or hyperglycemia particularly the non-ketotic hyperglycemia states. Tremor should resolve with correction of the glucose levels
Thyrotoxicosis	Proptosis, excessive sweating, hyperreflexia, weight loss
Pheochromocytoma	Signs and symptoms are predominantly caused by catecholamine excess, which includes palpitations, excessive sweating, pallor or flushing, headache, dizziness, anxiety, and weight change
Hypercortisolemia Iatrogenic use such as in chronic steroid use or due to a pituitary adenoma	Classic findings of Cushing's syndrome, diabetes, additionally hirsutism and menstrual changes are seen in women
Drugs: <u>Sympathomimetics:</u>	Drug-related tremors are usually

	<p><b>Sympathomimetics.</b>  beta agonists:  bronchodilators,  theophylline;  methylxanthines:  coffee, alcohol,  adrenaline  <b>Central-acting substances:</b>  antidepressants,  lithium,  amphetamines  <b>Antiarrhythmics:</b>  amiodarone  <b>Hormones:</b> thyroid hormone, steroids  <b>Toxins:</b> mercury, silver, arsenic, bismuth  <b>Miscellaneous:</b>  valproate, cyclosporine, interferon</p>	<p>tremors are usually postural, and can be reflective of an exaggeration of an underlying tremor tendency</p> <p>Risk factors include older age and polypharmacy</p> <p>It is particularly important to ask for a detailed drug history, any recent dose increases and consider other factors that could increase plasma drug levels such as renal or liver impairment, or co-prescription of enzyme-inhibiting drugs</p>
Idiopathic, hereditary and degenerative diseases	Essential tremor	<p>Predominantly symmetric bilateral postural and kinetic tremor</p> <p>± Family history</p> <p>± Alcohol sensitivity</p>
Motor neuron disease: Kennedy syndrome		<p>X-linked disorder</p> <p>Also known as bulbo-spinal muscular atrophy characterized by the presence of bulbar weakness, results in tongue weakness</p>

and atrophy,  
proximal and  
symmetric weakness  
of arms, legs, facial  
diplegia (involves  
both upper and  
lower face)

Peripheral neuropathies	Hereditary peripheral neuropathies: Charcot–Marie–Tooth, Roussy–Levy syndromes Demyelinating neuropathies, peripheral nerve injury	Muscle weakness, absent reflexes, and glove and stocking sensory deficits, sensory ataxia are clues that should be sought in neuropathic tremors
Cerebellar disorders of various etiologies		Usually, it is associated with other cerebellar signs such as nystagmus, dysarthria, and gait ataxia
Structural lesions (traumatic, vascular, neoplastic)		Structural lesions can be easily excluded by MRI findings
Demyelinating (multiple sclerosis), infectious		Classical multiple sclerosis is characterized by focal neurologic symptoms disseminated in time and space

In addition to clinical attacks, MRI, CSF, and visual evoked potentials are diagnostic

---

CSF, cerebrospinal fluid; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; MRI, magnetic resonance imaging.

## Parkinsonian tremor syndromes

Parkinsonism is a clinical syndrome characterized by bradykinesia, rigidity, and tremor. Classic parkinsonian tremor occurs in a resting limb with a low frequency, 4–6 Hz, frequently described as *pill rolling*. Characteristically, it diminishes with activity of the affected limb, but is exacerbated by stress, mental activity, or during coactivation of another body part. Parkinsonian tremor is not pathognomonic of Parkinson's disease (PD) and can be seen in other parkinsonian syndromes including drug-induced parkinsonism. Parkinson's disease tremor is frequently asymmetric, at least initially, which is a helpful hint to differentiate from symptomatic causes of parkinsonian tremor which are by far symmetric. Tremor is present in 75% but not all patients with PD.

Postural and action tremor can also be seen within the spectrum of PD. These tremor components can be within the same frequency as the resting tremor and often referred to as re-emergence tremor or can be non-harmonically related to the resting tremor .

## Cerebellar tremor

Cerebellar tremor signifies involvement of the cerebellum or cerebellar pathways. It is characterized by purely or predominantly intentional pattern, meaning that tremor amplitude increases with the limb approaching the target. Tremor can be either uni- or bilateral in presentation, with a frequency of 5 Hz, irregular in pattern. A postural tremor may be present but there should be no rest component. Another pattern of tremor seen with cerebellar pathology is titubation which is a slow-frequency oscillation of body trunk or head, amplitude of which increases with movement.

## **Holmes' tremor**

Holmes' tremor is a symptomatic tremor associated with a lesion within the central nervous system. Classically lesions are within the midbrain, cerebellum, or thalamus. It is characterized by a combination of a rest and intention tremor with an irregular pattern, slow frequency of less than 4.5 Hz. The most common etiology is vascular (e.g. cerebrovascular accident) with tremor emerging with a variable delay after the event (from 2 weeks to 2 years). It is frequently referred to as rubral tremor.

## **Palatal tremor syndrome**

Palatal tremor is characterized by rhythmic movements of the soft palate (levator veli palatini) but other brainstem-innervated or extremity muscles can be involved as well. It can either be symptomatic or essential. Symptomatic causes of tremor include preceding brainstem or cerebellum lesion, with presence of inferior olivary hypertrophy frequently demonstrated on magnetic resonance imaging (MRI).

Essential palatal tremor is seen in the absence of preceding lesions or olivary pseudohypertrophy. It is frequently accompanied by the presence of an ear click with rhythmic movements of soft palate mainly involving the tensor veli palatini.

## **Drug-induced and toxic tremor syndromes**

Clinically these tremors can present with a variable pattern. The most common pattern is EPT. The most common precipitating agents are listed in [Table 75.2](#).

These tremors will characteristically resolve with the withdrawal of the offending agent or correction of the metabolic abnormality. An exception is tardive tremor which is associated with prolonged exposure to neuroleptic agents.

## **Tremor syndromes associated with neuropathies**

Demyelinating neuropathies are the most common forms of peripheral neuropathy associated with tremor. The pattern can be postural or kinetic. See [Table 75.2](#).

## Psychogenic tremors

The diagnosis of a psychogenic movement disorder is always challenging even for the most experienced movement disorders neurologists. Clues to diagnosis include acute onset of symptoms, spontaneous remissions, inconsistent pattern of tremor, distractibility, suggestibility, history of somatization, and presence of other non-physiologic findings on neurologic exam.

Careful examination allows for a correct diagnosis as these cases are challenging ([Table 75.3](#)).

**Table 75.3 Stepwise approach to the diagnosis of tremor.**

---

1. Medical history review:
  - a. Mode of onset (acute or insidious)
  - b. Family history of tremor
  - c. Alcohol sensitivity
  - d. History of toxin or medication exposure
2. Pertinent findings on examination:
  - a. Does the patient have tremor?
  - b. Pattern of tremor (resting, postural, kinetic, goal directed)
  - c. Distribution of tremor (head, chin, voice, upper or lower limbs)
  - d. Frequency of tremors (fast > 7 Hz, medium 4–7 Hz, low, 4 Hz)
  - e. Impact on function, best assessed in the office by samples of handwriting, spiral drawing, cup drinking tasks
  - f. Additional neurologic manifestations (bradykinesia, rigidity, gait abnormality, pyramidal findings, cerebellar findings, dystonia, neuropathic signs)
  - g. Quantitative assessments of tremor including the use of electromyography (EMG), accelerometric (mostly used in research settings)
3. Define tremor syndrome (physiologic, parkinsonian, essential or other)
4. Review concomitant medications

5. Determine need for symptomatic work-up if clinically indicated:  
Imaging  
Thyroid testing, comprehensive chemistry panel, liver function tests  
24-hour copper excretion, ceruloplasmin, toxicologic tests
  6. Correct reversible cause if identified (metabolic, drugs, etc.)
  7. Determine need for treatment based on tremor syndrome, functional compromise
  8. Re-evaluate diagnosis based on treatment response and if appearance of new neurologic findings
- 

## **Case vignette**

A 70-year-old female presents with tremors, with onset in her late 20s. She experienced fine tremors on arm extension. Symptoms were not functionally interfering with daily activities and she was able to become an accomplished seamstress. With age tremors progressively worsened, and over the last 10 years, she has noted significant difficulty with tremor interfering with most activities including pouring from a cup, or eating soup with a spoon. Her handwriting has become illegible and she describes difficulty writing checks. There is no voice or head tremor. She reports significant functional impairment from her symptoms and is no longer able to accomplish her job as a seamstress. She no longer goes to restaurants and refuses invitations to visit with friends due to the social embarrassment.

Her family history is significant for a similar tremor in her father, brother, and sister. She has two children, one of whom has had tremors since age 19. She also reports a mild but symptomatic response of tremors to alcohol which she drinks socially. She presents to the office for symptomatic management.

## **Discussion**

Etiology: Benign familial essential tremor.

Diagnosis is based on the long duration of tremor, pattern of tremor, familial

history, and supporting evidence of alcohol sensitivity.

Diagnostic work-up is not warranted if there is an otherwise non-focal neurologic exam or there is classic history consistent with this tremor type. Thyroid testing and comprehensive chemistry panel should be considered.

Rationale regarding choice of treatment depends on the presence of functional compromise, other comorbid diseases (specifically hypertension or hypotension, diabetes), the patient's age, and risk of treatment side effects. Given these considerations propranolol would be a reasonable choice for treatment .

## **Further reading list**

Bain P, Brin M, Deuschl G *et al.* Criteria for the diagnosis of essential tremor. *Neurology* 2000; 54 (11 Suppl 4):S7.

Deuschl G, Bain P, Brin M. Consensus statement of the Movement Disorder Society on Tremor. Ad Hoc Scientific Committee. *Mov Disord* 1998; 13 (Suppl 3):2–23.

Deuschl G, Raethjen J, Lindemann M, Krack P. The pathophysiology of tremor. *Muscle Nerve* 2001; 24:716–35.

Fahn S. Classification of movement disorders. *Mov Disord* 2011; 26:947–57.

Zesiewicz TA, Elble R, Louis ED *et al.* Practice parameter: therapies for essential tremor: report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2005; 64:2008–20.

Zesiewicz TA, Elble RJ, Louis ED *et al.* Evidence-based guideline update: treatment of essential tremor: Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology* 2011; 77:1752–5.

## 76 Vertigo

---

Maroun T. Semaan *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Vertigo is an illusion of motion of self or surroundings that can be linear or rotatory.

The perception of balance requires the central integration of visual, proprioceptive, and vestibular inputs. Although present in visual and proprioceptive disorders, vertigo is often the result of a perturbation in the vestibular inputs.

An injury to the vestibular system causes an asymmetry in the baseline input from the vestibular centers and results in vertigo, nystagmus, nausea, and a sensation of falling towards the side of injury in destructive lesions or towards the contralateral side in irritative lesions.

The end organs of the vestibular system consist of the three semicircular canals and the otolithic organs (utricle and saccule) on each side. Each of the three semicircular canals transduces angular acceleration when the head is rotated in the plane of the corresponding canal. The utricle transduces lateral head tilt and translation whereas the saccule transduces front-to-back tilt and translation.

The peripheral vestibular system comprises the semicircular canals, the otolithic organs and the vestibular nerves. The neural output from the peripheral vestibular system is conveyed to the vestibular nuclei in the brainstem via the superior and inferior vestibular nerves. The central vestibular system integrates neural inputs from the vestibular nuclei. Principal afferent projections are transmitted to the oculomotor nuclei (CN III, IV and VI), the cerebellum, the interstitial nucleus of Cajal, the nucleus prepositus hypoglossi, the cerebral cortex, the thalamus, and the reticular nuclei [1–3].

The vestibulo-ocular reflex (VOR) maintains images on the fovea during high-velocity eye movements. Smooth pursuit and optokinetic eye movements function best with low-velocity head movements. The VOR depends on the direct projections from the vestibular nuclei in the brainstem to the abducens nucleus in the pons, and the indirect projections via the medial longitudinal fasciculus (MLF) to the third (oculomotor) and the fourth (trochlear) nerve nuclei in the midbrain [4,5].

An injury to the vestibular system creates an imbalance in the neural input originating from the injured organ. The brainstem interprets this asymmetry as a rotation or tilt of the head to one side (although the head is not moving). This results in a compensatory reflexive eye movement (slow phase of the nystagmus) and postural changes that are often present in an acute vestibular injury.

The evaluation of a patient with vertigo relies on obtaining a comprehensive medical history and performing appropriate physical examination.

## Medical history

A systematic approach to the evaluation of a patient presenting with vertigo narrows the list of differential diagnoses. A thorough medical history is essential in establishing the diagnosis. It is critical that the patient is asked to describe his chief complaint to differentiate “vertiginous dizziness” from “non-vertiginous dizziness” ([Table 76.1](#)). (The reader may also want to refer to [Chapter 19](#) on dizziness.) Further characterization of vertigo, focusing on the onset, periodicity, duration ([Table 76.2](#)), triggering factors ([Table 76.3](#)), and associated symptoms ([Table 76.4](#)), refines the differential diagnosis. The presence of auditory symptoms such as hearing loss, tinnitus, aural pressure, or hyperacusis suggests a peripheral vestibulopathy. The presence of ataxia, dysphonia, dysphagia, hemianesthesia to pain and temperature, and hemiparesis suggests a central lesion. Pressure and sound-induced vertigo are seen in conditions resulting in a “third window” such as superior semicircular canal dehiscence. The occurrence of vertigo in the presence of migraines, headaches with or without aura, phonophobia or photophobia, and a history of motion intolerance suggests migraine-associated vertigo. Inquiring about current and past medical conditions and the medications list is equally important. The chronic use of anti-vertiginous drugs or central suppressants delays central compensatory mechanisms and results in incomplete compensation. Determining the degree of disability and the limitations incurred

by the frequency and severity of the vertiginous spell provides a baseline assessment that allows the clinician to determine the efficacy of a therapeutic intervention in conditions with recurrent symptoms.

**Table 76.1 Suggested differential diagnosis based on the presenting symptom.**

Symptom	Possible etiology
Vertigo	Peripheral, central vestibular Cervical
Dysequilibrium	Peripheral, central vestibular Cervical Spinal
Rocking or swaying	Mal de débarquement
Motion sickness	Migraine-related vestibulopathy Vascular compression syndrome Peripheral vestibular
Swimming or floating	Psychogenic Vascular compression syndrome Bilateral vestibular hypofunction
Oscillopsia (Dandy's syndrome)	Bilateral vestibular hypofunction

**Table 76.2 Suggested differential diagnosis based on the duration of the episode.**

Time	No associated hearing loss	Hearing loss present
Seconds	BPPV	Perilymphatic fistula
Minutes	Vertebral basilar insufficiency	Cholesteatoma

Hours	Migraine vestibulopathy	Ménière's disease
Days	Vestibular neuronitis CVA	Labyrinthitis CVA
Weeks	CNS disease Lyme disease Multiple sclerosis	Acoustic neuroma Autoimmune Psychogenic

BPPV, benign paroxysmal positional vertigo; CNS, cerebrospinal fluid; CVA, cerebrovascular accident.

**Table 76.3 Suggested differential diagnosis based on the triggering or aggravating factors.**

Triggering or aggravating factors	Possible etiology
Head motion (all directions)	Central or peripheral vestibulopathy
Head motion (one particular position)	BPPV
Pressure (Hennebert's sign)	PLF SCC dehiscence LSCC fistula
Sound (Tullio phenomenon)	SCC dehiscence Otosyphillis
Valsalva maneuver	SCC dehiscence Chiari malformation

BPPV, benign paroxysmal positional vertigo; PLF, posterior longitudinal fasciculus; SCC,

semicircular canal.

**Table 76.4 Suggested differential diagnosis based on associated symptoms and signs.**

Associated signs and symptoms	Possible etiology
Hearing loss, tinnitus, aural pressure	Ménière's disease Acoustic neuroma Autoimmune diseases Labyrinthitis Perilymphatic fistula
Aural pressure, autophony, Tullio phenomenon, Hennebert's sign, hearing loss	Superior SCC dehiscence syndrome Otosyphilis
Photophobia, phonophobia, headache, motion intolerance, fatigue, depression	Migraine vestibulopathy
Aural drainage, hearing loss	Cholesteatoma
Ataxia, slurred speech, facial hemianesthesia, hemiparesis	TIA or VBI Demyelinating diseases
Auditory hallucinations, visual hallucinations, transient hemiparesthesia	Partial or complex seizures (mesio-temporal sclerosis)

SCC, semicircular canal; TIA, transient ischemic attack; VBI, vertebrobasilar insufficiency.

## **Physical examination**

A detailed physical examination should include a focused head and neck examination, a neurologic assessment of the cranial nerves and cerebellar function, and a bedside vestibular examination. The bedside vestibular examination assesses oculomotor function, positional and postural control testing.

In the head and neck examination, otoscopy identifies otologic disorders responsible for vertigo. A primary acquired cholesteatoma eroding through the lateral semicircular canal elicits short-lasting subjective vertigo when positive pressure is applied to the ear canal with manual tragal pressure or using a pneumatic otoscope (Hennebert's sign or fistula test). In the absence of visual fixation (patient wearing Frenzel's glasses or video goggles), a horizontal nystagmus is usually seen. A positive fistula test can also be seen in conditions resulting in a "third window" such as semicircular canal dehiscence or in perilymphatic fistulae.

## **Bedside vestibular testing**

Oculomotor function testing identifies the presence of nystagmus, the cardinal sign of acute vestibular dysfunction indicating a static imbalance in the resting outputs of the two peripheral vestibular systems. This asymmetrical response results in a compensatory VOR (slow phase) and a burst response bringing the eyes back into the center (fast phase – which defines its direction). Spontaneous nystagmus, seen in the acute phase, disappears after few days. Peripheral nystagmus is described as direction fixed, jerk-type, horizonto-rotatory eye movements that is decreased with visual fixation and increased by gazing away from the hypofunctional side – or gazing in the direction of the fast phase (Alexander's law). A peripheral nystagmus also increases post headshaking, a clinical finding that is reflective of the concept of velocity storage. In velocity storage, the cumulative excitatory effect of the non-injured vestibular system exceeds the cumulative inhibitory effect of that same system (Ewald's second law) resulting in an apparent stimulation of the non-injured side, which in normal conditions would be annulled by an intact contralateral vestibular system. Shaking the head at 10 degrees, 2 cycles per second for 20 seconds elicits a horizontal post-headshake nystagmus in peripheral vestibular disorders and occasionally a vertical nystagmus in central vestibular disorders. A head thrust, also known as head impulse test (HIT) or Halmagyi test, unmasks a compensated vestibular weakness. Relying on the "doll's eyes" reflex, the HIT is

performed by gently grasping the patient's head and guiding it through a quick abrupt turn to both sides. A refixation saccade when turning the head in the direction of the injured labyrinth denotes a positive test. Repositioning the head so that the plane of head movement is coplanar to the tested semicircular canal can test each individual canal. A central nystagmus changes with direction of gaze and is not abolished by visual fixation. It may be purely torsional (brainstem lesions), downbeating (cerebellar lesions or lesions of the craniocervical junction), upbeat (pontomedullary or pontomesencephalic lesions), pendular (cerebellar lesions), seasaw (midbrain lesions) or dissociated (in lesions causing internuclear ophthalmoplegia such as multiple sclerosis). Saccade eye movements bring an image onto the fovea and are tested by asking the patient to look to the right or left finger when asked. Dysmetric saccades suggest cerebellar disorders whereas slow saccade may be indicative of brainstem pathology. A disconjugate saccade is seen in demyelinating disorders such as multiple sclerosis. Smooth pursuit eye movements, tested by asking the patient to follow the examiner's fingers, allow the eyes to track an object moving across the field of view. Anything other than a smooth horizontal pursuit is indicative of central pathology. The Dix–Hallpike maneuver is a positional testing that is diagnostic of posterior canal benign paroxysmal positional vertigo (BPPV). The patient's head is rotated 45 degrees from the sagittal body plane and brought back quickly. The characteristic nystagmus of BPPV is downbeating, geotropic (beating towards the center of gravity), horizonto-rotatory, delayed in onset 2–3 seconds, and fatigable with repeated applications. Postural control assessment includes Romberg, tandem gait, past-pointing, and Fukuda tests.

Although diagnosing a patient with vertigo greatly relies on the medical history and the physical examination, certain adjunctive tests assist the clinician in confirming or supporting the diagnosis.

## Audiometric evaluation

A comprehensive audiogram is crucial in the evaluation of a patient with a history or physical examination suggesting a peripheral etiology of vertigo. Chronic otitis media with or without cholesteatoma often results in conductive, or mixed, hearing loss. A low-frequency sensorineural hearing loss is usually seen in Ménière's disease. A unilateral or asymmetrical sensorineural hearing loss can be indicative of retrocochlear pathology such as vestibular schwannomas or other tumors of the cerebellopontine angle.

## Vestibular function tests

Clinically relevant vestibular function tests are: videonystagmography (VNG), rotary chair, cervical vestibular evoked myogenic potentials (cVEMP), and computerized dynamic posturography (CDP).

The videonystagmogram includes testing of the oculomotor function, routine and custom (Dix–Hallpike) positional tests, and vestibular response to caloric stimulation. The visual response is typically recorded using a video eye-movement recording system. A detailed description of the available recording techniques and their limitations is beyond the scope of this chapter [6]. Oculomotor function testing includes the evaluation for the presence of spontaneous or gaze-evoked nystagmus, saccade and smooth pursuit eye movements, optokinetic nystagmus (OKN), and optokinetic after nystagmus (OKAN). Saccadic eye movements are assessed for latency, peak velocity, and accuracy (hypermetric or hypometric). Smooth pursuit eye movements are evaluated for gain (ratio of peak eye to target velocity), phase (difference in time between eye and target), asymmetry, and saccadic intrusions. The gain and phase of the OKN are assessed, whereas the initial velocity, time constant, and slow cumulative eye position are evaluated for the OKAN. These parameters are analyzed all together and interpreted to suggest a peripheral or central vestibular disturbance. The positional part determines the effects of different stationary head positions on eye movements. Although it does not have a localizing value, nystagmus that is direction fixed and suppressed by visual fixation is usually peripheral in origin. If BPPV is suspected, customization of the positional testing (i.e. performing a Dix–Hallpike maneuver) confirms the characteristic nystagmus. Caloric testing yields an aphysiologic stimulation of the lateral semicircular canal (SCC). The patient's head is tilted 30 degrees upward and bithermal caloric stimulation is conducted using water irrigation or air insufflation.

The reduced vestibular response (RVR) is measured by calculating the ratio of the difference in the peak slow-phase velocity of the “injured side” and the “non-injured side” to the sum of the peak slow phase velocity of both sides. Although it only evaluates the lateral SCC, its ability to localize the injury site makes it highly valuable in the evaluation of various pathologic peripheral vestibular conditions.

The rotary chair tests the angular VOR at different head accelerations. Head rotation is the physiologic stimulus of the SCC. Clinically available rotary chairs

test angular VOR generated by stimulation of both lateral SCC. Stimulus types can be sinusoidal harmonic acceleration or velocity step test. Tested parameters include phase (angle, lead, and lag), gain, symmetry, and time constant. Analysis of these parameters confirms bilateral vestibular impairment, provides evidence supporting central vestibular impairment, and quantifies progress of known vestibulopathy.

Computerized dynamic posturography (CDP) tests postural stability and measures postural sway by manipulating somatosensory (sway-preferred or fixed support conditions) and visual feedback (eyes fixed, eyes closed, and sway-referenced visual conditions). Three main protocols are used: sensory organization test (SOT), posture-evoked response, and motor control tests. The equilibrium score provided for each of the six sensory conditions and the sensory analysis suggest a particular pattern of dysfunction (vestibular, proprioceptive, or visual). Computerized dynamic posturography may be helpful in the evaluation of patients with persistent dizziness or vertigo despite treatment, in measuring baseline postural control prior to treatment, in selecting the most appropriate rehabilitation strategy, and in identification of malingering individuals.

Cervical vestibular evoked myogenic potentials (cVEMP) are short latency inhibitory potentials of the ipsilateral sternocleidomastoid muscle evoked by a brief and loud (>85 decibel [dB]) monaural click or tone burst stimuli. It is a recording of the vestibulo-colic reflex, which is generated in the saccule, and carried by the inferior vestibular nerve. The VEMP response is usually absent in patients with significant conductive hearing loss. In patients with superior SCC dehiscence syndrome, the cVEMP threshold is decreased and the amplitude is increased. The recording of a cVEMP in the presence of a significant conductive hearing loss suggests a “third window” [7]. In patients with Ménière's disease, the cVEMP threshold is increased and the amplitude is reduced. In advanced cases of Ménière's disease, the cVEMP response is absent. Abnormal cVEMP responses were noted in 27% of the contralateral asymptomatic ears of affected individuals with Ménière's disease [8].

Although not a vestibular test, electrocochleography (ECoG) is an evoked auditory response to condensation and rarefaction click or tone burst stimuli. Using a recording intratympanic or extratympanic electrode, the summating (SP) and the action potentials (AP) of the auditory nerve are recorded. An increased SP/AP ratio (greater than 0.4) suggests endolymphatic hydrops (ELH). An abnormal ECoG is found in approximately 71.6% of patients with Ménière's

disease [9].

## Radiographic evaluation

By providing excellent imaging detail of the bony anatomy and bone–soft tissue interface, high resolution computerized tomography (HRCT) of the temporal bone is helpful in the diagnosis of several otologic conditions. Current acquisition protocols allowing thin sections provide coronal reconstruction of high spatial resolution. The osteolytic effects of chronic otitis media with or without cholesteatoma are well demonstrated on HRCT. A soft tissue density filling the middle ear cleft and extending into the mastoid air cells with expansion and destruction of the bony septae is highly suggestive of cholesteatoma. Erosion of the lateral SCC is well apparent.

Pöschl (parallel to the superior SCC) and Stenver's (perpendicular to the superior SCC) views demonstrate dehiscence of the superior SCC.

Magnetic resonance imaging (MRI) of the brain and internal auditory canals (IAC) provide superb visualization of soft tissue details, greatly assisting the clinician in the diagnosis of various inflammatory, neoplastic, vascular, and degenerative conditions of the brain and cranial nerves. Gadolinium-enhanced MRI of the IAC is helpful in the evaluation of retrocochlear pathology. The differential diagnosis of lesions involving the cerebellopontine angle (CPA) is guided by their radiographic characteristics ([Table 76.5](#)). Cerebrovascular diseases and neuro-inflammatory conditions are readily diagnosed using various imaging sequences (T2 weighted MRI, fluid attenuated inversion recovery [FLAIR], diffusion weighted imaging [DWI]).

**Table 76.5 Radiographic characteristics of common lesions of the cerebellopontine angle.**

Characteristic	Vestibular schwannoma	Meningioma	Epidermoid
Shape	Globular	Sessile	Dumbbell
Internal auditory canal	Centered, penetrating	Eccentric, extrinsic	AL or PL to brainstem

Calcification	Absent	Present (25%)	Absent
Hyperostosis	Absent	Present	Absent
Tumor–bone angle	Acute	Obtuse (70%)	Variable
Meningeal tail	Absent	Present (70%)	Absent
T1	Iso/Hypointense	Iso/Hypointense	Hypointense
T1 + Gad	Enhance +++	Enhance +	No enhancement
T2	Iso/Hypointense	Iso/Hypointense	Hyperintense

---

## Etiologies

### Peripheral vestibular causes of vertigo

#### *Ménière's disease*

A 46-year-old female presents to urgent care with acute dizziness. She described a sensation of aural fullness developing in the left ear earlier in the morning followed by a roaring tinnitus and sudden onset rotatory vertigo that lasted 2 hours. She had two episodes of vomiting and felt nauseous. Although the spell has subsided, she admits feeling somewhat off balance and admits that her left ear feels muffled. The otolaryngologic examination is normal. The Weber test lateralized to the right ear and the Rinne was positive. Her neurologic examination was normal with the exception of a left beating horizonto-rotatory nystagmus. Her history is pertinent for a similar but much milder episode 4 months earlier.

Ménière's disease is characterized by episodic vertigo, fluctuating hearing loss, aural pressure, and tinnitus. The incidence varies between 4.3 and 15.3 per 100,000 with a slight female predominance (female/male ratio 1.3 : 1) [10]. The diagnostic guidelines published by the Committee on Hearing and Equilibrium of the American Academy of Otolaryngology – Head and Neck Surgery are

shown in Table 76.6 [11].

**Table 76.6 Guidelines for the diagnosis of Ménière's disease as proposed by the Committee on Hearing and Equilibrium from the American Academy of Otolaryngology – Head and Neck Surgery.**

Definition	Symptoms
Certain Ménière's disease	Definite Ménière's disease + histopathologic confirmation
Definite Ménière's disease	$\geq 2$ definitive spontaneous episodes of vertigo 20 min or longer Audiometrically documented hearing loss on at least one occasion Tinnitus or aural fullness in the treated ear Other causes excluded
Probable Ménière's disease	One definitive episode of vertigo Audiometrically documented hearing loss on at least one occasion Tinnitus or aural fullness in the treated ear Other causes excluded
Possible Ménière's disease	Episodic vertigo without documented hearing loss, or SNHL fluctuating or fixed, with dysequilibrium but non-episodic Other causes excluded

Ménière's disease remains a diagnosis of exclusion as several pathologic conditions may mimic Ménière's disease, causing Ménière's syndrome (i.e. otosyphilis, Cogan's syndrome, autoimmune inner ear diseases, vestibular schwannoma, intralabyrinthine schwannomas, endolymphatic sac tumors) [12].

Endolymphatic hydrops (ELH) is considered the pathologic substratum to Ménière's disease. Although the pathophysiology of ELH remains unknown,

several intrinsic (genetic, anatomic, autoimmune, or vascular) and extrinsic (trauma, viral, or allergic) factors have been implicated in the disturbance of the homeostasis of the endolymphatic fluid.

Episodic vertigo associated with nausea or vomiting is frequently present. The duration of the episode varies from 20 minutes to 4 hours. In milder forms or cases of longstanding disease, disequilibrium and imbalance may be present. Unlike in other peripheral causes of peripheral vertigo, fluctuating sensorineural hearing loss, roaring tinnitus, and aural fullness are often present. The hearing loss initially affects the lower frequencies. However, in advanced disease a flat hearing loss with poor word recognition score (WRS) is often seen. The severity of the attacks and the resultant disability vary greatly. In some patients, the attacks are mild and occur infrequently whereas in others the disease may relentlessly progress and cause substantial disability from the resultant recurrent and chronic vestibulopathy.

A spontaneous peripheral nystagmus can be seen in the acute phase of the disease. However, when examined beyond the acute phase, the physical examination is usually non-revealing. A baseline audiometric evaluation is essential to document hearing fluctuations. Although the diagnosis is based on a characteristic medical history and physical examination, in clinically challenging situations ECoG can be valuable. The value of VNG for the diagnosis of Ménière's disease is limited. Reduced response on caloric testing is seen in 42–73% of patients with Ménière's disease [13]. All patients with Ménière's disease should undergo a gadolinium-enhanced MRI for work-up of retrocochlear pathology.

Sodium restriction, avoidance of caffeinated products and excessive alcoholic consumption, and the regular use of diuretics are the mainstay of the medical management of Ménière's disease. In non-responsive patients, vestibular ablative and non-ablative procedures can be offered as effective means to control vertigo.

## ***Vestibular neuritis***

A 53-year-old male presents to urgent care with acute rotatory vertigo, nausea, and vomiting. The vertigo intensified over the course of the day. He denies any aural fullness or subjective hearing loss. He describes a left-sided tinnitus. He denies any slurred speech, dysphonia, dysphagia, or paresthesias. He admitted having had a cold 2 weeks prior. He appeared anxious during the encounter. He was afebrile and slightly tachycardic. The otolaryngologic and neurologic examinations were normal with the exception of a right-beating horizonto-

rotatory nystagmus and a head thrust test positive to the left. The vertigo spell resolved after 36 hours. Over the next several weeks he had a persistent sensation of disequilibrium that gradually improved with habituation exercises.

Vestibular neuritis is characterized by onset of acute vertigo with associated nausea and vomiting. Vestibular neuritis accounts for 3–10% of patients presenting for evaluation of dizziness with an incidence of 3.5 cases per 100,000 persons per year [14]. The acute phase is characterized by severe vertigo that lasts several hours to few days. The vertigo is associated with a tendency to fall or sway to the affected side, nausea, and vomiting. Typically auditory symptoms are minimal to absent. A residual sensation of imbalance or disequilibrium lasting several weeks often follows the initial vertiginous attacks. Sudden or quick head movements accentuate the acute and chronic imbalance.

Although the etiology remains unclear, most believe that a viral or vascular cause is causative in the majority of cases. Recurrent episodes of vestibular neuritis are rare and may support the pathophysiologic basis of latent viral reactivation (herpes simplex virus) [15]. Anatomical studies have suggested that the superior vestibular nerve is more frequently affected. Benign paroxysmal positional vertigo (BPPV) appears to be more prevalent after an episode of vestibular neuritis. A possible explanation is that the viral-induced degeneration of the utricle results in loosened otoconial debris, and in the presence of a functional inferior vestibular nerve may cause the typical symptoms of posterior canal BPPV [16].

The diagnosis is made through a detailed history and physical examination. In addition to vestibular neuritis, the differential diagnoses of an acute vestibular syndrome include cerebellar or brainstem hemorrhage or ischemia, vertebral artery dissection, first attack of Ménière's disease, or labyrinthitis [17]. Central causes of isolated vertigo are rare. Most central pathologies results in neurologic deficits depending on the neural territory affected. Vertigo is typically associated with ataxia, hemiplegia, facial droop, dysphonia, dysphagia, and/or facial hypoesthesia. Patients with Ménière's disease or labyrinthitis typically present with auditory symptoms.

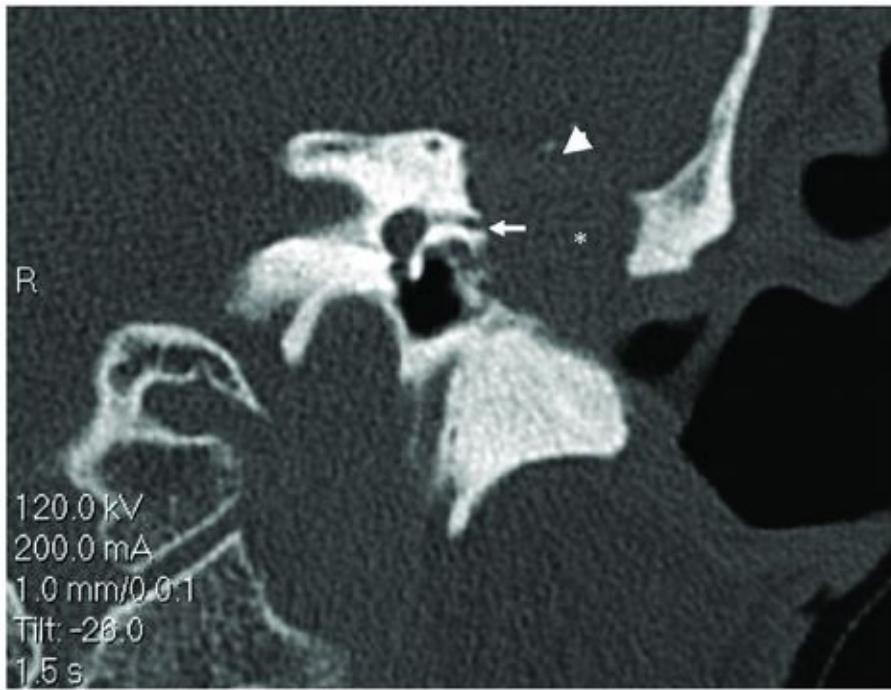
Treatment of vestibular neuritis is supportive. The acute phase is managed with vestibular suppressants, antiemetics, and hydration. Early administration of systemic steroid may improve recovery of vestibular function. The role of antiviral therapy remains controversial. Beyond the acute phase, patients with incompletely compensated vestibulopathy may benefit from formal vestibular rehabilitation.

## **Chronic otitis media**

A 47-year-old male with history of chronic right-sided intermittent otorrhea presented with recurrent episodes of dizziness. Blowing the nose and pushing on the auricle could also trigger the vertigo. He has a history of progressive right-sided hearing loss and occasional tinnitus. Examination showed a primary acquired cholesteatoma arising from an attic retraction, minimal amount of purulent debris, and a rim of granulation tissue posterior to the retraction. The attic was eroded. The malleus was seen but the incus was not well visualized. Fistula test was positive. The Weber lateralized to the right ear and the Rinne was negative in the right ear and positive in the left ear.

Cholesteatomatous and non-cholesteatomatous chronic otitis media can lead to disturbance of the vestibular apparatus and result in vertiginous and non-vertiginous dizziness. A large cholesteatoma may erode into the horizontal SCC. Vertigo may be pressure-induced (Hennebert's sign) or develops in the setting of active otorrhea and suppurative otitis. The history and physical examination often suggests the diagnosis. A history of chronic otorrhea and hearing loss are often present. Otoscopy is diagnostic. A positive fistula (Hennebert's sign) is present in approximately 50% of patients.

Audiometry provides a comprehensive assessment of hearing. Although most have conductive hearing impairment, a mixed hearing loss is often seen. A CT scan of the temporal bone shows an erosive soft tissue density extending into the mastoid with absent coverage of the horizontal SCC ([Figure 76.1](#)). Treatment of chronic otitis media is aimed at eradicating the underlying disease. In some instances, tympano-mastoid surgery is staged due to the relatively high risk of residual or recurrent disease. In intact canal wall mastoid surgery, an attempt is made to remove the cholesteatoma matrix and cover the fistula with a tissue graft. When a canal wall down procedure is being contemplated, the matrix is typically left and the disease is exteriorized.



**Figure 76.1** High resolution computed tomography of a left temporal bone showing a large mastoid cholesteatoma (asterisk) with erosion of the lateral semicircular canal (white arrow) and tegmen (arrowhead).

## ***Superior canal dehiscence syndrome***

A 56-year-old female presents for evaluation of episodic vertigo. While attending the orchestra and during the performance of a crescendo passage, she noticed a short-lasting rotatory vertigo. She also has autophony to her own voice and respirations in the left ear that have been ongoing for nearly 3 months. She denies any subjective hearing loss or tinnitus. The examination showed a vertical and torsional nystagmus with left-sided pneumoscopy. The audiogram showed supranormal hearing thresholds on the left. The cervical VEMP demonstrated decreased threshold and increased amplitude in the left ear.

Described by Minor and colleagues in 1998 [18], the superior canal dehiscence syndrome (SCD) syndrome is characterized by hyperacusis, autophony, and noise and/or pressure-induced vertigo. The dehiscence of the superior canal creates a “third mobile window” in the otic capsule.

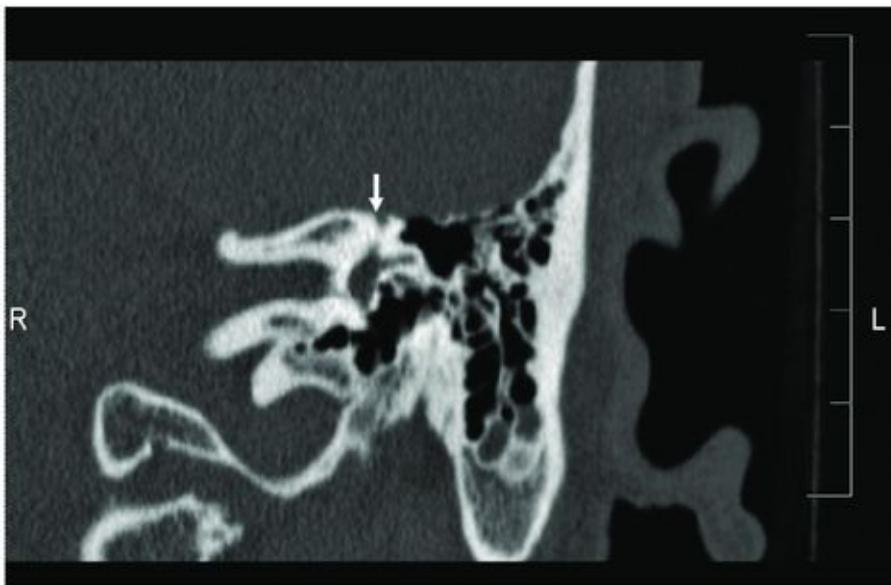
The pathophysiology remains controversial. Although rare in children and adolescents, a developmental or congenital anomaly has been proposed as a predisposing anatomical factor. An incidence of 0.4% was found on temporal bone anatomical studies. An additional 1.5% of temporal bone specimens had a

bone thinner than 0.1 mm. Both anatomical dissections and CT imaging showed a high incidence of thin bone overlying the superior canal contralateral to the dehiscent side [19]. The bone overlying the superior canal becomes progressively thicker during the first year of life. A failure of postnatal development may result in thin bony coverage. Presumably, the thin bony coverage is disrupted by the constant pulsations and pressure of the overlying temporal lobe and cerebrospinal fluid. Conversely, aberrant arachnoid granulations may cause progressive bony erosion and result in superior canal dehiscence.

Clinically, patients typically present with chronic disequilibrium, sound-evoked vertigo, pressure or straining-evoked vertigo, autophony to own voice or respiration, and hearing loss. Physical examination demonstrates the characteristic nystagmus. Maneuvers that cause excitation of the ipsilateral dehiscent canal (sound, nose blowing, or positive pneumoscopy) cause a vertical and torsional nystagmus with intorsion.

The audiogram may show supranormal bone hearing thresholds, a mild or a moderate conductive hearing loss. Unlike otosclerosis, which causes a mild to moderate conductive hearing loss, the stapedial reflexes are usually present in SCD. The cVEMP responses demonstrate decreased thresholds and increased amplitude. The responses are absent in ears with moderate conductive hearing loss. However, the presence of a normal cVEMP in an ear with conductive hearing loss is suggestive of “third window” or SCD [7].

High resolution CT of the temporal bones allows reconstructed images parallel (Pöschl) and perpendicular (Stenver's) to the plane of the superior canal. Absence of bony coverage over two or more cuts is usually suggestive ([Figure 76.2](#)). The diagnosis is not solely based on radiographic imaging as false positives occur due to the fact that current CT resolution does not differentiate bony coverage less than 0.1 mm from actual true dehiscence.



**Figure 76.2** High resolution computed tomography of a left temporal bone showing a dehiscent superior semicircular canal (white arrow).

Treatment is dictated by the severity of the clinical picture. Avoidance of inciting stimuli always should be recommended. Although placement of a tympanostomy tube may provide relief for some patients, a more definitive treatment requires plugging and resurfacing of the dehiscent canal via a subtemporal or transmastoid approach.

### ***Benign paroxysmal positional vertigo***

A 62-year-old male presents for evaluation of episodic vertigo. He stated that for the past 4 weeks he has been experiencing short-lasting vertigo that occurs when he rolls over in bed to the right. This is associated with nausea. He denies any aural fullness, hearing loss, or tinnitus. He mentioned that he had some dental work done the day prior to its onset. Physical examination showed a positive Dix–Hallpike test to the right side. The remainder of the bedside vestibular examination was normal. The audiogram was normal.

Benign paroxysmal positional vertigo (BPPV) is a common vestibular cause of vertigo. The true incidence of BPPV is unknown. Nevertheless, it is estimated that in the USA, 17–42% of all the patients presenting with dizziness per year are diagnosed with BPPV [20]. Although the condition occurs across all ages, affected individuals are typically in their 5th to 7th decade. Patients describe short-lasting vertigo spells that occur with specific head positioning. Typically, rolling over in bed, lying back or arising quickly, looking up, or reclining the

head are common triggering head positions. The vertigo may be associated with nausea and vomiting. Auditory symptoms are absent. Some patients describe a prior history of trauma or vestibular neuritis.

Benign paroxysmal positional vertigo occurs when otoconial debris becomes detached from the utricular macula and enters the posterior semicircular canal (PSC) or lateral semicircular canal (LSC).

Posterior semicircular canal BPPV is the most common variant (85–95%) [21]. The otoconial debris enters the non-ampulated end of the PSC and results in canalolithiasis. By rotating the head in the plane of the affected PSC, the inertia of the canaloliths causes an ampulofugal flow of endolymph, which causes an excitatory utriculofugal deflection of the cupula. With the head rotated down, excitation of the PSC causes a horizontal and torsional nystagmus, downbeating (geotropic), delayed in onset, and fatigable after several applications [22].

The Dix–Hallpike maneuver is diagnostic by demonstrating the characteristic nystagmus. The nystagmus reverses direction when moving from the supine to the upright position.

Lateral semicircular canal BPPV may be responsible for 5–15% of cases of BPPV [23]. Otolithic debris may be attached to the cupula (cupulolithiasis) at the ampulated end of the LSC. Depending on their position and the deflection of the cupula by the cupulolith, LSC-BPPV results in geotropic or apogeotropic nystagmus. The identification of the involved ear is more intricate as both LSC are coplanar and the nystagmus can be equally seen in both lateral supine positions. The Dix–Hallpike maneuver is not sensitive in diagnosing LSC-BPPV. In geotropic LSC-BPPV, the nystagmus is worse with the affected ear down. In apogeotropic LSC-BPPV, the nystagmus is worse with the unaffected ear down.

Specific canalith repositioning maneuvers are effective in the treatment of PSC-BPPV and LSC-BPPV. The Epley maneuver is used to treat PSC-BPPV [22]. The patient begins in the seated position with the head turned 45° towards the examiner. The patient is then placed in the Dix Hallpike position to the affected side and the nystagmus is observed. The patient remains supine and the head is rotated to the opposite ear. The patient then rolls onto the opposite shoulder and directs the head into a nose-down position. After the nystagmus subsides, the patient returns to the original sitting position. Geotropic LSC-BPPV is treated with 360° roll maneuvers towards the unaffected ear at 90°

increments every 30–60 seconds. Anterior semicircular canal BPPV is a controversial entity.

## Central vestibular and non-vestibular causes of vertigo

### ***Migraine-associated vertigo***

A 39-year-old female presents for evaluation of episodic dizziness of 3 months duration. She describes vertiginous dizziness associated with a sensation of feeling on a boat that occurs 5–6 times per month. The episodes last several hours and are frequently preceded by a throbbing headache. The dizziness is associated with phonophobia, photophobia, and nausea. She denies any auditory complaints. Her past medical history is significant for motion sickness and migraine. Physical examination is non-revealing; MRI is negative.

Migraine-associated vertigo (MAV) is defined as vertigo or dizziness caused by migraine. It is estimated that one third of patients with migraine experience dizziness [24]. Women are more commonly affected than men. Although there is no universally accepted definition for MAV, the most accepted criteria are those proposed by Lempert and Neuhauser [25] ([Table 76.7](#)).

**Table 76.7 The diagnostic criteria of migraine-associated vertigo proposed by Lempert and Neuhauser [25].**

---

#### Definite migrainous vertigo

- A.** Episodic vestibular symptoms\* of at least moderate severity **B.** Current or previous history of migraine according to the 2004 criteria of the HIS
- C.** One of the following migrainous symptoms during  $\geq 2$  attacks of vertigo: migrainous headache, photophobia, phonophobia, visual or other auras **D.** Other causes ruled out by appropriate investigations

#### Probable migrainous vertigo

- A.** Episodic vestibular symptoms\* of at least moderate severity **B.** One of the following:
  1. Current or previous history of migraine according to the 2004

criteria of the HIS

2. Migrainous symptoms during vestibular symptoms 3. Migraine precipitants of vertigo in more than 50% of attacks: food triggers, sleep irregularities, hormonal changes 4. Response to migraine medications in more than 50% of attacks

C. Other causes ruled out by appropriate investigations

---

\* Vestibular symptoms are rotational vertigo or another illusory self or object motion. They may be spontaneous or positional. Vestibular symptoms are moderate if they interfere with but do not prohibit daily activities and “severe” if patients cannot continue daily activities.

The pathophysiology of migraine remains poorly understood. It is now believed that migraine aura is caused by a spreading wave of cortical neuronal depression [26]. Current research suggests that the resultant change in blood flow demonstrated in the occipital cortex involves both vascular dysregulation and an abnormal electrical activity. The headache appears to implicate a vasodilator peptide, calcitonin gene-related peptide (CGRP), which is thought to modulate vascular nociception [27]. Migraineurs are more sensitive to unpleasant sensory inputs. Patients with MAV experience more motion sickness symptoms. The same mechanisms described in classic migraine have been proposed for MAV. Dizziness may occur with or without headache.

In patients with MAV [25], the most common vestibular symptom is rotational vertigo (70%), followed by intolerance of head motion (48%) and positional vertigo (42%). Other complaints include intolerance to visual motion, sensation of motion sickness, floating, rocking, or tilting. The duration of the episode varies from minutes to more than 24 hours. Six percent of patients with MAV do not experience migraine headaches. Of those who have migraine headaches, 45% consistently experience headache concomitant to the dizziness. Approximately two thirds of patients describe having photophobia and phonophobia. Migraine aura occurs in one third of patients.

Migraine-associated vertigo is a diagnosis of exclusion. Adjunctive audiometric, electrophysiologic, and radiographic testing helps in refining the differential diagnosis. There is a significant overlap between patients diagnosed with MAV and Ménière's disease. Episodic ataxia (EA) type 2, a dominantly inherited condition, can mimic MAV [28]. The disease manifests in the 2nd decade of life. Patients experience episodes of truncal ataxia, vertigo, nausea,

and vomiting. Half the patients have migraine headaches and family history of similar symptoms is often present.

Benign paroxysmal vertigo of childhood or BPVC (different from BPPV) is a common cause of recurrent vertigo in children [29]. The IHS classifies BPVC as a variant of migraine. The onset is between 2 and 12 years and most manifest the disease by age 6 years. The vertiginous spells last a few minutes and are not related to movement. A history of motion intolerance is common. Although 13% develop classical migraine, 43–68% of affected individuals have a family history of migraine [30]. The examination is normal between episodes. This is a diagnosis of exclusion and radiographic imaging is negative. The usual course is that of spontaneous remission in the teenage years; treatment is supportive and may include antimigraine therapy in severe cases.

Basilar artery migraine is the third most common type of vertigo in adolescents. Patients describe episodic vertigo associated with scotomata, paresthesias, tinnitus, drop attacks, lost of consciousness, and pounding headache.

The treatment of MAV is directed towards avoiding triggers when present and avoidable, and both prophylactic and abortive therapy. Effective prophylactic medications include various antidepressants, anticonvulsants, calcium channel blockers, and beta-blockers.

## ***Other central causes of vertigo***

Various vascular and neoplastic pathologies of the cerebellum and brainstem may present with acute vertigo. Although rarely isolated, associated signs and symptoms usually differentiate vestibulocerebellar and brainstem causes of vertigo from labyrinthine etiologies. A lateral medullary infarct or Wallenberg's syndrome presents with vertigo (medial and inferior vestibular nucleus), limb ataxia with difficulty sitting without support and veering to one side (restiform body and cerebellar peduncles), decreased pain and temperature sensation in the ipsilateral face (trigeminal nucleus and tract), contralateral trunk, and limbs (spinothalamic tract), Horner's syndrome (sympathetic tract), hoarseness, and dysphagia (nucleus ambiguus) [17]. Patients have cardiovascular risk factors and the neurologic symptoms often conceal the vestibular complaints.

Patients with demyelinating disease may develop vertigo. It is estimated that 5% of patients with multiple sclerosis present with vertigo and 50% will have vertigo at some point [31]. An MRI of the brain is diagnostic.

Vertigo may be a symptom of vestibular epilepsy, which is caused by epileptic activity of the temporal lobe [32]. This entity is rare and vertigo is almost always associated with other epileptic manifestations.

## Psychogenic vertigo

Psychogenic vertigo is often seen in patients with panic attacks or agoraphobia (fear of large open spaces or crowds). Patients are confined to their homes and appear incapacitated beyond the severity of their vertigo. Nystagmus is absent during the vertiginous spells unlike what is observed in “organic” vertigo. Psychogenic vertigo may follow an episode of “true” vertigo and the persistent complaints may be the manifestation of a maladaptive psychiatric behavior [33]. Although rarely vertiginous, most cases of chronic subjective dizziness secondary to psychiatric maladaptation are usually non-vertiginous and are manifested by constant imbalance for at least 3 months that is exacerbated in the context of complex visual motion stimuli [34]. Predisposing factors are a neurotic or phobic-anxious temperament or pre-existing anxiety disorder. The diagnosis is made after excluding other causes. The physical examination is typically non-revealing and radiographic imaging is normal.

## Conclusion

Vertigo is an illusion of motion of self or surroundings that can be linear or rotatory. It is indicative of a disturbance in the baseline input from the vestibular centers. The diagnosis relies on a detailed medical history and physical examination and may be assisted by adjunctive electrophysiologic and radiographic testing.

## References

1. Brodal A. Anatomy of the vestibuloreticular connections and possible ‘ascending’ vestibular pathways from the reticular formation. *Prog Brain Res* 1972; 37:553–65.
2. Ito J, Sasa M, Matsuoka I et al. Afferent projection from reticular nuclei, inferior olive and cerebellum to lateral vestibular nucleus of the cat as demonstrated by horseradish peroxidase. *Brain Res* 1982; 231:427–32.
3. McCrea RA, Baker R. Anatomical connections of the nucleus prepositus of

the cat. *J Comp Neurol* 1985; 237:377–407.

4. Gacek RR. Location of brain stem neurons projecting to the oculomotor nucleus in the cat. *Exp Neurol* 1977; 57:725–49.
5. Gacek RR. Afferent and efferent innervation of the labyrinth. *Adv Otorhinolaryngol* 1982; 28:1–13.
6. van der Geest JN, Frens MA. Recording eye movements with video-oculography and scleral search coils: a direct comparison of two methods. *J Neurosci Methods* 2002; 114:185–95.
7. Mikulec AA, McKenna MJ, Ramsey MJ *et al*. Superior semicircular canal dehiscence presenting as conductive hearing loss without vertigo. *Otol Neurotol* 2004; 25:121–9.
8. Lin MY, Timmer FC, Oriel BS *et al*. Vestibular evoked myogenic potentials (VEMP) can detect asymptomatic saccular hydrops. *Laryngoscope* 2006; 116:987–92.
9. Ge X, Shea JJ Jr. Transtympanic electrocochleography: a 10-year experience. *Otol Neurotol* 2002; 23:799–805.
10. Arenberg IK, Balkany TJ, Goldman G *et al*. The incidence and prevalence of Meniere's disease – a statistical analysis of limits. *Otolaryngol Clin North Am* 1980; 13:597–601.
11. Committee on Hearing and Equilibrium guidelines for the diagnosis and evaluation of therapy in Ménière's disease. American Academy of Otolaryngology–Head and Neck Foundation, Inc. *Otolaryngol Head Neck Surg* 1995; 113:181–5.
12. Semaan MT, Megerian CA. Ménière's disease: a challenging and relentless disorder. *Otolaryngol Clin North Am* 2011; 44:383–403, ix.
13. Park HJ, Migliaccio AA, Della Santina CC *et al*. Search-coil head-thrust and caloric tests in Ménière's disease. *Acta Otolaryngol* 2005; 125:852–7.
14. Neuhauser HK. Epidemiology of vertigo. *Curr Opin Neurol* 2007; 20:40–6.
15. Gacek RR, Gacek MR. The three faces of vestibular ganglionitis. *Ann Otol Rhinol Laryngol* 2002; 111:103–14.
16. Schuknecht HF. Positional vertigo: clinical and experimental observations.

*Trans Am Acad Ophthalmol Otolaryngol* 1962; 66:319–32.

17. Hotson JR, Baloh RW. Acute vestibular syndrome. *N Engl J Med* 1998; 339:680–5.
18. Minor LB, Solomon D, Zinreich JS *et al.* Sound-and/or pressure-induced vertigo due to bone dehiscence of the superior semicircular canal. *Arch Otolaryngol Head Neck Surg* 1998; 124:249–58.
19. Carey JP, Minor LB, Nager GT. Dehiscence or thinning of bone overlying the superior semicircular canal in a temporal bone survey. *Arch Otolaryngol Head Neck Surg* 2000; 126:137–47.
20. Hanley K, O'Dowd T, Considine N. A systematic review of vertigo in primary care. *Br J Gen Pract* 2001; 51:666–71.
21. Honrubia V, Baloh RW, Harris MR *et al.* Paroxysmal positional vertigo syndrome. *Am J Otol* 1999; 20:465–70.
22. Parnes LS, Agrawal SK, Atlas J. Diagnosis and management of benign paroxysmal positional vertigo (BPPV). *Can Med Assoc J* 2003; 169:681–93.
23. Cakir BO, Ercan I, Cakir ZA *et al.* What is the true incidence of horizontal semicircular canal benign paroxysmal positional vertigo? *Otolaryngol Head Neck Surg* 2006; 134:451–4.
24. Selby G, Lance JW. Observations on 500 cases of migraine and allied vascular headache. *J Neurol Neurosurg Psychiatry* 1960; 23:23–32.
25. Lempert T, Neuhauser H. Migrainous vertigo. *Neurol Clin* 2005; 23:715–30, vi.
26. Blau JN. Spreading cerebral hypoperfusion during migraine headache. *N Engl J Med* 1995; 332:1516–17; author reply 7–8.
27. Olesen J, Diener HC, Husstedt IW *et al.* Calcitonin gene-related peptide receptor antagonist BIBN 4096 BS for the acute treatment of migraine. *N Engl J Med* 2004; 350:1104–10.
28. Bertholon P, Chabrier S, Riant F *et al.* Episodic ataxia type 2: unusual aspects in clinical and genetic presentation. Special emphasis in childhood. *J Neurol Neurosurg Psychiatry* 2009; 80:1289–92.
29. Batson G. Benign paroxysmal vertigo of childhood: a review of the

literature. *Paediatr Child Health* 2004; 9:31–4.

30. Ralli G, Atturo F, de Filippis C. Idiopathic benign paroxysmal vertigo in children, a migraine precursor. *Int J Pediatr Otorhinolaryngol* 2009; 73(Suppl 1):S16–18.
31. Karatas M. Central vertigo and dizziness: epidemiology, differential diagnosis, and common causes. *Neurologist* 2008; 14:355–64.
32. Gordon AG. Link between vertigo and epilepsy. *Epilepsia* 1999; 40:1168–9.
33. Staab JP. Diagnosis and treatment of psychologic symptoms and psychiatric disorders in patients with dizziness and imbalance. *Otolaryngol Clin North Am* 2000; 33:617–36.
34. Ruckenstein MJ, Staab JP. Chronic subjective dizziness. *Otolaryngol Clin North Am* 2009; 42:71–7, ix.

## 77 Visual field deficits

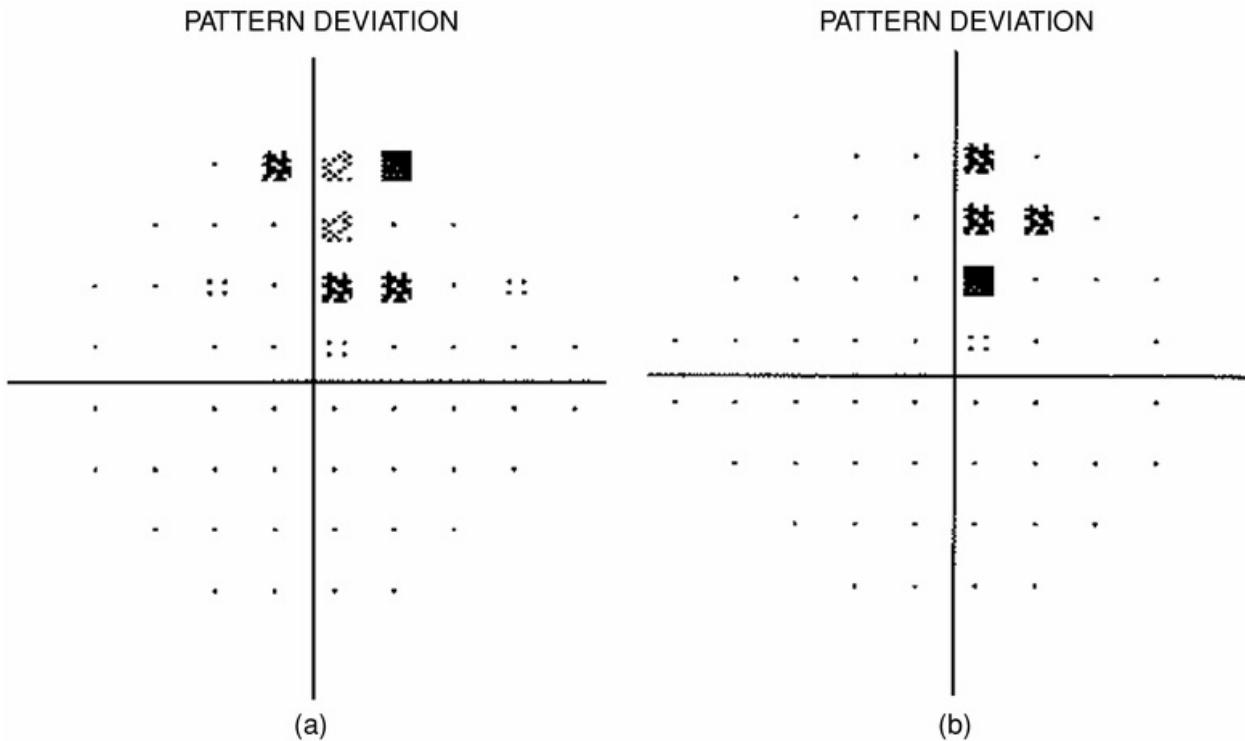
---

Scott Uretsky *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Examination of the visual field (VF) is one of the fundamental assessments of the afferent visual system, which extends from the cell bodies of the retinal ganglion cell, through the lateral geniculate body, to the primary visual (calcarine) cortex. Anatomically this includes the globe, orbit, cavernous sinus, extra-axial CSF spaces, and a significant portion of brain parenchyma (optic radiations and primary visual cortex). Thus VF testing is a cost-effective method in neurologic diagnoses [1]. A number of techniques can be employed for testing a patient's VF status, each with its advantages and disadvantages.

Visual field testing, including standard automated perimetry (SAP), has several important clinical functions [2]. Sensitivity loss detected by SAP in the peripheral VF may be the earliest sign of an abnormality in the afferent visual pathways (Figure 77.1). These defects are typically relative, indicating that an increased stimulus intensity compared with normal is required in that area of the VF to be perceived [3]. There are instances, depending on the extent of disease or the disease process itself, where VF deficits are present and central visual acuity is maintained. Asymptomatic vision loss can be detected by SAP, especially in cases with insidious visual decline. Visual field testing is employed in monitoring the progression of disease and response to treatment (e.g. glaucoma, compressive optic neuropathies). It is used for certain medications such as hydroxychloroquine, in early detection of potential toxic retinal and optic nerve effects [2].



**Figure 77.1** Relative sensitivity loss detected by standard automated perimetry. Central 24–2 visual field (VF) (OD (a), OS (b), pattern deviation) showing a relative right homonymous superior quadrantanopsia in a 64-year-old male presenting with vague visual complaints, diagnosed with left temporal--parietal glioblastoma. Key: OD, right eye; OS, left eye.

The pattern of VF loss and its presence in one or both eyes helps in the anatomic localization of the pathology within the afferent visual pathways: retina → optic nerve → optic chiasm → optic tract → optic radiations → primary visual cortex. The pattern of VF loss, the tempo of symptom onset and progression, and associated features guide the formulation of a differential diagnosis, refining the diagnostic work-up.

## Types of visual field tests

The most commonly used visual field tests in practice are confrontational VF (CVF) and SAP [2]. Confrontational VF testing should be part of *every* exam of the afferent visual system and can be done anywhere. Larger and denser defects, such as homonymous and altitudinal defects, are more easily detected, with a sensitivity up to 70%, in comparison to arcuate defects, typically detected with a sensitivity of 20% [2,3]. In comparison to SAP, confrontational visual field

deficits are highly specific, with a positive predictive value of 96% [2].

With SAP, sensitivities at each locus of the VF can be plotted and compared with age-matched normative data, with statistical analysis. Standardized test procedures are used. This allows detection of relative and absolute VF defects and asymptomatic depression of the VF can be detected. If reasonably reliable, SAP can be used for determination of disease progression and treatment response for optic neuropathies such as glaucoma and compressive optic neuropathies, among others. When employing SAP it is best to follow patients with the same strategy at each visit for the most reliable comparison [2]. Disadvantages include the difficulty some patients have performing automated testing, increased cognitive demands compared with other modalities, as well as learning and fatigue effects.

The Amsler grid, widely available and portable, is useful in detecting VF defects within the central 10° of fixation and metamorphopsia, typical of macular disease. Tangent (Bjerrum) screen and the Goldmann perimeter are kinetic VF testing modalities. These modalities may not be readily available and require a skilled perimetrist. Advantages include the interaction of the perimetrist with the patient, usefulness in patients in whom accurate automated testing cannot be obtained (e.g. patients with cognitive deficits), and ability to detect non-organic VF loss. Suprathreshold static perimetry is available as a screening test and can be obtained faster, but provides less diagnostic data than SAP. It is inferior to SAP in detection of certain types of VF deficits [2].

## How to assess visual fields at the bedside

Visual field testing, with few exceptions, *must* be performed one eye at a time, with the contralateral eye completely occluded. The VF of each eye can be divided into quadrants: superior-temporal, inferior-temporal, superior-nasal, and inferior-nasal. Attention should be paid to unilateral or bilateral involvement, to deficits that respect the horizontal or vertical meridian, and to homonymous deficits. Physiologically the ability to ascertain a static versus a moving target in the VF is different and I recommend at least static CVF. When performing CVF multiple techniques may increase sensitivity [2] and using a red stimulus testing may be the most sensitive CVF technique [3]. Stimuli can be presented simultaneously in two different quadrants to detect a relative difference indicating a subtle defect. Double simultaneous extinction can be tested for a neglect syndrome.

# Use of visual field deficits for localization: interpreting the exam

## Pre-chiasmal afferent visual pathways

The pattern of VF deficit allows localization of the pathology and initial formulation of potential diagnoses. The initial determination is whether one or both eyes are affected. Visual field deficits localized to only one eye indicate a pathologic process involving the ipsilateral retina or optic nerve prior to its connection with the contralateral optic nerve at the optic chiasm. [Table 77.1](#) reviews the differential diagnosis and patterns of defects based on anatomic location.

Generalized depression of the VF seen on SAP in one or both eyes can be of “ophthalmic” origin *i.e.* cataract, corneal disease, or other ocular media opacities ([Figure 77.2](#)). Visual field defects due to retinal disease typically correspond to the location of the pathology. Most defects are central and peripheral constrictions are seen ([Figure 77.3](#)) [2].

**Table 77. 1 Formulating a differential diagnosis in visual field (VF) loss.**

Afferent visual pathway lesion location	Patterns of VF loss	Clinical pearls
Retina	Most commonly central and paracentral scotomas	Amsler grids are helpful in identifying defects and metamorphopsia
Differential diagnosis [7]:	Occasionally nasal steps and wedge defects can be seen [1]	For automated perimetry, testing of the central 10° will better identify and delineate the defect
Central or branch retinal vascular occlusion	Advanced diabetic retinopathy	Retinal defects tend to have steep borders and be less variable than glaucomatous defects [1]
Retinal detachment		
Diabetic and hypertensive retinopathy		
Central serous chorioretinopathy		
Cystoid macular		

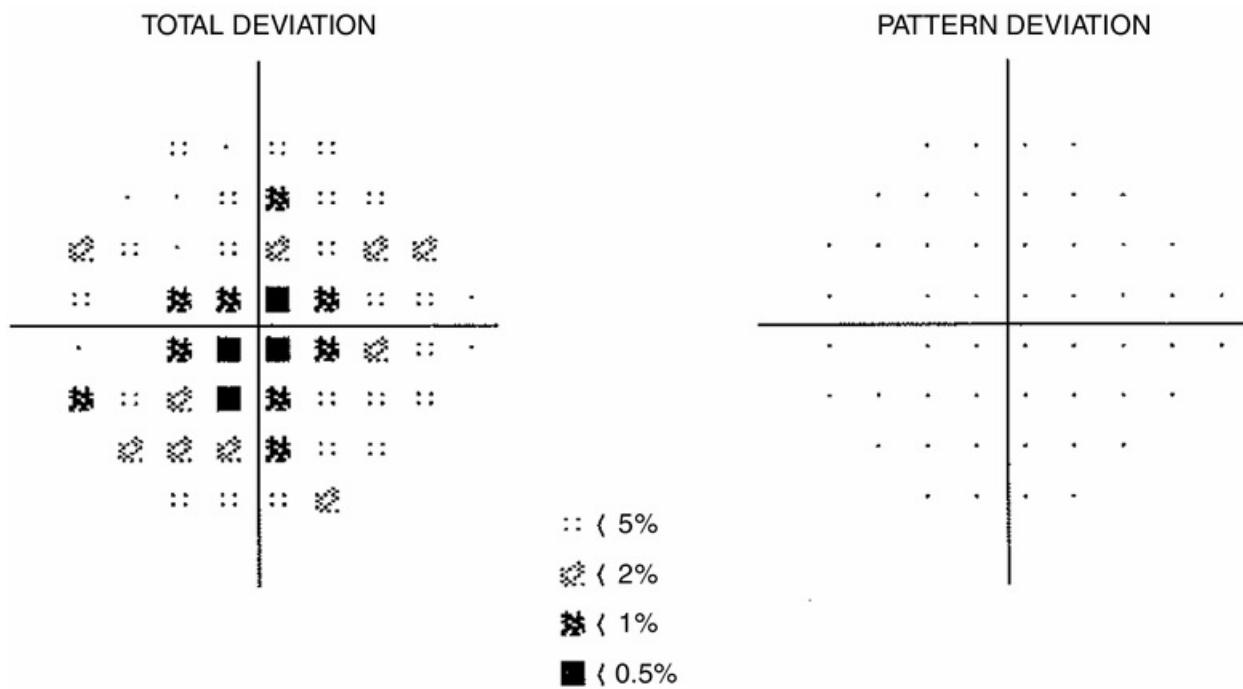
edema	“mottled” pattern	Neuroretinitis presents with vision loss, optic disc swelling, and a macular star → causative
Posterior uveitis and vasculitis	VF loss [1]	
Macular degeneration	Peripheral retinal degenerations	
Rod and cone dystrophies	such as retinitis pigmentosa typically cause peripheral field constriction	infections include <i>Bartonella</i> , syphilis, and Lyme [8]
Toxic retinopathy		
Paraneoplastic retinopathy		
Acute zonal occult outer retinopathies		
Hereditary retinal dystrophies		
Von Hippel--Lindau and Wyburn--Mason syndromes		
Metabolic and storage diseases		
Optic nerve Differential diagnosis [6,8]:	A variety of defects are possible [1,2]:	SAP can have variability over follow-up and visual field should be interpreted in the context of history and the remainder of the exam [2]
Ischemic optic neuropathy (nonarteritic and arteritic)	Central, paracentral, & cecocentral scotomas, with and without acuity loss	Commonly seen inferior nasal defects in anterior ischemic optic neuropathy may be due to watershed zones being commonly located in the temporal portion of the disc, with increased vulnerability to ischemia [4]
Demyelinating and inflammatory optic neuritis	Arcuate defects	
Neuromyelitis optica (NMO)	Nasal steps	
Trauma	Altitudinal defects	
Infectious optic neuritis (e.g. Lyme)	Enlargement of the blind spot	
Idiopathic and secondary intracranial hypertension	Generalized constriction	

Compressive optic neuropathies, including optic nerve sheath meningioma and vascular compression		prompt imaging, serum, and potentially CSF studies for demyelinating disease, mimickers of MS, as well as NMO when appropriate [8]
Leber's hereditary optic neuropathy and dominant optic atrophy		
Drusen		
Congenital anomaly		
Thyroid ophthalmopathy		
Idiopathic inflammatory orbital disease and Tolosa--Hunt		
Inflammatory, infectious and neoplastic sino-nasal disease		
Lymphoma, leukemia, sarcoidosis, plasmacytoma, carcinoma, and optic nerve glioma		
Optic chiasm	A variety of defects are possible [2]:	Homonymous defects: matching defects (quadrant or hemifield), congruous and non-congruous, with the same laterality in the VF of both eyes
Differential diagnosis [2,8]:	Bitemporal hemianopsia	On SAP, gray-scale and pattern deviation plots
Para-sella masses: pituitary adenoma, craniopharyngioma, Rathke's cleft cyst	Temporal scotoma,	
Meningioma	unilateral and bilateral	
Aneurysm and		

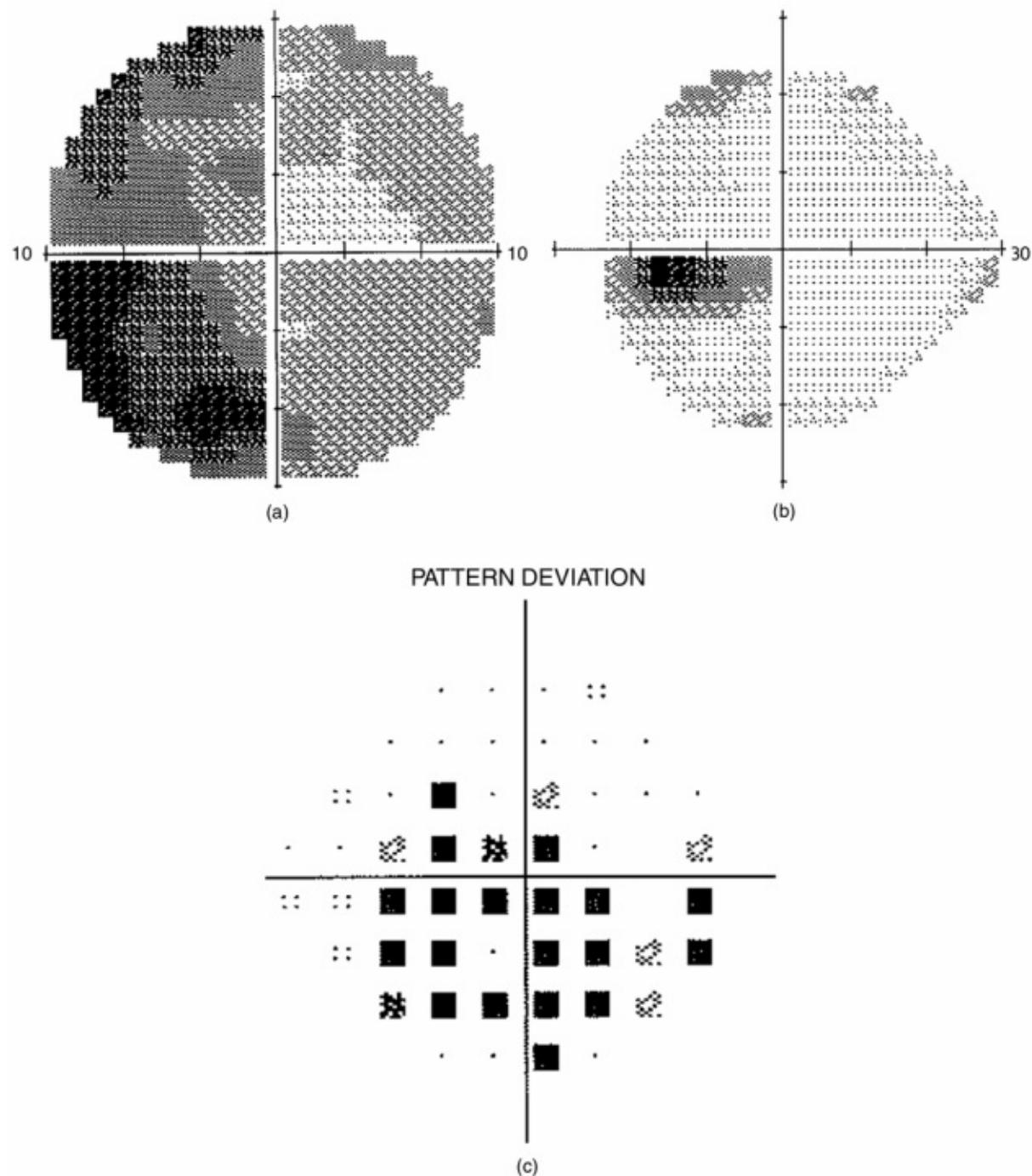
arteriovenous malformation NMO,  demyelinating and inflammatory chiasmopathy  Vascular malformations of the chiasm  Vasculitic ischemia Malignant glioma Hypothalamic tumors  Inflammatory masses: sarcoid, lymphocytic adenohypophysitis, idiopathic granulomatous hypophysitis  Tuberculosis	Junctional scotoma  Quadrantanopsia, unilateral and bilateral	Pattern deviation plots are useful in detecting subtle patterns respecting the vertical meridian, indicating chiasmal and post-chiasmal lesions [2]
Lateral geniculate body  Differential diagnosis: see retrochiasmal visual pathways	Homonymous sectoranopsia or incongruous homonymous hemianopsia [2,6,7]	Congruent and non-congruent lesions are possible [2]
Retrochiasmal visual pathways:  Optic tract, optic radiations, and primary visual cortex (occipital lobe)  Differential diagnosis [6,7]:	Homonymous VF defects with different patterns and congruity depending on the site of the lesion (see text)  Anterior occipital lobe: unilateral	Congruency of VF deficits increases with increasingly posterior locations [1,2]  Patients with homonymous defects due to stroke may not realize their deficits [6]  Homonymous VF

Mass lesion	loss of the temporal crescent	defects with an ipsilateral afferent pupillary defect help localize the lesion to the optic tract [6]
Ischemic and hemorrhagic stroke	[2]	
Trauma	Macular sparing	
Encephalitis	[6]: non-involvement of the central 5–25° of VF on the affected side	
Demyelination		
Reversible posterior leukoencephalopathy		
Vasculitis		
Congenital malformations	Occurs most commonly with stroke in the posterior cerebral artery territory	
Iatrogenic in neurosurgery	Homonymous scotomas: defects limited to the central 30° on the affected side, respecting the vertical meridian [6]	

---



**Figure 77.2** Generalized reduction in visual field (VF) sensitivity. Central 24–2 (OS, total (left) and pattern (right) deviation) of a 72-year-old male complaining of dimness of vision. Visual field shows a generalized reduction of sensitivity on the total deviation and no defects on the pattern deviation. Slit lamp exam revealed bilateral cataracts.  
Key: OD, right eye; OS left eye.

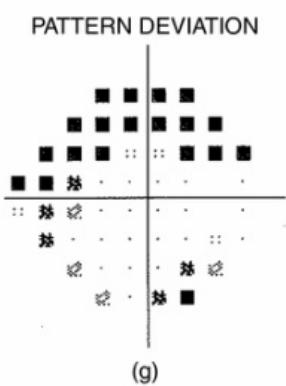
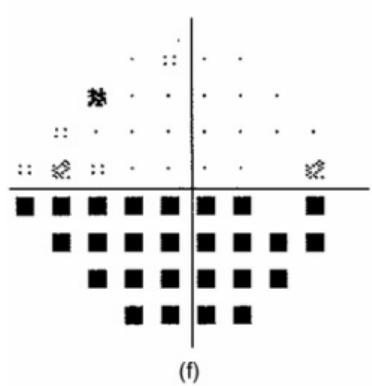
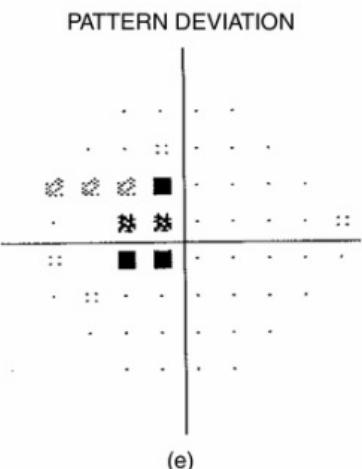
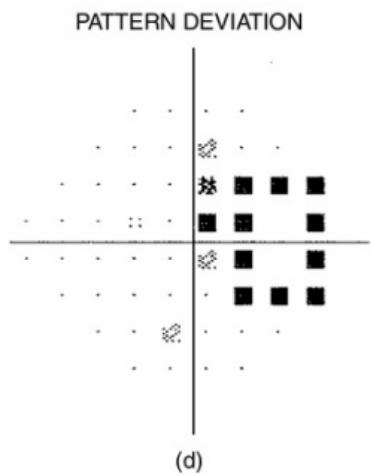
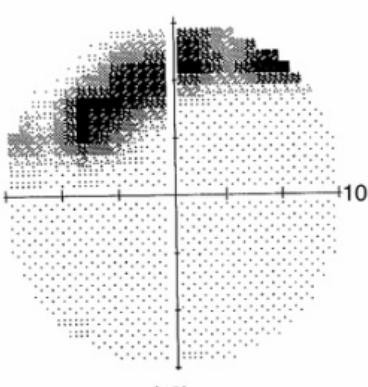
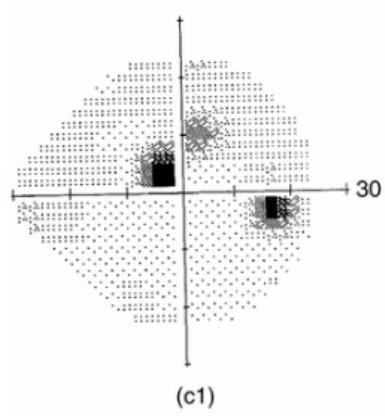
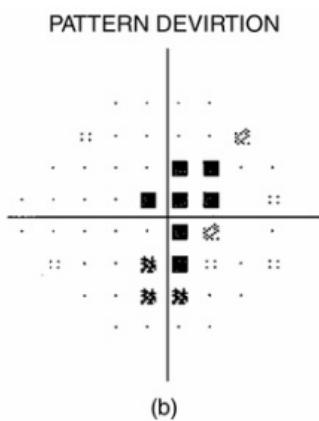
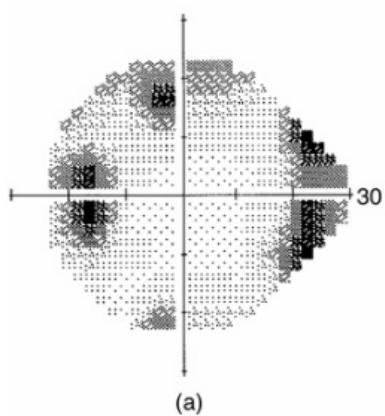


**Figure 77.3** Visual field (VF) defects of retinal origin. (a) Central 10-2 (OS, gray scale) VF of an 85-year-old female with sarcoidosis treated with hydroxychloroquine, diagnosed with toxic retinopathy. (b) Central 24-2 (OS, gray scale) VF showing a cecocentral defect in a 71-year-old female complaining of distorted vision, diagnosed with a macular hole. (c) Central 24-2 (OD, pattern deviation) showing central and diffuse defects in a 74-year-old male who awoke with vision loss, diagnosed with central retinal artery occlusion

(CRAO).

Key: OD, right eye; OS left eye.

Optic nerve disease can cause a variety of VF defects and particular pathologies have defects that are most commonly seen ([Figure 77.4](#)). Central and arcuate patterns are common. Arcuate defects extend from the blind spot, arcing around central fixation to the nasal hemifield, extending as far as the nasal horizontal meridian. They develop because of the arcing pathway taken by the axons of the temporal retinal ganglion cells as they course to the optic disc, respecting the temporal horizontal raphe. Altitudinal defects respect the horizontal meridian. They are commonly seen in anterior ischemic optic neuropathies which can also produce inferior nasal quadrantic defects and diffuse defects [[1,4](#)]. Altitudinal defects are typically large and involve both the nasal and temporal portions, sometimes with relative sparing of one or the other. Enlargement of the blind spot, detectable on SAP, may be due to either optic nerve (early stage) or retinal disease. The differential diagnosis is different if this is unilateral or bilateral, the latter indicating a process that must affect both eyes (e.g. papilledema from elevated intracranial pressure).



**Figure 77.4** Visual field (VF) defects of optic nerve origin. (a) Central 24–2 (OS, gray scale) showing peripheral constriction of the VF in a 31-year-old female diagnosed with idiopathic intracranial hypertension (IIH). (b) Central 24–2 (OD, pattern deviation) showing central and paracentral scotomas in a 77-year-old female presenting with bilateral vision loss, diagnosed with ethambutol toxic optic neuropathy. (c1) Central 24–2 (OD, gray scale) and (c2) central 10–2 (OD, gray scale) showing a central arcuate defect in a 62-year-old male with history of glaucoma and progressive VF loss, found to have low vitamin B1 levels. (d) Central 24–2 (OD, pattern deviation) showing enlargement of the blind spot in a 24-year-old female presenting with headache, transient visual obscurations, and blurred vision diagnosed with IIH. (e) Central 24–2 (OS, pattern deviation) showing a cecocentral defect in a 34-year-old female with a history of multiple sclerosis (MS) presenting with acute vision loss secondary to optic neuritis. (f) Central 24–2 (OD, pattern deviation) showing an inferior altitudinal defect in a 71-year-old male with history of hypertension, hyperlipidemia, coronary disease, and obstructive sleep apnea, presenting with acute vision loss, diagnosed with nonarteritic ischemic optic neuropathy (NAION). (g) Central 24–2 (OD, pattern deviation) showing a superior arcuate defect in a 76-year-old male with an eccentrically growing pituitary macroadenoma compressing the right optic nerve.

Key: OD, right eye; OS left eye.

Visual field loss of psychogenic origin also has typical patterns [5]. To confrontation or tangent testing, tunnel field, or the failure of the field to physiologically expand as testing distance increases, is seen. Spiraling and marked inconsistencies are the hallmarks on kinetic perimetry.

## Chiasmal and retrochiasmal afferent visual pathways

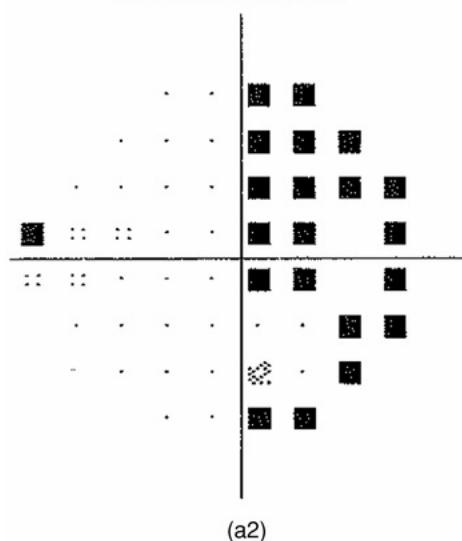
The pattern of VF loss secondary to chiasmal and retrochiasmal visual pathway lesions is used to determine anatomic location. [Figure 77.5](#) demonstrates the “classic” patterns of VF loss and their anatomic localization and [Figure 77.6](#) demonstrates clinical examples. Hemifield defects respect the vertical meridian and are considered homonymous when matching defects are seen in the same quadrant or hemifield of each eye. For example, the defect of a right homonymous superior quadrantanopsia is on the right side of VF of *both eyes*, superiorly. Homonymous defects are indicative of a retrochiasmal lesion. Their

pattern and congruency depend on location within the visual pathways, with congruency increasing with increasingly posterior locations [1,2]. However, it has been shown that lesions at a given location can cause a variety of defects typical of post-chiasmal lesions [6]. Bitemporal defects, complete and incomplete, are indicative of lesions of the optic chiasm. Sectoranopias are wedge-shaped and either point toward or away from fixation; they are caused by lesion of the lateral geniculate body [6].

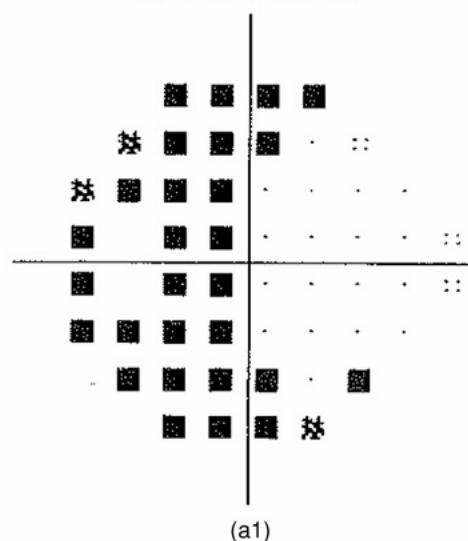
Location	Field Defect		
	Left Eye	Right Eye	Comment
1 Left Optic Nerve	●	○	No light perception left eye
2 Chiasm	○	○	Bitemporal hemianopsia
3 Right Optic Tract	○	○	Incongruous left homonymous hemianopia
4 Left Lateral Geniculate Nucleus	○	○	Right homonymous sectoranopia (lateral choroidal artery) - or -
	○	○	Incongruous right homonymous hemianopia
5 Left Temporal Lobe	○	○	Right homonymous upper quadrant defect ("pie in the sky")
6 Left Parietal Lobe	○	○	Right homonymous defect, denser inferiorly
7 Left Occipital Lobe (upper bank)	○	○	Right homonymous lower quadrantanopsia (macular sparing)
8 Left Occipital Lobe (lower bank)	○	○	Right homonymous upper quadrantanopsia (macular sparing)
9 Right Occipital Lobe	○	○	Left homonymous hemianopia (macular sparing)

**Figure 77.5** “Classic” patterns of visual field loss and their anatomic localization. Reprinted with permission from Liu GT, Volpe NJ, Galetta SL. *Neuro-Ophthalmology Diagnosis and Management*. New York, NY: W.B. Saunders Company, 2001.

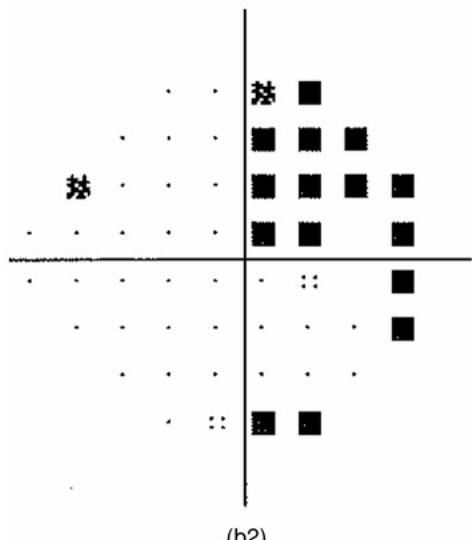
PATTERN DEVIATION



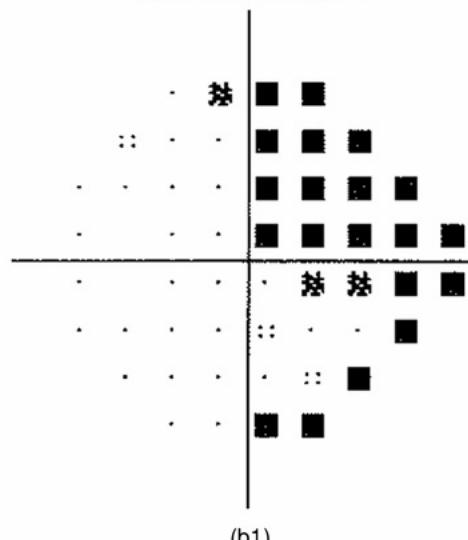
PATTERN DEVIATION



PATTERN DEVIATION



PATTERN DEVIATION

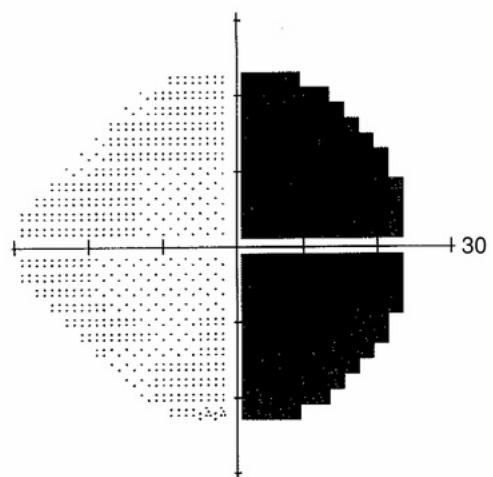
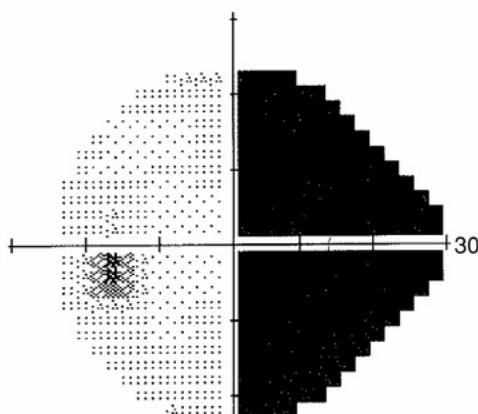


(b2)

(b1)

(c2)

(c1)



**Figure 77.6** Visual field defects in lesions of the optic chiasm and retrochiasmal afferent visual pathways. (a1 OD, a2 OS, pattern deviation) Bitemporal hemianopsia in a 66-year-old male presenting with lethargy, increased appetite and blurred vision, diagnosed with a compressive chiasmopathy from a pituitary macroadenoma. (b1 OD, b2 OS, pattern deviation) Right congruent homonymous superior quadrantanopsia in a 59-year-old female with a history of a left tentorial based recurrent meningioma, status post resection with adjacent encephalomalacia and enlargement of the left lateral ventricle. (c1 OD, c2 OS, gray scale) Complete right homonymous hemianopsia in a 60-year-old female presenting with difficulty seeing off to right, diagnosed with a left occipital ischemic stroke.

Key: OD, right eye, OS, left eye.

## Formulating a differential diagnosis

The VF deficit in conjunction with the history and the remainder of the exam leads to localization of the pathology and the underlying pathophysiology. Associated symptoms of particular importance include headache and symptoms of cardiac, vasculitic, arthritic, infectious, and neurologic origin. Acuity or insidiousness of onset and static versus progressive details should be obtained to delineate the underlying pathology. Assess if the complaint is truly unilateral or bilateral as this can only be definitively determined by closure of the contralateral eye and assessing each eye independently and is of great importance in determining localization.

The examination, ophthalmic, neurologic, and systemic, refines the differential and localization. A visual complaint localized subjectively to one eye and an examination showing a unilateral VF defect with a dyschromatopsia and afferent pupillary defect in the ipsilateral eye indicates optic nerve pathology. A unilateral complaint with abnormal retinal findings on the fundus exam indicates a retinal process. Motility disturbances or orbital signs on exam associated with symptoms of visual loss should focus the evaluation (e.g. orbital, superior orbital fissure, or cavernous sinus processes). Additional focal neurologic signs indicate a central nervous system (CNS) etiology. Referral for SAP should be obtained in patients with visual complaints not otherwise explained or with a normal ophthalmic exam.

After localization, testing can be directed toward the assumed

pathophysiology: ischemia and cardioembolic or atheroembolic, demyelinating and other inflammatory conditions, infectious, metabolic, and congenital or genetic, as listed in [Table 77.1](#), based on anatomic location. Additional ophthalmic testing including retinal fluorescein angiography, optical coherence tomography, B-scan, visual evoked potentials, and electroretinogram can be obtained if clinically warranted.

## Case vignette

A 64-year-old male presented with his wife, complaining of blurred vision. The patient had difficulty further delineating his symptoms. Upon occlusion of the left eye he reported normal vision in the right eye and upon occlusion of the right eye, reported “not perfectly clear” vision in the left eye. His wife reported cognitive decline with “decreased thought processes.”

Exam showed best corrected visual acuity of 20/20 OU. Color vision, red Amsler grid, pupil exam, orbital and lid exam, intraocular pressures, and motility and alignment were normal. Confrontation visual fields were full and there was no subjective red desaturation in either eye. Funduscopic exam revealed normal optic nerve and central and mid-peripheral retinal exam. The patient's VF is shown in [Figure 77.1](#). It indicates a relative right homonymous superior quadrantanopsia.

Neurologically the patient was alert and oriented. He had mild difficulty naming and more difficulty with spontaneous fluent speech. Cranial nerve exam was intact. There was no neglect or focal motor or sensory loss. Balance and gait were normal.

History and exam indicated a non-fluent aphasia and subtle VF defect detected on SAP. The pathology is localized to the left hemisphere, most likely the temporal or parietal area. Imaging is indicated and the tempo of onset and progression of symptoms indicate a relatively insidious process such as neoplastic disease. The patient underwent MRI imaging showing a glioblastoma and this was confirmed upon resection. In this case if an initial non-contrasted MRI was negative the localization should prompt a contrasted scan unless contraindicated.

## References

1. Heijl A, Patella VM. *Essential Perimetry: The Field Analyzer Primer*. Jena:

Carl Zeiss Meditec, 2002.

2. Kedar S, Ghate D, Corbett JJ. Visual fields in neuro-ophthalmology. *Indian J Ophthalmol* 2011; 59:103–9.
3. Pandit RJ, Gales K, Griffiths PG. Effectiveness of testing visual fields by confrontation. *Lancet* 2001; 358:1339–40.
4. Hayreh SS, Zimmerman B. Visual field abnormalities in nonarteritic anterior ischemic optic neuropathy: their pattern and prevalence at initial examination. *Arch Ophthalmol* 2005; 123:1554–62.
5. Burde RM, Savino PJ, Trobe JD. *Clinical Decisions in Neuro-Ophthalmology*, 2nd edn. St Louis, MO: Mosby-Year Book, 1992.
6. Zhang X, Kedar S, Lynn MJ et al. Homonymous hemianopias: clinical-anatomic correlations in 904 cases. *Neurology* 2006; 66:906–10.
7. Liu GT, Volpe NJ, Galetta SL. *Neuro-Ophthalmology Diagnosis and Management*. New York, NY: W.B. Saunders Company, 2001.
8. Selhorst JB, Chen Y. The optic nerve. *Semin Neurol* 2009; 29:29–35.

## **78 Visual loss, acute bilateral**

---

Robert M. Mallery and Misha L. Pless *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

A diverse set of ophthalmologic and neurologic disease processes may lead to binocular loss of visual field or visual acuity within the span of hours. Visual acuity loss is typically a result of lesions affecting the optic nerves, chiasm, or optic tracts (pre-geniculate visual pathway). Lesions affecting the lateral geniculate nucleus, the optic radiations, primary visual cortex, and association visual cortices (post-geniculate visual pathway) produce homonymous field loss with normal acuity, pupillary reactivity, and fundus examination. While several disease processes that cause acute monocular visual loss can present bilaterally, acute binocular visual loss is most often caused by intracerebral lesions. Visual field testing, ophthalmic examination, and co-localizing neurologic signs can be helpful in narrowing down the differential diagnosis for acute binocular visual loss.

### **Case vignette**

A 72-year-old male with history of hypertension presented with a headache and difficulty reading. His blood pressure was 180/110. On neurologic examination there was a left homonymous superior quadrantanopia. There was absence of a relative afferent pupillary defect. Visual acuity was 20/25 bilaterally with corrective lenses. While awaiting a computerized tomography (CT) of the head he had a generalized tonic-clonic seizure. The convulsion ended, after which he was confused and had transient left arm weakness. He was stabilized, and the head CT was performed showing a 12 cc right temporal lobe hyperdensity consistent with acute hemorrhage. He was treated with a nicardipine drip, levetiracetam, and admitted to an intensive care unit (ICU). He remained in the ICU for 48 hours, at which time brain MRI with susceptibility-weighted images

showed multiple cortical microhemorrhages in addition to the left temporal lobe hemorrhage.

This patient presented with homonymous visual field loss with relatively preserved visual acuity suggesting a process within the retro-geniculate visual pathway. The visual fields were consistent with a lesion in the right temporal lobe. At the time of presentation there was no associated weakness, but the presence of headache raised the possibility of increased intracranial pressure (ICP) or referred pain from the vessels or meninges. Head CT revealed a temporal lobe hemorrhage that was the cause of the visual deficit and the seizure. Multiple cortical microhemorrhages seen on MRI gave the final diagnosis of probable cerebral amyloid angiopathy (CAA). Systemic hypertension in the setting of CAA likely predisposed to hemorrhage.

**Table 78.1 Etiologies of pre-chiasmal visual loss.**

Location with visual field defects and pupil exam	Etiologic category	Specific etiology	Clinical signs
Ocular/retinal Visual field (VF): central, centrocecal, or altitudinal defect Pupils: no afferent pupillary defect (APD) (unless retinal damage is extensive)	Vascular	Central or branch retinal artery occlusion; amaurosis fugax if transient	Ophthalmologic signs: cherry-red spot in the macula, embolus in retinal artery, nerve fiber layer opacification, or attenuation of the retinal arterial tree
		Susac's syndrome	Ophthalmologic signs: branch

retinal artery occlusions with yellow retinal wall plaques in mid arteriolar segments of involved vessels [1]

Inflammatory	Acute posterior multifocal placoid pigment epitheliopathy (APMPPE)	Ophthalmologic signs: multifocal gray-white flat lesions of the retinal pigment epithelium with a predisposition for the macula [3]
Infectious	Acute retinal necrosis	Ophthalmologic signs: anterior uveitis, vitritis, retinal necrosis initially affecting the peripheral retina, and retinal

			detachment
	Systemic/pressure	Malignant hypertension	Ophthalmologic signs: optic disc edema, flame-shaped hemorrhages, cotton-wool spots, and lipid exudates
Optic nerves VF: central scotoma, centrocecal scotoma, arcuate defect, altitudinal defect, or constriction Pupils: relative APD present Other evidence of optic neuropathy: decreased visual acuity and dyschromatopsia	Vascular	Giant cell arteritis Arteritic anterior ischemic optic neuropathy (AION)	Ophthalmologic signs: optic nerve head pallor and edema, pale fundus suggests involvement of vessels supplying the choroid and posterior pole
		Posterior ischemic optic neuropathy (PION)	Not associated with acute changes on fundoscopy

Elevated intracranial pressure	Papilledema (optic nerve swelling secondary to elevated intracranial pressure)	Ophthalmologic examination: optic disc edema, obscuration of the vessels overlying the disc, peripapillary hemorrhages, cotton wool spots Visual acuity is relatively preserved compared with field loss
Inflammatory	Optic neuritis	Ophthalmologic signs: Optic disc edema if affecting the

optic nerve head (papillitis). If retrobulbar the optic disc may appear normal Pain with eye movements, Uthoff phenomena, signs of other demyelinating lesions in brain or spinal cord

AION, anterior ischemic optic neuropathy; CMV, cytomegalovirus; EBV, Epstein–Barr virus; HSV, herpes simplex virus; PRES, posterior reversible encephalopathy syndrome; VZV, varicella zoster virus.

**Table 78.2 Etiologies of chiasmal visual loss.**

Location with visual field defects and pupil exam	Etiologic category	Specific etiology	Clinical signs	Comments
Optic chiasm Visual field (VF): Bitemporal hemianopia, diffuse bilateral field loss, or junctional	Vascular	Optochiasmal apoplexy	Headache	Secondary hemorrhage within a cavernous involving chiasm or nerve

scotoma  
Pupils:  
relative  
afferent  
pupillary  
defect (APD)  
may or may  
not be  
present

	Giant intracerebral artery aneurysm	May have superimposed chronic nasal visual field loss	Acute vis loss occ secondary hemorrhage the chias from aneurysm thrombosis occlusion penetratin vessels
Inflammatory	Optic chiasmal neuritis	There may be signs of other concurrent demyelinating lesions	May occur neuromyelitis optica (NMO), systemic erythema (SLE), multiple sclerosis, neurosarco
Compressive	Pituitary apoplexy	Ocular motor palsies, monocular or binocular visual loss, systemic hypotension, headaches,	Pituitary dysfunction (amenorrhea, decreased libido, impotence, galactorrhea)


**Table 78.3 Etiologies of post-chiasmal/geniculate visual loss.**

Location with visual field defects and pupil exam	Etiologic category	Specific etiology	Clinical signs	Comments
Optic tract Visual field (VF): Incongruous or complete	Vascular	Stroke (lacunar or embolic)	May be accompanied by contralateral hemiplegia and hemihypesthesia	Vascular supply to optic tract from anterior anastomosis

<u>compression</u>	homonymous hemianopsia Pupils: relative afferent pupillary defect (APD) contralateral to the side of the lesion	from damage to the posterior limb of the internal capsule	network between anterior choroid artery (of the internal carotid and the posterior communicating artery)
Hemorrhage		Headache, signs of elevated intracranial pressure (ICP). Consider hypertensive bleed	Secondary vascular malformations or aneurysms. May occur from bleeding metastases
Inflammatory	MS, NMO, ADEM	May include signs of demyelination in other areas of the brain or spinal cord	Small lesions seen commonly on imaging often asymptomatic but large demyelinating lesions tumefactive lesions occur
Compressive	Sellar or suprasellar masses	Headache, signs of elevated ICP	Sellar nodules, suprasellar masses, rapidly expanding aneurysms

				result in compression and less frequent compressive vascular supply
Lateral geniculate nucleus (LGN)  VF: Horizontal sectoranopsia. Pupils: no APD	Vascular  Posterior choroidal artery stroke	Incongruous or complete homonymous hemianopsia; relative APD contralateral to the side of the lesion  Signs of elevated ICP: papilledema, headache  Seizure secondary to medial temporal lobe involvement	Compressive hemorrhage edema affecting optic tract be difficult distinguish from the process affecting temporal radiation	
LGN  VF: Sector-	Vascular  Anterior choroidal artery	Blindsight	Infarction LGN layer 3, and 4	

sparing homonymous hemianopsia Pupils: no APD	stroke	Well-preserved language and cognition	Associa structur lesions: posteric of the i capsule internal segmen globus pallidus tract, cl plexus i tempora of the l ventricl
---	--------	---	--

**Table 78.4 Localization and etiologies of post-geniculate visual loss.**

Location with visual field defects	Other localizing signs	Etiologic categories	Specific etiologies	C
Temporal optic radiations (Meyer's loop) Visual field (VF): homonymous superior quadrantanopsia (often incongruous)	Right hemisphere: Left-sided weakness, aprosodic speech Left hemisphere: Wernicke's or conduction aphasia	Vascular	Inferior division middle cerebral artery (MCA) stroke	T s p a a t s
			Hemorrhage	L a r +

u  
s  
a  
(  
f  
t  
a  
v  
n

Inflammatory      Multiple      T  
                      sclerosis      o

Tumor      Metastasis      A  
e  
h  
u  
C  
c  
p  
c  
h

Primary central      T  
nervous system      w  
(CNS) tumors      (  
(high grade      s  
glioma,      h  
primary CNS      v  
lymphoma)      C  
l  
e

Infectious      Abscess      A  
h  
s  
a  
a  
I  
s

p  
t  
o  
ii

Parietal optic radiations (Baum's loop)	Sensory loss, sensory extinction, hemispatial neglect, astereognosis, dysgraphesthesia, impaired visuospatial construction, anosognosia with non-dominant (usually right) parietal lobe lesion	Vascular	Stroke: Superior division MCA stroke, borderzone MCA/PCA stroke	C le l d to ra c
		Hemorrhage		S C a n
			Posterior reversible encephalopathy syndrome (PRES)	S s e w c a d
		Inflammatory	Multiple sclerosis	I ti
		Tumor	Metastasis	A e

				h
				u
				C
				c
				p
				c
				h
			Primary CNS tumors (high grade glioma, primary CNS lymphoma)	T
				w
				(i
				s
				h
				v
				C
				l
				e
	Infectious	Abscess		A
				h
				s
				a
				a
				I
				s
				p
				t
				o
				ir
Primary visual cortex – striate cortex (V1) VF: homonymous hemianopsia	Occipital lobe stroke may be accompanied by deficits in other areas of the brain supplied by the vertebrobasilar system (brainstem, ----1----1----	Vascular	Posterior cerebral artery stroke	M
				l
				c
				h
				fi
				n
				S]
				S]
				re
				--

cerebellum,  
thalamus)

S  
o  
b  
L  
e  
o  
fi  
p

Hemorrhage

S  
C

PRES

S  
S  
e  
w  
c  
a  
d

Headache

Migraine with  
aura

P  
p  
(  
p  
li  
h

Ictal

Occipital lobe  
seizure

P  
p  
l

Tumor

Metastasis

A  
e  
h  
u  
C  
c  
p  
c  
h

			--
		Primary CNS tumors (high grade glioma, primary CNS lymphoma)	T w ( s h v C l e
	Infectious	Abscess	A h s a a I s p t o ii
Association visual cortex VF: homonymous hemianopsia, visual extinction	May include visual aphasia, elements of Balint's syndrome (asimultagnosia, optic ataxia, oculomotor apraxia), achromatopsia, alexia, or Anton syndrome (visual confabulation)	Vascular	Stroke (including MCA/PCA watershed)
		PRES	S

S  
e  
w  
v  
d  
A  
E

Hemorrhage

S  
C

Inflammatory  
Multiple  
sclerosis

I  
t

Tumor

Metastasis

A  
e  
h  
u  
C  
c  
p  
c  
h

Primary CNS  
tumors (high  
grade glioma,  
primary CNS  
lymphoma)

T  
w  
(  
s  
h  
v  
C  
l  
e

Infectious

Abscess

A  
h  
s  
a  
a  
-

Non-organic visual loss VF: may or not be physiologic	Psychogenic	Secondary to malingering, factitious disorder, or somatization (hysteria)	M b n
--	-------------	---	-------------

---

## References

1. Egan RA, Ha Nyugen T, Gass JD, Rizzo JF 3rd, Tivnan J, Susac JO. Retinal arterial wall plaques in Susac syndrome. *Am J Ophthalmol* 2003; 135:483–6.
2. O'Halloran HS, Pearson PA, Lee WB *et al*. Microangiopathy of the brain, retina, and cochlea (Susac syndrome). A report of five cases and a review of the literature. *Ophthalmology* 1998; 105:1038–44.
3. Gass JD. Acute posterior multifocal placoid pigment epitheliopathy. *Arch Ophthalmol* 1968; 80:177–85.
4. Bonfioli AA, Eller AW. Acute retinal necrosis. *Semin Ophthalmol* 2005; 3:155–60.
5. Sadda SR, Nee M, Miller NR *et al*. Clinical spectrum of posterior ischemic optic neuropathy. *Am J Ophthalmol* 2001; 132:743–50.

## 79 Visual loss, monocular

---

Jeffrey Peterson, Rehan Ahmed, and and Rod Foroozan *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Transient monocular visual loss (TMVL) is the abrupt loss of vision in one eye lasting less than 24 hours. The terms “amaurosis fugax” (translating from Greek to mean “fleeting blindness”) and “transient monocular blindness” are sometimes used by clinicians interchangeably with “transient monocular visual loss.” However, “amaurosis fugax” implies visual loss secondary to ischemia, and does not specify whether the vision loss is in one or both eyes. The term “transient monocular blindness” implies a complete loss of vision, but most episodes of TMVL cause only a partial loss of vision. As TMVL may be incomplete, related to either ischemic or non-ischemic etiologies, and refers only to monocular visual loss, it has been suggested that this term be used in preference to others.

The most important step in the clinical evaluation of any patient presenting with TMVL is to obtain a thorough history. The age of the patient, the duration of visual loss, the pattern of visual loss and recovery, and any associated symptoms or additional signs are all used to formulate a differential diagnosis and initiate an appropriate management plan. Determining risk factors for retinal ischemia is also a critical component of the patient's history. As the retinal circulation arises from the internal carotid artery, the presence of carotid artery stenosis, hyperlipidemia, or cardiac arrhythmias may suggest a thrombo-embolic cause.

Establishing whether the visual loss is monocular or binocular helps to localize the lesion: monocular visual loss results from a lesion anterior to the chiasm (the eye or optic nerve). It is crucial to remember, however, that a patient's perception of monocular versus binocular visual loss can be misleading. For example, patients with binocular hemifield (homonymous) visual loss often

localize visual loss only to the eye that lost the temporal visual field. It is important to ask if visual loss was noted in the fellow eye when the affected eye was covered during the episode. In addition, patients with binocular visual loss also tend to have a more pronounced reading impairment, whereas monocular visual loss does not usually impair reading unless the unaffected eye has a prior visual impairment.

Despite the importance of obtaining a complete history, the approach to TMVL that we have found most useful is determining whether the patient has abnormal eye examination findings that can explain the visual loss.

## Case vignette

A 75-year-old male with a history of hyperlipidemia presented with several episodes of transient monocular visual loss in his right eye. He described the visual loss as a curtain rapidly coming down over his vision, lasting for approximately 10 minutes, and gradually resolving. The events occurred spontaneously, and there were no precipitating or alleviating factors. He denied pain. He had no other neurologic symptoms. He was seen by his primary care doctor but was asymptomatic and had normal funduscopy. The next day he experienced several more episodes of a similar nature, and presented to his nearest emergency room. An ophthalmologist was consulted, and a Hollenhorst plaque was identified on funduscopic examination of his right eye. The remainder of his complete eye exam was within normal limits. An echocardiogram was normal. Carotid Doppler revealed > 70% stenosis of the right internal carotid artery, and the patient was referred to a vascular surgeon for further management.

**Table 79.1 Differential diagnosis of transient monocular visual loss.**

Item	Specific type	Specific etiology	Possible clinical features
Abnormal eye examination	Anterior segment pathology	Irregular corneal tear film	Seen on slit lamp examination. Punctate keratopathy and abnormal Schirmer's test. <small>Symptoms improve</small>

**Symptoms improve**  
with blinking or  
application of tear  
supplements

Corneal epithelial basement membrane dystrophy	Seen on slit lamp examination. Associated with pain	
Uveitis– glaucoma– hyphema (UGH) syndrome	Uncommon complication of cataract surgery. Associated with pain, elevated intraocular pressure, erythropsia (perception of red in the vision). Gonioscopy may be required to make the diagnosis	
Angle closure glaucoma	Associated with pain, halos, nausea, and elevated intraocular pressure	
Retinopathy	Age-related macular degeneration	Anatomical derangement of retinal pigment epithelium– photoreceptor interaction results in abnormal processing of light. Drusen detected on funduscopy. Prolonged photostress test (> 45

		s to return to normal central acuity after 10 s exposure to bright light)
	Retinal detachment	Painless. Identified on funduscopic examination
Optic nerve pathology	Optic disc edema	Transient visual obscurations (“gray outs” lasting < 10 s), often precipitated by postural changes. Often associated with headache. Related to elevated intracranial pressure or compressive mass lesion
	Optic disc drusen	Transient visual obscurations. Drusen may be seen on ultrasound or computerized tomography
Other	Orbital mass or foreign body	May have unilateral proptosis. Gaze-evoked visual loss suggestive of optic nerve sheath meningioma or cavernous hemangioma, as mass may compress retinal or optic nerve circulation especially

in downgaze

Blepharospasm      In advanced cases, eyelids cannot be manually opened during an episode

Vascular                  Embolic

Typically causes a curtain of darkness descending over 5–10 minutes that then ascends or slowly disappears.

Appearance of emboli seen on funduscopy provides clues as to site of origin; most common types are cholesterol (yellow orange, refractile, rectangular), platelet–fibrin (dull gray–white, long and smooth), and calcium (chalky white)

Retinal vein occlusion (RVO)      Impending RVO associated with cloudiness of vision rather than vision loss. Funduscopy early shows dilated retinal veins, and within 2 weeks of occlusion shows scattered intraretinal hemorrhages.

Associated with hypertension, diabetes, and hypercholesterolemia

hypertension  
states, retinal artery  
occlusion, and  
arteriosclerosis

Giant cell  
arteritis

Typically short  
duration (< 2 min)  
visual loss.  
Associated with  
headache, jaw  
claudication, scalp  
tenderness,  
polymyalgia  
rheumatica, systemic  
symptoms (fever,  
anorexia, weight  
loss). Funduscopy  
may show cotton-  
wool spots,  
intraretinal  
hemorrhages, and  
optic disc edema.  
Elevated erythrocyte  
sedimentation rate,  
C-reactive protein,  
and platelet count.  
Confirmed with  
temporal artery  
biopsy

Ocular  
ischemic  
syndrome

Related to severe  
carotid artery  
stenosis. Described  
as gradual dark shade  
spreading across  
vision lasting  
seconds to minutes,  
triggered by bright  
light, meals, postural  
changes and activity

Normal eye examination.

Funduscopy shows signs of retinal ischemia

Normal eye examination	Other	Hypoperfusion	Associated with transient episodes of hypotension, especially orthostatic hypotension
		Retinal migraine	Variable presentation; vision loss lasts 5–20 minutes occurring multiple times per day. May also have positive visual phenomena (e.g. flashing lights, scintillating scotoma). May be associated with headache. Affects 1 in 200 patients with migraine, and patients tend to be younger (< 40 years old)
		Retinal artery vasospasm	Symptoms similar to retinal migraine but never occur with headache, are more frequent, and often involve transient complete vision loss. May have relative afferent pupillary

defect during attack

Demyelinating disease Uhthoff's phenomenon (visual loss with physical exertion)

Non-organic

---

Life-threatening cardioembolic causes and vision-threatening giant cell arteritis should be considered in any patient with TMVL. A careful eye examination along with a thorough history are important. In this case, the presence of a Hollenhorst plaque and the patient's description of altitudinal vision loss lasting minutes strongly suggest an embolic etiology, which requires a thorough vascular and cardiac evaluation.

## Further reading list

Biousse V, Trobe JD. Transient monocular visual loss. *Am J Ophthalmol* 2005; 140:717–21.

Bruno A, Corbett JJ, Biller J, Adams HP Jr, Qualls C. Transient monocular visual loss patterns and associated vascular abnormalities. *Stroke* 1990; 21:34–9.

Fisher CM. ‘Transient monocular blindness’ versus ‘amaurosis fugax’. *Neurology* 1989; 39:1622–4.

Miller N. Embolic causes of transient monocular visual loss. *Ophthalmol Clin North Am* 1996; 9:359–80.

Thurtell MJ, Rucker JC. Transient visual loss. *Int Ophthalmol Clin* 2009; 49:147–66.

Trobe JD. *The Neurology of Vision*. New York, NY: Oxford University Press, 2001.

## **80 Weakness, generalized acute**

---

Denis Ostrovskiy *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

Although not encountered every day in the clinical practice of neurology, acute generalized weakness usually represents a life-threatening problem requiring prompt diagnostic and therapeutic interventions. Every neurologist should be comfortable with the emergent decision making required in this situation. Unfortunately correct diagnosis can be rather challenging.

This chapter discusses disorders leading to the development of acute generalized weakness only. The term “acute” refers to development of the symptoms within minutes or hours up to 1–2 days, while “subacute” indicates progression of the symptoms from days to weeks. Most of the acute disorders can have a subacute course as well.

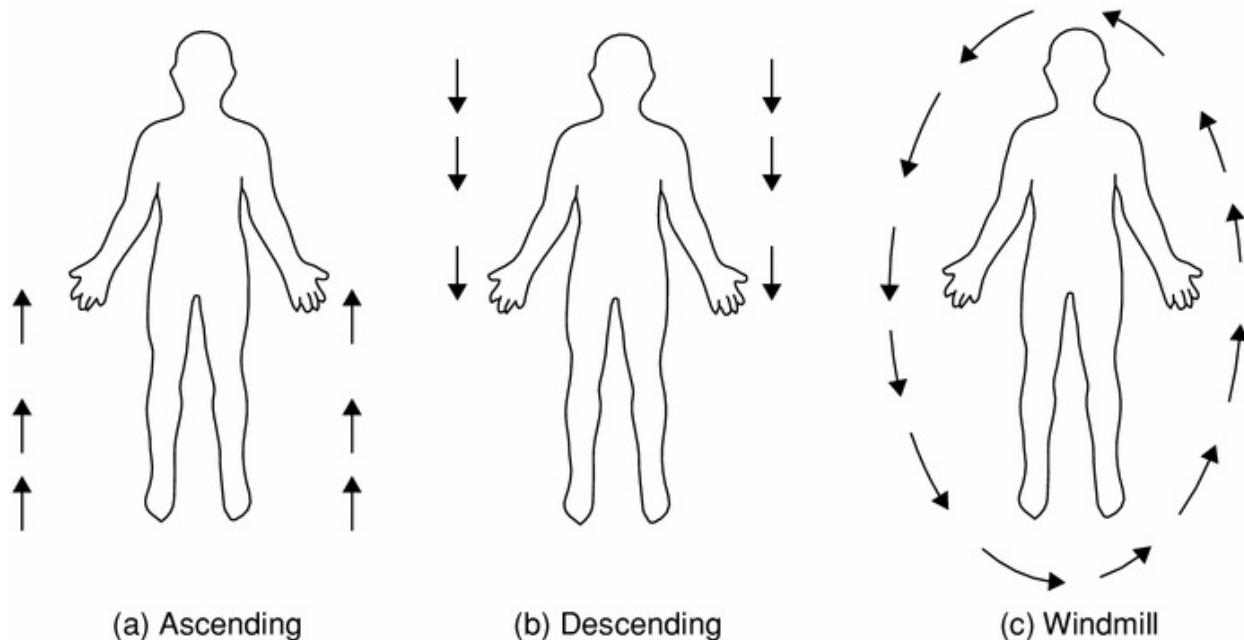
By definition, generalized weakness indicates involvement of the upper and lower extremities, axial and cranial muscles. Presence of sensory symptoms, bowel and bladder dysfunction, or dysautonomic symptoms may aid in differential diagnosis, but can be absent. Plegia, paralysis, or palsy refer to the complete loss of movement, while the term paresis indicates diminished motor power.

Generalized weakness can be localized to either the central or peripheral nervous systems. Within the central nervous system (CNS) there are only two potential locations of lesions:

1. Bilateral basal brainstem.
2. Bilateral higher segments of cervical spinal cord (C5 and above).

A pathologic process in the thoracic and lumbar segments of the spinal cord cannot affect the upper extremities or cranial muscles and thus cannot cause generalized weakness. The understanding of the development patterns and distribution of motor symptoms can be extremely helpful in diagnosis. The pattern of progression of the symptoms with CNS involvement will often affect sides of the body or separate limbs sequentially (i.e. the “windmill pattern,” see

Figure 80.1c) rather than in ascending or descending order.



**Figure 80.1** Patterns of progression of the symptoms of acute generalized weakness with central nervous system involvement.

## Case vignette 1

A 67-year-old male is transferred from a community hospital, where he was brought with rapidly progressive weakness in all four extremities with a presumed diagnosis of Guillain–Barré syndrome. Plasmapheresis treatments were initiated before the transfer. At the time of transfer to the tertiary facility the patient is intubated and sedated. On examination, conducted off of sedation, the patient is found to be plegic in all extremities as well as in the bulbar musculature. He is able to close and open his eyes. Extraocular movements are preserved. The patient is noted to have transient horizontal nystagmus on elective gaze. Additional history, obtained from the patient's family, revealed the stepwise progression of the symptoms within several hours. The weakness first affected the right and then later the left upper and lower extremities. Magnetic resonance imaging (MRI) of the brain is performed following his consultation revealed bilateral basal pontine strokes. The patient is therefore diagnosed with the “locked-in” syndrome, with plasmapheresis discontinued.

This case demonstrates the critical importance of the collection of history for a correct diagnosis. Although Guillain–Barré syndrome can rapidly involve all extremities and the face, a stepwise “windmill” progression with a hemiplegic

presentation suggests the presence of a CNS lesion.

As seen in the above case, the first decision-making step is to establish a clinical problem as related to either the central or peripheral nervous systems or both.

The classical presentation of upper motor neuron dysfunction includes hyperreflexia, increased muscular tone, and the presence of pathologic pyramidal signs. The first two findings are often absent in the acute setting. Careful examination for the presence of pathologic signs from the upper and lower extremities may provide clues aiding in the early diagnosis of CNS pathology. Modern advances in neuroimaging also allow much easier insight in involvement of the brain or cervical spinal cord once a careful history and physical examination has been performed to direct them.

The causes for acute generalized weakness resulting from involvement of the brain and high cervical spinal cord are reported in [Table 80.1](#).

**Table 80.1 Causes of acute generalized weakness involving the central nervous system.**

<b>Pathologic process</b>	<b>Clinical syndrome</b>	<b>Diagnostic considerations</b>
Bilateral basal brainstem stroke, ischemic or hemorrhagic	“Locked-in” syndrome: acute tetraplegia or tetraparesis with facial involvement, but sparing extraocular movement	Sudden onset or stepwise progression; magnetic resonance imaging (MRI) of the brain
Brainstem basal demyelination	Central pontine myelinolysis or demyelinating disease of the brainstem (multiple sclerosis, acute disseminated encephalomyelitis, neuromyelitis optica [NMO])	History of hyponatremia with rapid correction; cerebrospinal fluid (CSF) studies; MRI of the brain; positive NMO antibody

Brainstem compression	Rapidly developing epidural infection (empyema) or neoplasm; epidural or subdural hematoma	Presence or history of neoplasm History of cranial trauma Presence of a generalized or focal (usually bacterial) infection; MRI of brain
Cervical spinal cord injury	Spinal cord trauma	History of trauma MRI of cervical spinal cord
Cervical spinal cord compression	Epidural compression of cervical spinal cord with tumor, hematoma, infection, neoplasm, or disc herniation	Frequently associated with pain; MRI of cervical spinal cord
Spinal cord stroke	Anterior spinal artery syndrome: sudden tetraplegia and anesthesia with a sensory level and without cranial involvement	Sudden onset MRI of cervical spinal cord may not be diagnostic
Spinal cord demyelination	Transverse myelitis/NMO/multiple sclerosis/acute disseminated encephalomyelitis	MRI imaging of cervical spinal cord; CSF studies; positive NMO antibody

Within the peripheral nervous system (PNS) an acute generalized weakness may result from the involvement of:

1. Anterior horn cells of the spinal cord – poliomyelitis.
2. Multiple nerve roots – polyradiculopathy.
3. Multiple nerves – polyneuropathy.
4. Neuromuscular junction – myasthenic disorder.
5. Muscles – myopathy.

Sensory complaints or findings indicate involvement of neural roots or peripheral nerves, rather than the anterior horn cells, neuromuscular junction, or muscle. While bowel and bladder dysfunction do not help to differentiate between the lesions of the spinal cord and roots, the presence of these problems effectively rules out disorders of the anterior horn cells, neuromuscular junction, or muscle.

The pattern of weakness development is also helpful. Involvement of the lower extremities followed by the upper extremities and cranial muscles is more typical of acute polyradiculoneuropathy or polyneuropathy. This is known as an *ascending pattern* of weakness (see [Figure 80.1a](#)). Initial impairment of cranial musculature, especially bulbar and ocular muscles with subsequent involvement of the extremities is more suggestive of a disorder of the neuromuscular junction. This is a *descending pattern* of weakness (see [Figure 80.1b](#)). The “Windmill pattern,” mentioned above with CNS problems, may also be seen in poliomyelitic illnesses. Although helpful, these patterns are not absolutely diagnostic for any specific PNS problem.

## Case vignette 2

A 78-year-old male is brought by family to the emergency room with 24 hours of bilateral facial weakness and inability to raise his arms. There is no prior history of neurologic disease or neurologic symptoms. On examination the patient's speech is slurred. He is unable to close his eyes because of bilateral orbicularis oculi muscle weakness. He exhibits neck extensor weakness. Upper extremity strength is significantly diminished bilaterally. Lower extremity strength is normal. He is able to walk unassisted. Cerebrospinal fluid (CSF) study reveals highly elevated level of protein with normal white cell count; MRI imaging of the brain is normal. The patient is ultimately diagnosed with a crano-cervico-brachial form of Guillain–Barré syndrome and treated with plasma exchange with significant improvement.

In this case the absence of a past medical history of neurologic complaints or symptoms argues against myasthenia gravis, otherwise a very logical suspicion given the descending pattern of weakness. Lumbar puncture ultimately played a crucial role in forming a correct diagnosis in this case.

Causes for acute generalized weakness resulting from involvement of the PNS are reported in [Table 80.2](#).

**Table 80.2 Causes of acute generalized weakness involving the peripheral nervous system.**

Localization	Etiology	Clinical features
Acute motor neuronopathy – Poliomyelitis (from Greek <i>polios</i> – gray)	West Nile virus infection; Enteroviral infection	Seasonal illness develops general weakness
Acute polyradiculoneuropathy or generalized acute motor > sensory polyneuropathy	Guillain–Barré syndrome (GBS)	Most causes generalized weakness. Classic ascending symmetric
	Acute intermittent porphyria	Very distinctive, distinguishing from GBS past history similar abdominal cranial crises frequent
	Toxic: arsenic, thallium rodenticide Vacor, organophosphates, n-hexane	Arsenicals prominent component – pancreatic necrosis

Organic  
– fascic

Diphtheria

3rd–4th  
clinical  
present  
diphthe

Cytomegalovirus

In HIV  
immun  
patient

Buckthorn ingestion  
(*Karwinskia humboldtiana*)

Exposi  
buckth

Critical illness polyneuropathy

In the c  
critical

Carcinomatous polyradiculopathy

History  
malign

Tetrodotoxin exposure

Within  
of expo

Vasculitic neuropathy

Unusu  
progre  
multifc  
monon

Neuromuscular  
junction – myasthenic  
syndrome

Myasthenia gravis –  
myasthenic crisis

Highly  
develope  
Always  
of som  
weaknes  
Except  
exposu  
paralyti  
other d  
worsen

		neuron transm
	Botulism; exposure to toxin produced by <i>Clostridium botulinum</i>	With a route: descen pattern involve intraoc muscle mouth
	Hypermagnesemia	Rare. I in kidn with he associa cogniti and res suppre
Tick paralysis – likely affects presynaptic neuromuscular transmission	Exposure to <i>Dermacentor</i> ticks; possibly caused by toxin produced by the tick	Usually children search (hairy) the head parts o
Acute myopathy	Critical care myopathy	In the critical
	Rhabdomyolysis	Heavy exposu sustain immob myoto: medica exposu
	Infectious and autoimmune myopathies	Trichir

sarcos|  
acute  
inflamm  
necroti  
myopa

Periodic paralysis	Hypokalemic/hyperkalemic/Thyrotoxic periodic paralysis	Recurr ocular pharyn muscle precipi meals; resolve
--------------------	--	--

---

Electrodiagnostic testing is important in confirming the localization of acute generalized weakness to the PNS. This testing is not easily available in many hospitals, but if obtainable and performed by an experienced electromyographer, the studies often prove invaluable.

Despite common belief, nerve conduction studies are not always helpful early in the course of acute generalized weakness. In the case of Guillain–Barré syndrome, within 1 week of the presentation, definite diagnosis is possible only in 55% of cases on the basis of the nerve conduction studies of multiple nerves [1]. The absence of tibial H-reflexes is a positive finding in 97% of cases, although this may often be seen as a non-specific finding. Ultimately nerve conduction studies are often non-diagnostic until days 5 through 7 of illness or later, but can be quite helpful when available.

Repetitive nerve stimulation testing is important for diagnosis of disorders of neuromuscular transmission. Although requiring considerable technical skill and uncomfortable for the patient, this study is often positive in patients with severe generalized weakness resulting from myasthenia gravis or other myasthenic syndromes.

Unlike nerve conduction studies, needle electrode evaluation can provide very valuable information for detection of a PNS problem as cause for a generalized weakness from early in the course of illness. The most useful tool of identification of lower motor neuron involvement is needle electrode evaluation of weak muscles. The diagnostic interference pattern of neuropathic motor unit

action potential (MUAP) activation with rapid recruitment of a diminished number of motor unit potentials emerges early [2]. If found, this recruitment pattern is suggestive of involvement of the anterior horn cells, nerve roots, or peripheral nerves. Disorders of the CNS or incomplete voluntary effort (pain on effort, psychogenic weakness, sensory ataxia) will reveal an *incomplete activation pattern*. This pattern is characterized by diminished number of MUAPs without increase of their firing rate beyond the basal rate. A conclusion about the PNS origin of weakness can often therefore be made with confidence. Another important early finding on needle electrode evaluation is marked *instability of single MUAP firing*. In the acute setting this can be observed with disorders of neuromuscular transmission. Unfortunately both of these extremely useful findings cannot be elicited in completely paralyzed muscles and require considerable skill from the diagnostician.

## References

1. Gordon PH, Wilbourn AJ. Early electrodiagnostic findings in Guillain–Barré syndrome. *Arch Neurol* 2001; 58:913–917.
2. Levin KH, Lueders HO, Ed. *Comprehensive Clinical Neurophysiology*. Philadelphia, PA: W.B. Saunders, 2000.

# **81 Weakness, hemiparesis**

---

Amit M. Shelat, Shicong Ye, and and Malcolm H. Gottesman

*Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

## **Introduction**

Hemiparesis is defined as weakness on one side of the body. Therefore, the patient can move the impaired side of his/her body, but with reduced muscular strength. Hemiparesis is less severe than hemiplegia. Hemiplegia is defined as a total paralysis of limbs on one side of the body. There can be variable facial involvement depending on the location of the lesion. Regardless, these two terms will be used interchangeably in this chapter as they both relate to the same type of deficit except with a varying intensity of presentation.

Hemiparesis occurs secondary to the interruption of the motor fibers descending from the cortex. The primary motor pathway is also called the corticospinal tract. As all such pathways are named from beginning to end, this pathway starts in the cortex and ends in the spine. Specifically, it starts in the precentral gyrus, the fold of cortex just anterior to the central sulcus. The precentral gyrus has many names: primary motor cortex, Brodmann's area 4, and M1. It provides the bulk of the corticospinal tract, but other cortical areas contribute as well. These include: area 3a, part of primary somatosensory cortex, secondary motor cortex (precentral gyrus, area 6), and primary sensory cortex (postcentral gyrus, area 1, 2, and 3). All areas of cerebral cortex have six varying layers of cells, from the most superficial and cell-free layer I to the deeper layer VI.

The corticospinal tract originates as the axons of pyramidal neurons in layer V of primary motor cortex. Once the axons leave the pyramidal cells, they enter the white matter just below layer VI. Every gyrus in the brain has this core of white matter, which contains all of the axons entering or exiting the gyrus. Deeper into the brain, all of the bands of white matter coalesce to form a large body of axons called the corona radiata. As you get still deeper into the hemisphere, the corona

radiata courses between the deep nuclei of the brain: the caudate and putamen. At this point, all of the axons are called the internal capsule.

The internal capsule is composed of the anterior limb, posterior limb, and the genu. The motor information to the limbs travels through the posterior limb while the motor fibers for the face are in the genu. If one follows the horizontal sections down through the brainstem, at around the level where the midbrain begins, you would see the internal capsule coalesce into a tight bundle to exit the cerebral hemispheres. At this point the axons are called the cerebral peduncles. The peduncles make up the floor of the midbrain, and contain all the descending axons going to the brainstem and spine. Once midbrain gives way to the pons, two things happen to the peduncles. One: many of the axons from cortex form synapses with motor nuclei in the pons forming the corticopontine fibers. Two: the remaining corticospinal axons get a little fragmented in the pons and as such they are no longer visible as tight fiber bundles. They can be seen as several smaller bundles. In the medulla, the fibers come together again as the pyramids. The pyramids were actually named as landmarks on the surface of the brainstem as one can clearly see them as two ridges running down the ventral midline. The pyramids run the entire length of the ventral surface of the medulla.

At the very caudal-most end of the medulla, right about at the point where we begin to name it the cervical spinal cord, the fibers in the pyramids cross. The crossing event is called the “decussation of the pyramids” and one can identify it by the way the midline groove is suddenly way off the midline. After the decussation, the fibers take up residence in the lateral white matter of the spinal cord. By the time the decussation is completed, the corticospinal fibers reside in this new location, now called the lateral corticospinal tract. From this position they dive into the gray matter of the spinal cord at their target levels. Those fibers controlling the arms, for example, exit in the cervical levels of the cord. Once in the ventral horn they synapse either on interneurons (most common) or directly on the alpha-motor neurons. They preferentially innervate the limbs. A small number of fibers do not cross and descend as the anterior corticospinal tract. There is now some research which suggests that these fibers may cross at the spinal cord level.

The first step in determining the cause of the patient's hemiparesis is to determine whether the lesion is secondary to cortical, subcortical, bulbar, or spinal cord involvement. As can be seen in unusual cases of motor neuron disease or polymyelitis, lesions of the peripheral nervous system can also cause patients to develop weakness affecting the body to varying degrees. The

variation in the intensity of the weakness may make the patient appear weaker on one side more than the other, suggesting hemiparesis. In case of uncertainty, the presence of upper motor neuron signs such as hyperreflexia, spasticity, Babinski sign, and Hoffmann reflex may help favour the localization of a lesion that is at the level of the spinal cord or higher. **Table 81.1** is a comprehensive breakdown of the signs that are used to distinguish between an upper motor neuron versus a lower motor neuron lesion.

**Table 81.1 Comparison of the signs of upper motor neuron vs. lower motor neuron lesions.**

Sign	Upper motor neuron	Lower motor neuron
Weakness	Yes	Yes
Atrophy	No*	Yes
Reflexes	Increased	Decreased
Fasciculations	No	Yes
Tone	Increased	Decreased
Extensor response	Present	Absent

\* Only disuse atrophy is seen.

## Evaluation of hemiparesis

In evaluating hemiparesis, it is also important to consider the following possibilities and note them as part of the exam as they can confound the true nature of the patient's symptoms.

- The patient's pain level will have an impact on the patient's effort against resistance in motor testing.
- Lesions of the central nervous system (CNS) causing ataxia or apraxia can be mistaken for hemiparesis.

- Extrapyramidal symptoms seen in patients with movement disorders such as Parkinson's disease can mimic hemiparesis, but in fact are not true hemiparesis.
- Subtle signs of weakness should also be evaluated. These include:
  - Pronator drift.
  - Diminished fine finger movements.
  - Weak pincer grasp.
  - Weak thumb–pinky finger grasp.

A thorough neurologic examination is crucial to fully appreciate the phenomenology of the patient's disease process. Having a set of rules in mind to help make sense of the neurologic exam is ultimately very helpful in localizing the cause of the patient's hemiparesis and in formulating an optimal differential diagnosis. The following is a set of findings that helps in localizing the lesion.

## Cortical lesion

- Unable to name objects (anomia), unable to repeat phrases, unable to write (agraphia), unable to understand spoken language (aphasia), unable to understand written language (alexia), unable to recognize familiar faces (prosopagnosia), unable to recognize a deficit (anosognosia).
- Gaze preference or deviation.
- Homonymous visual field defect.
- Neglect on the side of the hemiparesis.
- Inability to recognize writing on one's skin (agaphesthesia) or recognize objects placed in the hand (astereognosis).
- Hemiparesis is not equally present in all limbs. A cortical convex lesion causes the arm to be weaker than the leg. A paramedian lesion produces weakness in the leg more than the arm. Facial weakness on the same side as the lesion and tongue deviation to the contralateral side are noted. Facial weakness and tongue deviation may not be obvious in some patients.
- Lesion at the central portion of the precentral gyrus causes upper limb monoparesis.
- Lesion at the parasagittal portion of the precentral gyrus causes lower limb monoparesis.
- Parasagittal lesion will cause a weakness in both legs known as paraplegia.
- Memory deficits.

## **Subcortical lesion**

- Hemiparesis is present equally in all the limbs since the fibers begin to converge into a small volume.
- The face may be involved if the lesion affects the genu of the internal capsule.
- Dense sensory loss may be present on the same side as the weakness. If the adjacent thalamus is involved, diminished sensitivity (hemihypesthesia) on the contralateral side may be present. Vibration sensory loss usually indicates subcortical rather than cortical lesion.
- Patients demonstrate evidence of abnormal movements or have increased tone.
- Aphasia is unusual.

## **Brainstem lesion**

- Facial weakness is on the side opposite the limb weakness (crossed hemiplegia).
- Anisocoria, ophthalmoplegia, double vision or blurred vision, nystagmus.
- Facial numbness on side opposite the hemiparesis.
- Deviation of uvula or tongue.
- Taste.
- Dysconjugate eye movements.
- Exaggerated gag reflex.
- Anosmia.

## **Spinal cord lesion**

- Sensory level is present.
- Pain and temperature sensation loss on side opposite the hemiparesis.
- Loss of bowel or bladder control.
- Face is not involved.
- No cranial nerve involvement.
- Epidural pain.

In order to standardize the grading of muscle strength or power, the classic neurologic exam includes a rating scale that rates power on scale of 0 to 5. The

significance of the scores is given [Table 81.2](#).

**Table 81.2 Assessment of muscle strength (power).**

Grade	Clinical significance
0	Flaccid; No evidence of muscle contraction
1	Muscle twitch
2	Side to side movement, movement with gravity eliminated
3	Movement against gravity with no resistance
4*	Movement against gravity with some resistance
5	Normal muscle strength

\* Some examiners will further subgrade into 4+ or 4– to better differentiate the patient's muscle strength.

## Differential diagnosis of hemiparesis

The differential diagnosis of hemiparesis is extremely long and includes many different etiologies. [Tables 81.3–81.7](#) provide an exhaustive review of various differential diagnoses that can lead patients to develop hemiparesis as one of the many symptoms of a disease process. These tables are by no means all-inclusive but highlight salient diagnoses encountered by the clinician.

**Table 81.3 Diagnoses involving the cerebral cortex, subcortical white matter, and posterior limb of internal capsule.**

Etiologic category	Specific etiology	Comment
Traumatic	Epidural hematoma	Usually acute, history of trauma, unconscious

	<b>Subdural</b> hematoma Subarachnoid hemorrhage Contusion	altered consciousness, headache, nausea, vomiting, unstable gait, slurred speech, blurred vision, unilateral hemiparesis/plegia, and seizure
Vascular	Infarction hemorrhage Migraine Aneurysm Arteriovenous malformation Carotid dissection Sickle cell crisis	Acute onset, change in mental status, lethargy, difficulty speaking and swallowing, writing, reading, headache, loss of balance, abnormal sensation, visual disturbance. Lesions of the middle cerebral and anterior cerebral arteries are responsible for most causes of hemiparesis/plegia. Lacunar stroke syndromes such as ataxic hemiparesis, clumsy hand dysarthria, and pure motor stroke affecting the posterior limb of the internal capsule can also lead to hemiparesis
Neoplastic	Primary brain	Subacute or

<u>Tumors</u>	<u>Primary brain tumor</u>	<u>Subacute or chronic onset.</u>
	tumor	
	Metastatic brain tumor	Headache (change in pattern, new onset, typically early in the morning), nausea, vomiting, visual TB change, one-sided loss of sensation and strength, personality change and behavioral change, difficulty with balance and seizure. Types of primary brain tumors include: astrocytoma, oligodendrogloma, ependymoma, meningioma, pituitary adenoma, and primary CNS lymphoma.
		Tumors most likely to metastasize include: lung, skin, renal cell, breast, prostate, colorectal, and lymphoma
Inflammatory	Vasculitis Sarcoidosis	May mimic other diseases such as stroke, viral encephalitis, tumor, tuberculosis, severe migraine

headaches, and multiple sclerosis. Acute, subacute, or chronic symptoms usually are similar to the disease it mimics

Autoimmune/demyelinating    Multiple sclerosis  
Acute (“flare up”), subacute, or chronic. Diversity is the rule.

Cognitive dysfunction, depression, mood instability, sensory changes (sensory loss, numbness, and tingling), muscle weakness, and increase of muscle tone, ataxia, difficulty in speech and swallowing, visual disturbance (blurry vision, nystagmus, and diplopia), bowel and bladder dysfunction

Acute disseminated encephalomyelitis

An autoimmune process that is typically seen after a viral infection by measles but can also be seen after other viruses such as influenza,

enterovirus, herpes, hepatitis A, cytomegalovirus, and coxsackie. It can also be seen after bacterial infections such as group B streptococcus, mycoplasma, *Borrelia*, and leptospirosis

Infectious	Brain abscess Tuberculosis Viral encephalitis Bacterial encephalitis	Fever, increased white blood cell count, altered mental status
Metabolic	Hypoglycemia Hyper-and hyponatremia	Almost always with pre-existing brain injury
Epileptic	Post-ictal state (Todd's paralysis)	Transient, seizure before the paralysis, EEG abnormality
Psychiatric/malingering	Hysterical or functional hemiplegia	Hoover sign (no clear downpressing weakness in paretic leg when asked to raise the normal leg); sensory loss precisely at midline; inconsistency of degree of weakness

Congenital	Intrauterine insult	Persists through life, some symptoms may improve over time
------------	---------------------	--

**Table 81.4 Diagnoses localizing to the midbrain (mesencephalon).**

Vascular	Ventral third nerve syndrome (Weber)	Contralateral hemiplegia and ipsilateral third nerve palsy (ptosis, inability to move the eye down or medially [if fibers from the Edinger-Westphal nucleus are involved], pupillary dilation)
	Dorsal third nerve syndrome (Benedikt's syndrome)	Contralateral hemiparesis, ipsilateral third nerve palsy, cerebellar ataxia (involvement of brachium conjunctivum), right tremor (involving red nucleus)
	Cavernous malformation/arteriovenous malformation	Hemorrhage secondary to this entity in the areas of the cortex, surface, subcortical regions, and brainstem involving motor tracts will lead to hemiparesis/hemiplegia

Neoplastic/paraneoplastic	<p>Neuroepithelial tumors: gliomas/ependymomas Germ cell tumors: teratoma, germinoma Ganglioglioma Meningioma Small cell lung cancer Adenocarcinoma of the lung Breast cancer Primary CNS lymphoma</p>	<p>Typically will cause symptoms such as diplopia or blurred vision, loss of pupillary light response, oculomotor deficit, light–near dissociation, convergence retraining, nystagmus, and hydrocephalus. Primary central nervous system (PCNS) lymphomas are most commonly B-cell, T-cell lymphomas, very rarely occur in brainstem</p>
Infectious/inflammatory	<p>Abscess</p> <p>Progressive multifocal leukoencephalopathy</p>	<p>Brainstem abscess may arise spontaneously, from hematogenous origin or contiguous spread, usually from the</p> <p>Typically seen in immunosuppressed patients who are positive for the JC Cunningham (JC)</p>
Demyelinating	<p>Neurosarcoidosis</p>	<p>Oculomotor deficit, light–near dissociation, convergence–retinoblastoma, nystagmus</p>
	<p>Neuromyelitis optica (Devic's disease)</p>	<p>Typical patient has acute and severe spastic paraparesis</p>

quadripareisis w/  
sensory signs w/  
are accompanied  
urinary incontinence.  
Optic neuritis may  
manifest as visual  
impairment with  
decreased visual

#### Multiple sclerosis

Typical symptoms  
include binocular  
diplopia, blurred  
vision, pupillary  
abnormalities. P<sub>1</sub>  
of oligoclonal bands  
in spinal fluid support  
this diagnosis.

#### Acute disseminated encephalomyelitis

Bilateral and  
symmetrical lesions  
with poorly defined  
borders that are more  
commonly seen in  
midbrain than in  
other areas in the  
brainstem.

#### Balo's concentric sclerosis

Demyelinating process  
that is more common  
in Chinese and French  
populations.

#### Marburg variant of multiple sclerosis

Also known as  
tumefactive multiple  
sclerosis or  
pseudotumoral MS.  
The lesions are atypical  
and look similar to  
gliomas on T2  
weighted MRI.

		<b>Weighted MRI</b> imaging. More commonly seen in women who are typically in the middle of their third decade of life
	Progressive multifocal leukoencephalopathy	A process most commonly seen in patients who are immunosuppressed due to reactivation of JC virus
Metabolic	Extrapontine myelinolysis	Typically secondary to rapid correction of metabolic disturbance such as hyponatremia. It can also be seen in patients with malnutrition, severe hepatic disease, alcoholism, severe burns, anorexia, hyperemesis gravidarum, and liver transplant. It can also be seen in other abnormalities such as oculomotor deficits, pupillary response deficits
Genetic	Von Hippel–Lindau disease (VHL)	Autosomal dominant genetic disorder secondary to mutation in tumor suppressor gene on chromosome 3. VHL leads to formation of brain tumors

		tumors
	Leigh's disease	A rare disease primarily that is caused by mitochondrial cytopathy secondary to <i>SURF1</i> gene mutation. It is typically seen in infants between 3 months and 2 years but also rarely in teenagers and adults. Leads to symptoms such as dorsal midbrain syndrome such as convergence-retraction nystagmus.
Traumatic	Kernohan–Woltman syndrome (Kernohan's notch)	False localizing sign ipsilateral hemiparesis in which the free edge of the tentorium compresses the contralateral crus cerebri in the midline due to a mass lesion causing herniation of the temporal lobe through the tentorial incisura.

**Table 81.5 Diagnoses localizing to the pons.**

Vascular:	Ventral pontine syndrome (Millard–Gubler)	Paralysis of the abducens nerve leads to diplopia due to disruption of
-----------	--	--

disruption of facial nerve leads to flaccid paralysis of the muscles of facial expression and loss of corneal reflex; and disruption of corticospinal tract leads to contralateral hemiplegia

Ventral medial pontine syndrome (Raymond)

Ipsilateral lateral rectus paresis (abducens nerve involvement) and contralateral hemiplegia, sparing the face (pyramidal tract involvement)

Pure motor hemiparesis

A lacunar syndrome leading to hemiparesis secondary to basis pontis involvement of corticospinal fibers

Clumsy hand dysarthria syndrome

A lacunar syndrome. The main symptoms are dysarthria and weakness of the hand, which

often are most prominent when the patient is writing

### Ataxic hemiparesis

A lucunar syndrome. It displays a combination of cerebellar and motor symptoms, including weakness and clumsiness, on the ipsilateral side of the body. It usually affects the leg more than it does the arm; hence, it is known also as homolateral ataxia and crural paresis. The onset of symptoms is often over hours or days

### Locked-in syndrome

Quadriplegia with maintained consciousness and ability to move facial muscles. Damage is isolated to the ventral pons

### Foville syndrome

Ipsilateral gaze palsy and facial nerve palsy with contralateral hemiparesis, hemisensory loss, and intranuclear ophthalmoplegia  
Lesion secondary to blockage of perforating branches of the basilar artery in the pons

Lesion of the cerebral peduncles that involves the red nucleus and causes speech disorders, paralysis of lateral conjugate gaze, ipsilateral 6th nerve palsy, and anaesthesia of the face and the remainder of the body, with contralateral hemiplegia

### Paramedian pontine syndrome

Contralateral spastic hemiparesis,

		contralateral loss of vibration and proprioception and ipsilateral lateral rectus muscle paralysis
Lateral pontine syndrome (Marie–Foix)	Ipsilateral cerebellar ataxia due to involvement of the cerebellar tracts, contralateral hemiparesis due to corticospinal tract involvement, and variable contralateral hemihypesthesia for pain and temperature due to corticospinal tract involvement	
Cavernous malformation/arteriovenous malformation	Well defined, grossly visible lesions that can lead to mass effect and hemorrhage. Involvement of the ventral pontine region can cause weakness	
Neoplastic/paraneoplastic	Nonneopithelial tumors	Mass lesion

	<b>Primary/secondary tumours.</b> gliomas/ependymomas Medulloblastoma (rare) Hemangioblastoma Breast cancer Lung cancer	<b>mass lesion</b> affecting the ventral aspect of the pons will lead to hemiparesis. As these lesions will lead to swelling they may affect nearby structures in the pons. Patient may present with abducens palsy, loss of vibration and proprioception. Patients may also have intranuclear ophthalmoplegia due to involvement of the medial longitudinal fasciculus
Infectious/inflammatory	Abscess	Infectious process leading to the development of an abscess can lead to symptoms similar to locked-in syndrome
	Progressive multifocal leukoencephalopathy	Rare cases of primary pontine

	(PML)	involvement in PML can present with hemiparesis, or abducens nerve palsy
Demyelinating	Neurosarcoidosis	Can mimic many different types of conditions; can have pontine involvement leading to hemiparesis and abducens nerve palsy
	Neuromyelitis optica	Also known as Devic's disease. This is a demyelinating process which can affect the spinal cord as well as the brainstem. Involvement of the ventral pons can lead to hemiparesis
	Multiple sclerosis	Demyelinating lesions of the pons can lead to hemiparesis, as well as involvement of the abducens and facial nerves

Metabolic	Central pontine myelinolysis	Typically secondary to rapid correction of a metabolic disturbance such as hyponatremia. It can also be seen in patients with malnutrition, severe hepatic disease, alcoholism, severe burns, anorexia, AIDS, hyperemesis gravidarum, and post liver transplant.
Genetic	Von Hippel–Lindau	Autosomal dominant genetic disorder secondary to mutation on tumor suppressor gene on chromosome 3. VHL leads to formation of brainstem tumor.
	Leigh's disease	A rare disease process that is caused by mitochondrial cytopathy secondary to

*SURF1* gene mutations typically seen in infants between 3 months and 2 years, but also rarely in teenagers and adults

---

**Table 81.6 Diagnoses localizing to the medulla oblongata.**

---

Vascular	Medial medullary syndrome	Vertebral artery and/or anterior spinal artery occlusion and/or dissection
	Opalski syndrome	Lesion of the corticospinal tract after pyramidal decussation
	Cavernous malformation/arteriovenous malformation	Well-defined, grossly visible lesions that can lead to mass effect and hemorrhage. Involvement of the pyramidal decussation can cause weakness. Patients are in imminent danger of death due to the risk of herniation

Neoplastic/paraneoplastic	Neuroepithelial tumors: gliomas/ependymomas Medulloblastoma Schwannomas Hemangioblastoma Small cell lung cancer Adenocarcinoma of the lung (rare) Prostate cancer Neuroblastoma Thymoma	Mass lesions of the medulla will typically lead to hemiparesis secondary to involvement of the pyramidal decussations. However, patients may also have tongue deviation, weakness of the sternocleidomastoid and trapezius muscles. Additionally, patients may have involvement of the respiratory drive with resultant periods of apnea. Patient may be in imminent danger of herniation.
Infectious/inflammatory	Abscess  Progressive multifocal leukoencephalopathy	Rapidly progressive multiple cranial nerve palsies and decreased level of consciousness. Patient is in imminent danger of death from herniation.
		Rare cases of PN involving the medulla can lead to hemiparesis as well.

as difficulty with swallowing, tongue movements, and weakness of the trapezius and sternocleidomastoid muscles; some lesions may only result in ataxia and dysmetria secondary to involvement of the inferior cerebellar peduncles.

#### Neurosarcoidosis Tuberculosis

In addition to hemiparesis, neurosarcoidosis and tuberculosis may present with progressive numbness and decreased sensation disturbance in bilateral lower extremities.

#### Demyelinating

#### Neuromyelitis optica

Typical patient has an acute and severe spastic paraparesis or quadriplegia with sensory signs which are accompanied by urinary incontinence.

#### Multiple sclerosis

Demyelinating lesions involving the medulla can lead to hemiparesis,

difficulty with swallowing, tongue movement problems, and weakness in the trapezius and sternocleidomastoid muscles. Patients can also display ataxia and dysmetria.

Metabolic

Extrapontine myelinolysis

Extrapontine myelinolysis is rare and commonly seen in patients with rapid correction of serum sodium. It can also be seen in patients with malnutrition, severe hepatic disease, alcoholism, severe burns, anorexia, AIDS, hyperemesis gravidarum, and post liver transplant.

Genetic

Leigh's disease

A rare disease process that is caused by mitochondrial cytopathy secondary to *SURF1* gene mutations typically seen in infants between 3 months and 2 years, but rarely in teenagers and adults.

	Von Hippel–Lindau	Autosomal dominant genetic disorder secondary to mutation on tumor suppressor gene on chromosome 3. VHL leads to formation of brainstem tumor
Traumatic	Syringobulbia	Syrinx formation in the medulla is seen in patients with Arnold–Chiari malformation. Traumatic cervical spine injury can lead to syrinx formation affecting the brainstem. Patients may have periods of apnea, have tongue movement abnormalities, weakness of the trapezius and sternocleidomastoid. Patients may also have loss of vibration, proprioception, secondary involvement of the medial lemniscus and ataxia secondary to damage to the

damage to the  
restiform body  
(inferior cerebellar  
peduncle)

Atlanto-occipital  
dislocation

Patients with  
connective tissue  
disorders such as  
Ehlers–Danlos  
syndrome, Marfan  
syndrome should  
be suspected of this  
condition. Further,  
patients with  
Down's syndrome  
are also susceptible  
to this condition

Abnormal development

Arnold–Chiari  
malformation

Herniation of the  
cerebellar tonsils  
can lead to  
compression of the  
cervical medulla  
junction causing  
hemiparesis.  
Patients can also  
complain of  
difficulty with  
swallowing and  
periods of apnea

---

## Case vignette 1

A 63-year-old male with past medical history of hypertension, hyperlipidemia, and atherosclerosis presented to the emergency room after he suddenly fell to the floor and was unable to get up. He found that his right arm and leg were paralyzed and he found it excessively difficult to speak or swallow.

Neurologic examination showed that he had paralysis of his right side with increased, exaggerated deep tendon reflexes. Motor examination of the face was normal, however upon protrusion his tongue pointed toward his left side; the left side of his tongue was atrophic.

The sensory exam indicated that pain and temperature were bilaterally normal from the body and face but there was loss of joint position sense (proprioception) from the right lower extremity. Examination of other cranial nerves was normal.

## **Discussion**

Spastic paralysis of the right arm and leg indicates injury to the corticospinal tract somewhere along its length. The additional tongue signs place the corticospinal lesion above the cord, in the medulla, on the left side. The tongue usually points to the side of a lesion of the nucleus or fibers of CN XII. Atrophy of its muscles confirms a lower motor neuron lesion of the fibers of CN XII on the left side.

Loss of proprioception from the right lower extremity is consistent with injury to the ventral-most fibers of the medial lemniscus on the left side. Absence of other sensory findings limits the area of involvement to the distribution of the penetrating branches of the vertebral or anterior spinal artery, which include the pyramids, exiting fibers of CN XII, and the medial lemniscus. The diagnosis for this patient is medial medullary syndrome.

## **Case vignette 2**

A 68-year-old female had coronary bypass surgery 2 weeks before she suddenly started to experience diplopia. She also felt a weakness in her left arm and leg. She was noted to have a ptosis of the right eye lid.

At the hospital she was alert, awake, and fully oriented. Her general physical condition was good. Her speech was articulate and the content was good. Her visual fields were normal but when asked to open her eyes the right eyelid did not open fully. When asked to look straight ahead the right eye was deviated to the right. On attempted lateral gaze to the left only the left eye responded. When asked to look at the tip of her nose, only the left eye was adducted and only the left eye showed pupillary constriction. Furthermore, only the left eye was reactive to light.

Upon smiling there was a minor weakness on the left. Her palate elevated symmetrically, gag reflex was normal, and corneal and jaw jerk responses were normal. The tongue protruded midline.

Motor strength was normal in the extremities on the right but was reduced on the left, especially in the arm where there was an increased biceps reflex and resistance to passive stretch.

Sensory examination was normal to all modalities for the face and the extremities.

**Table 81.7** *Diagnoses localizing to the spinal cord.*

Vascular	Arteriovenous malformation (AVM)	Two genera Spinal dura arterioveno (AVF) and intradural A dural AVF is commonly s patients old years and sp intradural A commonly s patients you 30 years. Sp AVF are typ painful and progressive over months. Dural AVFs bowel bladd and lower e weakness. H Alajouanine is an extre spinal dural which patie with a rapid .
----------	----------------------------------	---

progressive  
due to veno  
thrombosis  
venous stas.  
intradural A  
typically pr  
intraparencl  
subarachnoi  
hemorrhage  
will have ac  
neurologic c  
and mass ef

Infarct of the posterior spinal  
artery

Patients wil  
with compla  
of vibration  
propriocept  
the level of  
total anesthe  
level of the

Neoplastic

Intradural-extramedullary  
tumors

Meningiomas

Most comm  
thoracic spi  
complete re  
removal

Neurofibromas/schwannomas

Typically as  
with NF-1.  
commonly ]  
pain that is  
night or mo  
resolves du

Intramedullary tumors

Ependymoma

Peak age of  
presentatio

and 40 year  
have lower  
spasticity, l  
and tempera  
sensation, r  
vibration ar  
propriocept  
ataxia

#### Astrocytoma

Average age  
is 35 years.  
spinal cord  
astrocytoma  
pilocytic an  
infiltrative.  
astrocytoma  
typically lo  
have a bette

#### Lipoma

Typically as  
neurologic c  
leading to h  
and bowel/t  
deficits

#### Hemangioma

Seen in pati  
between 30  
benign tumo  
in thoracic &  
spine

#### Extradural tumors

Metastatic disease from bone,  
prostate, lung, breast,  
pancreas, uterus, brain

Can lead to  
at any site a  
neuro-axis c  
hemiparesis  
vibration/pr  
and pain/ter

		sensation
	Chordoma	Primarily seen at the sacral level, second most common site being the clivus
	Lymphoma	Patient presents with bone pain that is relieved by patients also with cord compression, typically a low-grade non-Hodgkin's lymphoma
	Sarcoma	Erosion of the bone can lead to spinal cord compression
	Plasmacytoma/multiple myeloma	An eosinophilic granulomatous process present in vertebral bodies
	Benign tumors	Osteoid osteoma, osteochondroma, osteoblastoma, chondroblastoma, giant cell tumor, vertebral hemangioma, and aneurysmal bone cysts
Traumatic	Brown–Sequard syndrome	Ipsilateral to lesion: Paralysis, Loss of vibration sense, position sense, Hyperreflexia, Babinski sign

Dandy-Walker  
contralateral  
Loss of pain  
temperature

### Syringomyelia

Traumatic spinal cord injury and Chiari malformation can both lead to formation of a syrinx. Early signs include loss of pain and temperature secondary to interruption of fibers that ascend in the anterior corticospinal tract. As the syrinx grows, the patient can experience vibration and proprioception loss and develop hemiparesis.

### Inflammatory/demyelinating diseases

### Mutiple sclerosis

Lesions may occur in any part of the spinal cord leading to a variety of symptoms such as pain, numbness, tingling, bowel/bladder dysfunction. Magnetic resonance imaging (MRI) with contrast will identify active lesions which enhance with gadolinium.

### Transverse myelitis

Secondary to infection

demyelination occurring after infection or trauma. Onset is typically sudden and progressive over hours to days. Lesions can affect both motor, sensory, and autonomic systems, including sphincter dysfunction.

#### Neuromyelitis optica (Devic's disease)

Typical presentation: acute and subacute onset of paraparesis, quadriplegia, sensory deficits, accompanied by headache, fever, and bladder control problems.

Infectious

#### Epidural abscess

Classical triad: back pain, fever, and neurologic deficits. Patients can present with deficits that include limb weakness, sensory changes, and bowel/bladder dysfunction. Neurological recovery less than 2 weeks suggests spinal cord involvement.

#### Tuberculosis/sarcoidosis

Back pain, fever, night sweats, and weight loss. Spinal mass lesions causing spinal cord compression. Spinal tuberculosis is known as Pott's disease. Involvement of the spinal cord in neu-

rare but can  
hemiparesis  
abnormaliti  
bowel/blad

### Neurosyphilis

Meningomy  
rise to pictu  
transverse r  
is the comm  
of spinal ne  
There are u  
symptoms c  
back spread  
and back. N  
weakness o  
limbs devel  
period rang  
few days to  
weeks. Initi  
flaccid para  
subsequentl  
paraplegia c  
with bladde  
dysfunction  
sensory loss

### Poliomyelitis

About 1–5 i  
cases of pol  
to paralytic  
which the n  
become wea  
and poorly c  
and, finally,  
paralyzed; t  
condition is  
acute flacci

### Aspergillosis

Patients wh  
spinal asper

		have hemip loss of vibr propriocept addition to l pain/temper sensation
Idiopathic	Amyotrophic lateral sclerosis	Affects both lower motor and sensory
	Primary lateral sclerosis	Affects only motor neurons
	Primary muscular atrophy	Affects only motor neurons (fasciculations, weakness), emotional labi spasticity, n reflexes

## Discussion

The patient's complaint of weakness of the left arm and leg and the confirmation of spastic paresis, most marked in the upper extremity, indicates involvement of the corticospinal tract, either at high cervical levels of the cord on the left or somewhere above the cord on the right. The finding of cranial nerve signs involving the right medial rectus and loss of pupillary light response places the lesion above the cord and into the brainstem. More specifically, the right side of the midbrain, where the third cranial nerve nuclei and fascicles are located.

The major cranial nerve sign involves the fibers of the right oculomotor nerve. The cause of the patient's complaint of diplopia is explained by the neurologic exam wherein the right medial rectus muscle is paralyzed upon attempted lateral gaze to the left and in convergence. Vision in optic nerves was normal but there was failure of the right pupil to constrict to light or upon convergence. This indicates injury to the parasympathetic component of the third nerve in addition to fibers supplying the extrinsic muscles of the eye and the eyelid (levator palpebrae). This places the lesion in the midbrain. The sensory examination was

normal indicating that the tegmentum of the midbrain was spared. Except for a minor facial weakness cranial nerve motor functions were unaltered.

These symptoms place the lesion in the crus cerebri, probably more medially since the arm was more severely affected than the leg, where oculomotor fibers exit into the interpeduncular fossa. The sudden onset after coronary bypass surgery suggests a vascular infarct. The vessels supplying this area are the short penetrating paramedian branches of the basilar and posterior cerebral arteries. The diagnosis for this patient is Weber's syndrome.

## **Case vignette 3**

A 57-year-old male suffered a sudden weakness of his left arm and leg which caused him to fall while shaving. He was helped to his feet but his left arm and leg felt stiff. In addition, he complained of seeing "double."

The neurologist found that the patient was alert with normal mental status. There was no evidence of increased intracranial pressure though his blood pressure was 210/110. There was a spastic paresis with a positive Babinski sign in the left extremities and loss of vibratory and positional sense on the left. The patient walked with an ataxic gait. Pain and temperature sensations were normal. There was diplopia when the patient looked toward the right side. At rest the right eye deviated toward the nose (internal strabismus or squint) while the left eye looked straight ahead. There was a paralysis of conjugate gaze toward the right (i.e. the right eye did not move laterally toward the right though the left eye did). Ocular convergence was normal.

## **Discussion**

The sudden onset suggests a lesion of vascular origin; the high blood pressure suggests the etiology. Though spastic paresis indicates involvement of the pyramidal tracts from the cerebrum on down, in this case, because of the sixth nerve injury at the level of the pons is indicated. In the pons the pyramidal tracts are in the basis pontis, and in this case the side opposite the weakness (i.e. the right side).

Ataxic gait, vibratory and positional deficits on the left suggest injury to the medial lemniscus, which lies near the midline in the ventral tegmentum, on the right. The ataxia could also have a cerebellar component due to injury of the basis pontis and the pontine nuclei. Normal pain and temperature perception

indicate that the lesion was more limited to the midline rather than lateral where the spinothalamic and fifth nerve components lie.

Gaze paralysis to the right and internal strabismus of the right eye indicate weakness of the right lateral rectus and injury to the fibers of the right abducens nerve. If the sixth nucleus had been involved the medial rectus of the left eye would have shown signs as well, due to involvement of the nearby pontine paramedian reticular formation (PPRF). Since convergence was preserved and only the lateral rectus of the right eye was paralyzed this was a lesion involving only the fibers of the sixth nerve.

This constellation of symptoms is consistent with the midline distribution of the paramedian branches of the basilar artery and occlusion of its branches in the caudal pons. The diagnosis for this patient is ventral medial pontine syndrome.

## Case vignette 4

A young female complained of pain in her left breast and progressive weakness of her left lower limb for a period of many months before finally visiting her physician.

The neurologic evaluation revealed weakness in the left lower limb. This was associated with spasticity (increased tone) and hyperreflexia (increased deep tendon reflexes) at the knee and ankle, which also demonstrated clonus. On the left side there was loss of two-point touch, vibratory sense, and proprioception at levels below the hip. The right side showed a loss of pain and temperature sensation below dermatome T7.

The patient was determined to have an extramedullary tumor expanding from the dorsal roots at spinal cord levels T5, 6.

## Discussion

Ipsilateral paralysis below the lesion. Paralysis is the “upper motor neuron” or spastic type; there is spasticity, slow (disuse) muscle atrophy, hypertonia, ankle clonus, and a positive Babinski sign. Superficial reflexes, *e.g.* the abdominal and cremasteric, are lost. Spastic paralysis is attributed to interruption of the lateral corticospinal tract and the accompanying lateral reticulospinal tract. Loss of these upper motor neurons deprives the anterior horn cells, *i.e.* lower motor neurons, of the impulses which generate contraction of skeletal muscle, hence, weakness (paresis) or paralysis. Hypertonia and hyperreflexia appear to result

from loss of the inhibitory effects of these two descending motor pathways on the stretch reflexes, leaving them hyperexcitable to segmental muscle afferents.

It may be possible to also demonstrate a “lower motor neuron syndrome” or flaccid paralysis ipsilaterally at the level of the lesion. If the anterior horn cells supplying the skeletal muscles are injured at the level of the lesion then these muscles are denervated. This paralysis is of the flaccid type; muscles undergo rapid atrophy due to loss of the trophic influence of the nerves as well as disuse. Tone and tendon reflexes are diminished since they are reflex responses and the injured lower motor neurons are the “final common pathway” to the muscle in the stretch reflex; hence, there is no reflex.

Loss of conscious proprioception, two-point discrimination, and vibratory sense ipsilaterally is due to interruption of the posterior white columns (fasciculus gracilis/cuneatus). This is frequently accompanied by a Romberg sign. A normal individual, standing erect with heels together and eyes closed, sways only slightly. Stable posture is achieved by (1) a sense of position from the vestibular system, (2) awareness of the position and status of muscles and joints by conscious proprioception, and (3) visual input regarding their position. Closing the eyes has only slight effect on the normal individual's stance since the vestibular and conscious proprioception systems are sufficient. In a patient with an impaired posterior column, conscious proprioception is diminished; when the eyes are closed loss of both systems renders the patient unstable and they are likely to sway or fall to the side.

*Pain and temperature sensation* is lost below the lesion, on the opposite side beginning about one dermatomal segment below the level of the lesion. These sensations are carried by the lateral spinothalamic tract whose fibers originated on the side opposite the lesion but which crossed in the anterior white commissure. Dorsal root afferents carrying pain and temperature synapse in the dorsal gray; the second order neuron crosses in the anterior white commissure along an ascending path for a distance of about one spinal segment. Because of the oblique ascent of the crossing fibers in the anterior white commissure, injury of the spinothalamic tract is not likely to be carrying sensation from that level.

A careful sensory evaluation may reveal that at the dermatomal level of the lesion there is a bilateral loss of pain and temperature sensation. Since the second order neurons from both sides cross in the midline below the central canal, a hemisection of the cord may interrupt the crossing fibers from both sides and produce this limited bilateral deficit.

The pain in the left breast was the result of the pressure of the tumor on the dorsal root.

The diagnosis of this patient is Brown–Séquard syndrome.

## Case vignette 5

A 50-year-old female awoke but couldn't get out of bed due to weakness of the right arm and leg. Her husband spoke to her and she understood him but she was unable to speak in response.

The patient was alert and oriented and followed commands well. She had bruits in both carotid arteries but otherwise the cardiovascular system was normal. Past medical history was unrelated to the present condition. There was no papilledema. The doctor found that the patient had a flattened nasolabial fold on the right and was unable to smile or show her teeth on the right; the brows could be wrinkled symmetrically upon command. When she was asked to protrude her tongue it deviated to the right. Other cranial nerve functions were unaffected. The upper right extremity was very weak, with spasticity and hyperreflexia. The lower limb was less weak with mild hypertonia, hyperreflexia, and a positive Babinski sign. Cerebellar function was unaffected. The sensory exam was normal.

Her speech was very halting. Its content was appropriate but she had difficulty finding the right words and her sentences were short and incomplete. When asked direct questions she would answer appropriately but only with a yes or no response or she would correctly point to an object. Her speech was also slurred, making words difficult to understand.

## Discussion

Spastic paralysis (on the right side) was more severe in the arms than the legs. This is suggestive of a left upper motor neuron lesion (corticospinals) at cortical levels rather than in the internal capsule where the fibers of both limbs are compact and so the weakness of upper and lower extremities is more likely to be of equal severity. Slurred, poorly articulated speech (dysarthria), and a tongue which deviated to the right upon protrusion suggest that corticobulbar on the left are also involved. Right-sided paralysis of the lower face indicates corticobulbar involvement on the left.

In addition to slurring of speech, which has to do with the mechanics of sound production, she had trouble with language itself (aphasia), *i.e.* there were problems in finding the right words to define objects and forming words into sentences. There was no indication of problems with comprehension of language but rather its expression, *i.e.* motor aphasia. Language functions are usually represented in the left hemisphere.

In addition to paresis and paralysis of the right limbs, due to the left-sided lesion, the patient had an apraxia of the left limbs. Apraxia is the inability to carry out a command for a motor act even though the patient understands the command and has no weakness or incoordination. This patient was asked to scratch her left knee with her left hand, which had no signs of weakness; she made a vague gesture toward her knee, demonstrating comprehension, but didn't complete the task. Later she used her left hand to adjust the hem on her skirt to cover her left knee. This apraxia is explained by the lesion to the motor cortices including Broca's motor speech area. The command to scratch is first comprehended in the Wernicke's speech area in the left temporal lobe. Connections exist (arcuate fasciculus) from Wernicke's area to Broca's area and the left motor cortex. The left arm responds to the command when the right motor cortex is activated by crossing fibers coming from the left motor cortex via the corpus callosum. In this case injury to the left motor cortex injures those crossing fibers and so the command is poorly executed.

The suddenness of the onset of the symptoms suggests that a vascular event has occurred rather than a slowly growing mass. The symptoms suggest that the most severely affected area is the lateral surface of the frontal lobe, *i.e.* the precentral gyrus (areas 4, 6) containing the motor cortex serving the head, arms (and to a lesser extent the legs) and in addition, Broca's motor speech area (area 44, 45). These areas are served by branches of the middle cerebral artery. An angiogram confirmed an occlusion in anterior branches of the middle cerebral artery .

## **Case vignette 6**

A 27-year-old male noticed that when playing volleyball his legs were becoming uncharacteristically tired and stiff feeling. At other activities he was less noticeably affected but over a period of weeks the weakness increased even with less strenuous tasks. Except for headaches, which awakened him from sleep, he had no other complaints.

His general physical condition was very good and he had no significant family history or past medical conditions of note. He was alert and well oriented with respect to time and place. He comprehended and spoke well. The cranial nerve exam was normal except for papilledema. His sensory exam was normal for pain, temperature, touch, proprioception, and vibration. His motor exam showed normal strength, tone, reflexes, etc. for both upper extremities but both lower extremities were weak, showed spasticity, and there were bilateral Babinski signs.

## Discussion

Weakness and spasticity of both lower extremities without involvement of the upper limbs indicate an upper motor neuron syndrome of the lower limbs suggesting a lesion in a location where the representation of both legs are close together but separated from the arms. Such locations would be the lateral funiculus of the spinal cord below T1 or the midline of the hemispheres. The spinal cord lesion would likely include the posterior white columns producing loss of conscious proprioception, which in this case was unaffected. The hemispheres are a more likely site since the leg area is far from the arm and motor and sensory functions are separated by the central sulcus.

Papilledema and headache suggested increased intracranial pressure. The gradual onset of symptoms plus radiographic evidence ruled out aneurysms, infarction, and hemorrhage but a midline mass growing on the falx cerebri was detected. A meningioma was diagnosed and removed.

## Further reading list

Brazis PW, Masdeau JC, Biller J. General principles of neurologic localization. In *Localization in Clinical Neurology*, 6th edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2011.

Gilman S, Newman SW. Motor pathways. In *Manter and Gatz's Essentials of Clinical Neuroanatomy and Neurophysiology*, 10th edn. Philadelphia, PA: F.A. Davis Publishers, 2003.

Gilman S, Newman SW. Lesions of the peripheral nerves, spinal nerve roots and spinal cord. In *Manter and Gatz's Essentials of Clinical Neuroanatomy and Neurophysiology*, 10th edn. Philadelphia, PA: F.A. Davis Publishers, 2003.

Gilman S, Newman SW. Lesions of the brainstem. In *Manter and Gatz's Essentials of Clinical Neuroanatomy and Neurophysiology*, 10th edn. Philadelphia, PA: F.A. Davis Publishers, 2003.

Querol-Pasqual MR. Clinical approach to brainstem lesions. *Semin Ultrasound CT MRI* 2010;31:220–9.

## **82 Weakness in the intensive care unit**

---

John J. Halperin *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

The differential diagnosis of weakness in the critically ill patient is vast. For the purposes of this chapter, central nervous system (CNS) causes such as stroke and trauma will be excluded, as will the wide array of metabolic abnormalities that cause weakness among their other manifestations. Acute myopathies will be included, as they often must be considered in the initial differential diagnosis. It is presumed that patients under consideration will have been screened with basic blood work including electrolytes, cardiac, hepatic, and renal studies. This section will deal primarily with acute neuromuscular disorders, a group best divided into those that result in admission to the intensive care unit (ICU), and those that develop after the patient is already there. Several elements are essential in the management of all – early airway protection at the earliest sign of failure of protective reflexes or of mechanical respiratory function, prophylaxis against venous thromboembolic disease, frequent repositioning to prevent skin breakdown as well as peripheral nerve compression, and splinting and physical therapy to prevent contracturing.

### **Case vignette**

This vignette is modified from Ginsberg *et al.* (2007), courtesy of the Centers for Disease Control (CDC). On June 29, two children had onset of illness that progressed to include difficulty chewing and swallowing, widely dilated pupils, dry mouth, and then symmetric, descending paralysis. The two were initially evaluated at two different hospitals, where multiple diagnoses were considered. After one child was transferred to the same hospital as the sibling, botulism was identified as the etiology of the shared symptoms. The two children required mechanical ventilation; botulinum antitoxin was requested on the evening of

July 7, released by CDC, and administered the next morning. Patient stool and serum specimens, collected 9 days after symptom onset, were negative for botulinum toxin by mouse bioassay. Initial stool cultures did not yield *Clostridium botulinum*.

The children had shared several meals in the days before symptoms began. They had eaten Hot Dog Chili Sauce for lunch on June 28. The opened can from this meal had been discarded and could not be located. However, one unopened can of this product, produced on May 7 at the same canning facility and purchased at the same time as the discarded can, was found in the children's home. The laboratory tested an aliquot from this can using an enzyme-linked immunosorbent assay (ELISA) for botulinum toxin and did not detect toxin. One child remains hospitalized and is on mechanical ventilation. The second child has been removed from mechanical ventilation and begun rehabilitation.

**Table 82.1 Etiologies of weakness in the intensive care unit (ICU) setting.**

Category	Subdivision	Specific entity	Possible mechanism
<b>Presenting disorder</b>			
Toxic. Medicines/drugs, toxic substances, withdrawal states	Neuromuscular junction	Botulism	Botulinum toxin blocks release of ACh at NMJ contaminated food peripherally cholinesterase causing muscle weakness decreased tone gastrointestinal motility dilation starts sweating extraocular muscle palsies tendon reflexes depressed

- sensor  
Diagn  
*Clostr*  
a wou  
botuli  
stool,  
Nerve  
demor  
amplit  
stimul  
an inc  
Treatn  
and su

### Dinoflagellate-derived neurotoxins

Dinofl wide r includ ciguat Dinofl fish; t progre concei becom diseas ingest (a) Bi contain axonal blocke in Nev the we Calif referre shellfi (b) Tr contain which channel occurs

fish are  
Paralytic  
produced  
paresthesia  
motor  
Ciguatera  
hyperesthesia  
distal sensory  
paralysis  
paresthesia  
after eating  
with a fish  
Diagnosis  
epidemic  
Treatment

### Organophosphates

Organophosphates used as  
chemical weapons irreversibly  
acetylate cholinesterase  
cause muscarinic  
syndrome  
muscular spasm  
(hyperactivity)  
GI/GU changes  
with onset of  
change in  
nicotinic receptors  
muscle weakness  
typical  
(respiratory  
weakness)  
patients  
axonal  
Neurodegenerative  
demyelinating  
hyperexcitability  
firing

and de  
repetit  
Treatn  
of resi  
gastric  
early i  
which  
from t  
molec  
with a  
essent

### Tick bite paralysis

Tick b  
media  
thoug  
at the  
produ  
*Derm*  
dog tic  
prolon  
Attack  
comm  
Paraly  
childr  
and ex  
pupils  
descer  
respira  
Progre  
hours)  
within  
This o  
in the  
Canad  
findin  
neurop  
shows  
potent

		Pseudocholinesterase deficiency	Fallen enzym pseudo have p neuroi after e succin by neu treatm
Immune/post infectious	Nerve	Guillain–Barré syndrome	Acute demye polyne media demye periph axonal anti-g occurs ascenc weakn to a fe cases t viral o <i>Camp</i> infecti preced Early Motor predom autonc chang sphinc infreq includ ophtha with le progre Diagn condit

conduc  
demon

demyel  
slightl  
demon  
albumin  
dissoci  
protein  
Treatm  
plasma

Infective/post-infective (meningitis, encephalitis, sinus, osteomyelitis, abscess); viral, bacterial, parasitic/protozoal, mycobacterial, fungal, spirochete, prion, post-infective	Nerve	Polio	Poliovirus ubiquitous well over eradicated worldwide efforts smallpox humans typical non-specific (minor) some, with epiphysi alterations dysautonomia dysfunctional invades leading to and flaccid Nervous peaks and Treatment supportive
		West Nile virus	WNV, transneuronal asymptomatic, most, .

illness  
sympt  
and an  
a subs  
develc  
motor  
togeth  
encepl  
menta  
occasi  
with o  
encepl  
to pea  
autum  
preval  
Diagn  
demon  
inflam  
IgM ir  
approi  
Treatn  
althou  
at usin  
high ti  
antibo

Immune

Spinal cord

Myelitis

Altho  
is a ce  
disord  
can so  
with a  
weakn  
of mye  
sensor  
functio  
functio  
freque  
diseas  
neuroi  
.

in spir  
extren  
typica  
planta  
severe  
reflexe  
hypoa  
the pic  
Howe  
patien  
rapid t  
neuroi  
neede  
can us  
inflam  
compr  
proces

Vascular

Spinal cord

Ischemic  
myelopathy

Spinal  
but is  
associ  
flow in  
artery.  
typica  
over h  
with c  
anterio  
spinal  
and in  
sensat  
posteri  
limited  
limited  
at the  
just a ]  
paraly  
Spinal  
arterio  
cause  
cord is

			coronary sympathetic
			months or exercise Diagnosis made by occasional angiogram or angiography needed
Metabolic	Muscle	Rhabdomyolysis	Rhabdomyolysis painful muscle can occur in participants in drinking alcohol underlying myopathy palmitoyl deficiencies followed by usually marked concentrations of creatine kinase and electrolytes (potassium magnesium) monitoring
		Malignant hyperthermia	Malignant hyperthermia an autonomic disorder abnormal release episodes by succinylcholine

inhala  
Result  
ultima  
rhabd  
hypert  
potent  
earlies  
an epis  
unexp  
tidal p  
includ  
dantro  
body t

Neuroleptic  
malignant

Neuro  
syndr  
resem  
hypert  
etiolο  
with d  
blockε  
of dop  
Symp  
after s  
dopan  
fever i  
manife

## **ICU acquired**

Pressure effects  
(increased intracranial  
pressure, herniation,  
hypertension,  
entrapment, increased  
local pressure)

Nerve

Pressure palsies

Patien  
with c  
suscep  
palsies  
as the  
fibulai  
reposit  
can be

to prev

Metabolic/inflammatory	Nerve and muscle	Critical illness neuromyopathy	Appro patient with s (systemic respor develc neurolog multic signifi critica (CIM) repres illness activel sensor CIM is myopa incons with c disord inflam contril quadri weanin and pr Diagn electric which sensor amplit veloci EMG indica compc increa activit motor
------------------------	------------------	--------------------------------	--

be pro  
disper  
consis  
underl  
avoidi  
neuroi  
agents  
worse  
Evide  
glucos  
freque  
CIN

---

## Further reading list

- Chawla J, Gruener G. Management of critical illness polyneuropathy and myopathy. *Neurologic Clin* 2010; 28:961–77.
- De Jonghe B, Lacherade JC, Durand MC, Sharshar T. Critical illness neuromuscular syndromes. *Neurologic Clin* 2008; 26:507–20, ix.
- Ginsberg M, Granzow L, Teclaw R *et al*. Botulism associated with commercially canned chili sauce – Texas and Indiana. *MMWR* 2007; 56:767–9.
- Green DM. Weakness in the ICU: Guillain–Barré syndrome, myasthenia gravis, and critical illness polyneuropathy/myopathy. *Neurologist* 2005; 11:338–47.
- McLaughlin J, Fearey D, Esposito T, Porter K. Paralytic shellfish poisoning – Southeast Alaska, May–June 2011. *MMWR* 2011; 60:1554–6.

## **83 Weakness, monomelic**

---

Casey A. Chamberlain and Michael Andary *Neurologic Differential Diagnosis*,  
ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge  
University Press. © Cambridge University Press 2014.

### **Introduction**

Monomelic weakness has a vast array of potential causes, both neurologic and non-neurologic, leading to disuse of the affected extremity. This is a relatively rare symptom, that when encountered requires immediate attention. Potential causes of monomelic weakness can involve injury to the central nervous system (CNS) including the brain or spinal cord, or distal structures including the anterior horn cell, spinal root, plexus (brachial or lumbosacral), and peripheral nerve. It may also involve injury to the musculoskeletal system.

### **Case vignette**

A 58-year-old male presents to the office with a chief complaint of weakness of the right upper extremity. He notes that his symptoms began approximately 4 weeks earlier with pain affecting the right shoulder girdle. This pain started insidiously, however it was preceded by 1 week of an upper respiratory infection. His symptoms then progressed to include weakness of the right arm. Differential diagnoses include disease processes that can affect upper or lower motor neuron systems or the musculoskeletal system. The work-up of this patient's symptoms should start with a history pertinent to the presenting complaint and thorough physical examination. Once clinical suspicion is raised for possible causes of the patient's symptoms, one should progress to further work-up in the form of imaging, electrodiagnostic testing, and laboratory data. One may start with magnetic resonance imaging of the brain and cervical spinal cord to rule out central lesions; electrodiagnostic testing to identify lesions affecting the nerve roots, brachial plexus, or peripheral nervous system as well as muscular system in the form of myopathies; vascular studies to rule out arterial disease; and laboratory studies. Cerebrospinal fluid studies may also be

useful to identify abnormalities if one suspects causes such as acute inflammatory demyelinating polyneuropathy. The most likely cause of the present patient's symptoms is neuralgic amyotrophy (Parsonage Turner syndrome). This would best be evaluated by electrodiagnostic testing to identify abnormalities of the brachial plexus.

**Table 83.1 Localizations and etiologies of monomelic weakness.**

Item	Subdivision	Specific entity	Possible clinical features
Diseases affecting the upper motor neuron (UMN) system	Vascular or traumatic	Cerebrovascular accident	Sudden focal neurologic deficit secondary to trauma or occlusion vs. rupture of blood vessel supplying brain
		Spinal cord infarction Intra-arterial injection resulting in spinal cord infarction	Traumatic injury or occlusion of the posterior spinal arteries, anterior spinal artery, or radicular arteries leading to sudden focal neurologic deficit
	Immunologic	Multiple sclerosis	Chronic progressive disease of the central nervous system (CNS) characterized by multiple areas of white matter demyelination. These inflammatory

sites lead to plaque formation that may recur and enlarge

leading to weakness and paresthesias with associated UMN signs [1]

#### Transverse myelitis (TM)

Demyelinating causes of TM include multiple sclerosis and neuromyelitis optica whereas idiopathic complete TM is often para-infectious. Incomplete cord lesion causes a Brown–Séquard type syndrome. Partial cord lesions cause unilateral sensory and motor dysfunction [2]

#### Neoplastic

#### Tumors (brain and spinal cord)

Expansile mass may compress motor axons or cell bodies leading to unilateral weakness with associated upper motor neuron signs

#### Infections

#### Abscess located within the CNS

Expansile mass may compress motor axons or cell bodies leading to unilateral weakness.

			Associated signs may include fever and encephalopathy
Diseases affecting the anterior horn cell	Infectious	Poliomyelitis with post-polio syndrome	History of poliomyelitis with partial or complete neurologic recovery that has been stable for > 15 years. Onset of fatigue, myalgias, and increased weakness usually secondary to musculoskeletal pathology [3]
		West Nile poliomyelitis	Acute onset of weakness that affects proximal greater than distal muscles that is asymmetric commonly affecting 1 limb with little sensory involvement. Other features include those related to general illness and meningoencephalitis [4]
Non- infectious		Amyotrophic lateral sclerosis (ALS; sporadic and hereditary) or variant syndromes including primary	UMN and lower motor neuron (LMN) disease that may present asymmetrically with upper extremity

	muscular atrophy and primary lateral sclerosis	(UE) weakness (flail arm) or lower extremity (LE) weakness (flail leg) and bulbar symptoms [5]
	Western Pacific ALS-like disorders	Presents with UMN and LMN symptoms (90%) vs. LMN symptoms only (10%) with associated bulbar symptoms [6]
	Primary muscular atrophy	Asymmetric weakness of the upper or lower extremities often involving paraspinal and respiratory muscles [7]
	Monomelic amyotrophy (Hirayama disease )	Progressive weakness of distal single limb over 1–4 years, then plateau. Possible etiologies include neck flexion-induced cervical myelopathy vs. motor neuron disease (MND) [8]
Focal spinal lesions	Syringomyelia	Development of a fluid-filled cavity within the spinal cord. Extension into the anterior horns of

the spinal cord damages motor neurons and causes diffuse muscle atrophy and weakness that begins in the hands and progresses proximally. Slowly progressive over months to years [9]

Intramedullary tumors

Expansile mass may compress motor axons or cell bodies leading to unilateral weakness

Hopkins syndrome

Age: 1–13 yrs  
Follows acute asthma attack with latency of 1–18 days  
Prognosis:  
permanent paralysis [10]

Toxic

Lead, mercury, arsenic, gold (heavy metals)

Slow or sudden onset asymmetric weakness with pain and sensory loss

Paraneoplastic

Subacute motor neuronopathy associated with cancer or lymphoma (especially Hodgkin's disease )

Asymmetric weakness with associated bulbar symptoms that is progressive over several months.  
Onset

Diseases affecting the spinal root	Structural	Root avulsion	approximately 4 months prior to diagnosis of neoplasm [11]
		Spinal dysraphisms with myelomeningocele, tethering of the spinal cord	Traumatic traction injury that disrupts the protective connective tissue support. The C8 and T1 roots have less protection and are the most common sites of injury. Presents with complaints of absent sensation and weakness from the muscles innervated by the roots involved [1]
Diseases affecting the brachial or lumbosacral plexus	Neoplastic	Malignant invasion of plexus (Pancoast tumor)	Weakness is the number one symptom followed by sensory deficit and bladder dysfunction, spasticity [1]
	Primary brachial	Affect upper or	Pain worse at night affecting the lower trunk of the brachial plexus. Horner's syndrome if T1 nerve root affected [12]

	plexus neoplasms (schwannomas or neurofibromas)	middle plexus and present as a painless mass with weakness in affected myotome <a href="#">[13]</a>
Structural	Thoracic outlet syndrome (neurogenic vs. vascular)	Pain and paresthesias of the upper extremity with associated weakness primarily affecting the lower trunk of the brachial plexus <a href="#">[14]</a>
	Trauma (avulsion, gunshot, etc.)	Weakness of proximal and distal muscles of upper or lower extremity with associated pain
	Burner syndrome	Sudden forceful depression of shoulder as occurs in football, affects upper extremity with dysesthesias most commonly affecting upper trunk of brachial plexus <a href="#">[15]</a>
	Obstetric injuries (Erb's palsy , Klumpke's palsy )	Erb's palsy: C5–6 distribution weakness with “waiter tip deformity” Klumpke's palsy:

C8–T1 distribution  
weakness  
Total plexus injury  
[16]

Postoperative  
paralysis associated  
with positioning

Immediate  
postoperative  
weakness with  
paresthesias (pain is  
not predominant)

Rucksack paralysis

Weakness primarily  
of the upper and  
middle trunks of  
brachial plexus with  
paresthesias in one  
who wears a pack  
without waist  
support [17]

Psoas hemorrhage  
or abscess

Results in  
lumbosacral  
plexopathy with  
weakness in the  
obturator and  
femoral nerve  
territory

Radiation  
plexopathy

Weakness and  
paresthesias (little  
pain) in C5–6  
distribution years  
after radiation [18]

Iatrogenic

Intra-arterial  
injections

Gluteal injection  
causing vasospasm  
resulting in sciatic  
nerve ischemia with  
resultant weakness

and paresthesias of the lower extremity  
Injection of cis-platinum or fluorouracil into internal iliac artery resulting in painless lumbosacral plexopathy [19]

Lumbosacral ischemic plexopathy

Surgery of aortic bifurcation and pelvic arteries resulting in weakness and paresthesias of LE [20]

Immunologic Parsonage Turner syndrome (neuralgic amyotrophy)

Sudden onset of pain commonly over the deltoid with associated patchy weakness, sensory loss and atrophy [21]

Flail arm syndrome (Vulpian–Bernhard syndrome )

Asymmetric weakness of the UE (shoulder > elbow) +/- bulbar changes with progression to neck and legs [22]

Diabetic amyotrophy

More frequently seen in type II diabetes presenting with asymmetric proximal weakness primarily affecting

the quadriceps, psoas, and adductors with associated pain in the hip, buttocks, or thigh. Prognosis reveals slow recovery over 6–24 months [23]

#### Lumbosacral plexopathy

Condition characterized by asymmetrical lower extremity pain, weakness, and muscle atrophy affecting commonly the thigh muscles; mild sensory symptoms are seen [23]

#### Ischemic

Peripheral artery disease of internal iliac arteries

Exercise provocation of pain, paresthesias, and weakness in the involved extremity [19]

#### Infections

Radiculoplexopathy with conduction block caused by acute Epstein–Barr virus infection

Present with pain, paresthesias, and monomelic weakness in the left C7–8, and T1 myotomes after infection caused by Epstein–Barr virus. The illness is monophasic with

rapid recovery [24]

Diseases affecting the peripheral nerve	Traumatic	Peripheral nerve injuries	Multiple causes of peripheral nerve injury presenting as pain, weakness, and paresthesias in the distribution of the affected peripheral nerve
	Ischemic	Ischemic monomelic neuropathy (IMN)	<p>Occurs after acute arterial occlusion or low blood flow to an extremity.</p> <p>Patients with IMN usually complain of pain in the distal limb with associated weakness. This pain generally occurs after hours of arterial occlusion.</p> <p>This commonly presents after surgical intervention, examples including after arteriovenous fistula formation or prolonged tourniquet time [25]</p>
	Immunologic	Multifocal motor neuropathy with conduction block	Asymmetric weakness affecting distal greater than proximal, upper greater than lower extremity that

typically presents in a slowly progressive pattern over 1–30 years (90%) [26]

#### Leprosy

Pure neural leprosy most commonly presents as mononeuritis multiplex with asymmetric weakness and sensory loss with ulnar nerve most commonly affected [27]

#### Acute inflammatory demyelinating polyneuropathy

Commonly presents after prodrome of illness (gastrointestinal, respiratory) with distal weakness, paresthesias, autonomic dysfunction, hyporeflexia, and cranial nerve involvement with nadir occurring at 9 days [28]

#### Hereditary neuropathy with liability to pressure palsies (HNPP)

*PMP-22* deletion with recurrent neuropathies leading to weakness and paresthesias in distribution of affected peripheral

affecting peripheral nerve [29]

### Diseases affecting the muscular system

#### Focal myositis and inclusion body myositis

Slowly progressive course of weakness both proximally and distally, asymmetry is common. Early involvement of the knee extensors, ankle dorsiflexors, and wrist/finger flexors is characteristic. Weakness of the wrist and finger flexors is often disproportionate to that of their extensor counterparts. Hence, loss of finger dexterity and grip strength may be a presenting or prominent symptom. Dysphagia is common [30]

#### Diabetic myonecrosis

Acute painful swelling affecting the lower extremity most commonly with weakness of the affected extremity [31]

## References

1. Cuccurullo S. *Physical Medicine and Rehabilitation Board Review*. New York, NY: Demos Medical Publishing, 2004.
2. Scott TF, Bhagavatula K, Snyder P *et al*. Transverse myelitis. Comparison with spinal cord presentations of multiple sclerosis. *Neurology* 1998; 50:429–33.
3. Trojan DA, Cashman NR. Post-polio-myelitis syndrome. *Muscle Nerve* 2005; 31:6–19.
4. Li J, Loeb JA, Shy ME *et al*. Asymmetric flaccid paralysis: a neuromuscular presentation of West Nile virus infection. *Ann Neurol* 2003; 53:703–10.
5. Hu MT, Ellis CM, Al-Chalabi A *et al*. Flail arm syndrome: a distinctive variant of amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1998; 65:950–1.
6. Al-Sarraj S. A clinical and pathological study of motor neurone disease on Guam. *Brain* 2001; 124:2215–22.
7. Kim W-K, Liu X, Sandner J *et al*. Study of 962 patients indicates progressive muscular atrophy is a form of ALS. *Neurology* 2009; 73:1686–92.
8. Andreadou E, Christodoulou K, Manta P *et al*. Familial asymmetric distal upper limb amyotrophy (Hirayama disease): report of a Greek family. *Neurologist* 2009; 15:156–60.
9. Falci SP, Indeck C, Lammertse DP. Posttraumatic spinal cord tethering and syringomyelia: surgical treatment and long-term outcome. *J Neurosurg Spine* 2009; 11:445–60.
10. Nakano Y, Kohira R, Yamazaki H *et al*. Hopkins syndrome: oral prednisolone was effective for the paralysis. *Brain and Development* 2001; 33:69–73.
11. Ferracci F, Fassetta G, Butler MH *et al*. A novel antineuronal antibody in a motor neuron syndrome associated with breast cancer. *Neurology* 1999; 53:852–5.
12. Khosravi Shahi P. Pancoast's syndrome (superior pulmonary sulcus tumor): review of the literature. *Ann Med Intern* 2005; 22:194–6.

13. Binder DK, Smith JS, Barbaro NM. Primary brachial plexus tumors: imaging, surgical, and pathological findings in 25 patients. *Neurosurg Focus* 2004; 16:E11.
14. Watson LA, Pizzari T, Balster S. Thoracic outlet syndrome part 1: clinical manifestations, differentiation and treatment pathways. *Man Ther* 2009; 14:586–95.
15. Sallis RE, Jones K, Knopp W. Burners: offensive strategy for an underreported injury. *Physician Sportsmed* 1992; 20:47–55.
16. Evans-Jones G, Kay SP, Weindling AM *et al*. Congenital brachial palsy: incidence, causes, and outcome in the United Kingdom and Republic of Ireland. *Arch Dis Child Fetal Neonatal Ed* 2003; 88:F185–9.
17. Knapik JJ, Reynolds KL, Harman E. Soldier load carriage: historical, physiological, biomechanical, and medical aspects. *Mil Med* 2004; 169:45–56.
18. Gosk J, Rutowski R, Reichert P *et al*. Radiation-induced brachial plexus neuropathy – aetiopathogenesis, risk factors, differential diagnostics, symptoms and treatment. *J Folia Neuropathol* 2007; 45:26–30.
19. Wohlgemuth WA, Rottach KG, Stoehr M. Intermittent claudication due to ischaemia of the lumbosacral plexus. *J Neurol Neurosurg Psychiatry* 1999; 67:793–5.
20. Abdelhamid MF, Sandler B, Awad RW. Ischaemic lumbosacral plexopathy following aorto-iliac bypass graft: case report and review of literature. *Coll Surg Engl* 2007; 89:W12–13.
21. van Alfen N. Clinical and pathophysiological concepts of neuralgic amyotrophy. *Nat Rev Neurol* 2011 10;7(6): 315–22.
22. Katz JS, Wolfe GI, Andersson PB *et al*. Brachial amyotrophic diplegia: a slowly progressive motor neuron disorder. *Neurology* 1999; 53:1071–6.
23. Bhanushali MJ, Muley SA. Diabetic and non-diabetic lumbosacral radiculoplexus neuropathy. *Neurol India* 2008; 56:420–5.
24. Vucic S, Palmer W, Cros D. Radiculoplexopathy with conduction block caused by acute Epstein–Barr virus infection. *Neurology* 2005;64: 530–2.
25. Andary MT, Fankhauser MJ, van der Harst CL. Ischemic monomelic neuropathy with involvement of sacral nerves and sparing of sympathetic skin

response. *Muscle Nerve* 1993; 16:1105(A).

26. Kiernan MC, Guglielmi J-M, Kaji R, Murray NMF, Bostock H. Evidence for axonal membrane hyperpolarization in multifocal motor neuropathy with conduction block. *Brain* 2002; 125:664–75.
27. Jardim MR, Illarramendi X, Nascimento OJ *et al*. Pure neural leprosy: steroids prevent neuropathy progression. *Arq Neuropsiquiatr* 2007; 65:969–73.
28. George A, Abdurehiman P, James J. “Finger drop sign” in Guillain-Barré syndrome. *Neurol India* 2009; 57:282–6.
29. Hui-Chou HG, Hashemi SS, Höke A, Dellon AL. Clinical implications of peripheral myelin protein 22 for nerve compression and neural regeneration: a review. *J Reconstr Microsurg* 2011; 27:67–74.
30. Lederman RJ, Salanga VD, Wilbourn AJ. Focal inflammatory myopathy. *Muscle Nerve* 1984; 7:142–6.
31. Iyer SN, Drake AJ III, West RL, Tanenberg RJ. Diabetic muscle infarction: a rare complication of long-standing and poorly controlled diabetes mellitus. *Case Report Med* 2011; 2011:Art. 407921.

## 84 Weakness, neck

---

Sindhu Ramchandren and and Aashit K. Shah *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

Neck weakness is a descriptive term, indicating the effect of various neurologic conditions that result in weakness of the neck extensor and flexor muscles. It has been classified under various names in the past: since it is characterized by anterior curvature of the spine, reports of camptocormia , or bent-spine disorders marked by flexion of the thoracolumbar spine, may perhaps be the earliest descriptions of this condition [1]. Other descriptive names used in the literature to characterize disorders with neck weakness include floppy head syndrome [2], dropped-head syndrome [3,4], head ptosis , or head drop [5].

It is important to distinguish the neurologic causes of neck weakness described under these various names from the spinal rigidity seen in ankylosing spondylitis or other arthritic conditions, which is fixed, regardless of whether the patient is erect or supine. In contrast, patients with neurologic etiologies of neck weakness are unable to voluntarily correct the head drop, but a change in position, such as lying supine, can correct the neck flexion.

Neck weakness can result from central and peripheral nervous system disorders. Centrally, the putative mechanism is involvement of the striatum and its projections to the reticulospinal tract or the thalamus [6]. Peripherally, weakness of the antigravity neck and trunk extensor muscles due to motor neuron disease [7], peripheral neuropathies [8], neuromuscular junction disorders [9], or myopathy [10–12] has been reported. The work-up of neck weakness, after a detailed clinical history and neurologic examination, often includes imaging of the cervical spine with gadolinium to look for active paraspinal muscle necrosis or enhancement of nerve roots, repetitive nerve stimulation conduction studies to look for neuromuscular junction disorders, electromyography (EMG) to look for myopathic features, and laboratory

evaluation for abnormal electrolyte or creatine kinase (CK) values. Endocrinologic tests such as thyroid function test, or immunologic testing such as anti-acetylcholine receptor antibody (anti-AChR-Ab) for suspected myasthenia gravis antinuclear antibodies, anti-Jo-1 antibodies for suspected polymyositis, are therefore often part of the standard work-up of patients presenting with neck weakness. In [Table 84.1](#), we present the common neurologic etiologies of this condition, along with their clinical features.

## Case vignette

A 54-year-old male presents with a 6-month history of progressive weakness of the right hand, and a stooped posture. He notes that he has to prop his head up while working at his computer. He denies any sensory symptoms, tremor, diplopia, or ptosis. On neurologic examination, he has normal mentation and cranial nerves. There is marked atrophy of the intrinsic muscles of his right hand as well as his left calf, with intrinsic hand muscle strength of 3/5, and ankle dorsiflexion strength of 4/5. Neck flexor strength is 4/5. Gait is normal with no festination or retropulsion. He has 4+ hyperreflexia with a positive left Babinski sign .

The clinical history and exam were not suggestive of a neurodegenerative disorder such as Alzheimer's, Parkinson's, or multiple system atrophy. An EMG was done, which showed normal repetitive nerve stimulation studies, which, combined with the lack of clinical features, made a neuromuscular junction disorder unlikely. Nerve conduction studies did show markedly low amplitudes of several motor nerves, without sensory abnormalities, making a peripheral neuropathy unlikely. The EMG showed spontaneous activity with changes suggesting neurogenic atrophy in three segments (cervical, lumbar, and thoracic paraspinal muscles). Magnetic resonance imaging of the entire spine was done, which showed no nerve impingement in any of the segments. The most likely diagnosis based on this presentation is amyotrophic lateral sclerosis .

**Table 84.1 Differential diagnosis for causes of neck weakness.**

Classification	Localization	Specific etiology	Clinical features
Peripheral nervous system	Muscle	Primary myopathies (myotonic dystrophy, Duchenne muscular dystrophy)	Neurologic examination reveals proximal limb weakness

**system  
disorders**

myopathy,  
mitochondrial  
myopathy, nemaline  
myopathy)

Initial physical  
muscle weak  
as well as  
myotonia in th  
case of myoto  
dystrophy.  
Electromyogr  
(EMG) shows  
myopathic  
features. Crea  
kinase (CK)  
values are  
elevated. Biof  
or genetic test  
is diagnostic

Secondary myopathies  
(hypothyroid  
myopathy, Cushing  
syndrome, severe  
hypokalemic  
myopathy)

While exam  
shows myopa  
features, EMG  
may be normal.  
Electrolyte  
abnormalities  
muscle biopsy  
may be needed  
diagnosis

Inflammatory  
myopathies  
(polymyositis,  
dermatomyositis,  
inclusion body  
myositis)

Neurologic  
examination  
shows proxim  
weakness. EMG  
often shows  
abnormal  
spontaneous  
activity. Musc  
biopsy is  
diagnostic

Toxic myopathies  
(olanzapine, valproic  
acid, statins,

Usually after  
few days of  
treatment wit

intermediate syndrome  
of organophosphate  
poisoning)

offending age  
Patients prese  
with  
camptocormic  
posture,  
paraspinal mu  
tenderness, an  
elevated CK  
levels suggest  
of  
rhabdomyoly<sup>s</sup>  
In cases of  
organophosph  
poisoning,  
intermediate  
syndrome  
typically occu  
1–4 days into  
illness and  
presents with  
acute weaknes  
neck muscles,  
respiratory  
muscles, and  
proximal lim<sup>t</sup>  
muscles

Inherited myopathies  
(congenital muscular  
dystrophy,  
oculopharyngeal  
muscular dystrophy,  
myotonic dystrophy,  
limb-girdle muscular  
dystrophy)

Neurologic ex  
and presentati  
are variable  
depending up  
the type of the  
inherited  
myopathy.  
However, the  
family history  
genetic testing  
key in  
establishing th

diagnosis

Neuromuscular junction      Myasthenia gravis

Neurologic examination may show fatigability and eye muscles are frequently involved. Repetitive nerve stimulation studies or single fiber EMG may also be helpful. Anti-acetylcholine receptor antibodies are seen in over 80% of patients.

Lambert–Eaton myasthenic syndrome (LEMS)

Patients are often over 40, and there is increased incidence in patients with malignancy, especially small cell lung cancer. Augmentation of strength can be seen in proximal muscles on examination. Repetitive nerve stimulation also shows increments in motor amplitudes. Detection of voltage-gated

calcium channel antibodies is diagnostic

Peripheral nerve	Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP)	Classic cases CIDP present rapid, progressive symmetric weakness of cranial and proximal muscles, in legs and arms, over period of 2 months or greater. Magnetic resonance imaging with contrast can show enhancement of nerve roots, with lumbar puncture showing albuminocytological dissociation (elevated protein without concomitant increase in white blood cells)
Motor neuron	Amyotrophic lateral sclerosis	Patients present in their 40s or later with asymmetric limb, leg, arm, or eye muscle weakness. Sensory symptoms are usually lacking. EMG shows spontaneous activity.

			spontaneous activity in the paraspinal muscles
Central nervous system disorders	Degenerative	Parkinson's disease (PD), Multiple system atrophy (MSA)	Patients present with marked stooped posture along with other cardinal features such as masked facies, tremor, festinating gait and retropulsion (PD) or postural instability and supranuclear (upgaze) palsies (MSA). Unlike the peripheral nervous system disorders, there is some resistance attempted passive extension of the neck or back, but it can be overcome with change in position.
		Amyotrophic lateral sclerosis	Corticospinal involvement makes this a central as well as peripheral disorder. Clinical examination can reveal upper motor neuron signs such as

signs, such as  
hyperreflexia  
positive Babinski  
sign

---

## References

1. Southard EE. *Shell shock and other neuropsychiatric problems presented in 589 case histories from the war literature, 1914–1918*. Boston, MA: WM Leonard, 1919.
2. Lange DJ, Fetell MR, Lovelace RE, Rowland LP. The floppy head syndrome [abstract]. *Ann Neurol* 1986;20:133.
3. Suarez GA, Kelly JJ. The dropped head syndrome. *Neurology* 1992; 42:1625–7.
4. Katz JS, Wolfe GI, Burns DK *et al*. Isolated neck extensor myopathy: a common cause of dropped head syndrome. *Neurology* 1996; 46:917–21.
5. Umapathi T, Chaudhry V, Cornblath D *et al*. Head drop and camptocormia. *J Neurol Neurosurg Psychiatry* 2002; 73:1–7.
6. Djaldetti R, Melamed E. Camptocormia in Parkinson's disease: new insights. *J Neurol Neurosurg Psychiatry* 2006; 77:1205.
7. Gourie-Devi M, Nalini A, Sandhya S. Early or late appearance of “dropped head syndrome” in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 2003; 74:683–6.
8. Hoffman D, Gutmann L. The dropped head syndrome with chronic inflammatory demyelinating polyneuropathy. *Muscle Nerve* 1994; 17:808–10.
9. Ueda T, Kanda F, Kobessho H, Hamaguchi H, Motomura M. “Dropped head syndrome” caused by Lambert-Eaton myasthenic syndrome. *Muscle Nerve* 2009; 40:134–6.
10. Finsterer J. Dropped head syndrome in mitochondriopathy. *Eur Spine J* 2004; 13:652–6.
11. Robert F, Koenig M, Robert A *et al*. Acute camptocormia induced by olanzapine: a case report. *J Med Case Reports* 2010; 4:192.

12. Kiuru S, Iivanainen M. CAMPTOCORMIA, A NEW SIDE EFFECT OF SODIUM VALPROATE. *Epilepsy Res* 1987; 1:254–7.

## **85 Weakness, paraparesis**

---

Friedhelm Sandbrink *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

Paraparesis indicates (partial) paralysis in the lower extremities, *i.e.* incomplete loss of motor function in the legs. Paraplegia denotes complete loss of motor function in the legs.

Tetraparesis (or quadriparesis) and tetraplegia (quadriplegia) are the terms for partial and complete loss of motor function in all four extremities, respectively.

### **Anatomy and clinical correlation**

The clinical findings are key to localization of the lesion and guide the differential diagnosis and the selection of appropriate diagnostic studies including magnetic resonance imaging (MRI).

Important steps are to differentiate between upper or lower motor neuron lesions, and to determine any accompanying sensory and bladder/bowel involvement.

Patients with spastic paraparesis have upper motor neuron (UMN) damage from lesions of the pyramidal tract (corticospinal tract). Upper motor neuron signs (long tract signs) are increased tone (spasticity), hyperreflexia, and upgoing plantar response (Babinski sign). In spastic paraparesis, the leg weakness is typically greater in the leg flexor muscles (hip and knee flexors, and foot dorsiflexors) than the extensor muscles (including quadriceps and plantar flexor muscles). The presence of upper motor neuron signs localizes the lesion to the central nervous system (CNS) above (*i.e.* proximal to) the lumbosacral cord, *i.e.* above the lower motor neurons for the lower extremities.

Spinal cord lesions manifest with bilateral motor and/or sensory symptoms

without cranial nerve involvement and without change in mental status. In patients with paraparesis and UMN signs on examination, the lesion is likely within the thoracic cord. If the upper extremities are also affected, the lesion is likely within the cervical cord. Occasionally, a chronic cervical cord lesion may not cause any detectable weakness in the upper extremities. Rarely, a midline cortical lesion affecting the cortical motor presentation of the legs (such as parasagittal falx meningeoma) may cause spastic paraparesis.

Patients presenting with flaccid paraparesis usually have lower motor neuron (LMN) involvement, either within the lower spinal cord (lumbar cord or conus medullaris), or peripherally. An important exception, however, is an acute upper motor neuron lesion from spinal infarction or trauma that may present initially also as flaccidity with decreased muscle tone and hyporeflexia ("spinal shock"). The presence of fasciculation potentials indicates lower motor neuron involvement. Muscle atrophy occurs in chronic or slowly progressive lower motor neuron disorders, neuropathies, and myopathies. The pattern of leg weakness (distal versus proximal, symmetric versus asymmetric, segmental or focal) should be determined carefully.

Lumbar cord and conus medullaris lesions are less common than peripheral lesions of the nerve roots or peripheral nerves. In conus medullaris syndrome, there is early sphincter involvement and saddle anesthesia. Cauda equina syndrome may present similarly, if acute and severe. The pattern of weakness depends on the lesion level: upper cauda lesions affect the proximal leg muscles in addition to the distal musculature. The pattern of bilateral distal leg weakness suggests motor neuron disorders, polyradiculopathy affecting the lower lumbosacral nerve roots on both sides, and axonal polyneuropathies. Proximal leg weakness occurs in motor neuron disorders, upper cauda equina lesions, demyelinating polyneuropathies, neuromuscular junction disorders, and myopathies.

There are several distinct spinal cord syndromes whose recognition is important to localize the spinal cord lesion within the transverse plane.

In segmental cord syndrome, all spinal cord functions at one or several levels are affected. There is paraparesis associated with sensory dysfunction of all qualities below the lesion and sphincter impairment. Dysesthesias surrounding the trunk in a band or girdle-like fashion may mark the sensory level. Examples are transverse myelitis, spinal cord trauma, and spinal hemorrhage.

In anterior (ventral) cord syndrome, paraparesis is associated with decreased

sensation for pain and temperature and neurogenic bladder. Light touch, vibration and position sensation are preserved, as mediated through the dorsal columns. Examples are spinal cord infarction and anterior cord compression from disc herniation or epidural abscess.

In posterior (dorsal column) cord syndrome, there is no weakness, but impaired sensation for light touch (paresthesias), position (gait unsteadiness), and vibration. An example is tabes dorsalis.

In posterolateral cord syndrome, paraparesis results from the additional corticospinal tract involvement. Examples are vitamin B12 deficiency, copper deficiency, AIDS myelopathy, Friedreich ataxia.

In central cord syndrome, loss of pain and temperature occurs in a dermatomal distribution, followed by weakness in a myotomal pattern. Long tract signs followed later as the lesion expands within the cord. Examples are syringomyelia and intramedullary tumor.

Brown–Séquard syndrome is a hemi-cord syndrome characterized by ipsilateral weakness and loss of light touch, vibration, and position, with contralateral loss of pain and temperature sense. The full syndrome is rare and typically caused by penetrating trauma (knife or bullet wounds). Asymmetric myelopathy resembling incomplete Brown–Séquard syndrome occurs in multiple sclerosis.

Paraparesis as a pure motor syndrome, without any sensory or bladder involvement, limits the differential diagnostic considerations greatly.

A pure upper motor neuron syndrome occurs in primary lateral sclerosis variant of amyotrophic lateral sclerosis and hepatic myelopathy. Hereditary spastic paraplegia, HTLV-I associated myelopathy/spastic paraparesis (HAM/TSP), and adrenomyeloneuropathy have mild sensory deficits in addition to prominent spastic paraparesis.

A pure mixed upper and lower motor neuron syndrome suggests amyotrophic lateral sclerosis.

A pure lower motor neuron syndrome occurs in progressive muscular atrophy variant of amyotrophic lateral sclerosis, poliomyelitis and related viral infections, and post-polio syndrome. The differential diagnosis includes inflammatory demyelinating neuropathies (Guillain–Barré syndrome), neuromuscular junction disorders, and myopathies.

Other causes of paraparesis include parasagittal lesions in the brain.

Alternatively, neuropathies and myopathies may present with predominant weakness in the lower extremities. In particular, the paraparetic variant of Guillain–Barré syndrome is a regional variant with isolated leg weakness and areflexia simulating a cauda equina or spinal cord syndrome. Inflammatory myopathies, including inclusion body myositis, may cause isolated leg weakness. Psychogenic causes are also in the differential diagnosis.

## Case vignette

A 58-year-old male presents with a 2-year history of gradually increasing difficulty walking and rather acute worsening in the last few days. He is now at the point of having to use a cane, due to weakness in his legs and gait unsteadiness. In retrospect, he recalls fluctuating severity of paraparesis with worsening after prolonged walking. He reports chronic tingling of his legs, in particular in his feet, and pain in his low back radiating to the posterior thighs bilaterally, for years. He admits to erectile dysfunction, but denies bladder symptoms. On examination, his cranial nerves and the upper extremities are normal. He has moderate paraparesis in both legs minimally worse on the right than left side and rated as 3 to 4/5. There is slight spasticity in both legs. Deep tendon reflexes at the knees are hypoactive, and ankle jerks are absent. The toe responses are upgoing bilaterally. He has decreased sensation to light touch, vibration, and proprioception in both legs with distal gradient. The gait is unsteady and mildly spastic. The clinical findings of upper and lower motor neuron signs in both legs with accompanying sensory deficits and without involvement of the arms localize the lesion to the thoracic and lumbar cord or myeloneuropathy. The MRI shows extensive T2 central cord signal change with cord edema and swelling, from T7 to the conus medullaris. CSF is normal except mild increase in protein. The immune parameters (IgG index and oligoclonal bands) are normal. Cytology does not show abnormal cells. Viral serologies are normal including HTLV-1, HIV, HSV, HZV and West Nile virus. Screening for collagen vascular disorders and sarcoid is normal. B12, copper and vitamin E levels are normal. The fluctuating course suggests the diagnosis of spinal dural arteriovenous fistula (SDAVF), but there is concern for intramedullary tumor (astrocytoma, ependymoma). A spinal arteriogram documents a typical SDAVF at the L1 level supplied by the right L1 lumbar artery. The treatment with embolization results in improvement of symptoms.

**Table 85.1 Differential diagnosis of paraparesis.**

---

<b>Item</b>	<b>Subdivision</b>	<b>Specific entity</b>
Structural	Degenerative spine disease	Cervical spinal stenosis (degenerative spine disease including disc herniation, often superimposed upon congenital canal narrowing)
		Lumbar central spinal stenosis (degenerative spine disease including disc herniation, facet joint arthropathy, ligamentum flavum hypertrophy, epidural lipomatosis; often superimposed upon congenital canal narrowing)

Thoracic central spinal stenosis (degenerative spine disease, disc herniation)

Syringomyelia

Toxic

Food toxins

Konzo (from improperly processed cassava, *Manihot esculenta*)

Lathyrism (over-consumption of grass pea, *Lathyrus sativus*)

	Drugs: chemotherapy	Methotrexate, cytosine arabinoside (Ara-C)
Infective	Bacterial	Epidural abscess ( <i>Staphylococcus aureus</i> in >50%, <i>Streptococcus</i> , gram-negative bacilli, coagulase-negative staphylococci, anaerobes, <i>Actinomyces</i> )
		Bacterial myelitis ( <i>Staphylococcus</i> , <i>Streptococcus</i> , <i>Escherichia coli</i> , <i>Nocardia</i> , and others)
		Syphilis ( <i>Treponema</i>

*pallidum*)

Lyme disease (*Borrelia burgdorferi*)

Mycobacterial

Tuberculosis (TB)  
(*Mycobacterium tuberculosis*)

Viral

Poliomyelitis – acute viral myelitis  
Enteroviruses:  
poliovirus, coxsackie and echovirus;

Flaviviruses including  
West Nile virus

Flaviviruses: West Nile  
virus and others

Viral myelitis – varicella  
zoster, herpes simplex,  
cytomegalovirus, human  
herpes types 6 and 7,  
hepatitis C, Epstein–  
Barr

HIV myelitis

AIDS myelopathy

HTLV-1 associated  
myelopathy (HAM) or  
tropical spastic  
paraparesis (TSP)

Fungal

*Aspergillus,*  
*Blastomyces,*  
*Coccidioides*

*Cryptococcus*  
*neoformans*

Parasitic/protozoal    *Schistosoma mansoni* or

*Schistosoma  
haematobium*

Cysticercosis (*Taenia  
solium*)

Inflammatory

'Idiopathic'  
(autoimmune)

Transverse myelitis  
(TM)

Guillain–Barré  
syndrome

Granulomatous      Sarcoidosis

	Connective tissue disorders	Systemic lupus erythematosus , Sjögren syndrome , mixed connective tissue disease, systemic sclerosis /scleroderma , antiphospholipid antibody syndrome, Behçet's syndrome
Post vaccinial		Rabies, diphtheria–tetanus–polio, smallpox, measles, mumps, rubella, pertussis, influenza, hepatitis B, Japanese encephalitis
Radiation		Post-radiation myelopathy
Demyelinating	Inflammatory acquired	Multiple sclerosis , relapsing remitting form

Multiple sclerosis,  
primary progressive  
form

Neuromyelitis optica  
spectrum disorders  
(NMO disease, Devic's  
syndrome)

Acute disseminated  
encephalomyelitis  
(ADEM)

Neoplastic/paraneoplastic    Extradural tumors    Metastasis: lung, breast carcinoma

Metastasis: prostate cancer

Intradural  
extramedullary  
tumors

Primary tumors:  
meningioma,  
neurofibroma, and  
schwannoma, rarely

chordoma

Focal metastatic lesions from medulloblastoma, pinioblastoma, primitive neuroectodermal tumor, germ cell tumor

Leptomeningeal metastasis (meningeal carcinomatosis or lymphomatosis)

Intramedullary tumors

Primary tumors:  
ependymoma >  
astrocytoma >  
lymphoma,  
hemangioblastoma

Secondary: metastasis.  
Lung > breast >  
melanoma > lymphoma,  
renal, others

Paraneoplastic

Paraneoplastic motor neuron syndrome

## Paraneoplastic myelopathy

Degenerative

Motor neuron  
disorders

Amyotrophic lateral  
sclerosis

Primary lateral sclerosis

Spinal muscular atrophy  
(SMA)

Bulbospinal muscular atrophy (Kennedy syndrome )

Vascular

Ischemic

Spinal cord infarction – anterior spinal artery, due to aortic dissection, embolic, hypotensive, vasculitic (polyarteritis nodosa)

Spinal cord infarction – posterior spinal artery

Hemorrhage

Hematomyelia  
(intramedullary

hemorrhage)

Epidural hematoma

Vascular  
malformations

Spinal dural  
arteriovenous fistula  
(SDAVF)

Intramedullary spinal  
arteriovenous  
malformation (AVM)

Metabolic

Nutritional  
deficiency

Subacute combined  
degeneration (SCD) in  
vitamin B12 deficiency  
= cobalamin deficiency  
myeloneuropathy

Nitrous oxide (NO)  
toxicity  
myeloneuropathy

Copper deficiency  
myeloneuropathy

Zinc toxicity

Folic acid deficiency  
myeloneuropathy

Vitamin E deficiency  
myeloneuropathy

Hepatic myelopathy

Mitochondrial

Mitochondrial disorders

Urea cycle  
disorder

Hyperargininemia

Congenital

Cerebral palsy

Spastic diplegia

Heredo-familial

Hereditary spastic  
paraplegias (HSP) –  
'uncomplicated' or  
'pure'

HSP – 'complicated'

Adrenomyeloneuropathy  
(AMN) variant of

~~variant~~, variant of  
adrenoleukodystrophy  
(ALD)

Friedreich ataxia

Spinocerebellar ataxias  
(SCAs)

Segawa disease  
(levodopa-responsive  
dystonia)

Trauma associated

Mechanical  
trauma

Spinal cord injury (SCI)

Deep sea diving

Decompression sickness  
myelopathy

Electrical injury      Lightning strike

---

## Further reading list

Borchers AT, Gershwin ME. Transverse myelitis. *Autoimmun Rev* 2012; 11:231–48.

Eisen A. Disorders affecting the spinal cord. [www.uptodate.com](http://www.uptodate.com). Accessed 1/5/2012.

Engelen M, Kemp S, de Visser M *et al.* X-linked adrenoleukodystrophy (X-ALD): clinical presentation and guidelines for diagnosis, follow-up and management. *Orphanet J Rare Dis* 2012; 7:51.

Flanagan EP, Lennon VA, Pittock SJ. Autoimmune myelopathies. *Continuum Lifelong Learning Neurol* 2011; 17:776–99.

Flanagan EP, McKeon A, Lennon VA *et al.* Paraneoplastic isolated myelopathy: clinical course and neuroimaging clues. *Neurology* 2011; 76:2089–95.

Fugate JE, Lanzino G, Rabinstein AA. Clinical presentation and prognostic factors of spinal dural arteriovenous fistulas: an overview. *Neurosurg Focus* 2012; 32:E17.

Goodman BP. Diagnostic approach to myeloneuropathy. *Continuum Lifelong Learning Neurol* 2011; 17:744–60.

Hedera P. Hereditary myelopathies. *Continuum Lifelong Learning Neurol* 2011; 17:800–15.

Jaiser SR, Winston GP. Copper deficiency myelopathy. *J Neurol* 2010; 257:869–81.

Katz JN, Harris MB. Clinical practice. Lumbar spinal stenosis. *N Engl J Med* 2008; 358:818–25.

## 86 Weakness, proximal

---

Georgios Manousakis and and Glenn Lopate *Neurologic Differential Diagnosis*,  
ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge  
University Press. © Cambridge University Press 2014.

### Introduction

Proximal weakness is a sign elicited by physical examination. Patients often use the term “weakness” to describe fatigue (asthenia) or abnormal stance and gait resulting from sensory, proprioceptive loss or various central disorders. True weakness usually interferes with specific activities of daily living. For example, patients with shoulder weakness report difficulties combing or washing their hair, or getting objects from high shelves. Patients with biceps or triceps weakness have difficulties pushing or pulling objects respectively. With hip flexion weakness, a patient cannot go upstairs; hip extension weakness leads to problems getting up from a deep-seated chair. Knee extension weakness leads to buckling upon walking and inability to walk downstairs. Hip abductor weakness leads to waddling (Trendelenburg) gait. Paraspinal muscle weakness can lead to head drop (cervical) or bent posture (thoracolumbar). Lastly, diaphragmatic weakness leads to respiratory failure, often manifesting first at night (orthopnea, insomnia, night sweats, non-refreshing sleep, morning headaches, etc.).

The differential diagnosis of proximal weakness is vast and spans disorders of the upper motor neuron (UMN) and peripheral neuromuscular disorders, anywhere from the anterior horn to the muscle itself. Upper motor neuron disorders produce increased tone and reflexes, selective weakness of upper limb extensors and lower limb flexors, and slowing of coordinated movements; for their differential diagnosis, the reader is referred to other chapters in this book. To differentiate between neuromuscular disorders causing proximal weakness, specific elements of the history (e.g. time course, fluctuating versus steady deterioration, presence or absence of pain and sensory symptoms) and the examination (symmetric versus asymmetric weakness, stretch reflexes, involvement of bulbar, extraocular and/or respiratory muscles, associated sensory abnormalities) are critical. Some key clinical features that allow

differentiation between each anatomic localization and disease group are outlined in [Table 86.1](#). The list is not exhaustive; for more details on specific diseases, further reading is suggested at the end of the chapter.

## Case vignette

A 46-year-old male was referred to our center for weakness and suspicion of “motor neuron disease versus motor neuropathy or myopathy,” based on electromyography results and after he had a muscle biopsy which was interpreted as “non-diagnostic.” He reported a 3-year history of progressive difficulties with gait, particularly getting up from chairs, walking upstairs, and also lifting his chainsaw with his arms. His weakness and fatigue was fluctuating through the day, and was severely exacerbated in the evening. He also reported dry mouth, erectile dysfunction, dysesthesias and paresthesias, and a 30 lb unintentional weight loss over the last year. He was a heavy smoker (> 1 pack per day). Neurologic examination showed normal mental status and normal cranial nerve exam; there was no ptosis, ophthalmoplegia, or facial or bulbar weakness. Motor examination showed normal tone and bulk. There was no muscle atrophy or fasciculations. Symmetric proximal weakness was noted at the deltoids, iliopsoas, quadriceps, all at 4/5 on the Medical Research Council (MRC) scale with normal distal strength. Tendon reflexes were absent, but were markedly facilitated after a brief (10 s) sustained isometric contraction of muscle. Despite his dysesthetic complaints, sensory examination to vibration, proprioception, light touch, and temperature was normal. He had difficulty getting out of a chair but was walking without ataxia.

**Table 86.1 Proximal weakness: key clinical features that allow differentiation between each anatomic localization and disease group.**

Location	Signs of that localization	Etiologic category	Specific
Anterior horn	Flaccid weakness; fasciculations and cramps; early atrophy; areflexia (except ALS) No sensory signs	Degenerative	ALS (familial)

(except Kennedy's)  
No ophthalmoplegia

Spinal  
atroph  
(SMA)

Kenne  
(Bulb  
atroph

Other  
ataxia

Infectious

Polio  
West ]

Radiculopathy      Myotomal pattern of weakness and reflex loss  
Complete paralysis rare with single root disease, due to innervation of muscles by different roots; pain and sensory symptoms in corresponding dermatome(s); positive Spurling signs (cervical) or straight leg raising signs (lumbosacral disc herniation)

EMG, MRI, and CSF examination

Inflammatory

Vascu  
Sarcoi  
Diseas

neuron for diagnosis			Diagnoses
	Traumatic		Root avulsion, speed
	Infectious		Lyme, CMV, coxsackie, comm.
	Neoplastic/other		Epidural (primary, metastatic), Nerve (schwannoma, Leptomeningeal carcinomatosis, lymphoma)
Plexopathy (brachial or lumbosacral)	Weakness in distribution of affected division of plexus	Traumatic	Shoulder girdle fractures
	Typically unilateral or asymmetric bilateral weakness and loss of sensation/reflexes. Most are painful initially	Immune-mediated	Parsonage-Turner syndrome, amyotrophic lateral sclerosis

Trophic/autonomic changes in affected limb in chronic conditions  
(differentiate from polyradiculopathies)  
EMG, MRI, and CSF examination helpful

Diabe  
lumbo  
radicu  
neuroj  
amyot

Vascular

Hema  
with a  
Ischer  
abdon  
aneury  
athero  
vascul

Neoplastic/infiltrative

Lung,  
pelvic  
(color  
comm  
Infecti  
(absce

Radiation

Compression

Rucks

palsy/  
injury  
Postop  
Postpr  
plexop  
Conge  
plexus

Hereditary  
Hered  
amyot  
Hered  
with s  
pressu  
(HNP)

Proximal mononeuropathy	Suprascapular, axillary, musculocutaneous, long thoracic neuropathy (upper extremity) Femoral, obturator, sciatic, superior gluteal nerve (lower extremity) Motor +/- sensory deficits in individual nerve pattern; often residual pain EMG/NCS critical to identify mechanism and prognosis (neurapraxic vs. axonal injury);	Trauma Infiltrative/compressive Ischemic Immune mediated	Fractu compr iatrog Nerve (e.g. n Vascu typica nerves Forme Parsoi syndr
-------------------------	--	---	--

serial studies may  
be needed

Polyneuropathy	Early hypo-/areflexia, sensory loss (except multifocal motor neuropathy [MMN], some toxic neuropathies) Distal > proximal weakness is the rule in most neuropathies. Proximal weakness suggests a non-length-dependent neuropathy which could be treatable EMG key for diagnosis	Immune-mediated	Guilla syndr
----------------	---	-----------------	--------------

Chron  
demye  
polyne  
(CIDP)

Multif  
neuroj

Vascu  
isolate  
nervo  
vascul  
nodos  
Straus  
syndr  
micro  
polyar  
cryogl

Infectious

Diphth

Metabolic

Porph

Neuromuscular  
junction

Fluctuations of  
weakness (between  
examiners, diurnal –  
evening worse than  
morning)  
No atrophy  
Patterns of  
weakness vary  
between disorders  
(see comments)  
Normal sensory  
exam (may not be

Immune-mediated

Myast  
(MG)  
May h  
categc  
MuSK  
Anti-s  
antibo  
with tl  
also h  
respir

true with LEMS)  
Antibody testing  
(AChR, MuSK for  
MG, VGCC for  
LEMS) and  
electrodiagnosis  
(repetitive  
stimulation,  
SFEMG) useful

## Lamb<sup>o</sup> myast (LEM)

Infectious

Botuli

Heredity

## Congenital myasthenic syndrome

Toxic

pois or  
Tick p

Myopathy	Limb-girdle pattern of weakness; usually symmetric (except IBM, FSHD, occasionally LGMD2B, acid maltase); reflexes preserved until later stages; no sensory symptoms/signs CK often elevated (especially inflammatory, DMD, LGMD 2A/2B, glycogen storage, toxic, central core), EMG – myopathic (except metabolic and mitochondrial myopathies -- often normal) Muscle biopsy necessary for specific diagnoses, except FSHD, OPMD, DM2, DM1, periodic paralyses, EDMD (genetic testing first)	Acquired: 1. Inflammatory/ Immune	Polymyopathy Dermatomyopathy
----------	--	---	---------------------------------

Inclusion  
myopathy

Necrosis

2. Toxic/Metabolic  
Severe  
(statin  
amphi  
AZT,  
etc.)

Hypotonia

Electro  
(hypotonia  
hypop-

Genetic/inherited  
1. Congenital  
myopathies  
(usually infantile onset,  
biopsy is characteristic)  
Criticisms  
myopia  
myopia  
Central

Nemaline  
myopathy

Central  
myopathy

2. Muscular  
dystrophies  
Duchenne

Facioc  
muscu

Oculo  
muscu

Emery

Limb-  
dystro  
type 1  
LGMD

Myotc  
type 1

### 3. Metabolic

Glyco  
disord  
Myop  
defici

Acid r  
defici

Lipid  
disord  
defici  
defici

4. Mitochondrial  
disorders

Kearn  
syndr  
Isolate  
due to  
in mtI

5. Ion channel  
disorders

Hypol  
paraly

Hyper  
period  
Myotc  
(AR f  
AD fo  
Ander  
syndr

5. Other myopathies

Myofi  
myop;

---

AChR, acetylcholine receptor; ALS, amyotrophic lateral sclerosis; CK, creatine kinase; CMAP, compound muscle action potential; CMV, cytomegalovirus; COLQ, collagen-like tail subunit; CRP, C-reactive protein; CSF, cerebrospinal fluid; DM1 and DM2, myotonic dystrophy types 1 and 2; DMD, Duchenne muscular dystrophy; EDMD, Emery–Dreifuss muscular dystrophy; EMG, electromyography; ESR, erythrocyte sedimentation rate; FSHD, facioscapulohumeral muscular dystrophy; IBM, inclusion body myositis; IVIG, intravenous immunoglobulin; LMN, lower motor neuron; LP, lumbar puncture; MGUS, monoclonal gammopathy of undetermined significance; MRI, magnetic resonance imaging; MuSK, muscle-specific kinase; NCS, nerve conduction studies; OPMD, oculopharyngeal muscular dystrophy; POEMS, polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes syndrome; PMN, polymorphonuclear leukocytes; SFEMG, single fiber electromyography; SLR, straight leg raise; UMN, upper motor neuron; VGCC, voltage gate calcium channel; VZV, varicella zoster virus; WPW, Wolff–Parkinson–White syndrome.

## Discussion

This patient had subacute/chronic, fluctuating symmetric proximal weakness with areflexia and normal sensory examination. The diagnoses suspected by the referring physician may fit with this pattern; for instance, non-amyotrophic lateral sclerosis motor neuron diseases, such as Kennedy's or adult-onset spinal muscular atrophies. Immune motor neuropathies usually present with distal, asymmetric rather than symmetric proximal weakness. Symmetric proximal weakness is the classic pattern in several myopathies, but reflexes are usually lost in proportion to the degree of weakness, and one would not expect loss of ankle reflexes with strong gastrocnemius muscles. Clues to the correct diagnosis include several details in the history (dry mouth, erectile dysfunction indicating autonomic involvement, weight loss and smoking history indicating possible malignancy, fluctuating nature of the weakness indicating possible disease of the neuromuscular junction) and the physical examination (facilitation of reflexes after brief exercise), all pointing to Lambert–Eaton myasthenic syndrome (LEMS). Electrodiagnosis is critical for the confirmation of the suspected diagnosis. The characteristic finding is small CMAP amplitudes that increase in

size (facilitate) with 30 Hz repetitive nerve stimulation (RNS) or after sustained muscle contraction for 10 seconds. In our patient, CMAP increment of > 200% was noted after brief isometric exercise. Repetitive nerve stimulation at 2 Hz produced a significant (> 10%) decrement, another characteristic finding. Voltage-gated calcium channel antibodies were positive from serum. Computerized tomography (CT) of the chest and positron emission tomography (PET) scan were negative for malignancy, but because of the high index of clinical suspicion, they should be repeated at 6–12 month intervals. Note that about 60% of LEMS are paraneoplastic, with small-cell lung cancer being the most common malignancy. The remaining 40% are likely immune mediated and usually occur in younger patients without underlying malignancy; they may be associated with other autoimmune diseases .

## Further reading list

- Amato AA, Russell JA. *Neuromuscular Disorders*, 1st edn. New York, NY: McGraw-Hill, 2008.
- Bertorini TE. *Neuromuscular Disorders: Treatment and Management*, 1st edn. Philadelphia, PA: Elsevier-Saunders, 2011.
- Preston DC, Shapiro BE. *Electromyography and Neuromuscular Disorders: Clinical-electrophysiologic Correlations*, 2nd edn. Philadelphia, PA: Elsevier, 2005.
- Titulaer MJ, Lang B, Verschuur JJ. Lambert-Eaton myasthenic syndrome: from clinical characteristics to therapeutic strategies. *Lancet Neurol* 2011; 10:1098–107. [www.neuromuscular.wustl.edu](http://www.neuromuscular.wustl.edu).

## **Section 2 Differential Diagnosis within Specific Localizations**

---

## 87 Cavernous sinus syndrome

---

Vladimir Dadashev, Jonathan L. Brisman, and and John Pile-Spellman  
*Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

The cavernous sinus syndrome is defined by the presence of multiple cranial neuropathies as the result of involvement/compression of cranial nerves within the cavernous sinus (CN III, IV, V1, V2, VI).

### Cavernous sinus anatomy

The cavernous sinus is the collection of venous plexi within the two layers of skullbase dura and is bordered by temporal bone inferiorly, the sella turcica medially, and the sphenoid wing anteriorly. The carotid arteries on each side pass through the cavernous sinus on each side forming the carotid siphon. Five cranial nerves are located lateral to the carotid artery within the cavernous sinus. Those include, superior to inferior: cranial nerves III, IV, and VI (innervate the eye muscles, and parasympathetics for CN III). Additionally autonomic sympathetic fibers surround the carotid artery on the way to the orbit as well as CN V branches (V1 and V2).

### Case vignette (pituitary apoplexy)

A 64-year-old male presented with 24 hours of acute onset subtle confusion, headache, nausea, and inability to see out of the right eye. The vital signs were significant for hypotension (ultimately deemed to be secondary to hypocortisolism) and low-grade fever. On neurologic examination, the patient was verbalizing but disoriented to place. On cranial nerve exam, the right eye was deviated laterally and down with ptosis (eyelid drooping) and he could not move it medially (CN III and IV palsies). On visual exam, he had some light

perception but was unable to count fingers out of the right eye and had a temporal visual field loss out of the left eye. He also had a right afferent pupillary defect (decreased pupillary response to light).

Computerized tomography (CT) of the head showed a lesion suggestive of a pituitary macroadenoma with evidence of hemorrhage. The patient was started on stress-dose hydrocortisone. Pituitary protocol magnetic resonance imaging (MRI) was consistent with hemorrhagic pituitary macroadenoma with cavernous sinus invasion on the right and suprasellar extension with right optic nerve and chiasmal compression. Endocrine work-up revealed panhypopituitarism. The patient was taken for urgent surgical decompression. An endoscopic trans-sphenoidal adenomectomy was performed. Some visual improvement was noticed on postoperative day two. At 3-month follow-up, the vision has further improved, with near complete ophthalmoplegia resolution. The patient continued hormonal replacement.

**Table 87.1 Differential diagnosis of cavernous sinus syndrome.**

Item	Subdivision	Specific entity	Possible feature
Structural (tumors)	Tumors within the cavernous sinus	Meningiomas Schwannomas	Progressive ophthalmoplegia Retrograde amnesia
	Tumors from outside compressing/invasive cavernous sinus	Pituitary adenomas Meningiomas Schwannomas Chordomas Chondrosarcomas Nasopharyngeal carcinomas Esthesioneuroblastomas Metastatic lesions	Progressive ophthalmoplegia Retrograde amnesia Endocrinopathy Visual field defects
Structural (vascular)	Aneurysms	Cavernous segment aneurysms	Progressive ophthalmoplegia Post-gangrene limb syndrome

		ptosis)
	Proximal intradural intracranial aneurysms	As per Subarachnoid hemorrhage
	Carotid--cavernous fistulas	Exophthalmos Conjunctival chemosis Visual loss
	Cavernous sinus thrombosis	Retro-orbital pain Horner's syndrome Ophthalmoplegia
Infection	Mucormycosis, phycomycosis	Fungal infections, usually in diabetics
	Herpes-zoster virus (HZV) ophthalmicus	Reactivation of HZV in V1 branch of trigeminal nerve/nucleus
Inflammatory	Tolosa--Hunt syndrome	Forehead and eyelid/rhinopharyngeal HZV lesions Conjunctival injection
	Sarcoidosis	Inflammation within the cavernous sinus and superior orbital fissure
		Unilateral headache Ophthalmoplegia
		Facial palsy Optic disc swelling Ophthalmoplegia Hypothalamic abnormalities Uveitis Systemic disease
Traumatic	Variety of skull base fractures that involve the cavernous sinus	Symptoms of fracture

## **Further reading list**

Greenberg M. *Handbook of Neurosurgery*. New York, NY: Thieme, 2010.

Oyesiku NM, Tindall GT. Endocrine-inactive adenomas: surgical results and prognosis. In Landolt AM, Vance ML, Reilly PL, Eds. *Pituitary Adenomas*. New York, NY: Churchill-Livingstone, 1996: 377–83.

Winn HR, Ed. *Youmans Neurological Surgery*, 6th edn. New York, NY: Elsevier, 2012.

## 88 Facial nerve palsy

---

Philip Ragone *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

The seventh cranial nerve or facial nerve originates in the pons. The major function of the facial nerve is control of the muscles of facial expression. It also innervates the stapedius muscle in the middle ear. Dysfunction of the stapedius muscle results in hyperacusis. The facial nerve also provides parasympathetic innervation to the salivary glands and taste sensation to the anterior two thirds of the tongue.

Facial nerve palsy can be the result of supranuclear, nuclear, or infranuclear dysfunction. Supranuclear lesions of the facial nerve affect motor function of the lower two thirds of the face sparing the frontalis (which is bilaterally innervated). Hyperacusis and impaired lacrimation and taste which occur in nuclear and infranuclear lesions are lacking in supranuclear lesions. With brainstem processes, there can be accompanying long tract signs and gaze palsies. Nuclear lesions of the facial nerve are the result of disease processes occurring in the brainstem (pons and medulla). Infranuclear lesions are usually due to injury in the subarachnoid space, skull base, and distally. In cases of nuclear and infranuclear dysfunction, other usually proximally located cranial nerves can be involved.

The differential diagnosis in [Table 88.1](#) focuses on nuclear and infranuclear etiologies.

**Table 88.1** *Differential diagnosis of facial nerve palsy.*

---

Category	Clinical features
Idiopathic	Retroauricular pain, hyperacusis, vague

Bell's palsy	facial numbness, lacrimation, and facial weakness. 90% recover completely 80% of all peripheral facial palsies are idiopathic. Herpes simplex virus (HSV) suspected as cause
Trauma	All occur due to trauma to the facial nerve. In particular, obtain comprehensive dental history. The most common cause of dental malpractice
Skull and facial fracture	
Parotid surgery or other procedures	
Dental procedure/anesthesia	
Infection	Facial palsy occurs during the early disseminated stage and is associated with rash at areas remote from bite, headache, migratory arthralgias, limb tingling and numbness, fever, and malaise. Frequent cause of bilateral facial palsy
Lyme disease	Can be seen, sometimes bilaterally, in early disease associated with aseptic meningitis
HIV	Subacute course manifested by headache, neck stiffness, irritability and weight loss. Basilar meningitis can result in cranial neuropathies. Concern heightened in immune compromised e.g. HIV and populations at increased risk particularly from Asia, Latin America, and Africa
<i>Mycobacterium tuberculosis</i>	Painful facial palsy associated with eruption and induration of external auditory canal and pinna
Herpes zoster (Ramsay Hunt syndrome)	Complications include headache, vertigo, hearing loss, facial palsy, meningitis, brain abscess, hydrocephalus
Bacterial otitis media	Meningeal neurosyphilis occurs within
Syphilis	
Epstein–Barr virus	
Cytomegalovirus (CMV)	
Mycoplasma	

a year of primary infection.  
Manifestations include headache, fever, neck stiffness. CSF pressure elevated with lymphocytosis, increased protein, and low glucose. Facial diplegia and hearing loss can occur  
CNS involvement < 1%. Aseptic meningitis, encephalitis, myelitis, optic neuritis, facial neuropathy, and other cranial neuropathies  
Consider especially in immune compromised patients, *e.g.* HIV  
Usually causes acute respiratory illness.  
Neurologic manifestations include meningoencephalitis, meningitis, and cranial neuropathies

Neoplasm	Parotid mass; 30% can be painful; 7–20% of malignant tumors present with weakness
Parotid tumor	85% are vestibular schwannomas, lipomas, vascular malformations, and hemangiomas. Less frequently meningiomas, epidermoids, facial and lower cranial nerve schwannomas, and arachnoid cysts
Cerebellopontine angle (CPA)	Rare but relevant in patients previously treated for advanced disease
Nasopharyngeal carcinoma	Almost exclusively in non-Hodgkin's lymphoma and carcinomas, in particular lung, breast, melanoma, renal cell, bladder, germ cell tumors, <i>e.g.</i> testicular, and certain sarcomas
Lymphoma, carcinoma, and leptomeningeal carcinomatosis and lymphomatosis	
Vascular	Ischemic cranial mononeuropathy as part of a mononeuritis multiplex
Vasculitis	
Stroke	Median pontine infarction (Foville syndrome) due to basilar artery thrombosis manifested by ipsilateral

	peripheral facial palsy, ipsilateral gaze palsy due to dysfunction of paramedian pontine reticular formation and/or abducens nucleus, and contralateral hemiplegia sparing face
Endocrine Diabetes	Probably the result of nerve ischemia
Granulomatous Sarcoidosis Melkersson–Rosenthal syndrome	Inflammatory disease typically with chest symptoms. Nervous system involvement in 5%. Cranial nerves can be involved most frequently and sometimes bilaterally the facial nerve Rare disorder occurring in childhood or early adolescence. Recurrent facial paralysis with swelling of face and lips and development of folds and furrows in tongue. Sometimes associated with sarcoidosis or Crohn's disease
Demyelinating AIDP/Guillain–Barré syndrome	Acute ascending paralysis with milder sensory symptoms, ataxia, hypo-or areflexia and often bilateral facial palsy
Inflammatory/autoimmune Sjögren's syndrome	Can present with multiple recurrent cranial nerve palsies even if prominent sicca symptoms are absent
Infiltrative Amyloid	Two forms: (1) light chains with primary amyloidosis and (2) transthyretin in hereditary amyloidosis. Often causes small fiber painful and autonomic neuropathy. Most common focal neuropathy is carpal tunnel syndrome
Mimickers Botox <del>Mycophenolate</del>	Can cause inadvertent facial weakness particularly eyelid drooping <small>Typically progressive and associated with other neurological findings</small>

### **Primary progressive and associated**

**Myasthenia gravis**

### **Primary progressive and associated**

**with other weakness, e.g.**

**facioscapulohumeral muscular dystrophy**

**Common autoimmune neuromuscular disorder most frequently heralded by ptosis and ophthalmoparesis. Facial weakness is common**

**Congenital  
Moebius syndrome**

**Congenital bilateral sixth and seventh  
nerve palsies**

---

AIDP, acute inflammatory demyelinating polyneuropathy; CNS, central nervous system; CSF, cerebrospinal fluid.

## **Case vignette**

A 36-year-old right-handed female was referred for neurologic consultation at the suggestion of her primary care physician.

The patient was well until a week ago when she developed right retroauricular discomfort. The following day she noticed a distorted smile and drooling from the right side of her mouth when she drank. Her right cheek felt tight and tingling. Sounds in her right ear seemed muffled. She had mild difficulty swallowing. She had been experiencing chills for the previous 3 days. She denied headache, neck pain or stiffness, fever, chills, cognitive, motor, sensory, or sphincteric difficulties. She denied rash or tick bites, although she lived in a rural area with a large deer population in Long Island, New York.

On examination, the pulse was 56 and blood pressure was 130/100. Respiratory rate was 20. Lungs were clear and cardiac rhythm was regular without murmur. Neck was supple. There were no palpable masses or tenderness in the neck, submandibular region, or jaw. Spine was non-tender. Tympanic membranes were clear. There was no eruption about the right pinna or external canal. There was no pedal edema or carotid bruits. Pedal pulses were full. She was alert and appropriate. Her speech was mildly slurred. Visual acuity was 20/25 bilaterally with glasses with normal pupillary responses, fundi, visual fields, and eye movements. Facial sensation was normal. There was complete

weakness on the right side of the face including the frontalis and there was poor eyelid closure. There was distortion of hearing in the right ear, described as high pitched and tinny. Tongue, palate, sternocleidomastoids, and trapezii were normal. Motor examination revealed normal bulk and tone with full strength. Sensory examination was notable for intact pinprick, light touch, joint position, and vibration sensation. Reflexes were 2 throughout. Plantar responses were flexor. Gait and tandem were normal. Romberg was negative.

The patient presents with a severe right peripheral facial palsy. Although there are no obvious long tract signs or gaze palsy, the presence of mild dysarthria and vague right cheek numbness raise concern regarding a brainstem process. Magnetic resonance imaging of the brain and internal auditory canals with and without contrast was obtained and failed to reveal any parenchymal brainstem lesion but did reveal enhancement of the geniculate ganglion. Complete metabolic panel (CMP) and complete blood count (CBC) were normal. Lyme titer was negative.

A clinical diagnosis of Bell's palsy was made. Treatment was initiated with valacyclovir and prednisone, lubricating ointment use during sleep to prevent exposure keratitis, and eye protection particularly when outdoors to avoid foreign body injury to the cornea.

Facial nerve stimulation study was performed 8 days after symptom onset to quantitate the severity of axonal injury and predict timing and expected extent of recovery.

## Further reading list

Blum AS, Rutkove SB, Eds. *The Clinical Neurophysiology Primer*. Totowa, NJ: Humana Press, 2007.

Goldman L, Schafer AI. *Goldman's Cecil Medicine*, 24th edn. New York, NY: Elsevier, 2011.

Herskovitz S, Scelsa SN, Schaumburg HH. *Peripheral Neuropathies in Clinical Practice. Contemporary Neurology Series*, 76. New York, NY: Oxford University Press, 2010.

Rowland LP, Pedley TA. *Merritt's Neurology*, 12th edn. Philadelphia, PA: Lippincott Williams & Wilkins, 2009.

## **89 Fourth nerve palsy**

---

Kristina Y. Pao and Mark L. Moster *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

The cranial nerve (CN) IV nucleus lies within the gray matter caudal to the CN III nucleus in the dorsal midbrain just below the cerebral aqueduct. The CN IV fascicles run dorsal to the medial longitudinal fasciculus then course posteroinferiorly around the cerebral aqueduct and cross within the anterior medullary velum just caudal to the inferior colliculus [1]. The trochlear nerve is the only cranial nerve to emerge from the dorsal surface of the brainstem and the only one that crosses to the contralateral side. It is particularly susceptible to trauma as it crosses.

The cisternal segment of CN IV courses anteriorly over the lateral aspect of the brainstem where it pierces the dura entering the postero-lateral aspect of the cavernous sinus just inferior to CN III and superior to CN VI. CN IV shares a common connective tissue sheath with CN III, V1, and V2 within the lateral wall of the cavernous sinus before crossing anteriorly over CN III to enter the superior orbital fissure. CN IV courses superomedial to the annulus of Zinn and crosses the optic nerve before innervating the superior oblique. The actions of the superior oblique are depression (especially when adducted) and intorsion of the eyeball.

### **Symptoms**

Symptoms of fourth nerve palsy may include binocular vertical and/or oblique diplopia worse in downgaze and the sensation that objects may appear tilted.

### **Signs**

Ocular motility may grossly appear normal or reveal a mild inability to depress the eye when it is in the adducted position. Alternate cover testing reveals an incomitant (varies with different eye positions) hypertropia that may become comitant over time. Seventy percent of patients will have a contralateral head tilt away from the hypertropic eye, while 3% will have a paradoxical head tilt towards the hypertropic eye.

The Parks–Bielschowsky three-step test using the cover–uncover or Maddox rod is the way to demonstrate the ocular deviation characteristic of a fourth nerve palsy [1].

## Parks–Bielschowsky three-step test

The Parks–Bielschowsky three-step test is an algorithm used to determine the paretic muscle using the cover–uncover or Maddox rod test and measuring the amount of vertical deviation in different head positions. The three steps are:

1. Determine which eye is hypertropic (deviated upward) using the cover–uncover or Maddox rod test.
2. Determine if the hypertropic eye is deviated upwards more on left or right gaze.
3. Determine if the hypertropic eye is deviated upwards more on left or right head tilt.

A fourth nerve palsy will have a hypertropia in the eye on the side of the fourth nerve lesion that is worse in contralateral gaze and ipsilateral head tilt. This may be confirmed with an extra fourth step: demonstrating that it is worse in downgaze than upgaze.

Suspect a bilateral superior oblique palsy when a “V” pattern esotropia (eyes appear abducted or deviated towards the nose when looking downward) is present in conjunction with hypertropia of the right eye when looking left and hypertropia of the left eye when looking right and excyclotorsion of 10° or more.

## Isolated fourth nerve palsy

When a fourth nerve palsy occurs in the setting of other neurologic findings one can localize the lesion and often narrow the differential diagnosis based on those other findings. When there are no other findings, the lesion may be anywhere between the dorsal midbrain and orbit. The main causes of an isolated fourth nerve palsy are listed in [Table 89.1](#) and include trauma, vasculopathic,

congenital, compressive, or a structural brainstem lesion (e.g. stroke, demyelination, tumor, infection).

**Table 89.1 Causes of fourth nerve palsy.**

Etiology	Work-up	Treatment	Clinical Features
Trauma (e.g. accidental, iatrogenic)	CT scan of head and orbits without contrast	Occlude either eye, as needed. If deviation stable for 6 months, consider prism glasses or strabismus surgery if patient symptomatic in primary gaze	May be isolated unilateral or bilateral common bilateral fourth nerve palsies [5]. Progression
Vasculopathic	None if age > 50 with microvascular disease risk factors (e.g. hypertension, diabetes mellitus, hypercholesterolemia) [6]. Check blood pressure, random blood glucose, hemoglobin A1c, lipid panel. ESR if over 55. CTA or MRA of brain and brainstem, CBC, ANCA panel	Microvascular causes: spontaneously resolve in 3 weeks to 6 months. Blood pressure, blood glucose, and cholesterol control Refer to neurosurgery if fistula or aneurysm is present	Typically 3–6 months with partial attention if new neurological symptom or persist for 6 months LP if MR
Demyelinating disease (e.g. multiple sclerosis)	MRI of brain with gadolinium	Immunomodulatory agents for multiple sclerosis	

Congenital

Examiner aid

Pointing to lesion

Patient's t

Congenital	Examine via photographs for long-standing head tilt and measure vertical fusion capacity, which is increased to greater than 6 prism diopters in congenital fourth nerve palsy	Assume, unless symptomatic. If deviation stable for 6 months, consider prisms or strabismus surgery if symptomatic in primary gaze. If head tilt is cosmetically significant, consider strabismus surgery	Patient is not comp subjectively. Typically decompen to 6th dec when ver fusional & diminish
Idiopathic	Work-up negative and does not resolve after 6 months	If deviation stable for 6 months, consider prisms or strabismus surgery if patient symptomatic in primary gaze	
Inflammatory (e.g. sarcoidosis, Wegener granulomatosis, Tolosa–Hunt syndrome)	Check ESR, ANA, ACE, CXR, RF, ANCA panel	May require referral to pulmonologist	Tolosa–Hunt syndrome diagnosis exclusion associated with severe bo
Infectious (e.g. tuberculosis, herpes zoster, mucormycosis, zygomycosis, cavernous sinus thrombosis)	CT/MRI of brain and orbits Early surgical debridement and biopsy of necrotic tissue if fungal infection suspected. Check CBC, random blood glucose, hemoglobin A1c.	Immediate admission and evaluation by otolaryngology, neurosurgery, endocrinology, and infectious disease if sinusitis is present Consider systemic anticoagulation if	Suspect fungal infection in immunocompetent patients (uncontrolled diabetics, patients with multiple comorbidities) and neurooncology

	PPD, CXR, 2–3 sets of peripheral blood cultures from different sites, cultures from presumed primary source of infection	cavernous sinus thrombosis present	Invasive sinusitis (aspergillosis) present in immunocompetent patients
Compressive lesions in brainstem, subarachnoid space, cavernous sinus, or orbit (e.g. neoplasm, dural arteriovenous fistula, aneurysm, mucocele, pituitary adenoma)	CT or MRI of brain and orbits. May require MRA/CTA or cerebral angiography	Refer to neurosurgery or oculoplastics specialist. Refer to neurosurgery if fistula or aneurysm is present	Orbital tumors may involve cranial nerves (e.g. III, IV, V) and may present with painful proptosis

ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; CBC, complete blood count; CT, computerized tomography; CTA, computerized tomography angiography; CXR, chest X-ray; ESR, erythrocyte sedimentation rate; LP, lumbar puncture; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; PPD, purified protein derivative; RF, rheumatoid factor.

## Differential diagnosis

The differential diagnosis of fourth nerve palsy includes myasthenia gravis, thyroid eye disease, idiopathic orbital inflammatory syndrome, orbital fracture, skew deviation due to a posterior fossa or brainstem lesion, incomplete third nerve palsy, Brown syndrome, and giant cell arteritis.

Skew deviation is a comitant or noncomitant vertical strabismus caused by a

supranuclear lesion in the brainstem, cerebellum, or peripheral vestibular system. It is often associated with other neurologic signs and can mimic a fourth nerve palsy. However, if cyclotorsion is present, the hypertropic eye incyclotorts (rotated toward contralateral shoulder), while the hypotropic eye excyclotorts in skew deviation. Another way to differentiate a skew deviation from a fourth nerve palsy is by performing the upright–supine test [2]. A positive test favors a diagnosis of skew deviation when the vertical deviation decreased by  $\geq 50\%$  from the upright position to the supine position [2].

## **Non-isolated fourth nerve palsy**

### **Symptoms**

Symptoms of a non-isolated fourth nerve palsy vary depending on the involvement of other cranial nerves, long tracts in the brainstem, meningeal inflammation, or structures in the cavernous sinus or orbit. Symptoms may include a different pattern of diplopia, ptosis, pupil asymmetry, facial pain or numbness, sensory loss, ataxia, visual loss, proptosis, or conjunctival injection.

### **Signs**

Involvement in the midbrain can be associated with a variety of long tract and other cranial nerve signs. Meningeal involvement will often be associated with headache and other cranial nerve deficits that may not be anatomically near the fourth nerve. Cavernous sinus involvement may be associated with a third or sixth nerve palsy, involvement of V1 and/or V2, Horner's syndrome, and – if due to an arteriovenous fistula – proptosis, chemosis, and arterialization of vessels on the conjunctiva. Orbital involvement may be accompanied by other ocular motility defects, optic neuropathy, proptosis, and conjunctival chemosis and injection.

### **Differential diagnosis**

The differential diagnosis of non-isolated fourth nerve palsies includes the entities described above in the differential diagnosis of isolated fourth nerve palsies. Additional considerations in the differential diagnosis depend on the associated findings and may also include chronic progressive external ophthalmoplegia (CPEO), idiopathic orbital inflammatory syndrome, carcinomatous meningitis, progressive supranuclear palsy, myotonic dystrophy,

Miller–Fisher variant and/or Guillain–Barré syndrome, skullbase tumors (e.g. nasopharyngeal carcinoma, clivus lesions), mass lesions in the cavernous sinus, and brainstem lesions [3].

## Case vignette 1

A 60-year-old female with a history of diabetes mellitus and hypertension presents to the emergency room with sudden onset of double vision. She states that the double vision occurs with both eyes open, but resolves when closing either eye. The double vision is worse when reading and objects appear tilted. She has no history of trauma and no associated neurologic symptoms.

The patient's blood pressure is 165/95 and her random blood glucose is 245. Visual acuity is 20/20 in both eyes. There is no mass, proptosis, lid lag, or lid retraction, but the patient appears to have a left head tilt. Pupils are briskly reactive without an afferent pupillary defect or Horner's syndrome, and visual fields are full by confrontation. Parks–Bielschowsky three-step test reveals 3 prism diopters of right hypertropia on primary gaze, 1 prism diopter of right hypertropia on right gaze, 5 prism diopters of right hypertropia on left gaze, 6 prism diopters of right hypertropia on right head tilt, and 2 prism diopters of right hypertropia on left head tilt.

## Discussion

This patient likely has a microvascular isolated right fourth nerve palsy. She has a history of hypertension and diabetes without other neurologic symptoms. The Parks–Bielschowsky test demonstrates a right hypertropia in primary gaze that is worse in opposite gaze and better in opposite head tilt. She also appears to have a left head tilt. Blood pressure and blood glucose should be optimized in this patient and a fasting lipid panel should be obtained. Because of her age, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and platelet count should be obtained to rule out giant cell arteritis.

The patient should be followed every 3 months. If she develops new symptoms or if her present symptoms worsen or persist for longer than 6 months, magnetic resonance imaging (MRI) of the brain and brainstem should be obtained.

## Case vignette 2

A 41-year-old female with a past medical history of migraines and hypothyroidism presents with a 2-month history of binocular vertical diplopia, initially on left head tilt only. However, the diplopia now occurs in other positions. Her diplopia is worse in downgaze, right gaze, and left head tilt. Her diplopia improves with right head tilt. Her symptoms are associated with a headache that is worse than her usual migraines.

The patient's ocular examination reveals a visual acuity of 20/20 in the right eye and 20/25 in the left eye. There is no proptosis, lid lag, or lid retraction. Pupils are briskly reactive without an afferent pupillary defect or Horner's syndrome, and visual fields are full by confrontation. She identifies 14 of 14 color plates briskly in each eye. Ocular motility is full. However, Parks–Bielschowsky three-step test reveals 5 prism diopters of left hypertropia on primary gaze, 12 prism diopters of left hypertropia on right gaze, 1 prism diopters of left hypertropia on left gaze, 2 prism diopters of left hypertropia on right head tilt, and 18 prism diopters of left hypertropia on left head tilt ([Figure 89.1](#)). She also exhibits a spontaneous right head tilt. Vertical fusion capacity is 2 prism diopters. Examination of an old photograph reveals absence of a head tilt.

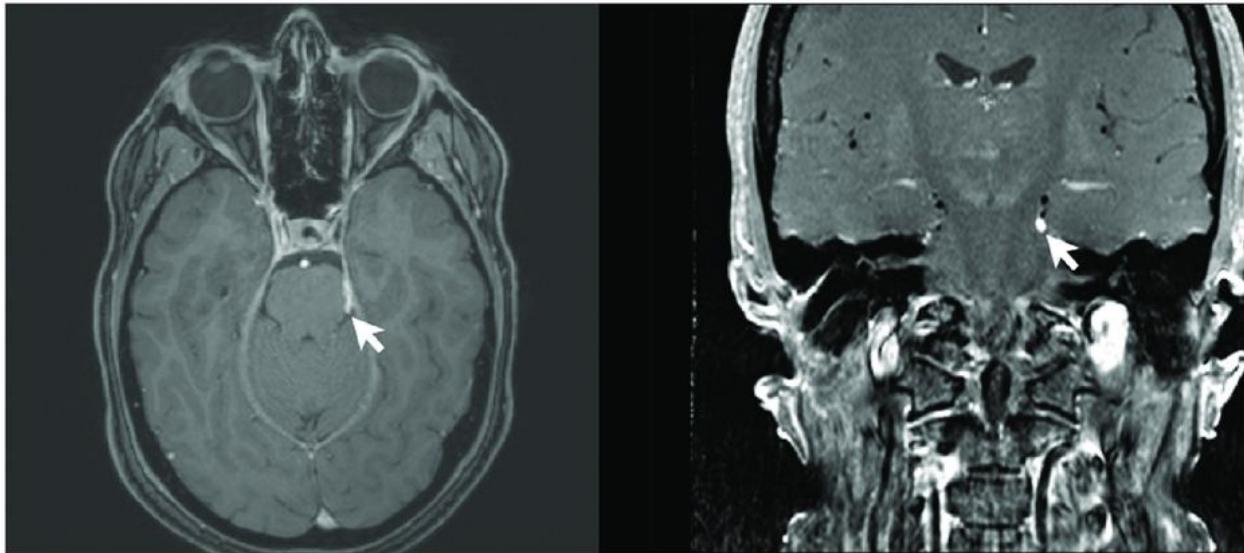


**Figure 89.1** External photograph. Left hypertropia is present in primary gaze, worse in right gaze, downgaze, and left head tilt. The patient prefers right head tilt to minimize her diplopia.

## Discussion

This patient has a new isolated left fourth nerve palsy. She does not have clinical risk factors for a microvascular event and she is too young for giant cell arteritis. An MRI of the brain and orbits revealed a lesion along the left fourth nerve in

the perimesencephalic cistern consistent with a schwannoma ([Figure 89.2](#)) [4]. After further worsening of her fourth nerve palsy and enlargement of the lesion on MRI, neurosurgery and radiation oncology were consulted, and the patient underwent fractionated stereotactic radiotherapy.



**Figure 89.2** T1-weighted magnetic resonance image of brain and orbits with fat suppression. A lesion was noted along the left fourth nerve in the perimesencephalic cistern (arrow).

## References

1. Brazis PW. Isolated palsies of cranial nerves III, IV, and VI. *Semin Neurol* 2009; 29:14–28.
2. Wong AMF. Understanding skew deviation and a new clinical test to differentiate it from trochlear nerve palsy. *J AAPOS* 2010; 14:61–7.
3. Prasad S, Volpe NJ. Paralytic strabismus: third, fourth, and sixth nerve palsy. *Neurol Clin* 2010; 28:803–33.
4. Elmalem VI, Younge BR, Bioussse V *et al*. Clinical course and prognosis of trochlear nerve schwannomas. *Ophthalmology* 2009; 116:2011–6.
5. Mollan SP, Edwards JH, Price A *et al*. Aetiology and outcomes of adult superior oblique palsies: a modern series. *Eye* 2009; 23:640–4.
6. Murchison AP, Gilbert ME, Savino PJ. Neuroimaging and acute ocular motor mononeuropathies: a prospective study. *Arch Ophthalmol* 2001; 129:301–5.

## 90 Myelopathy

---

Amanda R. Bedford and and Randall J. Wright *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

“Is it in the Dura or outside the Dura, that is the Question!”

### Introduction

The 2:00 a.m. call from the emergency room stating “we have a 45-year-old male who is coming in for a 3-day complaint of progressive weakness in his legs and is not able to feel anything below his waist...” is a call that will send a shock down the spine of most neurologists. The possible causes are vast and many require emergent attention. At first glance, such a complaint can set off an exploration of conditions as simple as B12 deficiency to as complex as Foix–Alajouanine syndrome. However, with some basic understanding of the anatomy of the spinal column and how a few key disease states can affect it, one can readily narrow the search and arrive at a precise cause of the myelopathy (lesion affecting the spinal cord).

The vertebral column consists of 31 vertebra in total, 7 cervical, 12 thoracic, and 5 in the lumbar region. The sacrum is composed of five vertebra that are fused, and two coccygeal. The vertebral column's purpose is to protect the spinal column from injury. Each vertebral body is separated by a cartilaginous joint known as the intervertebral disc. Various conditions can affect the discs or other parts of the vertebral body. The spinal cord runs down the center of the vertebral columns and is composed of long tracts that relay information to and from the brain.

Basic vertebral column anatomy is divided into four main sections aligned vertically starting with cervical, followed by thoracic, lumbar, and sacral.

Cervical spine: C1–C7 begins at the base of the skull and runs down the length of the spinal cord to about midline of the shoulders.

Thoracic spine: T1–T12 picks up where C8 stops between the shoulders and

continues down to around the middle of the waist or hip level.

Lumbar spine: L1–L5 starts right below T12 around the hips and runs a short distance to the right above the tailbone in the gluteus maximus.

Sacral spine: S1–S5 runs the length of the gluteus maximus. In healthy adults these sections are fused together to make up one single bone structure.

Coccyx: Co1 is the very last subdivision of the spinal cord and is also fused together completing the spinal cord track.

## Basic anatomy of single vertebrae

The largest portion of any vertebrae is called the body. The body is a circular thick portion of bone; in a healthy spinal cord these are aligned one on top of another. From cervical down to lumbar the body, as with all spinal cord structures, becomes larger and thicker to accommodate the increase in load. The body of each vertebra carries the weight within the spinal cord.

Moving from the body posteriorly (towards the back) are long protrusions on either side called the transverse process and one long protrusion in the middle known as the spinous process. The transverse processes along with the spinous process form a triangle shape that is the point of attachment for joints and muscles.

Contained in the middle of every vertebra is a wide hole called the vertebral foramen. The vertebral foramen exists to protect the actual spinal cord which runs the length within it. This area is also home to adipose tissue, blood vessels, and spinal nerves that project through the vertebrae and into specific areas of the body.

## Long tracts in the spinal cord

Long tracts contained within the spinal cord carry information between the brain and the rest of the body. The tracts are classified based upon whether they send information to the brain (**ascending** – adding information) or from the brain (**descending** – delegating instructions).

The main tracts of the spinal cord are:

Dorsal column (ascending tract) Fasciculus gracilis medial: carries proprioception (position in space) from the legs and middle thoracic region to the brainstem. Information in this tract enters the spinal cord and travels up the

spinal cord ipsilateral to location of entry. It then crosses midline in the brainstem and travels to the thalamus and cerebral cortex. Lesions that occur at a certain level will cause ipsilateral proprioceptor loss based on location of lesion. Fasciculus cuneate: this tract is responsible for relaying information about light pressure and proprioception from the upper extremities to the brain. Lesions here also cause ipsilateral proprioceptor loss based on location of lesion.

Lateral spinothalamic (ascending tract): runs from the spinal cord to the thalamus of the brain providing sensory input about pain and temperature. This tract will immediately (within 1–2 levels) cross midline contralateral from origin and travel to the brain on the contralateral side of the spinal cord. Therefore lesions in this location will cause pain and temperature loss on the contralateral limbs and below the point of entry.

Spinocerebellar (ascending tract): runs from the spinal cord to the cerebellum of the brain with information about the position of the body respective to limbs. This tract does not cross midline; its fibers enter the cerebellum ipsilateral to their site of origin.

Cortical spinal tract or pyramidal tract (descending tract): this tract originates in the primary motor area of the cerebral cortex, more specifically the precentral gyrus. Its fibers cross in the brainstem and travel down the spinal cord. Lesions in the spinal cord thus cause ipsilateral weakness below the level of the lesion.

## Vascular supply of the spinal cord

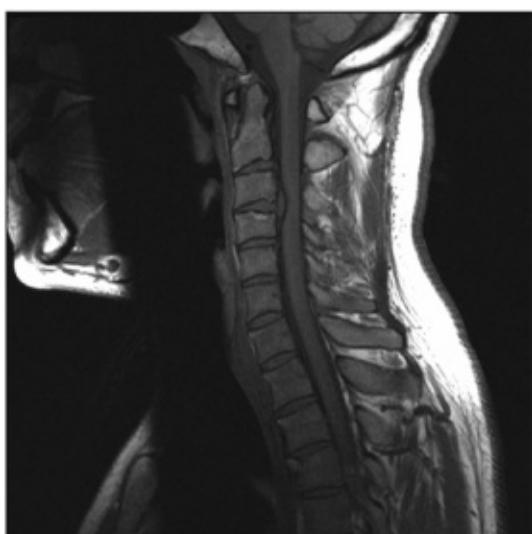
The vascular supply to the spinal cord is important to know due to possible ischemia (blood restriction) events within the spinal cord; these events can lead to a variety of clinical symptoms.

Once the blood enters the spinal cord it is distributed to four types of arteries. These arteries are:

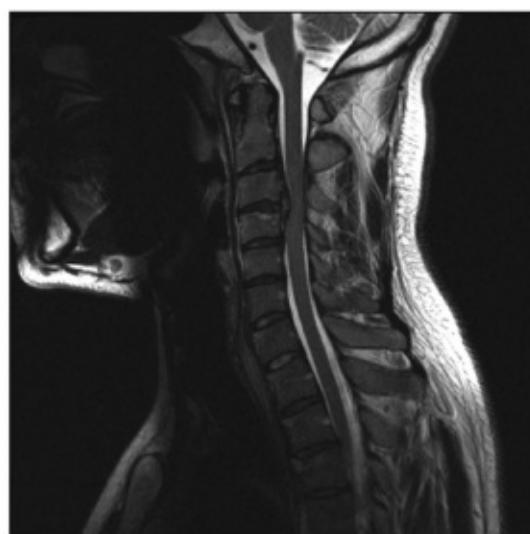
1. Anterior spinal artery: supplies two-thirds of blood to the anterior spinal cord in the cervical region.
2. Posterior spinal arteries: the two posterior spinal arteries together supply one-third of blood to the posterior cervical spinal cord.
3. Segmental artery: supplies blood to the thoracic and lumbar regions of the spinal cord.
4. Artery of Adamkiewicz: supplies the caudal cord portion of the spinal cord to the extent of almost two-thirds.

## Nerves attaching to the spinal cord

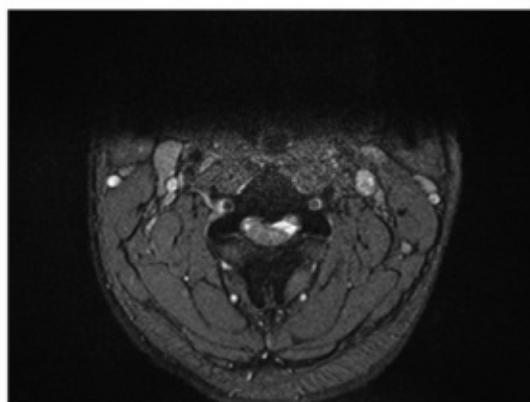
From each spinal cord region nerve roots attach to the spinal cord. Those that attach from the posterior lateral sulcus are called the dorsal roots and those that attach on the ventral side of the spinal cord are called ventral roots. When nerve roots exit the vertebral column, they do so through a space called the intervertebral foramen. The first seven cervical nerve roots exit above the corresponding vertebral body and C8 exits below the C7 vertebra. I like to call the first seven cervical nerves the “Heavenly Seven” for they are above the rest.



(a)



(b)



(c)

**Figure 90.1**

[Table 90.1](#) details specific conditions that may cause weakness, sensory changes, or other symptoms in patients suffering from spinal cord-related illnesses.

## Case vignette

A 28-year-old female athlete presents with extreme neck pain and an inability to move her neck without sharp pain. Patient denies any recent trauma and states she “just woke up unable to move.”

On exam, she was alert and oriented to person, place, and time. Cranial nerves 2–12 were grossly intact. Her motor exam was 5/5 throughout, except for mild give-way weakness in her right shoulder abductors and biceps due to pain. She did complain of pain in her neck with turning left or right. The pain radiated down her right neck, arm, and into her right thumb. Her reflexes were 3+ in her biceps and patellas bilaterally. Sensation was grossly intact.

Magnetic resonance imaging (MRI) without contrast is obtained to determine any structural changes. Results indicate a disc protrusion at the C5–C6 level. The disc protrusion is clearly seen in the MRI as impinging upon the C6 nerve root with mild contact of the spinal cord at that level.

The patient is referred to neurosurgery to assess the possibility of surgery. She is also prescribed muscle relaxants to halt the muscular neck spasms and relieve pain. After discussing results with the patient, she reported that in fact a few months earlier, she was thrown from a wave runner and hit the water hard enough to cause shoulder pain for days. This admission indicates the disc protrusion is probably caused by the trauma associated with this incident.

**Table 90.1 Differential diagnosis of myelopathy.**

Item	Area affected	Etiology	Possible clinical features
<b>Structural (congenital or acquired)</b>			
Spina bifida	A neural tube defect that results in incomplete closure of the bones of the spinal canal	Birth defect that affects about 1 in 800 newborns May be due to maternal folic acid deficiency during early pregnancy	Meningoformatio where the tissue co the spina protrudes through t

		bony def forming a external j visible or examinat the infant back
		Loss of sensation legs
		Paralysis legs
		Loss of b or bladder control, weakness incontine
		Hydroce
		Tuft of h dimpling sacral are
		Feet abnormal
Tethered cord syndrome	Typically affects the conus medullaris of the spine	Malformation causing tissue to attach to spinal cord, which over time stretches the cord May occur after trauma
		Limited movemei spinal co Sensory & motor fu loss
		Bowel or bladder incontine
		Tuft of h dimpling sacral are
		Feet abnormal

<b>Trauma</b>	Posterior and anterior column	Compression, impact, hyper/hypoextension	Pain and weakness loss of function, numbness based on segment involved
Hyperlordosis (swayback)	Exaggerated curvature of the lumbar region of spinal canal	Hereditary, birth defect, obesity, osteoporosis, discitis	Inward curvature spinal cord Low back pain Limited range of motion
Scoliosis	May affect any of the natural curvature regions of the spine (cervical, thoracic, lumbar, sacral)  Kyphoscoliosis is abnormal front to back curvature, given a “rounded back” appearance	Congenital, neuromuscular causes, idiopathic	Outward curvature Pain Uneven shoulders Twist in spine leading to uneven rib cage Compression of lungs may occur in some cases
Spondylolisthesis	The anterior or posterior slippage of one disc on another	Trauma	Pain and limited range of motion

### Toxic: Medicines/drugs, toxic substances, withdrawal states

Vitamin B12	Posterior	Vitamin B12	Paresthesias
-------------	-----------	-------------	--------------

	column	deficiency	nerve los of large f modalitiē
Nitrous oxide	Posterior column	Excessive exposure to nitrous oxide	Hypoxia, degenera spinal co

## Ischemic

Anterior spinal	Loss of blood supply to the anterior 2/3 of the spinal cord	Ischemic	Sudden b pain follo by bilater weakness sensory l Sparing o position and vibra
Posterior spinal	Loss of blood supply to the posterior 1/3 of the spinal cord	Ischemic	Loss of proprioce and vibra
Artery of Adamkiewicz	Enlarged lumbar vessel artery	Spinal cord infarction Commonly affected by thoracic aortic aneurysm	Loss of b control Impaired extremity motor fu
Foix-Alajouanine	Typically involves thoracic and lumbosacral regions of spinal cord	Arterial venous malformation (AVM) of artery supplying parts of the spinal cord	Progressi weakness lower extremiti Bowl an bladder dysfuncti Sensory l lower

extremiti  
Recurren

### Infectious /post-infectious

Tabes dorsalis	Posterior column	May be a manifestation of neurosyphilis	Loss of sensation and vibration Unsteady
Tropical spastic paraparesis	Mainly posterior column	Infection, half of cases caused by human T-lymphotropic virus type 1 (HTLV-1)	Increasing weakness lower extremities followed by increased muscle tone and extensor plantar responses Spastic paraparesis Some patients may also develop peripheral neuropathy, cerebellar ataxia, and polyneuritis Urinary dysfunction
Transverse myelitis	Inflammation of a horizontal section of the spinal cord that may span several levels	Typically a monophasic illness resulting from viral infection of the spinal cord May also be seen in multiple sclerosis or sarcoidosis	Paresthesias in back pain, even leg weakness based upon portion of spinal cord involved

		<b>SCLEROSIS OR SYSTEMIC INVOLVED</b>	
		<b>vasculitis</b>	
Spinal epidural abscess	Infection in the epidural space by direct spread of vertebral osteomyelitis, soft tissue infections, and penetrating trauma	Local or systemic infections	Fever Mental status changes Back or radicular pain Paraparesis/quadriplegia

## Pressure effects

Disc herniation	Most commonly affects the cervical and lumbar regions	Trauma Degenerative disc disease	Radiculopathy in neck or lower back based upon level of herniation
Osteophyte formation	Calcifications of supporting spinal canal ligaments that result over time May affect any vertebral level of spinal canal	Degenerative disc disease Trauma	Can result in radicular neck and pain
Brown–Séquard syndrome	Unilateral lesion of the spinal cord	Traumatic mass lesions	Ipsilateral weakness Ipsilateral loss of touch position & vibration Contralateral

			loss of pain and temperature sensation
Central cord syndrome	Lesion affecting center of spinal cord, affecting the crossing spinal thalamic tracts	Syrinx Tumors Trauma	Weakness upper extremities more than lower extremities May be loss of sensation cape-like distribution Vibration position sense is spared
Extramedullary – extradural lesions	Originate outside both the dural covering and the spinal cord	Herniated disc Epidural metastases Epidural abscess Epidural hematoma	Ascending deficits distributed somatotopically along arrangement of the cord
Extramedullary – intradural lesions	Originate inside dural covering but outside spinal cord	Neurofibroma Meningoma Schwannoma	Ascending deficits distributed somatotopically along arrangement of the cord
Intramedullary intradural lesions	Originate from inside the spinal cord	Primary spinal cord tumor Metastatic tumor Syrinx	May cause sacral sparing sensory level lesion is at cervical level Descending deficits distributed somatotopically

arrangement  
cord

## Psychiatric

Psychiatric paraplegia/conversion disorder	Physical condition with no found root in physical nature. Generally found to be an emotional transference observed by a physical condition	Mental illness	Paraplegia symptom resulting perceived inability patient to control the lower extremities
--	---	----------------	---

## Inflammatory (post-radiation, granulomatous, collagen vascular, autoimmune)

Granulomatous	Immune system responds to items within the body perceived as foreign by isolating them	Genetic	Abscesses recurrent and skin infection
Collagen vascular	Immune system attacks collagen surrounding tissue, bone, and tendons	Auto immune	Fever Rashes Shortness of breath Back pain Weakness

## Degenerative (acquired) such as demyelinating Heredofamilial: dyskinetic syndromes – phakomatoses

Multiple sclerosis	Demyelination of nerves in brain and spinal cord	Auto immune	Varying degrees of weakness in arms or legs based upon which area of brain and spinal cord is affected Paresthesia Ataxia Lhermitte's sign if high cervical lesion spinal lesions are present
Devic's syndrome	Form of multiple sclerosis and affects solely cervical spinal cord and optic nerve	Auto immune	Vision loss from bilateral optic neuritis Symptoms transverse myelitis (paraparesis, paresthesia) Paraparesis Variable sensory changes based upon location of lesions
Compression fracture	May affect any vertebral body	Fracture of a vertebral body typically due to trauma and osteoporosis	Localized pain typical in affected area

---

## **Further reading list**

- Anderson GBJ. The epidemiology of spinal disorders. In Frymoyer JW, Ed. *The Adult Spine: Principles and Practice*. Philadelphia, PA: Lippincott-Raven, 1997: 93–141.
- Greenberg MS. Myelopathy. In *Differential Diagnosis by Signs and Symptoms*, 6th edn. New York, NY: Thieme, 2006: 902–43.
- Keller S, Smith J. Back pain. In Oliveira G, Nesbitt G, Murphy J, Eds. *Mayo Clinic Medical Manual*. Rochester, MN: Mayo Clinic Scientific Publications, 2006: 25–39.
- Mihai C, Mattson DH. Myelitis and myelopathy. In Joynt RJ, Griggs RC, Eds. *Clinical Neurology*. Philadelphia, PA: J.B. Lippincott, 1997: 1–31.
- Rolak LA. *Neurology Secrets*, 4th edn. New York, NY: Elsevier Mosby, 2005: 109–29.
- Rowland LP, Pedley TA, Eds, *Merritt's Neurology*, 12th edn. Philadelphia, PA: Lippincott Williams and Wilkins, 2010.

# **Chapter 91 Nerve, cranial: multiple deficit**

---

David Solomon and Jee Bang *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

## **Introduction**

Multiple cranial neuropathy refers to a myriad of conditions that involve more than one cranial nerve deficit, either simultaneously or in sequence. When diagnosing multiple cranial neuropathy, the two most important factors to determine are the location of the problem and its etiology. Usually, the combination of nerve deficits helps to narrow down the list of possible locations. Determining the etiology can be more difficult, given the vast array of differential diagnostic possibilities ([Table 91.1](#)). However, many conditions can often be ruled out from imaging and cerebrospinal fluid (CSF) analysis. [Table 91.2](#) summarizes the common locations and etiologies that can give rise to multiple cranial neuropathies.

## **Tumor**

Neoplastic processes are a significant cause of multiple cranial neuropathy. In a study describing 979 cases of multiple cranial nerve palsies, tumors were the most common cause, accounting for 30% of the cases (see Keane 2005 in the further reading list). Primary malignancies may initially present with multiple cranial deficits, whereas metastatic tumors usually occur late in the course of the disease. In addition to primary and metastatic malignancies, one should also consider paraneoplastic syndrome, as well as secondary effects (such as compression) from benign tumors.

## **Malignancies at the base of the skull**

Many neoplasms occurring at the base of the skull may present with multiple cranial nerve palsies. Paraganglioma (a rare neuroendocrine neoplasm) may

compress the cranial nerves which can result in a multiple cranial nerve deficit. Carotid paraganglioma, the most common of the head and neck paragangliomas, may cause cranial nerve palsies, usually of the vagus nerve and hypoglossal nerve. Glomus tympanicum and glomus jugulare (which is most common in adult females) present with pulsatile tinnitus, pain below the ear, and may show involvement of nerves VII, VIII, IX, and XII. Primary osteosarcomas that involve craniofacial bones have been reported to produce unilateral paralysis of several cranial nerves. Tumors involving the temporal bone, such as adenocarcinoma and adenoid cystic carcinoma , can present with facial nerve palsies, and may extend to the lower cranial nerves. Chordoma , a rare slow-growing malignant neoplasm thought to arise from cellular remnants of the notochord, is histologically benign but may become locally invasive and cause cranial nerve damage and compression. Nasopharyngeal carcinoma , which is more common in certain regions of East Asia and Africa, can spread to the skull base, where it may infiltrate the maxillary nerve, the pterygopalatine fossa, and the cavernous sinus. Leukemia , which may cause multiple neuropathies by infiltrating the cranial nerves, may not be visible when imaged, but may be suggested if the CSF shows lymphocytosis consisting of monoclonal B cells. Metastatic tumors that have been seen to cause multiple cranial neuropathies include breast cancer, lung cancer, and late-stage prostate cancer.

## Malignancies in the jugular foramen

The jugular foramen is a large irregular opening from the posterior cranial fossa that is bounded anteriorly by the petrous part of the temporal bone and posteriorly by the jugular notch of the occipital bone. It transmits cranial nerves IX, X, and XI. Jugular foramen syndrome (or Vernet's syndrome ) is characterized by the ipsilateral paralysis of these three cranial nerves, and is commonly caused by paraganglioma . Although this tumor is slow growing, it may erode through bone and extend into the jugular foramen or even into the hypoglossal canal.

**Table 91.1 *Differential diagnosis of multiple cranial neuropathies.***

Item	Subdivision	Specific entity	Possible clinical features
Infection			

Bacterial infections

Lyme disease

Facial nerve palsy which may be associated with aseptic meningitis and painful radiculitis. Less often, cranial nerves II, V, and VII can be affected as well. Horner's syndrome and Argyll Robertson pupils, optic neuropathy, and retinal vasculitis pseudotumor-like syndrome can occur, but with cerebrospinal fluid (CSF) abnormalities. Neurologic involvement is seen in 10% of infected individuals. Neurologic symptoms usually occur during Stage III infection, often several weeks after inoculation. Central nervous system, often with CSF or magnetic resonance imaging (MRI) abnormalities, and may cause severe encephalomyopathy.

Neurosyphilis

Cranial nerve palsy

are seen in about 10% of neurosyphilis cases. Occurs in people who have had untreated syphilis for many years (typically about 10–20 years after first infection).

#### Tuberculous meningitis

Fever, headache, vomiting, encephalopathy, photophobia, nerve palsies on admission. About 40% of adults with tuberculosis affect the cranial nerve system. Cranial nerve VI is most often involved, and usually affects it. Papilledema is frequently observed, and, on occasion, fundoscopic examination may reveal choroidal tubercles, yellowish lesions with irregular borders presenting singly or in clusters.

#### Diphtheritic polyneuropathy

Bilateral weakness from involvement of cranial nerves III, VI, VII, IX, and X. Can present several weeks after onset of diphtheria.

diphtheria wi  
dysphagia or  
dysphonia

Listeriosis (primarily  
in newborn infants,  
elderly, and  
immunocompromised  
patients)

Prodrome of  
headache, na  
vomiting, anc  
followed by  
asymmetrical  
nerve palsies,  
cerebellar sig  
hemiparesis c  
hypesthesia, a  
impairment o  
consciousnes  
frequently re  
ventilation. S  
be considered  
patient has  
rhomencepha  
meningitis wi  
negative rout  
bacterial culti

Fungal  
meningitis

*Cryptococcus  
neoformans*

More commo  
immunosuppi  
or  
immunocomp  
patients

*Coccidioides immitis*

As per above

Histoplasmosis

As per above

Blastomycosis

As per above

*Aspergillus*

As per above

*Candida*

As per above

## Mucormycosis

Ominous cause of rapidly evolving cranial neuropathy which must be recognized and treated promptly to avoid a fatal outcome. The eschar or black crusting of the mucosa in a debilitated or immunocompetent patient with exophthalmos, chemosis, stroke, cranial nerve palsies demands an urgent otolaryngologic evaluation and possible antifungal treatment or surgery.

## Viral infections

### HIV

Persistent memory and HIV-1 and -2 have both been shown to present with multiple neuropathies.

### Herpes zoster

Reactivation of varicella zoster virus. Example is herpetic zoster ophthalmicus.

### Epstein–Barr

Cranial nerve VII particularly vulnerable

### Cytomegalovirus

Rule out HIV

Parasites	Neurocysticercosis	Occurs after exposure to eggs of the tapeworm <i>Taenia solium</i> . Most common tape infection of the brain worldwide
-----------	--------------------	--

## Inflammatory

Guillain–Barré syndrome	Acute inflammatory demyelinating polyneuropathy (AIDP)	Characterized by ascending painless weakness. 50% of patients develop cranial palsies following ascending limb weakness. But symptoms are common, which include facial ptosis, ophthalmoplegia, oropharyngeal, lingual weakness and weakness of muscles of mastication
Miller–Fisher syndrome (MFS)		Manifests as descending pain proceeding in reverse order more common than Guillain–Barré syndrome. Present with a triad of ataxia, ophthalmoplegia, and areflexia.

ataxia, and ar  
and anti-GQ1  
antibodies are  
in 90% of cas

### Sarcoidosis

Neurosarcoidosis  
(develops in 5–15%  
of systemic  
sarcoidosis)

Bilateral nerv  
palsies (CN V  
followed by  
reduction in v  
perception du  
II involveme  
commonly in  
nerves are IX  
XII. Cranial n  
deficits are pi  
50–75% of ca  
many of those  
patients will c  
multiple neur

### Immune- mediated

Behçet's syndrome (a  
rare systemic  
vasculitis)

Often present  
mucous mem  
ulceration and  
involvements  
all patients pi  
with some fo  
painful oral  
mucocutaneo  
ulcerations in  
form of aphth  
ulcers or non-  
oral lesions. C  
nerve involve  
has been repc  
3–20% of cas  
cranial nerves;  
VIII most coi  
affected

### Vasculitis

### Neurooncology

### Neurology

**VASCULITIS****WEGENER'S  
GRANULOMATOSIS**

Neurologic involvement manifest as mononeuritis multiplex or sensorimotor neuropathy, and multiple cran neuropathies been reported. 34% of cases neuropathies commonly affect optic nerve, abducens, and nerves, but may involve the vestibulocochlear nerve as well. Diagnosis is suggested by upper respiratory disease, and is by a very specific cytoplasmic antineutrophil cytoplasmic autoantibodies (ANCA).

Lymphomatoid granulomatosis (a malignant lymphoreticular disorder which may be induced by Epstein-Barr virus )

Cranial nerves occur in 11% cases. Polyarteritis nodosa, a vasculitis of medium and small-sized arteries which become swollen and necrotic from attack by immune cells.

**immune cells**  
result in cranial neuropathies,  
cranial nerves  
VIII most often affected

Other	Tolosa–Hunt syndrome	Painful ophthalmoplegia may involve cranial nerves III, IV and VI. The second common cause cavernous sinus syndrome, after tumor
	Rosai–Dorfman disease	Usually associated with lymphadenopathy but can present isolated central nervous system (CNS) findings in young adults resulting from leptomeningeal involvement. Enhancing dural-based lesions mimic meningitis on imaging, but actually fibrohistiocytic lesions with inflammatory changes and the typical histiocytes
	Idiopathic hypertrophic cranial osteitis	Chronic inflammatory condition

pachymeningitis	thickening
Amyloidosis	Rule out plasma dyscrasias
Rheumatoid arthritis	Cranial nerves less common peripheral neuropathy
Sjögren's syndrome	Look for dry eyes and dry mouth
Scleroderma	Vasculitis often seen Also known as systemic sclerosis
Systemic lupus erythematosus (SLE)	Look for classic diagnostic criteria for SLE. May cause painful cranial neuropathies

## Neoplastic

Base of skull	Paraganglioma (rare neuroendocrine neoplasm)	May compress cranial nerves
	Carotid paraganglioma	May cause cranial nerve palsies, including the vagus and hypoglossal nerve
	Glomus tympanicum and glomus jugulare	Most common in adult females Presents with pulsatile tinnitus

pain below m  
and may shov  
involvement o  
nerves VII, V  
and XII

Primary  
osteosarcomas that  
involve craniofacial  
bones

Have been re  
to produce ur  
paralysis of s  
cranial nerves

Adenocarcinoma,  
adenoid cystic  
carcinoma, and other  
tumors involving the  
temporal bone

Can present v  
facial nerve p  
and may exte  
the lower cra  
nerves

Chordoma (a rare  
slow-growing  
malignant neoplasm  
thought to arise from  
cellular remnants of  
the notochord)

Histologically  
but may beco  
locally invasi  
cause cranial  
damage and  
compression

Nasopharyngeal  
carcinoma

More commo  
certain regior  
East Asia and  
Can spread to  
skull base, wh  
may infiltrate  
maxillary ner  
pterygopalati  
and the caver  
sinus

Leukemia

Can cause mi  
neuropathies  
infiltrating th  
nerves. May b  
visible when

but may be seen if the CSF shows lymphocytosis consisting of monoclonal IgG

	Breast cancer, lung cancer, and late-stage prostate cancer	Metastatic tumor
Jugular foramen	Jugular foramen syndrome (or Vernet's syndrome)	Ipsilateral palsies of cranial nerves X, and XI. Commonly caused by paraganglioma. Tumor may extend through bone and extend into the jugular foramen and the hypoglossal canal.
Subarachnoid space	Neoplastic meningitis (may arise from breast cancer, small lung cell cancer, myeloblastic leukemia, lymphoma, melanoma, or more rarely from gastrointestinal or gynecologic cancers)	Commonly involves cranial nerves IV, VI, and V. May be bilateral. Headache, stiffness, increased intracranial pressure, and meningeal signs. Should especially be considered for patients that present subacutely in absence of pain.
Cavernous sinus	Primary tumors (meningioma, lymphoma)	Cranial nerve IV, V (branch and V2), and III

	Extensions of local tumors (nasopharyngeal carcinoma, pituitary adenoma, or craniopharyngioma)	Cranial nerve IV, V (branch and V2), and
	Metastatic disease	Cranial nerve IV, V (branch and V2), and
Cerebellopontine angle (CPA)	Acoustic schwannoma	Arises from the intracanalicular segment of the vestibular portion of the vestibulocochlear nerve (CN VI). Typically presents with sensorineural hearing loss and tinnitus. As it enlarges, it invades cranial nerve function. Deficits include CN VII (causing lower motor neuron facial paresis and hyperacusis) and CN VIII (causing facial sensory loss). Common. Cranial nerves VI, IX, and X are less commonly involved, but become affected in the course.
Other	Paraneoplastic syndrome	Remote effects of cancer unrelated to the brain

metastasis. ▶  
types

Secondary effects  
from benign tumors  
(e.g. compression)

Examples are  
meningioma  
schwannoma

## Vascular

Stroke	Infarcts involving the lateral pons or medulla	Gaze palsies, tract signs, internuclear ophthalmoplegia, “crossed” syndrome and complex spontaneous movement abnormalities
Cavernous sinus syndrome	Other infarct locations	Aneurysms, thromboses, and cavernous fistulas of the carotid artery that occur in or near the cavernous sinus
Internal carotid artery	Spontaneous dissection of the internal carotid artery	Relatively common cause of ischemic stroke in the young. Multiple CN palsies reported in many. 10% of patients have neurologic

hemispheric cerebral hemorrhage typically follows a period of relative stability. The onset of unilateral headache or rectal pain after some initial delay. Elements of Horner's syndrome are often present, while bruits are a variable finding. Infrequently, cranial nerves are involved, probably due to compression by a mural hematoma, causing dysarthria, dysphagia, drooling, gag, or hoarseness. Dissection occurs in the subadventitial layer without significant carotid stenosis, the result of a lower cranial nerve palsy may remain obscure, but has some advantage over arteriography in evaluating this condition in the absence of luminal narrowing, or if the aneurysm is thrombosed.

Giant intracranial aneurysms

Cavernous sinus, circle of Willis

Giant intracranial aneurysms causing pressure on cranial

nerves, which give rise to cranial nerves in multiple locations with concentration in the cranial nerves as the cavernous sinus or the circle of Willis. Affecting cranial nerves II, III, IV, VI and V

<b>Bone disorders</b>	<b>Other</b>	<b>Diabetes</b>	Rare cause of multiple cranial neuropathy
		Sickle cell disease	Rare cause of multiple cranial neuropathy
	Bone malformation in an area with multiple nerves	Osteopetrosis Paget's disease of bone Fibrous dysplasia of the cranium Hyperostosis cranialis interna	Inherited disorder Bones become thickened and hardened Localized abnormal bone break down and rebuilding Abnormal replacement of normal tissue with fibrous tissue Hereditary bone disease of hyperostosis or osteosclerosis bony overgrowth

can entrap cranial nerves

## Metabolic

Wilson's disease

Dysarthria and drooling. Should be considered in younger patients with bulbar weakness especially if there are associated movement disorders or psychiatric symptoms

Hypothyroidism

May lead to mucopolysaccharide deposition around nerve sheaths resulting in axonal degeneration and entrapment

## Trauma

Automobile and motorcycle accidents; gunshot wounds; falls and beatings; surgical trauma

May be accompanied by CSF rhinorrhea. May occur in traumatic injuries with or without fractures to the base of the skull

Iatrogenic

Surgical procedures on the head and neck such as endarterectomy and posterior cranial fossa surgery

**Table 91.2 Common locations and causes of multiple cranial neuropathy.**

Common locations		Common etiologies	
Cavernous sinus	Subarachnoid space	Tumor	Vascular disease
Brainstem	Cerebellopontine angle	Infection	Inflammatory disease
Nerve	Psychogenic	Trauma	Bone disease
Clivus & skull base	Neck		

## Malignancies in the subarachnoid space

Neoplastic meningitis is a common oncologic complication representing metastasis to the subarachnoid space. It is an important cause of cranial multineuropathy, and should be considered especially in patients that present subacutely in the absence of pain. Commonly involved cranial nerves include II, III, IV, VI, and VII, and involvement may be bilateral. Symptoms may include headache, signs of increased intracranial pressure, and meningeal signs. Neoplastic meningitis may arise from breast cancer, small lung cell cancer, myeloblastic leukemia, lymphoma, melanoma, or more rarely from gastrointestinal or gynecologic cancers. Diffuse leptomeningeal gliomatosis originating from occult anaplastic ectopic glia or astrocytoma may present with papilledema and hydrocephalus or multiple cranial neuropathies.

## Malignancies in the cavernous sinus

The cavernous sinuses are a pair of venous channels bordered by the temporal bone of the skull and the sphenoid bone, lateral to the sella turcica. Cranial nerves III, IV, V (branches V1 and V2), and VI all pass through this blood-filled space. Neoplasms in the cavernous sinus may affect one or more of these nerves,

and in severe cases may affect all of them. In Keane's study of 979 cranial multineuropathy patients, cranial nerve involvement represented 25% of the cases overall, and 26% of the tumor cases. Malignancies in the cavernous sinus that may cause multiple cranial neuropathy include primary tumors (meningioma, lymphoma), extensions of local tumors (nasopharyngeal carcinoma, pituitary adenoma, or craniopharyngioma), and metastatic disease.

## Malignancies in the cerebellopontine angle

The cerebellopontine angle (CPA) spans the lateral aspect of the pons and the inferior surface of the cerebellar hemisphere, and spans longitudinally from cranial nerves V through X. It is a relatively frequent site of intracranial masses, many of which are relatively specific for the region. The most common type is acoustic schwannoma (75–90% of CPA masses), which arises from the intracanalicular segment of the vestibular portion of the vestibulocochlear nerve (CN VIII), and typically presents with sensorineural hearing loss or tinnitus. As the mass expands, it interferes with cranial nerve function. Deficits in CN VII (causing a lower motor neuron facial paresis without hyperacusis) and V (causing facial sensory loss) are common. Cranial nerves VI, IX, and X are less commonly involved, but can become affected later in the course.

## Vascular disease

Vascular disease accounts for about 10% of cranial multineuropathy cases.

## Stroke

Brainstem infarcts involving the lateral pons or medulla account for about two thirds of vascular cranial multineuropathy cases. Most brainstem cases that involve multiple cranial nerves will include signs such as gaze palsies, long tract signs, internuclear ophthalmoplegia, “crossed” syndromes, and complex spontaneous eye movement abnormalities. The reader is referred to [Chapters 70–72](#) on stroke for further details.

## Cavernous sinus syndrome

Aneurysms, thromboses, and cavernous fistulas of the carotid artery that occur in or near the cavernous sinus may give rise to ipsilateral cranial multineuropathy involving the cranial nerves that pass through the cavernous sinuses (cranial

nerves II, IV, VI, and branches V1 and V2 of cranial nerve V).

## **Internal carotid artery**

Spontaneous dissection of the internal carotid artery is a relatively common cause of ischemic stroke in the young, and may cause cranial nerve palsies. Multiple cranial nerve palsies are reported in more than 10% of patients. Neurologic hemispheric deficits typically follow the onset of unilateral headache or neck pain after some delay. Elements of a Horner's syndrome are often present, while bruits are a variable finding. Infrequently, lower cranial nerves are involved, probably due to compression by a mural hematoma, causing dysarthria, dysphagia, depressed gag, or hoarseness. If dissection occurs in the subadventitial layer without causing significant carotid stenosis, the etiology of a lower cranial nerve palsy may remain obscure. Magnetic resonance imaging (MRI) has some advantages over arteriography in evaluating this condition in the absence of luminal narrowing, or if an aneurysm is thrombosed.

## **Giant intracranial aneurysms**

Giant intracranial aneurysms can cause pressure on cranial nerves, which may give rise to cranial multineuropathy in locations with high concentrations of cranial nerves, such as the cavernous sinus or the circle of Willis. Affected cranial nerves include II, III, IV, VI, VII, and also V.

## **Other vascular diseases**

Diabetes and sickle cell disease have both been reported as rare causes of multiple cranial neuropathies.

## **Traumatic brain injury**

Head injuries are an important diagnostic consideration, and may account for about 10% of multiple cranial neuropathies. Automobile and motorcycle accidents and gunshot wounds are common causes, followed by falls and beatings. Cranial neuropathy may occur in traumatic injuries with or without fractures to the base of the skull, and may be accompanied by cerebrospinal fluid (CSF) rhinorrhea. Iatrogenic causes, including surgical procedures on the head and neck, such as endarterectomy and posterior triangle lymph node biopsies, should also be considered.

## **Inflammatory diseases**

### **Guillain–Barré syndrome**

Guillain–Barré syndrome is an acute polyneuropathy affecting the peripheral nervous system. Acute inflammatory demyelinating polyneuropathy (AIDP), the most common form of Guillain–Barré syndrome, is characterized by ascending paralysis. Half of these patients develop cranial nerve palsies following the ascending limb weakness. Bulbar symptoms are common, which include facial palsy, ptosis, ophthalmoparesis, oropharyngeal and lingual weakness, and weakness of the muscles of mastication. Miller–Fisher syndrome is a less common variant of Guillain–Barré syndrome, constituting 5% of cases, and manifests as a descending paralysis, proceeding in the reverse order of the more common forms of Guillain–Barré syndrome. It presents with a triad of ophthalmoplegia, ataxia, and areflexia, and anti-GQ1b antibodies are present in 90% of cases.

### **Neurosarcoidosis**

Neurosarcoidosis develops in 5–15% of systemic sarcoidosis. Cranial nerve deficits are present in 50–75% of cases, and many of those patients will develop multiple neuropathies. Neurosarcoidosis commonly presents with bilateral nerve palsies (CN VII), followed by reduction in visual perception due to CN II involvement. Other commonly involved nerves are IX, X, and XII.

### **Behçet's syndrome**

Behçet's syndrome is a rare immune-mediated systemic vasculitis that often presents with mucous membrane ulceration and ocular involvements. Nearly all patients present with some form of painful oral mucocutaneous ulcerations in the form of aphthous ulcers or non-scarring oral lesions. Cranial nerve involvement has been reported in 3–20% of cases, with cranial nerves II and VIII most commonly affected.

### **Vasculitis**

Several forms of vasculitis may cause multiple cranial neuropathies. In Wegener's granulomatosis, neurologic involvement usually manifests as mononeuritis multiplex or a distal sensorimotor neuropathy, but multiple cranial

neuropathies have been reported in 8–34% of cases. Cranial neuropathies most commonly affect the optic nerve, abducens, and facial nerves, but may involve the vestibulocochlear nerve as well. Diagnosis is suggested by renal or upper respiratory disease, and is aided by a very specific test for cytoplasmic antineutrophil cytoplasmic autoantibodies (c-ANCA). In lymphomatoid granulomatosis , a malignant lymphoreticular disorder which may be induced by Epstein–Barr virus , cranial neuropathies occur in 11% of cases. Polyarteritis nodosa , a vasculitis of medium and small-sized arteries, which become swollen and damaged from attack by rogue immune cells, may result in cranial neuropathies, with cranial nerves III and VIII most often affected.

## **Other inflammatory diseases**

Tolosa–Hunt syndrome is an idiopathic inflammatory granulomatous disorder characterized by severe and unilateral headaches with extraocular palsies. It typically presents with a painful ophthalmoplegia, and may involve cranial nerves III, IV, V, and VI. It is the second most common cause of cavernous sinus syndrome, after tumor. Other inflammatory conditions that might cause multiple cranial neuropathies include idiopathic hypertrophic cranial pachymeningitis , amyloidosis , rheumatoid arthritis , Sjögren's syndrome , scleroderma , and systemic lupus erythematosus . Rosai–Dorfman disease is a rare condition usually associated with lymphadenopathy, but can present with isolated central nervous system (CNS) findings in young adults resulting from leptomeningeal involvement. Enhancing dural-based lesions can mimic meningioma on imaging, but are actually fibrotic lesions with inflammatory cells and the typical pale histiocytes.

## **Infection**

Infectious diseases (especially infections of the meninges) may give rise to multiple cranial nerve palsies.

## **Bacterial infections**

Lyme disease, the most common tick-borne disease in the northern hemisphere, leads to neurologic involvement in about 15% of infected individuals. Neurologic symptoms usually occur during the second stage of infection, often several weeks after inoculation. The most common neurologic deficit is facial nerve palsies (especially cranial nerve VII), which may be associated with an

aseptic meningitis and painful radiculitis. Less often, cranial nerves II, V, and VIII may be affected as well. A pseudotumor cerebri-like syndrome may occur, but with CSF abnormalities. Horner's syndrome and Argyll Robertson pupils , optic neuropathy , and retinal vasculitis may occur. Stage III disease affects the CNS, often without CSF or MRI abnormalities, and may cause a severe encephalomyelitis .

Neurosypilis, an infection of the brain or spinal cord caused by the bacterium *Treponema pallidum* , usually occurs in people who have had untreated syphilis for many years (typically about 10–20 years after first infection). Cranial nerve palsies are seen in about one third of neurosyphilis cases.

While tuberculosis usually attacks the lungs, in 25% of cases it may spread to extrapulmonary sites, including the meninges. Tuberculous meningitis most often presents with fever, headache, vomiting, encephalopathy, and photophobia. Cranial nerve palsies are seen on admission in 15–40% of adults with tuberculosis affecting the cranial nervous system. Cranial nerve VI is most often involved, and is usually affected first. Papilledema is frequently observed and, on occasion, funduscopic examination may reveal choroid tubercles, yellow lesions with indistinct borders present either singly or in clusters. Their presence is convincing evidence of the disease, but they appear in only about 10% of cases of tuberculous meningitis not associated with miliary tuberculosis.

Diphtheritic polyneuropathy can present several weeks after onset of diphtheria with dysphagia or dysphonia and most frequently causes bilateral weakness from involvement of cranial nerves III, IV, VI, VII, IX, and XII.

Listeriosis is a rare disease that occurs primarily in newborn infants, elderly patients, and patients who are immunocompromised . It should be considered when a patient has rhombencephalitis (encephalitis of the hindbrain) and meningitis with negative routine bacterial cultures. It presents with a prodrome of headache, nausea or vomiting, and fever, followed by asymmetrical cranial nerve palsies, cerebellar signs, hemiparesis or hypesthesia, and impairment of consciousness frequently requiring ventilation.

## Fungal infections

While fungal infections in the CNS are rare, they should be considered as possible causes of multiple cranial neuropathies, especially in immunosuppressed or immunocompromised patients. The most common cause of CNS fungal meningitis is *Cryptococcus neoformans* . Other common CNS

fungal infections include *Coccidioides immitis*, histoplasmosis, and blastomycosis. *Aspergillus* and *Candida* species should also be considered in patients who are at risk for opportunistic infections. An ominous infectious cause of rapidly evolving cranial neuropathy is mucormycosis, which must be recognized and treated promptly to avoid a fatal outcome. The classic eschar or black crusting of the nasal mucosa in a debilitated or diabetic patient with exophthalmos, chemosis, stroke, or cranial nerve deficits demands an urgent otolaryngologic evaluation and possible antifungal treatment or surgery.

## Viral infections

Human immunodeficiency virus (HIV) often causes a persistent meningitis, and HIV-1 and HIV-2 have both been shown to present with multiple cranial neuropathies. Other viral infections that may lead to multiple cranial nerve palsies include herpes zoster, Epstein–Barr, and cytomegalovirus.

## Parasites

Neurocysticercosis, which occurs after exposure to eggs of the pork tapeworm *Taenia solium*, is the most common tapeworm infection of the brain worldwide, and has been observed to produce multiple cranial neuropathies.

## Bone disorders

Bone disorders may occasionally give rise to multiple cranial nerve palsies, especially when bone growth or malformation occurs in an area containing multiple nerves (such as the cavernous sinus or the jugular foramen). Bone disorders that have been observed to produce cranial multineuropathy include osteopetrosis, Paget's disease, fibrous dysplasia of the cranium, and hypertrosis cranialis interna.

## Metabolic causes of cranial multineuropathy

Dysarthria and drooling may be an early sign of Wilson's disease, which should be considered in younger patients with bulbar weakness, especially if there is an associated movement disorder or psychiatric symptoms. Hypothyroidism may lead to mucopolysaccharide deposition around nerve sheaths, resulting in axonal degeneration or nerve entrapment.

## **Diagnostic work-up**

For patients that present with multiple cranial nerve deficits, radiologic and cerebrospinal fluid studies should be used to narrow the set of differential diagnoses. The initial work-up should include computerized tomography (CT) and MRI of the brain, with special attention to the base of the skull. If chronic meningitis is suspected, neuroimaging may be used to check for alternative causes such as neoplasm, abscess, and parameningeal focus of infection. In cases where bony detail is important, such as trauma or neoplastic processes with erosion or extension into the cranial foramina, CT scans may be helpful. A general physical exam should be performed to establish or exclude the diagnosis of cancer. If the evaluation reveals evidence for a tumor, then an imaging search for the primary source may be necessary. Cerebrospinal fluid testing can help evaluate the likelihood of inflammatory, infectious, and neoplastic causes. Many meningeal disorders will cause a lymphocytic predominance. High volumes of CSF should be examined microscopically, cultured, and subjected to polymerase chain reaction (PCR) analysis. An ear, nose, and throat examination may be helpful for diagnosing nasopharyngeal carcinoma. If the etiology remains unknown, a meningeal biopsy should be considered in cases where neoplastic processes, chromic meningitis, or CNS vasculitis is suspected. The yield of meningeal biopsy is significantly higher if the biopsy can be obtained from an enhancing area noted on the MRI.

## **Case vignette**

An 84-year-old male with atrial fibrillation, hypertension, and recent thyroid cancer with radioactive iodine treatment presents with a 6-week history of double vision, facial numbness, facial weakness, articulation, and swallowing difficulties. Exam reveals pupil-sparing third nerve palsy, right facial numbness along the V3 distribution, and dysarthria.

Work-up: An MRI brain and C-spine, CT chest, abdomen, and pelvis with unrevealing etiology. A CSF analysis reveals lymphocytosis and flow cytometry suggests B-cell lymphoma. Peripheral blood and bone marrow flow cytometry consistent with B-cell lymphoproliferative disorder.

Diagnosis: Lymphomatous meningitis with a B-cell lymphoproliferative disorder.

Treatment: A combination of immunosuppression, antiviral therapy,

debulking, chemotherapy, and radiotherapy.

## Further reading list

Beal MF. Multiple cranial-nerve palsies – a diagnostic challenge. *N Engl J Med* 1990; 322:461–3.

Carroll CG, Campbell WW. Multiple cranial neuropathies. *Semin Neurol* 2009; 29: 53–65.

Jain KK. Multiple cranial neuropathies. *Neurobase MedLink*. [www.medlink.com](http://www.medlink.com).

Keane JR. Multiple cranial nerve palsies: analysis of 979 cases. *Arch Neurol* 2005; 62:1714–17.

## **92 Neuropathy, axonal versus demyelinating**

---

Michael T. Pulley and Alan R. Berger *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

Peripheral nerve disorders may be classified in many different ways, including, among others, differentiation based on etiology, distribution, and physiology. One important element that helps define the scope of the work-up, and may suggest the etiology of the peripheral neuropathy, is to distinguish axonal neuropathies from those that are demyelinating. The most reliable differentiation is usually based on electrophysiologic testing (nerve conduction studies), but clinical features may provide important clues.

Individual peripheral nerve fibers are divided into subtypes. These include the small, unmyelinated C-fibers, small thinly myelinated A delta, and the large, heavily myelinated A alpha. These fibers have different functions and these differences explain some of the variation of clinical manifestations seen in axonal versus demyelinating neuropathies. The unmyelinated C-fibers transmit pain and temperature sensation, while the larger, thickly myelinated fibers transmit proprioception, vibration sense, and motor function.

Demyelination is a term used to describe a condition in which there is a lack of the normal relationship between the large diameter axons and their myelin sheath. Although demyelination is the term used for any variation of this relationship, the term should probably be applied to situations in which there is an active process involving removal of myelin as opposed to one in which myelin is formed improperly, which might be termed dysmyelination, or in which there is secondary myelin disruption due to axonal shrinkage or injury.

Many peripheral neuropathies involve a combination of axonal loss and demyelination. In primary demyelinating neuropathies, axons may be damaged secondarily. In axonal neuropathies, axonal shrinkage may lead to the loss of the intimate relationship between axon and myelin, resulting in some demyelination.

When describing a neuropathy that has mixed features, it is best to list the predominant physiologic abnormality first (e.g. mixed demyelinating and axonal neuropathy indicates demyelination with secondary axonal loss).

## How is demyelination defined?

The physiologic definition for demyelination is based on speed of conduction. Most neurophysiology laboratories use onset latency to calculate conduction velocity. The onset of a sensory or motor potential is determined by the fastest conducting fibers. The speed of conduction in an individual axon is determined by its cross-sectional area and also by the presence or absence of myelin. Therefore, large, heavily myelinated axons conduct the fastest. If there is significant loss of these large, heavily myelinated axons, there will be a prolongation of the onset latency and a reduction of conduction velocity due to conduction primarily occurring in thin, more slowly conducting nerve fibers. Since slowing of conduction velocity can occur in severe axonal neuropathies in which there is significant large fiber loss, it becomes important to have physiologic criteria (e.g. velocity, latency) that can differentiate primary demyelination from slowing of conduction due to large axon loss. In research trials this needs to be very strictly defined, while in clinical practice some rough guidelines will suffice. Research trials have used cut-offs of less than 80% of the lower limit of normal for conduction velocity and greater than 125% of the upper limit of normal for latency (both assuming there is normal amplitude of responses) as unequivocal indications that there is demyelination. Most neurophysiologists apply these criteria only to motor nerves or late responses as sensory nerve responses are much smaller in amplitude, and errors in measurement are less likely to occur in motor than sensory nerves. Also, sensory nerves are much more susceptible to the effects of temperature, which can significantly influence conduction velocity. Other electrophysiologic clues to the presence of demyelination include the presence of conduction block or temporal dispersion. These physiologic characteristics are found predominantly in acquired demyelinating neuropathies in which the demyelinating process is non-uniform (i.e. some fibers affected, while others less involved), rather than in hereditary demyelinating neuropathies in which all axons within the nerve are similarly affected. When some axons within a nerve are demyelinated and others are not, there is variability of conduction velocities among the many axons within the nerve, with a resultant spreading out of the waveform, a phenomenon known as temporal dispersion. This is only demonstrated clearly when

conduction is measured over a longer nerve segment, thereby allowing time for the differential slowing of conduction within the many fibers to be evident. Conduction block occurs when an impulse traveling through a myelinated fiber reaches a demyelinated segment, and is not able to be transmitted. As a result, the summated distal nerve action potential, or the compound muscle action potential, will not reflect the impulses carried by that nerve fiber, and the resultant summed potential will be of lower amplitude. Conduction block is only evident when the stimulation is applied proximal to the demyelinated nerve segment, with recordings distal to the site of demyelination. The underlying axon must be intact in order to have a larger amplitude distally (assuming no anatomical variants and adequate stimulation proximally).

## **How is an axonal neuropathy defined?**

Axonal neuropathies are defined electrophysiologically by reduced amplitude of sensory and/or motor responses. The correlation of amplitude with number of axons is more definitive in sensory nerve conduction, in which the response is recorded from the nerve. However, sensory nerve action potentials are very small (microvolts) and cannot be reliably recorded in proximal parts of the limbs. Also, edema may make it difficult to obtain responses and this is more of an issue with sensory than motor responses, which are much larger (millivolts). In motor nerve conduction, the response is recorded from the muscle. One can see that if axonal sprouting takes place and reinnervation is successful, it is possible to have no reduction of the motor potential amplitude in spite of axonal loss. Thus motor axon loss is more reliably identified by changes on electromyography (EMG). Axonal loss will result in denervated muscle fibers firing spontaneously (spontaneous activity; fibrillations and positive sharp waves) during the early stages. As remaining axons sprout and reinnervate the orphaned muscle fibers, the amplitude of the motor unit action potentials recorded with voluntary activation on EMG increases. The electrophysiologic changes seen in axonal neuropathy are usually in a length-dependent pattern. Involvement of proximal muscles raises the possibility of nerve root involvement. Axonal neuropathies should have normal conduction velocity but there may be mild slowing due to loss of large heavily myelinated axons as previously discussed.

## **Case vignette 1**

A 52-year-old male presented with a 6-month history of difficulty walking. He noted that he tended to trip over his toe. The symptoms had been slowly progressive. He denied any pain in the lower back or legs. He had noticed some mild weakness of grip as well. He reported occasional tingling in his feet but denied any numbness. The past medical history was negative. On examination, he had moderate weakness (MRC grade 4/5) in his ankle and toe dorsiflexors bilaterally with minimal weakness of the hip flexors (5-/5). The intrinsic hand muscles were also mildly weak at 4+/5, but normal at the ankle. Pin prick, light touch, and proprioception were intact. Reflexes were absent throughout the upper and lower extremities bilaterally. There was a mild steppage quality of his gait. Nerve conduction studies revealed normal motor potential amplitude but marked slowing of conduction velocity in the common peroneal motor nerves (25 m/s; normal > 40 m/s) with evidence for temporal dispersion of the waveform on proximal stimulation. In the upper extremity, median and ulnar motor amplitudes were normal but the conduction velocities were also markedly slowed (36 m/s; normal > 50 m/s). The sensory nerve conduction studies were normal.

This is a typical example of an acquired demyelinating neuropathy, most likely chronic inflammatory demyelinating polyradiculoneuropathy (CIDP). The case also points out that although many cases of demyelinating neuropathy present with either diffuse or patchy neurologic deficits, there may be a distal predominance, mimicking a length-dependent pattern. As in this case, most demyelinating neuropathies have predominant motor deficits with only mild sensory symptoms or signs. The key clinical features differentiating this case from an axonal neuropathy are the diffuse areflexia and the mild proximal weakness. The most important differential here would be to exclude a demyelinating neuropathy caused by a monoclonal gammopathy, most likely IgM. Although one might consider a lumbar puncture to look for evidence of elevated protein in the absence of white blood cells, most would agree that this is not necessary and a normal CSF would not change the decision to initiate treatment with immunomodulatory therapy.

**Table 92.1 Features of axonal and demyelinating neuropathies.**

	<b>Axonal</b>	<b>Demyelinating</b>
Distribution of deficits	Length dependent (stepping and glove)	Usually diffuse (proximal and distal)

<b>Sensations</b>	(stocking and glove or distal symmetric); multifocal (vasculitic)	(proximal and distal) or patchy (multifocal); occasionally length dependent
Clinical findings	Length-dependent loss (ankle reflexes lost initially)	Usually diffusely reduced or absent; can be patchy or length dependent
Reflexes		
Sensation	Depending on type of fibers involved – pain, temperature, light touch, vibration; length-dependent distribution	Usually mild. Prominent proprioception and vibration loss. May have sensory ataxia; pain and temperature sense not lost alone
Weakness	Distal, symmetric	Diffuse; can mimic length-dependent process
Autonomic involvement	Yes, with small fiber loss (diabetes, amyloidosis)	Only in Guillain–Barré or autoimmune dysautonomia
Electrophysiology	Normal or mild slowing (not out of proportion to axonal loss)	Marked slowing (< 80% of lower limit of normal)
Conduction velocity		
Conduction block; temporal dispersion	No	Yes, with acquired demyelination
Cerebrospinal fluid protein	Normal	Often elevated
Onset	Acute – ischemia; high dose toxin; critical illness Subacute – toxic;	Acute – Guillain–Barré Subacute – chronic inflammatory demyelinating

	nutritional; paraneoplastic Chronic – metabolic; hereditary	polyneuropathy (CIDP); monoclonal gammopathy Chronic – hereditary; CIDP; monoclonal gammopathy
CNS involvement	Occasional; especially toxic in which dorsal columns affected	Rare; hereditary metabolic disorders (leukodystrophy)
Recovery: rate (relative)	Slow	Rapid
Mechanism	Axon regrowth guided by schwann cell and basal lamina tubes	Schwann cell proliferation and remyelination with shortened internodes

---

## Case vignette 2

A 63-year-old female presented with complaints of numbness and pain in her feet. This initially began with involvement of the toes only and had spread over the course of about a year to involve the foot into the lower leg. There was no weakness. She felt mildly unsteady but had not had any falls. The arms and hands were unaffected. There was mild, chronic lower back pain that had not changed with the onset of the sensory symptoms. Her past medical history was positive for type II diabetes, diagnosed about 10 years ago. She indicated that her blood sugars were fairly well controlled. Her most recent hemoglobin A1C was 8.2. On examination, she had normal muscle strength throughout, including distal foot and leg muscles. Her sensory examination revealed a moderate reduction of vibratory appreciation at the toes bilaterally and symmetric. There was shading of pin to the mid-shin level bilaterally. Proprioception was intact. Reflexes were absent at the ankles and otherwise 1+ throughout. Nerve conduction studies revealed absent sural and superficial peroneal sensory responses bilaterally. Sensory nerve conductances in the upper extremities were

normal. Motor nerve conductions revealed normal motor potential amplitudes and conduction velocities in the tibial and peroneal nerves bilaterally. Needle EMG examination revealed high amplitude motor unit potentials in distal leg muscles (tibialis anterior and gastrocnemius) but was normal on proximal muscles.

**Table 92.2 Etiologies of axonal and demyelinating neuropathies.**

	Axonal	Assoc featur
Hereditary	Charcot–Marie–Tooth 2,	Famil
Non-metabolic	X (female)	pes ca
	Adrenomyeloneuropathy	Myelc
	Neuroacanthocytosis	(spast
	Adult onset Tay–Sachs	parap
	disease	sensoi
		Chore
		Ataxia
Metabolic	Porphyria	Abdo
	Uremia	psych
	Hypothyroidism	Usual
	Bariatric surgery	creatii
	Hepatic failure	cleara
	Acromegaly	< 5 m
		“Hun
		dry sk
		consti
		Multij
		Jaund
		Large
		suprac
		ridges
Ischemic	Diabetic focal neuropathies or plexopathy	Good Evalu system

	<b>vasculitis</b>	<b>lung, r eosinc</b>
Acute autoimmune	Axonal Guillain–Barré Vasculitis	Worse than a inflam demye polyne (AIDI rapid Patchy
Chronic autoimmune	Lupus erythematosus Sjögren's syndrome Sarcoidosis Vasculitis Cryoglobulinemia Celiac disease Primary biliary cirrhosis	List o joint, <i>etc.</i> Sicca Pulmc involv Patchy can be With l leukoc vascul GI syi may b Senso autono
Nutritional deficiency	Vitamin B12 Vitamin E Folate Thiamine Copper	Lab “ too lo methy acid; e with r Centra peripl axono ataxia malab Rare; malnu

		(intra vomit alcoh Myelc bariatr
Toxic environmental/occupational	Acrylamide Arsenic Carbon disulfide Ethylene oxide Lead Organophosphates Thallium	Skin c Gastric (GI), i alopec Headache dizzin Agitatio insom Mees' anemi Delay Hair, i
Medication	Dapsone (motor predominant) Nucleoside analogs (ddI, ddC, d4T) Disulfiram Colchicine (with myopathy) Isoniazid (INH) Metronidazole Nitrofurantoin Cisplatin Thalidomide Vincristine	Chron Painfu than F neuroj Metal carboi More renal insuff If vita not gi Chron > 50 g Usual g Senso depen Senso Senso may s

extrem

Infectious

Lyme (multifocal)

HIV

Whipple disease

Hepatitis/HIV

Hepatitis C virus

Human T-lymphotropic  
virus type 1 (HTLV-1)

Leprosy

Bulls-

arthra

With

HIV r

also

Arthr

centra

system

malab

With

cryog

Spasti

parap

bladd

dysfui

Patchy

loss o

areas

Paraprotein/Hematologic/Malignancies

IgG

IgM

IgA

Multiple myeloma;  
leukemia; lymphoma

Amyloidosis

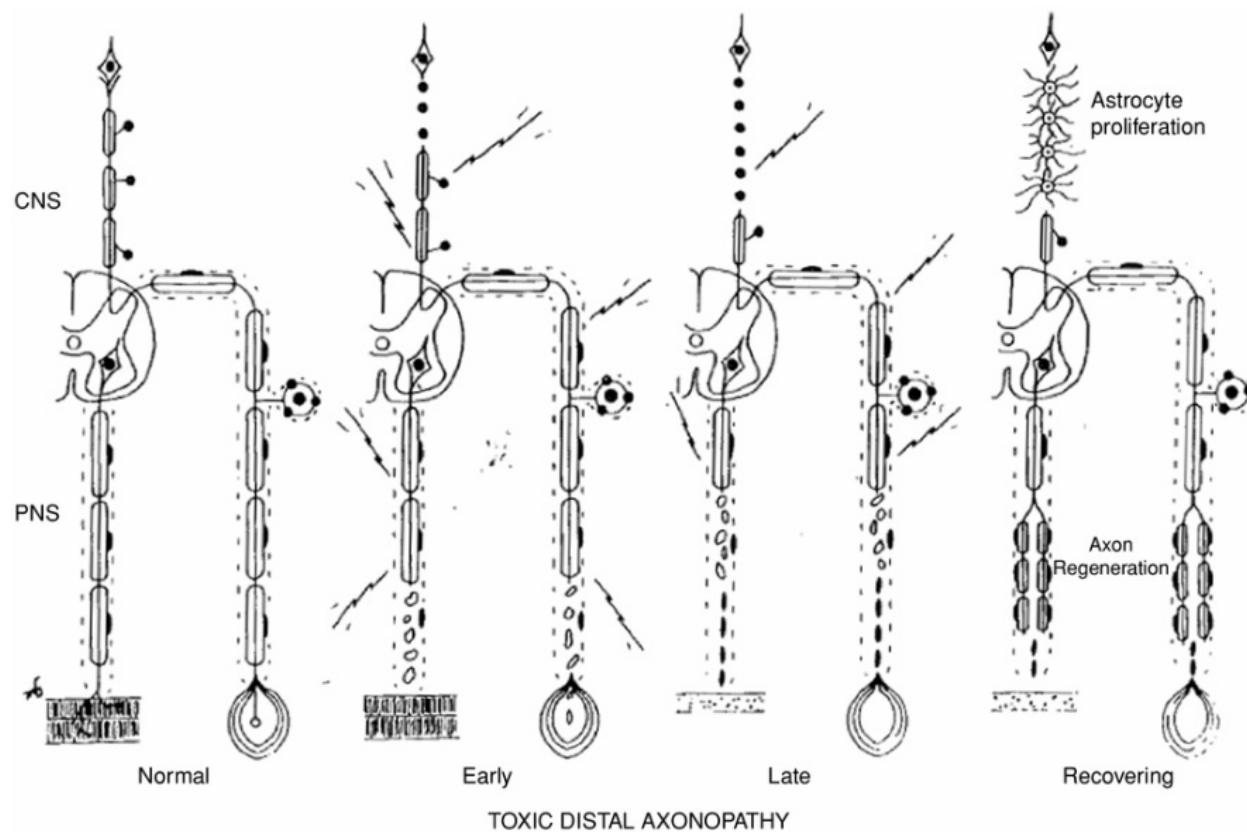
Diabetes

Most

Many mixed

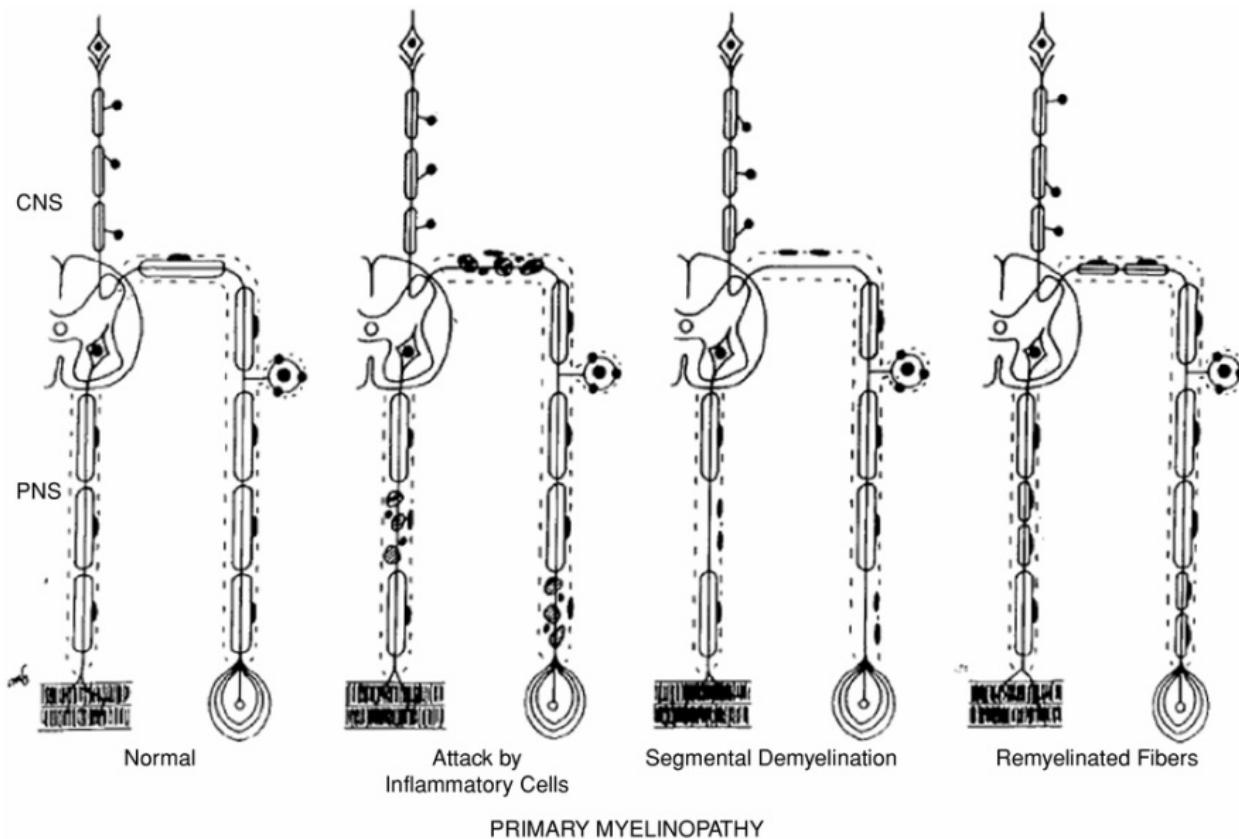
axonal/demyelinating

This case represents a typical axonal neuropathy. The key features are that there is a length-dependent process affecting the distal lower extremities first and then progressing more proximally over time. The features distinguishing this case from a demyelinating neuropathy are the preservation of all reflexes except the ankle jerks and the absence of weakness. The normal motor nerve conduction with abnormal EMG points out the importance of performing EMG to look for evidence of motor axon loss. The etiology of the neuropathy in this case is most likely the patient's diabetes. However, it is important to exclude other etiologies of neuropathy, even in a diabetic patient. The American Academy of Neurology Guidelines for laboratory evaluation of distal symmetric neuropathy include: a test for diabetes in a patient without a history of diabetes; vitamin B12 level; and serum immunofixation electrophoresis to evaluate for a monoclonal gammopathy. These three tests have the highest yield for uncovering the etiology of a distal, symmetric peripheral neuropathy.

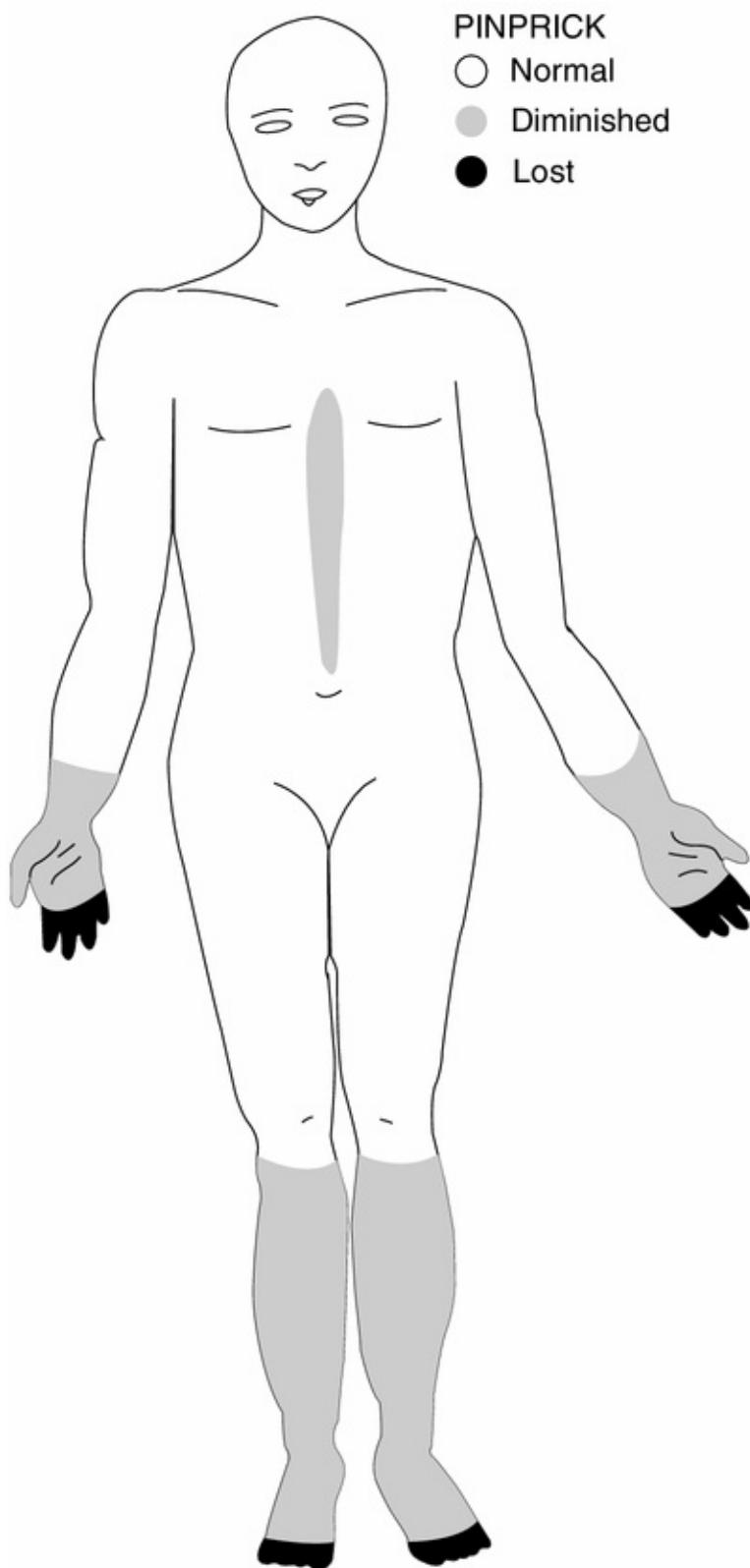


**Figure 92.1** A diagram of the cardinal pathologic features of a toxic distal axonopathy. The jagged lines (lightning bolts) indicate the toxin is acting at multiple sites along motor and sensory axons in the peripheral and central nervous systems (PNS and CNS). Axon degeneration has moved proximally (dying-back) by the late stage. Recovery in the CNS is impeded by astrogliosis.

proliferation. Reproduced with permission of Oxford University Press; Mendell JR, Kissel JT, Cornblath DR. *Diagnosis and Management of Peripheral Nerve Disorders*. New York, NY: Oxford University Press, 2001.



**Figure 92.2** A diagram of the cardinal pathologic features of an inflammatory peripheral nervous system (PNS) myelinopathy. Axons are spared as is central nervous system (CNS) myelin. Following the attack, the remaining Schwann cells divide. The denuded segments of axons are remyelinated, leaving them with shortened internodes. Reproduced with permission of Oxford University Press; Mendell JR, Kissel JT, Cornblath DR. *Diagnosis and Management of Peripheral Nerve Disorders*. New York, NY: Oxford University Press, 2001.



**Figure 92.3** Stocking-glove pattern of sensory loss of an advanced stage of distal axonopathy. The area of diminished sensation over midthorax reflects

involvement of distal ends of intercostal nerves. Reproduced with permission of Oxford University Press; Mendell JR, Kissel JT, Cornblath DR. *Diagnosis and Management of Peripheral Nerve Disorders*. New York, NY: Oxford University Press, 2001.

## Further reading list

- Hermann DN, Logigian EL. Approach to peripheral nerve disorders. In Preston DC, Ruff RL, Shapiro B, Eds. *Neuromuscular Disorders in Clinical Practice*. Boston, MA: Butterworth Heinemann, 2002.
- Mendell JR, Kissel JT, Cornblath DR. *Diagnosis and Management of Peripheral Nerve Disorders*. New York, NY: Oxford University Press, 2001.
- Schaumburg HH, Berger AR, Thomas PK. *Disorders of Peripheral Nerves*, 2nd edn. Philadelphia, PA: F. A. Davis, 1992.

## 93 Neuropathy, femoral

---

Eva Sahay *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

The femoral nerve is formed from the L2–L4 nerve roots. (Please refer also to [Chapter 100](#) on lumbar plexopathy.) It travels in the psoas muscle where it branches to innervate the muscle, and emerges from the lower third of the lateral border of the psoas, approximately 4 cm above the inguinal ligament. It courses through the groove between the psoas anteriorly and the iliacus muscle posteriorly to enter the femoral triangle just lateral to the femoral artery and vein. It leaves the pelvis, passes beneath the inguinal ligament where it emits a branch, the saphenous nerve, the sensory nerve to the anterior thigh and medial leg, and motor branch to the quadriceps and the sartorius muscles.

Damage to an individual nerve is called a mononeuropathy, which can occur with the femoral nerve. A mononeuropathy typically results from local nerve damage. Systemic disorders can also cause mononeuropathy nerve damage, as can occur with mononeuropathy multiplex (seen commonly with diabetes mellitus).

The frequency of femoral neuropathy in the USA is approximately 1% of all mononeuropathies. It is reported in all age groups and there is no race or sex predilection.

### Causes

The femoral nerve is predisposed to compression within the psoas muscle. This is commonly associated with hemorrhage into the muscle or in the retroperitoneal space. Thus, an underlying coagulopathy or active anticoagulation may be important contributors. Compression can also be due to local masses, *i.e.* aortic or iliac aneurysms, abscesses, or pelvic tumors.

Direct trauma to the femoral nerve can occur as a result of penetrating wounds or related to fractures of the hip or pelvis.

Lithotomy positioning during delivery or gynecologic procedures (especially if spinal anesthesia is used) can also compress the femoral nerve. There are two mechanisms for the compression: pressure-induced ischemia versus stretch of the nerve from excessive hip abduction and external rotation. These injuries are usually self-limited, with spontaneous resolution within weeks to months.

Iatrogenic causes include trauma during pelvic or abdominal surgery, with damage within the pelvis often caused by the retractors used during these operations.

Diabetic patients have an unusual predilection for femoral nerve distribution weakness, though this is more diffuse and often involves the entire lumbar plexus and lumbar root, hence the name diabetic radiculoplexus neuropathy or amyotrophy. The etiology is most likely ischemic in nature.

## History and physical signs

Patients with femoral neuropathy complain of knee buckling and difficulty with climbing stairs and report frequent falls . The onset is typically acute to subacute, which contrasts with a myopathic process, in which the onset is subacute to chronic and typically bilateral in distribution. Patients complain of numbness, tingling, burning, and severe pain in the groin, thigh, and sometimes in the lower abdomen when associated with a retroperitoneal hematoma. Rarely, painful paresthesias are present in the lateral femoral cutaneous nerve distribution. Patients may also experience a sensory disturbance in the saphenous nerve distribution (the medial and posterior leg).

Physical examination reveals weakness of the knee extensors and hip flexors. This results in difficulty in rising from a chair or climbing stairs. If the neuropathy is chronic, there is wasting of the quadriceps muscles. In isolated femoral mononeuropathies, the thigh adductors have normal muscle strength. These muscles are innervated by the obturator nerve, which is formed from the same lumbar nerve roots as the femoral nerve. There is decreased pinprick and temperature sensation in an oval pattern around the anterior surface of the knee, extending approximately 10 cm above and below the knee. Femoral nerve compression may result in debilitating pain requiring medical therapy or surgical intervention.

## **Differential diagnosis**

Lumbar radiculopathy Lumbar plexopathy Diabetic proximal neuropathy (radiculoplexus neuropathy, amyotrophy) Diabetic muscle infarction HIV-associated multiple mononeuropathies Inclusion body myositis Leprosy Systemic lupus erythematosus Sarcoidosis Metabolic myopathies Polyarteritis nodosa Leptomeningeal carcinomatosis

## **Diagnostic work-up**

Imaging studies: magnetic resonance imaging (MRI) or computerized tomography (CT) scan of the pelvis. A CT scan is the investigation of choice when hematoma is suspected. Emergent CT scan of pelvis should be performed in cases of suspected retroperitoneal hematoma.

Electrophysiologic studies: Nerve conduction study (NCS) and needle electromyography (EMG) of the femoral nerve. The quadriceps needle EMG demonstrates neuropathic changes. The adductor magnus and brevis are spared as described above. The femoral motor NCS should be performed bilaterally, comparing the symptomatic and asymptomatic sides. The compound muscle action potential (CMAP) amplitude obtained after a week is the best determinant of extent of axon loss and prognosis. Of note, EMG may not show fibrillation potentials for 1–3 weeks post nerve injury, and NCS may be normal for 5–10 days.

## **Treatment**

In some cases no treatment is required and spontaneous recovery occurs within weeks to months.

Medical treatment is an option depending on the etiology of the lesion. Most patients can be treated conservatively with physical therapy and a knee brace to prevent knee buckling. In patients with a hematoma who are on anticoagulant therapy, anticoagulation agents must be stopped until the hematoma is resolved. If the compression is due to a tumor, treatment is geared toward mass reduction with chemotherapy, radiation therapy, or operative options. In diabetic or vasculitic causes, immunosuppressive therapy is indicated. In cases of painful femoral neuropathy, pain medication may be beneficial.

Surgery is recommended if the neurologic deficit is progressive. Surgical decompression of the nerve is performed in the case of compression from local hematomas or mass lesions. Occasionally surgery is indicated for penetrating wounds or fascial bands. Exploration of the retroperitoneum carries the risk of further bleeding, however. There is also a potential for iatrogenic nerve injury and infection.

## **Prognosis**

If the cause of the femoral nerve dysfunction is identified early and treated successfully, it is possible to recover fully. In some cases there may be complete or partial loss of movement or sensation resulting in some degree of disability and potential complication of repeated injury to the leg.

## **Prevention**

Prevention depends on the etiology of the femoral neuropathy. Maintaining better diabetes control and administration of antiplatelet agents in vasculitic causes may prevent the neuropathy. Close monitoring of the international normalized ratio (INR) to avoid supratherapeutic levels in patients on warfarin may help prevent retroperitoneal bleeds. Avoiding prolonged static positioning during surgical or gynecologic procedures may help prevent compression of the nerve as well .

## **Case vignette**

A 46-year-old male underwent a revision of a colostomy. He had a prior colectomy for diverticulitis. When he awoke from surgery, he noted severe left leg weakness and thigh/leg numbness. He had pain in the left groin and thigh. When examined a month later, he had severe weakness of left hip flexion and knee extension (4/5). Knee flexion and ankle strength was normal. Left knee jerk was absent while the ankle jerk was normal. There was sensory loss in the left anterior thigh and medial leg. Gait was impaired with collapsing left leg. An EMG study showed low femoral CMAP and absent saphenous sensory nerve action potential (SNAP) on the left only. Needle EMG showed fibrillation potentials and reduced motor unit action potential recruitment in left iliocaudis and quadriceps while the thigh adductors, tibialis anterior, and the lumbar paraspinal

muscles were normal. This was consistent with a left femoral neuropathy, proximal to the iliacus branch in the pelvis with evidence of axonal loss. The patient showed slow improvement of weakness and sensory loss. At 6 months, he had mild weakness of left quadriceps and sensory loss in the medial leg.

## Further reading list

- al Hakim M, Katirji B. Femoral mononeuropathy induced by the lithotomy position: a report of 5 cases with a review of literature. *Muscle Nerve* 1993; 16:891–5.
- Kim JE, Kang JH, Choi JC, Lee JS, Kang SY. Isolated posterior femoral cutaneous neuropathy following intragluteal injection. *Muscle Nerve* 2009; 40:864–6.
- Krendel DA, Zacharias A, Younger DS. Autoimmune diabetic neuropathy. *NeurolClin* 1997; 15:959–71.
- Naroji S, Belin LJ, Maltenfort MG *et al*. Vulnerability of the femoral nerve during complex anterior and posterior spinal surgery. *J Spinal Cord Med* 2009; 32:432–5.
- Parmer SS, Carpenter JP, Fairman RM, Velazquez OC, Mitchell ME. Femoral neuropathy following retroperitoneal hemorrhage: case series and review of the literature. *Ann Vasc Surg* 2006; 20:536–40.
- Peirce C, O'Brien C, O'Herlihy C. Postpartum femoral neuropathy following spontaneous vaginal delivery. *J Obstet Gynaecol* 2010; 30:203–4.
- Phang IS, Biant LC, Jones TS. Neurostenalgia of the femoral nerve: a treatable cause of intractable hip pain in a young adult. *J Arthroplasty* 2010; 25:498.e15–7.
- Williams FH, Johns JS, Weiss JM. Neuromuscular rehabilitation and electrodiagnosis. 1. Mononeuropathy. *Arch Phys Med Rehabil* 2005; 86:S3–10.

## **94 Neuropathy, median and carpal tunnel**

---

Huiying Yu *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

Median neuropathies occur in the wrist and the hand, the proximal forearm, the elbow region, the upper arm, and the axilla. Median neuropathy at the wrist – carpal tunnel syndrome (CTS) – is by far the most common.

### **Median neuropathy at the wrist – carpal tunnel syndrome**

Carpal tunnel syndrome is the result of compression of the median nerve within the carpal tunnel, a closed space bounded on the volar surface by the thick transverse carpal ligament. In the carpal tunnel, the median nerve is extremely vulnerable and damage at this level is the commonest peripheral nerve lesion encountered.

### **Etiology**

The normal cause of CTS is enlargement or hypertrophy of the nine flexor tendons that pass through this closed space.

Carpal tunnel syndrome is usually sporadic and is related to recurrent activity. There are numerous etiologies, although most are idiopathic. Idiopathic cases were considered to be tenosynovitis of the transverse carpal ligament due to repeated stress to connective tissue. Multiple predisposing etiologies can be identified ([Table 94.1](#)).

**Table 94.1 Predisposing etiologies of median neuropathy at the wrist.**

---

## Idiopathic

Reduced space in the carpal tunnel

Ganglia, osteophytes

Gout tophi

Lipomas

Vascular anomalies

Anomalous muscles and tendons

Congenital narrow carpal canal

Increased susceptibility of nerve to pressure

Diabetes

Other neuropathies

Hereditary neuropathy with liability to pressure palsies

Other conditions

Repetitive hand use (knitting, meat cutting, playing a musical instrument)

Pregnancy

Obesity

Systemic disorders

Endocrine (e.g. hypothyroidism)

Connective diseases (e.g. rheumatoid arthritis, sarcoid, systemic lupus erythematosus, scleroderma)

Mass or infiltrating lesions of the carpal tunnel

Various infectious diseases such as Lyme

Amyloidosis

Hemodialysis

Acromegaly

Multiple myeloma

Trauma especially Colles' fracture

Familial carpal tunnel syndrome

---

## Clinical presentation

Carpal tunnel syndrome may present with a variety of symptoms and signs. Although usually bilateral, the dominant hand is usually more severely affected. Patients complain of wrist and arm pain associated with paresthesias in the hand.

The pain may be localized to the wrist, or may radiate to the forearm, or rarely, the shoulder. Some patients may describe a diffuse, poorly localized ache involving the entire arm. Paresthesias, typically burning and unpleasant, are frequently present in a median nerve distribution (i.e. first three and a half fingers). Many patients report that the entire hand falls asleep. If asked specifically about little finger involvement, most will subsequently say the little finger is spared.

Symptoms are often provoked with either a flexed or extended wrist posture such as driving or holding a newspaper. Nocturnal exacerbation is a common feature. Patients are frequently awakened from sleep, and describe relief by shaking their hands.

Pain and paresthesia initially are intermittent; as the condition progresses, symptoms become persistent and weakness of thumb abduction and opposition may develop, followed by atrophy of the thenar eminence. Some patients describe difficulty buttoning shirts, opening a jar, or tying a shoelace.

On examination, sensory impairment is usually detectable only in the fingertips. The quickest and easiest method is to rub the patient's fingertips with one's own hand to compare the sensation in the tips of the first three digits with that of the fifth. Patients often describe a feeling like sandpaper or as if their fingertips are covered by a glove. If this abnormality is not present, more careful examination with pinprick and light touch may reveal subtle abnormalities. Few patients have hyperesthesia in the fingertips, particularly to pinprick. Two-point discrimination is less useful than those methods of sensory testing. Sensation over the thenar eminence area is spared owing to the anatomy of the median nerve (i.e. the palmar cutaneous arises proximal to the carpal tunnel). Often paresthesia may be elicited by tapping over the median nerve at the wrist (Tinel's sign) or by wrist flexion (Phalen's sign). Motor examination involves inspection of the hand, looking for wasting of the thenar eminence and testing the strength of thumb abduction and opposition. Atrophy of the abductor pollicis brevis (APB) is a late sign of CTS and is less often seen now because of early diagnosis. Severe atrophy of the APB muscle is most often seen in elderly patients with long-standing but relatively minor sensory symptoms, who finally present with hand clumsiness due to weakness and finger numbness.

## Differential diagnosis

There are several peripheral and central nervous system (CNS) lesions that may result in symptoms similar to CTS. The peripheral lesions that may mimic CTS

include median neuropathy in the region of elbow, brachial plexopathy, C6 or C7 cervical radiculopathy. Cervical radiculopathy is the most common disorder confused with CTS.

The tips listed in [Table 94.2](#) would be helpful regarding what questions should be asked and what exam should be focused on when assessing a patient.

**Table 94.2   *Helpful tips in localizing diagnosis of median neuropathy.***

---

Carpal tunnel syndrome

Clinical features: Nocturnal paresthesia; awaking patient from sleep; shaking the hands; pain or paresthesia with driving or holding book; sensory disturbance of digits 1, 2, 3, and 4, splitting the fourth digit; positive Phalen's sign; positive Tinel's sign; isolated atrophy of thenar muscle

Pronator syndrome

Clinical features: Aching and pain on the flexor compartment of the forearm; aggravation of pain by pronation--supination movements; weakness of median innervated forearm and intrinsic hand muscles; Tinel's sign over the pronator teres muscle; the pronator teres may be firm or enlarged

Brachial plexopathy

Clinical features: Diffuse arm pain; sensory impairment beyond the first three and a half digits; motor weakness involving muscles beyond the abductor pollicis brevis; reduced biceps or triceps reflexes

C6 or C7 radiculopathy

Clinical features: Neck pain, and the pain radiates to the arm; preponderance of pain proximally as opposed to distally (seen in CTS); unequivocal numbness over the thenar eminence; weakness of arm muscles (arm pronation and/or elbow flexion or extension); reduced biceps, brachioradialis, or triceps reflexes

CNS lesions

Transient paresthesia in the hand seen in seizures, migraines, and transient ischemic attacks, small thalamic or internal capsule infarct

---

---

## **Investigation**

### ***Electrophysiology studies***

The best way to confirm the clinical diagnosis of CTS is to perform median sensory and motor nerve conduction studies across the transverse carpal ligament. The most sensitive criterion for diagnosis of CTS is the demonstration of slowing of sensory or mixed nerve conduction at the wrist.

### ***Imaging***

Plain radiography of the wrist will show osteophytes or calcific deposition in the carpal tunnel. Computerized tomography (CT) provides more detail not only of the bones but of the soft tissue structure as well. Magnetic resonance imaging (MRI) is even better at demonstrating structures within the carpal tunnel. Specific lesions such as tendon sheath edema in traumatic tenosynovitis, synovial hypertrophy in rheumatoid arthritis, ganglia, tumors, excessive fat, and abnormal arteries and muscles can all be seen to cause median nerve compression. It is clear that MRI can identify space-occupying lesions in the tunnel causing median nerve compression, but most patients with CTS do not have mass lesions in the tunnel. High-resolution sonography is another effective method of demonstrating mass lesions in the carpal tunnel and is a low-cost alternative to MRI.

### ***Blood tests***

Thyroid function, a fasting glucose, a hematologic profile, and serum protein electrophoresis may lead to the discovery of undiagnosed thyroid dysfunction, diabetes mellitus, or multiple myeloma. However, the diagnostic yield of such blood tests is low in patients with CTS who have otherwise normal medical history and general examination.

## **Management**

Conservative management of CTS involves splinting the wrist in a slightly extended position, reduction of the activity that might have caused the syndrome to develop, steroid injection underneath the volar carpal ligament, and oral medications including non-steroidal anti-inflammatory medications, diuretics,

and corticosteroids. The objective of conservative management is to reduce the tissue pressure within the carpal tunnel, which will rise with wrist extension or flexion or as a consequence of inflammation of the flexor tendons.

The patients who have progressive symptoms and have not responded to conservative measures should be referred to a surgeon for carpal tunnel release. Patients who have late-stage carpal tunnel syndrome with advanced atrophy sensory loss and few symptoms do not respond to surgery.

## Median neuropathy above the wrist

Median neuropathy occurs much less frequently in the axilla, in the upper arm, at the elbow and in the forearm compared with median neuropathy at the wrist. Damage to the median nerve at various regions above the wrist has many causes ([Table 94.3](#)).

**Table 94.3 Etiology of median neuropathy at different locations of the arm.**

---

### Axilla

- Pressure from misuse of crutches
- Sleep palsies associated with drunkenness or drug overdose
- Stab injury or missile injury
- Anterior shoulder dislocation
- Fascial sheath hemorrhage
- False aneurysm
- Radiation treatment
- Idiopathic

### Upper arm

- Arteriovenous fistulas
- Stab wounds or missile injury
- Fracture of the humerus
- Tourniquets
- Sleep palsy associated with drunkenness or drug overdose

### Elbow and forearm

- Fracture of the humerus
- Supracondylar

#### Supracondylar

Medial epicondyle

Fractures of the ulnar and/or radius

Elbow dislocation

Direct trauma

Casting

Bleeding to the flexor compartment of the forearm

Arteriovenous fistulas

Venipuncture

Angiography-related trauma

Supracondylar spurs and ligament (ligament of Struthers)

Compression by:

The bicepital aproneurosis

Anomalous ligamentous bands

The pronator teres muscle (pronator teres syndrome)

Tumors and masses of the nerve and adjacent structures

---

## **Case vignette**

A 35-year-old right-handed female presented to her primary care physician complaining of intermittent numbness and tingling in fingers of both hands associated with pain for about 3 years, worse for 2 months.

Her problem started during her pregnancy with her son 3 years ago. Symptoms gradually improved after delivery, but intermittently she still experiences numbness and tingling mainly in the first three fingers, right more than left. Symptoms are worse at night. At times, she would wake up and had to shake her hands to relieve the symptoms. Two months ago, she bought an apartment. She and her husband painted all the rooms. Since then her symptoms have worsened. She experiences burning pain in fingers and wrists, and at times the pain affects bilateral forearms. The symptoms are aggravated when driving or holding a phone. She noted difficulty opening jars. She has chronic neck tightness, but no pain radiating from her neck to either arm.

Her physician examined her a month ago and noted decreased pinprick and light touch sensation in the first three and a half fingers of the right hand and paresthesia in the first three and a half fingers of the left hand. No muscle weakness was detected. Her physician suspected carpal tunnel syndrome. She was instructed to use wrist braces and see a neurologist. Her neurologist

confirmed her physician's finding on examination and recommended a nerve conduction and needle EMG study, which she had a week ago. She was told that she has bilateral median neuropathy at the wrists, moderate on the right and mild on the left, which is consistent with carpal tunnel syndrome. She does not have cervical radiculopathy.

She had a follow-up visit after the EMG test with her neurologist. She reports that since she started using the wrist braces, her pain and numbness have significantly improved. Her neurologist recommended continuing wearing wrist braces as much as she could, avoid excessive wrist flexion or extension movement. She was told that her symptoms should continue improving. However, if her pain persists, gabapentin can be used; another option is a steroid injection to her wrist at the carpal tunnel. No surgery is indicated.

## Further reading list

- Bland J. Treatment of carpal tunnel syndrome. *Muscle Nerve* 2007; 36:167–71.
- Calandro P, Giannini F, Pazzaglia C *et al.* A new clinical scale to grade the impairment of median nerve in carpal tunnel syndrome. *Clin Neurophysiol* 2010; 121:1066–71.
- Cartwright M, Hobson-Webb L, Boon AJ *et al.* Evidence-based guideline: neuromuscular ultrasound for the diagnosis of carpal tunnel syndrome. *Muscle Nerve* 2012; 46:287–93.
- Padua L, Di Pasquale A, Pazzaglia C *et al.* Systematic review of pregnancy-related carpal tunnel syndrome. *Muscle Nerve* 2010; 42:697–702.
- Werner R, Andary M. Electrodiagnostic evaluation of carpal tunnel syndrome. *Muscle Nerve* 2011; 44:597–607.

## 95 Neuropathy, radial

---

Padmaja Aradhya

*Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

The radial nerve is derived from C5--T1 root fibers. It is the terminal nerve of the posterior cord. It supplies the triceps and the extensors of the wrists and hands. It divides into a deep branch, which is known as the posterior interosseous nerve and continues as the superficial branch and innervates the dorsum of the hand. The radial nerve enters the arm behind the axillary artery. It descends to the forearm between the distal portion of the triceps and brachioradialis muscles. The branches of the radial nerve are as follows:

Sensory:

1. Posterior cutaneous nerve of arm.
2. Inferior cutaneous nerve of arm.
3. Posterior cutaneous nerve of forearm.
4. Superficial radial nerve.

Motor:

1. Radial nerve.
2. Posterior interosseous branch.

The radial nerve can be injured anywhere along its course, but the following sites are more prone to compression. In the axilla, fracture of the humerus is one of the most common causes of radial nerve injury and it results in wrist drop. [Figure 95.1](#) shows a 40-year-old male who was involved in a trauma resulting in a left humeral fracture, resulting in wrist drop and atrophy of the extensor muscles. Use of crutches is another common cause of radial neuropathy at the

axilla. A radial nerve lesion could also be a part and parcel of more widespread processes like vasculitis, or cryoglobulinemia. Other common causes are Saturday night palsy , which usually occurs as a result of compression of the radial nerve in the spiral groove in a patient who is intoxicated, ill, or bed-bound. Posterior interosseous neuropathy , which is a pure motor neuropathy, causes weakness of the wrist and finger extensors. This neuropathy usually spares sensation. This can be due to trauma, rheumatoid arthritis, vasculitis, idiopathic brachial plexus neuropathy (neuralgic amyotrophy , Parsonage--Turner syndrome ), and as part of generalized processes such as multifocal motor neuropathy or multifocal acquired demyelinating sensory and motor neuropathy (MADSAM ).



**Figure 95.1** A 40-year-old male involved in a trauma resulting in a left humeral fracture, resulting in wrist drop and atrophy of the extensor muscles.

Superficial radial neuropathy is a pure sensory branch, which causes sensory loss in the dorsum of the hand. The common causes are compression due to handcuffs, casts, tight wristbands, or venipuncture. De Quervain's tendonitis may rarely be associated with superficial radial neuropathy.

## Treatment of radial nerve lesions

The management of radial nerve palsy is usually conservative with finger and

wrist splints, pain control, and physical/occupational therapy. Posterior interosseous neuropathy is also treated conservatively unless there is an open trauma, especially with laceration, which requires surgical exploration. Of course, lesions due to tumors can also be explored for a surgical solution.

A tendon transplant to improve the position of the wrist drop is sometimes recommended. Re-anastomosis is an option if no regeneration or inadequate regeneration is noted.

Prognosis depends on the degree and type of radial nerve injury. In most mild cases, recovery after several months is noted.

## Case vignette

A 40-year-old male was involved in a trauma 10 years ago resulting in fracture of the left humerus. As seen in [Figure 95.1](#), the patient has atrophy of the extensor muscles of the left forearm. The differential diagnosis includes radial neuropathy or brachial plexopathy involving the posterior cord. Cervical radiculopathy, particularly C7 radiculopathy, also needs to be considered. Since this patient had no ulnar nerve involvement the diagnosis was of radial neuropathy. Please refer to [Table 95.1](#) for further information.

**Table 95.1 Etiology and signs of radial neuropathy.**

Site	Etiology	Pattern of weakness	Sensory loss
Axilla	1. Crutches 2. Trauma 3. Stretch injury – hyperabduction of arm during surgery 4. Honeymoon palsy 5. Vasculitis 6. Arteriovenous	Triceps, brachioradialis and all finger and wrist extensor muscles NCS – decreased radial CMAP (rarely conduction block between axilla and Erb's point) and decreased	Present. May be minimum or inconspicuous Extends into posterior forearm and arm

	(AV) fistula 7. Multifocal motor neuropathy 8. Multifocal acquired demyelinating sensory and motor neuropathy	radial SNAP EMG – denervation in triceps, brachioradialis, and all finger and wrist extensor muscles	
Arm (spiral groove)	1. Saturday night palsy 2. Fracture of humerus	Brachioradialis and all finger and wrist extensor muscles. Normal triceps NCS – decreased radial CMAP or conduction block across the spiral groove and decreased radial SNAP EMG – denervation in brachioradialis and all finger and wrist extensor muscles. Normal triceps and anconeus	Present. May be minimal or inconspicuous
Forearm (posterior interosseous nerve)	1. Trauma 2. Idiopathic brachial plexus neuropathy 3. Multifocal motor neuropathy or	Normal triceps and brachioradialis NCS – SNAP normal and decreased CMAP EMG –	Absent

	MADSAM	Denervation in extensor muscles.	
4.	Ganglion	Spares triceps.	
	cysts	Anconeus and brachioradialis	
5.	Lipoma		
6.	Compression by the arcade of Frohse		
7.	Compression within the supinator muscle		
8.	Peripheral nerve tumor		
9.	Vasculitis		
10.	AV fistula		
11.	Rheumatoid arthritis		
Superficial radial neuropathy	Compression – tight wristbands, casts, handcuffs, venipuncture, De Quervain's tendonitis, trauma, tumors	No weakness detected NCS – decreased SNAP and normal CMAP EMG – normal	Dorsum of the hand

---

CMAP, compound muscle action potential; EMG, electromyography; MADSAM, multifocal acquired demyelinating sensory and motor neuropathy; NCS, nerve conduction studies; SNAP, sensory nerve action potential.

## Further reading list

Lotem N, Fried A, Levi M *et al*. Radial palsy following muscular effort: a nerve compression syndrome possibly related to a fibrous arch of the lateral head of the triceps. *Bone Joint Surg* 1971; 53B: 500–6.

## **96 Neuropathy, sciatic**

---

Julius Bazan and Pedro J. Torrico *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

#### **Sciatic nerve**

The sciatic nerve is the longest and widest nerve in the human body. It is derived from spinal nerves L4, L5, S1, S2, and S3. (Please also refer to [Chapter 100](#) on lumbar plexopathy). These nerve roots intermingle to form the lumbosacral plexus. The sciatic nerve leaves the pelvis through the sciatic notch (greater sciatic foramen) under the piriformis muscle covered by gluteus maximus muscle and then it runs in the posterior thigh compartment. The two divisions (peroneal/tibial) physically separate in the midthigh to form their respective nerves. The sciatic nerve innervates all thigh muscles in the posterior compartment, the semitendinosus, semimembranosus, biceps femoris (the long head is tibial innervated and the short head peroneal innervated), and adductor longus.

#### **Posterior femoral cutaneous nerve (S1, S2, S3)**

Also known as the small sciatic nerve, it originates from the sacral plexus. It travels with the sciatic nerve (via the sciatic notch) and innervates the skin of the posterior thigh.

#### **Tibial nerve**

Also known as the posterior tibial nerve, the tibial nerve runs deep in the calf compartment and innervates the following muscles: soleus, gastrocnemius, posterior tibialis, and plantar/toe flexors. Finally, the tibial nerve passes through the tarsal tunnel and innervates the foot flexors and the skin of the sole of the foot (sensory nerves – lateral plantar, medial plantar, and calcaneus).

## **Peroneal nerve**

Also known as the common peroneal nerve, the peroneal nerve wings around the knee at the fibular head. The deep branch runs in the anterior tibial compartment and innervates the anterior tibialis, extensor digitorum longus, peroneus tertius, and extensor hallucis longus, and below the ankle the extensor digitorum brevis and extensor hallucis Brevis. The DPN terminal sensory branch innervates the webbing between the first and second toes. The superficial branch (superficial peroneal nerve) innervates the peroneus longus and peroneus brevis muscles and provides sensory innervation to the lateral calf and dorsum of the foot.

## **Sural nerve**

The sural nerve is formed by posterior cutaneous branches of the tibial and peroneal nerves. They unite above mid-calf and provide sensory innervation to the posterior-lateral calf. The medial calf/foot region is innervated by the saphenous nerve (L3, L4) – a branch of the femoral nerve.

## **Symptoms**

Pain (sciatica, lumbago) : Sciatic pain, sciatica or lumbago. The typical syndrome is a sharp pain that arises in the gluteal or proximal thigh region, radiating posteriorly and laterally to the leg, ankle, and foot/toes. It usually does not affect the back. This can be accompanied by paresthesias in the calf, foot, and toes. Sitting or walking may worsen the pain. Other sensations like ache, throbbing, pulling, burning can also occur.

Weakness: It has long been recognized that the peroneal fibers are preferentially affected in most sciatic nerve lesions. So, it is not unusual to have a sciatic neuropathy presenting as a peroneal neuropathy (foot drop with sensory dysfunction on the dorsum of the foot). More severe lesions will show obvious deficits like depressed ankle jerks, knee flexion/plantar flexion weakness, and sensory deficits below the knee level sparing the medial aspect of the calf and foot.

Numbness/paresthesias/dysesthesias: Sensory symptoms will involve the anterolateral, posterior calf, dorsum of the foot and plantar region sparing the medial aspect of the calf/foot (saphenous nerve). Sensory symptoms will be more commonly seen in the peroneal nerve distribution preferentially.

Loss of reflexes, knee jerk (L3, L4), ankle jerk (L5, S1): A sciatic nerve dysfunction will only affect ankle jerks. Note that in mild sciatic neuropathies ankle jerks can be normal or slightly diminished. Patellar jerks should always be spared.

## Differential diagnosis

Peroneal neuropathy, lumbosacral plexopathy, or L4/L5/S1 radiculopathy.

Meralgia paresthetica (lateral femoral cutaneous nerve): Compression of the lateral femoral cutaneous nerve at the inguinal ligament. Contributing factors include obesity, tight belts, positioning during surgery (lithotomy position), cesarean section, groin surgery, or idiopathic. Symptoms are burning sensation, tingling, and numbness in the lateral thigh region. Deficits to pinprick sensation on the lateral thigh region.

Piriformis syndrome (pseudosciatica, Wallet syndrome, hip socket neuropathy): Initially described in 1929. This is a rare clinical entity and does not differ from other sciatic neuropathies in terms of symptomatology. In 10–17% of the population the sciatic nerve pierces the piriformis muscle. The piriformis muscle laterally rotates the extended thigh and abducts the flexed thigh. Theoretically, muscle spasms or hypertrophy of the piriformis muscle can produce sciatic nerve dysfunction. Clinically, the pain is more intense with sitting than standing. The pain can be reproduced by manual compression of the mid-gluteal region. Flexion, adduction, and internal rotation of the hip can worsen symptoms. Contributing factors include very thin body habitus, local trauma, and occupation related (e.g. athletes, individuals who stand for prolonged periods of time).

Shin splints (medial tibial stress syndrome): Shin splints are very common. They account for 13% of running injuries. This is usually due to muscular fatigue during exercise (overpronation of the foot). It can be triggered by mild or moderate exercise if leg conditioning is poor.

Pediatric sciatic neuropathies: There are no significant differences between adult and pediatric sciatic neuropathies ([Table 96.2](#)).

**Table 96.1** *The lumbosacral plexus.*

Nerve	Root	Muscle	Function
-------	------	--------	----------

Sciatic	L4	Adductor magnus	Thigh	Adduction
Sciatic	L5, S1, S2	Biceps femoris	Knee	Flexion
Sciatic	L5, S1, S2	Semimembranosus Semitendinosus	Knee	Flexion
Peroneal deep	L4, L5	Anterior tibial	Foot	Dorsiflexion
Peroneal deep	L5, S1	Extensor digitorum	Dig. 2–5	Dorsiflexion
Peroneal deep	L5, S1	Extensor hallucis	Dig. 1	Dorsiflexion
Peroneal superficial	L5, S1	Peroneus	Foot	Eversion
Tibial	L5, S1	Posterior tibial	Foot	Plantarflexion
Tibial	S1, S2	Gastrocnemius	Foot	Plantarflexion
Tibial	S1, S2	Soleus	Foot	Plantarflexion

Note: Adductor magnus also innervated by obturator nerve (L2, L3).

Gluteal muscles innervated by gluteal nerves (L5, S1, S2).

It is commonly accepted that the peroneal division is more susceptible to damage in sciatic nerve injuries (compression/trauma/ischemia). This is due to different reasons: The peroneal division runs

more superficial relative to the tibial division in hip and proximal thigh; the peroneal division has fewer and larger fascicles and less supportive endoneurium and perineurium; the peroneal division has smaller blood supply compared with the tibial division; the peroneal division is securely fixed to the sciatic notch and fibular head; and finally reinnervation process occurs more efficiently in the tibial division.

**Table 96.2 Etiologies of sciatic neuropathies.**

Trauma	25%
Iatrogenic (surgery)	25% Mostly orthopedic
Vascular	13%
Prolonged compression and immobilization	11%
Idiopathic progressive	7%
Idiopathic non-progressive	5%
Presumed postviral	3%
All other etiologies	1%

### **Case vignette**

A 71-year-old male with a history of diabetes mellitus, hypertension, and osteoarthritis presents to the office for evaluation of left foot drop noted after knee replacement surgery for 4 weeks. He complains of weakness on ankle dorsiflexion and plantar flexion. This is accompanied by shooting-type pain originating from the posterior aspect of the midthigh that radiates down to the foot associated with numbness/paresthesias in the calf. He does not have lumbar pain. General exam shows left lower extremity edema (below the knee). Neurologic exam shows normal cranial nerves; strength and sensory examination in upper limbs is unremarkable. Lower limb exam is relevant for decreased tone in left calf and foot. Right lower extremity strength is 5/5 in all muscle groups. Left lower extremity: hip flexion and extension 5/5, knee flexion

4/5, knee extension 5/5, foot dorsiflexion 1/5, plantar flexion 2/5, toe extension/flexion 1/5, foot inversion/eversion 1/5. Deep tendon reflexes are +1 bilaterally except for left patellar (pain limited), and absent left ankle jerk. Plantar response was flexor bilaterally. Sensory exam revealed decreased sharp perception in right foot (circumferential sensory loss) and decreased sensation to sharp perception, and vibration sense in left calf sparing the medial aspect of calf and foot. Joint position is abnormal in left foot.

The patient had a femoral nerve block for the knee replacement surgery. He also had a tourniquet placed in midthigh.

Nerve conduction studies of both lower limbs showed diffuse sensorimotor abnormalities in both lower limbs, left lower extremity significantly worse than right (peroneal/tibial/sural/superficial peroneal nerves). Needle electromyography (EMG) revealed active denervation in left posterior thigh muscles (semitendinosus, semimembranosus, short head of biceps), and anterior/posterior calf muscles (tibial and peroneal innervated muscles), and normal findings on the gluteus maximus and tensor of the fascia lata. Right tibialis anterior and paraspinal musculature showed no electrical instability.

## Discussion

Based on the patient's complaints, it is clear that there is more than an isolated peroneal nerve dysfunction, which can be seen in patients with history of knee replacement surgery and foot drop. The neurologic exam shows deficits in the sciatic nerve distribution. At this point it is difficult to differentiate an isolated sciatic nerve problem versus a lumbosacral plexopathy or lumbosacral radiculopathy (L4–L5–S1), which are still in the differential diagnosis. This becomes even more challenging given the history of diabetes mellitus. Note that the patient does not complain of radiating lumbar pain.

The nerve conduction studies were very helpful in localizing the problem. First, there are diffuse abnormalities in sensory and motor nerves in both legs, left worse than right, which suggests a pre-existent sensorimotor neuropathy likely secondary to diabetes mellitus. The EMG showed abnormalities in all sciatic innervated muscles sampled. Anterior thigh muscles (femoral innervated), gluteus maximus (inferior gluteal nerve – branch of lumbosacral plexus), and tensor of the fascia lata (innervated by superior gluteal nerve – branch of the lumbosacral plexus) are all spared which exclude a possible lumbosacral plexopathy. The absence of electrical instability in lumbosacral paraspinal musculature excludes the possibility of radiculopathy.

The patient also underwent magnetic resonance imaging (MRI) of the lumbosacral spine that showed diffuse degenerative changes with mild spinal stenosis without nerve root involvement. Doppler studies of the left lower extremity did not show a deep venous thrombosis. An MRI of the thigh was also performed to exclude a possible lesion in the posterior compartment of the thigh. No compressive lesion in the thigh was found and there were T2 abnormalities in biceps femoris and semitendinosus muscles suggestive of denervation. No abnormal enhancement of sciatic nerve was reported.

It was determined that the etiology of sciatic neuropathy in this patient was secondary to a tourniquet in the setting of pre-existent diabetic neuropathy (likely ischemic ).

**Table 96.3 Differential causes of sciatic neuropathy by location.**

Mechanism	Example	Clinical features/clues
<b>Lumbar radiculopathies</b>		
Compression	Disk herniation (herniated nucleus pulposus) Osteophytes (bone spurs) Osteoarthritis Spinal stenosis Spondylolisthesis	Radicular lumbar pain with or without motor and sensory symptoms within the affected nerve root distribution. Associated muscle spasm is common
Sprain	Trauma – whiplash injuries	Radicular lumbar pain, history of trauma
Ischemia	Diabetes mellitus (DM) Arteriovenous (AV) malformation	DM: Rapid onset of symptoms including radicular pain, it can be bilateral. No history of trauma. Difficult to differentiate from compressive radiculopathy. Imaging studies necessary

Radiation	Iatrogenic – cancer treatment	Radicular lumbar pain. Multilevel nerve root involvement is not uncommon. This can be unilateral or bilateral
Inflammation	CMV, Epstein–Barr virus, HSV, HZV Lyme disease Syphilis Mycoplasma Sarcoidosis	CMV/HSV/HZV: Usually associated with severe back pain, sensory/motor symptoms and may be accompanied by myelopathy
Epidural abscess	Any bacterial infection (most commonly <i>Staphylococcus</i> ) Tuberculosis Osteomyelitis	Fever, back pain, history of intravenous (IV) drug abuse, mechanical valves, indwelling catheters (chemotherapy port/dialysis catheter/PICC line)
Tumors – benign	Meningioma Neurofibroma Ependymoma Neural sheath tumors	Symptoms develop insidiously. Low back pain may or may not be present. Motor/sensory deficits in lower extremity (myotomal/dermatomal distribution)
Tumors – malignant	Carcinomatous meningitis Lymphoma (lymphomatous meningitis)	History of cancer, +/- meningismus, back pain, LM syndrome in lower limbs, unilateral or bilateral. Bladder function may be compromised. Contrast imaging studies/CSI analysis are helpful
Cysts	Perineurial cyst (Tarlov cyst)	Radicular lumbar/leg pain. Need imaging study to aid in diagnosis

Trauma – iatrogenic	Epidural nerve block Lumbar puncture Lumbar anesthesia	Back pain and deficits in the affected nerve root distribution History of recent epidural injection
---------------------	--	--

## Lumbosacral plexopathies

Compression	Pregnancy – fetal head (3rd trimester) Delivery – perinatal injuries, protracted labor, forceps delivery Uterus – fibroma, myoma Uterus – retroflexion	Clinical clue in pregnancy: large babies (petite mothers can have large babies). Injury may happen during vaginal delivery which can damage the lumbosacral plexus. This results in foot drop with associated radicular pain
Trauma	Pelvic – fractures	Usually peroneal division is more affected than tibial division resulting in foot drop. Tibial involvement is variable.
Ischemia	Diabetes – diabetic amyotrophy HIV Vasculitis Iliac artery – stenosis, spasm Idiopathic Proximal iliac vein thrombosis Heroin IV users (lumbosacral plexus necrosis)	Diabetic: severe lancinating pain in pelvic region/thigh muscles with sensory and motor deficits in proximal LE usually unilateral Vascular arterial: look for accompanying sx, pallor, pulseless, pain, paresthesias, and weakness Vascular venous: LE edema, skin changes, pain, paresthesias, and weakness
Radiation	Iatrogenic – cancer treatment	Pelvic pain – Motor and sensory complaints in affected area

ЛЕ, ЕМГ нервов, преходяща myokymia on EMG recording

Inflammation	Viral – CMV, Epstein–Barr virus, HSV, HIV Sarcoid	Lumbar/pelvic pain associate with ant/post lumbosacral plexus sensory/motor deficits Laboratory, EMG, imaging studies needed
Abscess	Retroperitoneal, pelvic	Pelvic – upper thigh/lower thigh pain or sciatic-like symptoms. Imaging studies necessary, +/- EMG
Aneurysm	Iliac artery (unruptured large aneurysms/ruptured aneurysms)	May present as a sudden onset of lumbar pain/pelvic pain associated with sensory/motor symptoms in the L2–L4 or L4–S1 distributions. Urinary retention is not uncommon
Hemorrhage	Retroperitoneal Ruptured aneurysm, warfarin therapy	As above
Tumors – benign	Schwannoma, neuroma, neurofibroma Retroperitoneal – fibroma, myxoma Round ligament – leiomyoma	Usually insidious onset with or without pain and motor/sensory symptoms in the L2–L4/ L4–S1 distributions. Imaging studies necessary
Tumors – malignant – local	Carcinoma – rectum, prostate, bladder, uterus, ovary, testicles Sarcoma	Symptoms depend on the extent of involvement. Clinic exam can be challenging given the severity of pain. EMG/imaging studies are helpful

Tumors – malignant – metastatic	Invasive tumors	Pain in lumbar, gluteal, pelvic/thigh region associated with sensory/motor symptoms, unilateral 90% of cases. Possible autonomic dysfunction due to involvement of sympathetic nerves
Endometriosis	Ectopic endometrial tissue	+ Gynecologic history. Deficits will depend upon location. Rare.
Idiopathic	Non-diabetic amyotrophy	Presentation similar to diabetic amyotrophy
Iatrogenic – Injections	Iliac artery – angiography, chemotherapy	Usually presents as a femoral neuropathy syndrome
Iatrogenic – Surgery Compression, retraction, hematoma	Retroperitoneal, pelvic surgery Aorto-iliac bypass Kidney surgery – nephrectomy, transplant Gynecologic surgery – hysterectomy	Lumbar/pelvic/upper thigh pain. Deficits will depend on the location/type of surgery and proximity to compromised neural structures

## Sciatic neuropathy

Compression – external	Prolonged bedrest Perioperative buttock pillow wedge Lithotomy (flexed hips) position Toilet seat neuropathy	Pain in gluteal/posterior thigh region with radiation to the foot. Back pain is usually not present. Peroneal fibers are usually more affected than tibial fibers
------------------------	---	---

Compression – internal	Piriformis syndrome Gluteal compartment syndrome Thigh compartment syndrome Entrapment (myofascial band in thigh) Obturator internus spasm Ossification of sacrospinous ligament	Piriformis syndrome: rare, seen in athletes, very thin individuals, or patients who spend long hours standing. The pain is more intense with sitting than standing; worsening of symptoms with flexion, adduction, and internal rotation of the hip; history of local trauma; tenderness on palpation of mid-gluteal region reproducing the pain
Trauma	Hip, femur, pelvis, thigh Fractures – hip, femur, pelvis Avulsion fracture – ischial tuberosity Hip dislocations – posterior Thigh injuries – posterior	History of trauma. Peroneal fibers are usually more affected than tibial (see Note to Table 96.2).
Ischemia	Sciatic nerve Diabetes Vasculitis Femoral artery – stenosis, spasm Heroin use Tourniquet used in surgery	Note that diabetics are more prone to mononeuropathies/neuropathy. In vasculitis, associated systemic symptoms like fever, myalgias, skin rash, pericarditis, pleuritis, etc. are usually already present
Amyloidosis	Sciatic nerve	Rare cause of mononeuropathy
Abscess	Thigh – posterior	Sciatic nerve dysfunction due to abscess

		<b>SCIATIC NERVE DYSFUNCTION, HIGH INDEX OF SUSPICION</b>
		<b>SCIATIC NERVE DYSFUNCTION, HIGH INDEX OF SUSPICION</b>
Aneurysm/dissection	Deep femoral artery/popliteal artery/knee trauma	High clinical suspicion for vascular pathology in the context of sciatic nerve dysfunction
Hematoma	Thigh – posterior Ruptured aneurysm Warfarin therapy	Look for LE pulses. Thigh diameter enlargement and signs of distal ischemia (pallor, decrease in peripheral pulses, pain)
Tumors – nerve	Sciatic nerve Schwannoma, neuroma, neurofibroma Peripheral nerve sheath tumor, neurofibrosarcoma	Slow growing tumors. Presentation is insidious. Sensory and motor deficits distal to the tumor. Imaging studies/biopsy/resection for final diagnosis.
Tumors – local – benign	Thigh, femur Lipoma Osteochondroma, fibrous dysplasia, desmoplastic fibroma	Sensory and motor deficits distal to the tumor Imaging/resection/biopsy
Tumors – local – malignant	Thigh, sacrum, femur Sarcoma, liposarcoma, chondrosarcoma, giant-cell tumors	Sciatic nerve dysfunction distal to the tumor Imaging/resection/biopsy
Tumors – metastatic	Bone metastases	Isolated sciatic involvement

	Breast cancer, hypernephroma, lung cancer, prostate cancer	rare
Inflammation	Trochanteric bursa – bursitis	
Iatrogenic – injections	Buttocks, intramuscular (IM) injections	Sciatic nerve dysfunction, history of recent IM injection
Iatrogenic – surgery (Traction, compression, retraction, hematoma)	Hip, buttock, thigh Orthopedic surgery: preoperative hip traction, hip arthroplasty, replacement Knee replacement – tourniquet Endovascular surgery: buttock, thigh – aneurysm, AV malformation – obliteration	Sciatic nerve dysfunction dist to the insult

### **Bilateral sciatic neuropathy**

Compression – External	Prolonged sitting position – sleeping Bench, toilet – toilet seat neuropathy Usually in alcoholics (Saturday night palsy) Yoga lotus position	Bilateral sciatic nerve dysfunction symptoms peroneal > tibial
---------------------------	--	--

	Karely bilateral proximal iliac vein thrombosis
Compression – Iatrogenic	Surgery Lithotomy (Flexed hips) position – gynecologic surgery Sitting position – craniotomy
Metabolic	Diabetes Alcoholism Thyroid dysfunction Porphyria Kidney failure Sepsis Vitamin deficiencies (B12, E, B1)
Immune	Cryoglobulinemia

---

CMV, cytomegalovirus; CSF, cerebrospinal fluid; EMG, electromyography; HIV, human immunodeficiency virus; HSV, herpes simplex virus; HZV, herpes zoster virus; LE, lower extremities; LMN, lower motor neuron syndrome; PICC, peripherally inserted central catheter.

## Further reading list

Ducray F, Guillevin R, Psimaras D *et al.* Postradiation lumbosacral radiculopathy with spinal root cavernomas mimicking carcinomatous meningitis. *Neuro Oncol* 2008; 10:1035–9.

Geiringer SR. *Anatomic Localization for Needle Electromyography*, 2nd edn. Philadelphia, PA: Hanley & Belfus, 1999.

Kim DH, Murovic JA, Tiel R, Kline DG. Management and outcomes in 353

surgically treated sciatic nerve lesions. *J Neurosurg* 2004; 101:8–17.

Preston DC, Shapiro B. *Electromyography and Neuromuscular Disorders: Clinical-Electrophysiologic Correlations*, 3rd edn. Philadelphia, PA: Saunders, 2012.

Sethi RK, Thompson LL. *The Electromyographer's Handbook*. Boston, MA: Little, Brown and Company, 1989.

Srinivasan J, Ryan MM, Escolar DM, Darras B, Jones HR. Pediatric sciatic neuropathies: a 30-year prospective study. *Neurology* 2011; 76:976–80.

Sunderland S. The relative susceptibility to injury of the medial and lateral popliteal divisions of the sciatic nerve. *Br J Surg* 1953; 41:300–2.

Van Langenhove M, Pollefliet A, Vanderstraeten G. A retrospective electrodiagnostic evaluation of footdrop in 303 patients. *Electromyogr Clin Neurophysiol* 1989; 29:145–52.

Yuen EC, So YT. Entrapment and other focal neuropathies: sciatic neuropathy. *Neurol Clin* 1999; 17:617–31.

## **97 Neuropathy, tibial**

---

Reema Maindiratta *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### **Introduction**

The complaint of difficulty standing and walking from painful burning sensation in one or both feet is common, but definitive diagnosis is often difficult, resulting in persistent discomfort and delay in treatment. While investigating various diagnostic differentials and solving the maze, the clinical presentation often opens the window to possibilities. Tibial neuropathy, a rare syndrome, is one of the likely possibilities that presents with unilateral, and occasionally bilateral, burning pain in the foot, numbness and paresthesias in the sole, difficulty ambulating, and weakness of plantar flexion and inversion of the foot as well as flexion of the toes. Tinel's sign is commonly present at the site of compression. The absence of sensory complaints, findings on the dorsum of the foot and sparing of peroneal nerve-innervated muscles assists in solving the diagnostic dilemma.

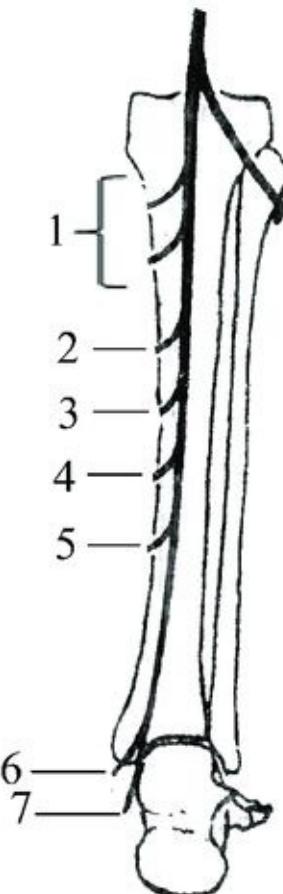
### **Anatomic localization and clinical presentation**

The tibial nerve is derived from the L4 to S3 nerve roots, and its fibers descend initially within the sciatic nerve that branches into the tibial and peroneal nerves in the posterior thigh. The tibial nerve descends, lying deep, and exits the popliteal fossa between the two heads of the gastrocnemius muscle to innervate the muscles in the posterior compartment of the lower leg. The nerve then continues deep to the soleus muscle towards the foot and ankle. At about halfway down the lower leg, the medial cutaneous nerve of the calf, a branch of the tibial nerve, joins the lateral cutaneous nerve of the calf, a branch of the peroneal nerve, to form the purely sensory sural nerve. This supplies sensation to the distal posterolateral third of the lower leg and lateral border of the foot. In the upper leg and above the knee, the tibial nerve innervates the hamstring

muscles, semitendinosus, semimembranosus and long head of biceps femoris, while the peroneal nerve innervates the short head of biceps femoris. In the lower leg and above the ankle, it also innervates the popliteus, both heads of gastrocnemius, soleus, tibialis posterior, flexor hallucis longus, and flexor digitorum longus muscles ([Figure 97.1](#)).

### Muscles Innervated by Tibial Nerve

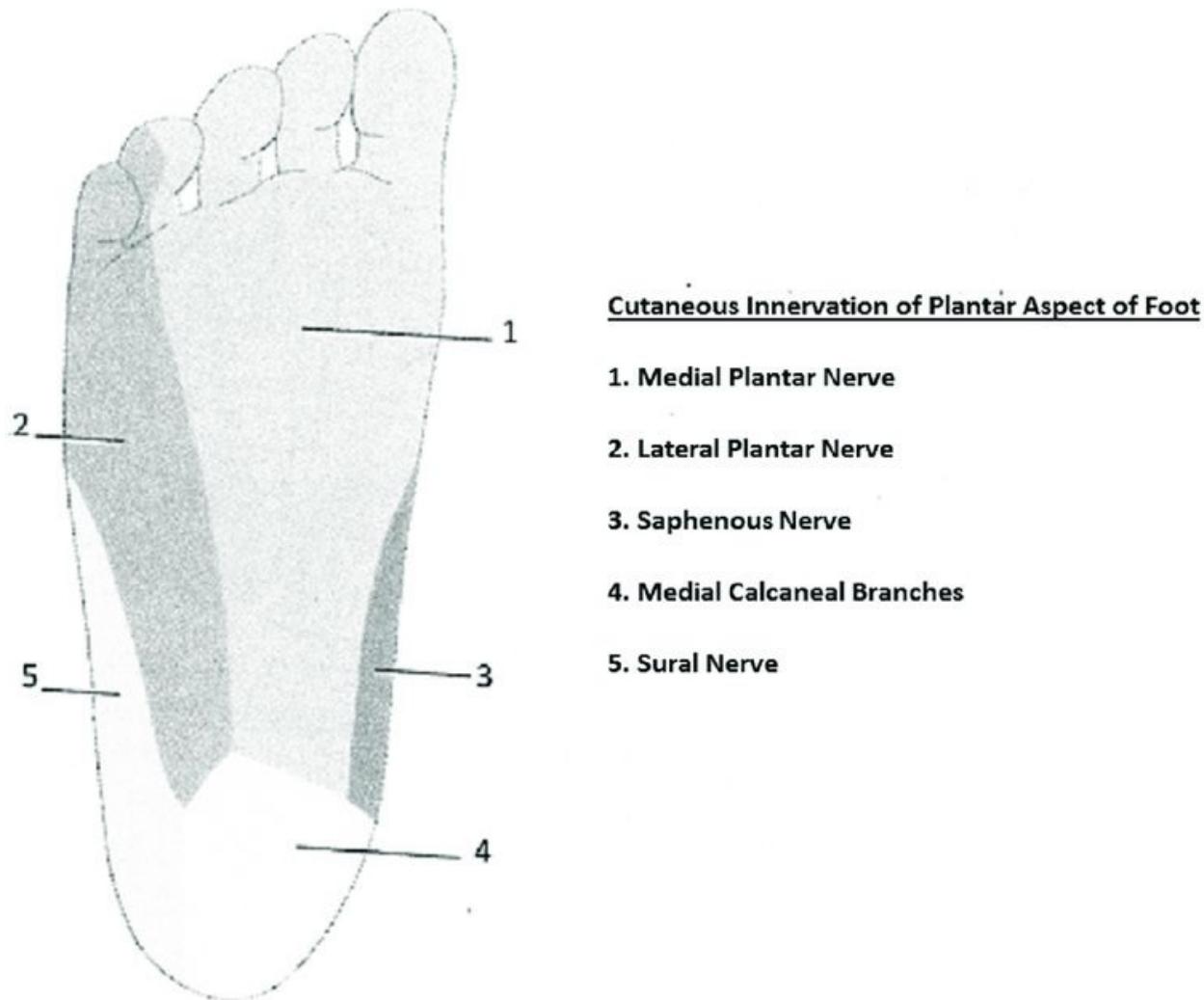
1. Gastrocnemius (Both Heads)
2. Soleus
3. Tibialis Posterior
4. Flexor Digitorum Longus
5. Flexor Hallucis Longus
6. Medial Plantar Nerve  
*(Innervates Abductor Hallucis and Short Flexor Digitorum Muscles)*
7. Lateral Plantar Nerve  
*(Innervates Flexor Digiti Minimi, Abductor Digiti Minimi, Adductor Hallucis, and Interossei)*



**Figure 97.1** Muscles innervated by the tibial nerve.

At the ankle, the tibial nerve runs posterior to the medial malleolus and under the flexor retinaculum. The flexor retinaculum is a fibrous band that forms the tarsal tunnel and has several structures passing through it and posterior to the medial malleolus. These are the tibialis posterior tendon, flexor digitorum tendon, posterior tibial artery, posterior tibial veins that are usually one on either side of the artery, tibial nerve, and the flexor hallucis longus tendon. The nerve then divides into four branches, the medial and lateral plantar nerves, and the medial and inferior calcaneal nerves ([Figure 97.2](#)). The two plantar nerves supply sensation to the sole of the foot and innervate its intrinsic muscles. The medial plantar nerve supplies sensation to the medial sole and medial three or

four toes, and innervates the abductor hallucis, flexor digitorum brevis, and lumbrical muscles. The lateral plantar nerve supplies sensation to the lateral sole and the little toe, and sometimes the adjacent toe. It innervates the abductor digiti minimi, flexor digiti minimi, adductor hallucis, and the dorsal and plantar interossei muscles. The purely sensory medial and inferior calcaneal nerves branch out with the plantar nerves and supply the heel of the foot.



**Figure 97.2** Cutaneous innervation of plantar aspect of foot.

Injury to the tibial nerve at different levels results in varying clinical syndromes. Motor deficits may include plantar flexion and inversion of the foot, as well as weakness of toe flexors. The gastrocnemius and tibialis posterior muscles are the plantar flexors, tibialis posterior muscles are the invertors, and flexor digitorum longus and intrinsic muscles of the feet are the toe flexors. Sensory deficit may be present over the lateral aspect and sole of the foot.

Atrophy of the gastrocnemius and intrinsic muscles may be noted. In moderate to severe cases, weakness of the interossei muscles of the feet can result in claw-like deformity. Tinel's sign is usually present at the site of irritation, which is behind the medial malleolus for tarsal tunnel syndrome. Differential diagnosis includes polyneuropathy, radiculopathy, myopathy, plexopathy, plantar fasciitis, Morton's neuroma, and other degenerative and systemic disorders.

Proximal tibial neuropathy may present with motor weakness of the plantar flexors/invertors of the foot and flexors of the toes, numbness and tingling of the lateral border and sole of the foot, and absence of Tinel's sign at the tarsal tunnel. Injury distal to the branches to the gastrocnemius muscle may result in weakness of the toe flexors and sensory changes of the sole of the foot. Plantar flexion and sural nerve distribution are spared. Distal tibial neuropathy at and below the ankle includes tarsal tunnel syndrome and distal tarsal tunnel syndrome. Tarsal tunnel syndrome is an underdiagnosed entrapment neuropathy caused by involvement of the posterior tibial nerve when it passes under the flexor retinaculum in the tarsal tunnel and behind the medial malleolus. It presents with burning, electric-like radiating pain, numbness, and paresthesias in the ankle and sole of the foot, occurring at rest but worse on weight bearing, resulting in difficulty standing and walking, and possible accompanying weakness and atrophy of the intrinsic muscles of the foot. There is often Tinel's sign behind the medial malleolus. Distal tarsal tunnel syndrome is usually clinically isolated to the nerve affected, medial or lateral plantar nerves, and/or medial or inferior calcaneal nerves.

## Etiology

Tibial neuropathy is rare, especially proximally where the nerve runs deep for most of its course. Nerve damage may also result from injury to the tibial fibers in the sciatic nerve trunk. Causes include trauma, ischemia, and direct compression of the nerve from a space-occupying lesion at the back of the knee, lower leg, ankle, or sole of foot, such as tumor, hematoma, edema, congenital band, bakers cyst, fracture, knee dislocation, ganglion cyst, or lipoma. Other etiologies include infectious, autoimmune, inflammatory, and systemic illnesses, which may involve either one (mononeuropathy) or multiple nerves (mononeuropathy multiplex), such as diabetes mellitus, Lyme disease, lupus, and scleroderma. Nevertheless, several cases are idiopathic in origin.

Prolonged external pressure, an example of which is the lower extremity

equivalent of “Saturday night palsy,” is uncommon, but can be seen after lying supine for an extended period of time with the lower legs over a footboard or end of the bed. Just as its counterpart in the upper extremity, this can be seen in patients with impaired consciousness from alcohol and drugs. The deficit is noted upon awakening, and may involve both the tibial and peroneal nerves, depending on the level of compression. Length of recovery varies from hours to weeks and months.

## **Diagnostic testing and treatment**

Diagnostic testing can be used to confirm clinical suspicion, evaluate co-existent or other causally related conditions, check for extent of neurogenic changes, and determine the underlying etiology. This may help manage the patient's symptomatology and prevent progression with appropriate treatment modalities.

Electrophysiologic testing can assist in the study of neurogenic disorders, sorting the clinically generated differential diagnosis, and differentiating from non-neurogenic disorders when necessary. Nerve conduction studies and needle EMG studies may be helpful in the diagnosis of both proximal tibial neuropathy and tarsal tunnel syndrome, and can help differentiate tibial neuropathy from peripheral neuropathy, lumbosacral radiculopathy and plexopathy, sciatic neuropathy, and co-existent peroneal neuropathy. Injury to the tibial nerve can be axonal and/or demyelinating, thus effectively slowing conduction of impulses and resulting in the clinical syndrome. It is important to localize lesions superior and inferior to the popliteal fossa, above and below the ankle, or in the tarsal tunnel. Nerve conduction studies, both motor and sensory, may reveal prolonged distal latencies, reduced amplitudes, and/or decreased conduction velocities. Late responses are useful in differentiating from other conditions, but do not have to be tested in a tarsal tunnel study in which the H reflex is normal, and F response may or may not be normal. Needle electromyography (EMG) testing of the long head of biceps femoris and gastrocnemius/soleus muscles helps localize the lesion above or below the popliteal fossa. Biceps femoris (long head) is the tibial innervated hamstring muscle that originates at the ischial tuberosity and inserts into the head of the fibula, causing thigh extension, and flexion and rotation of the leg medially. Tarsal tunnel syndrome is usually unilateral, although may be present bilaterally. Electrodiagnostic studies can be unreliable, but it is important to do bilateral testing for comparison, using the unaffected or less affected foot as control.

Radiologic studies including X-rays may be performed to evaluate stress and other fractures, dislocations, avascular necrosis, and bony changes from systemic disorders or compressive lesions. Computerized tomography (CT) and magnetic resonance imaging (MRI) studies can demonstrate space-occupying lesions, degenerative disease, and infectious/inflammatory sequelae. Ultrasound may be useful when neuromas are suspected. Laboratory testing including blood work is useful for evaluation of metabolic and systemic illnesses, infections, and inflammatory disorders.

Treatment consists of conservative management with anti-inflammatory medications (oral and topical), neurogenic pain medications, physical therapy, acupuncture, and advice on choice of shoes especially if there is an existing biomechanical condition. Local injections of corticosteroids and local anesthetics may provide temporary relief of symptoms by reducing edema and inflammatory changes. Surgical intervention to decompress the tibial nerve at the site of injury in both proximal neuropathy and tarsal tunnel syndrome may prove beneficial with good outcome.

Prevention of possible complications is important and can be obtained by routine follow-up visits and patient education. The consequences of loss of sensation to the sole of the foot include ulcerations and delayed recognition of small cuts and bruises. Low back, hip, and knee pain, as well as problems with balance and gait, may develop with secondary compensation.

## **Case vignette**

A 44-year-old nurse complained of occasional burning left heel pain, worse after a long work day in the pediatric intensive care unit (ICU). The neurologic exam was unremarkable except for Tinel's sign behind the left medial malleolus. X-rays of the foot were normal, and there was mild relief with topical anti-inflammatory medications. Over the following year the pain spread to involve the sole of the foot, shooting into the little toe. The symptoms were accompanied by intermittent paresthesias, and were now present at rest as well. On examination, there was mild loss of sensation over the sole of the left foot. Nerve conduction and EMG testing of both feet revealed increased distal latency of the left lateral plantar sensory nerve when compared with the right, consistent with mild left tarsal tunnel syndrome. An MRI scan of the left foot was significant for a lipoma compressing the nerve under the flexor retinaculum. Surgical decompression of the nerve with excision of the mass resulted in gradual

resolution of disabling symptoms, and consequent improvement in function.

**Table 97.1 Tibial neuropathy: location, clinical and specific features, and etiologies.**

Location	Clinical features	Specific features	Etiologies	Muscles supply)
Posterior thigh (above the knee)	Weakness of knee flexion (+ listed below)	Weakness of knee flexion Burning in sole of foot (++) Tinel's sign at site of compression	At all levels: Trauma Ischemia Space-occupying lesion: tumor, lipoma, edema, hematoma, fracture Infection (Lyme disease) Inflammation (rheumatoid arthritis) Autoimmune (lupus, scleroderma) Systemic illness (diabetes) Mononeuropathy (multiplex) Idiopathic	Tibial nerve biceps femoris (long head) Inner hamstrings (semimembranosus and semitendinosus) (+ listed below)
Knee (popliteal fossa)	(+ listed below)	Burning in sole of foot (++) Tinel's sign at site of injury	At this level: Knee dislocation Mass: Baker cyst	Tibial nerve popliteus below)

Lower leg/calf (between the knee and ankle)	Weakness foot plantar flexion and inversion Sensory loss lateral foot, distal third posterolateral leg (+ listed below)	Burning in sole of foot (++) Tinel's sign at site of compression	At this level: Saturday night palsy (drugs/alcohol)	Tibial nerve gastrocnemius soleus, tibial posterior hallucis longus (+ listed)
Ankle/tarsal tunnel syndrome (behind medial malleolus)	Weakness toe flexion Sensory loss sole of foot Difficulty walking Burning in sole of foot Tinel's sign behind medial malleolus	Burning in sole of foot (++++) Tinel's sign present over tarsal tunnel	At this level: Mass: Entrapment Arthritis Tendinitis	Medial plantar nerve: abductor hallucis, digitorum profundum, lumbricals Lateral plantar nerve: abductor digiti minimi, flexor digitorum minimi, flexor hallucis, interosseous, interosseous
Distal to ankle (sole of foot)	Nerve(s) injured: plantar and calcaneal nerve	Depends on branches affected		

## Further reading list

Chen WS. Lipoma responsible for tarsal tunnel syndrome. Apropos of 2 cases.  
*Rev Chir Orthop Reparatrice Appar Mot* 1992; 78:251–4.

Cione JA, Cozzarelli J, Mullin CJ *et al.* Tarsal tunnel surgery secondary to a tarsal ganglion: be prepared before performing this complicated operation. *Foot Ankle Spec* 2009; 2:35–40.

Dellon AL. The four medial ankle tunnels: a critical review of perceptions of tarsal tunnel syndrome and neuropathy. *Neurosurg Clin N Am* 2008; 19:629–48.

Franson J, Baravarian B. Tarsal tunnel syndrome: a compression neuropathy involving four distinct tunnels. *Clinical Podiatric Med Surg* 2006; 23:597–609.

Gould JS, Myerson MS. *Nerve Problems of the Lower Extremity. Foot and Ankle Clinics*. Philadelphia, PA: Saunders Elsevier, 2011: 234–93.

Spinner RJ, Amrami KK, Wolanskyj AP *et al.* Dynamic phases of peroneal and tibial intraneuronal ganglia formation: a new dimension added to the unifying articular theory. *J Neurosurg* 2007; 107:296–307.

Spinner RJ, Winfree CJ, Parsa AT, McCormick PC. Peripheral Nerves: Tumors and Entrapments. *Neurosurgery Clinics of North America*. Philadelphia, PA: Saunders Elsevier, 2008: 604–5, 629–48.

Stall A, Van Gijn J, Spaans F. *Mononeuropathies: Examination, Diagnosis and Treatment*. Philadelphia, PA: W.B. Saunders, 1999: 126–32, 143–5.

Tacconi P, Manca D, Tamburini G *et al.* Bed footboard peroneal and tibial neuropathy. A further unusual type of Saturday night palsy. *J Peripheral Nerv Syst* 2004; 9:54–6.

Waldman SD. *Atlas of Uncommon Pain Syndromes*, 2nd edn. Philadelphia, PA: Saunders Elsevier, 2008: 293–320.

## 98 Neuropathy, ulnar

---

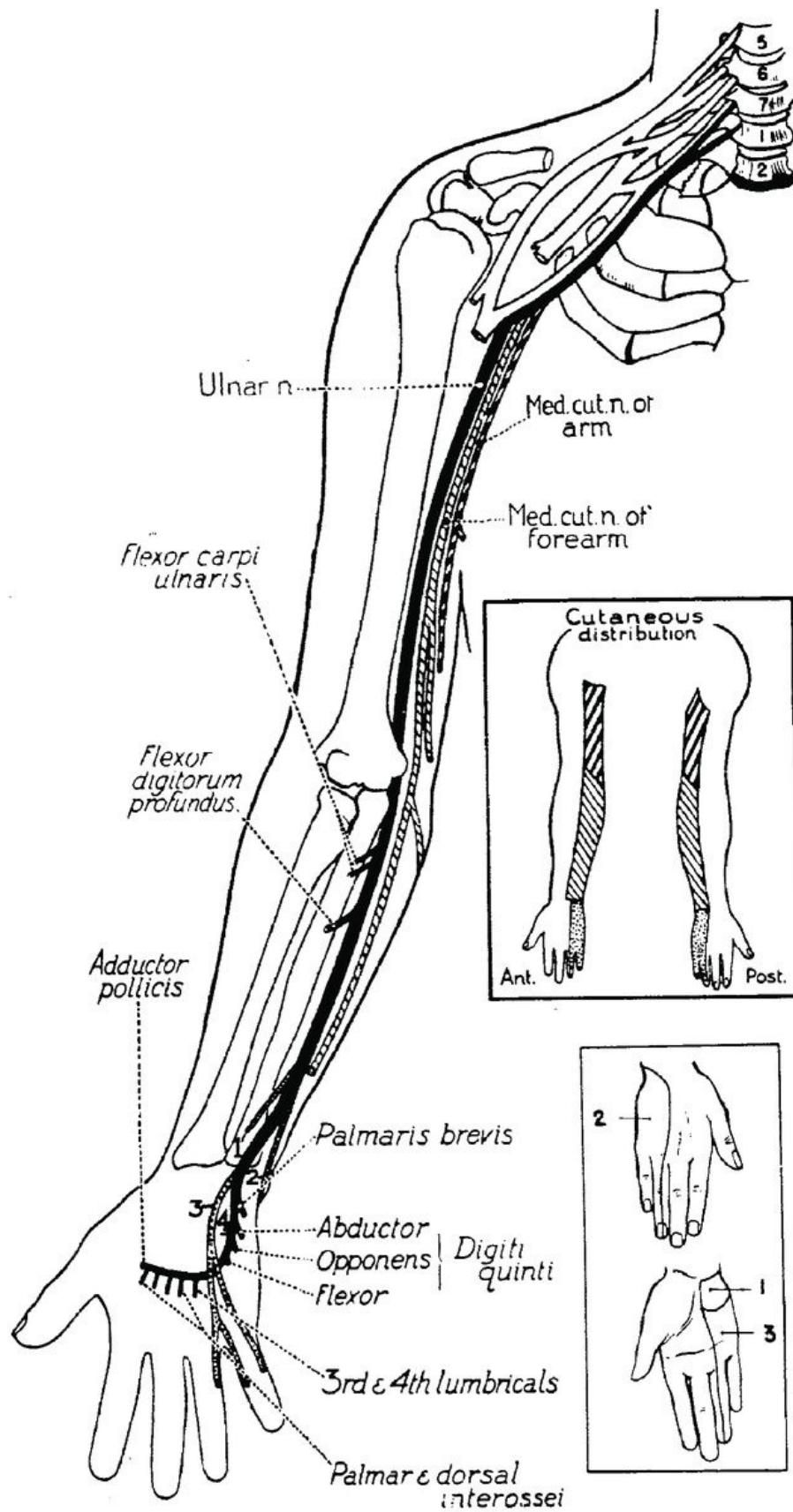
Steven Ender *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

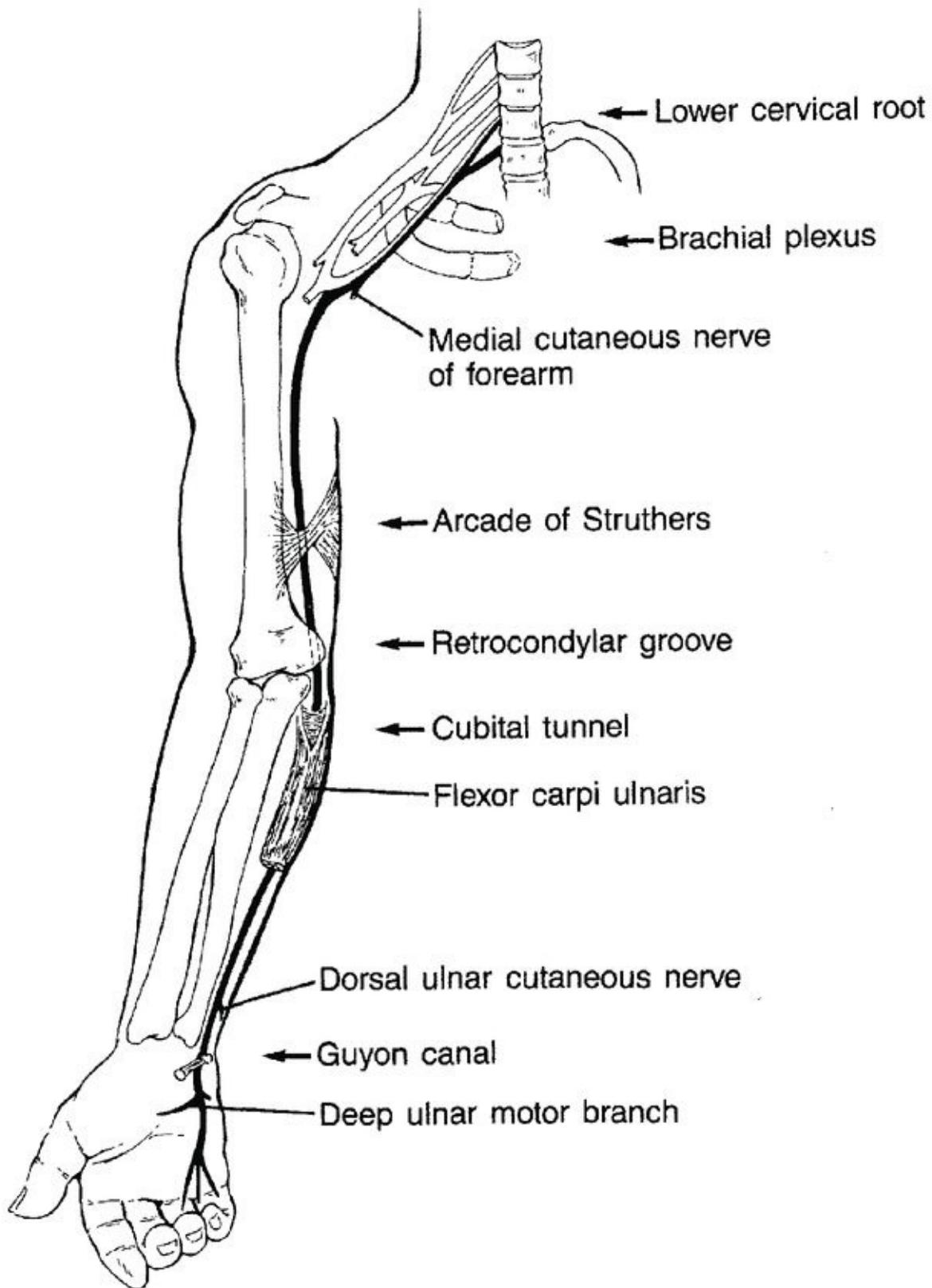
This chapter on the ulnar nerve is divided into separate sections that discuss the arm segment, the elbow/forearm segment, and the wrist/palm segment. In each section the anatomy is reviewed, followed by the different types of lesions of the nerve. This is followed by a discussion of the differential diagnosis/clinical pearls and finally some treatment options.

### Arm segment

The ulnar nerve originates from the cervical nerve roots C8 and T1, and sometimes C7. Within the brachial plexus the fibers pass through the lower trunk, and then travel through the medial cord to form the ulnar nerve. Within the medial cord, the medial cutaneous nerve to the arm and the medial cutaneous nerve to the forearm branch off to innervate their respective cutaneous regions in the arm and forearm (see [Figure 98.1](#)). The nerve then travels down the arm, posteriorly and medially along the medial head of triceps muscle. Distally in the arm, the ulnar nerve travels underneath the arcade of Struthers in about 70% of the population (see [Figure 98.2](#)). The arcade of Struthers is a deep fascia band that lies about 8 cm proximal to the medial epicondyle. It extends from the medial head of the triceps to the medial intermuscular septum, which connects the posterior and anterior compartments. This is a potential yet uncommon entrapment site and should be considered in a case of a failed ulnar nerve transposition, since the nerve can be under tension here as well.



**Figure 98.1** The origin and distribution of the ulnar nerve, the medial cutaneous nerve of the forearm, and medial cutaneous nerve of the arm. The numbered nerves are as follows: (1) palmar branch, (2) dorsal branch, (3) superficial terminal branch, (4) deep terminal branch. The fields of innervation of 1, 2, and 3 are detailed in the inset. (From Haymaker W, Woodhall B. *Peripheral Nerve Injuries*. Philadelphia, PA: WB Saunders, 1953, with permission.)



**Figure 98.2** The arcade of Struthers is a fascial band that can be a source of secondary ulnar entrapment in the transposed ulnar nerve. (Reprinted from

*Occupational Medicine: State of the Art Reviews* 1992;7:765–83, with permission, Hanley and Belfus Inc.) Entrapment of the ulnar nerve within the arm segment is rare. It may occur from compression due to pressure from a tourniquet, the head of a sleeping partner, improper arm positioning during a coma, improper use of crutches, an aneurysm of the brachial artery as it runs medial to the vessel, or a supracondylar fracture of the humerus. The radial and median nerves run closely to the ulnar nerve in the arm, therefore a triad or involvement of multiple nerves may occur.

The pattern of sensory loss from a lesion in the arm segment usually involves the medial palm, dorsum of the palm, digit 5, and the median half of digit 4. The first motor branch from the ulnar nerve is to the flexor carpi ulnaris muscle (FCU) and usually is distal to the elbow region. Therefore a lesion in the arm segment leads to weakness of all the ulnar innervated muscles. (See [Table 98.1](#) below for the ulnar innervated muscles.) This includes the FCU, flexor digitorum profundus  $\frac{3}{4}$  (FDP  $\frac{3}{4}$ ), all the hypothenar muscles (abductor digiti minimi [ADM], opponens digiti minimi [ODM], flexor digiti minimi [FDM]), both of the interossei (dorsal and palmar), lumbricals III and IV, a portion of the flexor pollicis brevis (FPB), and adductor pollicis (AP). Typically the distally innervated intrinsic hand muscles are involved earliest with the FDI being the most common muscle involved. However depending on the involvement of different nerve fascicles from patient to patient, the pattern of weakness varies from case to case. Weakness of the III and IV lumbricals leads to a classic “claw hand” or ulnar claw hand deformity due to hyperextension of MCP joints and flexion of the IP joints of digits 4 and 5 ([Figure 98.3](#)).

**Table 98.1 Ulnar innervated muscles.**

<b>Ulnar innervated muscles</b>	<b>Action</b>	<b>Clinical significance</b>
Flexor carpi ulnaris (FCU)	Flexes and adducts the wrist	Weakness leads to decreased strength of wrist flexion and may cause radial deviation of the hand
Flexor digitorum	Flexion of the distal interphalangeal	Decreased ability to flex the distal joints of digits 4 and 5

<b>Flexor pollicis profundus III/IV (FDP 3/4)</b>	<b>Interphalangeal joints of digits 4 and 5</b>	<b>Weakness of these muscles may reduce the appearance of a claw-hand deformity</b>
<b>Abductor digiti minimi (ADM)</b>	<b>Abduction of digit 5</b>	<b>Decreased ability to abduct digit 5</b>
<b>Opponens digiti minimi (ODM)</b>	<b>Opposes (flexes with slight rotation) the carpometacarpal joint of digit 5 to the first digit</b>	<b>Weakness results in flattening of the palm and difficulty opposing digit 5 to the first digit</b>
<b>Flexor digiti minimi (FDM)</b>	<b>Flexes the metacarpophalangeal joint of digit 5 and opposition towards the first digit</b>	<b>Weakness leads to inability to flex digit 5 and oppose it towards the first digit</b>
<b>Lumbrical III/IV</b>	<b>Extension of the interphalangeal joints and simultaneously flexes the metacarpophalangeal joints of digits 4 and 5</b>	<b>Weakness results in a claw-hand deformity</b>
<b>Dorsal interossei</b>	<b>Abducts digits 2, 3, and 4</b>	<b>Weakness leads to decreased ability to abduct digits 2, 3, and 4</b>
<b>Palmar interossei</b>	<b>Adducts digits 1, 2, 4, and 5</b>	<b>Weakness leads to decreased ability to adduct digit 1, 2, 4, and 5</b>
<b>Flexor pollicis longus</b>	<b>Flexion of the interphalangeal joint of the thumb</b>	<b>Weakness leads to difficulty</b>

pollicus brevis (FPB)	metacarpophalangeal and the carpometacarpal joints of the thumb	gripping objects firmly between the thumb and fingers. Marked weakness may result in hyperextension deformity of the metacarpophalangeal joint
Adductor pollicis (AP)	Adduction of the carpometacarpal joint of the thumb towards the palm	Weakness results in inability to clench the thumb firmly over a closed fist

---

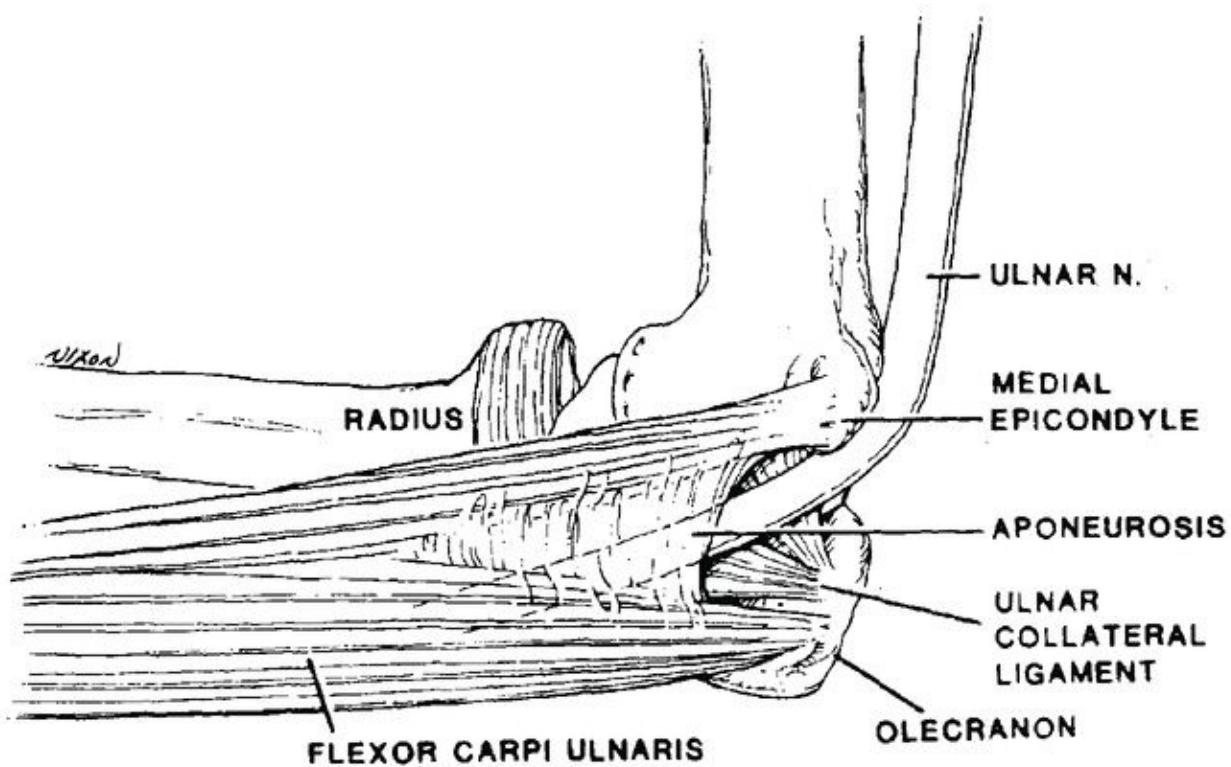


**Figure 98.3** Ulnar claw hand.

## Elbow segment

The most common site where the ulnar nerve can become compressed is in the elbow region and this is the second most common entrapment in the upper extremity, after compressions of the median nerve at the wrist. As the ulnar nerve passes into the elbow region it travels into the condylar (ulnar) groove, behind the medial epicondyle of the humerus ([Figure 98.4](#)). The groove can vary in its size and if very shallow it can cause the nerve to sublux or slip out with elbow flexion and therefore be more susceptible to potential trauma or compression. The nerve then passes under the humeroulnar arcade, named by Sutherland, which is an aponeurotic band of the FCU muscle that stretches from the medial epicondyle to the olecranon ([Figure 98.4](#)). The thickness as well as the location of this aponeurotic band varies from patient to patient. It is thought

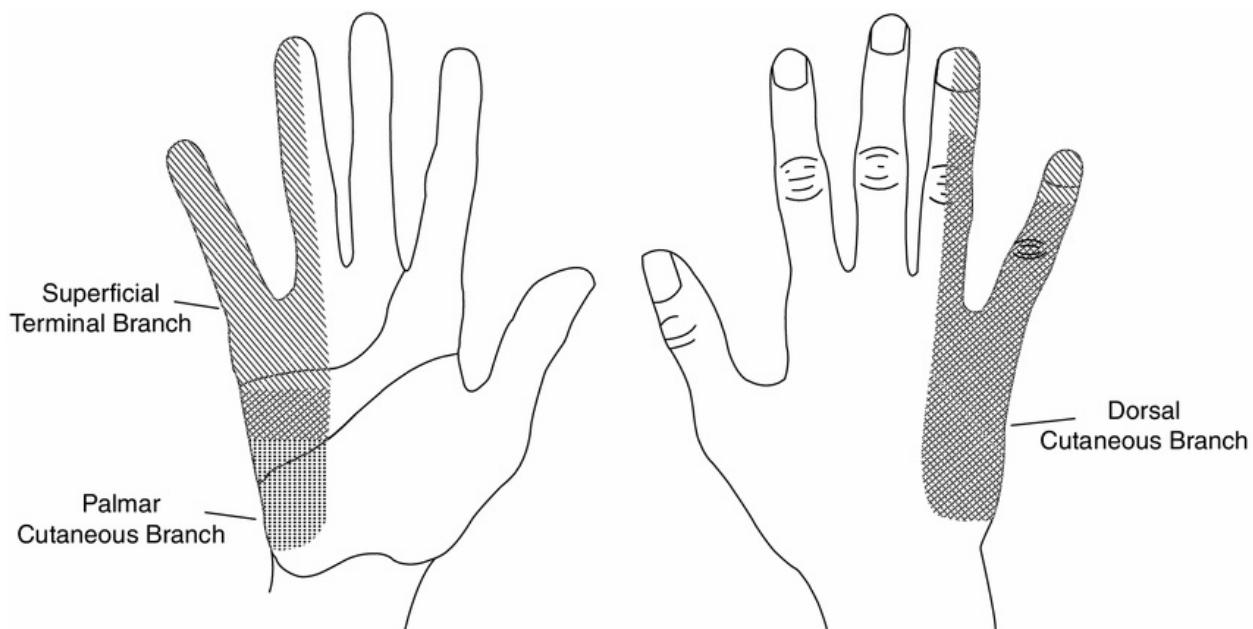
that a thicker and more rigid band leads to a narrowed and unyielding structure that can predispose a person to a nerve entrapment. Once the nerve transverses the muscle fibers of the FCU, it enters the cubital tunnel. The floor of the tunnel is formed by the medial ligament of the elbow and muscle fibers of the FCU. The roof is formed by the humeroulnar arcade and other muscle fibers of the FCU. The dimensions of the cubital tunnel change very significantly between extension and flexion of the elbow joint, as the epicondyle and the olecranon move away from each other. This can lead to about a 50% reduction in the cubital tunnel and therefore compression of the nerve. In addition the medial elbow ligament bulges into the tunnel with elbow flexion and further narrows the dimensions.



**Figure 98.4** View of the medial surface of the elbow, showing the course of the ulnar nerve through the ulnar groove and cubital tunnel. (From Kincaid JC. The electrodiagnosis of ulnar neuropathy at the elbow. *Muscle Nerve* 1988;11:1005–15, 1988, with permission.) After entering the cubital tunnel the ulnar nerve travels between the two heads of the FCU muscle and then through an aponeurosis lining the deep surface of the FCU and separating it from the FDP and FDS muscles. Due to this protected location, entrapment and exposure to trauma are uncommon.

The first sensory branch of the ulnar nerve, the palmar cutaneous branch,

comes off in the mid forearm and travels ventrally to the palm without passing through Guyon's canal, to innervate the proximal portion of the palm ([Figure 98.5](#)). The second sensory branch, the dorsal cutaneous nerve, usually comes off about 5 cm proximal to the wrist and travels into the distal aspect of the hand to innervate the dorsal medial aspect of the hand, digit 5, and one half of digit 4. With nerve conduction studies, the presence or absence of these nerves helps to further localize a lesion proximal or distal to the wrist/hand. For example a preserved palmar cutaneous nerve or dorsal cutaneous nerve suggests an ulnar lesion that is distal to the wrist.



**Figure 98.5** The cutaneous distribution of the three sensory branches of the ulnar nerve. (From Stewart JD. The variable clinical manifestations of ulnar neuropathies at the elbow. *Neurol Neurosurg Psychiatry* 1987;50:252–8, ©BMJ Publishing Group.) There are two motor branches off from the elbow segment of the ulnar nerve. The first one, to the FCU muscle, usually occurs about 10 cm distal to the medial epicondyle and less often before the nerve enters the elbow region. The second motor branch is to the FDP muscle that flexes the interphalangeal joint of the 4th and 5th digits. Due to the fascicular arrangement of these axons in the nerve they are usually spared early with a compressive lesion, but later on involvement can lead to atrophy of these forearm muscles.

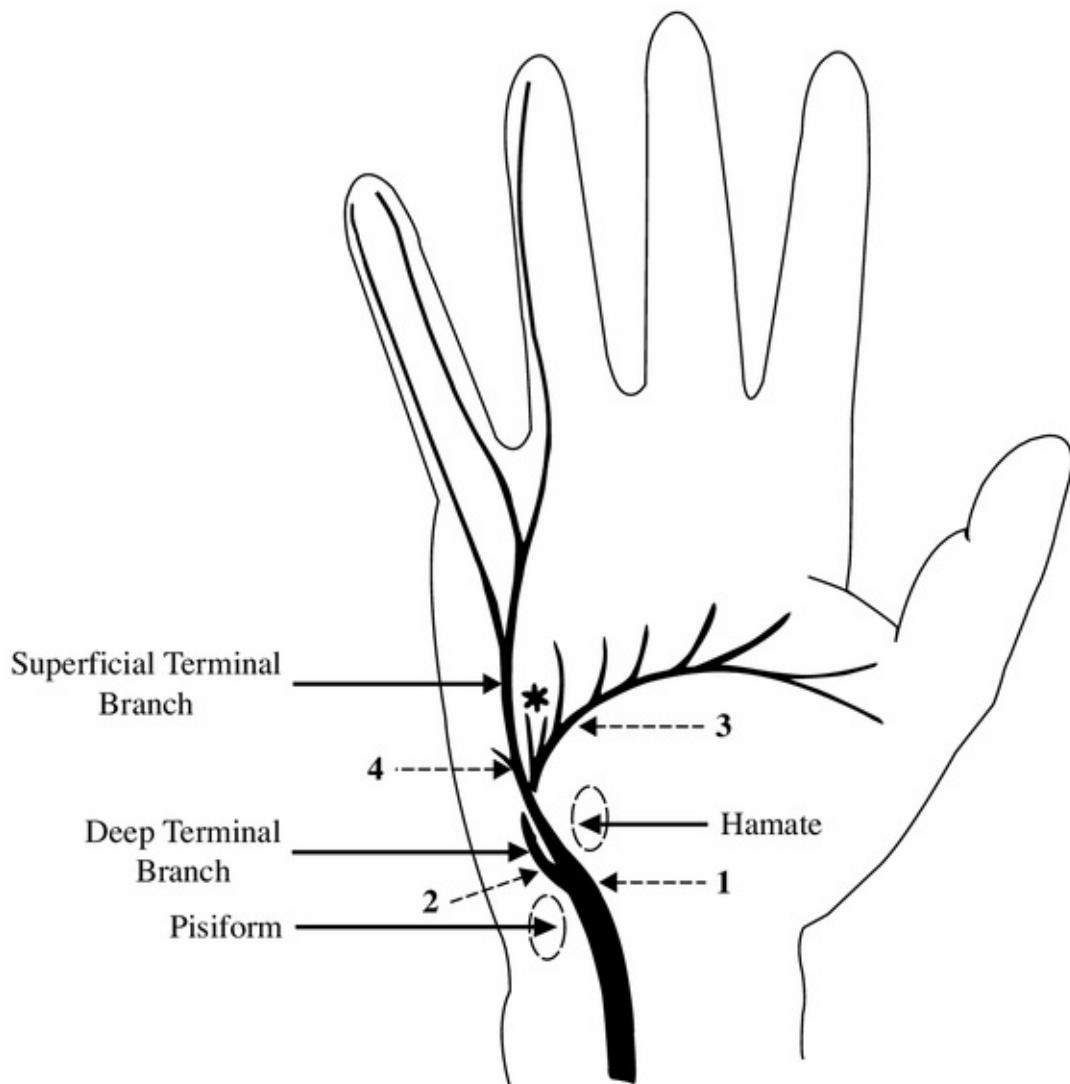
Helpful clues to localizing an entrapment around the elbow segment include sensory complaints involving the medial aspect of the palm and digits 4 and 5, but may be limited to just the fingertips. Again this can be explained by the fascicular arrangement of the sensory axons and certain fibers are more

susceptible to damage, with the terminal digital branches most commonly involved. Initially there may be weakness of the FDI muscle, but typically in chronic cases there is weakness and atrophy of all the ulnar innervated intrinsic hand muscles. Pain, tenderness, and a strongly positive Tinel's sign at the elbow are other helpful clinical clues to an entrapment at this site.

The elbow segment has the potential to have multiple entrapment sites. Occupations that involve repetitive or prolonged flexion of the elbow are a common cause. Flexion of the elbow joint while sleeping, habitual elbow leaning, driving for a long distance while leaning the elbow on an arm rest, rheumatoid arthritis, and chronic subluxation are all potential causes. During surgery, postoperatively or while in a coma, the arm may remain in the flexed position for a prolonged time and the nerve can be compressed by external pressure. A delayed entrapment from an old fracture of the supracondylar of the humerus (tardy ulnar palsy), or the medial or lateral epicondyle are other known etiologies. This is felt to be caused by an abnormal carry angle of the elbow or the nerve being stretched over a bony callus. Unfortunately idiopathic cases are fairly common and therefore remain a problem for proper management.

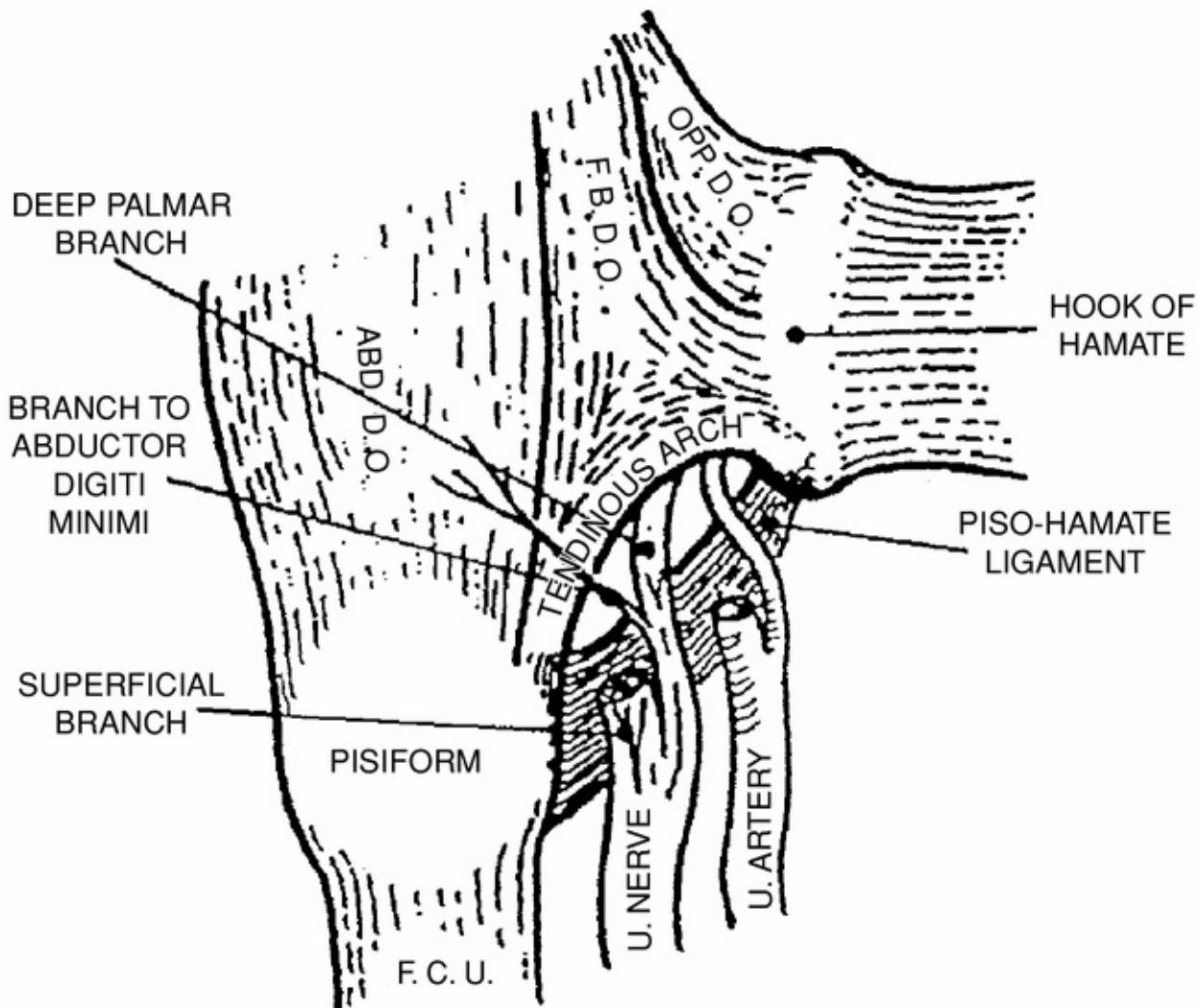
## **Wrist segment**

At the wrist the ulnar nerve enters the Guyon's canal with the ulnar artery. Guyon's canal is formed by the pisiform bone medially, the hook of the hamate bone laterally, the transverse carpal ligament and the pisohamate ligament form the floor, and the roof is formed by the volar carpal ligament and the palmaris brevis muscle. As the nerve leaves the canal it gives off the superficial terminal branch (primarily sensory branch, except for a small motor branch to the palmaris brevis) and a deep terminal branch (pure motor nerve) ([Figure 98.6](#)). The superficial terminal branch innervates the distal-medial palm, the ventral aspect of digit 5, and the ventromedial half of digit 4. The deep terminal branch innervates all the hypothenar muscles and then turns laterally to innervate all the interossei (dorsal and palmar), the lumbricals III and IV, the AP muscle, and part of the FPB muscle (with the median nerve).



**Figure 98.6** Palmar aspect of the right hand, showing the course and branching of the distal ulnar nerve. The asterisk denotes the branches to the hypotenar muscles (abductor opposens and flexor digiti minimi muscles). The numbers refer to the four main sites of ulnar nerve lesions in the wrist and hand.

In the distal portion of Guyon's canal the pisohamate hiatus (PHH) is formed, superficially by the tendonous arch of the FDM and posteriorly by the pisohamate ligament ([Figure 98.7](#)). After the deep terminal branch gives off the nerve to the ADM it passes through the arch before making the turn laterally and is a potential entrapment site.



**Figure 98.7** The pisohamate hiatus (PHH) in the distal portion of Guyon's canal. U., Ulnar; F.C.U., flexor carpi ulnaris; ABD.D.Q., abductor digiti quinti (or minimi); F.B.D.Q., flexor brevis digiti quinti (or minimi); OPP.D.Q., opponens digiti quinti. (Modified from Uriburu IJF, Morchio FJ, Marin JC. Compression syndrome of the deep motor branch of the ulnar nerve [pisohamate hiatus syndrome]. *Bone Joint Surg* 1976;58A:145–7, with permission.)

Entrapments at the wrists are less common than they are at the elbow. There are four patterns of an ulnar nerve entrapment at the wrist/hand segment (the most common are sites 2 and 3 mentioned below). Etiologies include work-related repetitive trauma/external pressure at the wrist or in the palm from tools, the handle of a cane, bicycling, lipoma, cyst, giant cell tumor, fracture of the hook of the hamate bone/other carpal bones, a hand laceration (since the nerve is superficial near Guyon's canal), or idiopathic. The most common cause is a ganglion which is reported in 28–45% of series. These lesions spare the sensory nerves to the dorsal and palmar surface of the hand as these nerves come off the

proximal to the wrist. The second most common cause is compression at the PHH from work-related repetitive trauma or activities such as bicycling.

Patterns of potential entrapment sites of the ulnar nerve in the wrist:

1. The ulnar nerve may be compressed or entrapped at or just before Guyon's canal. A lesion at this site would lead to weakness of all the ulnar intrinsic hand muscles and sensory loss in the distribution of the superficial terminal branch.
2. A lesion of the deep terminal branch, proximal to the branches to the hypothenar muscles. This would lead to weakness of all the ulnar innervated intrinsic hand muscles, sparing the sensory branches to the hand.
3. A lesion of the deep terminal branch, distal to the branches to the hypothenar muscles. A lesion at this point would lead to weakness of the ulnar innervated intrinsic hand muscles, sparing the hypothenar muscles, and no sensory loss.
4. The least common lesion involves just the superficial terminal branch leading to only distal sensory loss, involving the medial palm and digits 4 and 5.

## Clinical pearls

The diagnosis and proper management of an ulnar nerve lesion is derived from performing a thorough neuromuscular history and examination, followed by an electromyography/nerve conduction study to confirm the diagnosis and rule out other possible etiologies. The differential diagnoses of an ulnar nerve lesion include a C8/T1 radiculopathy, cervical myelopathy, brachial plexopathy/thoracic outlet syndrome, syringomyelia, and motor neuron disease.

With a lesion of the cervical roots or brachial plexus, there usually is a history of pain and possible trauma to the cervical, scapular, or shoulder region.

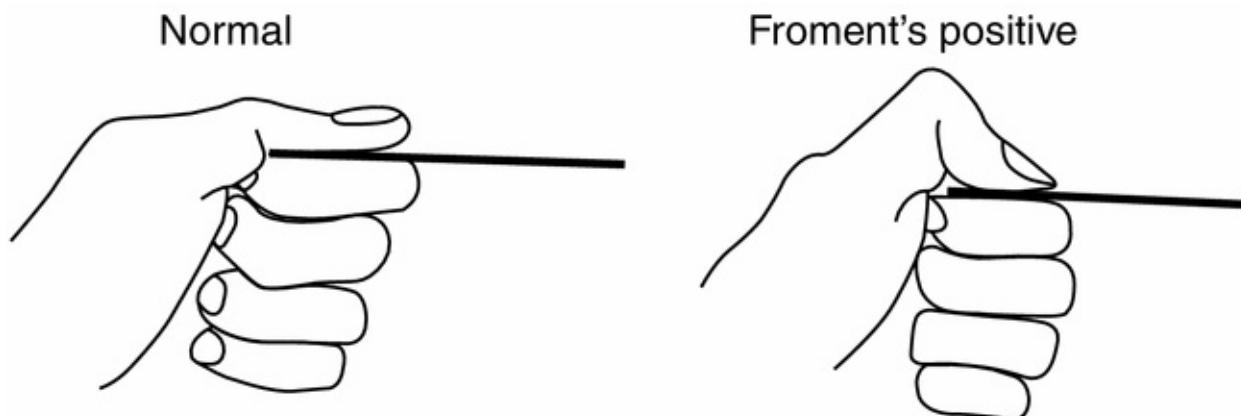
Radiating pain down the medial aspect of the arm and forearm into the hand is a symptom that helps to localize the lesion proximally in the arm. Since there are no ulnar nerve sensory branches in the arm, sensory complaints and objective sensory loss proximal to the wrist are useful signs that help to localize a diagnosis at the root or less often involving the lower trunk or medial cord. A Horner's sign (ptosis, miosis, and anhidrosis) is another localizing sign to the lower plexus.

The median cutaneous nerve of the arm and forearm branches off from the medial cord of the brachial plexus to innervate its respective cutaneous region. It is not until the mid forearm that the first sensory branch, the palmar cutaneous branch, branches off to innervate the medial palm and digits 4 and 5. Therefore a lesion of the ulnar nerve at the elbow or arm segment will have sensory loss

involving the medial aspect of the hand extending into digits 4 and 5 and sparing the medial forearm and arm. Actual splitting of digit 4 is highly indicative of an ulnar nerve lesion and less so a C8/T1 lesion.

In a patient that presents with wasting of the intrinsic hand muscles, the differential diagnosis includes an ulnar nerve lesion, a cervical myelopathy, syringomyelia, or motor neuron disease (MND). With MND sensory loss is a rare finding. Also with MND there is more diffuse motor involvement of the arms and legs, with fasciculations of the extremities and bulbar muscles, as well as upper motor neuron signs. With cervical syringomyelia the sensory findings usually involve the smaller fiber pain and temperature tracts, in a capelike distribution (suspended), as they cross to the contralateral spinothalamic tract and spare the large fiber vibration and position sense tracts (dissociated sensory loss). There may be segment weakness, atrophy, and fasciculations out of the distribution of the ulnar nerve. If there is involvement of the corticospinal tracts there may be spasticity, incontinence, and hyperreflexia. Like syringomyelia, a cervical myelopathy has extensive motor, sensory, and reflex changes out of the ulnar nerve distribution. Neuroimaging of the cervical spine is essential for the work-up to determine any structural lesion of the cervical spinal cord.

When examining patients with an ulnar nerve lesion they may perform a trick maneuver to compensate for weakness of the hand. The Froment's sign is helpful to detect weakness of adductor pollicus brevis muscle and a normal flexor pollicis longus muscle (median innervated muscle), both of which are innervated by the C8/T1 roots. The patient is asked to grasp a piece of paper between the thumb and the second finger while the examiner attempts to pull out the paper. Due to adductor pollicus brevis weakness, the patient flexes the thumb to compensate in trying to keep the paper from sliding out (see [Figure 98.8](#)).



**Figure 98.8** Froment's sign. Reproduced with permission from [mims.com](#).

## **Electrophysiology**

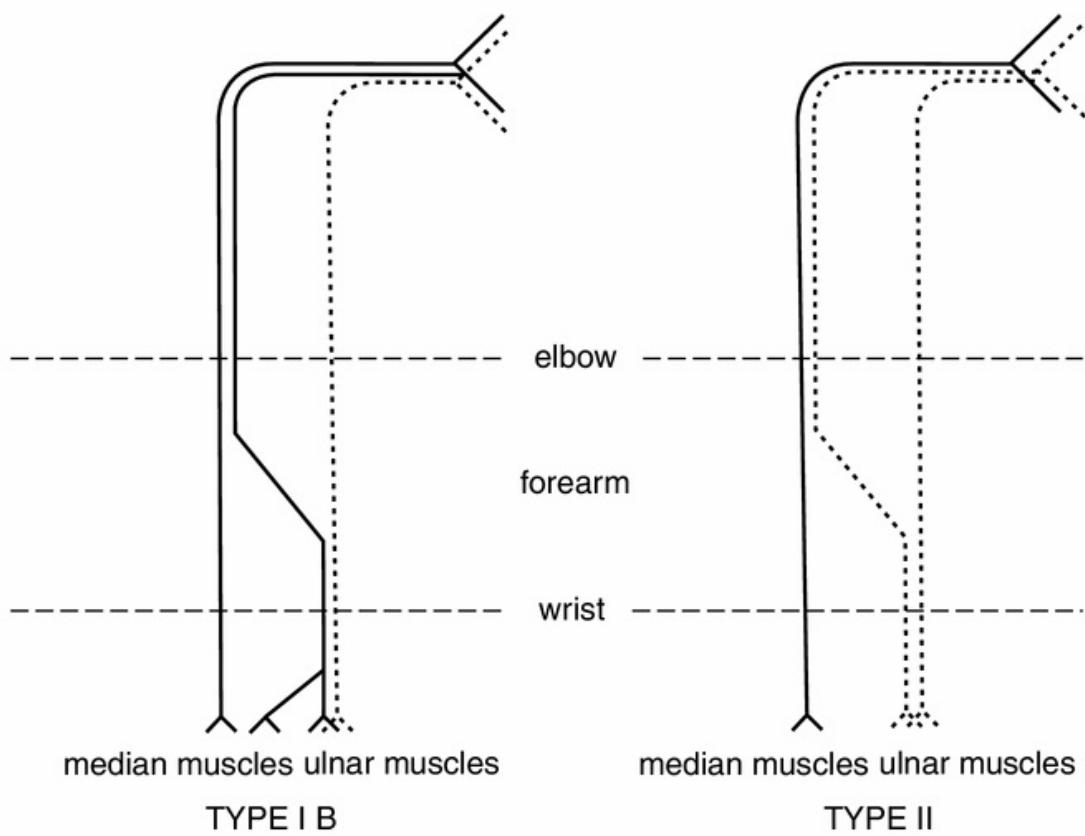
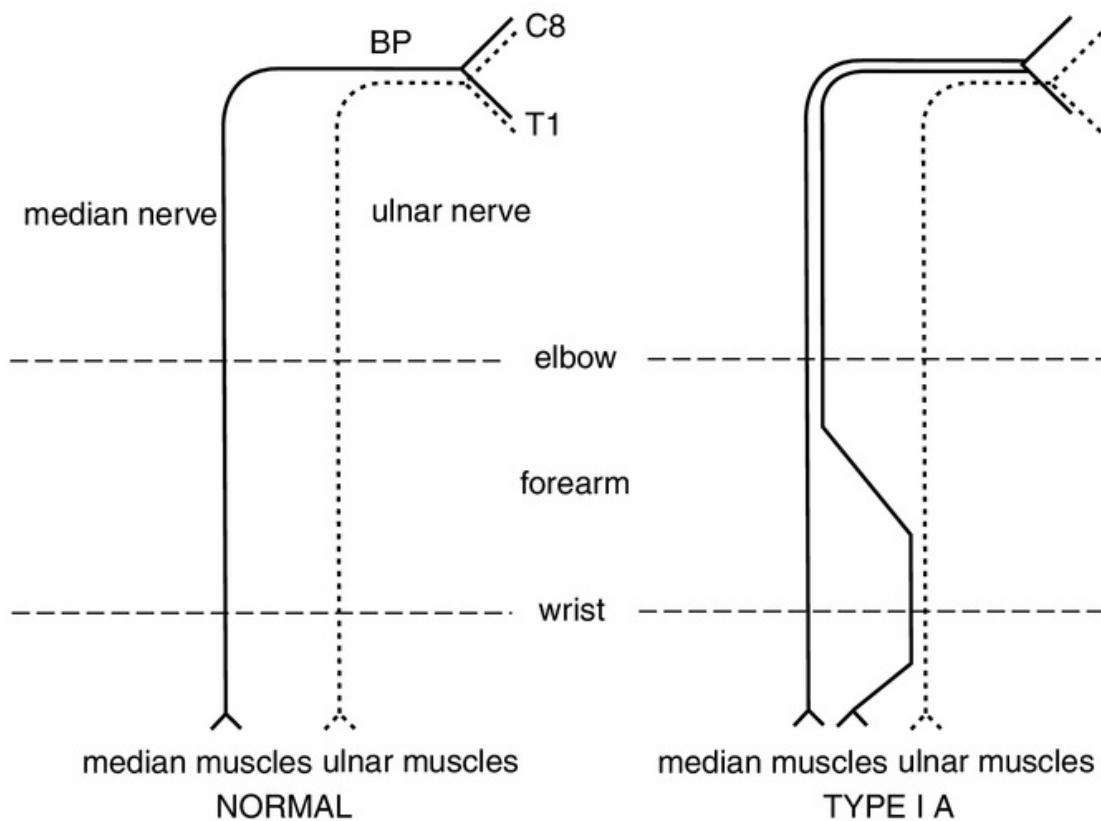
Electrophysiologic testing is an important component in the work-up for weakness suspected to involve the peripheral nervous system. Nerve conduction studies (NCS) in a patient with a cervical radiculopathy should reveal preserved sensory nerve potential as the lesion is proximal to the dorsal root (sensory) ganglion. As compared with a brachial plexus or peripheral nerve lesion, the sensory potentials should be low amplitude or absent depending on the severity of the lesion as the lesion is distal to the dorsal root ganglion.

Motor NCS are usually the most helpful to localize ulnar nerve lesions at the elbow or wrist. Slowing of the ulnar nerve around the elbow segment compared with the forearm segment (greater than 10 m/s difference) or reduced motor nerve amplitude by 20–30% are usually reliable findings to localize an entrapment at the elbow. Sometimes inching techniques are useful to further localize the lesion to the ulnar groove or cubital tunnel. There is increased sensitivity when recording motor conductions from both the ADM and FDI muscles. One reason is that there may be predominate involvement of the FDI due to fascicular arrangement in the nerve. Secondly, a lesion of the deep motor branch can be assessed as the distal latency to the FDI muscle will be prolonged compared with the distal latency recording from the ADM (greater than 1.5 ms).

Further localization of a cervical radiculopathy with needle EMG may reveal active denervation of the cervical paraspinal muscles in a more acute case and less often in a chronic condition. It is necessary to sample muscles that are innervated not only by the ulnar nerve, but by other C8/T1 nerves. For example, the ABP and FPL can be sampled for the median nerve and EIP and ECU for the radial nerve in order to determine whether the lesion involves the cervical root, plexus, or peripheral nerve. In the majority of the population the first motor branch of the ulnar nerve is distal to the elbow and innervates the FCU muscle. Therefore if there is sparing of the FCU muscle, the lesion is less likely to be at the level of the nerve root, brachial plexus, or arm, although this does not entirely rule out an ulnar nerve lesion at the elbow. The second motor branch of the ulnar nerve is to the FDP 3/4 muscle, and needle EMG denervation detecting involvement of this muscle and not the FCU supports a lesion within the cubital tunnel.

It is important to be aware of some of the anomalies in the innervation of the upper extremity because this can lead to confusion with the neurologic exam as well as the EMG/NCS. The most common anomaly is a branch from the median

to the ulnar nerve in the forearm, called the Martin–Gruber anastomosis. This occurs in about 10–40% of the population, and involves mainly motor fibers traveling to the ulnar innervated intrinsic hand muscles. There are several patterns of anastomosis and [Figure 98.9](#) demonstrates three of the most common patterns. Type 1A is where the median nerve fibers cross over to the ulnar nerve and innervate muscle usually supplied by the median nerve. Type 1B is where the fibers travel to the hand and supply both the ulnar and median innervated muscles. Type II is where some of the ulnar nerve fibers enter the median nerve from the brachial plexus and then cross over in the forearm to innervate muscles normally supplied by the ulnar nerve. Other less common anomalies include anastomosis from the ulnar nerve to the median nerve, or an all ulnar or median innervated intrinsic hand. These are rare but can lead to patterns of weakness and EMG/NCS changes that require very detailed electrophysiologic testing analysis.



**Figure 98.9** Median and ulnar nerves showing the common neural anastomoses between these nerves in the forearm. C8, T1, eighth cervical and first thoracic spinal nerve ventral rami respectively; BP, brachial plexus. Median and ulnar muscles, those intrinsic hand muscles normally supplied by these nerves. See text for details.

## Treatment

The treatment of an ulnar nerve entrapment at the elbow depends on the etiology and degree of injury. Conservative treatments for mild to moderate entraptments include the use of a soft cushioning device at the elbow (e.g. Heelbo), non-steroidal anti-inflammatory drugs (NSAIDS), and education about the problem and how to avoid positions that lead to further injury. Correction of occupational or recreational hazards may be helpful to prevent further injury and restore nerve function. Adding physical therapy for strengthening and pain management can be beneficial. Conservative treatments are usually continued for about 6–12 weeks for mild to moderate lesions. Educating the patient about the etiology of the process cannot be over stressed as the majority of cases are related to activities during day, at work, and/or common sleeping positions. Most mild to moderate compressive nerve lesions usually show improvement within 2–3 months after removal of the causative factors.

Severe lesions at the elbow or at the wrist may require more aggressive treatment with surgical intervention. For a severe lesion, precise localization with EMG/NCS and sometimes the addition of an MRI of the region are necessary to maximize a good surgical outcome. Surgical treatment of an entrapment at the elbow falls into two categories: decompression *in situ* and decompression with anterior transposition. For lesions at the wrist, surgery is usually required for ganglia, fractures, or a mass lesion. Deep surgical exploration into the pisohamate hiatus should be considered in cases where there is progression of weakness and confirmation from electrophysiologic testing of a lesion at the wrist.

## Case vignette

The patient is a 35-year-old right-handed male with complaints of tingling and numbness of the left hand. This is worse in digits 4 and 5 and is associated with a dull pain in the left forearm. His symptoms started a few months ago and have

gradually progressed to where his hand feels weak and unable to grasp objects. He has intermittent neck pain but no radicular pain. There were no recent injuries, fevers, chills, weight loss, or night sweats. Past medical and surgical history is unremarkable. He drinks alcohol socially and denies any use of tobacco or drugs.

Physical examination revealed a well-nourished and well-developed male. Mental status and cranial nerve examination were normal. There was no ptosis or miosis. The motor examination was remarkable for weakness of the left FDI, ADM, and distal phalangeal flexors of digits 3 and 4 that was 4/5. The remainder of the strength was 5/5. There was no atrophy or fasciculation. Deep tendon reflexes were 2+ in the upper and lower extremities. Plantar response was flexor bilaterally. Sensory examination revealed intact pinprick and cold sensation. There was moderately reduced vibration sensation in digit 5 of the left hand. The coordination and gait examination were both normal. The musculoskeletal examination showed full range of motion of the cervical spine. There was no cervical muscle spasm or tenderness. There was a positive Tinel's sign at both cubital tunnels.

An EMG/NCS demonstrated a low amplitude ulnar nerve sensory potential of the left side where on the right it was normal. Both medial and radial sensory nerve potentials were normal. The ulnar nerve motor nerve conduction studies revealed a conduction block of the ulnar nerve stimulating above the elbow segment and recording from both the ADM and FDI muscles. The amplitude was reduced by 80% compared with distal stimulation below the elbow and at the wrist. The median and radial motor nerve potentials were normal bilaterally. Needle EMG sampling of the left arm revealed reduced recruitment of all the ulnar innervated intrinsic hand muscles, but no evidence of active or chronic denervation. The FCU and FPD muscles were normal. There was no denervation of the cervical paraspinal muscles or radial or median innervated muscles.

The electrophysiologic study was consistent with a focal demyelinating lesion of the left ulnar nerve at the elbow. Further review of the patient's history found out that he had started a new job about 4 months earlier where he would make phone calls about 8 hours per day leaning on his left elbow and dialing the phone with his right hand. The patient was initially treated with a soft elbow pad and physical therapy, and advised to avoid prolonged leaning and flexion of the left elbow joint. A follow-up NCS was performed 2 months later that demonstrated an improvement and the conduction block improved to approximately 20% reduction. The sensory nerve amplitude remained mildly low and there were no signs of denervation potentials on needle EMG testing of the ulnar innervated

muscles.

## Further reading list

Katirji B. *Electromyography in Clinical Practice. A Case Study Approach*. St Louis, MI: Mosby, 1998.

Kendall FP, McCreary EK, Provance PG. *Muscles: Testing and Function*, 4th edn. Baltimore, MD: Williams and Wilkins, 1993.

Kimura J. *Electrodiagnosis in Diseases of Nerves and Muscle: Principles and Practice*, 2nd edn. Philadelphia, PA: F.A. Davis, 1989.

Schaumburg HH, Berger AR, Thomas PK, Eds. *Disorders of Peripheral Nerves*, 2nd edn. Philadelphia, PA: F.A. Davis, 1992.

Stewart JD. *Focal Peripheral Neuropathies*, 3rd edn. Philadelphia, PA: Lippincott-Raven, 2000.

## 99 Plexopathy, brachial

---

Michael Amoashiy, Prajwal Rajappa, and and Caitlin Hoffman *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

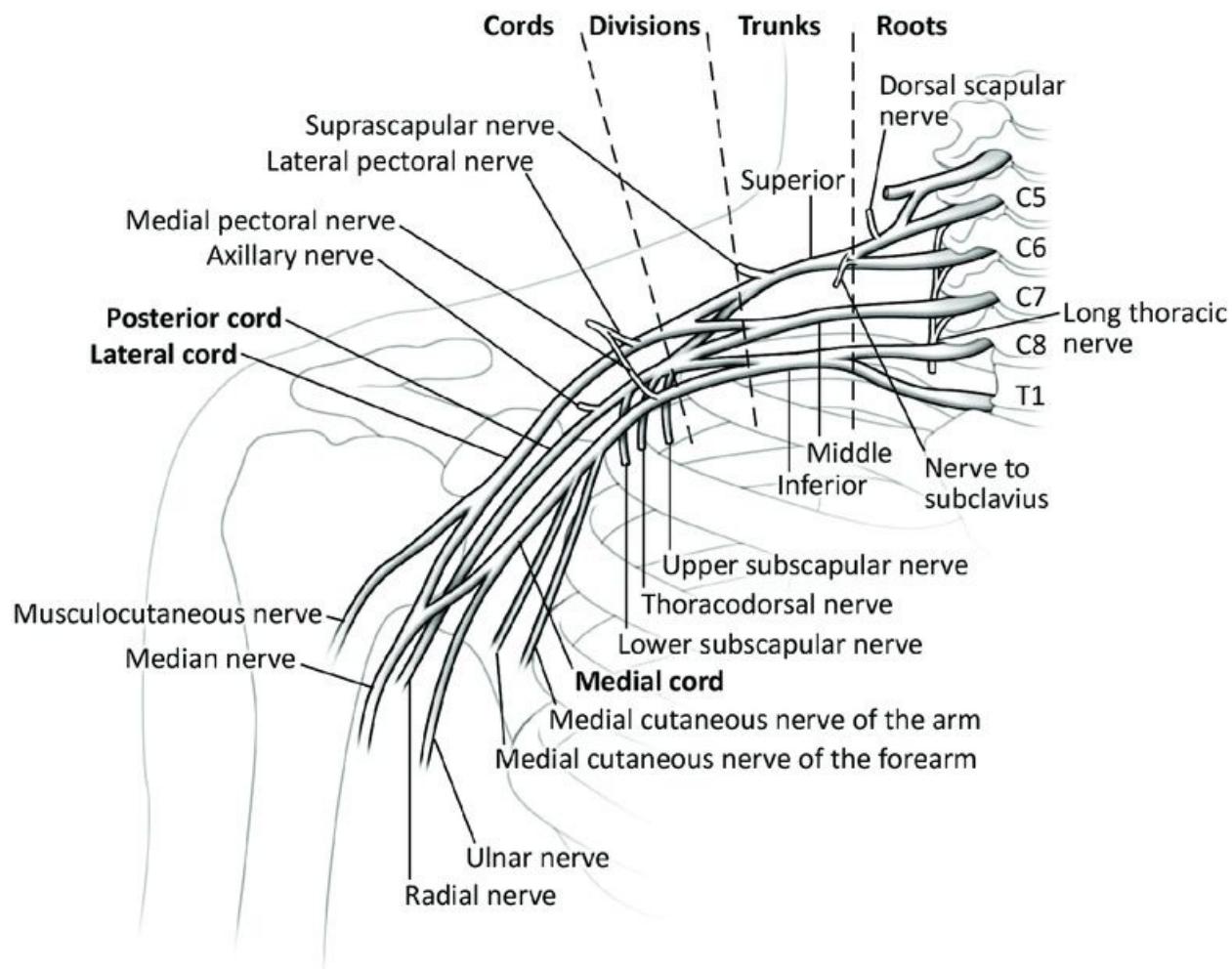
### Introduction

The brachial plexus is an intricate network of nerve divisions that supply motor and sensory function to the muscles and skin of the upper extremities. A fundamental anatomical understanding of the brachial plexus is vital in distinguishing between the various plexopathies encountered in the clinical setting. In this chapter, we aim to provide a brief overview of the underlying anatomy, and offer a concise discussion of the clinical presentation, etiology, differential diagnosis, and treatment of disorders of the brachial plexus. The pathogenesis of brachial plexus lesions encompasses a wide spectrum including infectious, traumatic, iatrogenic (postoperative), radiation-induced, metabolic, neoplastic, inflammatory, and congenital causes. We also explore currently utilized diagnostic tools that enhance distinction between differential diagnoses and subsequent treatment paradigms.

### Anatomical considerations

The brachial plexus is approximately 15 cm long in an adult. The plexus extends from the spinal column to the axilla, passing under the clavicle. The overall structure of the plexus involves division into five major components: roots, trunks, divisions, cords, and branches. (Mnemonic: Robert Taylor Drinks Cold Beer.) The roots are the anterior rami of C5–C8 and T1. These roots combine to form three trunks described as the upper trunk (C5–C6), middle trunk (C7), and lower trunk (C8–T1). Each trunk then splits into correlating divisions which are further subdivided into lateral, posterior, and medial cords, named in accordance to their relationship to the axillary artery. The lateral cord is comprised of fused anterior divisions of the upper and middle trunks whereas the posterior cord is a composite of all three posterior divisions. The medial cord arises from the

anterior division of the lower trunk. These cords continue beyond the brachial plexus as peripheral nerves or branches. Nerves exiting the plexus include the radial nerve, axillary nerve, median nerve, ulnar nerve, musculocutaneous nerve, dorsal scapular nerve, suprascapular nerve, subscapular nerve, and thoracodorsal nerve (Figure 99.1).



**Figure 99.1** Brachial plexopathy.

These exiting branches, as well as two nerves that originate proximal to the formation of the plexus, innervate the shoulder girdle, upper extremity, and hand. The nerves that originate proximal to the plexus are the long thoracic nerve (C5/6/7) and the dorsal scapular nerve (C4/5). The long thoracic nerve descends behind the plexus and innervates the serratus anterior muscle. This muscle stabilizes the shoulder during arm movement. Long thoracic neuropathy manifests as shoulder pain and weakness in abducting the arm and raising it above the head, and results in winging of the scapula when the arms are

extended away from the body. It is important to assess the function of these muscles and cervical paraspinal muscles both clinically and electrodiagnostically to locate lesions to the level of nerve roots versus plexus. Electromyography (EMG) demonstrates fibrillation potentials in these respective muscles in cases of denervation injury. Nerve conduction studies (NCS) are difficult in assessing nerve injury in both cases.

The nerves exiting the anterior division of the brachial plexus supply the flexors of the upper extremity. The nerves exiting the posterior division of the brachial plexus supply the extensors of the upper extremity. Exiting peripheral nerves, or branches, provide sensory and motor innervation to the forearm and hand. Anatomical variations of the brachial plexus are not uncommon, leading to different nomenclature for the plexus based on predominant nerve root contributions. When the plexus is formed predominantly from the C4–C7 roots, it is called prefixed. When the primary contribution is from the C6–T2 roots, it is post-fixed. With a post-fixed plexus, there is a risk that the inferior trunk may be compressed by the first rib, resulting in neurovascular symptoms consistent with an inferior plexopathy, as discussed below.

## Clinical presentation

Diagnosing brachial plexus injury can be challenging. Brachial plexopathy commonly presents with muscle weakness, atrophy, paresthesias, numbness, or pain correlating to the distribution of the trunk, cord, or division of the plexus affected. Brachial plexus pathology can be classified into pan-plexus (C5–T1), upper trunk (C5–C6), middle trunk (C7), or lower trunk (C8–T1) injury and further subdivided by traumatic or non-traumatic mechanisms (refer to [Table 99.1](#)).

**Table 99.1 Differential diagnosis of brachial plexopathy lesions.**

		Trunk lesions	
		Above the clavicle	
Localization	Pan-plexopathy	Superior trunk plexopathy	Middle trunk plexopathy

Focal muscle weakness	Proximal and distal arm and hand weakness or paralysis	Deltoid, biceps, pectoralis major, supraspinatus, infraspinatus, subscapularis and teres major in various combinations. If lesion is proximal near the roots also serratus. Rhomboids and levator scapulae are also involved	Forearm pronators, radial hand flexion	]
Sensory impairment	Sensation impaired throughout the entire upper extremity	Lateral arm, lateral forearm, lateral hand, and 1st digit	Posterior forearm and 1st–3rd digits	]
Deep tendon reflexes (DTR)	Decreased or absent triceps, biceps, and brachioradialis	Decreased biceps and brachioradialis. Triceps preserved	Decreased triceps. Brachioradialis and biceps preserved	]
Comments	Flail arm, pallor, or swelling. Most common in	Waiter's tip: arm in internal rotation and	Rare solitary. Usually comcomitant of	]

	obstetric/children. Uncommon in adults. Usually occurs with severe trauma	pronation, thumb and finger flexion, interrupted digit extension	the upper or lower plexopathy
Eponym	Global palsy	Erb–Duchenne palsy	
Cervical spinal nerve roots involved	C5–T1	C5–C6	C7
Peripheral nerves involved	All brachial plexus nerves involved	Dorsal scapular nerve, long thoracic nerve, suprascapular nerve	Long thoracic, lateral pectoral, musculocutaneous, lateral head of median

When assessing the severity of these types of lesions, it is essential to ascertain the degree of peripheral nerve damage. In 1943, Seddon first classified nerve damage into three primary categories: neuropraxia (Class 1), axonotmesis

(Class 2), and neurometesis (Class 3).

Neuropraxia, the mildest form of peripheral nerve injury, involves a physiologic nerve conduction block due to damage to the axon and occasionally partial myelin sheath injury while axonotmesis is usually the result of a more extensive crush or contusion injury, resulting in axonal and myelin injury. The nerve sheath, consisting of the endoneurium, perineurium, and epineurium, is left intact. Neurometesis involves a complete disruption of the entire nerve fiber, including the axon, myelin, and the endoneurium, perineurium, and epineurium.

This nerve injury classification scheme continues to play a major role when determining if surgical intervention or supportive management will be utilized in contemporary brachial plexopathy treatment.

## Pan-plexopathy

Pan-plexus or global lesions present with abnormality in all aspects of upper limb function and involve partial or complete damage to all the nerve roots of the brachial plexus [1]. Clinical presentation may include flail arm, swelling, and pallor of the upper extremity, and diffusely involves upper, middle, and lower trunks. This injury is most commonly observed in infants with pan-plexus lesions accounting for 25–50% of obstetric brachial plexus palsies (OBPP) [1,2]. Although rare in adults, pan-plexopathy may be observed as a result of traumatic injuries.

## Upper trunk plexopathy

In 1861, Guillame Duchenne first published his findings on obstetric brachial palsy followed by Wilhelm Einrich Erb, who in 1874 further described these lesions to be localized to the C5–C6 roots of the brachial plexus. Now more commonly referred to as Erb–Duchenne palsy, the patient presents with the arm held in internal rotation with pronation. This is often referred to as a “waiter's tip” presentation, and it has been associated with weakness in the bicep and deltoid muscles [3]. More distally, patients usually maintain thumb and finger flexion while digit extension can be interrupted. Sensory loss is frequently observed in the lateral forearm and lateral deltoid and along the trapezius ridge and medial scapular border [4].

## Middle trunk plexopathy

Lesions affecting the middle trunk are rare. Clinical presentation usually involves both motor and sensory deficits. Motor deficits include forearm and wrist weakness; weakness in forearm pronation and radial hand extension have also been described [4]. Sensory loss has been reported at the dorsal portion of the thumb, index, and long finger. There is also a decreased triceps reflex [4].

## Lower trunk plexopathy

The lower plexus palsy (Klumpke's paralysis) was named after Augusta Dejerine-Klumpke, the first American intern at a Parisian hospital. This lesion usually presents with C8–T1 nerve root involvement. Clinical presentation includes intrinsic hand muscle weakness resulting in a clenched hand deformity, often referred to as “claw hand,” and sensory loss in the distribution of the ulnar nerve [3]. The upper extremity is often described to have a swollen and pale appearance due to neurovascular sensorimotor disturbance. In fact, a majority of postganglionic sympathetic fibers are distributed along C8–T1 roots [3]. Additionally, T1 root involvement may present with a Horner's syndrome presenting with miosis, ptosis, and anhydrosis [4].

## Cord plexopathy (lateral, posterior, and medial)

Most cord plexus injuries result from insults below the clavicle. Lateral cord injury is typically observed with humeral dislocation, involving the musculocutaneous nerve and lateral part of the median nerve [4]. These lesions most often present with weakness of the biceps, coracobrachialis, and muscles supplied by the median nerve (refer to anatomy section). Patients also experience loss of flexion of the forearm and wrist, and sensory loss of the radial forearm due to injury of the musculocutaneous and lateral root of the median nerve along with the median nerve [3,4]. Posterior cord injury results in compromise of radial and axillary nerve branches. Damage to the posterior cord presents with weakness in forearm extension and decreased ability to abduct the shoulder. Loss of sensation may be reported along the anatomical snuff box and the dorsum of the hand [4]. Medial cord injury results in median and ulnar nerve deficits. Common presentation includes paralysis of the intrinsic muscles of the hand (“LOAF”), and sensory loss of the ulnar and median distribution of the hand [4]. (Refer to [Table 99.1](#).)

## Etiology of brachial plexopathy

A multifactorial approach must be utilized when differentiating the causes of brachial plexopathy. Brachial plexus injury can be localized and categorized into two major subtypes: traumatic and non-traumatic (refer to [Table 99.2](#)).

## Electrophysiologic evaluation

The main goal of the neurologic investigation in brachial plexopathy lesions is to localize the lesion and estimate the severity. In addition, in every clinical situation the differential should include the possibility of other lesions that are closely mimicking brachial plexus pathology. It is very important for the clinician to be familiar with brachial plexus anatomy and perform a thorough neurologic exam in conjunction with nerve conduction studies (NCS) and electromyography (EMG) investigation.

**Table 99.2** *Brachial plexopathy treatment.*

Etiology	Brachial plexopathy treatment		
Traumatic – Open or closed injury animal bite, compression, cold, electric shock, shearing forces	Pain management	Corticosteroids	Physical therapy
Neuropraxia – expected improvement within 6–8 weeks (e.g. backpack palsy, Burner syndrome)	Gabapentin, pregabalin, carbamazepine, dilantin, lidocaine patches, tricyclic antidepressants, lamotrigine	Corticosteroids are optional depending on severity	Initial rest for 3–5 days followed by early mobilization and aggressive physical therapy
.	.	.	.

Axonotmesis – expected improvement from 6–8 months	Gabapentin, pregabalin, carbamazepine, dilantin, lidocaine patches, tricyclic antidepressants, opiates, lamotrigine. Local and regional blocks, infusion pumps, sympathetic ganglion blocks. Ultrasound guided rhizotomy. Radiofrequency neurotomy	Oral or local corticosteroids in the acute–subacute stage	Initial rest. Followed by aggressive physical therapy, transcutaneous electrical nerve stimulation
Neurometesis Poor prognosis (i.e. root avulsion)	Gabapentin, pregabalin, carbamazepine, dilantin, lidocaine patches, tricyclic antidepressants, opiates, lamotrigine. Local and regional blocks, infusion pumps,	Necessary to reduce neuroedema in the acute and subacute phase	Not expected to provide relief unless a curative surgery was performed

	<p>sympathetic ganglion blocks. Ultrasound-guided rhizotomy. Radiofrequency neurotomy</p>
Infectious Influenza, Coxsackie virus, Epstein–Barr virus, Q fever, <i>Mycoplasma pneumoniae</i> , bacterial pneumoniae, TB, typhoid, syphilis, HIV, and Lyme borreliosis	<p>Organism-specific antibiotic or antiviral regimen Physical therapy Pain management – gabapentin, pregabalin, carbamazepine, lidocaine patches, tricyclic antidepressants, opiates. Local and regional blocks, infusion pumps, sympathetic ganglion blocks. Ultrasound-guided rhizotomy, radiofrequency neurotomy cases. Incision and drainage of abscess if present</p>
Congenital Thoracic outlet syndrome, rudimentary cervical rib, fibrous band compressing C8 and T1 fibers of the lower plexus	<p>Surgical division of fibrous band or transaxillary first rib resection Pain management if severe pain/dysesthesias are present – gabapentin, pregabalin, carbamazepine, dilantin, lidocaine patches, tricyclic antidepressants, opiates, lamotrigine Local and regional blocks, infusion pumps, sympathetic ganglion blocks. Ultrasound-guided rhizotomy, radiofrequency neurotomy cases Physical therapy if motor weakness is present</p>
Radiation-induced plexopathy – peripheral nervous system is resistant to radiation. Incidence of damage increases	<p>Preventative – administer lower total doses over a longer period of time Neurolysis has been performed with improvement of symptoms but also may cause greater motor and sensory deficits Supportive treatment with opiates, gabapentin, pregabalin, carbamazepine, dilantin, lidocaine patches, tricyclic antidepressants, opiates, lamotrigine for pain control Physical therapy to improve motor deficits These treatments are employed but there is no definitive answer</p>

	<del>These treatments are empirical, but there is no definitive treatment</del>
with higher total dose, greater fraction sizes, and shorter treatment times. Commonly in breast cancer patients post-axillary lymph node radiation	
Radiation induced nerve sheath tumor – typically will cause malignant nerve sheath tumor. Rarely occurs, but should be a consideration in patients with plexopathy post-radiation	Treatment is listed below under “Primary neoplastic br plexopathies”
Obstetric Traction injury – shoulder dystocia impedes vertex delivery, excessive lateral deviation of the head in efforts to free the shoulder. Can also occur with use of vacuum and forceps extraction	Expected spontaneous recovery in at least 90% of cases Surgical repair yields the best results when performed Observational period is controversial and ranges from 6 months to 2 years cases that do not show any signs of significant improvement
Hereditary	Initial: non-steroidal anti-inflammatory drugs (NSAID)
Hereditary	Secondary phase: gabapentin, carbamazepine, and tricyclic antidepressants

neuralgic amyotrophy – autosomal dominant. May also involve lower cranial nerves, lumbosacral plexus, and isolated peripheral nerves. Sensory loss. Motor strength and DTRs preserved. Onset in 4th and 5th decade. Deletion or mutation on the *SEPT9* (septin) gene on chromosome 17

Idiopathic Neuralgic amyotrophy (Parsonage–Turner syndrome). Acute onset of shoulder or arm pain. Typically involves axillary, suprascapular, long thoracic, anterior interosseous, and musculocutaneous nerves. Severe pain, weakness, and muscle wasting. Acute

antidepressants, pregabalin, dilantin, lidocaine patches lamotrigine

Chronic phase: support the glenohumeral joint (sling),

Opiates for pain management  
Short course of corticosteroids  
Recovery depends upon the severity of the lesion  
Gabapentin, carbamazepine, and tricyclic antidepressants  
dilantin, lidocaine patches, opiates, lamotrigine are used for chronic pain

pain usually lasts  
7–10 days  
followed by a dull  
ache

Postoperative  
Classical  
postoperative  
(positional) –  
Trendelenberg  
position, arm  
board restraint in  
abducted extended  
and externally  
rotated position  
with contralateral  
deviation of the  
head.  
Postoperative  
painless  
weakness,  
paresthesias may  
also be noted.  
Most common  
location – upper  
plexus

Postoperative  
(post-median  
sternotomy  
plexopathy). Most  
common –  
coronary artery  
bypass surgery.  
Chest wall  
retraction pushes  
clavicle into  
retroclavicular  
space – rotating

Expected recovery within 6 weeks  
Physical therapy increases the rate of improvement

Physical therapy  
Corticosteroids  
Pain management – gabapentin, carbamazepine, and ti  
antidepressants, pregabalin, dilantin, lidocaine patches  
lamotrigine  
Permanent disability is not expected

first rib into C8  
anterior and  
primary ramus

Neoplasm  
Primary  
neoplastic  
brachial  
plexopathies.  
Schwannoma –  
most common.  
Solitary, slow  
growing. Painless  
mass occasionally  
with paresthesias

Neurofibromatosis  
type 1 – multiple  
plexiform. Pain,  
associated with  
weakness and/or  
numbness

Malignant nerve  
sheath tumors –  
malignant  
transformation of  
plexiform  
neurofibroma  
(most common).  
Less commonly

Schwannoma  
Excision of mass  
Recurrence is unusual, even if surgical excision is incom-

Neurofibroma  
Surgical excision for pathology and decompression  
Recurrence of mass is expected following surgical excision  
Chemotherapy and radiation therapy are recommended to prevent malignant transformation  
Gabapentin, pregabalin, carbamazepine, dilantin, lidocaine, tricyclic antidepressants, opiates, lamotrigine  
Local and regional blocks, infusion pumps, sympathetic blocks, ultrasound guided rhizotomy, radiofrequency rhizotomies  
Physical therapy for supportive treatment  
Surgical options which should also be considered in selected cases where pain and deficits persist: neurolysis, nerve transfer, stem cell blocks, stellate ganglionectomies, dorsal column stimulators, cordotomies, dorsal root zone entry ablations, nerve arachnoid releases, sympathectomies

Malignant nerve sheath tumor  
Surgical excision for pathology and decompression  
Recurrence of mass is expected following surgical excision  
Chemotherapy and radiation therapy are recommended to prevent malignant transformation  
Gabapentin, pregabalin, carbamazepine, dilantin, lidocaine, tricyclic antidepressants, opiates, lamotrigine  
Physical therapy for supportive treatment

**Less common**  
solitary  
neurofibroma and  
schwannoma.  
Painful enlarging  
mass associated  
with motor and/or  
sensory deficit. 5-  
year survival rate  
is 10–50%

Secondary  
neoplastic  
brachial  
plexopathies –  
breast and lung  
most common.  
Neoplasm causing  
extrinsic  
compression or  
infiltration upon  
the brachial  
plexus. Severe,  
persistent  
shoulder and arm  
pain. Occasional  
sympathetic  
involvement.  
Example:  
Pancoast  
syndrome –  
cancer within the  
lung apex  
compressing the  
lower plexus.  
Shoulder region  
pain radiating to  
the medial aspect  
of the elbow and  
digits 4 and 5.

**Physical therapy for supportive treatment**

Surgical removal of tumor  
Radiation therapy and chemotherapy as appropriate for  
Physical therapy if motor weakness is present  
Gabapentin, pregabalin, carbamazepine, dilantin, lidocaine  
tricyclic antidepressants, opiates, lamotrigine  
For patients with persistent pain more aggressive treatment  
Local and regional blocks, infusion pumps, sympathetic nerve blocks, ultrasound guided rhizotomy, radiofrequency rhizotomy  
Surgical options which should also be considered in selected cases  
pain and deficits persist: neurolysis, nerve transfer, stellate ganglion blocks, stellate ganglionectomies, dorsal column stimulation, cordotomies, dorsal root zone entry ablations, nerve arachnoid release, sympathectomies

Horner's  
syndrome.  
Commonly non-  
small cell  
carcinoma

---

The electrodiagnostic evaluation of the brachial plexus pathology relies primarily on sensory nerve action potentials (SNAPs) and detailed needle EMG examination. It is important to remember that all sensory nerve fibers are localized distal to the dorsal root ganglia (DRG), thus making SNAPs the most important diagnostic tool in differentiating between plexus and nerve root pathology. Motor NCS are less useful in differentiating between a plexopathy and radiculopathy, although may be helpful in multiple upper extremity entrapment neuropathies.

## Sensory nerve conduction studies

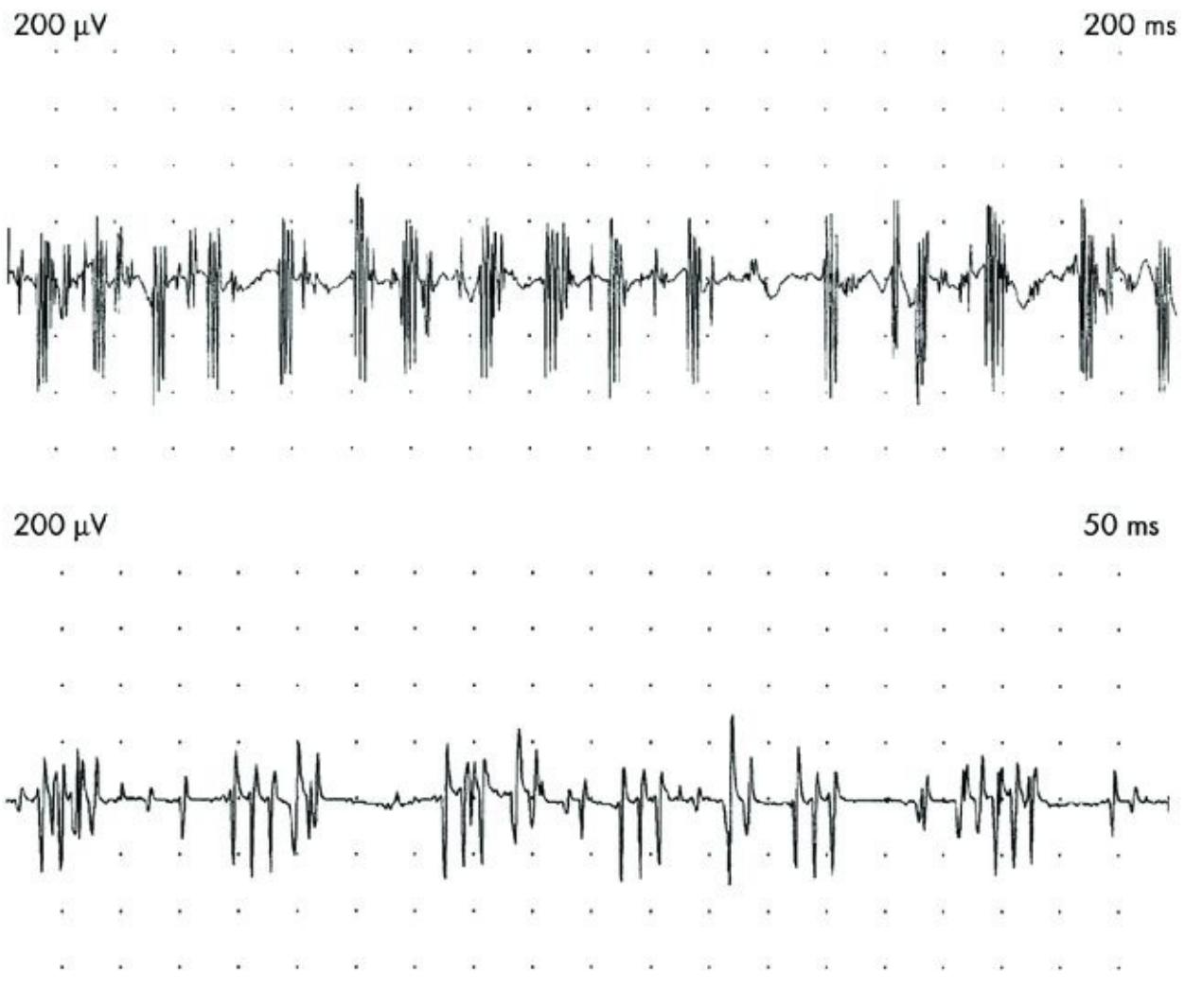
The SNAPs' decreased amplitude is the most useful indicator of an axonal damage in a brachial plexopathy. Bilateral studies should be performed and comparison is made with usually 50% difference in amplitude to consider it abnormal. For brachial plexopathy diagnosis lateral and medial antebrachial cutaneous, radial, median, and ulnar sensory conduction studies are recommended.

## Motor nerve conduction studies

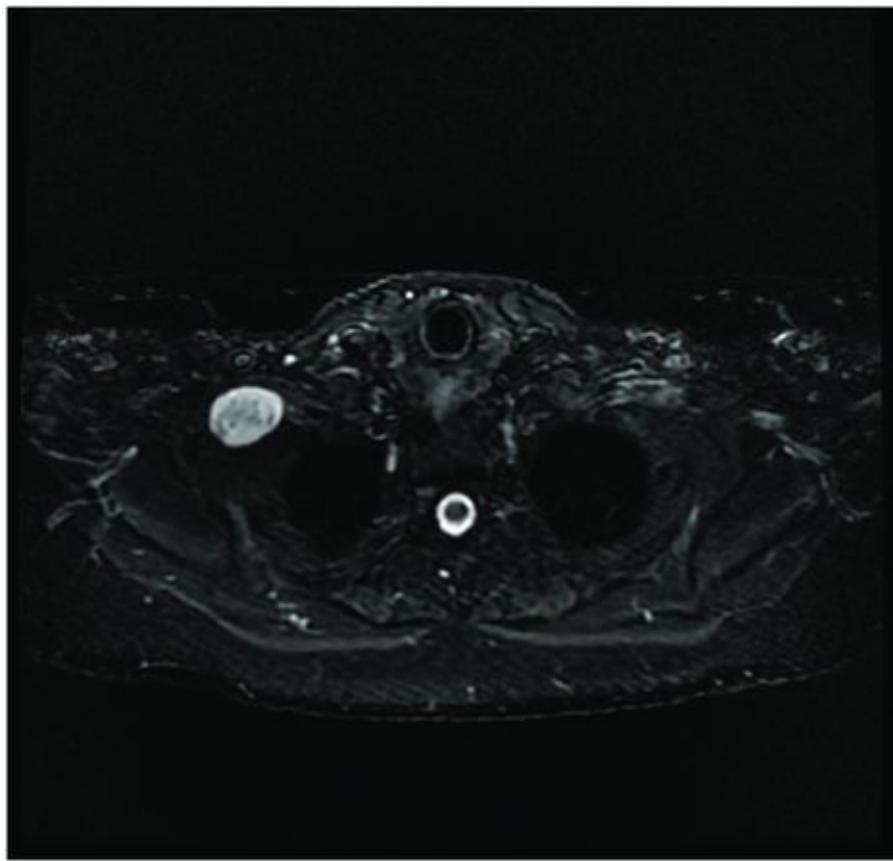
In general, motor NCS are less useful. They help to distinguish between a brachial plexopathy and multiple entrapment neuropathies. Motor NCS in suspected brachial plexopathies are usually performed in median motor recorded at the abductor pollicis brevis (APB) with distal and proximal stimulation. Ulnar motor NCS are recorded at the abductor digiti minimi (ADM) with distal and proximal stimulation at and above the elbow. Radial motor NCS may be useful in lower trunk or posterior cord lesions with recording from the extensor indicis proprius (EIP). When suspecting upper or middle trunk lesions, Erb's point stimulation can be applied with recording at the biceps, triceps, and deltoid or spinatus muscles bilaterally. Median and ulnar F waves can be useful in suspected lower trunk or medial cord lesions.

## **Electromyography**

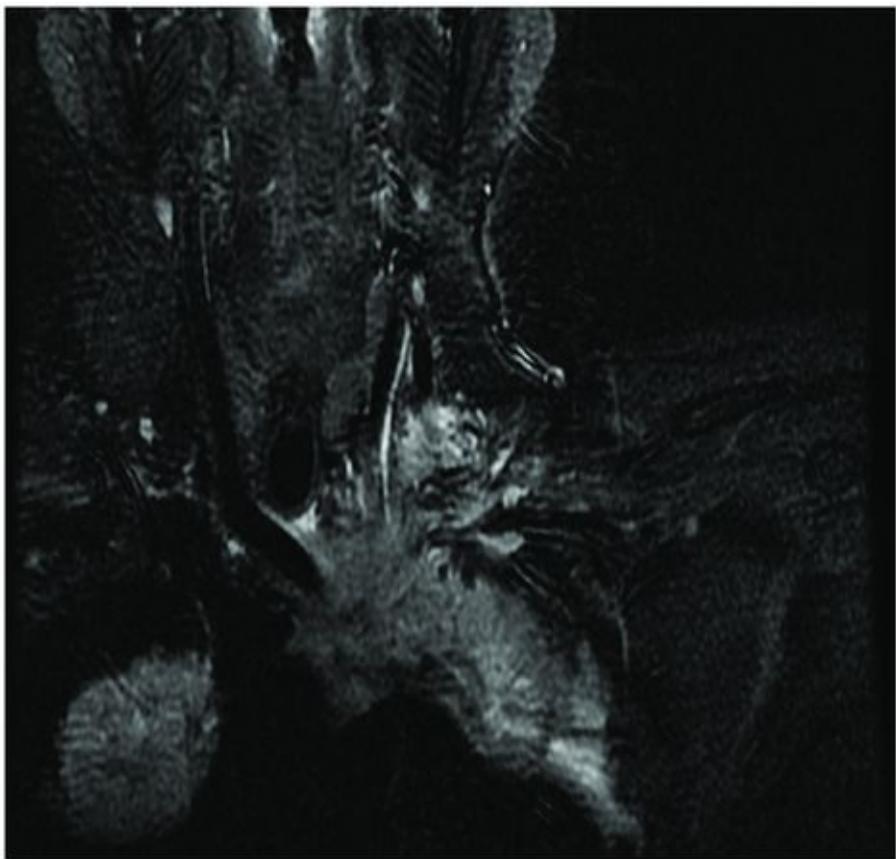
Electromyography should be performed extensively including the proximal paraspinal muscles that help differentiate between a brachial plexus and a cervical root lesion. The brachial plexus is composed of nerve fibers derived from different spinal cord segments and in electrodiagnosis of the brachial plexus injuries standard myotomal charts are used to localize the lesion [1]. Abnormal EMG and preserved sensory responses would indicate a cervical radiculopathy; however, in the absence of paraspinal muscular electromyographic abnormalities this distinction is difficult. Electromyography is useful in demonstrating denervation, motor unit action potential abnormalities (MUAP), recruitment pattern, unusual spontaneous discharges, and axonal continuity. Myokymic discharges are important in differentiating a neoplastic infiltration of the brachial plexus from radiation-induced plexopathy. These discharges are recognized as spontaneous bursts of single amplitude MUAP firing every 0.5–2.0 s with a frequency of 20–70 Hz ([Figure 99.2](#)).



**Figure 99.2** Myokymic discharges.



**Figure 99.3** Solitary schwannoma.



**Figure 99.4** Pancoast tumor.

Mild compressive, traction, or inflammatory plexopathies can lead to a focal demyelination that results in conduction slowing or conduction block. Electrophysiologic evaluation reveals reduced recruitment of MUAPs in the affected muscles. The prognosis for recovery in such lesions is favorable. In more severe plexopathies axonal loss is present with associated reduced number of MUAPs, positive sharp waves (PSW), and fibrillation potentials in the affected muscles. These electromyographic changes usually develop after 5–7 days and the prognosis is usually poorer. It is important to determine if the plexus remains in functional continuity. Axonal disruption is strongly suspected in the absence of any MUAPs with volitional control and absence of F waves. In such cases consideration should be given to surgical exploration, nerve grafts, and other surgical options. The clinical and electrophysiologic manifestation of a brachial plexopathy depends on the level of severity of injury and generally extends beyond the distribution of an isolated nerve root or peripheral nerve.

In a pan-plexopathy the entire plexus is affected and the arm is completely paralyzed. With partial lesions of the supraclavicular brachial plexus

abnormalities may demonstrate a radicular distribution that depends on whether the upper (C5–6), middle (C7), or lower trunk (C8–T1) of the plexus is involved. Infraclavicular lesions affect the cords and derived nerves.

Upper trunk lesions may result in abnormal lateral antebrachial cutaneous sensory responses. The median and radial sensory responses may also be abnormal. Motor nerve conduction studies obtained from median and ulnar nerves as well as F waves are normal. An EMG is usually abnormal with deltoid, biceps, brachioradialis, supraspinatus, and infraspinatus muscles studied. Other muscles such as pronator teres, triceps, and flexor carpi radialis may also be partially affected. The cervical paraspinals, rhomboids, and serratus anterior muscles are normal.

Middle trunk plexopathy is relatively rare in isolation. This type of lesion demonstrates abnormal median SNAPs (C7) particularly with recording from the middle finger. Motor nerve conductions and F responses are normal. Electromyography shows abnormalities in C7 innervated muscles such as triceps, pronator teres, and flexor carpi radialis. Brachioradialis muscle is entirely spared.

Lower trunk plexopathy (Klumpke palsy) affects the ulnar, dorsal ulnar, and medial antebrachial cutaneous SNAPs (C8–T1). Motor median and ulnar conduction studies and F-wave responses are also abnormal. Radial motor study from EIP is often abnormal, however may be spared in partially lower trunk lesions. If radial motor nerve is abnormal this will exclude a middle trunk lesion. Electromyography shows abnormality in all ulnar, median, and radial innervated muscles that contain C8–T1 fibers such as flexor pollicis longus, APB, intrinsic hand muscles, flexor digitorum, and EIP.

Brachial cord lesions can demonstrate motor and sensory loss mimicking two or more peripheral nerves injuries.

Lateral cord demonstrates abnormalities in the lateral antebrachial and median SNAPs. Median and ulnar motor nerve conduction and F waves are normal. Electromyography may show abnormalities in biceps, pronator teres, and flexor carpi radialis. Distal median innervated muscles in the forearm and hand are normal.

Posterior cord plexopathy demonstrates abnormal radial SNAPs. Median and ulnar motor conduction studies and F-wave responses are normal. Electromyography may show abnormalities in distal and proximal radial innervated muscles such as extensor indicis proprius, extensor carpi radialis, and

brachioradialis muscles. Occasionally EMG may be abnormal in deltoid, teres minor, and latissimus dorsi muscles.

Medial cord plexopathy is similar to lower trunk plexopathies. In these cases it mimics combined injury to the ulnar and medial head of the median nerve (finger flexion weakness). Medial cord lesions may involve the ulnar, dorsal ulnar, and medial antebrachial cutaneous SNAPs. The median and ulnar motor studies and F-wave responses are abnormal. With axonal loss present SNAP amplitude may be reduced with prolongation of the distal latency and mild slowing of conduction velocities. Electromyographic abnormalities include all ulnar innervated muscles and the median innervated muscles that contain C8–T1 fibers such as APB and flexor pollicis longus, however radial innervated C8 muscles are spared.

## Treatment

Treatment paradigms of brachial plexopathy focus on managing the underlying cause of the pathology with supportive or surgical intervention. With milder injury, a conservative approach is recommended as spontaneous resolution is reported to occur in neonatal, pediatric, and adult plexopathy, often within 3–4 months from initial insult [1]. Plexopathies secondary to systemic (autoimmune), radiation-induced, infectious, and metabolic causes are offered supportive treatment with pain management along with physical therapy. Pain management pharmacotherapy includes analgesics, opioids, local anesthetics, and gabapentin [5]. In the setting of severe injury, where symptoms often persist longer than 3–6 months, surgery may be indicated. These injuries are secondary to traumatic etiology presenting with complete or partial avulsion of cervical roots. Microsurgical techniques offered may include neurolysis, nerve grafting, or nerve transfer. Neurolysis involves clearing scar tissue. The utility of nerve grafting with the sural nerve or nerve transfer (anastomosis) depends on the degree of avulsion involved. With upper root (C5 and C6) avulsion, neurotization by nerve transfer is recommended [1]. Pan-plexus lesions may be amenable to nerve transfer procedures but this does vary institutionally and depends on a case-specific basis [1].

## Imaging of the brachial plexus

Several techniques are used in imaging of the brachial plexus including X-ray, myelography, computerized tomography (CT), magnetic resonance imaging

(MRI), and high-resolution sonography [6]. X-ray may be useful to diagnose the presence of cervical ribs, elongated C7 transverse process, or trauma to the clavicle and cervical spine. Computerized tomography and CT myelography may also be utilized to diagnose brachial plexus lesions, especially diagnosing bony changes and hemorrhages or intradural C5–6 root injuries; however there are limitations to their use due to the desire to avoid high radiation exposure. The imaging of choice for brachial plexus involvement is MRI [6]. Short T1 inversion recovery (STIR) (fat suppression) sequences can demonstrate high signal intensity from trunks and cords of the brachial plexus. In root avulsions, a pseudomeningocele appears hyperintense and easily identifiable on T2 sequences. An MRI scan can also be very useful in distinguishing between a neoplastic process involving the brachial plexus and post-radiation plexopathy.

High-resolution ultrasound is inexpensive and readily available. This technique in experienced hands can provide additional information in diagnosing root avulsions and scarring, however with proximal injuries shadowing from the bone can preclude visualization of the attachment of the nerve rootlets to the spinal cord [7].

## Case vignette

A 48-year-old right-handed female was referred for evaluation of right-hand numbness and weakness for the past 3 years. She noted slowly worsening numbness over the fourth and fifth digits of the right hand. In addition she started dropping things from her hand and has been experiencing difficulties with fine right-hand movements such as tying shoelaces, or turning keys. The patient denied any pain. Initially the symptoms were intermittent but have become more persistent in the past 3 months. She also noticed swelling in her right arm and hand. Past medical history is significant for breast cancer 12 years ago that was treated with surgery followed by breast and axillary radiation and chemotherapy. Follow-up imaging and clinical studies did not reveal recurrent tumor.

Examination was notable for normal cranial nerves with no signs of a Horner's syndrome. There was slight atrophy in the right thenar and hypothenar areas, with weakness of the right thumb adduction and interossei muscles. There was slight edema of the dorsal aspect of the right hand and forearm. Hypoesthesia was present in the right fifth and the medial aspect of the fourth finger. The muscle strength and sensation were normal in the left arm. Deep tendon reflexes

demonstrate absent right triceps, brachioradialis, and carporadial reflexes on the right. Muscle strength, sensation, and reflexes were normal in both lower extremities. In addition there were undulating worm-like movements seen in the distal right forearm and hand.

Electrodiagnostic study showed evidence of chronic brachial plexus lesion on the right, primarily affecting the lower trunk. Electromyography showed myokymic discharges in the distal right forearm and hand muscles that corresponded to the worm-like, undulating movements on clinical exam.

An MRI of the arm and plexus was performed that demonstrated localized edema within the soft tissues without a mass and T2 hyperintensity within the trunks and nerve roots on the right plexus. There was no nodular enhancement.

A diagnosis of a radiation-induced brachial plexopathy was made. A history of insidious onset of numbness and weakness in the upper extremity in a patient who received prior radiation therapy should suggest a delayed radiation-induced plexopathy. Distinguishable features of the radiation-induced plexopathy include the gradual onset over several years, the lack of pain on presentation, lymphedema, and myokymia.

## References

1. Midha R. Nerve transfers for severe brachial plexus injuries: a review. *Neurosurg Focus* 2004;16:E5.
2. Gilbert A, Whitaker I. Obstetrical brachial plexus lesions. *J Hand Surg Br* 1991;16:489–91.
3. Greenberg MS, Arredondo N. *Handbook of Neurosurgery*, 6th edn. New York, NY: Thieme, 2006.
4. Schwartzman RJ. *Differential Diagnosis in Neurology*. Washington, DC: IOS Press, 2006.
5. Galecki J, Hicer-Grzenkowicz J, Grudzien-Kowalska M, Michalska T, Zalucki W. Radiation-induced brachial plexopathy and hypofractionated regimens in adjuvant irradiation of patients with breast cancer – a review. *Acta Oncol* 2006;45:280–4.
6. Castillo M. Imaging the anatomy of the brachial plexus: review and self-assessment module. *AJR Am J Roentgenol* 2005;185:S196–204.

7. Haber HP, Sinis N, Haerle M, Schaller HE. Sonography of brachial plexus traction injuries. *AJR Am J Roentgenol* 2006;186:1787–91.

# 100 Plexopathy, lumbar

---

Jean Robert Desrouleaux and Alan B. Ettinger *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrod. Published by Cambridge University Press. © Cambridge University Press 2014.

## Introduction

A brief review of anatomical considerations helps guide a better understanding of the clinical presentation of lumbosacral plexopathy (LSP). Lumbar roots L2, L3, and L4 form the lumbar plexus and are located within the psoas muscle. The major branch from the lumbar plexus is the femoral nerve in addition to the obturator nerve. Affectation of these nerves within the pelvic region is often included in discussion of LSP. (The reader may also want to refer to [Chapter 93](#) on femoral neuropathy.) Lesions of the lumbar plexus segments may produce deficits in hip flexion and adduction, knee extension, and, sometimes, ankle dorsiflexion, along with a depressed patellar reflex [1].

Both the femoral and obturator nerves arise in the substance of the psoas muscle which lies in the floor of the retroperitoneal space. A space-occupying lesion in the muscle such as a hemorrhage or abscess can cause a femoral entrapment. The femoral nerve (L2–L4) comes out of the lateral psoas muscle and descends from the abdomen laterally below the inguinal ligament along with the femoral artery [2]. It innervates the quadriceps femoris muscle. (The adductor of the thigh muscle and the skin of the medial thigh are innervated by the obturator nerve originating from nerve roots L2–L4.) Distinction of femoral neuropathy from LSP can be made through demonstration of weakness of adductor muscles in LSP and sensory deficits in the medial thigh (because of additional involvement in the obturator nerve component) which will not be present in pure femoral neuropathy.

The sacral plexus evolves from the L4, L5 roots and ventral rami of S1–S4 and is located on the posterior area of the pelvis. The major branch off the sacral plexus is the sciatic nerve which leaves the pelvis through the greater sciatic foramen. The superior and inferior gluteal nerves come off the sciatic nerve.

Lesions of the sacral segments can produce deficits in hip extension, abduction, and internal rotation of the thigh. Additional problems in flexing the knee and all motions involving the foot may occur along with a depressed ankle jerk reflex [1]. Distinction of a sacral plexopathy from a sciatic nerve problem is facilitated through the demonstration of weakness of abduction and internal rotation of the thigh, or sensory deficits in the posterior thigh (posterior femoral cutaneous nerve distribution), none of which are seen in a pure sciatic neuropathy [1].

While the brachial plexus is more exposed and more vulnerable to trauma (please refer to [Chapter 99](#) on brachial plexopathy), the lumbosacral plexus is more protected by the pelvis. This protective barrier, however, makes it more difficult to palpate tumors in that region. Other differences between brachial plexopathy and LSP is the latter's lower tendency to be afflicted with idiopathic plexitis [3].

Lumbosacral plexopathy should be suspected in the presence of motor and sensory loss involving more than one peripheral nerve or dermatome. Lumbosacral plexopathy should be distinguished from a multiple root syndrome. In the latter, pain associated with multiple roots may be radiating and increased with Valsalva maneuver or with bending or lifting. Lumbosacral plexopathy is less likely to have these features. (Please refer to [Chapter 101](#) on radiculopathy.) Root pain is also more likely to be provoked with straight leg raising or reverse straight leg raising (although there are notable exceptions), and will be more vulnerable to local percussion tenderness along the spine. Root pathology is more associated with paraspinal muscle spasm and reduction of normal lordosis. On the other hand, root pain may be more readily relieved with bedrest compared with LSP. Another distinguishing clue is the lack of impairment in sweating in multiple root syndromes whereas sweating may be impaired in LSP.

## Physical examination

Aspects of testing of relevant muscle groups are described here.

- (a) Iliopsoas: T12; L1, 2, 3. This is the main flexor of the hip.

The patient sits on the edge of the table with his legs hanging. The pelvis is stabilized by placing the examiner's hand over the iliac crest and the patient is required to actively raise his thigh off the table. The examiner places his other hand over the distal femoral portion of the patient's knee and the patient is again asked to raise his thigh as the examiner resists. Muscle strength is compared with the other side.

- (b) Quadriceps: L2, L3, L4 (femoral nerve). The examiner should instruct the patient to extend his knee while he places one hand just above the knee and the second hand above the ankle to offer resistance.
- (c) Hip adductor group (L2, L3, L4) obturator nerve. The patient lies supine or on his back and he is instructed to abduct his legs. The examiner places his hands on the medial sides of both knees and the patient is asked to adduct his legs against the examiner's resistance.

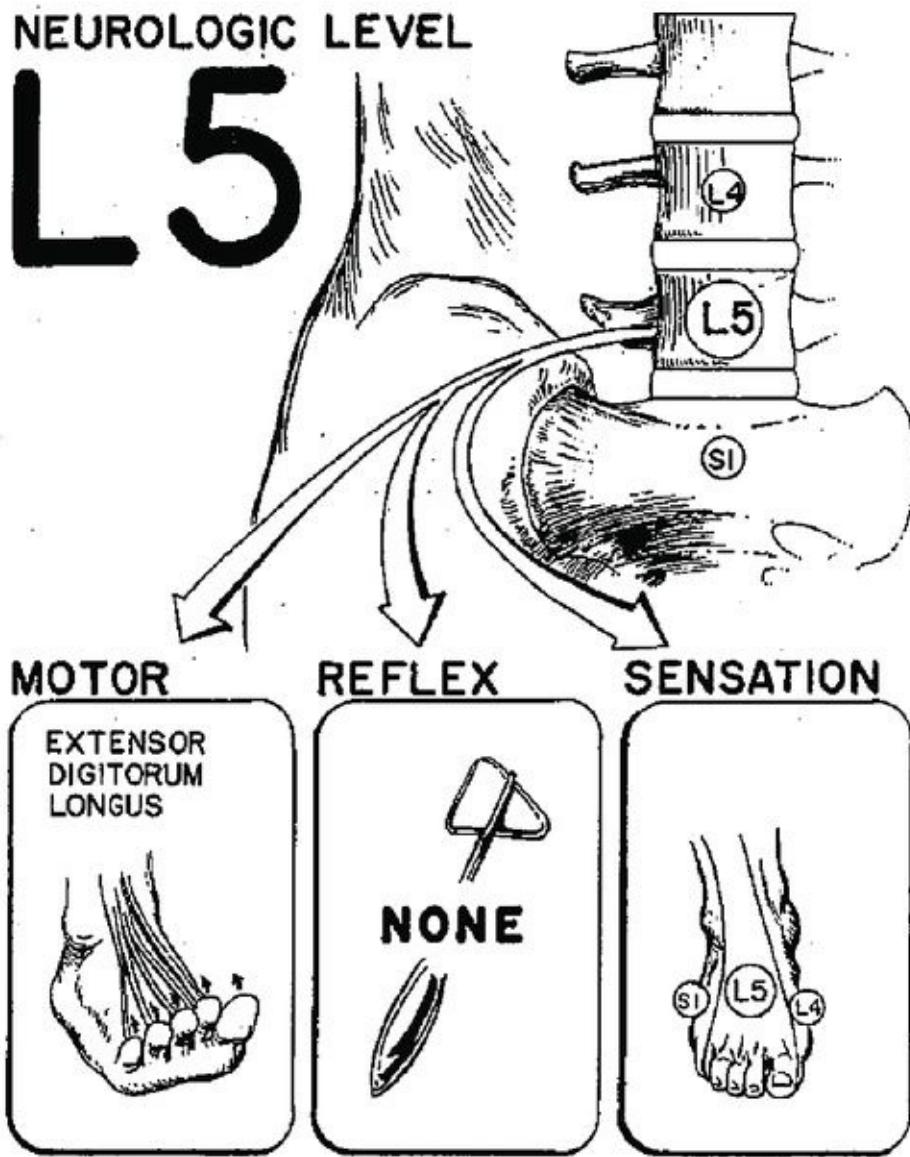
## **Muscle testing: L4 nerve root**

Tibialis anterior: L4 (deep peroneal nerve) is mainly innervated by the L4 nerve root with minimal innervations from L5. Functionally to test the muscle the patient should walk on his heels with his feet inverted. If the tibialis anterior muscle is weak, the patient is unable to perform the dorsiflexion–inversion test and if the deficit is severe, may show drop foot or steppage gait.

## **Manual testing**

Dorsiflex and inversion of foot.

Deep tendon reflex: Patellar tendon reflex. (L4 nerve root.) L5 nerve root



(Figure 100.1)

Figure 100.1 L5 nerve root.

Muscles: Extensor hallucis longus; extensor digitorum longus and brevis; gluteus medius; tensor fascia lata.

(a) Extensor hallucis longus

Testing: Ask the patient to walk on his heels with feet neither inverted nor everted.

(b) Extensor digitorum longus and brevis

Testing: Same as for extensor hallucis longus and the tendon of the extensor digitorum longus should be palpable on the dorsum of the foot.

(c) Gluteus medius L5 (Superior gluteal nerve)

Testing: Patient should lie on his side; stabilize the pelvis with one hand and ask the patient to abduct his leg. After full abduction by the patient, the examiner should push down against the thigh, applying pressure at the lateral aspect of the knee.

Sensory testing: lateral aspect of the leg.

- (d) Tensor fascia lata (Superior gluteal nerve)

Testing: Patient should lie on his side; stabilize the pelvis with one hand and ask the patient to elevate the foot while keeping the knee down. The examiner should push down against the lower leg.

S1 level:

Muscles: Peroneus longus and brevis.

Gastrocnemius–soleus muscles.

Gluteus maximus.

- (a) The peroneal muscles (S1) are evertors of the ankle and foot. To test these muscles, ask the patient to walk on the medial border of his feet.
- (b) Gastrocnemius-soleus muscles (S1, S2): Ask the patient to walk on his toes. There is weakness if he is unable to do so.
- (c) Gluteus maximus (S1): The gluteus maximus can be tested by asking the patient to stand from a sitting position without using his hands.

Reflex: Achilles tendon reflex.

Sensory: The S1 dermatome covers the lateral aspect of the dorsum of the foot and a portion of the plantar aspect of the foot.

## Case vignette

A 52-year-old right-handed female is seen for evaluation because of back and right lower extremity pain. The patient was in her usual state of health until approximately 3 weeks ago when she started experiencing discomfort in the anterior aspect of the right thigh associated with increasing difficulty walking up the stairs. A few days later, she started developing low back pain described as a tingling and burning sensation in the lumbosacral region, radiating to the right thigh and the right leg. The pain at first was mild at an intensity up to “3” and it is now up to “9” (zero being no pain and 10 the most imaginable pain). The pain radiates to the anterior aspect of the thigh and the lateral and posterior aspects of the leg. She also complains of weakness of the leg and she fell twice when the right leg gave way. The pain is worse at night, but there is no increase in pain with walking, coughing, or sneezing.

Past medical history: history of hypertension, diabetes mellitus type 2, and hypercholesterolemia. She denies any history of trauma or connective tissue disorder.

Current medications include insulin (started 3 months prior for poorly controlled diabetes), meto-prolol, and aspirin.

On review of system, she had a 30 pounds weight loss over 6 months. She had no sphincteric dysfunction. Physical examination is unremarkable except for mild increase of arterial blood pressure: 140/82 and a weight of 225 pounds for a 5 foot 2 inch height.

Neurologic examination was unremarkable except for the following: motor strength in the right lower extremity is 4+/5 for right hip flexion, 3/5 for right knee extension, and 4/5 for right foot dorsiflexion.

Sensory exam shows allodynia in the anterior aspect of the right thigh and there was decrease of sensation to pinprick and temperature in the inner and lateral aspect of the right leg and dorsal aspect of the right foot. There was absent patellar reflex on the right, and overall deep tendon reflex was +2 throughout and +1 at both ankles. The neurologic examination was otherwise unremarkable.

## Discussion

The patient is an obese diabetic 52-year-old female with pain, weakness, and abnormal reflexes in the right proximal lower extremity. The pain has been progressively worsening and started in the anterior aspect of the thigh muscles. She was experiencing difficulty walking up the stairs and had a few falls. The pain progressively worsens. The absence of pain during Valsalva maneuvers makes the diagnosis of acute lumbar disc herniation less likely, a remote possibility. Additional night pain is not typical of lumbar spinal canal stenosis or disc herniation. The absence of symptoms to the other side and the fact that she retains good bladder and bowel function makes a cauda equina dysfunction unlikely.

This case is classical for a presentation of diabetic amyotrophy, also called diabetic lumbosacral radiculoplexus neuropathy or subacute diabetic proximal neuropathy. It is supported by the acute unprovoked pain including night pain, weakness and sensory disturbance in the lumbar plexus distribution, and recent history of poorly controlled diabetes, recent initiation of insulin therapy, and

weight loss.

Lab result was unremarkable except for mild elevation of screen cholesterol and an elevated HgAC to 10% (down from 12% 3 months prior). An MRI of the lumbosacral spine only showed mild disc degeneration, no disc herniation, no foraminal narrowing or central canal stenosis. The normal prothrombin time (PT), partial thromboplastin time (PTT), and international normalized ratio (INR) discard the possibility of a coagulopathy. Examination of the cerebrospinal fluid (CSF) showed no abnormality except for a very mild elevation of protein content. No signs of any infectious process or neoplastic disease were found.

**Table 100.1 Clinical presentation and management of lumbosacral plexopathy (LSP). Case vignettes in tabular form: assorted presentations of LSP. Information from references 2 and 3 contributed to this table.**

Symptoms	Signs	Localization	Etiology
<b>I.</b>			
Pain in the groin or lower iliac fossa (unilateral)	Pain on passive rotation of hip joint  No pain on passive rotation of hip joint. Patient lies with hip flexed  Extension of the knee is weak  Patellar reflex weak or absent  Numbness in inner aspect of ipsilateral leg and foot, and anteromedial thigh	Hip joint  Lumbar plexus lesion (lower part femoral nerve)	Septic arthritis or hemarthrosis of hip joint  Infectious (abcess) stati post  laparotomy/appendecto  Hematoma: Patient receiving anticoagulati therapy and minimal hemophilia. Disseminat intravascular coagulati  Hemophilia, leukemia  Rupture of aneurysm  Localized blunt trauma
<b>II.</b>			

Sport injuries with hip hyperextension and avulsion of the iliacus muscle from the ilium  
Very rarely from injection sites in the buttock in patients with a coagulopathy. Retractor blade injury following renal transplantation or abdominal hysterectomy  
Neoplastic disease unlikely (too localized: involvement of only L4 component of the plexus)

### III.

Difficulty standing straight, difficulty walking up the stairs, difficulty crossing the legs, pain in the buttock, difficulty	Weakness of knee extension Weakness of leg adduction Weakness of foot dorsiflexion and inversion Weakness of foot dorsiflexion Difficulty evertting the foot and ankle Difficulty	→(L2–L3–L4) →(L2–L3–L4) →(L4) →(L5) →S1 →S1 →S1 →S2, S3	Vascular: Aortoiliac vascular disease: aneurysm, stenosis, or post-operative vascular lesion. Ischemic lesion following renal transplant in diabetic patients (mainly leg weakness below the knee and buttock pain)
---	--	--	--

walking  
due to foot  
weakness

performing toe  
walking  
Difficulty  
performing hip  
extension  
Possible clawing of  
toes on inspection  
(if chronic)

#### IV.

Difficulty urinating	Increased urinary frequency and nocturia (rarely occurs because innervation is bilateral and impairment is not symmetric) (in addition) Impairment of superficial anal reflex (in addition) (same as above) Decreased or absent patellar and/or Achilles tendon. Non- uniform decrease of sensation to the thigh, leg, and foot	S2, S3, S4 S2, S3, S4	Neoplastic: direct invasion from primary sites, colorectum, prostate, uterus, ovary, metastatic spread (sarcoma, lymphoma, bronchus, breast, myeloma, testes, thyo melanoma) Post-radiation: usually occurs 5 years after radiation, (painless, bilateral, progressive distal leg weakness) Infectious: most commonly caused by anogenital herpes simp[ or herpes zoster infections. Very rarely localized infections, osteomyelitis, tuberculosis, abcess invading the psoas muscle, appendicitis, pyelonephritis status pc laparotomy with secondary abcess
-------------------------	---	--------------------------	---

#### V

v.

Pain, skin eruption (zoster)	Urinary retention due to sacral involvement (S2, S3, S4)	Infectious: Herpes simplex and zoster are the most common infection
Pain, numbness in perineum, buttocks, and lower extremities	Paresthesia of perineum, buttocks, and posterior thigh with urinary retention, constipation, and erectile impotence, reduced anal tone, meningism (mild)	Acute anogenital herpes simplex: involvement of lumbosacral and sacrococcygeal plexi occasionally Agent: Herpes simplex virus type II

## VI.

Anterior thigh pain and weakness at first in proximal thigh muscles and later in the legs	Asymmetric weakness of thighs and legs at first affecting proximal and later distal muscles  Loss of patellar reflexes, and also Achilles tendon reflex  Sensory deficit affects at first anterior thigh and	Lumbosacral plexus	Diabetic amyotrophy, subacute diabetic proximal neuropathy, or diabetic radiculoplexus neuropathy
---	--	--------------------	---

inner aspect of  
legs, and later  
stocking  
distribution

## VII.

Unilateral severe pain in the anterior thigh (lumbar plexus) or in the buttock or posterior thigh (sacral plexus) As pain is fading, weakness becomes prominent	Various degrees of weakness in all lumbar and sacral innervated muscles Absent patellar and Achilles tendon reflexes Patchy sensory deficit	Lumbar plexus Sacral plexus	Idiopathic lumbosacral plexus neuropathy
--	---	--------------------------------	--

## VIII.

Acute pain with stepwise worsening	Other manifestations of systemic vasculitis (on top of signs of lumbosacral plexus involvement): purpura, arthritis, glomerulonephritis, respiratory tract	Systemic vasculitis
------------------------------------	---	---------------------

granuloma,  
eosinophilia  
associated with  
weight loss and  
elevated ESR

---

CBC, complete blood count; CSF, cerebrospinal fluid; CT, computerized tomography; EMG, electromyography; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; NCS, nerve conduction studies; SEPS, somatosensory evoked potentials.

Nerve conduction studies (NCS) and needle electromyography (EMG) study of the lower extremity was done. The NCS showed decrease in amplitude of the right femoral compound muscle action potential (CMAP) with normal CMAP on the left. In addition, the tibial and peroneal nerve CMAPs were low with slight slowing of conduction velocities, distal latencies, and F wave latencies bilaterally. The sensory nerve action potentials (SNAPs) of the saphenous nerve were absent on the right and normal on the left and low in amplitudes of the sural nerves bilaterally. A needle EMG showed active denervation with early reinnervation in the right quadriceps femoris, iliocostalis, adductor longus, tibialis anterior, and the lumbar paraspinal muscles. Mild chronic reinnervation changes were seen in the flexor digitorum longus, extensor hallucis, and medial head to the gastrocnemius bilaterally. This is consistent with a lumbar radiculoplexopathy (supported by fibrillation potentials in the paraspinal muscles and asymmetrically absent right saphenous SNAP) superimposed on a mild chronic sensorimotor polyneuropathy.

**Table 100.2 Lumbosacral plexopathy (LSP).**

---

<b>Pathology category</b>	<b>Subdivision</b>	<b>Possible clinical features</b>
Pressure effects	Obstetric injuries	Classic presentation with postpartum foot drop. (Please refer to <a href="#">Chapter 27</a> on foot drop.) Compression at pelvic brim causes ankle dorsiflexion and eversion deficits noted after delivery when mother attempts to ambulate.

		Typical recovery within 3 months. Cephalopelvic disproportion a risk factor for LSP or intrapartum entrapment neuropathies
Surgery		Self-retaining retractors on psoas muscles used in some abdominal surgeries such as renal transplant or abdominal hysterectomy or hip surgeries may affect femoral nerve component Lumbar sympathectomy may also cause LSP
Inflammatory	Idiopathic neuritis	Idiopathic LSP. Resembles diabetic proximal neuropathy with unilateral acute anterior thigh pain if lumbar plexus predominates or posterior thigh pain if sacral plexus more involved. Pain resolves as paresis develops. Varying paresis patterns. Recovery over months to years and often not complete
Post-radiation (post-RT)		Radiation dose related. Relevant in treatment of uterine, cervical, ovarian, testicular, or lymphomatous neoplasms. A distinction from recurrence of cancer in the same region is the higher likelihood of initial painless bilateral asymmetric motor deficits with post-RT. May have sphincter dysfunction
Neoplastic		Neoplasms detectable on MRI. Sacrococcygeal plexus vulnerable to invasive local cancers such as from rectum, prostate, uterus, inferior

## kidney

Vascular	Hemorrhage	Retroperitoneal hemorrhage. Look for evidence of coagulopathies, bleeding diathesis, anticoagulant usage Compression of lumbar plexus within the psoas muscle produces deficits relating to femoral nerve. Obturator division involvement causes thigh adductor weakness. Relatively pain free Should distinguish from femoral nerve compression within iliacus muscle associated with groin pain, exacerbated by hip extension. Quadriceps paretic. Depressed patellar reflex. Needs to be distinguished from hip joint pathology. Neuroimaging is vital
	Ischemia	Aortoiliac vasculopathy. Use of internal iliac artery to supply blood flow to the renal transplant grafts. Pelvic pain and buttock and lower extremity musculature affected Episodic ischemic LSP distinguished from cauda equina lesion in that former worsened with walking uphill and has pain and sensory deficits both proximal and distal. Symptoms of cauda equina lesion exacerbated by walking downhill and pain and sensory deficits are mostly distal. Peripheral artery disease is also in the differential diagnosis and loss of pulses should be ascertained Vasotoxic agents introduced into inferior gluteal artery during buttock injection. LSP neurologic deficits and <del>buttock discoloration</del>

#### **Buttock misnomeration**

Aneurysm		Aneurysm of iliac or hypogastric arteries may cause pressure on lumbosacral plexus. Sudden sciatic pain may lead to false conclusion of herniated disc. May be able to palpate pulsatile mass on rectal exam. Aneurysmal hemorrhage as from abdominal aorta requires immediate surgical treatment
Vasculitis		Vasculitis more likely to cause mononeuritis multiplex rather than LSP but painful LSP can occur. More easily diagnosed in context of established inflammatory disorder such as rheumatoid arthritis but vasculitic presentations restricted to LSP may occur
Other	Tissue deposition	Endometriosis involving the LSP or sciatic nerve may induce sciatic neuropathy and catamenial sciatic symptoms including perimenstrual pain in the posterior thigh and buttock
Metabolic	Diabetes mellitus (DM)	Called diabetic amyotrophy, subacute diabetic proximal neuropathy, or diabetic radiculoplexus neuropathy. Males more than often than females. Mostly over age 50. Sudden asymmetric burning pain in the hip, buttock, or thigh. As pain attenuates, proximal weakness develops in quadriceps, hip adductors, and iliopsoas muscles. Proximal lower limb muscle weakness and wasting are characteristic. Minimal sensory loss. Association with DM. type 1 or

		2 in poor control. Patient usually on insulin, and with significant weight loss can lead to profound atrophy of the proximal lower limb muscles
Trauma associated	Motor vehicle accidents	With major pelvic fractures such as with motor vehicle accidents. Often overlooked until it is apparent that lower extremity recovery is delayed. Neurologic deficits tend to persist
Infectious	Abscess	Lower extremity paresis which may be bilateral, assortd sensory deficits and sphincteric dysfunction if coccygeal plexus also involved. Other infectious signs such as fever, and leukocytosis may be present. Other known infections such as lumbar osteomyelitis, pyelonephritis, or appendicitis may be a cause. Very rare in USA
Viral		Herpes zoster affecting the sacrococcygeal plexus may cause paresis and sphincteric problems Herpes simplex type 2 infections are also described

## References

1. Hammerstad JP. Strength and reflexes. In Goetz CG, Ed. *Textbook of Clinical Neurology*, 3rd edn. Philadelphia, PA: Saunders Elsevier, 2007.
2. Lindsay KW, Bone I, Callander R. *Neurology and Neurosurgery Illustrated*, 4th edn. New York, NY: Churchill Livingstone, 2004.
3. Donaghy M, Ed. *Brain's Diseases of the Nervous System*, 12th edn. New York, NY: Oxford University Press, 2009.

# **101 Radiculopathy**

---

Amtul Farheen and Bashar Katirji *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

## **Introduction**

A radiculopathy is a pathologic process affecting the nerve root within the spinal canal. It usually causes pain, paresthesias, and weakness in the distribution of the nerve root (myotomes and dermatome). Radiculopathy may be caused by compressive etiologies at the neural foramina or within the spinal canal (such as spondylosis or disc herniation) or rarely non-compressive processes (infections, infarction, avulsion, infiltration by tumor or granulomatous tissue, or immune-mediated inflammation).

Radiculopathy may occur in any part of the spine, but is most common in the lumbar and cervical regions. Radiculopathies often present with limb pain with sensory manifestations, reflex changes, and weakness. Sometimes they are painless, presenting with sensory manifestations and/or weakness only.

The diagnosis of radiculopathy is based on history and neurologic examination and is supported by diagnostic studies. The electrodiagnostic studies are important in establishing the diagnosis and localizing the location of the lesion. Two criteria are necessary to establish the electrodiagnosis of radiculopathy:

1. Normal sensory nerve action potential (SNAP) of the corresponding dermatome on nerve conduction studies. The lesion in radiculopathy is preganglionic (i.e. within the spinal canal) which results in normal SNAP since it does not interfere with the peripheral axon of the unipolar dorsal root ganglion. In contrast, postganglionic lesions (such as brachial or lumbosacral plexopathy) disrupt the peripheral axon and result in low amplitude or absent SNAP of the corresponding dermatome.
2. Denervation in a segmental myotomal distribution. Fibrillation potentials and/or reinnervation motor unit action potentials and/or reduced recruitment in at

least two muscles innervated by the same root via more than one peripheral nerve, with or without denervation of the paraspinal muscles.

Two provocative bedside tests are useful in the confirmation of radiculopathy:

1. Straight leg raise test: This is a maneuver that causes stretching of the L5 and S1 nerve roots, and also the sciatic nerve and sacral plexus. It is considered positive if the pain is reproduced between 30 and 70 degrees with passive straight leg rising while the patient is supine. A useful and as reliable test is a reverse straight leg raise test. This test stretches the upper lumbar roots (L2, L3, or L4), and also the femoral nerve and lumbar plexus. It is performed by passive hip extension while the patient is prone and is considered positive if pain is reproduced in the groin or anterior thigh.
2. Spurling maneuver: This test is useful in the diagnosis of cervical root compression. During this maneuver, the head is first slightly extended, rotated and laterally flexed, and then compressed downwards. This maneuver produces significant reduction of the surface area and shape of the cervical intervertebral foramina, particularly at the midcervical spine. A positive sign (reproducible radicular pain) is diagnostic of cervical radiculopathy.

[Tables 101.1](#) and [101.2](#) list the clinical features and electrodiagnostics of cervical and lumbosacral radiculopathies.

**Table 101.1 Cervical radiculopathies.**

Root	Pain distribution	Sensory manifestations	Weakness	Reduced reflex(es)	Ob no sen ner act pot
C5	Neck pain radiating to upper arm, shoulder, scapula	Shoulder, upper arm	Shoulder abduction and external rotation, elbow flexion, scapular fixation	Biceps, brachioradialis	No app (no av SN

### TESTS

C6	Neck pain radiating to shoulder, arm, forearm	Thumb, index finger, lateral forearm	Shoulder abduction, elbow flexion, forearm pronation	Biceps, brachioradialis	Medrec thind finlate antner
C7	Neck pain radiating to arm, forearm	Index, middle finger	Elbow extension, wrist extension, forearm pronation	Triceps	Medrec midfin indfin radrec theana snu
C8	Neck pain radiating to medial arm, forearm, hand	Ring, little finger, medial forearm	Long finger extension and flexion, hand grip and finger abduction	Not applicable (no reproducible reflex)	Ultrarecthefinmeantner
T1	Neck pain radiating to axilla, medial arm, anterior chest, and/or axilla	Medial forearm, medial arm, axilla	Thumb abduction (thenar muscles)	Not applicable (no reproducible reflex)	Medcutnerarm

**Table 101.2 Lumbosacral radiculopathies.**

<b>Root</b>	<b>Pain distribution</b>	<b>Sensory manifestations</b>	<b>Weakness</b>	<b>Reduced reflex(es)</b>	<b>Obnor senact pot</b>
L1	Back pain radiating to groin	Inguinal region	Not applicable	Not applicable	Not (no SN)
L2	Back pain radiating to anterior thigh, groin	Anterolateral thigh	Thigh flexion	Not applicable	Not (no SN)
L3	Back pain radiating to groin, anterior thigh, knee	Medial thigh and knee	Thigh flexion and adduction, knee extension	Knee	Not (no SN)
L4	Back pain radiating to buttock, anterior thigh, knee, medial lower leg	Medial lower leg	Knee extension of knee, thigh adduction, ankle dorsiflexion	Knee	Sap
L5	Back pain radiating to buttock, lateral thigh, calf, dorsum foot, great toe	Lateral lower leg, dorsum of foot, great toe	Toe and ankle dorsiflexion, foot eversion and	Not applicable (no reproducible reflex)	Sup per

	or root		inversion, hip abduction		
S1	Back pain radiating to posterior thigh and leg, lateral foot	Lateral two toes, lateral foot and ankle, sole of foot, posterior thigh	Plantar flexion and toe flexion	Ankle	Sur abs del asy low H r

---

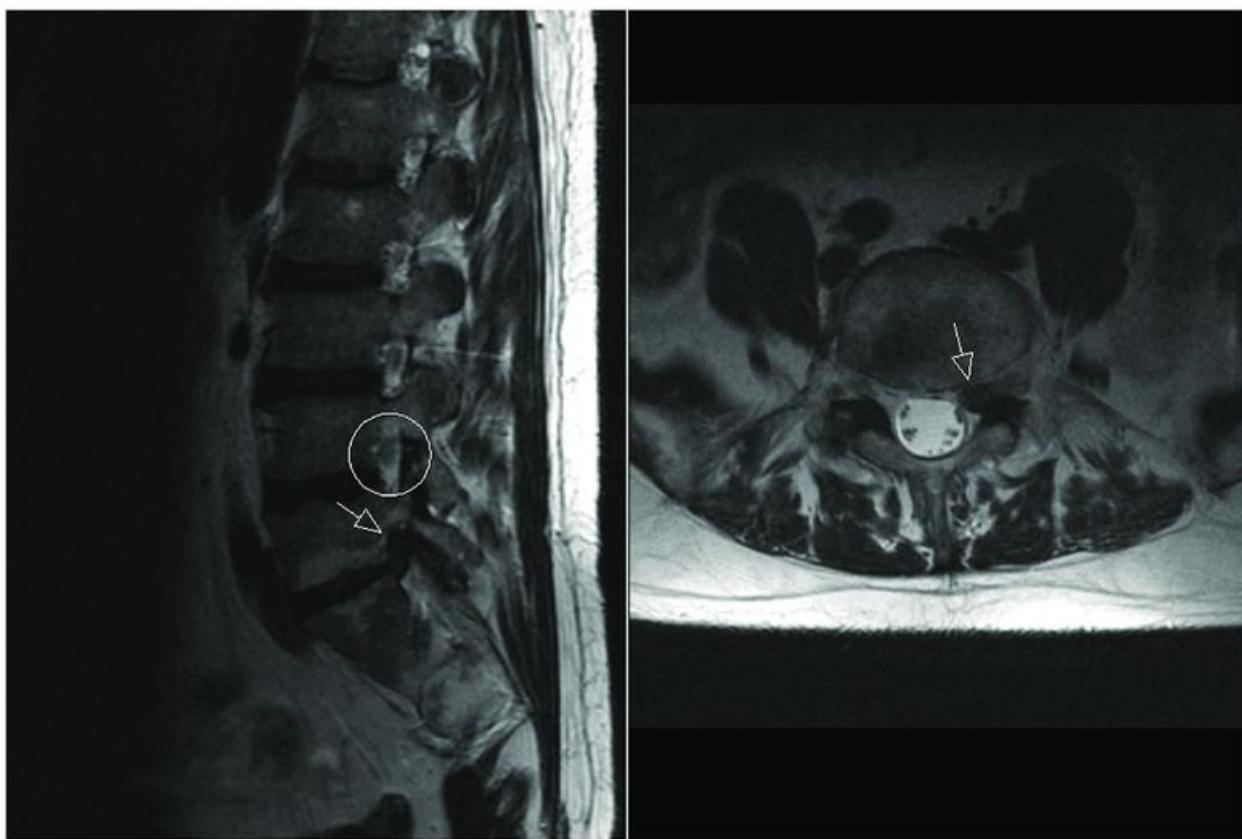
## Case vignette

A 53-year-old man in otherwise good health presented with a 3-week history of severe left buttock pain radiating to posterior thigh, lateral leg, and into the medial foot. He also had numbness predominantly in the left lateral leg and left big toe. A week prior to this, he worked in his garage and carried several heavy objects. He did not recall having back pain or other symptoms during the work. The pain is worse when he stands or walks a short distance. Coughing, sneezing, or Valsalva maneuver does not worsen the pain. He was taking ibuprofen 800 mg 3 times a day without any effect on the intensity of the pain. He had no bladder or bowel symptoms. He was treated with a course of oral steroids for 10 days with no change in symptoms.

On examination, he was in modest distress and walked with an antalgic gait. Straight leg raise was positive at 60 degrees on the left and negative on the right. There was no muscle atrophy or fasciculations. He had slight tenderness in the left buttock. Manual muscle examination revealed weakness of the left ankle dorsiflexion (Medical Research Council scale (MRC) 5-/5), ankle eversion (MRC 5-/5), and great toe extension (MRC 4+/5). Plantar flexion was normal. There was no weakness of hip abduction, flexion, or extension, or knee extension and flexion. His deep tendon reflexes were +2 and symmetric throughout, including the ankle jerks and knee jerks. His plantar responses were both flexors. The sensory examination revealed decreased pin and touch sensation in the left lateral leg and the great toe. Vibration and position senses

were normal.

An electrodiagnostic study showed normal sensory and motor nerve conduction studies (NCS) including left sural and superficial peroneal sensory studies, left peroneal motor and tibial motor studies, and bilateral H-reflexes. Needle EMG revealed fibrillation potentials in the tibialis anterior, tibialis posterior, extensor hallucis longus, tensor fascia lata, and low lumbar paraspinal muscles. Motor unit action potentials were normal in morphology and recruitment. An MRI of the lumbar spine showed a left intraforaminal disc herniation at L5–S1 interspace ([Figure 101.1](#)).



**Figure 101.1** Sagittal and axial T2 weighted images of the lumbar spine showing a left lateral disc herniation at L5–S1 with complete obliteration of the intervertebral foramen at that level (arrows). Note the well visualized roots within the corresponding foramina above L5–S1 (sagittal view), including at L4–L5 (circle).

The patient underwent an epidural block with no effect on pain or weakness. He then underwent a left L5 microlumbar discectomy successfully. He had rapid improvement of pain and his weakness and numbness had resolved when

examined 2 months later.

## Further reading list

- Katirji MB, Agrawal R, Kantra TA. The human cervical myotomes. An anatomical correlation between electromyography and CT/myelography. *Muscle Nerve* 1988; 11:1070–3.
- Katz JN, Harris MB. Clinical practice. Lumbar spinal stenosis. *N Engl J Med* 2008; 358:818–25.
- Levin KH, Maggiano HJ, Wilbourn AJ. Cervical radiculopathies: comparison of surgical and EMG localization of single-root lesions. *Neurology* 1996; 46:1022–5.
- Tsao B. The electrodiagnosis of cervical and lumbosacral radiculopathy. *Neurol Clin* 2007; 25:473–94.
- Tsao BE, Levin KH, Bodner RA. Comparison of surgical and electrodiagnostic findings in single root lumbosacral radiculopathies. *Muscle Nerve* 2003; 27:60–4.
- Wilbourn AJ, Aminoff MJ. The electrodiagnostic examination in patients with radiculopathies. *Muscle Nerve* 1998; 21:1612–31.
- Yoss RE, Corbin KB, MacCarty CS, Love JG. Significance of symptoms and signs in localization of involved root in cervical disk protrusion. *Neurology* 1957; 7:673–83.

## 102 Sixth nerve palsy

---

Scott Uretsky *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

The sixth (VI, abducens) cranial nerve innervates the lateral rectus muscle and is responsible for abduction of the eye. Palsy of the abducens nerve causes an incomitant ocular misalignment manifesting most commonly with diplopia. It is the most common of the isolated ocular motor palsies [1,2]. The abducens nucleus serves as the ipsilateral horizontal gaze center and thus nuclear lesions cause ipsilateral gaze palsy and not pure unilateral abduction deficits. When the ipsilateral medial longitudinal fasciculus (MLF) is involved the one-and-a-half syndrome results. The nucleus contains large motor neurons innervating the ipsilateral lateral rectus and smaller interneurons that ascend in the MLF to innervate the contralateral medial rectus sub-nucleus of the third nerve nucleus.

### Anatomic considerations

Precise knowledge of the course of the sixth nerve and the structures it keeps company with at various locations frequently allows localization of the pathologic process in non-isolated sixth nerve palsies.

The abducens nucleus is located in the lower pons, separated from the floor of the fourth ventricle by the genu of the facial nerve, in proximity to the vestibular nuclei and the MLF. The sixth nerve exits the brainstem anterolaterally at the pontomedullary junction, medial to the exit of the seventh and eighth cranial nerves.

The nerve enters the subarachnoid space and ascends in the prepontine cistern and along the clivus. It travels over the petrous apex, beneath the petroclinoid ligament, through Dorello's canal entering into the substance of the cavernous sinus. Here it is the cranial nerve closest to the internal carotid artery. The third,

fourth, and first two divisions of the fifth cranial nerves travel in the lateral wall of the cavernous sinus. The postganglionic oculosympathetics travel on the carotid artery but briefly join the sixth nerve, accounting for reports of sixth nerve paresis and Horner's syndrome associated with cavernous sinus lesions. The sixth nerve, along with the third and fourth nerves, then enters the orbit through the superior orbital fissure.

The trigeminal or fifth cranial nerve course is also useful in localization. The first division exits the intracranial cavity through the superior orbital fissure along with the third, fourth, and sixth cranial nerves. The second division exits the skull base at the level of the cavernous sinus. The third division exits the skull base prior to entry into the cavernous sinus.

The long course of the sixth nerve makes it susceptible to pathologic processes of various kinds. Elevated intracranial pressure as a cause of sixth nerve paresis is known as a false localizing sign. Its course through the subarachnoid space makes it vulnerable to pathologic processes involving the cerebrospinal fluid (CSF) and meninges. Given the proximity of the sixth nerve to other structures in the brainstem, lesions here rarely cause isolated sixth nerve palsy. Syndromes of the cavernous sinus, superior orbital fissure, and the orbit typically, but not always, are accompanied by additional symptoms or signs, allowing localization of pathology to these structures.

## Symptoms

Patients with a sixth nerve palsy typically complain of diplopia, the awareness of seeing the same object located at different places in visual space. Patients may alternatively describe a vague visual difficulty when attempting a saccade in the direction of action of the palsied lateral rectus. Others may describe blurred vision if the images are close or there is intermittent fusion of images. Some patients may not report diplopia because of poor visual clarity, suppression of images from the non-fixating eye, or misinterpretation or lack of appreciation of the sensory experience.

The initial consideration is to determine if the diplopia is binocular (resolves with cover of either eye). The orientation of the doubled images (vertical, horizontal, or oblique) and the gaze in which it is worse, along with the motility exam, help determine the ocular muscles and cranial nerves involved. Monocular diplopia of neurologic origin is rare.

Assess for a past history of childhood strabismus (patching), ocular surgery,

ischemic risk factors, neoplastic history, and other systemic, neurologic, and ophthalmic diseases. Are there symptoms of elevated intracranial pressure (ICP: headache, transient visual obscurations, loss of vision, pulsatile tinnitus, nausea), or myasthenia gravis (dysphagia, dysarthria, ptosis, fatigable weakness, shortness of breath, diurnal variation)? Inquire about orbital symptoms (periocular pain, erythema, lid edema, proptosis) and thyroid-related diseases. Is pain or headache involved (e.g. orbital inflammatory syndromes, giant cell arteritis)? Finally, are there other neurologic symptoms (dysphagia, dysarthria, motor, gait or balance dysfunction, limb ataxia, vertigo, sensory loss, etc.)?

## **Examination: the motility exam**

The hallmark of an isolated, unilateral sixth nerve palsy is an abduction deficit of one eye, even partially, in attempted lateral gaze. This causes an esodeviation of the eyes that is worst when the patient looks in the direction of action of the palsied sixth nerve.

Assess abduction, adduction, depression, and elevation of each globe. Ensure no concomitant third or fourth nerve involvement. Is the motility dysfunction from a restrictive process? Forced ductions may be used to confirm this. Ensure there is no gaze palsy indicating a more centrally located process. Assess saccades, as this may highlight a gaze palsy, the adduction lag of an internuclear ophthalmoplegia, or other subtle ocular motility abnormality. If diplopia resolves with pin-hole the cause is refractive aberrations. Comitant phorias can decompensate causing intermittent diplopia. In these cases the exam shows relatively small-angle, comitant deviations. Symptoms resolve with and are treated by prisms.

## **Examination: signs to assess**

Rule out additional cranial neuropathies. Perform a visual examination: acuity, confrontational visual fields, and afferent pupillary defect. Every patient with a sixth nerve palsy should have a fundoscopic exam for papilledema. Check for ptosis (including fatigable ptosis), lid lag and retraction, neck and orbicularis oculi weakness. Assess for orbital signs: proptosis, conjunctival erythema, arteriolarization of scleral vessels, and chemosis. Check the pupils for anisocoria, particularly a Horner's (sympathetic) syndrome or third nerve (parasympathetic) involvement. Finally assess for other neurologic signs: focal motor weakness or sensory change, limb or gait ataxia, nystagmus, etc.

## Differential diagnosis and evaluation

We will focus on isolated sixth nerve palsies; diagnostic criteria have been proposed [3]. Multiple cranial neuropathies and patients presenting with multiple neurologic symptoms and signs require neuroimaging and in many cases CSF analysis; this is beyond the scope of this chapter.

The most common causes for sixth nerve palsies are microvascular ischemia (the most common cause [1]), trauma, elevated ICP, and neoplastic and compressive etiologies (e.g. metastatic disease, skull base, cavernous sinus, orbital and pituitary fossa tumors). Myasthenia gravis and restrictive myopathies (e.g. thyroid ophthalmopathy) can mimic a sixth nerve palsy. Additional considerations include: temporal arteritis, multiple sclerosis, Lyme disease, sarcoid, migraine, meningitis, and aneurysm. In the pediatric population consider acute otitis media, Möbius syndrome, and Duane's retraction syndrome. Iatrogenic cases after neurosurgery, spinal anesthesia, and myelography are reported.

The initial consideration is the patient's age and ischemic risk factors. Those less than 14 years of age may have benign sixth nerve palsy (~13%) [4]. However in the pediatric population the most common causes are tumors (~40%) [4], trauma, and elevated ICP. Thus the recommendation is to obtain neuroimaging, preferably with magnetic resonance imaging (MRI). If the imaging is negative, decision for subsequent lumbar puncture can be made on a case-by-case basis. The patient should be followed closely.

In those 15 to approximately 50 years of age neuroimaging should be obtained with contrast [5] and ischemic risk factors screened for (e.g. hypertension, diabetes mellitus) [3]. Common causes include mass lesion and demyelination [6]. Blood work should include anti-acetylcholine receptor antibodies (binding and blocking), Lyme titers, antinuclear antibody (ANA), angiotensin-converting enzyme (ACE) level, fasting lipid profile, HgbA1c, and/or 2-hour glucose tolerance test and syphilis serology. If these are negative, CSF analysis is appropriate including opening pressure. In addition to routine CSF studies, include cytology, studies for multiple sclerosis, ACE level, and Lyme testing.

In patients older than ~50 years and in those with ischemic risk factors, isolated sixth nerve palsies are most commonly due to microvascular ischemia [1]. Neuroimaging is not required at initial evaluation, although it is my practice to obtain imaging in the setting of neoplastic history. Imaging should be obtained in cases of non-resolution by 4–6 months and for progression of

symptoms and signs. Assess for the presence of arteritic symptoms and if suspicious obtain erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and complete blood count (CBC). Anti-acetylcholine receptor antibodies should be checked. If negative, in the presence of clinical suspicion for myasthenia, edrophonium testing or electrophysiology (repetitive stimulation and single-fiber EMG) can be obtained. Treatment of microvascular ischemic VI nerve palsies includes patching for symptomatic relief and risk-factor management. Prognosis for spontaneous recovery is very good [2,7].

In general, orbital signs on exam should prompt dedicated orbital imaging with CT or MRI. At any age, bilateral sixth nerve palsies require neuroimaging as microvascular ischemic disease is not the etiology. If imaging is negative, lumbar puncture is warranted, including opening pressure. Laboratory studies are as noted above. Chest X-ray and/or CT of the chest, abdomen, and pelvis to assess for adenopathy (sarcoid) and occult malignancy should be obtained.

Differential diagnosis is listed in [Table 102.1](#).

## Case vignette 1

A 17-year-old male was referred for acute onset of double vision that was binocular and horizontal in orientation. The patient initially denied any precipitating factors. Review of systems was negative for systemic, neurologic, and other visual symptoms. Exam revealed visual acuity of 20/20 OU, full color vision, and no afferent pupillary defect. The eyelid, orbital, and slit lamp exams were normal. Motility exam ([Figure 102.1](#)) revealed an esodeviation worse on left gaze and a left abduction deficit. A dilated fundus exam revealed mild bilateral optic disc edema *i.e.* papilledema ([Figure 102.2](#)). The remainder of the neurologic exam was normal.

**Table 102.1 Differential diagnosis of sixth nerve palsy.**

Etiology	Evaluation	Treatment	Clinical pearls
Microvascular ischemia, Vasculopathic Risk factors: diabetes (most)	Determine status of current risk factors and assess appropriately for others	Observation, typically with excellent prognosis for full recovery	Patients may complain of periocular or retrobulbar pain. Typically ful

<p>proven and common risk factor [2]), hypertension, hyperlipidemia, tobacco use, obstructive sleep apnea</p> <p>Typically patients &gt;~50 years old and/or with noted risk factors</p>	<p>Assess review of systems for giant cell arteritis → if over 55 years check ESR, CRP, and CBC/platelets [3]</p> <p>Neoplastic history warrants neuroimaging (MRI) [5]</p> <p>Always consider myasthenia gravis: Evaluate with anti-acetylcholine receptor antibodies → edrophonium test or repetitive stimulation/single fiber EMG if high suspicion and negative antibodies</p> <p>Additional considerations: Lyme disease, sarcoid, syphilis</p> <p>In patients &gt; 50 years with ischemic risk factors it is reasonable to observe without imaging in purely isolated cases → pursue imaging for non-</p>	<p>[1,7]</p> <p>Patching to alleviate symptomatic double vision</p> <p>Incomplete recovery: prisms, botulinum toxin injection, strabismus surgery (motility exam must be stable at least 6 months) [7]</p>	<p>resolution in 6 months [2, Giant cell/temporal arteritis: Review of systems → headache, scalp tenderness, jaw claudication, fever, rash, sweats, myalgia, arthralgia, appetite and weight loss Clinical suspicion (+/− review of systems, +/− inflammatory markers) → place on corticosteroids and obtain temporal artery biopsy</p> <p>Indicators of recovery not clearly identified → control of underlying ischemic risk factors likely helpful</p> <p>For incomplete resolution or progression obtain</p>
--	---	--	--

	improvement or progression [2,3,5]	additional lab work-up (see text), neuroimaging and consider lumbar puncture (with opening pressure)
Demyelination Multiple sclerosis (MS)	Obtain MRI to assess for new causative lesion → use gadolinium (absent contraindications) to assess, for enhancement (active inflammation)	Pulse intravenous corticosteroids, followed by quick oral taper
Traumatic	CT orbits, paranasal sinuses, and brain without contrast, include bone windows & coronal & sagittal planes	Isolated sixth nerve palsy at the presentation sign of MS is unusual but is reported → Consider follow-up MRI for surveillance of new demyelinating lesions
	Observation, surgery for operative indications (unusual in isolated palsy) Patching to alleviate symptoms Incomplete recovery: prisms, botulinum toxin injection, strabismus	Spontaneous resolution reported in 173% at 6 months [8] Inability to abduct past the midline at presentation associated with non-recovery 6 months [3]

		surgery (motility exam must be stable at least 6 months) [7]	
Vascular Ischemic & hemorrhagic stroke, cavernous malformation, aneurysmal or dolichoectatic compression, cavernous sinus thrombosis, cavernous–carotid fistula, carotid arterial dissection	CT and MRI of the brain Multimodal vascular imaging may be used including: MR- and CT-based angiogram and venogram, catheter-based cerebral angiography	Dependent on causative pathology	Aneurysmal isolated sixth nerve palsy is rare → initial evaluation should not be focused on aneurysmal causes [3] Use of diagnostic cerebral angiography rare in isolated sixth nerve palsy
Infectious Herpes zoster ophthalmicus, meningitis, tuberculosis, Lyme disease, <i>Listeria</i> <i>monocytogenes</i> meningoencephalitis, meningitis (bacterial, viral, spirochetal, or neoplastic)	Neuroimaging as appropriate followed by lumbar puncture (LP)	Treatment of underlying infection	In acquired immune deficiency syndrome (AIDS): <i>Mycobacteri</i> <i>Cryptococcu</i> <i>Toxoplasma</i> <i>gondii</i> , cytomegalovirus and herpes simplex virus
Inflammatory Idiopathic orbital inflammatory	Laboratory: ESR, CRP, CBC, ANA, Anti-	Treatment of the underlying condition	Typically has good prognosis for partial to

disease, Tolosa–Hunt syndrome, sarcoid, Wegener's granulomatosis, mastoiditis (Gradenigo's syndrome), Miller–Fisher syndrome, systemic lupus erythematosus, idiopathic hypertrophic cranial pachymeningitis	dsDNA Ab, RF, C-ANCA, P-ANCA, ACE, Anti GQ1B Ab Sarcoid: CXR and/or CT chest to r/o hilar and mediastinal lymphadenopathy Consider gallium scan for high suspicion of sarcoid to assess for biopsy amenable lesion	Typically initial pulse intravenous corticosteroids Steroid-sparing immune suppression is dependent on etiology, response to initial therapy, relapse, and recurrence	complete recovery with control of underlying etiology [1]
Neoplastic, infiltrative, compressive Meningioma, schwannoma, cerebellopontine angle masses, neurofibroma, lymphoma, pituitary adenoma and other parasellar masses, metastatic carcinoma, invasive nasopharyngeal carcinoma, chordoma, brainstem glioma	Neuroimaging, CSF for cytology and flow cytometry, consider biopsy if lesion is anatomically approachable Evaluate for primary neoplastic disease if metastatic lesion is suspected	Surgical resection, chemotherapy and/or radiotherapy, depending on the pathology and location of disease Patching for symptomatic relief Incomplete recovery: prisms, botulinum toxin injection, strabismus surgery (motility exam must be stable at least 6 months) [7]	Imaging should be with special attention to the palsied sixth nerve, with focus on the cavernous sinus where a small lesion can be overlooked [7] Abducens nerve palsy after minimal head trauma suggests a compressive lesion

<p>Idiopathic (negative evaluation)</p> <p>In children &lt; 14 years consider benign sixth nerve palsy</p> <p>Idiopathic intracranial hypertension (IIH) (pseudotumor cerebri)</p>	<p>Neuroimaging and additional work-up as per text:</p> <p>IIH criteria: negative imaging (MRI and MRV), elevated opening pressure on LP in lateral decubitus position, and normal CSF labs, no other causative or precipitating etiology</p> <p>In adults consider obstructive sleep apnea as ischemic etiology</p> <p>Repeat imaging in 6–12 months and for any progression [3]</p>	<p>Observation, patching for symptomatic relief</p> <p>Incomplete recovery: prisms, botulinum toxin injection, and strabismus surgery (motility exam must be stable at least 6 months) [7]</p>	<p>Benign sixth nerve palsy childhood: 5–16% of patients, may recur [4]</p> <p>May follow viral illness, fever, or vaccination</p> <p>Intracranial hypotension cause unilate or bilateral sixth nerve palsy - can occur post LP, spinal anesthesia, myelography CSF shunting procedure or spontaneously</p>
<p>Congenital birth trauma, cerebral palsy, Möbius syndrome (congenital bulbar palsy), Duane's retraction syndrome</p>	<p>Möbius syndrome: facial diplegia with absent abduction or absent horizontal gaze bilaterally</p> <p>Duane's retraction syndrome: marked limitation of abduction, variable</p>	<p>In isolation birth trauma is suspected and spontaneous resolution is typical</p> <p>With occurrence in congenital disorders and syndromes management is a component</p>	<p>Congenital isolated absence of abduction rarely occurs</p> <p>Duane's retraction syndrome: May show absence or hypoplasia of the abducens nerve</p>

limitation of adduction, palpebral fissure narrowing and globe retraction on attempted adduction of the syndrome management

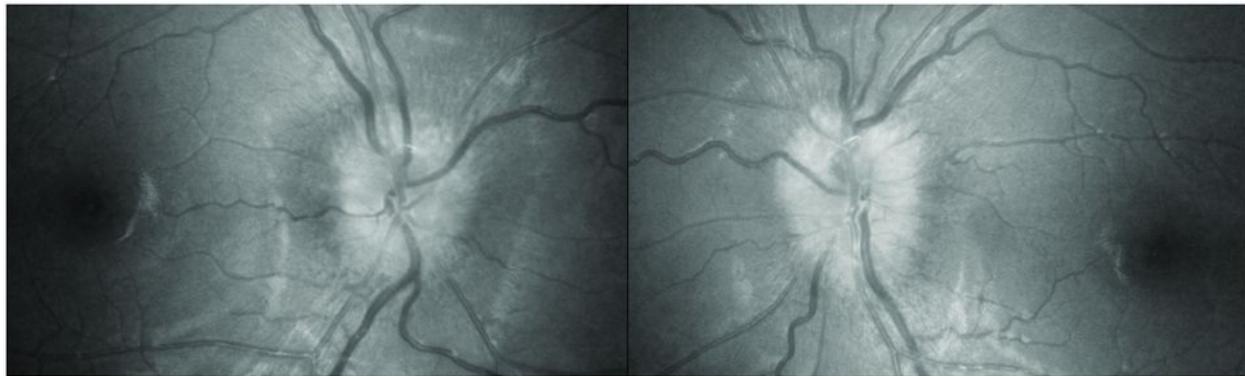
---

ACE, angiotensin-converting enzyme; ANA, antinuclear antibody; ANCA, anti-neutrophil cytoplasmic antibodies; anti-dsDNA Ab, anti-double stranded DNA antibody; C-ANCA, cytoplasmic anti-neutrophil cytoplasmic antibodies; CBC, complete blood count; CRP, C-reactive protein; CSF, cerebrospinal fluid; CT, computerized tomography; CXR, chest X-ray; EMG, electromyography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; P-ANCA, perinuclear anti-neutrophil cytoplasmic antibodies; RF, rheumatoid factor



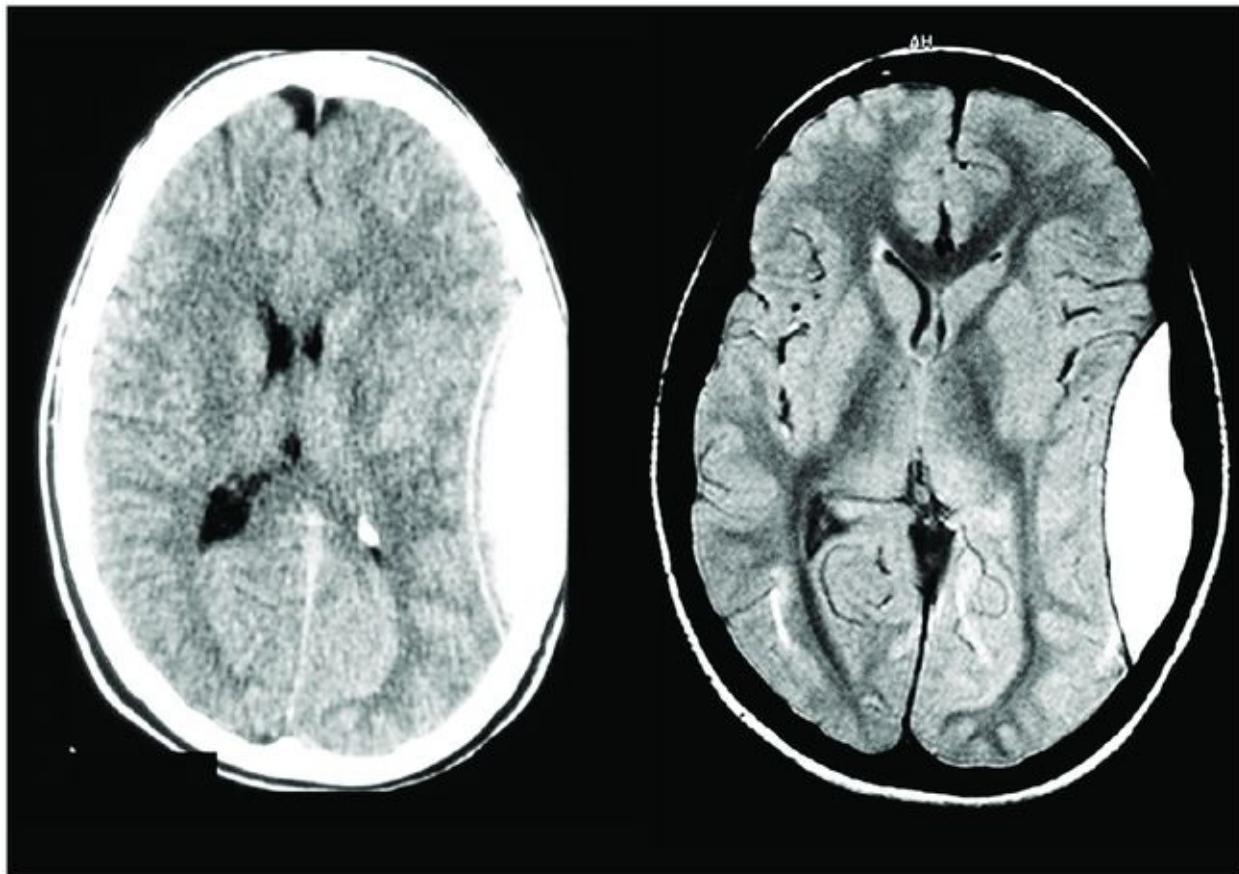
**Figure 102.1** Motility exam of a 17-year-old male with a complaint of binocular, horizontal diplopia. In primary gaze an esodeviation is noted. Elevation, depression, and adduction of both globes are full, as in abduction on

the right. There is a left abduction deficit.



**Figure 102.2** Fundoscopic exam of a 17-year-old male presenting with diplopia revealing papilledema with mild swelling and elevation of the optic nerves bilaterally without hemorrhages.

The findings of a sixth nerve palsy and papilledema should raise suspicion for elevated ICP, prompting urgent neuroimaging. Further questioning revealed that the patient was kicked in the head 1 week ago; CT and MRI were obtained ([Figure 102.3](#)). An epidural hematoma was found with mass effect and midline shift. Neurosurgical evacuation was performed. On follow-up the diplopia, abduction deficit, and papilledema had completely resolved.



**Figure 102.3** Axial computerized tomography (left) and axial fluid attenuated inversion recovery magnetic resonance imaging (FLAIR MRI) (right) of a 17-year-old male with mild papilledema and a left sixth nerve palsy, revealing a left-sided epidural hematoma with mass effect and midline shift, without hydrocephalus.

## Case vignette 2

A 63-year-old female was referred for vague visual complaints of blurred vision on right gaze. This followed 1 week of constant, binocular, horizontally oriented diplopia. History and review of systems were not consistent with myasthenia or giant cell arteritis. Past medical history included hypertension, hyperlipidemia, and poorly controlled diabetes with recent HgbA1c of ~10.

Examination revealed visual acuity of 20/20 OU, full color vision, normal pupil reactions, normal intraocular pressure, no orbital signs, and normal lid and slit lamp exam. Fundoscopic exam revealed normal-appearing optic nerves bilaterally and findings consistent with diabetic retinopathy. Motility showed an abduction deficit of the right eye. Alignment testing revealed a 25 diopter

esotropia in primary gaze, decreasing to 16 diopters on left gaze and increasing to 30 diopters on right gaze. These finding were consistent with a right sixth nerve palsy. The remainder of the cranial nerve and neurologic exam was normal.

Evaluation revealed negative anti-acetylcholine receptor antibodies and normal CBC, ESR, and CRP. Given the isolated sixth nerve palsy in the presence of appropriate risk factors (most notably uncontrolled diabetes) the patient was referred to an endocrinologist and was observed neuro-ophthalmic-wise. At 2-month follow-up symptoms had completely resolved and the right eye had regained full abduction. Alignment testing at follow-up revealed a 1 diopter esodeviation in primary and right gaze with no misalignment on left gaze, indicating essentially complete recovery. This is consistent with the generally good prognosis for complete recovery of ocular motor palsy from microvascular ischemia [2,7]. Ischemic risk factor management was encouraged.

## References

1. Park UC, Kim SJ, Hwang JM *et al*. Clinical features and natural history of isolated third, fourth and sixth cranial nerve palsy. *Eye* 2008; 22:691–6.
2. Chi SL, Bhatti MT. The diagnostic dilemma of neuroimaging in acute isolated sixth nerve palsy. *Curr Opin Ophthalmol* 2009; 20:423–9.
3. Brazis PW. Isolated palsies of cranial nerves III, IV, and VI. *Semin Neurol* 2009; 29:14–28.
4. Mahoney NR, Liu GT. Benign recurrent sixth (abducens) nerve palsy in children. *Arch Dis Child* 2009; 94:394–6.
5. Murchison AP, Gilbert ME, Savino PJ. Neuroimaging and acute ocular motor mononeuropathies. *Arch Ophthalmol* 2011; 129:301–5.
6. Peters III GB, Bakri SJ, Krohel GB. Cause and prognosis of nontraumatic sixth nerve palsy in young adults. *Ophthalmology* 2002; 109:1925–8.
7. Sanders SK, Kawasaki A, Purvin VA. Long-term prognosis in patients with vasculopathic sixth nerve palsy. *Am J Ophthalmol* 2002; 134:81–4.
8. Mutyala S, Holmes JM, Hodge DO *et al*. Spontaneous recovery rate in traumatic sixth nerve palsy. *Am J Ophthalmol* 1996; 12:898–9.

## 103 Third nerve palsy

---

Claire A. Sheldon and Jason J. S. Barton *Neurologic Differential Diagnosis*, ed. Alan B. Ettinger and Deborah M. Weisbrot. Published by Cambridge University Press. © Cambridge University Press 2014.

### Introduction

The oculomotor nerve (cranial nerve III) innervates the superior rectus, medial rectus, inferior rectus, and inferior oblique extraocular muscles, as well as the levator palpebrae superioris. Thus, it controls elevation, depression, adduction, and excyclotorsion of the globe, as well as elevation of the eyelid. It also innervates two internal ocular muscles (muscles within the globe): the ciliary muscles that generate accommodation, the ability to focus clearly at near distance, and the pupillary sphincter, which constricts the pupil.

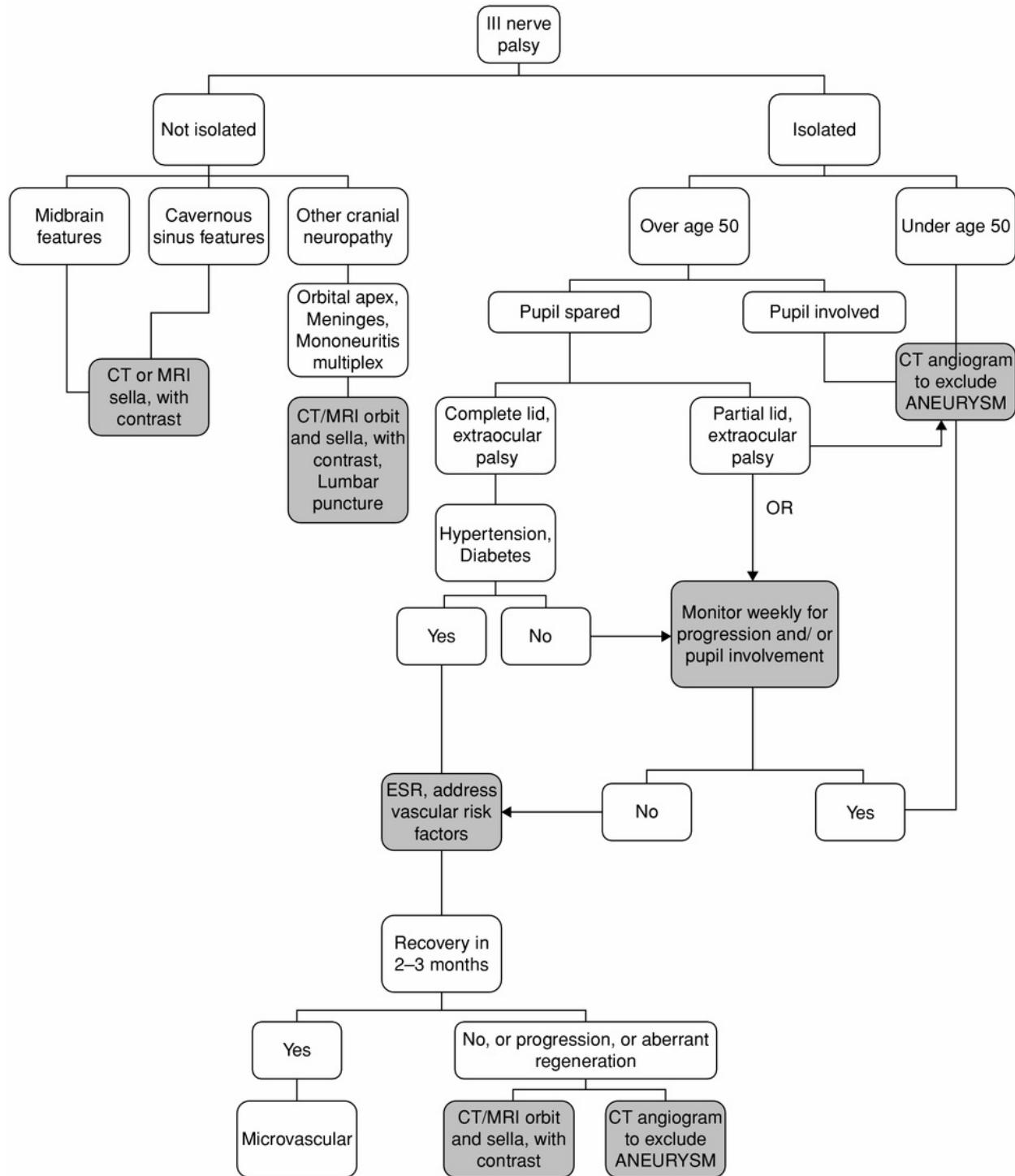
Knowledge of the anatomic location and organization of the oculomotor nuclear complex and the trajectory of the oculomotor nerve through the midbrain, subarachnoid space, cavernous sinus, and, ultimately, the orbit is critical to localizing pathology. The oculomotor nuclear complex is in the midbrain, near the Sylvian aqueduct. It has six subnuclei. In the most caudal and dorsal location is the central caudate nucleus, a single structure that controls both right and left levators of the eyelid. In the most rostral and dorsal location is the Edinger-Westphal nucleus, also a single structure that innervates the pupillary sphincter and ciliary muscles of both eyes. Ventral to these two are the paired subnuclei for the four extraocular muscles that move the eye. All innervate the ipsilateral eye with the exception of the superior rectus, which projects to the contralateral eye.

The fascicle of the oculomotor nerve then passes forward through the midbrain close to the decussation of the superior cerebellar peduncles, the red nucleus, and the cerebral peduncle. The oculomotor nerve exits the midbrain in the inter-peduncular fossa, sandwiched between the superior cerebellar and posterior cerebral arteries. It then travels in the subarachnoid space alongside the posterior communicating artery: at this point the pupillomotor fibers are located

on the periphery of the nerve, vulnerable to compression from posterior communicating artery aneurysms. The oculomotor nerve pierces the dura to enter the cavernous sinus. As it reaches the end of the sinus, it divides into a superior division, which innervates the superior rectus and levator palpebrae superioris, and an inferior division, which innervates the rest of the muscles. Both branches enter the orbit through the superior orbital foramen, through the annulus of Zinn.

Symptoms of an oculomotor palsy include diplopia, ptosis, a dilated pupil, and blurred near vision. Partial palsies are common, and thus not all patients will have all of these symptoms. The diplopia is binocular and may have tilt, horizontal, and/or vertical components, depending on how many muscles are involved in the palsy. The signs include ptosis, sometimes complete, sometimes partial; anisocoria, with the affected pupil larger, and the difference between the pupils greatest in bright light; and ocular misalignment, which in a complete palsy is characterized by the affected eye pointing “down and out.” The signs and symptoms may progress, depending on etiology.

A step-wise approach should be taken when evaluating patients with oculomotor nerve palsies (see [Table 103.1](#) and [Figure 103.1](#)) [1]. On history, enquire about preceding trauma, headache, and constitutional symptoms such as fever and weight loss. On examination, first look for the different features of oculomotor nerve palsy, to decide if the palsy is complete or partial. If partial, determine whether the pattern fits with damage limited to either the superior or inferior division: this should first point to the cavernous sinus, though a midbrain fascicular palsy can less commonly mimic this. Second, determine if other cranial nerves are involved: the causes of multiple ocular motor palsies, bilateral palsies, and multiple cranial neuropathies are very different from a unilateral isolated III nerve palsy. To examine for concomitant IV nerve palsy, place the affected eye in abduction and then have the patient look down: the eye should intort if the superior oblique is still working ([Figure 103.3](#)). Third, perform a neurologic exam looking for other signs of midbrain damage, such as ataxia, tremor, and spastic weakness of the limb contralateral to the affected eye.



**Figure 103.1** Clinical step-wise approach to oculomotor nerve palsies. CT, computerized tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging.

**Table 103.1 Anatomical classification of oculomotor nerve palsies.**

Location	Signs of that localization	Etiology	Comment	S in
Oculomotor nerve nucleus	<p>Unilateral third nerve palsy with bilateral ptosis and/or bilateral elevation palsy</p> <p>Bilateral oculomotor nerve palsies without ptosis</p>	<p>Most common: ischemic stroke (branches of the basilar artery)</p> <p>Less common: midbrain hemorrhage, tumor, inflammation, compression</p>	<p>Features that <i>may</i> suggest a III nuclear palsy:</p> <ul style="list-style-type: none"> <li>Isolated bilateral weakness of levator, superior rectus, or pupil constriction</li> <li>Features that <i>exclude</i> a nuclear site for third nerve palsy:</li> <ul style="list-style-type: none"> <li>Unilateral ptosis</li> <li>Unilateral elevator palsy</li> <li>Unilateral mydriasis</li> </ul> </ul>	C bi co  L pi m sy pi
Oculomotor nerve fascicle	<p>May be isolated or with neurologic signs:</p> <ol style="list-style-type: none"> <li>1. Cerebellar ataxia</li> <li>2. Tremor</li> <li>3. Contralateral hemiparesis</li> </ol>	<p>Same as III nuclear lesions above, as well as multiple sclerosis rarely</p>		C bi co
Oculomotor nerve	Normal pupil with complete	Pupil-sparing oculomotor	Oculomotor nerve palsies	E bl

through subarachnoid space	external ophthalmoplegia	nerve palsy with <i>complete</i> ophthalmoplegia: most common cause is microvascular occlusion [2]	caused by microvascular occlusion display mild (< 1 mm) anisocoria in up to 38% of cases [10]	p di va m E W hi h o fc m o] fæ s€ sc p ne W cl o h o ei ne (s ol w s€ [1]
Normal pupil with incomplete external ophthalmoplegia	Microvascular or compression	Intracranial, posterior communicating artery aneurysms may present with <i>pupil-</i> <i>sparing,</i> <i>incomplete</i>	C ai ne p co lu p A re	

oculomotor  
nerve palsy in  
14% of cases

[11]

Pupil-involving  
oculomotor  
nerve palsy

Microvascular or  
compression

C  
ai  
n  
p  
c  
lu  
p  
A  
re  
m  
fc  
e

Oculomotor  
nerve  
through  
cavernous  
sinus

Ipsilateral  
paralysis of III,  
possibly with:  
IV, VI, or V1,  
V2 involvement  
Small fixed  
pupil from  
additional  
Horner's  
syndrome  
Lid edema,  
proptosis, or  
chemosis  
Superior  
division palsy  
Inferior division  
palsy

Three most  
common:  
Neoplasm  
(meningioma)  
Vascular lesion  
(giant aneurysm,  
arteriovenous  
fistula, or venous  
thrombosis)  
Inflammation  
(infection,  
Tolosa–Hunt)

C  
o  
se  
co

Oculomotor  
nerve within  
orbital apex

Ipsilateral  
paralysis of III,  
IV, VI, V1, or

Five most  
common:  
Neoplasm

Only  
involvement of  
the orbital apex

C  
o  
se

optic neuropathy	Inflammation	can have optic nerve and oculomotor nerve involvement
Superior division palsy	Infection (e.g. fungal)	
Inferior division palsy	Mucocele	
Lid edema, proptosis, or chemosis	Trauma	

---

CRP, C-reactive protein; CT, computerized tomography; ESR, erythrocyte sedimentation rate; MRI, magnetic resonance imaging.

If the oculomotor palsy is sudden and isolated and does not fit a divisional palsy, it should be classified into one of three clinical patterns: (i) complete external ophthalmoplegia with normal pupil constriction, (ii) incomplete external ophthalmoplegia with normal pupil constriction, and (iii) complete or partial external ophthalmoplegia and impaired pupil constriction [2]. The “pupil rule” states that an isolated, atraumatic oculomotor nerve palsy with complete external ophthalmoplegia and normal pupillary involvement has a greater than 90% probability of being secondary to microvascular ischemia, usually in the setting of age, diabetes, or hypertension, and is almost never due to compression by an aneurysm of the posterior communicating artery [2]. Thus, with a clear history of diabetes or hypertension, patients can be followed at least monthly, without imaging. Without this history, patients should be assessed for diabetes and hypertension, or less common vasculitic risk factors, and can then be followed closely. In both cases, if symptoms change or the pupil does become involved, imaging is required. In the second clinical pattern, the case of an isolated, incomplete, pupil-sparing oculomotor nerve palsy, the option exists to either arrange neuroimaging or to follow closely (i.e. weekly) for progression or involvement of the pupil and, if seen, to then arrange urgent neuroimaging. Finally, the clinical pattern of a complete or partial external ophthalmoplegia and impaired pupil constriction requires urgent imaging. It is important to note that neither the presence or absence of pain nor the extent of ophthalmoplegia adequately distinguishes microvascular or compressive oculomotor nerve palsies in this last scenario [3]. Furthermore, as mentioned, a story of progressive worsening mandates imaging regardless of the status of the pupil.

Adequate neurovascular imaging, read by trained radiologists [4], is directed primarily at urgently excluding aneurysmal compression of the oculomotor nerve, though in progressive or more chronic palsies, compression by other lesions such as tumours needs to be addressed with imaging of the sella and midbrain. Most aneurysms causing isolated oculomotor nerve palsies are  $\geq$  4 mm and a CT angiogram can detect 97% of these intracranial aneurysms [5,6]. Magnetic resonance angiography (MRA) is a reasonable alternative when a CT angiogram is contraindicated; however, its ability to detect small aneurysms may be limited [6]. Few patients these days require formal angiography with its associated risk of iatrogenic stroke. Twenty percent of posterior communicating aneurysms present with isolated oculomotor nerve palsies prior to rupture [7]. The need for urgent neuroimaging is due to the fact that with surgical treatment of unruptured aneurysms, rates of adverse events are about 10% [7], while patients with ruptured intracranial aneurysms have mortality rates over 25% [8].

The time course and extent of recovery from oculomotor nerve palsy varies with etiology and severity. Microvascular palsies tend to recover completely in most, over 2–4 months. Unless diagnosed and managed within the first 2 weeks of symptoms, recovery from traumatic or compressive palsies is often slow and incomplete, beginning within 2–4 months, and sometimes continuing for up to a year [9]. Aberrant regeneration may complicate recovery from traumatic or compressive oculomotor palsies, with nerves regrowing to innervate the wrong muscle. Examples include lid elevation with attempted adduction or downgaze, adduction with attempted upgaze or downgaze, or pupil constriction with adduction, downgaze, or upgaze. If aberrant regeneration is seen or if recovery does not begin by 2 months in a patient with a presumptive diagnosis of a microvascular oculomotor nerve palsy, the diagnosis should be questioned and the patient should have neuroimaging to exclude a compressive lesion.

## Case vignette

A 62-year-old male first noted horizontal diplopia while driving, after a few days of mild frontal headache. The next day, his wife noted right lid droop, and the diplopia became vertical and horizontal, varying in different gaze positions. After a few days the lid droop became complete, at which point he no longer noted diplopia. The headache was continuous for about a week, and then became intermittent.

He had had diabetes mellitus for more than 10 years, as well as

hypercholesterolemia and borderline hypertension. His medications included clopidogrel, aspirin, insulin, ramipril, rosuvastatin, and metformin.

Visual acuity, colour vision, peripheral fields, and fundoscopy were normal. His pupils were symmetric in size in both light and dark. He had nearly complete right ptosis ([Figure 103.2](#)).



**Figure 103.2** Extraocular movements seen on examination of the patient described in the case vignette. The right eye had absent elevation, depression, and adduction, but good abduction. There was nearly complete ptosis of the right eyelid.

His left eye had full range. The right eye had absent elevation, depression, and adduction, but good abduction ([Figure 103.2](#)). On attempted depression when the right eye is abducted, the globe intorted, indicating good IV nerve function ([Figure 103.3](#)).



**Figure 103.3** Illustration of preserved fourth nerve function seen on examination of the patient described in the case vignette. The right eye is placed in abduction and, on attempted depression, the globe intorted, as indicated by examining movement of a large conjunctival vessel (arrow).

Motor and sensory functions of the trigeminal nerve were intact. Corneal reflex was symmetric. Upper and lower functions of the facial nerve were

normal. Motor examination showed normal tone, power, and dexterity in all limbs, including the left arm and leg. Sensory examination was normal. Coordination was symmetric and normal. Deep tendon reflexes were symmetric.

## Discussion

The patient has a painful, isolated pupil-sparing complete III palsy of the right eye. He has no involvement of the VI, IV, or V nerve to raise suspicion of a lesion of the cavernous sinus. He has no tremor, ataxia, or pyramidal weakness or spasticity of the left arm or leg, to point to a midbrain lesion. After the first few days, the palsy did not progress, and the pain improved over a week. All these latter points are reassuring against a compressive lesion, and more consistent with microvascular damage in a man with predisposing conditions of diabetes and hypertension. The pattern of a pupil-sparing III palsy with otherwise complete involvement of the extraocular muscles and levator also strongly suggests a microvascular palsy, rather than compression by an aneurysm at the junction of the internal carotid artery and posterior communicating artery.

He had arrived already having a normal CT scan of his head. Given the physical findings, a CT angiogram was not felt necessary, and he was followed with repeated assessments over the next few months. At about 3 months after onset his palsy began to improve and returned to normal over the course of 1 week.

## References

1. Bruce B, Bioussse V, Newman N. Third nerve palsies. *Semin Neurol* 2007; 27:257–68.
2. Trobe JD. Isolated third nerve palsies. *Semin Neurol* 1986; 6:135–41.
3. Jacobson DM. Relative pupil-sparing third nerve palsy: etiology and clinical variables predictive of a mass. *Neurology* 2001; 56:797–8.
4. Elmalem VI, Hudgins PA, Bruce BB, Newman NJ, Bioussse V. Underdiagnosis of posterior communicating artery aneurysm in noninvasive brain vascular studies. *J Neuro-Ophthalmol* 2011; 31:103–9.
5. Trobe JD. Searching for brain aneurysm in third cranial nerve palsy. *J Neuroophthalmol* 2009; 29:171–3.

6. Chaudhary N, Davagnanam I, Ansari SA *et al.* Imaging of intracranial aneurysms causing isolated third cranial nerve palsy. *J Neuro-Ophthalmol* 2009; 29:238–44.
7. Britz G, Golshani K, Ferrell A, Zomorodi A, Smith T. A review of the management of posterior communicating artery aneurysms in the modern era. *Surg Neurol Int* 2010; 1:88.
8. Knuckey NW, Stokes BA. Subarachnoid haemorrhage: epidemiology, natural history, and surgical treatment. *Med J Aust* 1981; 2:651–4.
9. Hamer J. Prognosis of oculomotor palsy in patients with aneurysms of the posterior communicating artery. *Acta Neurochir (Wien)* 1982; 66:173–85.
10. Jacobson DM. Pupil involvement in patients with diabetes-associated oculomotor nerve palsy. *Arch Ophthalmol* 1998; 116:723–7.
11. Kissel JT, Burde RM, Klingele TG, Zeiger HE. Pupil-sparing oculomotor palsies with internal carotid-posterior communicating artery aneurysms. *Ann Neurol* 1983; 13:149–54.

# Index

---

- Abadie sign 400  
abducens nerve palsy *see* sixth nerve palsy  
abetalipoproteinemia 301  
abulia 5  
acalculia 39, 433  
achalasia 153  
achromatopsia 5  
acquired hepatocerebral degeneration 229  
acquired neuromyotonia 282  
acrophobia 349  
acute cardiogenic shock 378  
acute disseminated encephalomyelitis 226, 532  
acute inflammatory demyelinating polyneuropathy (AIDP) 9, 523, 551, 565, 569  
acute intermittent porphyria 229  
acute pulmonary edema 378  
acute stress disorder 22, 137  
acute stress reaction 267  
Addison's disease 351  
adenocarcinoma 563  
adenoid cystic carcinoma 563  
adrenoleukodystrophy 535  
adrenomyeloneuropathy 535  
Adson's sign 305  
aggression definition 12  
aggressive behavior differential diagnosis 13–17  
aggressive impulsivity 5  
agitated excitement 84  
agitation acute 4  
  clinical vignette 12  
  definition 12  
  differential diagnosis 13–17  
  in catatonia 84  
  in patient with developmental disability 12

neuroanatomy 12  
urinary tract infection 12

agnosia 3

- anosagnosia 21
- auditory agnosias 20–21
- case vignette 18–19
- classification of types 19
- definition 18, 39, 408
- differential diagnosis 19
- distinction from aphasia 39
- for scenes 19
- for words 19
- tactile agnosia 21
- visual agnosias 18–20

agnostic alexia 20

agoraphobia 22

agraphesthesia 5

agraphia 433

- definition 39
- distinction from aphasia 39

Aicardi syndrome 353

AIDS 83, 400

- cognitive impairment 109
- AIDS myelopathy 531

akathisia 84, 243

akinesia 243

akinetic mutism 5, 102, 432

alcohol cognitive effects 108

- hallucinations related to 189
- intoxication 14
- polyneuropathy associated with alcoholism 178

alcohol-related complex motor activity 254

Alexander syndrome 383

alexia 20

- definition 39
- distinction from aphasia 39

alexia without agraphia 4, 5, 433

alien hand syndrome 4, 254

allodynia definition 304, 396

Alpers' disease 392  
alternating leg muscle activation (ALMA) 258, 259  
Alzheimer's disease 106, 111  
  dysphagia 153  
  hallucinations 189  
  memory impairment 233  
  myoclonus related to 277  
  psychosis related to 352  
amaurosis fugax 494  
amnesia 5  
  approach to diagnosis 223  
  case vignette (scopolamine-related amnesia) 234  
  case vignettes (transient global amnesia) 223–234  
  definition 223  
  differential diagnosis 224–233  
  dissociative amnesia 135–136  
  distinction from delirium 223  
  distinction from dementia 223  
  etiological factors 224–233  
  for non-verbal material 5  
  for verbal material 5  
  transient global amnesia 225  
amusia 5  
amyloidosis 73, 75, 551, 565, 570  
amyotrophic lateral sclerosis (ALS) 8, 9, 83, 152, 154, 179, 377, 520, 526, 527, 533, 538  
  case vignette 82, 526–527  
  effects on speech 150  
anarchic hand syndrome 254  
Andermann syndrome 353  
Andersen Tawil syndrome 545  
anesthesia definition 396  
anesthesia dolorosa 396, 402  
Angelman syndrome 381, 392  
anhedonia 119  
anhidrosis 75  
anisocoria 360  
  definition 359  
  physiological 359

anomic aphasia 5, 37  
anorexia nervosa 164  
anosmia 5  
    definition 408  
anosognosia 5, 21  
antalgic gait 185  
anterior cord syndrome 7  
anterior inferior cerebellar artery (AICA) infarction 144  
anterior spinal artery insufficiency 7  
antibody screening 94  
antiphospholipid antibody syndrome 90, 232, 351, 532  
antipsychotic medications side effects 238–240  
anti-Yo antibody 53  
Anton's syndrome 433  
anxiety 14, 74, 84, 146  
    case vignette (related to Parkinson's disease) 31–32  
    classification of anxiety disorders 22  
    definition 22  
    differential diagnosis 23–31  
    etiologies 22, 31  
    neuroanatomy and neurotransmitters 22–31  
    prevalence 22  
anxiety disorder 143  
    mutism 267  
apallic syndrome 102  
Apert syndrome 353  
aphasia 3, 4, 5, 149, 433  
    acute 34  
    anomic aphasia 37  
    Broca's aphasia 37–38  
    case vignette 40  
    conduction aphasia 35–37  
    definition 34  
    differential assessment of aphasic syndromes 34–35  
    differential diagnosis 36, 38–39  
    etiologies 34  
    features of 36  
    fluent aphasias 35–37  
    global aphasia 38

localization of lesion 36  
mixed transcortical aphasia (MTcA) 38  
neuroanatomy 34  
non-fluent aphasias 37–38  
primary progressive aphasia 38  
progressive 34  
subcortical aphasia 38  
transcortical motor aphasia (TcMA) 38  
transcortical sensory aphasia (TSA) 37  
transient 34  
Wernicke's aphasia 35

aphemia 5  
apneustic breathing 376, 377  
appendicular ataxia 45  
apperceptive agnosia 18–19  
apraxia 3, 4, 5  
    clinical vignette (normal pressure hydrocephalus) 41–44  
    description 41  
    differential diagnosis of apraxia 42  
    differential diagnosis of gait apraxia and NPH 43  
    etiologies 41  
    neuroanatomy 41  
    subtypes 41  
    synonyms and related terms 41  
    tests for 41  
apraxia of speech definition 39  
    distinction from aphasia 39  
Argyll Robertson pupils 361, 363, 570  
arm pain case vignette (lung tumor) 305  
    differential diagnosis 306–307  
    neuroanatomy 304  
    pain descriptions 304  
    pain terminology 304–305  
    provocative tests for upper extremity pain 305  
arsenic poisoning 229  
artery of Adamkiewicz 560  
Ashkenazi Jewish population 159  
asomatognosia 5  
*Aspergillus* spp. 571

aspiration risk associated with dysphagia 152, 154  
associative agnosia 18–19  
astasia abasia 243  
astereognosis 5, 402  
asterixis 274, 275–276  
asymptomatic autonomic dysfunction 70  
ataxia 6  
    gait ataxia 45  
    hereditary ataxias 277  
    of breathing 100  
    sensory ataxia 45  
        with oculomotor apraxia 301  
ataxia, acute clinical vignette (stroke) 53–54  
    definition 45  
    description 45–53  
    differential diagnosis 45–53  
    differential diagnosis of episodic ataxia 46  
    differential diagnosis of non-episodic ataxia 47–52  
    in children 53  
    neurologic examination 45–53  
    patient history 52–53  
    toxic etiology 53  
ataxia, chronic acquired causes 55–56  
    autosomal recessive ataxias 56, 57  
    clinical approach 55  
    clinical signs 55  
    clinical vignette (fragile X tremor ataxia syndrome) 59  
    definition 55  
    epidemiology 55  
    episodic ataxias (EA) 57–58  
    in recessively inherited or X-linked metabolic errors 56–57  
    inherited causes 56–59  
    mitochondrial diseases with ataxia 59  
    neuropathology 55  
    SCAs related to nucleotide expansion 58  
    SCAs resulting from conventional mutations 58  
    sensory ataxia 55  
    spinocerebellar ataxias (SCAs) 57  
    X-linked ataxias 58–59

ataxia, subacute acquired causes 55–56  
autosomal recessive ataxias 56, 57  
clinical approach 55  
clinical signs 55  
clinical vignette (fragile X tremor ataxia syndrome) 59  
clinical vignette (stroke) 53–54  
definition 45, 55  
description 45–53  
differential diagnosis 45–53  
differential diagnosis of episodic ataxia 46  
differential diagnosis of non-episodic ataxia 47–52  
epidemiology 55  
episodic ataxias (EA) 57–58  
in children 53  
in recessively inherited or X-linked metabolic errors 56–57  
inherited causes 56–59  
mitochondrial diseases with ataxia 59  
neurologic examination 45–53  
neuropathology 55  
patient history 52–53  
SCAs related to nucleotide expansion 58  
SCAs resulting from conventional mutations 58  
sensory ataxia 55  
spinocerebellar ataxias (SCAs) 57  
toxic etiology 53  
X-linked ataxias 58–59  
ataxia telangiectasia 56  
ataxic breathing 376, 377, 378  
ataxic gaits 184  
ataxic hemiparesis syndrome 4  
athetoid movements 4  
athetosis 254  
atrophy 8, 9  
attention deficit disorder (ADD) 74  
attention deficit hyperactivity disorder (ADHD) 14, 74, 383  
case vignette 61–69  
attentional problems case vignette (ADHD) 61–69  
definition of attention 61  
neurologic basis 61

atypical sensory syndrome 404  
auditory agnosias 5, 20–21  
autism 85  
autoimmune disorders myalgia related to 271  
autoimmune malignant catatonia 87  
automatic obedience 84  
autonomic dysfunction 140, 450  
    assessment and monitoring 76  
    associated with dizziness or lightheadedness 73  
    associated with general neurology 72–74  
    associated with pain management 72–74  
    associated with sleep 72–74  
    asymptomatic 70  
    autonomic neuropathy 70  
    cardiovascular autonomic neuropathy (CAN) 70, 72–76  
    case vignette (postural orthostatic tachycardia syndrome, POTS) 77–80  
    caveats with autonomic dysfunction 80  
    clinical parasympathetic and sympathetic assessment 70–72  
    description of the autonomic nervous system 70  
    diabetes mellitus 76–77  
    dizziness or lightheadedness disorders 76  
    features of 72  
    general forms 72  
    in catatonia 84  
    measures of autonomic function 70  
    measures of parasympathetic and sympathetic activity 70  
    recommendations for autonomic testing 70–72  
autonomic neuropathy 70  
autosomal recessive ataxias 56, 57  
axonal neuropathy case study 575–579  
    definition 574  
axonotmesis 613

Babinski sign 3, 5, 7  
back pain 7  
    *see also low back pain*  
bacterial infections multiple cranial neuropathy 570  
bacterial otitis media 550  
balance definition 182

Balint's syndrome 5, 20, 433  
Baltic myoclonus 384  
basilar artery migraine 474  
Beck Depression Inventory (BDI) 120  
Becker's disease 285, 545  
behavioral variant fronto-temporal dementia 233  
Behçet's syndrome 83, 532, 565  
    multiple cranial neuropathy 569  
Bell's palsy 153, 550  
    case vignette 549–551  
Benedikt syndrome 6  
benign neonatal sleep myoclonus 259  
benign paroxysmal positional vertigo (BPPV) 142, 467, 468, 471, 472–473  
benign paroxysmal vertigo of childhood (BPVC) 474  
benign sleep myoclonus of infancy 258  
bent-spine disorders 525  
benzodiazepines 85, 87, 240  
bilateral corticobulbar disease effects on speech 150  
bilateral hemispheric disturbances 5  
bilateral vestibulopathy 143  
Binswanger disease 83, 170–177  
Biot's breathing 100  
bipolar affective disorder 119  
bipolar disorder 74, 107, 267  
bipolar disorder–manic psychosis 353  
bipolar I disorder 214  
bladder dysfunction 7, 8  
blastomycosis 571  
blepharoptosis 355  
blepharospasm 159, 251  
blow-out fracture 303  
body dysmorphic disorder differential diagnosis 221  
bone disorders cause of multiple cranial neuropathies 571  
Botox treatment 551  
botulism 9, 153, 302, 357, 377, 542  
bowel dysfunction 7, 8  
brachial plexopathy 9, 584, 612  
    anatomy of the brachial plexus 612–613  
    case vignette (radiation-induced brachial plexopathy) 622

clinical presentation 613  
cord plexopathy 615  
differential diagnosis of lesions 614  
electromyography 619–621  
electrophysiologic evaluation 615–621  
etiologies 615  
imaging the brachial plexus 621–622  
localization 615  
lower trunk plexopathy 615  
middle trunk plexopathy 615  
motor nerve conduction studies 619  
nerve injury classification scheme 613  
pan-plexopathy 615  
sensory nerve conduction studies 619  
treatment 616–618, 621  
upper trunk plexopathy 615

Bradbury–Eggleston syndrome 74  
bradykinesia 4  
brain hemorrhage 414  
brain injury 74, 83  
    agitation/aggression caused by 16  
    cognitive dysfunction 110  
brain lesions mutism related to 267  
brainstem lesions localization 6  
brainstem stroke 433–434  
brainstem syndromes 6  
brainstem tumor 83  
breath holding 377  
breathing disorders during sleep 258  
brief psychotic disorder 267, 353  
Briquet's syndrome 219  
Broca's aphasia 37–38  
Brody's disease 282, 285  
Brown–Séquard syndrome 7, 8, 399, 529, 560  
    case vignette 511–512  
Brun's frontal lobe ataxia 432  
bruxism sleep related 258, 259, 264  
bulbar palsy neuroanatomy 82  
bulbar polio 152

bulbar reflexes hyperactive 5  
bulbospinal muscular atrophy 533, 538  
bulimia nervosa 164  
Burner syndrome 521

CADASIL 83, 114  
Call–Fleming syndrome 224  
callosal apraxia 41  
camptocormia 525  
*Candida* spp. 153, 571  
Capgras syndrome 349  
carbon monoxide poisoning 229  
    symptoms of low level exposure 108  
cardiac arrhythmias 140, 146  
cardiac output low 113  
cardiovascular autonomic neuropathy (CAN) 70  
    risk assessment 72–76  
cardiovascular disorders drop attacks 147  
    enlarged left atrium 153  
    lightheadedness caused by 140  
    tonic-clonic activity related to 264  
carpal tunnel syndrome 337, 396  
    case vignette 585–586  
    clinical presentation 583–584  
    description 583  
    diagnostic investigations 584–585  
    differential diagnosis 584  
    etiologies 583  
    localization of median neuropathy 584  
    management 585  
    predisposing etiologies 583  
carphology 256  
catalepsy 84, 243  
cataplexy 146, 147, 243  
catatonia 243  
    and mutism 266  
    association with schizophrenia 84  
    case vignette 87–88  
    classification 84

description 84  
diagnosis 85–87  
diagnostic signs and symptoms 84  
endocrine model 85  
epidemiology 85  
epilepsy model 85  
etiologies 85  
excited type 16  
genetics 85  
malignant catatonia 84, 85  
neuroleptic malignant syndrome 84  
neurotransmitter model 85  
pathophysiology 85  
serotonin syndrome 84–85  
subtypes 84–85  
treatment 87  
catatonic schizophrenia 267  
cauda equina anterior cord syndrome 7  
cauda equina syndrome 8  
cavernous sinus malignancies 568  
cavernous sinus syndrome case vignette (pituitary apoplexy) 547  
cavernous sinus anatomy 547  
definition 547  
differential diagnosis 548  
multiple cranial neuropathy 567, 568  
CDKL5 382  
celiac disease 277  
Center for Epidemiology Studies Depression Scale (CES-D) 120  
central cord syndrome 7, 560  
central nervous system (CNS) lesions differentiation from PNS lesions 3  
    intra-axial and extra-axial lesions 3  
central nervous system (CNS) syphilis 352  
central pontine myelinolysis 83  
central sleep apnea 378  
cerebral flexibilitas 243  
cerebellar ataxia 45  
    differential diagnosis 45–53  
cerebellar degenerative ataxias 147  
cerebellar dysfunction imbalance caused by 143

cerebellar syndromes 6  
cerebellar tremor 463  
cerebellopontine angle malignancies 568  
cerebral cortex lesions 3–4  
cerebral hemisphere lesions 3–4  
cerebral malaria 352  
cerebral palsy 83  
cerebral vasculitis 111  
cerebral venous thrombosis 436  
cervical dystonia 159  
cervical radiculopathies 631, 632  
cervicocerebral arterial dissection 435  
Charcot–Marie–Tooth 180  
Charcot's triad 53  
Charles Bonnet syndrome 189  
chemotherapy side effects 108  
Cheyne–Stokes respiration 99, 376  
Chiari malformation type 1 146, 147  
childhood disintegrative disorder 385  
childhood trauma dissociative amnesia 135–136  
    dissociative identity disorder (DID) 136  
children ataxia 53  
chlorpromazine 240  
cholesteatoma 467, 471  
chordoma 563  
chorea 4, 251, 254, 256, 274  
    case vignette 89–95  
    description 89  
    differential diagnosis 91–93  
    distinction from other movement disorders 89, 158  
    effects on speech 150  
    pathophysiology 89  
chorea–acanthocytosis 90  
choreoathetosis 251  
chronic fatigue syndrome 74, 115  
chronic hypotension 74  
chronic inflammatory demyelinating polyneuropathy (CIDP) 541  
chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) 526, 574–  
    575

chronic monoarthritis 153  
chronic otitis media 467, 471  
chronic progressive external ophthalmoplegia 302, 356  
chronic regional pain syndrome (CRPS) 75  
citrullinemia 384  
Claude syndrome 6  
clonic motor activity case vignette 250  
    description 250  
    differential diagnosis 251  
cluster breathing 376  
cluster headache 194, 362  
cocaine use cognitive effects 108  
*Coccidioides immitis* 571  
Coffin–Lowry syndrome 146, 147  
Cogan's lid twitch 355  
cognitive deficits 5  
cognitive difficulties 3  
cognitive map formation problems 20  
color agnosia 5  
coma acute coma evaluation 100  
    case vignette 103–104  
    clinical presentation 97  
    components of the examination 97–100  
    definition of coma 96  
    definition of impaired states of consciousness 96  
    degrees of coma 96  
    disorders of consciousness and syndromes 103  
    displacement of midline structures on CT scan 103  
    etiologies 101–102  
    eye movement examination 132–133  
    Glasgow Coma Scale (GCS) 97  
    locked-in syndrome 100–102  
    neuropathology 100  
    pathophysiology 96–97  
    psychogenic unresponsiveness 103  
    reasons for reduced consciousness with structural lesions 100  
    spontaneous abnormal eye movements 168  
    vegetative state 102–103  
coma vigil 102

combined spinal cord and peripheral nerve lesions 9  
combined upper and lower motor neuron deficits 9  
command automatism 255  
common peroneal nerve anatomy 589  
compartment syndrome 180  
complex motor activity case vignette (REM sleep behavior disorder) 253  
    description 253  
    differential diagnosis 254–257  
compulsions 255  
conduction aphasia 35–37  
confusion definition 96  
confusional arousals 258, 260  
confusional state 5  
congenital central hypoventilation syndrome 377  
congenital disorders agitation/aggression 16  
congenital myotonic dystrophy (CMD) 283  
consciousness disorders 103  
constructional apraxia 4  
contralateral deficits 4  
contralateral paresis 3  
conus medullaris 8  
conversion disorder 107, 137, 179, 267, 561  
    case vignette 218–222  
    differential diagnosis 219  
cord plexopathy 615  
coronary artery by-pass graft (CABG) risks associated with 73  
corpus callosum agenesis 353  
cortical deafness 5, 20  
cortical sensory syndrome 404  
corticobasal ganglionic degeneration 277, 343  
    case vignette 344  
corticobasal syndrome 233  
corticospinal tract lesions 3–4  
corticospinal tract neuroanatomy 502–503  
Cotard's syndrome 349  
cranial nerve lesions effects on speech 150  
cranial nerve palsies 52  
cranial nerves 4  
cranial neuropathies *see under* cavernous sinus syndrome and specific cranial

*nerves* Creutzfeldt–Jakob disease 83, 189, 227, 277, 280, 300, 352  
classical 110  
cognitive symptoms 233  
variant CJD 110  
crutches cause of radial neuropathy 587  
cryptococcal infection 109  
*Cryptococcus neoformans* 571  
culture-bound syndromes 255  
Cushing's disease 351  
cysticercosis 352, 531  
cytomegalovirus 382, 550, 564, 571  
cytomegalovirus encephalitis 226

De Clerambault syndrome 349  
De Quervain's tendonitis 587  
deafness 5  
decerebrate posturing 99  
decompression sickness myelopathy 535  
decorticate posturing 99  
deep tendon reflexes diminished 8  
increased 3, 4  
degenerative cerebellar ataxias 146  
degenerative diseases cognitive impairment 111  
diagnosis and therapeutics 112  
dehydration 140  
déjà entendu 135  
déjà vu 135  
Dejerine and Roussy thalamic syndrome 402  
delirium 14, 189, 256  
case vignette 240–241  
clinical approach 237–238, 241  
clinical presentation 236  
definition 96, 236  
differential diagnosis 238, 240  
distinction from amnesia 223  
etiologies 236–237, 238  
management 238–240  
pathophysiology 236–237  
screening tools 237–238

terminal delirium 240  
delirium tremens 254  
delusional disorder 353  
delusional disorder, somatic type 221  
delusions 84  
    content-specific types 349  
    definition 349  
    hallucination as 349  
    in psychosis 349  
dementia 5, 9  
    apraxia 41  
    case vignette 115–117  
    definition 106  
    differential diagnosis 107–115  
    distinction from amnesia 223  
    etiologies 106  
    hallucinations 189  
    mutism related to 268  
    parkinsonian features 343  
    prevalence 106  
dementia–parkinsonism–amyotrophic lateral sclerosis complex of Guam 343  
dementia patient differential diagnosis for agitation/aggression 13–17  
dementia with Lewy bodies *see Lewy body dementia*  
demyelinating disorders 73  
    ataxia caused by 52  
    behavioral changes 16  
demyelination definition 573–574  
denial 4  
dentatorubral–pallidoluysian atrophy (DRPLA) 277  
depersonalization disorder 136–137  
depression 5, 14, 74, 107, 146, 267  
    depression in medical illness approach to treatment 126–127  
        case vignette 120  
        classification of mood disorders 119  
    CNS illness 120  
        comorbidity of depression 119  
        definitions 119–120  
    diagnostic and screening tools 120  
    differential diagnosis 120, 121–126

etiologies 121–126  
nature of depression 119  
Neurological Disorders Depression Inventory in Epilepsy (NDDI-E) 120  
potential for suicide 120  
dermatomyositis 152, 272  
developmental agnosia 19, 20  
developmental disability case vignette (agitation) 12  
case vignette (urinary tract infection) 12  
differential diagnosis for agitation/aggression 13–17  
Devic's syndrome 561  
dexmedetomidine 240  
diabetes mellitus and multiple cranial neuropathy 569  
autonomic dysfunction 76–77  
facial palsy 550  
falls 171  
polyneuropathy 178  
risk of CAN 73  
diabetic amyotrophy 522, 539  
diabetic autonomic neuropathy 76–77  
diabetic ketoacidosis 268  
diabetic myonecrosis 523  
diabetic neuropathy 398  
diabetic non-ketotic hyperglycemia 89  
diabetic polyneuropathy 397  
dialysis dementia 350  
diffuse cortical disturbances 5  
diffuse leptomeningeal gliomatosis 568  
Di-George syndrome 381  
diphtheria 153, 541  
diphtheritic polyneuropathy 564, 570  
diplopia 6, 635  
approach to patient evaluation 129  
clinical vignette 133–134  
examination (comatose patient) 132–133  
examination (conscious patient) 131–132  
localization based on patient history 130  
patient history 129–131  
disc herniation 560  
 disinhibition 5

disseminated encephalomyelitis 268  
dissociative disorder acute stress disorder 137  
    clinical vignette 137–138  
    conversion disorder 137  
    definition of dissociation 135  
    depersonalization disorder 136–137  
    differential diagnosis 135  
    dissociative amnesia 135–136  
    dissociative fugue 136, 231  
    dissociative identity disorder (DID) 136  
    post-traumatic stress disorder (PTSD) 137  
Dix–Hallpike maneuver 467, 468, 473  
dizziness 45, 73, 76  
    case vignette 144  
    definition of symptoms 139  
    differential diagnosis of imbalance 143  
    differential diagnosis of lightheadedness 140  
    differential diagnosis of non-specific dizziness 140  
    differential diagnosis of vertigo 141–143  
    imbalance 139  
    lightheadedness 139  
    non-specific 139  
    vertigo 139  
    vestibular system anatomy and physiology 139  
Djerine anterior bulbar syndrome 400–401  
Doose syndrome 146, 147  
dopa-responsive dystonia 160, 342  
dorsal root ganglion lesions 8  
double vision 6  
Down's syndrome 381  
Dravet syndrome 278  
drop attacks 176  
    case vignette 145–148  
    classification 146  
    definition 145  
    diagnostic approach 145  
    differential diagnosis 146  
    distinction from syncope 147  
dropped-head syndrome 525

drowsiness definition 96  
drug toxicity ophthalmoparesis related to 300  
drug-induced dangerous behavior 254  
drug-induced mutism 268  
drug-induced myalgia 270, 271, 272  
drug-induced parkinsonism 242–245  
drug-induced tremor syndromes 463  
drug-related psychosis 350  
drugs of abuse cognitive effects 229  
    hallucinations related to 189  
Duane syndrome 302  
dysarthria 5, 6, 82, 90  
    case vignette 149, 151  
    definition 39, 149  
    differential diagnosis 150  
    distinction from aphasia 39  
    laryngeal symptoms of disease 150  
    neurology and physiology of speech production 149–150  
    oral symptoms of disease 150  
    patient examination 150–151  
    signs of abnormal speech 150–151  
    symptoms of abnormal speech 150  
    terminology relating to abnormal speech 149  
    velopharyngeal (palate) symptoms of disease 150  
dysarthria clumsy hand syndrome 4  
dyscalculia 5  
dysdiadochokinesia 6, 46  
dysesthesia 396  
    definition 304  
dysferlinopathies 282, 285  
dysgeusia 321  
dyskinesia paroxysmal dystonia/dyskinesia 160–162  
dysmetria 6  
dysmophobia differential diagnosis 221  
dysosmia 408  
dysphagia 4, 9, 82  
    anatomical localization 155–156  
    and nutritional problems 152  
    aspiration risk 152, 154

aspiration risk predictors 155  
classification 152  
clinical swallowing evaluation structure examination 155  
clinical vignette 156  
definition 152  
differential diagnosis 152–154, 156  
esophageal dysphagia 152  
functional–anatomical model of swallowing 155–156  
oropharyngeal dysphagia 152  
post-stroke dysphagia 155–156  
swallowing evaluation 152–154  
treatment 154–155

dysprosody 5

dysthymia 119

dystonia 84, 274–275  
acute 243  
adult onset 158  
age-of-onset classification 158  
as a feature of another neurologic disease 158–159  
blepharospasm 159  
body distribution classification 158  
case vignette 163, 344  
cervical dystonia 159  
classification systems 158–159  
description 158  
differential diagnosis 161–162  
distinction from chorea 89  
distinction from other movement disorders 158  
dopa-responsive dystonia 160  
dystonia-plus syndromes 158–160, 161–162, 342  
early onset 158  
early-onset PTD 159  
effects on speech 150  
etiological categories 158–159  
focal dystonias 158, 159  
generalized dystonia 158  
genetic factors 158–159, 160  
hemidystonia 158  
heredodegenerative disorders 158–159, 160

laboratory and radiographic evaluation 162  
laryngeal dystonia 159  
late-onset dystonias 159  
mirror dystonia 158  
multifocal dystonia 158  
neurodegenerative etiologies 160  
oculogyric crisis 160  
oromandibular dystonia 159  
overflow feature 158  
paroxysmal dystonia/dyskinesia 160–162  
phenomenology 158  
primary torsion dystonia (PTD) 159  
primary torsion with or without tremor 158–159  
rapid-onset dystonia parkinsonism 160  
secondary dystonia 158–159  
secondary etiologies 160, 161–162  
segmental dystonia 158  
sensory tricks 158, 159  
sporadic neurodegenerative disorders 160  
task-specific dystonias 159  
treatment 162–163  
tremor 158, 459  
use of *geste antagoniste* 158  
writer's cramp 159  
dystrophic myotonias 282–285

early myoclonic encephalopathies 278  
eating disorders anorexia nervosa 164  
bulimia nervosa 164  
case vignette 164  
classification 164  
differential diagnosis 165–166  
etiologies 165–166  
Eaton–Lambert syndrome 74  
echolalia 84  
echopraxia 84, 244  
Ekbom syndrome 349  
electrical myotonia 282  
electroconvulsive therapy (ECT) 85, 87

cognitive side effects 231  
electrolyte imbalance 90  
embouchure dystonia 159  
emotional dysregulation 82  
emotional lability 84  
encephalic hemorrhage 414  
encephalitis 13, 225, 300, 377, 382  
encephalitis, lethargic 227  
encephalomyelitis 570  
encephalomyelitis with rigidity 277  
encephalopathy 256  
encephalopathy with potassium channel antibody/VGKC antibodies (LGI1 antigen) 232  
endocrine disorders 15  
    causes of respiratory failure 377  
    mutism related to 268  
endocrine model of catatonia 85  
endocrine-related cognitive impairment 114  
endolymphatic hydrops 470  
eosinophilia–myalgia syndrome 271  
eosinophilic esophagitis 153  
epilepsy agitation/aggression caused by 16  
    causes of intellectual disability 384  
    cognitive dysfunction 108  
    cognitive effects 230  
    complex motor activity 257  
    definition 387  
    drop attacks 146, 147  
    juvenile myoclonic epilepsy 280–281  
    mutism related to 267  
    myoclonus related to 278  
    Neurological Disorders Depression Inventory in Epilepsy (NDDI-E) 120  
    nocturnal epilepsy 260  
    prevalence of depression 120  
    psychosis related to 352  
    sleep movements 260  
        *see also* clonic motor activity; seizures; tonic-clonic activity  
epilepsy model of catatonia 85  
episodic ataxias (EA) 57–58

Epley maneuver 473  
Epstein–Barr virus 522, 550, 564, 565, 570, 571  
Erb's palsy 521  
Erb–Duchenne palsy 615  
Erb–Duchenne plexopathy 9  
erotomania 349  
esophageal cancer 153  
esophageal diverticulum 153  
esophageal dysphagia 152  
    aspiration risk 154  
    swallowing evaluation 152–154  
    treatment 154–155  
esophageal webs 153  
essential tremor 90, 113, 242, 458–459  
evening edema 74  
excessive daytime sleepiness (EDS) 202  
executive function impairment 5  
exophthalmos 346  
extra-axial CNS lesions 3  
extradural (epidural) hematoma 414  
extrapyramidal syndromes case vignette (corticobasal ganglionic degeneration)  
    344  
    case vignette (dystonia) 344  
    case vignette (Huntington's disease) 344–345  
    case vignette (Parkinson's disease) 340–344  
    case vignette (progressive supranuclear palsy) 344  
    clinical features 340  
    differential diagnosis 340, 341–344  
    extrapyramidal tract anatomy and function 340  
eye disorders oculogyric crisis 160  
eye movements, abnormal 167  
    case vignette (opsoclonus myoclonus syndrome) 167–169  
    components of normal eye movements 167  
    convergence retraction 'nystagmus' 169  
    description 167  
    differential diagnosis 167–169  
    identification and localization 167–169  
    in coma patients 168  
    interrupt fixation 168

lateropulsion 169  
ocular flutter 168  
ocular neuromyotonia 169  
oculogyric crisis 169  
oculomasticatory myorhythmia 169  
oculopalatal tremor 169  
opsoclonus 168  
psychogenic flutter 168  
saccadic corrections 168  
saccadic intrusions 168  
superior oblique myokymia 169  
symptoms caused by 167  
tics 169  
transient ocular deviations 169  
voluntary 'nystagmus' 168  
*see also* [nystagmus](#)

eye pain approach to diagnosis 312  
assessment of pain 312  
case vignette (demyelinating disease) 315  
differential diagnosis 313–314  
etiologies 312–315  
neuroanatomy of the eye 312

facial movement abnormalities *see* [hemifacial spasm](#); [movement disorders \(facial\)](#)

facial nerve palsy 434–435  
anatomy of the facial nerve (seventh cranial nerve) 549  
case vignette (Bell's palsy) 549–551  
differential diagnosis 549  
etiologies 440, 549

facial numbness 6

facial pain differential diagnosis 406

facial paresis 4

facial sensation loss 4

facial sensory deficits case vignette 407  
differential diagnosis 406  
etiologies 405–407  
forms of 405  
localization of lesions 405–407

trigeminal neuralgia 405  
facial weakness 6  
    stroke 434–435  
facio-mandibular myoclonus 259  
factitious disorder differential diagnosis 221  
falls 580  
    Binswanger disease 170–177  
    case vignette 170–177  
    central disorders 172  
    description 170  
    differential diagnosis 171–176  
    drop attacks 176  
    motor disorders 175  
    muscular disorders 176  
    non-syncopal falls 170  
    prevalence 170  
    risk from gait abnormalities 182  
    sensory etiologies 171  
    syncopal falls 170  
    vestibular system disorders 171  
    visual system disorders 172  
familial idiopathic basal ganglia calcification (FIBGC) 341  
fasciculations 3, 8, 9  
fatal catatonia 84  
fatigue 74  
    definition 202  
femoral neuropathy anatomy of the femoral nerve 580  
    case vignette 582  
    diagnostic work-up 581  
    differential diagnosis 581  
    etiologies 580  
    frequency 580  
    mononeuropathy 580  
    patient history 580  
    physical examination 581  
    prevention 581–582  
    prognosis 581  
    treatment 581  
festinating gait 4, 185

fetal alcohol syndrome 382  
fibromyalgia 75, 272  
fibrous dysplasia of the cranium 571  
fibular neuropathy 178–180  
Filipino X-linked dystonia parkinsonism, DYT3 342  
finger agnosia 5, 39, 433  
flaccid paresis 8  
flail arm syndrome 522  
floccillation 256  
floppy head syndrome 525  
focal myoclonus 252  
focal seizures 275  
focal structural lesions paresthesias 338  
Foix–Alajouanine syndrome 560  
folate deficiency 351  
foot painful burning sensation 596  
foot drop 184  
    case vignette 181  
    central disorders 179  
    description 178  
    differential diagnosis 179  
    etiologies 178–180  
    fibular neuropathy 178–180  
    lumbar plexopathy 179  
    lumbar radiculopathy 179  
    neuropathy 179  
    physical examination 178–180  
    sciatic neuropathy 179  
forebrain lesions localization 5  
formication-reaching 254  
Foster Kennedy syndrome 332  
fourth nerve palsy anatomy of the trochlear nerve 552  
    case vignettes 553–555, 556  
    differential diagnosis (isolated) 553  
    differential diagnosis (non-isolated) 553  
    etiologies 553, 554  
    isolated fourth nerve palsy 553  
    non-isolated fourth nerve palsy 553  
    Parks–Bielschowsky three-step test 552

signs 552  
signs of non-isolated fourth nerve palsy 553  
symptoms 552  
symptoms of non-isolated fourth nerve palsy 553  
treatments 553, 554

fragile X carriers 115

fragile X FMR1 381

fragile X syndrome 16

fragile X tremor ataxia syndrome (FXTAS) 58–59, 342

frailty and cognitive decline 115

Fregoli syndrome 349

Friedreich's ataxia 56, 353, 535

frontal lobe epilepsy 260

fronto-temporal dementia 112

- behavioral variant 233
- hallucinations 189
- psychosis related to 352

fugue states 135, 136

fungal infections multiple cranial neuropathy 570–571

fungal meningitis 564, 570

gag reflex diminished 82

- enhanced 82

gait abnormalities alterations in gait 4

- antalgic gait 185
- biomechanical determinants of gait 186
- case vignette (elderly patient) 187
- clinical vignette (normal pressure hydrocephalus) 41–44
- definition of balance 182
- definition of gait 182
- definition of locomotion 182
- differential diagnosis 183–186
- effects on energy consumption 186
- etiologies 182
- festinating gait 4, 185
- gait disorders 183–186
- gait evaluation 187
- hemiplegic gaits 183
- localization schema 182–186

magnetic gait 5, 44, 185  
neurologic aspects of gait 182  
neurologic causes 182  
neuromuscular gaits 183  
non-neurologic causes 182  
normal gait cycle 186  
normal gait cycle (new and old terminology) 186  
prevalence 182  
psychogenic gait 186  
risk of falls 182  
shuffling gait 185  
spastic gaits 183  
steppage gait 184

gait apraxia differential diagnosis 43  
gait ataxia 6, 45, 184  
*see also* ataxia  
gastroesophageal reflux disease (GERD) 153, 260  
Gaucher disease 301  
Gaucher type II 383  
gegenhalten 5, 84  
generalized anxiety disorder 22  
genetic counseling 94  
genetic disorders causes of intellectual disability 381  
genetic testing for autosomal dominant disease 94–95  
    for Huntington's disease 94–95  
Geriatric Depression Scale 120  
Gerstmann syndrome 4, 39, 433  
*geste antagoniste*  
    use in dystonia 158  
giant intracranial aneurysms 567  
    multiple cranial neuropathy 569  
Glasgow Coma Scale (GCS) 97  
    score in coma 97  
glaucoma 333  
    effects of pilocarpine treatment 359–362  
global aphasia 38  
glomus jugulare 563  
glomus tympanicum 563  
glycogenosis type V 282, 285

GM2 gangliosidosis, juvenile form 383  
graphesthesia 4, 402  
grimacing 84  
Guillain–Barré syndrome 9, 147, 153, 303, 378, 398, 499, 531, 540, 551, 565, 569  
case vignette 498–499

Hallervorden–Spatz syndrome 341

hallucinations 84  
definition 349  
in psychosis 349  
psychiatric 189  
scopolamine side effect 234  
*see also* visual hallucinations

haloperidol 240  
side effects 238–240

Hashimoto's encephalopathy 228

head drop 525  
head ptosis 525  
head tilt 6, 7  
headache 75  
afternoon 74  
approach to diagnosis 191  
case vignette 195–196  
classification of causes 191  
cluster headache 194, 195  
definition 191

diagnosing a specific headache syndrome 192–193

differential diagnosis 196

distinction from orofacial pain 316

etiologies 191

hemicrania continua 195

identifying secondary headache disorder 191–192

International Classification of Headache Disorders, second edition (ICHD-2)  
191

migraine 193–194

new daily-persistent headaches 195

paroxysmal hemicrania 194, 195

prevalence 191

primary headache diagnosis by syndromic group 193  
red flags for secondary disorders 192  
Short-lasting Unilateral Neuralgiform headache attacks with Conjunctival injection and Tearing (SUNCT) 194, 195  
Short-lasting Unilateral Neuralgiform headache attacks with cranial Autonomic symptoms (SUNA) 194  
symptoms 191  
tension-type headache 194  
trigeminal autonomic cephalgias 194, 195  
heading disorientation 20  
hearing loss auditory system structure and function 197  
case vignette 200  
classification of etiologies 197  
conductive hearing loss 197, 198–199  
differential diagnosis 198–200  
etiologies 198–200  
mixed hearing loss 197  
patient history 197  
physical examination 197–200  
prevalence 197  
sensorineural hearing loss 197, 199–200  
heavy metal exposure cognitive impairment 108  
hemianesthesia 433  
hemianopsia 433  
hemiballismus 4, 251, 274  
hemicrania continua 195  
hemifacial spasm 251  
causes 412  
description 412  
differential diagnosis 413  
epidemiology 412  
hemifield visual field cuts 3  
hemiparesis 5, 6, 21, 433  
case vignette (Brown–Séquard syndrome) 511–512  
case vignette (medial medullary syndrome) 504–505  
case vignette (meningioma) 513  
case vignette (right-sided paralysis and dysarthria) 512–513  
case vignette (ventral medial pontine syndrome) 510–511  
case vignette (Weber's syndrome) 505–510

definition 502  
diagnostic approach 503–504  
differential diagnosis 504  
etiologies 504  
lesion localization 503–504  
localization of lesions 504  
neuroanatomy of the corticospinal tract 502–503  
hemiparkinsonism–hemiatrophy (HPHA) syndrome 342  
hemiplegia definition 502  
hemiplegic gaits 183  
hemiplegic migraines 147  
hemisection of the spinal cord 399  
hemisensory loss 3  
hepatic encephalopathy 146, 350  
hereditary ataxias 277  
hereditary hemorrhagic telangiectasia (HHT) 436  
hereditary neuralgic amyotrophy 540  
hereditary neuropathy with liability to pressure palsies (HNPP) 523, 540  
herpes encephalitis 83  
herpes simplex encephalitis 109, 351  
herpes viral encephalitis 225  
herpes zoster 398, 564, 571  
heutoscopy 349  
hip socket neuropathy 590  
Hirayama disease 520  
histoplasmosis 571  
HIV 83, 109, 564  
cognitive impairment 109  
facial palsy 550  
multiple cranial neuropathies 571  
HIV-associated dementia (HAD) 109  
HIV encephalopathy 226, 352  
HIV myelitis 531  
Hodgkin disease 521  
Hoffman's disease 282, 285  
Holmes' tremor 463  
homonymous hemianopsia 4, 5  
Hoover's sign 3  
Hopkins syndrome 521

horizontal gaze palsy 401  
horizontal gaze palsy with scoliosis 302  
Horner's syndrome 6, 52, 98, 305, 356, 357, 360, 363, 399, 521, 570  
case vignette 364  
Hospital Anxiety and Depression Scale 120  
HTLV-1 associated myelopathy 400, 531  
Hunter syndrome 383  
Huntington's disease 112, 277, 301, 341, 353  
case vignette 344–345  
dysphagia 154  
genetic testing 94–95  
Huntington's disease-like 2 95  
Hurler syndrome 383  
hydrocephalus 300, 302, 343, 568  
hypercalcemia 350  
hypercapnea 375  
hyperekplexia 275  
hyperesthesia 396  
hyperexplexia 146  
hyperglycemia 90  
hyperhidrosis 75  
hyperhomocysteinemia 53  
hyperkalemic periodic paralysis 286  
hyper-lordosis 559  
hyperparathyroidism 351  
hyperpathia 396  
hyperreflexia 3, 9  
hypersomnia 75  
hypersomnolence case vignette (difficulty falling asleep) 203  
case vignette (poor quality sleep) 204  
case vignette (sleep fragmentation and cataplexy) 206–207  
categorizing etiologies 202–203  
classification 202  
definition 202  
differential diagnosis 205–206  
disorders of arousal 204–207  
distinction from fatigue 202  
etiologies 202–207  
hypersomnias of central origin 202

neuroanatomy of sleepiness 202  
quality of sleep 203–204  
quantity of sleep 203  
hypertensive encephalopathy 13  
hyperthyroidism 351  
hypertrosis cranialis interna 571  
hyperventilation syndrome 140  
hypesthesia 396  
hypnagogic foot tremor 258, 259  
hypnic jerks 258, 259  
hypoactive delirium 87  
hypochondriasis differential diagnosis 220  
hypogesia 321  
hypoglycemia 140, 350  
hyponatremia 350  
hypoparathyroidism 351  
hyposmia 408  
hypothalamic–pituitary–adrenal dysfunction 85  
hypothyroidism 228, 344, 351, 571  
hypotonia 46  
hypotonicity 8  
hypoxemia 375

ideas of reference 349  
idiopathic basal ganglia calcification 353  
idiopathic hypertrophic cranial pachymeningitis 565, 570  
idiopathic orthostatic hypotension 74  
illness unawareness of (anosognosia) 21  
imbalance definition 139  
    differential diagnosis 143  
immunocompromised patient bacterial infection risk 570  
    fungal infection risk 570–571  
immunosuppressed patient fungal infection risk 570–571  
impulse control disorder 14  
impulsivity 84  
inborn errors of metabolism 277  
    causes of intellectual disability 382  
incontinence 4, 5, 84  
    case vignette 209–212

definition 208  
differential diagnosis 209, 210–212  
etiologies 208  
functional incontinence 208, 212  
mixed incontinence 208  
neuroanatomy of the lower urinary tract 208–209  
overflow incontinence 208, 211  
stress incontinence 208, 212  
types of 208  
urgency incontinence 208, 210

incubus syndrome 349

infarction vertigo caused by 142

infection agitation/aggression 13  
as cause of ataxia 47  
causes of dysphagia 153  
causes of respiratory failure 377  
cognitive dysfunction caused by 109  
multiple cranial neuropathy 570–571  
mutism related to 268  
myalgia related to 271

inflammatory conditions as cause of ataxia 48

inflammatory neurologic diseases 73

inherited causes of ataxia 56–59

insomnia 75, 258, 259

integrative agnosia 18–19

intellectual disability academic and functioning potential 380  
case vignette 380–385  
definition 380  
etiologies 380, 385  
IQ classification 380  
prevalence 380

intensive care unit (ICU) *see* weakness, ICU patient

intensive care unit psychosis 351

intention tremor 6, 46, 53

intermittent explosive disorder 255

internal carotid artery dissection 567  
multiple cranial neuropathy 569

International Classification of Headache Disorders, second edition (ICHD-2)  
191

internuclear ophthalmoplegia 6  
intra-axial CNS lesions 3  
intracerebral hemorrhage definition 414  
    pathophysiology 442  
intracranial hemorrhage 435–436  
    as cause of stroke 414  
    classification 422  
    classification by anatomic location 414  
    definition 414  
    etiologies 423–431  
    imaging 414  
intracranial hypertension and papilledema 332  
intraventricular hemorrhage 414  
invasive fungal sinusitis 302  
ipsilateral gaze palsy 6, 635  
iron accumulation syndromes 160  
Isaacs' syndrome 285

*jamais entendu* 135  
*jamais vu* 135  
James, William 61  
jaw jerk reflex brisk 82  
    diminished 82  
jugular foramen malignancies 563–568  
jugular foramen syndrome 568  
juvenile absence with myoclonus 278  
juvenile myoclonic epilepsy 258, 259, 278, 280–281  
juvenile Parkinson's disease 342

K<sup>+</sup> aggravated myotonia 286  
kathisia 15  
Kearns–Sayre syndrome 59, 356, 544  
Kennedy syndrome 533, 538  
Klinefelter syndrome 381  
Klein–Levin (Sleeping Beauty) syndrome 256  
Klumpke's palsy 521  
Klumpke's paralysis 615  
knee buckling 580  
konzo 530

Korsakoff's syndrome 115  
Krabbe disease, late onset 383

L-dopa-induced dyskinesia 89  
labyrinthine ataxia 45  
labyrinthitis 141, 471  
lacunar stroke 4, 433  
Lafora body epilepsy 278  
Lafora disease 385, 393  
Lambert–Eaton myasthenic syndrome (LEMS) 339, 357, 377, 526, 537–546  
landmark agnosia 20  
language deficit *see* aphasia  
language difficulties 3  
laryngeal dystonia 159  
laryngospasm 260  
lateral medullary syndrome 401  
lathyrism 530  
Leber's hereditary optic atrophy 353  
leg cramps sleep related 258, 259  
Leigh disease 382, 383  
Lennox–Gastaut syndrome 146, 147, 278, 384  
leprosy 180, 523  
lethargy definition 96  
leukemia 563  
leukodystrophies 16, 83  
Lewy body dementia 106, 112, 342  
    hallucinations 189  
    memory impairment 233  
    psychosis related to 352  
Lewy body syndromes 73, 74  
Lhermitte sign 400  
lightheadedness 73, 76  
    definition 139  
    differential diagnosis 140  
lightning strike 535  
limb weakness 6  
listeriosis 564, 570  
lithium toxicity myoclonus 279  
locked-in syndrome 87, 100–102

locomotion definition 182  
logopenic variation of progressive aphasia 38  
loss of inhibition 5  
low back pain 8  
    approach to investigation 308, 309  
    clinical vignette 308–311  
    red flags 308  
lower motor neuron dysfunction signs of 82  
lower motor neuron lesions localization 8  
lower motor neuron syndromes 8–9  
lower trunk plexopathy 615  
Lubag syndrome 342  
lumbago 589  
lumbar plexopathy 179  
lumbar plexus lesions 180  
lumbar radiculopathy 179, 180  
lumbosacral plexopathy 9, 522  
    anatomy 623  
    case vignette 625–630  
    clinical presentation 623–624, 626–628  
    differential diagnosis 623–624, 626–628  
    etiologies 626–628, 629  
    physical examination 624–625  
lumbosacral plexus 589  
lumbosacral radiculopathies 631, 632  
lupus 87  
Lyme disease 109, 153, 398, 530, 550, 564, 570  
Lyme encephalopathy 226  
lymphomatoid granulomatosis 565, 570  
lysosomal storage disease 160

Machado–Joseph's disease (MJD) 341  
macrocytic anemia 53, 54  
magnetic gait 5, 44, 185  
major depressive disorder (MDD) 119  
malignancy cognitive effects 232  
malignant catatonia 84, 85  
malignant hyperthermia 263  
malingering 107, 179

differential diagnosis 222, 231  
mania 14, 267  
    case vignette 214  
    description 214  
    differential diagnosis 215–216  
    etiologies 215–216  
manic depression 74  
maple syrup urine disease 301  
marche à petits pas 432  
Marchiafava–Bignami disease 228, 352  
Marcus Gunn jaw-winking syndrome 356  
marijuana use cognitive effects 108  
McArdle disease 282, 285, 544  
medial lemniscus deficit 6  
medial medullary syndrome 400–401  
    case vignette 504–505  
medial tibial stress syndrome 590  
median neuropathy above the wrist 585  
    carpal tunnel syndrome 583–585  
    case vignette (carpal tunnel syndrome) 585–586  
    description 583  
    etiology at different locations in the arm 585  
    localization 584  
    predisposing etiologies for carpal tunnel syndrome 583  
medically unexplained symptoms case vignette (conversion disorder) 218–222  
    definition 218  
    psychiatric differential diagnosis 219–222  
medications agitation/aggression side effects 13  
    cognitive side effects 229  
    complex motor activity side effects 254  
    depression caused by 121  
    dizziness caused by 140  
    extrapyramidal effects 343  
    hallucinations caused by 189  
    parkinsonian side effects 343  
    side effects 107  
    systemic reaction to 84  
megaloblastic anemia 53  
Meige's syndrome 247

Melkersson--Rosenthal syndrome 550  
memory disturbance 5  
memory loss approach to diagnosis 223  
    definition of amnesia 223  
    differential diagnosis 224–233  
    etiologies 224–233  
Ménière's disease 142, 146, 147, 467, 469–470, 471  
    diagnosis 470  
meningioma case vignette 513  
meningitis 13, 301, 377, 382, 570  
meningoencephalitis 109  
Menke's disease 384, 392  
menstrual psychosis 351  
mental retardation academic and functioning potential 380  
    case vignette 380–385  
    definition 380  
    etiologies 380, 385  
    IQ classification 380  
    prevalence 380  
mental status change, acute definition of delirium 236  
meralgia paresthetica 9, 590  
metabolic disorders agitation related to 15  
    causes of ataxia 51  
    causes of intellectual disability 384  
    causes of multiple cranial neuropathy 571  
    causes of respiratory failure 377  
    cognitive impairment 114  
    ophthalmoparesis related to 301  
metabolic myopathy 271  
metachromatic leukodystrophy, juvenile form 383  
metastasis cognitive effects 232  
metastatic tumors multiple cranial neuropathy 563, 568  
methylphenidate 69  
microsmia 408  
middle trunk plexopathy 615  
migraine 75, 189, 193–194, 362, 393  
    amnesia related to 225  
    distinction from seizure 387  
paresthesias 338

timescale of symptom evolution 387  
migraine associated vertigo 473–474  
    diagnosis 474  
Miller–Fisher syndrome 303, 565, 569  
mirror dystonia 158  
mitochondrial cytopathies with striatal necrosis 342  
mitochondrial disorders 160  
    causes of intellectual disability 382  
    with ataxia 59  
mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) 59, 115, 232, 383  
mitochondrial encephalopathy with ragged red fibers (MERRF) 277  
mixed transcortical aphasia (MTcA) 38  
Möbius syndrome 302, 551  
monomelic weakness case vignette 519  
    etiologies 519, 520–523  
    localization 520–523  
mononeuropathy 8  
    localization 9  
mononeuropathy multiplex 9, 396  
monosymptomatic hypochondriacal psychosis 221  
mood disorders 14, 267  
    classification 119  
    psychosis related to 353  
mood episodes 119  
motor agnosia 41  
motor ataxia 6  
motor neuron disease 9, 83, 179, 503  
motor sequencing impairment 5  
movement abnormalities (facial) case vignette (Meige's syndrome) 247  
    clinical approach 247  
    description 247  
    differential diagnosis 248–249  
movement disorders ataxia in 52  
    distinction between hyperkinetic movement disorders 158  
movement disorders in psychiatry approach to diagnosis 242  
    case vignette (drug-induced parkinsonism–tardive dyskinesia) 242–245  
    differential diagnosis 243–245  
    essential tremor 242

prevalence 242  
mucopolysaccharidosis 160  
mucormycosis 564, 571  
mucositis 153  
multifocal acquired demyelinating sensory and motor neuropathy (MADSAM) 587  
multifocal mononeuropathy 396  
multifocal motor neuropathy 587  
multiple cranial neuropathy acute inflammatory demyelinating polyneuropathy (AIDP) 569  
bacterial infections 570  
Behçet's syndrome 569  
case vignette 571–572  
caused by bone disorders 571  
caused by diabetes 569  
caused by HIV 571  
caused by metabolic disorders 571  
caused by neurocysticercosis 571  
caused by parasites 571  
caused by sickle cell disease 569  
cavernous sinus syndrome 568  
common etiologies 568  
common locations 568  
definition 563  
diagnosis 571  
differential diagnosis 563, 567  
etiologies 563  
fungal infections 570–571  
giant intracranial aneurysms 569  
Guillain–Barré syndrome 569  
infections 570–571  
inflammatory diseases 569–570  
internal carotid artery dissection 569  
localization 563  
malignancies at the base of the skull 563  
malignancies in the cavernous sinus 568  
malignancies in the cerebellopontine angle 568  
malignancies in the jugular foramen 563–568  
malignancies in the subarachnoid space 568

metastatic tumors 563, 568  
Miller–Fisher syndrome 569  
neurosarcoidosis 569  
paraneoplastic syndromes 563  
stroke 568  
Tolosa–Hunt syndrome 570  
traumatic brain injury 569  
tumor 563–568  
vascular diseases 568–569  
vasculitis 569–570  
viral infections 571

multiple personality disorder *see under* dissociative identity disorder multiple sclerosis 45, 83, 115, 142, 301, 467, 532, 561  
dysphagia 152, 154  
memory impairment 231  
movement disorders 252  
paresthesias 338  
psychosis related to 352  
weakness 520

multiple system atrophy 73, 74, 113, 342, 527

Munchausen's syndrome 221  
Munchausen's syndrome by proxy 221

muscle atrophy 8, 9  
muscle tone diminished 6  
muscle weakness 10  
muscular atrophy 3  
muscular dystrophy 152, 179, 543  
musician's hand dystonia 159  
mutism 84  
and catatonia 266  
case vignette 266–269  
definition 39, 266  
differential diagnosis 267–268  
distinction from aphasia 39  
neuropathology 266

myalgia case vignette (statin-induced myalgia) 270  
causes 270  
description 270  
differential diagnosis 271–272

drug-induced myalgia 270, 271, 272  
testing for myopathy/myositis 270  
myasthenia gravis 74, 302, 357, 377, 378, 526, 541  
  effects on speech 150  
  facial weakness 551  
  oropharyngeal dysphagia 152  
mycoplasma 550  
myelopathy 45  
  anatomy of a single vertebra 557–558  
  anatomy of the vertebral column 557  
  approach to evaluation 557  
  case vignette (disc protrusion) 558–559  
  definition 557  
  differential diagnosis 559  
  dorsal and ventral nerve roots 558–561  
  long tracts in the spinal cord 558  
  vascular supply of the spinal cord 558  
myocardial infarct (MI) risk assessment 72  
myoclonic astatic epilepsy 146, 147  
myoclonic epilepsy with ragged red fibers (MERRF) 59, 385  
myoclonic jerks sleep related 258  
myoclonus approach to diagnosis 274  
  asterixis 274, 275–276  
  case vignette (juvenile myoclonic epilepsy) 280–281  
  case vignette (lithium toxicity) 279  
  case vignette (myoclonus associated with CJD) 280  
  case vignette (post-anoxic myoclonus) 279–280  
  clinical classification 276  
  definition 274  
  diagnostic approach 274  
  differential diagnosis 274–275  
  distinction from other movement disorders 158  
  etiological diagnosis 277–278  
  etiological diagnosis of myoclonic syndromes 276  
  etiologies 274  
  key clinical questions for diagnosis 278  
  laboratory tests 281  
  negative myoclonus 274, 275–276  
  neurophysiologic classification 274–276

palatal myoclonus 274  
pathological classification 275–276  
positive myoclonus 274  
prevalence 274  
systematic approach to clinical diagnosis 276–279

myofascial pain definition 305

myokymia 252

myopathy 10, 179  
causes of proximal weakness 542  
effects on speech 150  
facial weakness 551

myositis effects on speech 150

myotonia action myotonia 282  
case vignette 286  
classification of myotonic muscle diseases 282–283  
clinical features of myotonic disorders 284  
description 282  
differential diagnosis 282–283, 285  
dystrophic myotonias 282–285  
grip myotonia 282  
myotonic disorders 283  
non-dystrophic myotonias 282–283, 285–286  
percussion myotonia 282

myotonia congenita 285

myotonic dystrophy 303, 356  
type 1 (DM1) and type 2 (DM2) 282, 283–285

narcolepsy 75, 147, 352

nasopharyngeal carcinoma 563

neck pain 7  
anatomy and physiology of the neck 325–326  
case vignette (intervertebral disc protrusion) 326–331  
differential diagnosis 327–330  
prevalence 325

neck weakness case vignette (amyotrophic lateral sclerosis) 526–527  
descriptive terminology 525  
differential diagnosis 525, 526  
neurologic etiologies 525

negative myoclonus 274, 275–276

negativism 84, 244  
neglect 4, 5  
neonatal epileptic encephalopathy 278  
neoplasms 9  
    behavioral symptoms 14  
    causes of dysphagia 153  
    causes of facial palsy 550  
    causes of multiple cranial neuropathy 563–568  
    causes of paraparesis 532  
    cognitive dysfunction caused by 110  
    mutism related to 268  
    ophthalmoparesis related to 300, 302  
    paresthesias 338  
    psychosis related to 352  
neoplastic meningitis 568  
nerve conduction velocity (NCV) studies 76  
nerve injury classification scheme 613  
nerve root lesions 9  
neuralgic amyotrophy 587  
neuroacanthocytosis 342  
neurocysticercosis 564  
    multiple cranial neuropathy 571  
neurodegenerative disorders hallucinations 189  
    mutism related to 268  
    myoclonus related to 277  
neurofibromatosis 385  
neurogenic weakness, retinitis pigmentosa and ataxia (NARP) 59  
neuroleptic malignant syndrome 16, 84, 244, 263, 282, 285  
neurologic differential diagnosis 1–11  
    challenges with psychiatric disorders 3  
    generating a differential diagnosis 10–11  
    lesions in the cerebral hemispheres and cerebral cortex 3–4  
    neurologic examination 2  
    neurologic history 1–2  
    neurologic localization 1  
    neurologic localization approach 2–3  
    step-by-step approach 1  
neurologic examination 2–10  
    approach to 2

neurologic history 1–2  
neurologic localization affectation of specific lobes of the brain 4  
    approach to 2–3  
    bilateral hemispheric disturbances 5  
    brainstem lesions 6  
    brainstem syndromes 6  
    cerebellar syndromes 6  
    cerebral cortex lesions 3–4  
    cerebral hemisphere lesions 3–4  
    differentiating CNS lesions and PNS lesions 3  
    diffuse cortical disturbances 5  
    dorsal root ganglion 8  
    forebrain lesions 5  
    intra-axial and extra-axial CNS lesions 3  
    lower motor neuron lesions 8  
    lower motor neuron syndromes 8–9  
    mononeuropathies 9  
    muscle weakness 10  
    myopathy 10  
    nerve root 9  
    neuromuscular junction 9  
    peripheral nerve deficits 9  
    plexus lesion 9  
    role in diagnosis 1  
    specific nerve deficits 9  
    spinal cord lesions 7  
    spinal cord syndromes 6–8  
    subcortical gray matter lesions 4  
    subcortical white matter disturbances 4  
    syndromes with combined spinal cord and peripheral nerve lesions 9  
    syndromes with combined upper and lower motor neuron deficits 9

Neurological Disorders Depression Inventory in Epilepsy (NDDI-E) 120  
neuromodulator imbalance 22–31  
neuromuscular gaits 183  
neuromuscular junction disease 9  
neuronal ceroid lipofuscinosis 277, 342, 385  
neuropathic pain 396  
    definition 304  
neuropathy paresthesias related to 338

tremor associated with 463  
    *see under specific nerves/locations* neuropraxia 613

neurosarcoidosis 565  
    multiple cranial neuropathy 569

neurosyphilis 13, 109, 226, 564, 570

neurotmesis 613

neurotransmitter imbalance 22–31

neurotransmitter model of catatonia 85

new daily-persistent headaches 195

niacin deficiency 351

Niemann–Pick disease 353

Niemann–Pick disease type C 301, 383

NMDA receptor encephalitis 231

nocturnal epilepsy 260

non-convulsive status epilepticus 85  
    clinical vignette 103–104

non-dystrophic myotonias 282–283

non-epileptic seizures clinical vignette 137–138

non-fluent aphasias 37–38

non-fluent progressive aphasia 38

non-ketotic hyperglycinemia 382

non-verbal auditory agnosia 5, 20

normal pressure hydrocephalus 107  
    clinical vignette 41–44  
    differential diagnosis 43

nutritional problems and dysphagia 152

nystagmus 6, 7, 45, 53  
    case vignette 288–298  
    clinical approach 288  
    clinical evaluation 288  
    definition 287  
    forms of 287, 289–297  
    jerk forms 287  
    mechanisms 287–288  
    mimics 287  
    non-nystagmus ocular oscillations 287, 289–297  
    patterns and causes 289–297  
    pendular forms 287

obsessive-compulsive disorder 22, 143  
obstetric brachial plexus palsies 615  
obstructive sleep apnea 260  
ocular apraxia 5, 433  
ocular dysmetria 45  
ocular malalignment 6  
oculogyric crisis 160, 169  
oculomotor (third cranial) nerve anatomy 642  
oculomotor apraxia 56, 301  
oculomotor palsy *see* third nerve palsy  
oculopharyngeal dystrophy 302, 356  
Odor Memory Test 410  
Ohtahara syndrome 278, 384  
olanzapine 240  
Ondine's curse 376  
one-and-a-half syndrome 6, 635  
ophthalmoparesis case vignette 299  
    differential diagnosis 299, 300–303  
    location of the lesion 299  
    nuclear–intranuclear (lower motor neuron) lesions 299  
    supranuclear (upper motor neuron) lesions 299  
ophthalmoplegia 6  
opsoclonus–myoclonus syndrome 277  
optic ataxia 5  
optic neuropathy 570  
organophosphate poisoning 542  
orofacial pain approach to diagnosis 323  
    burning face or mouth 320–322  
    case vignette (joint pain) 319  
    case vignette (burning face) 321  
    case vignette (burning mouth) 321  
    case vignette (facial pressure) 318–319  
    case vignette (facial tightness) 317  
    case vignette (jaw pain) 319–320  
    case vignette (shooting/jabbing/stabbing pain) 322–323  
    classification systems 316–317  
    definition 316  
    definition of chronic orofacial pain 316  
    diagnosis of chronic orofacial pain 316

differential diagnosis 323  
distinction from headache 316  
etiologies 323  
facial tightness or pressure 317–319  
jaw pain 319–320  
joint pain 319  
prevalence of chronic orofacial pain 316  
shooting, jabbing or stabbing pain 322–323  
underlying mechanisms 316

oromandibular dystonia 159  
oropharyngeal dysphagia 152  
aspiration risk 154  
swallowing evaluation 152–154  
treatment 154–155

oropharyngeal weakness *see pseudobulbar palsy*  
orthostatic hypotension 450  
oscillopsia 6, 287  
osmotic demyelination 83  
osteopetrosis 571  
osteophyte formation 560  
osteosarcoma 563  
Othello syndrome 349  
otolithic crisis 146, 147  
otosclerosis 141

Paget's disease 571  
pain 8  
    agitation/aggression related to 15  
    contralateral severe 4  
    peripheral neuropathy 9  
    radiating 9  
    sensory deficit 8  
    sensory loss 6  
    thalamic pain 402  
    pain descriptions 304  
    pain disorder differential diagnosis 220  
    pain management autonomic dysfunction associated with 72–74  
    pain terminology 304–305  
    palatal myoclonus 274

palatal tremor syndrome 463  
palsy definition 497  
PANDAS 254  
panic attacks 136, 140, 146, 260  
panic disorder 22, 259, 260  
panic symptoms case vignette (anxiety related to Parkinson's disease) 31–32  
    classification of anxiety disorders 22  
    definition 22  
    differential diagnosis 23–31  
    etiologies 22, 31  
    neuroanatomy and neurotransmitters 22–31  
    prevalence 22  
pantothenate kinase-associated neurodegeneration (PKAN) 341  
papilledema 568, 570  
    appearance with ophthalmoscope 333  
    approach to diagnosis 335  
    case vignette 335  
    clinical manifestations 332–333  
    definition 332  
    diagnostic testing 334–335  
    differential diagnosis 334  
    head symptoms 332–333  
    neurologic causes 332  
    physiology 332  
    treatment 335  
    visual prognosis 335  
    visual symptoms 333  
paraganglioma 563, 568  
parakinesias 89  
paralysis definition 497  
paramyotonia congenita 286  
paraneoplasms causes of ataxia 49  
    causes of dysphagia 153  
    causes of paraparesis 532  
    ophthalmoparesis related to 300, 302  
paraneoplastic-limbic encephalitis memory impairment 231  
paraneoplastic syndromes 73, 75, 94  
    multiple cranial neuropathy 563  
paranoid delusions 349

paraparesis 7, 8, 9  
anatomy and clinical correlation 528–529  
case vignette 529–535  
definition 528  
differential diagnosis 528–529

paraplegia definition 528

parasites cause of multiple cranial neuropathy 571

parasitophobia 349

parasomnias 256

parasympathetic nervous system *see* autonomic dysfunction

paratonic rigidity 5

parenchymal hemorrhage 414

paresis 4, 7, 8, 9  
definition 497

paresthesia 8  
case vignette (carpal tunnel syndrome) 337  
definition 304, 337, 396  
differential diagnosis 338–339  
etiologies 337

Parinaud syndrome 6

Parkinson's disease 74, 83, 106  
case vignette 340–344  
case vignette (anxiety disorders) 31–32  
clinical features 340  
dementia 113  
differential diagnosis 340, 341–344  
drop attacks 146, 147  
dysphagia 154  
effects on speech 150  
extrapyramidal tract anatomy and function 340  
focal dystonia 160  
hallucinations 189  
juvenile Parkinson's disease 342  
neck weakness 527  
oropharyngeal dysphagia 152  
post-encephalitic 353  
prevalence of depression 120  
risk of CAN 73  
secondary REM sleep behaviour disorder 260–261

tremor 462–463  
Parkinson's-plus syndromes focal dystonia 160  
parkinsonian symptoms 4  
    differential diagnosis 340  
parkinsonian tremor syndromes 462–463  
parkinsonism drug-induced 242–245  
    psychosis related to 353  
paroxysmal dystonia/dyskinesia 160–162  
paroxysmal hemicrania 194, 195  
paroxysmal kinesogenic choreoathetosis 251  
Parsonage–Turner syndrome 338, 519, 522, 539, 540, 587  
partial seizures 3  
patient history 1–2  
pellagra 351  
pemphigus 153  
peptic stricture 153  
perineal hypesthesia 7, 8  
perineal pain 8  
periodic leg movements of sleep (PLMS) 252  
periodic limb movement disorder 258  
periodic limb movements of sleep 259  
peripheral nerve deficits 9  
peripheral nerve disturbances 3  
peripheral nerve lesions 396–398  
peripheral nerves paresthesias 338  
peripheral nervous system (PNS) lesions differentiation from CNS lesions 3  
peripheral neuropathy 9, 90, 143  
    axonal versus demyelinating neuropathies 573  
    case study (axonal neuropathy) 575–579  
    case study (CIDP) 574–575  
    definition of axonal neuropathy 574  
    definition of demyelination 573–574  
    effects on gait 183  
    etiologies of axonal and demyelinating neuropathies 575–577  
    features of axonal and demyelinating neuropathies 575  
    types of peripheral nerve fibers 573  
pernicious anemia 54  
peroneal nerve anatomy 589  
persecutory thoughts 349

perseveration 5, 84  
Phalen's maneuver 305  
phantosmia 408  
phenylketonuria 382  
pheochromocytoma 75  
phobia 22  
phonagnosia 21  
pill-rolling resting tremor 4  
pilocarpine miosis produced by 359–362  
pinprick perception 402  
piriformis syndrome 590  
pituitary apoplexy 302  
    case vignette 547  
plegia definition 497  
plexopathy 180, 538  
    *see under* specific locations plexus lesions 9  
Plummer–Vinson syndrome 154  
pneumonia 13  
poliomyelitis 153, 520, 531, 538  
polyarteritis nodosa 570  
polycythemia 113  
polycythemia rubravera 90  
polymyalgia rheumatica 272  
polymyelitis 503  
polymyositis 272  
polyneuropathies 8, 9, 396–398  
    and falls 171  
pontine hemorrhage 364  
porphyria 350, 541  
post-anoxic myoclonus 277, 279–280  
post-encephalitic Parkinson's disease 353  
post-hypoxic parkinsonian symptoms 344  
post-operative psychosis 351  
post-partum psychosis 351  
post-traumatic stress disorder (PTSD) 22, 74, 136, 137, 236  
posterior column syndromes 8  
posterior cortical agnosia 19  
posterior cortical atrophy hallucinations 189  
posterior femoral cutaneous nerve anatomy 589

posterior interosseous neuropathy 587  
posterior reversible encephalopathy syndrome 228  
posterior tibial nerve anatomy 589  
postural loss 4  
postural orthostatic tachycardia syndrome (POTS) 140  
    case vignette 77–80  
posturing 84  
Prader–Willi syndrome 16, 85, 381  
pressure effects as cause of ataxia 48  
primary autonomic failure 73, 74  
primary lateral sclerosis 9, 83, 533  
primary progressive aphasia 38  
prion diseases 48, 110, 227, 277  
progressive external ophthalmoplegia 59  
progressive multifocal leukoencephalopathy 226  
progressive supranuclear palsy 83, 146, 154, 301, 342  
    case vignette 344  
    falls 147  
pronator syndrome 584  
proprioceptive sensory deficits 9  
propriospinal myoclonus at sleep onset 258  
propriospinal myoclonus of sleep 259  
proptosis case vignette 346–348  
    definition 346  
    differential diagnosis 347–348  
    differential diagnosis by anatomical structure 346  
    distinction from pseudoptosis 346  
    etiologies 347–348  
    history and examination 346  
prosopagnosia 5, 19, 20  
proximal myotonic myopathy (PROMM) 285  
proximal weakness case vignette (LEMS) 537–546  
    consequences for patients 537  
    description 537  
    differential diagnosis 537, 538  
    etiologies 538  
    localization 538  
    potential locations 537  
pseudobulbar affect 82

pseudobulbar palsy 5, 152  
case vignette (amyotrophic lateral sclerosis, ALS) 82  
definition 82  
differential diagnosis 83  
dysphagia 154  
neuroanatomy 82  
upper motor neuron dysfunction 82

pseudodementia 107

pseudoproptosis 346

pseudosciatica 590

pseudothalamic sensory syndrome 404

pseudothalamic syndrome 402

psychiatric disorders challenges for differential diagnosis 3

psychiatric etiology of ataxia 48

psychiatric paraplegia 561

psychogenic causes of seizure 387

psychogenic gait 186

psychogenic movement disorders 244

psychogenic non-epileptic seizure (PNES) 257, 263

psychogenic paroxysmal movements 275

psychogenic tremors 463

psychogenic unresponsiveness 103

psychogenic vertigo 475

psychological causes of seizures 394

psychosis 14, 189  
case vignette 354  
content-specific delusions 349  
definition 349  
definition of delusions 349  
definition of hallucinations 349  
definition of thought disorganization 349  
delusions 349  
differential diagnosis 350–353, 354  
hallucinations 349  
pathophysiology 349–354  
prevalence 349  
thought disorganization 349

psychosomatic pain 75

psychotic major depression 353

ptosis anatomy of the eyelid 355  
blepharoptosis 355  
case vignette 355–358  
description 355  
differential diagnosis 355–358  
pounding 244  
pupil abnormalities 6  
pupil constriction anatomic localization 359, 360–362  
Argyll Robertson pupils 361, 363  
case vignette (Horner's syndrome) 364  
cavernous sinus lesions 363  
clinical features 359, 360–362  
description 359  
differential diagnosis 360–362  
etiologies 359, 360–362  
Horner's syndrome 360, 363  
oculo-sympathetic pathway lesions 363  
pharmacologic effects 359–362  
physiologic anisocoria 359  
pontine hemorrhage 364  
uveitis 360, 363  
visual neuroanatomic pathway 359  
pupil dilation approach to examination 365  
case vignette (episodic unilateral mydriasis) 373  
differentiating vasculopathic CN III palsy from compressive CN II palsy 369–371  
neurologic and non-neurologic causes 367–368  
pathway of the parasympathetic fibers 365  
pharmacologic assessment 371–373  
pupil examination 365–368  
testing the dilated pupil 373  
pure alexia 20  
pure motor stroke 4  
pure word blindness 39  
pure word deafness 20  
definition 39  
distinction from aphasia 39  
pyramidal (corticospinal tract) lesions 3–4  
pyridoxine dependency 384

pyruvate dehydrogenase complex deficiency 383

quadrantanopsia 5

quadripareisis 528

quadriplegia 528

quetiapine 240

rabies 351

radial neuropathy anatomy of the radial nerve 587

case study 588

etiologies 587, 588

localization of radial nerve lesions 588

superficial 587

radiation-induced brachial plexopathy 622

radiation therapy side effects 108

radicular pain 8

radiculopathy 538

C6 or C7 584

case vignette 633–634

cervical radiculopathies 631, 632

clinical presentations 631

definition 304, 631

diagnosis 631

etiologies 631

locations 631

lumbosacral radiculopathies 631, 632

symptoms 631

Ramsay Hunt syndrome 277, 550

rapid-onset dystonia parkinsonism 160

Raynaud's syndrome 153

reading deficit *see* alexia

recessively inherited metabolic errors 56–57

recognition impairment *see* agnosia

reflex sympathetic dystrophy (RSD) 75

reflexes diminished 3, 9

diminished deep tendon reflexes 8

hyperreflexia 9

increase deep tendon reflexes 3

loss of 8

REM sleep behavior disorder 256, 258, 259, 260  
case vignette 253, 260–261  
respiratory compromise 52  
respiratory difficulties 9  
respiratory failure case vignette 378–379  
definition of ventilation 375  
description 375  
differential diagnosis for neurologic causes 376–378  
hypercapnea 375  
hypoxemia 375  
neural control of respiration 375–376  
neurologic causes 376–378  
respiratory system anatomy and physiology 375  
restless legs syndrome 74, 258, 259  
restlessness 85  
retinal vasculitis 570  
Rett syndrome 382  
rhabdomyolysis 271  
rheumatoid arthritis 570  
rhombencephalitis 570  
rhythmic movement disorder 259  
ridigity 84  
right–left confusion 5, 39, 433  
rigors 263  
risperidone 240  
Romberg sign 400  
Rosai–Dorfman disease 565, 570  
rubella 382  
rubral tremor 463

saccadic pursuit distortion 6  
saccadic pursuit eye movements 45  
saddle hypesthesia 8  
sarcoidosis 111, 351, 531, 550, 565  
Saturday night palsy 587  
scanning speech 6, 45, 53  
schizoaffective disorder 353  
schizophrenia 14, 107, 267, 353  
association with catatonia 84

distinction from aphasia 39  
genetics 85  
hallucinations 189  
schizophreniform disorder 353  
sciatic nerve anatomy 589  
sciatic nerve injury 180  
sciatic neuropathy 179  
case vignette 591–595  
differential diagnosis 590–591, 594  
localization 590–594  
neuroanatomy 589  
symptoms 589–590  
scleroderma 153, 532, 565, 570  
scoliosis 559  
scopolamine hallucinations and amnesia side effects 234  
Segawa disease 535  
seizures aphasia 34  
case vignette 387  
complex motor activity 257  
definition 387  
definition of epilepsy 387  
differential diagnosis 387, 388–394  
dissociative-like symptoms 135  
drop attacks 147  
etiologies 388–394  
evaluation 387  
paresthesias 338  
psychogenic causes 387, 394  
timescale of symptom evolution 387  
underlying causes 387  
visual hallucinations 189  
*see also* epilepsy  
selective attention definition 61  
semantic dementia 38  
sensory ataxia 45, 55  
sensory deficits 5  
anatomy of the sensory system 395–396  
brainstem lesions 400–401  
case vignette 404

contralateral effects 4  
differential diagnosis of mononeuropathy multiplex 396  
differential diagnosis of small fiber sensory neuropathies 397  
distal 9  
dorsal nerve root lesions 398  
lesions of the cerebrum 401–404  
localization of lesions affecting somatosensory pathways 403  
peripheral nerve lesions 396–398  
polyneuropathies 396–398  
profound, contralateral 4  
radicular (root) pain 398  
sensory ataxic neuropathies and neuronopathies 397  
signs and symptoms of sensory disorders 396  
spinal cord lesions 398–400  
terminology 396  
thalamic lesions 401–404  
*see also* facial sensory deficits  
sensory neuronopathies 8  
sensory polyganglionopathy 397  
sensory polyneuropathies 8  
serotonin syndrome 16, 84–85, 244  
seventh nerve palsy 52  
sexual abuse psychogenic seizures 387  
sexual dysfunction 7  
shin splints 590  
shoulder pain *see* arm pain  
shuffling gait 185  
Shy–Drager syndrome 73, 74, 342, 450  
sialidosis type I 278, 385  
sialidosis type II 278  
sickle cell disease and multiple cranial neuropathy 569  
simultanagnosia 5, 20, 21, 433  
sixth nerve palsy 52  
anatomical considerations 635  
case vignettes 637–641  
description 635  
differential diagnosis 636–637, 638  
evaluation 636–637  
examination 636

symptoms 635–636

Sjögren's syndrome 111, 153, 532, 551, 565, 570

skew deviation 6

skull basal malignancies 563

sleep autonomic dysfunction associated with 72–74

sleep apnea 75, 260

sleep disorders agitation caused by 16

- central sleep apnea 378
- psychosis related to 352

REM sleep behavior disorder 253, 256

- see also* complex motor activity; hypersomnolence

sleep movements case vignette (REM sleep behavior disorder) 260–261

- description of abnormal movements 258
- differential diagnosis 259–260
- disorders that can cause ambulation during sleep 260
- disorders that can cause jerking movements 258, 259
- disorders that can cause restlessness 258, 259
- disorders that can cause rhythmic movements 258, 259
- disorders that can cause sudden sitting up 258–260

sleep-related cognitive dysfunction 109

sleep-related rhythmic movement disorder 258

sleep starts 258, 259

sleep terror 260

Sleeping Beauty (Klein–Levin) syndrome 256

sleepwalking 260

smell deficit agnosia 408

- anatomy of olfactory dysfunctions 409
- anosmia 408
- case vignette 410–411
- definitions of terminology 408
- differential diagnosis 409
- dysosmia 408
- etiologies 408, 409
- hyposmia 408
- microsmia 408
- patient evaluation 408–410
- patient management 410
- phantosmia 408
- potential consequences for the patient 408

prevalence 408  
smooth pursuit distortion 6  
social anxiety disorder 22  
social phobia 22  
somatization disorder differential diagnosis 219  
somnolence definition 96  
spasm, hemifacial causes 412  
    description 412  
    differential diagnosis 413  
    epidemiology 412  
spastic gaits 183  
spasticity 3, 7, 9  
specific nerve deficits 9  
specific phobia 22  
speech abnormalities terminology related to 149  
speech articulation alterations 4  
speech articulation difficulties 6  
speech development failure 268  
speech dysfunction pseudobulbar palsy 82  
speech production neurology and physiology 149–150  
sphincter dysfunction 6, 7, 8  
spina bifida 559  
spinal cord dorsal and ventral nerve roots 558–561  
    long tracts 558  
    vascular supply 558  
spinal cord hemisection 399  
spinal cord injury 74, 535  
    respiratory failure 378  
spinal cord lesions 398–400  
    localization 7  
spinal cord syndromes 6–8  
spinal epidural abscess 560  
spinal muscular atrophy 9, 533, 538  
spinocerebellar ataxias (SCAs) 57, 400, 535, 538  
    cognitive impairment 113  
    related to nucleotide expansion 58  
    resulting from conventional mutations 58  
type 2 300  
type 7 300

spinocerebellar degeneration 141  
    type 3 341

spondylolisthesis 559

spondylosis 9

Spurling's test 305

stairs difficulty with climbing 580

staring 84

startle myoclonus 251

statin-induced myalgia 270, 271, 272

Steele–Richardson–Olszewski syndrome *see* progressive supranuclear palsy

steppage gait 178, 184

stereognosis 4

stereotypies 16, 85, 255

steroid responsive encephalopathy associated with autoimmune thyroiditis (SREAT) 232

stiff person syndrome 263, 282, 285

stiffness in lower extremities 7

striato-nigral degeneration 342

stroke 3, 4, 393

- anatomical localization of lesion causing dysphagia 155–156
- anatomy 432
- apraxia 41
- behavioral symptoms 14
- brainstem strokes 433–434
- brainstem vascular syndromes 440
- case vignette 415–416, 436–443
- causes of intellectual disability 385
- causes of respiratory failure 377
- cerebral venous thrombosis 436
- cervicocerebral arterial dissection 435
- characteristics of main stroke types 417–418
- classification of intracranial hemorrhages 422
- classification of types 432
- clinical vignette 53–54
- conditions that may mimic 442
- definition 432, 444
- differential diagnosis 417–418, 435, 436, 442
- dissection syndromes 441
- distinction from seizure 387

distinguishing hemorrhagic from ischemic stroke 414–415  
drop attacks 146  
etiologies of facial nerve palsy 440  
facial weakness 434–435  
hemorrhagic stroke 414, 444  
hereditary hemorrhagic telangiectasia (HHT) 436  
imaging intracranial hemorrhage 414  
incidence 444  
internal carotid artery dissection 569  
intracerebral hemorrhage pathophysiology 442  
intracranial hemorrhage 414, 435–436  
intracranial hemorrhage etiologies 423–431  
ischemic stroke 444  
ischemic stroke territories 419–421  
lacunar syndromes 433, 439  
localization 432  
major cerebral artery syndromes 432–433  
multiple cranial neuropathy 567, 568  
ophthalmoparesis related to 301  
oropharyngeal dysphagia 152  
paresthesias 338  
pathophysiology 437–439  
post-stroke dementia 113  
post-stroke dysphagia 155–156  
prevalence 432  
prevalence of depression 120  
risk assessment 72  
risk factors 432  
simultanagnosia 20, 21  
symptoms of large artery occlusion 439  
timescale of symptom evolution 387  
types of 444  
vertigo 435  
vertigo differential diagnosis 441  
vomiting 52  
*see also* transient ischemic attack  
stroke in children case vignette 449  
clinical presentations 447  
definition of stroke 444

diagnostic evaluation 448  
differential diagnosis 448  
differential diagnosis of neurological impairment 448  
etiologies 445–447  
evaluation of stroke syndromes 448  
incidence 444  
risk factors for hemorrhagic stroke 444–447  
risk factors for ischemic stroke 444  
stroke evaluation (after 24 hours) 449  
stroke evaluation (first 24 hours) 448  
Structured Clinical Interview for DSMIV (SCID) 120  
strychnine toxicity 263  
stupor definition 96  
Sturge–Weber syndrome 385  
subacute necrotizing encephalomyopathy (SNEM) 382  
subacute sclerosing panencephalitis 227, 277  
subarachnoid hemorrhage 414  
subarachnoid space malignancies 568  
subcortical aphasia 38  
subcortical grey matter lesions 4  
subcortical white matter disturbances 4  
subdural hematoma 414  
sudden cardiac death risk assessment 72  
suicidal ideation case vignette (depression with seizures) 120  
suicide potential in depression with medical illness 120  
suicide rate depression in CNS illness 120  
SUNA 194  
SUNCT 194, 195  
superior canal dehiscence syndrome 472  
sural nerve anatomy 589  
surgery post-surgical mutism 268  
swallowing difficulties *see* dysphagia  
swayback 559  
Sydenham's chorea 90, 254, 353  
sympathetic nervous system *see* autonomic dysfunction  
syncope approach to diagnosis and treatment 450–451  
case vignette 451–453  
definition 450  
distinction from drop attack 147

etiologies 450, 452  
falls 170  
pre-syncope etiologies 450  
synkinesis 254  
syphilis 45, 109, 530, 550  
systemic lupus erythematosus 90, 111, 232, 272, 351, 532, 565, 570  
systemic sclerosis 153, 532

tabes dorsalis 8, 45, 400, 530, 560  
tactile agnosia 21, 402  
Tangier disease 398  
tapeworm (*Taenia solium*) infection 571  
tardive dyskinesia 87, 89, 90, 242–245, 254, 275  
Tay–Sachs disease 277, 301, 383, 538  
temperature sensory deficit 6, 8  
tension-type headache 194  
terminal delirium 240  
tetanic attacks 264  
tetanus 263, 282, 285, 377  
tethered cord syndrome 559  
tetraparesis 528  
tetraplegia 528  
thalamic lesions 4  
thalamic pain 402  
thiamine deficiency 238, 351  
third nerve palsy 356, 357  
anatomical classification 642, 643  
anatomy of the oculomotor (third cranial) nerve 642  
case vignette 645–647  
evaluation and diagnosis 642–645  
prognosis 645  
signs and symptoms of oculomotor palsy 642  
Thomsen disease 285, 545  
thought disorganization definition 349  
in psychosis 349  
thyroid eye disease 302  
tibial nerve anatomy 589  
tibial neuropathy anatomical localization 596–598  
case vignette 600

clinical presentation 596–598  
description 596  
diagnostic testing and treatment 598–600  
etiologies 598, 599  
location-specific clinical features 599  
tibialis anterior muscle damage to 180  
    muscle or tendon tear 179  
tick paralysis 377, 542  
tics 16, 245, 254, 255, 274  
    abnormal eye movements 169  
    description 251  
    distinction from other movement disorders 158  
Tinel's sign 305  
tinnitus approach to diagnosis 454  
    case vignette 455–457  
    definition 454  
    differential diagnosis 455  
    objective type 454  
    pathophysiology 454  
    prevalence 454  
    related anatomy 454  
    subjective type 454  
Tolosa–Hunt syndrome 565, 570  
tongue atrophy/fasciculations 82  
    stiff/spastic 82  
tonic-clonic activity case vignette 262  
    description 262  
    differential diagnosis 263–264  
    etiologies 263–264  
tonic-clonic seizure 264  
topographic agnosia 20  
Tourette's syndrome 16, 251, 255, 274  
toxic–metabolic encephalopathy 5  
toxic withdrawal syndrome 350  
toxicity as cause of ataxia 47, 53  
    causes of dysphagia 153  
    causes of respiration failure 377  
    effects of toxic substances 122  
    parkinsonian effects 343

toxic metal-induced psychosis 350  
tremor syndromes 463  
toxoplasma encephalitis 226  
toxoplasmosis 382  
transcortical aphasia 4  
transcortical motor aphasia (TcMA) 38  
transcortical sensory aphasia (TSA) 37  
transcortical sensory aphasia dysgraphia 5  
transient global amnesia 225  
transient ischemic attack 142, 147, 251, 338, 393  
    definition 444  
    distinction from seizure 387  
    timescale of symptom evolution 387  
transient monocular blindness 494  
transient monocular visual loss case vignette 494–496  
    clinical evaluation 494  
    description 494  
    differential diagnosis 495–496  
    terminology used to describe 494  
translocation Down's syndrome 381  
transverse cord syndrome 7  
transverse myelitis 377, 520, 531, 532, 560  
transverse myelopathy 398  
trauma agitation/aggression caused by 16  
    and dissociative disorders 135  
    cognitive effects 229  
    depersonalization disorder 136–137  
    dissociative amnesia 135–136  
    dissociative fugue 136  
    dissociative identity disorder (DID) 136  
    mutism related to 268  
    myoclonus related to 277  
    psychosis related to 353  
    respiratory failure caused by 378  
    vertigo caused by 143  
traumatic brain injury multiple cranial neuropathy 569  
tremor 6, 46, 158, 245  
    action tremor 458  
    associated with neuropathies 463

case vignette 463–464  
cerebellar tremor 463  
classification systems 458  
definition 274, 458  
description 251  
differential diagnosis 460–462  
distinction from other movement disorders 158  
drug-induced syndromes 463  
dystonic tremor syndromes 459  
enhanced physiologic tremor 458  
essential tremor 458–459  
etiologies 458, 460–462  
Holmes' tremor 463  
intention tremor 458  
isometric tremor 458  
kinetic tremor 458  
oculopalatal tremor 169  
palatal tremor syndrome 463  
Parkinson's disease 462–463  
parkinsonian tremor syndromes 462–463  
physiologic tremor 458  
pill-rolling resting tremor 4  
position specific tremor 459  
postural tremor 458  
prevalence 458  
primary orthostatic tremor 459  
psychogenic tremors 463  
rest tremor 458  
rubral tremor 463  
stepwise approach to diagnosis and treatment 464  
syndromic classification 458, 459  
task specific tremor 458, 459  
toxic tremor syndromes 463  
*Treponema pallidum* 570  
trigeminal autonomic cephalgias 194, 195  
trigeminal neuralgia 405  
trochlear nerve see *fourth nerve palsy*  
tropical spastic paraparesis 400, 531, 560  
truncal ataxia 46

truncal titubation 6  
trypanosomiasis 352  
tuberculosis 530, 550  
tuberculosis meningitis 564, 570  
tuberous sclerosis complex 381  
Tumarkin falls 147  
tumors as cause of ataxia 49  
    posterior fossa 146  
    third ventricle 146  
two-point discrimination 4, 402

ulnar nerve anatomy arm segment 601  
    elbow segment 601–606  
    wrist segment 606–607  
ulnar neuropathy arm segment lesions 601  
    case vignette 609–611  
    clinical pearls 607–608  
    elbow segment lesions 601–606  
    electrophysiologic testing 608–609  
    treatment 609  
    ulnar innervated muscles 604  
    wrist segment lesions 606–607  
unexplained symptoms *see* medically unexplained symptoms  
University of Pennsylvania Smell Identification Test (UPSIT) 408  
Unverricht–Lundborg disease 278, 384, 393  
upper motor neuron dysfunction signs of 82  
upper motor neuron injury signs 3  
upper trunk plexopathy 615  
uremia 350  
urinary incontinence *see* incontinence  
urinary retention 84  
urinary tract infection 12, 13  
    in patient with developmental disability 12  
uveitis 360, 363

vascular dementia 106  
    dysphagia 153  
vascular disorders causes of ataxia 49  
    causes of dysphagia 154

causes of facial palsy 550  
cognitive impairment 113  
drop attacks 146  
psychosis related to 352  
vertigo caused by 142  
vasculitis 180  
    multiple cranial neuropathy 569–570  
vegetative state 102–103  
ventilation definition 375  
ventral medial pontine syndrome case vignette 510–511  
ventriculoperitoneal shunt malfunction 300, 302  
verbigeration 84  
Vernet's syndrome 568  
vertebral anatomy 557–558  
vertebral body fracture 561  
vertebral column anatomy 557  
vertical gaze palsy 401  
vertigo 6, 45  
    benign paroxysmal positional vertigo (BPPV) 471, 472–473  
    benign paroxysmal vertigo of childhood (BPVC) 474  
    case vignette (AICA infarction) 144  
    case vignette (benign paroxysmal positional vertigo) 472–473  
    case vignette (Ménière's disease) 469  
    case vignette (migraine associated vertigo) 473  
    case vignette (superior canal dehiscence syndrome) 472  
    case vignette (vestibular neuritis) 470  
    case vignette (cholesteatoma) 471  
    case vignette (chronic otitis media) 471  
    central vestibular causes 473–475  
    cholesteatoma 471  
    chronic otitis media 471  
    definition 139, 465  
    differential diagnosis 141–143, 441  
    differential diagnosis based on duration of episode 466  
    differential diagnosis based on presenting symptoms 466  
    differential diagnosis based on signs and symptoms 466  
    differential diagnosis based on triggering or aggravating factors 466  
    endolymphatic hydrops 470  
    etiologies 469–475

Ménière's disease 469–470, 471  
Ménière's disease diagnosis 470  
migraine-associated vertigo 473–474  
migraine-associated vertigo diagnosis 474  
neuroanatomy of balance 465  
non-vestibular causes 473–475  
patient evaluation 465–469  
patient medical history 465–466  
peripheral vestibular causes 469–473  
physical examination 466–467  
psychogenic vertigo 475  
radiographic characteristics of common lesions 469  
related to stroke 435  
superior canal dehiscence syndrome 472  
vestibular injury 465  
vestibular neuritis 470–471  
vestibular system anatomy 465  
vestibular testing 467–469  
vestibulo-ocular reflex (VOR) 465  
vestibular migraine 142  
vestibular neuritis 141, 470–471  
vestibular seizures 142  
vestibular system anatomy and physiology 139, 465  
testing 467–469  
vestibular system disorders and falls 171  
drop attacks 147  
vestibulocerebellar ataxia 6  
vestibulo-ocular reflex (VOR) 45, 103, 139, 299, 465  
videofluoroscopic swallow study (VFSS) 152, 154  
viral encephalitis 225, 277  
viral infections multiple cranial neuropathy 571  
viral myelitis 531  
visual agnosia 5  
case vignette 18–19  
classification of types 18–19, 20  
differential diagnosis 19  
visual amnesia 5  
visual deficits 9  
visual dysfunction imbalance caused by 143

visual field cuts 3  
visual field deficits anatomy of the afferent visual system 477  
    bedside visual field assessment 478  
    case vignette 485  
    chiasmal afferent visual pathways 483–485  
    clinical functions of visual field testing 477  
    differential diagnosis 478, 479–485  
    lesion localization 478, 479  
    pre-chiasmal afferent visual pathways 478–483  
    retrochiasmal afferent visual pathways 483–485  
    types of visual field testing 477–478  
    use for localization 478–485  
visual hallucinations case vignette 188–190  
    definition 188  
    differential diagnosis 189  
    etiologies 188  
    in psychosis 349  
    nature of 188  
    pathophysiology 188  
visual loss, acute bilateral case vignette 487  
    etiologies 487  
    etiologies of chiasmal visual loss 487, 489  
    etiologies of post-chiasmal/geniculate visual loss 487, 490  
    etiologies of post-geniculate visual loss 487, 491  
    etiologies of pre-chiasmal visual loss 487, 488  
    lesion localization 487  
    localization of post-geniculate visual loss 487, 491  
visual loss, transient monocular see [transient monocular visual loss](#)  
visually selective progressive posterior cortical atrophy 20  
visuospatial localization impairment 5  
vitamin deficiencies and dementia 115  
    symptoms 15  
    vitamin B12 8, 9, 53, 54, 351, 399  
vomiting 52  
Von Economo's encephalitis 353  
Vulpian–Bernhardt syndrome 522  
  
Wallenberg syndrome 6, 52, 401  
wallet syndrome 590

waxy flexibility 84  
weakness 3, 5, 7, 8, 9  
    fluctuating 9  
    myopathy 10  
weakness, generalized acute case vignette (Guillain–Barré syndrome) 498–499  
    case vignette ('locked-in' syndrome) 497  
    CNS etiologies 498, 499  
    CNS pathology 497–498  
    definition 497  
    Guillain–Barré syndrome 499  
    PNS etiologies 499, 500  
    PNS pathology 498–501  
weakness, hemiparesis *see* hemiparesis  
weakness, ICU patient acute neuromuscular disorders 514  
    case vignette 514  
    differential diagnosis 514, 515  
weakness, monomelic *see* monomelic weakness  
weakness, neck *see* neck weakness  
weakness, paraparesis *see* paraparesis  
weakness, proximal *see* proximal weakness  
Weber's syndrome 6  
    case vignette 505–510  
Wegener's granulomatosis 565  
Wernicke's aphasia 35  
Wernicke's encephalopathy 115, 228, 302  
Wernicke–Korsakoff syndrome 228, 351  
West Nile poliomyelitis 520  
West Nile virus 531, 538  
West syndrome 384  
Whipple disease 226, 277, 300  
whispering dysphonia 159  
wide-based gait 6, 45  
Williams syndrome 381  
Wilson's disease 113, 160, 341, 353, 571  
withdrawal states 13, 84, 254  
Wolf–Hirschorn syndrome 381  
writer's cramp 159  
writing deficit *see* agraphia  
    *see under* alexia with agraphia

X-linked ataxias 58–59

X-linked metabolic errors 56–57

Zenker's diverticulum 153