42nd Annual Meeting of the Child Neurology Society

Austin, Texas

October 30 - November 2, 2013

E. Steve Roach, MD; President, CNS
Mustafa Sahin, MD, PhD; Chair, CNS Scientific Selection and Program Planning Committee

This activity has been planned and implemented in accordance with the Essential Areas and Policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint sponsorship of Nationwide Children's Hospital and the Child Neurology Society. Nationwide Children's Hospital is accredited by the ACCME to provide continuing medical education for physicians.

NCH designates this educational activity for a maximum of 26.0 AMA PRA Category 1 credits™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

PROGRAM

Wednesday, October 30

7:30 AM – 5:00 PM **Symposium I: Neurobiology of Disease in Children: Mitochondrial Disease**
Organizer: Bernard L. Maria, MD, MBA; Georgia Regents University, Augusta, GA

Supported by the National Institutes of Health (NIH grant 5R13NS040925-09), the Child Neurology Society and United Mitochondrial Disease Foundation

7:30 AM – 7:40 AM **Opening Comments**
Bernard L. Maria, MD, MBA, Principal Investigator

7:40 AM – 9:40 AM **SESSION I: CLINICAL ASPECTS**
Co-Director and Moderator: Bruce H. Cohen, MD; Akron Children's Hospital, Akron, OH

7:40 AM – 8:05 AM *Natural Histories and Classification of Mitochondrial Disease*
Eric Schon, PhD; Columbia University, New York, NY

8:05 AM – 8:30 AM *Diagnosis and Treatment of Mitochondrial Diseases*
Bruce H. Cohen, MD

8:30 AM – 8:55 AM *Mitochondrial DNA Disorders*
Patrick Chinnery, PhD/MRCPath/MRCP; New Castle upon Tyne, UK

8:55 AM – 9:20 AM *POLG: Primary and Secondary Disorders*
Robert K. Naviaux, MD, PhD; University of California, San Diego, San Diego, CA

9:20 AM – 9:40 AM *Question and Answer Session*

9:40 AM – 9:55 AM **Coffee Break**

9:55 AM – 11:30 AM **SESSION II: Molecular Mechanisms**
Co-Director and Moderator: William Copeland, PhD; NIEHS, Research Triangle Park, NC

9:55 AM – 10:20 AM *Defects of Mitochondrial DNA Replication*
William Copeland, PhD

10:20 AM – 10:45 AM *Mitochondrial Dynamics and Parkinsons*
Richard Youle, PhD; NINDS, Bethesda, MD

10:45 AM – 11:10 AM *Systems Biology Approach to Mitochondrial Disease*
Vamsi Mootha, MD; Harvard Medical School, Boston, MA

11:10 AM – 11:30 AM *Question and Answer Session*

11:30 AM – 1:00 PM **Lunch and Presentation by the United Mitochondrial Disease Foundation**

1:00 PM – 2:40 PM **SESSION III: TRANSLATIONAL SCIENCE AND CLINICAL FRONTIERS**
Co-Director and Moderator: Greg Enns, PhD; Stanford University School of Medicine, Stanford, CA

1:00 PM – 1:25 PM *Gene Therapy and Enzyme Replacement*
Michio Hirano, MD
Columbia University Medical Center, New York, NY

1:25 PM – 1:50 PM *Exercise Therapies in Attenuating Mitochondrial Disease*
Mark Tarnopolsky, MD, PhD, FRCPC; McMaster University, Hamilton, ON

1:50 PM – 2:15 PM *Clinical Trials: Edison Pharmaceuticals, EPI-743*
Greg Enns, PhD

2:15 PM – 2:40 PM *Occupational, Environmental and Therapeutically Acquired Mitochondrial Disorders*
Kendall Wallace, PhD; University of Minnesota-Duluth, Duluth, MN

2:40 PM – 3:00 PM *Question and Answer Session*

3:00 PM – 3:15 PM **In-Room Coffee Break**

3:15 PM – 3:45 PM *Executive Summary of the Day*
Bruce H. Cohen, MD and William Copeland, PhD

3:45 PM – 4:45 PM **SESSION IV: FUTURE DIRECTIONS PANEL DISCUSSION**
Moderator: Doug Wallace, PhD; Children's Hospital of Philadelphia, Philadelphia, PA

PANELISTS:
Amy Goldstein, MD; Children's Hospital of Pittsburgh, Pittsburgh, PA
Andrea Gropman, MD; Children's National Medical Center, Washington, DC
Richard Haas, MD; University of California, San Diego, San Diego, CA
Sumit Parikh, MD; Cleveland Clinic, Cleveland, OH
Russ Saneto, DO, PhD; Seattle Children's Hospital, Seattle, WA

4:45 PM – 5:00 PM *Closing Comments and Thanks*
Bernard L. Maria, MD, MBA

Additional Wednesday Meetings/Sessions

8:00 AM – 4:30 PM *Association of Child Neurology Nurses*

2:00 PM – 5:00 PM *Professors of Child Neurology*

6:00 PM – 8:00 PM **OPENING RECEPTION**
Austin Hilton Hotel, 6th Floor
Supported by Texas Children's Hospital, Houston, TX

8:00 – 10:00 PM *SIG Meetings (including Movement Disorders)*

Thursday, October 31

7:00 – 8:15 AM **CONTINENTAL BREAKFAST AND SEMINARS**

Breakfast Seminar 1: Shifting Models of Health Care Delivery and the Child Neurologist: The Sky is Falling

Organizer: Mark Mintz, MD; The Center for Neurological and Neurodevelopmental Health (CNNH) and the Clinical Research Center of New Jersey (CRCNJ), Gibbsboro, NJ

Introduction: The Sky is Falling: Survival and Sustainability
Mark Mintz, MD

Shifts in Reimbursements: Global Payments, Accountable Care Organizations and Medical Homes
Bruce Cohen, MD; Akron Children's Hospital, Akron, OH

Hospital-Employed Physicians: Impact of Diminishing Hospital Admissions
Ram Kairam, MD; Columbia University Medical Center, New York, NY

Innovative Models of Specialty Care Delivery
Mark Mintz, MD

Breakfast Seminar 2: Tourette Syndrome - Novel Treatments at the Ends of the Spectrum

Organizer: Leon Dure, MD; University of Alabama at Birmingham, Birmingham, AL

Medical and Surgical Approaches to TS
Leon Dure, MD

Examining the Outcomes Associated with Behavior Therapy for TS
Douglas Woods, PhD; Texas A&M University

Practical Application of Cognitive/Behavioral Therapy for TS: an OT Perspective
Jan Rowe, DrOT; Children's Hospital of Alabama, Birmingham, AL

Breakfast Seminar 3: Refractory Status Epilepticus: An Update

Organizer: James J. Riviello, Jr., MD; Columbia University Medical Center/Children's Hospital of New York, New York, NY

Refractory Status Epilepticus: Definition, stages, etiologies, and therapeutic implications
James J. Riviello, Jr., MD

The pathophysiology of Refractory Status Epilepticus: how understanding the pathophysiology impacts treatment
Mohamad Mikati, MD; Duke University Medical Center, Durham, NC

Standard and alternative treatments for refractory status epilepticus and the importance of a specific protocol.
Nicolas S. Abend, MD; University of Pennsylvania, Philadelphia, PA

8:45 AM – 8:50 AM **Association of Child Neurology Nurses Claire Chee Award for Excellence**

- Cheryl Fischer, PNP; Memorial Sloan Kettering Cancer Center, New York, NY

8:50 AM – 9:00 AM **CNS Lifetime Achievement Awards:**

- Arthur Rose, MD; SUNY Downstate, Brooklyn, NY
- A. David Rothner, MD; Cleveland Clinic, Cleveland, OH

9:00 AM – 9:05 AM **CNS Bernard D'Souza International Fellowship Award**

- Samson Gwer, MBChB, MRCPCH; Kenyatta University, Nairobi, Kenya

9:05 AM – 9:10 AM **Arnold P. Gold Foundation Humanism in Medicine Award at the Child Neurology Society:**

- Douglas Postels, MD; Michigan State University, East Lansing, MI

9:15 AM – 12:00 PM **Symposium II: Presidential Symposium: Gene Therapy for Childhood Neurological Disease**

Organizer: Mustafa Sahin, MD, PhD; Boston Children's Hospital, Boston, MA

Introduction
Mustafa Sahin, MD, PhD

Gene therapy for muscular dystrophy: moving forward to new levels
Jerry R. Mendell, MD; Nationwide Children's Hospital, Columbus, OH

Treatment of Ventilatory Failure in Pompe Disease by Gene Therapy: Next Generation Therapy
Barry Byrne, MD, PhD; University of Florida, Gainesville, FL

Developing Gene Delivery approaches for Spinal Muscular Atrophy and Translating to the Clinic
Brian K. Kaspar, PhD; Nationwide Children's Hospital, Columbus, OH

Combination Therapy for Neurodegenerative Lysosomal Storage Diseases
Mark S. Sands, PhD; Washington University, St. Louis, MO

11:00 AM – 6:00 PM: **Exhibits**

12:00 PM – 12:30 PM: **CNS Business Meeting**

12:30 PM – 1:30 PM: **Maintenance of Certification and Lifelong Learning in Child Neurology**
Lawrence Faulkner, MD; President, American Board of Psychiatry and Neurology, Lake Forest, IL

12:30 – 1:45 PM: **Lunch, Exhibit & Poster Viewing**

1:45 PM – 4:00 PM **Symposium III: Little Brains, Big Problems: Lasting Effects of Pediatric Traumatic Brain Injury**

Organizer: Heidi Blume, MD, MPH; Seattle Children's Hospital and Research Institute, Seattle, WA

Who Gives a Rat's…Brain? Understanding the Translational Science of Pediatric TBI
Chris Giza, MD; Mattel Children's Hospital, UCLA, Los Angeles, CA

Little Brains, Big Pains: Headache after Pediatric Concussion and TBI
Heidi Blume, MD, MPH

Waiting for the Other Shoe to Drop: Pediatric Post-traumatic Epilepsy
Howard Goodkin, MD, PhD; University of Virginia, Charlotesville, VA

Trajectories of Recovery and Predictors of Neurocognitive Outcome Following Pediatric TBI
Talin Babikian, PhD, ABPP; David Geffen School of Medicine at UCLA, Los Angeles, CA

4:00 PM – 6:00 PM **Child Neuro News Break: Poster Walkaround/Wine & Cheese Reception (Non-CME)**
Supported by Eisai, Inc.

Friday, November 1

7:00 – 8:15 AM **CONTINENTAL BREAKFAST AND SEMINARS**

Breakfast Seminar 4: Beyond "Seizure Disorders": the New Classification of the Epilepsies
Organizers: Renée Shellhaas, MD and Sucheta Joshi, MD; University of Michigan, Ann Arbor, MI

The 2010 ILAE Proposed New Organization of the Epilepsies: What You Need to Know
Elaine Wirrell, MD; Mayo Clinic, Rochester, MN

What Happens When a Patient Doesn't Fit in One of the New Boxes? Criticisms and Potential Difficulties with the New System

Peter Camfield, MD; Dalhousie University, Halifax, NS

How Do I Use this in my Practice? What is "Done" and What is Up for Discussion? Practical Implementation in Clinical Practice and Research Proposals
Dennis Dlugos, MD, MSCE; Children's Hospital of Philadelphia, Philadelphia, PA

Breakfast Seminar 5: Next Generation Sequencing, Genomics, and Neurogenetics

Organizer: Tyler Mark Pierson, MD, PhD; Cedars-Sinai Medical Center, Los Angeles, CA

Next Generation Sequencing and Genomics: a Technological Introduction
David Adams, MD, PhD; NIH-Undiagnosed Diseases Program, Bethesda, MD

Neurogenetics and Genomics: Undiagnosed Cases in Pediatric Neurology
Tyler Mark Pierson, MD, PhD

Clinical Applications of Exome Sequencing: from the NICU to the Neurogenetics Clinic
Eric Marsh, MD, PhD; Children's Hospital of Philadelphia, Philadelphia, PA

Breakfast Seminar 6: Ethical Considerations in Gene Therapy

Organizer: Pedro Weisleder, MD, PhD; Nationwide Children's Hospital, Columbus, OH

Panel Discussion: "Gene Therapy: Proceed with Extreme Caution"

- Leon Epstein, MD; Ann & Robert Lurie Children's Hospital of Chicago, Chicago, IL
- William Graf, MD, PhD; Yale University School of Medicine, New Haven, CT
- Geoffrey Miller, MD, PhD; Yale University School of Medicine, New Haven, CT
- Pedro Weisleder, MD, PhD

8:30 AM – 10:15 AM **Platform Sessions 1 & 2**

Platform Session 1:

8:30 AM – 8:45 PS1-1 Darras BT et al
Results of a First-in-Human Phase I Study to Assess the Safety, Tolerability, and Dose Range Finding of a Single Intrathecal Dose of ISIS-SMNRx in Patients with Spinal Muscular Atrophy

8:45 AM – 9:00 AM PS1-2 Raymond GV et al
Efficacy and Safety of Hematopoietic Cell Therapy in X-linked Adrenoleukodystrophy: a Multinstitutional Study (ALD-101)

9:00 AM – 9:15 AM PS1-3 Karacay B et al
Viral Vector-based RNAi Gene Therapy for Alexander Disease

9:15 AM – 9:30 AM PS1-4 Stasheff SF et al
Early Rpe65 Gene Therapy More Effectively Restores Precise Visual Responses to Retinal Ganglion Cells of Rpe65-/- Mice in vitro

9:30 AM – 9:45 AM PS1-5 Schor NS et al
The p75 Neuurotrophin Receptor and Autism

9:45 AM – 10:00 AM PS1-6: Kaufmann WE et al
Randomized, Controlled, Phase2 Trial of STX209 (Arbaclofen) for Social Function in Autism Spectrum Disorder

10:00 AM – 10:15 AM LATE BREAKING ABSTRACT:
PL1-7 Shirley MD et al
A Somatic Mosaic Mutation in GNAQ causes Sturge-Weber syndrome and Isolated Port-wine Birthmarks

Platform Session 2:

8:30 AM – 8:45 PS2-1 Tully HM
A New Approach to the Classification of Developmental Hydrocephalus

8:45 AM – 9:00 AM PS2-2 Kuban KCK
Extremely Low Gestational Age Newborns (ELGANs) with Repeatedly Elevated Blood Concentrations of Inflammation-Related Proteins within 15 days of Birth are at Higher Risk of Cerebral Palsy

9:00 AM – 9:15 AM PS2-3 Harbert MJ et al
Therapeutic Hypothermia is Associated with Improved Outcomes in Perinatal Stroke

9:15 AM – 9:30 AM PS2-4 Schulz A
The Natural History of Late Infantile CLN2 Disease: Striking Homogeneity of Clinical Progression in Two Independently Obtained Large Clinical Cohorts

9:30 AM – 9:45 AM PS2-5 Mallick AA et al
The Presenting Features of Arterial Ischaemic Stroke in a Population-Based Cohort

9:45 AM – 10:00 AM PS2-6 McKnight D et al
A 53-gene Sequencing and Deletion/ Duplication Panel Reveals a Broader Spectrum of Genotype-Phenotype Correlations in Epilepsy.

10:00 AM – 10:15 AM LATE BREAKING ABSTRACT:
PS2-7 Anderson HM et al
Preventable Infections in Children with Leukodystrophies

10:45 AM – 10:55 AM *Child Neurology Society Awards Announcements:*

Outstanding Junior Member Awards

- Anuja Jindal, MD; Children's Hospital Pittsburgh, Pittsburgh, PA
- Archana Patel, MD; Children's Hospital Boston, Boston, MA
- Pilar Pichon, MD; Loma Linda University Medical Center, Loma Linda, CA
- Mark Schomer, MD; Children's Hospital Boston, Boston, MA
- Mitchel Williams, MD; Children's Hospital of Michigan, Detroit, MI

M. Richard Koenigsberger Scholarship Award

- Louis Dang, MD, University of Michigan, Ann Arbor, MI

10:55 – 11:00 AM **CNS/PCN Blue Bird Circle Training Program Director Award:**

- Harvey Singer, MD; Johns Hopkins University, Baltimore, MD

11:00 AM – 11:10 AM **Child Neurology Foundation Scientific Awards Announcements**

11:10 AM – 11:40 AM **Philip R. Dodge Young Investigator Award Lecture:**
Peter T. Tsai, MD, PhD; Boston Children's Hospital, Boston, MA
Mechanisms Underlying the Cerebellar Contribution to Autism in Mouse Models of Tuberous Sclerosi

11:40 AM – 12:40 PM Bernard Sachs Lecture:
Tallie Z. Baram, MD, PhD; University of California Irvine, Irvine, CA
Shaping the 4-Dimensional Brain

9:00 AM – 2:30 PM: **Exhibits**

12:45 – 2:30 PM: **Lunch & Poster/Exhibit Walkaround**

2:30 – 4:45 PM **Symposium IV: Treatable Genetic-Metabolic Epilepsies**
Organizer: Phillip L. Pearl, MD; Children's National Medical Center, Washington, DC

Treatable Genetic-Metabolic Epilepsies: Overview and Case Studies
Phillip L. Pearl, MD

Pyridoxine-Dependencies--Clinical and Research Update
Sidney M. Gospe, Jr., MD, PhD; Seattle Children's Hospital, Seattle, WA

Glucose Transporter I Deficiency--DeVivo Disease
Darryl C. DeVivo, MD; Columbia University, New York, NY

New Genes in Early Onset Epileptic Encephalopathies
Annapurna Poduri, MD; Boston Children's Hospital, Boston, MA

4:45 – 6:00 PM: **Junior Member Seminar 1: Meet the Editors**
Organizer: Renée Shellhaas, MD; University of Michigan, Ann Arbor, MI

Panel Members:

- John Bodensteiner, MD
- Amy Brooks-Kayal, MD, PhD
- Tobias Loddenkemper, MD, PhD
- E. Steve Roach, MD

Junior Member Seminar 2: Private Practice Child Neurology
Organizer: Jasna Kojic, MD; Orlando, FL
Discussant: Ashraf El-Bohy, MD; Orlando, FL

7:00 – 10:00 PM: **RECEPTION**

Saturday, November 2

7:00 – 8:15 AM **CONTINENTAL BREAKFAST AND SEMINARS**

Breakfast Seminar 7: Updates on Inherited Neuromuscular Disorders
Organizer: Peter Kang, MD; Boston Children's Hospital, Boston, MA and University of Florida, Gainesville, FL

Duchenne Muscular Dystrophy: exon skipping strategies
Edward M. Kaye, MD; Sarepta Therapeutics, Cambridge, MA

Spinal Muscular Atrophy: emerging therapies
Basil T. Darras, MD; Boston Children's Hospital, Boston, MA

Myotonic Dystrophy: genetic and therapeutic advances
Peter Kang, MD

Breakfast Seminar 8: Neuro-ophthalmology for the Child Neurologist: Practical clinical pearls
Organizer: Steven F. Stasheff, MD, PhD; University of Iowa, Iowa City, IA

Examining the Back of the Eye to Help Diagnose and Treat Pediatric Neurologic Disease
Steven F. Stasheff, MD, PhD

Updates on the Diagnosis of Papilledema, Pseudopapilledema, and IIH
Robert Avery, MA, DO; Children's National Medical Center, Washington, DC

Congenital Ocular Motor Apraxia and Associated Neurodevelopmental Abnormalities
Michael S. Salman, MRCP, PhD; University of Manitoba, Winnipeg, MB

Breakfast Seminar 9: To Err is Human: Reducing Medical Errors by Better Handoffs with I-PASS

Organizer: James F. Bale, Jr., MD; University of Utah and Primary Children's Hospital, Salt Lake City, UT

Panel Discussion:

- James F. Bale, Jr., MD
- David K. Urion, MD; Boston Children's Hospital, Boston, MA
- Ann Yeh, MD; Hospital for Sick Children, Toronto, ON

9:00 – 9:50 AM **Hower Award Lecture:** *Genetic Bottlenecks and the Neurologic Diseases of the Navajo Native Americans*
John Bodensteiner, MD; Mayo Clinic, Rochester, MN

10:00 AM – 12:15 PM **Symposium V: Paroxysmal Disorders**

Organizer: Jonathan W. Mink, MD, PhD; University of Rochester Medical Center, Rochester, NY

Topics/ Speaker:

Mechanistic Insights on Hypokalemic Periodic Paralysis Reveal a New Therapeutic Strategy
Stephen C. Cannon, MD, PhD; University of Texas Southwestern, Dallas, TX

Episodic Ataxias
Abigail Collins, MD; Children's Hospital Colorado, Denver, CO

Alternating Hemiplegia of Childhood
Kathryn Swoboda, MD; University School of Medicine, Salt Lake City, UT

Paroxysmal Dyskinesias
Jonathan W. Mink, MD, PhD

ACNN
ASSOCIATION OF CHILD NEUROLOGY NURSES

Agenda for 2013 ACNN Conference Program
Austin Hilton Hotel
Austin, Texas
October 29 – November 1, 2013

Tuesday October 29,2013

7:00 PM – 9:00 PM ACNN Welcome Reception (Nurses only)

Wednesday October 30, 2013

7:00 AM – 8:00 AM **Registration and Continental Breakfast**

8:00 AM – 8:15 AM **Welcome and Introduction**

8:15 AM – 9:00 AM **Janet Brucker Keynote Address: TBA**

9:00 AM – 10:00 AM *Duchenne Muscular Dystrophy: Early Diagnosis and Care*
Kathi Kinnet, MSN, CNP

10:00 AM – 10:15 AM **Break**

10:15 AM – 10:45 AM *Myasthenia Gravis: OMG X 3*
Jennifer Boyd RN, MHSc, CNN(C)

10:45 AM – 11:30 AM *Stroke in Children: Now you see it, now you don't*
Ivanna Yau RN, MN, NP-Peds, CNN (C)

11:30 AM – 12:00 PM **Awards and Annual Business Meeting**

12:00 PM – 1:00 PM **Lunch and Networking Opportunity**

1:00 PM – 1:45 PM **Innovative Practice Award Presentation**
Seizure Safety School- Simple but Significant
Chelsey Stillman

1:45 PM – 2:45 PM *Sexual Maturation in Special Needs Female Populations: A "right" of passage*
Jane Lane RN, BSN

2:45 PM – 3:00 PM **Break**

3:00 PM – 3:30 PM *B6 or Not to B6*
W. Byron Cook MN, PNP

3:30 PM – 4:00 PM *Reflex Epilepsy*
Marian J. Kolodgie MSN, CPNP

4:00 PM – 4:15 PM **Wrap up**

Thursday October 31, 2013

12:00 PM – 1:00 PM **Lunch**
Ketogenic Diet Therapy Pilot Survey Abstract
Julie M. Sprague-McRae MS, RN, PPCNP-BC

1:00 PM – 2:00 PM *Is Intranasal or Buccal Midazolam as Effective as Rectal Diazepam in the Treatment of active Convulsive Seizures in the Pediatric Setting Outside the Hospital?*
Ann Morgan MS, RN, CPNP, CPN and Vicki Netzke-Doyle MSN, RN, CPN

4:30 PM **5k Run/Walk Fundraiser for ACNN/CNF Nursing Research Grant**

Friday November 2, 2012

12:00 PM – 12:30 PM **Lunch-SIG**
Topics to be announced

12:30 PM – 1:00 PM *A Randomized Controlled Trial of the Acceptability, Feasibility, and Preliminary Effects of Cognitive Behavioral Skills Building Intervention in Adolescents with Chronic Daily Headaches*
Carolyn Hickman, PhD, RN, CPNP

1:00 PM – 1:30 PM *Improving Headaches Self-management Skills Using Medical Media in Children and Adolescents Age 8-18*
Ruth Rosenblum DNP, RN, PNP-BC

Platform Session 1

PS1 - 1. Results of a First-in-Human Phase I Study to Assess the Safety, Tolerability, and Dose Range Finding of a Single Intrathecal Dose of ISIS-SMNRx in Patients with Spinal Muscular Atrophy

Darras BT (Boston, MA), Chiriboga C, Swoboda K, Iannaccone S, Montes J, Rausch N, Robert G, Johnson S, De Vivo D, Norris D, Alexander K, Bennett CF, Bishop K

Objective: ISIS-SMNRx is an antisense oligonucleotide designed to enhance inclusion of SMN2 exon 7 mRNA and increase the amount of functional SMN protein. A first-in-human, open-label, escalating-dose clinical study was conducted to evaluate the safety, tolerability, and pharmacokinetics of ISIS-SMNRx.

Methods: A single dose (1, 3, 6, or 9 mg) was delivered by intrathecal injection to medically stable SMA patients 2–14 years of age (n=28). Subjects were monitored for drug safety and tolerability. Post-dosing drug levels in CSF and plasma were measured. Exploratory endpoints, including the Hammersmith (HFMSE), were performed to gain further experience with these measures.

Results: Overall, ISIS-SMNRx was well tolerated in this study. No serious adverse events or dose-limiting toxicities were reported. All adverse events were mild or moderate in severity; none were related to dose level of ISIS-SMNRx. No drug-related changes in neurological exams, CSF laboratory assessments, or systemic evaluations were reported. Intrathecal injections were also well tolerated in SMA children and shown to be feasible. Pharmacokinetics in plasma and CSF indicate that drug levels in SMA patients were dose-dependent; observations were consistent with preclinical data and support infrequent administration (i.e. every 6–9 months). Although the study was not designed to provide evidence of functional improvement, an increase in the HFMSE was observed in the highest dose cohort at 3 months (mean increase = 3.1 points, or 17.6%; 6/10 subjects with a >4 point change).

Conclusions: Results from this study support continued development of ISIS-SMNRx, and we have initiated multiple-dose clinical studies in patients with SMA.

Sources of Funding: Isis Pharmaceuticals Inc., Carlsbad, CA, USA Spinal Muscular Atrophy Foundation, New York, NY, USA.

Keywords: Neuromuscular disorders

PS1 - 2. Efficacy and Safety of Hematopoietic Cell Therapy in X-linked Adrenoleukodystrophy: a Multiinstitutional Study (ALD-101)

Raymond GV (Minneapolis, MN), Orchard P, Aubourg P, Escolar ML, Kurtzberg J, Paedre S, Balsar J

Objective: The only therapy for childhood cerebral adrenoleukodystrophy (CCALD) is hematopoietic cell therapy (HCT), but there is limited outcome information compared to untreated boys.

Methods: We conducted a retrospective study (ALD-101) to characterize subjects with untreated CCALD and collect efficacy and safety data from HCT treated boys. Data was collected on 136 cases (72 untreated/ 65 HCT) from diagnosis till either 2 years post-diagnosis or death from 5 centers, 4 in the US and 1 in France. Established measures of neurologic function (NFS) and MRI (Loes) were used in all cases.

Results: In the untreated, 70 of 72 (97%) had at least one NFS score and an MRI; 30 (42%) with gadolinium (23 Gad+/7Gad-). Enhancement was highly predictive of rapid progression. Of the Gad+, 19 had more than one NFS score recorded and the majority showed significant decline in 6–18 months and no resolution of enhancement in the untreated group. In the 65 HCT-treated boys, all were evaluated with NFS and MRI with contrast. In the treated cohort there was resolution of enhancement (median 3.4 months) and stabilization of MRI and NFS. Engraftment failure occurred in 18.5% and the rate of severe acute and chronic GVHD was 11% and 5% respectively. The highest incidence of death occurred in those boys undergoing an HLA mismatched, non related transplant (12/32; 37.5%).

Conclusions: We report here the largest retrospective, multi-institutional study of untreated and treated CCALD, demonstrating that MRI enhancement is predictive of progression, and that it rapidly resolves following HCT. Successful HCT improved all measures of disease.

Sources of Funding: Bluebird Bio (Cambridge, MA).

Keywords: Demyelinating disorders, Genetics, Translational/experimental therapeutics

PS1 - 3. Viral Vector-based RNAi Gene Therapy for Alexander Disease

Karacay B (Iowa City, IA), Bonthius DJ

Objective: Alexander Disease (AlxD) is a leukodystrophy, caused by dominant mutations of glial fibrillary acidic protein (GFAP) in astrocytes. Gene therapy for AlxD will require selective targeting of astrocytes and allele-specific silencing of the mutant gene. Lymphocytic choriomeningitis virus (LCMV) has a strong tropism for astrocytes, while feline immunodeficiency virus (FIV) can be a gene therapy vector. RNA interference (RNAi) is a process to specifically silence targeted genes. Our objective is to develop RNAi - mediated allele-specific gene therapy for AlxD , using an LCMV-pseudotyped FIV vector.

Methods: Astrocyte cultures were infected with LCMV-pseudotyped FIV vectors carrying green fluorescent protein (eGFP) as a reporter. Cos7 cells were transfected with vectors expressing the wild type or AlxD mutant form of GFAP alone or in combination with in vitro-transcribed siRNAs targeting the mutation. As a negative control, cells were transfected with in vitro transcribed mismatched siRNA. Silencing was tested with TaqMan and Western Blot assays.

Results: LCMV-pseudotyped FIV infected astrocytes and expressed eGFP. GFAP expression vectors alone induced substantial levels of wild type or mutant GFAP. The missense siRNA did not reduce GFAP expression. In contrast, siRNA directed against the AlxD mutation substantially suppressed expression of the mutant, but not the wild type, allele.

Conclusions: LCMV-pseudotyped FIV can be used as a gene therapy vector to deliver genes to astrocytes. RNAi can suppress expression of mutant GFAP in an allele-specific manner. These results suggest that LCMV-pseudotyped FIV, carrying siRNA against GFAP mutations, can be an effective gene therapy approach for AlxD.

Sources of Funding: Supported by NIH grant R21 NS052432-01A2 from NINDS to DJB.

Keywords: Translational/experimental therapeutics

PS1 - 4. Early Rpe65 Gene Therapy More Effectively Restores Precise Visual Responses to Retinal Ganglion Cells of Rpe65-/- mice in vitro

Stasheff SF (Iowa City, IA), Blodi FR, Shankar M, Bennicelli J, Bennett J, Bhatarrai S, Thompson S, Drack AV

Objective: To help further improve Rpe65 gene therapy for Leber's congenital amaurosis (LCA), we sought to better understand its effectiveness at the resolution of single cells and retinal circuits. Here we report substantial improvements in retinal ganglion cell (RGC) responsiveness to light in vitro, but persistent background hyperactivity that is ameliorated only by treatment early in development. Further understanding of underlying mechanisms may help explain the better response of children than adults seen in early clinical trials.

Methods: We measured RGC activity in rd12 (Rpe65-/-) mouse retinas using in vitro multielectrode recording, after subretinal injection with a viral vector to restore normal RPE65 expression (AAV2/1-hRPE65). We compared in vitro spontaneous and light-evoked activity in treated and untreated eyes at various time points following injection.

Results: Ganglion cell responses were robust in treated eyes, including multiple recognizable response types and reliable receptive field maps in many cells. However, others had weak or imprecise responses. Retinotopic regions receiving gene therapy corresponded to regions with light responsiveness. Spontaneous hyperactivity persisted after gene therapy, except when treatment was instituted at P4.

Conclusions: In vitro multielectrode recording evaluates the effectiveness of gene therapy at high resolution not possible in human patients. It can provide more detailed understanding of mechanisms underlying imperfect responsiveness to gene therapy, and guide further improvements in treatment. Our current results suggest that spontaneous hyperactivity corrupts the neural code of RGCs, decreasing the precision of some RGC responses and thus the quality of vision. However, very early treatment may prevent RGC hyperactivity.

Keywords: Translational/experimental therapeutics

PS1 - 5. The p75 Neuurotrophin Receptor and Autism

Schor NF (Rochester, NY), Lotta LT, Conrad K, Cor-Slechta DA

Objective: To test the hypothesis that the p75 neurotrophin receptor (p75NTR) plays a role in the pathogenesis of autism.

Methods: We have created a cerebellar Purkinje cell p75NTR conditional knockout mouse (with cre driven by the Purkinje cell protein 2 promotor) and have compared its motor and social behavior with that of cre-only and wild type mice.

Results: In knockout mice, motor behaviors associated with exploration of a foreign environment or stranger mice (sniffing and grooming) are decreased both as a percent of total study time ($p<0.01$) and as an absolute number of incidents per unit time ($p<0.05$) relative to cre-only controls. Conversely, stereotypies (as exemplified by perseverative behaviors) are increased both as a percent of total study time ($p<0.05$) and as an absolute number of incidents per unit time ($p<0.05$). Both social investigation and allogrooming are significantly ($p<0.05$) decreased in knockout mice relative to cre-only controls, even though cre-only controls also differ significantly ($p<0.01$) from wild type mice solely in social investigation.

Conclusions: Autism involves difficulty "reading" social cues; paucity of interpersonal interaction; and repetitive, stereotyped motor behaviors. It typically becomes clinically robust in the late toddler years and has been associated with inflammation, oxidative stress, and cerebellar Purkinje cell dysgenesis or apoptosis. The p75NTR exhibits anatomic restriction of expression at the same time as the appearance of and has been associated with the same biological factors as autism. The present findings support the importance of cerebellar Purkinje cell p75NTR for autistic behavior.

Sources of Funding: William H. Eilinger Endowment of the Department of Pediatrics, University of Rochester Medical Center.

Keywords: Translational/experimental therapeutics

PS1 - 6. Randomized, Controlled, Phase2 Trial of STX209 (Arbaclofen) for Social Function in Autism Spectrum Disorder

Kaufmann WE (Boston, MA), Walton-Bowen KL, Kuriyama N, Cherubini M, Carpenter RL, Bear MF, Wang P

Objective: STX209 is a selective GABA-B agonist showing disease-modifying effects in animal models of fragile X syndrome. It is hypothesized to modulate mGluR5 receptor signaling, and to augment inhibitory neurotransmission. In an open-label study of 32 subjects with Autism Spectrum Disorder (ASD), STX209 was associated with improvement in social withdrawal.

Methods: A 12-week randomized controlled trial was conducted in 150 subjects with ASD of unknown cause, age 5–21 years, and an ABC-Lethargy/Social Withdrawal (ABC-LSW) score ≥ 8. Other assessments included the CGI-I, CGI-S, and Vineland-II scales.

Results: 130 subjects completed the study, with 10 (8 on STX209) discontinuing due to adverse events (AEs), which were predominantly behavioral. There was 1 serious AE on STX209 (suicidal ideation). Suicidal ideation also occurred in 1 placebo subject. STX209 was well-tolerated overall, with 9% incidence of somnolence. On the primary endpoint (ABC-LSW), there was similar improvement on STX209 and on placebo ($p=0.5$). On the CGI-S, there was greater improvement on STX209 (-0.6 ± 0.1 vs. -0.2 ± 0.1, mean$\pm$SEM, $p=0.006$), and STX209 showed better scores on multiple other secondary endpoints. A post-hoc analysis showed significant improvement on the Vineland-Socialization scale (7.2 ± 1.4 vs. 1.8 ± 1.3,

p=0.006) among the 93 subjects who were assessed by the same evaluator at the start and end of treatment, as specified in the protocol. Many measures of social and global function showed numerically larger improvements in subjects with IQ≥70 than in those with IQ<70.

Conclusions: STX209 was well-tolerated and showed unprecedented potential for improvement in social function in ASD. Further prospective trials are needed.

Keywords: Case studies/case series, Translational/experimental therapeutics

LATE BREAKING ABSTRACT: PS1 - 7. A Somatic Mosaic Mutation in GNAQ Causes Sturge-Weber Syndrome and Isolated Port-wine Birthmarks

Shirley MD (Baltimore, MD), Tang H, Gallione CJ, Baugher JD, Frelin LP, Cohen B, North PE, Marchuk DA, Comi AM, Pevsner J

Objective: To determine the somatic mutation causing Sturge-Weber syndrome (SWS) and isolated port-wine birthmarks (PWB).

Methods: Whole genome sequencing followed by functional annotation and ranking was used to compare the DNA from unaffected and affected tissue from the three individuals with SWS. Confirmation of a candidate somatic mutation was done in two laboratories by targeted amplicon sequencing and by a primer extension based assay, with tissue from subjects with SWS, isolated PWB, and both post-mortem and Cavernous Capillary Malformation (CCM) controls. Function of the mutation was assessed by western analysis and luciferase assays of phosphorylated proteins in transfected T293 cells.

Results: A single variant was identified by analysis of the WGS data, a c.548G→A nucleotide transition in GNAQ on chromosome 9q21. The same somatic mutation was present in 1–18% of calls in 15 of 18 of SWS brain samples, 9 of 9 of SWS port-wine skin samples, 1 0f 7 normal skin SWS samples, 12 of 13 isolated port-wine samples, and in none of the controls. Phosphorylated ERK was significantly increased in both the mutant p.Gln209Leu and p.Arg183Gln transfected cells, although the increase was less in the cells with the p.Arg183Gln mutation.

Conclusions: The somatic mosaic mutation in GNAQ is predicted to "lock" the protein in the activated state thereby promoting constitutive activation of downstream pathways as supported by increased phosphorylation in cells transfected with the mutation. This breakthrough provides new opportunities for development of in vitro and animal models of SWS and the development of novel treatment strategies.

Keywords: Epilepsy and other paroxysmal disorders, Genetics, Stroke

Platform Session 2

PS2 - 1. A New Approach to the Classification of Developmental Hydrocephalus

Tully HM (Seattle, WA), Browd SR, Doherty D, Dobyns WB

Objective: Hydrocephalus is an established consequence of acquired events such as intraventricular hemorrhage and infection, but the causes of non-acquired forms are less well defined. Moreover, the division of hydrocephalus into communicating and obstructive subtypes dates from 100 years ago, with few refinements despite remarkable advances in imaging. We therefore studied a large group of infants with hydrocephalus, focusing on the radiographic and clinical features of hydrocephalus without an obvious extrinsic cause.

Methods: We searched the Seattle Children's Hospital imaging database for patients diagnosed with hydrocephalus within the first year of life and reviewed their MRIs and clinical records.

Results: 155 children had hydrocephalus attributable to an extrinsic cause, most often prematurity-associated hemorrhage. 238 patients had no recognizable extrinsic cause. Among these children, 5 clinical subtypes emerged: meningomyelocele-associated Chiari II malformations (N=78); primary aqueductal obstruction, often accompanied by additional mid- and hindbrain malformations (N=60); cysts, sometimes with associated skull defects (N=40); posterior fossa crowding, usually in the setting of skeletal dysplasia or megalencephaly (N=25); and hydrocephalus with no clear point of obstruction (communicating hydrocephalus, N=31). These groups exhibited differences in time of onset and severity.

Conclusions: In a large cohort of infants with hydrocephalus, 60% had no clear extrinsic cause. Based on imaging features, these patients could be divided into 5 subgroups that reflect pathogenesis and differ in time of onset and severity. We propose to use these categories to help identify genetic causes of congenital hydrocephalus and to evaluate differences in outcomes and response to treatment.

Keywords: Case studies/case series, Neonatal neurology, Neuroimaging

PS2 - 2. Extremely Low Gestational Age Newborns (ELGANs) with Repeatedly Elevated Blood Concentrations of Inflammation-related Proteins within 15 Days of Birth are at Higher Risk of Cerebral Palsy

Kuban KCK (Boston, MA), O'Shea TM, Leviton A, Allred EN, Paneth N, Hirtz D, Fichorova R

Hypothesis: Extremely preterm infants with elevated postnatal blood levels of inflammation-related proteins are more likely than their peers to develop quadriparetic, diparetic, and hemiparetic CP by age 2.

Method: Concentrations of 25 blood proteins obtained within 3 days of birth and at one and two weeks of life from 939 infants born < 28th week gestation were evaluated for their ability to predict CP at 2 years. We defined a protein elevation as a concentration in the top quartile for gestational age and postnatal day. Multinomial logistic regression models adjusting for GA provided odds ratios for each CP diagnosis.

Results: No single protein concentration elevation within three days of birth was associated with CP. On day 14, 1

protein was associated with diparesis (OR 3.8) and 3 with hemiparesis (OR 4.0–4.2). Quadriparesis was more likely when levels of MCP-1 and IL-8 were elevated on at least two days (OR 2.1–2.5). Diparetic CP was more likely when TNF-α, TNF-R1, IL-8, ICAM-1 were elevated on ≥2 days (OR 2.4-3.5) as was hemiparetic CP when IL-6, E-SEL, or IGFBP-1 were elevated on ≥2 days (OR 3.1–7.1). Recurrent-persistent elevations of any four of nine proteins (IL-6, TNF-α, TNF-R1, IL-8, ICAM-1, E-SEL, CRP, SAA and IGFBP-1) were associated with increased diparetic and hemiparetic CP risk (OR 3.0–4.2)).

Conclusion: Extremely preterm newborns with repeatedly elevated concentrations of a number of inflammation-related proteins in their blood during the first two postnatal weeks are at increased risk of a cerebral palsy diagnosis two years later.

Sources of Funding: This study was completed as a cooperative agreement with the National Institute of Neurological Disorders and Stroke (5U01NS040069-05 and 2R01NS040069-06A2).

Keywords: Neonatal neurology

PS2 - 3. Therapeutic Hypothermia is Associated with Improved Outcomes in Perinatal Stroke

Harbert MJ (San Diego, CA), Haeusslein LA, Bonifacio SL, Rogers EE, Glass HC, Cilio MR, Jeremy RR, Barkovich AJ, Ferriero DM, Tam EWY

Objective: We have previously demonstrated association between therapeutic hypothermia in perinatal stroke and decreased risk for neonatal seizures. Here we evaluated these children in follow-up to determine if hypothermia was correlated with improved outcomes.

Methods: In a prospective cohort study of MRI in neonatal encephalopathy, 14 of 330 subjects had focal ischemic infarcts in the neonatal period. Subjects at 12 and 30 months of age were assessed using the Bayley Scales of Infant Development (BSID-II or Bayley-III) and graded using a neuromotor score. Bayley-III cognitive and language scores were adjusted using a published algorithm to reflect the BSID-II MDI score.

Results: Five of 14 stroke subjects received therapeutic hypothermia. 93% were seen in follow-up at 12 months and 71% at 30 months. There was no difference in mean MDI scores at 12 months of age ($p=0.8$) between cooled and uncooled groups. However, a 31-point higher mean MDI score was found in the cooled group by 30 months of age ($p=0.1$, non-cooled group MDI mean score 67 +/- SD 18, cooled group mean 98 +/- SD 33). A difference in neuromotor scores was seen at 12 months of age ($p=0.05$, median non-cooled group 2.0 (IQR = 1.25) and median cooled group 0.0 (IQR = 0.0)) but not at 30 months ($p=0.2$.)

Conclusions: Possible association between therapeutic hypothermia and improved outcomes was identified in children who suffered perinatal stroke associated with encephalopathy. This potential association should stimulate larger prospective studies to determine if therapeutic hypothermia improves outcome after perinatal stroke.

Sources of Funding: National Institutes of Health [P50 NS35902, UL1 RR024131, NINDS 1K23NS066137 (HCG)] Cerebral Palsy International Research Foundation Ethel & Jack Hausman Clinical Research Scholar (EWYT).

Keywords: Neonatal neurology, Stroke

PS2 - 4. The Natural History of Late Infantile CLN2 Disease: Striking Homogeneity of Clinical Progression in Two Independently Obtained Large Clinical Cohorts

Schulz A (Hamburg, Germany), Nickel M, Downs M, Mezey J, Landy H, Sondhi D, Jacoby D, Wittes J, Crystal RG, Kohlschuetter A

Objective: Late infantile CLN2 disease (CLN2) is a lysosomal storage disease and characterized by progressive psychomotor and language decline. A disease-specific rating scale was developed 10 years ago and now used in an expanded cohort of 29 genetically confirmed patients.

Methods: This new study focused on (i) first symptoms to support early diagnosis, (ii) prospective longitudinal data acquisition covering a period of 26 years, and (iii) quantification of rate of decline as a means to measure disease progression.

Results: (1) Early symptoms of CLN2 comprise delayed language acquisition and seizures (73% of patients; median age of onset 37 months). (2) Disease progression was measured longitudinally by the sums of 3-point motor and language subscales of the Hamburg-LINCL score. Onset of neurological decline occurred at a median of 39 months of age. Onset of symptoms leads to a rapid, progressive clinical decline with a linearized mean rate of decline of 2.2 units/year (SD±1.1). Slowly progressing patients were uncommon and mostly related to unusual genotypes. The age-specific level of functioning was similar in an independent dataset of 62 observations in 43 patients from the Weill Cornell CLN2 cohort. Further, quantification of CNS MRI parameters of the Weill Cornell subjects showed similar status.

Conclusion: This analysis of CLN2 natural history shows high homogeneity in the population across time and geography. The data underscore the rapid decline in this disease, and therefore the importance of early diagnosis for potential therapies. CLN2 should be considered in young children with new onset seizures of uncertain etiology.

Keywords: Genetics, Neuroimaging

PS2 - 5. The Presenting Features of Arterial Ischaemic Stroke in a Population-Based Cohort

Mallick AA (Bristol, UK), Ganesan V, Kirkham FJ, Fallon P, Hedderly T, McShane MA, Parker AP, Wassmer E, Wraige E Amin S Edwards HB O' Callaghan FJ

Objective: To describe the presenting features of childhood arterial ischaemic stroke (AIS) and analyse factors associated with such features.

Methods: Records of a population-based cohort of 96 children (aged >28 days to <16 years) with AIS onset between July 2008 and June 2009 were analysed. Presenting features and risk factors were categorised according to schemes used by the International Pediatric Stroke Study.

The commonly used adult stroke recognition tool, the FAST (Face Arm Speech Time) test was applied retrospectively.

Results: Focal features were present in 85% of children, diffuse features in 61% and seizures in 29%. A hemiparesis was present in 72% of children. 78% of children had a least one positive variable (facial weakness, arm weakness, or speech disturbance) on the FAST test. Diffuse features occurred more frequently with increasing age (odds ratio 1.14 [95%CI 1.03 - 1.26], p=0.015). Seizures were less likely with increasing age (OR 0.83 [95%CI 0.72 - 0.96], p=0.012). A positive FAST test was not associated with age. Diffuse features were independently associated with acute systemic risk factors (OR 5.36 [95%CI 1.72 - 16.7], p=0.0004). Arteriopathy was independently associated with reduced odds of seizures (OR 0.18 [95%CI 0.04 - 0.86], p=0.031). Children with acute systemic risk factors had reduced odds of a positive FAST test (OR 0.23 [95%CI 0.08 - 0.69], p=0.009). Presenting features did not significantly vary with gender.

Conclusions: The presenting features of childhood AIS are similar to those in adult AIS. However, presenting features vary according to age and underlying risk factors.

Keywords: Stroke

PS2 - 6. A 53-gene Sequencing and Deletion/Duplication Panel Reveals a Broader Spectrum of Genotype-Phenotype Correlations in Epilepsy.

McKnight D (Gaithersburg, MD), Butler E, Shanmugham A, Downtain C, Entezam A, Aradhya S

Objective: Mutations in many genes and biological pathways have been linked to epilepsy in the past decade. However, the discovery of many of these genes occurred in small populations with restricted and homogeneous phenotypes and often with analysis of a single gene. As a result, the full phenotypic spectrum associated with many epilepsy-related genes remains unknown. We report the expanded genotype-phenotype correlation of multiple epilepsy-related genes through the clinical use of a 53-gene sequencing and deletion/duplication panel.

Methods: A cohort of 1,400 individuals with isolated or syndromic forms of epilepsy was tested using a targeted epilepsy panel that combines Next Generation sequencing and deletion/duplication testing by exon-level array CGH of up to 53 genes simultaneously.

Results: Our data illuminates a broader phenotypic spectrum for some genes previously thought to have limited involvement in one type of epilepsy. Consequently, genes previously known to be associated with specific non-syndromic forms of epilepsy are proving to have a more complicated phenotypic impact. Patients reported to have encephalopathy had mutations identified in SLC2A1, KCNQ2 and GABRG2, some patients with reported movement disorders had mutations in the GABRA1 and SCN2A, and others with autism/intellectual disability in GABRA1, GABRG2, KCNQ2 and SCN2A. In addition, our data also highlight the complexity contributed by reduced penetrance associated with mutations in several epilepsy genes, including ion channel genes, CNTNAP2, NRXN1, LGI1, and others.

Conclusions: Corroborating the well-described genetic heterogeneity in epilepsy, our data emphasize the need for a multi-gene analysis to obtain meaningful molecular diagnoses in a clinical population.

Sources of Funding: GeneDx.

Keywords: Genetics

LATE BREAKING ABSTRACT: PS2–7. Preventable Infections in Children with Leukodystrophies

Anderson HM (Salt Lake City, UT), Wilkes J, Korgenski EH, Bonkowsky JL

Objective: Leukodystrophies are inherited diseases of the myelin of the brain with significant morbidity and mortality. 1/3rd of children die before age 8 years; and costs for treatment are high, averaging more than $100,000 per patient. Despite having such high healthcare needs and high mortality, there are no standards of care. Infections have been shown previously to be a significant cause of hospital admissions and costs. Our objective was to determine whether leukodystrophy patients had potentially modifiable risk factors for infections, and what those risk factors were.

Methods: We conducted a retrospective, hospital- and clinic-based surveillance of inherited leukodystrophies among children less than 18 years of age presenting to a children's hospital from January 1, 1999 through June 30th, 2013; clinical information was abstracted from medical records.

Results: 160 children with an inherited leukodystrophy were identified. There were 232 hospitalizations with infection. 75 out of 160 patients were hospitalized with infections (47%). Statistically significant risk factors for infection included bulbar insufficiency, bone marrow transplant, in-dwelling central iv access, in-dwelling urinary catheter, tracheostomy and/or ventilator, and no influenza vaccine received. These risk factors were significant in both immune-suppressed patients (bone marrow transplant) and immune-competent patients. Odds ratios (OR) for sepsis were 9.8 from a central line, 3.7 from a urinary catheter; and 1.7 from in-dwelling hardware. In-dwelling urinary catheter had an OR for urinary tract infection of 9.0. Not receiving an influenza vaccine had an OR for influenza of 6.4. Tracheostomy and/or ventilator had an OR for pneumonia of 2.7.

Conclusions: We identified modifiable risk factors for infection in leukodystrophy patients. Modifiable risk factors include administering influenza vaccination every year, improved care for in-dwelling iv lines, urinary catheters, tracheostomies, ventilators, and in-dwelling hardware, and more aggressive prophylactic care for patients with bulbar insufficiency and bone marrow transplant.

Posters

1. Fatal Necrotizing Leukoencephalopathy Associated with Proton Beam Radiation Therapy and Intensive Chemotherapy in Young Children with Brainstem Region Tumors

Wells EM (Washington, DC), Kilburn L, Rood B, Crozier F, Tryggestad-Codispoti K, Hwang E, Lustig R, Mahajan A, Vezina G, Packer RJ

Objective: Proton beam radiation (PBR) is a new technique of radiation delivery being employed in pediatrics due to its potential to cause less toxicity to surrounding tissue. We report three autopsy-confirmed treatment-related deaths in 3 out of 33 pediatric patients with brain tumors referred from our institution for PBR in the past four years.

Methods and Results: All patients were less than 3 years of age with high grade posterior fossa tumors (AT/RT, disseminated anaplastic medulloblastoma, anaplastic ependymoma). Two patients received 54Gy focal radiation, one (medulloblastoma) received 39Gy whole brain and 36Gy spinal. Two children were treated with pre-PBR alkylator and cisplatin-based chemotherapy regimens (one with methotrexate); both received post-PBR high dose thiotepa-based chemotherapy, supported by stem cell rescue. The third child (ependymoma) received post-PBR alkylator and cisplatin-based therapy. MRI scans 2–6 weeks post-PBR showed no immediate radiation-induced changes. MRI evidence of brainstem damage was detected at 2, 3, and 3 months; clinical evidence of brainstem damage including irritability and apnea emerged at 3, 6, and 3 months; the patients died at 3, 7, and 6 months post-PBR, respectively for AT/RT, medulloblastoma, and ependymoma. All children were treated with dexamethasone and two received Avastin; one had transient clinical improvement. Autopsy demonstrated multifocal necrotizing leukoencephalopathy and areas of demyelination. One child (medulloblastoma) also had residual disease at autopsy.

Conclusion: Proton beam therapy is increasingly recommended to spare long term adverse effects of radiation but further investigation of early risks is warranted given these deaths, especially if intensive chemotherapy is also administered.

Keywords: Brain tumors/oncology

2. Massive Soft Tissue Neurofibroma (Elephantiasis Neuromatosa) – Case Report and Review of Literature

Santos Pinheiro F (Cleveland, OH), Rothner AD

Objective: Describe a case of Massive Soft Tissue Neurofibroma - MSTN (also known as elephantiasis neuromatosa) and review the literature.

Methods: We describe the clinical management of a 22 year-old male with MSTN. We also gathered 71 case reports (total of 91 patients), in order to compare the clinical findings and management of this rare condition. This is the largest review of literature on MSTN.

Results: A total of 71 case reports were reviewed. The mean age by the time of evaluation was 21 years (66% male). The onset was predominantly reported during childhood years, whereas in 39% of cases the tumor was present since birth. The commonest affected body segment was the lower extremity (46%) followed by head/neck (30%), trunk (including back, abdomen and genitalia −15%) and upper extremity (9%). CT and MRI were the preferred imaging modality for assessment. Surgical approach was pursued in the majority of cases (79%) while conservative (no biopsy/surgical intervention) was reported 7%. Bleeding was the most frequent complication during surgery. Recurrence of tumors was described in 12% of cases. Malignant transformation into MPNST occurred in 5%.

Conclusions: MSTN affects only patients with neurofibromatosis type 1. Although initial findings are noticed during the first years of life, it is hard to predict its progression or whether surgery is beneficial in early stages. Massive tumor overgrowth may take years to develop and patients may not be surgical candidates until further progression. Surgical management is associated with high bleeding risk. Malignant transformation is rare.

Keywords: Brain tumors/oncology

3. Bilateral Internuclear Ophthalmoplegia Associated with Pediatric Brain Tumor Progression: A Case Series and Review of the Literature.

Rismanchi N (San Diego, CA), Crawford JR

Objective: Internuclear ophthalmoplegia (INO) is a rare disorder of conjugate lateral gaze that has been described in a number of neurologic conditions including multiple sclerosis, stroke and less commonly brain tumors. We describe a series of three children who developed bilateral INO as a manifestation of brain tumor progression.

Methods: The clinical presentation, neuroradiographic findings, histopathology, neurologic examination and outcome are described in a series of three neuro-oncology patients diagnosed with bilateral INO at Rady Children's Hospital San Diego. A literature review on the association of INO and brain tumors was performed.

Results: Three boys (ages 11, 12, 15 y) diagnosed with primary central nervous system tumors (pilomyxoid variant astrocytoma, anaplastic oligoastrocytoma, gliomatosis cerebri) developed bilateral INO as a manifestation of progressive disease. Time from diagnosis to development of bilateral INO ranged from 13–36 months. All children died of their disease 1–9 months following diagnosis of bilateral INO and had significant dorsal pontine invasion on magnetic resonance imaging at progression. Only one child had brainstem involvement at diagnosis.

Conclusions: Our case series highlights the importance of INO as a potential marker of poor prognosis signifying brainstem invasion in children with progressive central nervous system tumors.

Keywords: Brain tumors/oncology, Case studies/case series

4. Histopathologic Diagnosis of Neurofibroma in Lesion with Clinical and Imaging Features Resembling Vascular Anomalies

Yilmaz S (Pittsburgh, PA), Zammerilla L, Osman M, Ozolek J, Davis A, Fitz C, Crowley JJ, Grunwaldt L, Gardner K, Goldstein AC

Objective: Although rare, the initial clinical and imaging presentations of plexiform neurofibromas can mimic those of vascular anomalies, particularly if the characteristic clinical features of neurofibromatosis-1 are not present.

Methods: Patients with histopathologic diagnosis of neurofibroma were seen at the Neurofibromatosis Clinic. These patients were initially misdiagnosed and followed as vascular anomalies and initially referred to the Vascular Anomalies Center (VAC) for evaluation.

Results: We report the clinical, imaging, and pathologic features of a case series of plexiform neurofibromas, resembling the clinical and imaging characteristics of vascular anomalies including infantile hemangioma, non-involuting congenital hemangioma, microcystic lymphatic malformation, and venous malformation. One patient had Kasselbach-Merritt syndrome in the newborn period, thought to be secondary to a large vascular malformation. He developed further symptoms of NF1 and had several more vascular-appearing plexiform neurofibromas. Patients were followed longitudinally in NF Clinic, and other features of NF1 were identified or evolved over time in some of the patients. Confirmation of NF1 was made based on clinical criteria or molecular confirmation.

Conclusions: The clinical and imaging differences between plexiform neurofibromas and vascular anomalies are highlighted with the goal of preventing diagnostic pitfalls in the future. Clinicians should consider initial evaluation and ongoing surveillance for NF1 related plexiform tumors in the differential diagnosis of mass lesions with highly vascularized features.

Keywords: Brain tumors/oncology, Case studies/case series, Genetics

5. Dysembryoplastic Neuroepithelial Tumor (DNET): A Retrospective Review at Memorial Sloan Kettering Cancer Center (MSKCC)

Fischer C (New York, NY), Young RJ, Huse JT, Khakoo Y

Objective: DNET is a rare benign glioneural tumor in children and young adults associated with intractable seizures. The purpose of this study is to review imaging studies, operative and pathology reports, and clinical features of DNET, in patients whose pathology was evaluated at MSKCC from 1993–2012.

Methods: IRB approval was obtained and a Dataline search conducted. Available imaging studies and medical records were reviewed for each patient and a de-identified database was formed.

Results: We identified 33 patients with a diagnosis of DNET with an age range of 2 to 62 years old. Twenty were female. Most patients presented with seizures, but headache and dizziness were also noted. The majority of tumors were confined to an isolated lobe of the brain. All patients had pathologic confirmation of diagnosis at MSKCC. Surgical intervention included biopsy, partial resection, or gross total resection. Three patients had documented progression of disease before initial resection and another 5 developed recurrent disease requiring re-resection; of these 2 received external beam radiation therapy. Detailed medical records were available for 10 patients, all of whom are alive and continue to require anti-epileptic medications. Five patients were noted to have persistent neurocognitive deficits.

Conclusions: Our data are consistent with previous reports that DNET is typically low grade and commonly causes seizures. Interestingly we had two patients with recurrent tumors who went on to receive external beam radiation therapy. Further study is required to assess the effect of seizures and neurocognitive deficits on quality of life in patients with DNET.

Keywords: Brain tumors/oncology, Case studies/case series, Neuroimaging

6. Subacute Methotrexate Leukodystrophy: A Case Series

Kanaan SH (Oklahoma City, OK), Belbeissi TA, Chrusciel DG, Khan O, Ng YT

Objective: We aim to familiarize pediatric neurologists with the clinical and radiographic features of subacute methotrexate (MTX) leukodystrophy (neurotoxicity).

Methods: The clinical and magnetic resonance imaging (MRI) findings of 4 children with subacute MTX leukodystrophy were reviewed. All 4 patients had acute lymphocytic leukemia and were treated with intrathecal MTX. The first patient was a 13-year-old girl who developed acute right hemiparesis and dysarthria. Brain MRI revealed restricted diffusion in the left centrum semiovale. Her symptoms resolved after 24 hours but then almost immediately developed left hemiparesis. Repeat MRI 48 hours later showed resolution of the prior MRI changes and the development of new restricted diffusion in the right parietal white matter. The second patient was a 17-year-old boy who developed acute-onset encephalopathy, dysarthria, and right facial weakness. Brain MRI revealed restricted diffusion bilateral posterior white matter. The third patient was a 9-year-old girl who developed acute left hemiparesis. Brain MRI revealed restricted diffusion in bilateral posterior white matter. The fourth patient is a 2.5-year-old boy who presented with complex partial status epilepticus. MRI revealed T2 FLAIR hyperintensity in the left putamen.

Results: In view of the clinical history and the non-vascular distribution of the MRI findings, the patients were diagnosed with subacute MTX leukodystrophy. All 4 of our patients had complete recovery within a few days.

Conclusion: Subacute MTX leukodystrophy can mimic acute ischemic stroke in its clinical and radiographic features. The clue to diagnosis lies in the history of MTX administration and the non-vascular distribution of MRI changes.

Sources of Funding: YT Ng is a consultant for Lundbeck, Inc. and Questcor Pharmaceuticals, and is on the speakers bureau for UCB Pharma, Lundbeck Inc. and Cyberonics Inc.

Keywords: Brain tumors/oncology, Case studies/case series, Neuroimaging

7. Everolimus Long-Term Safety and Efficacy in Patients with Subependymal Giant Cell Astrocytomas (SEGAs) Associated with Tuberous Sclerosis Complex

Krueger DA (Cincinnati, OH), Care MM, Holland-Bouley K, Agricola K, Tudor C, Prestifilippo J, Berkowitz N, Franz DN

Objective: To examine the long-term safety and efficacy of the mTOR inhibitor everolimus in a prospective, open-label, phase 1/2 trial (NCT00411619) using data available as of 14 Dec 2011 (original cut-off 09 Dec 2009). The original 6-month study demonstrated a significant reduction in SEGA volume and patient-reported seizure frequency.

Methods: Patients ≥3 years of age with a definitive TSC diagnosis and confirmed radiological evidence of serial SEGA growth received oral everolimus starting at 3 mg/m2/day (titrated to blood trough levels of 5–15 ng/mL). The primary endpoint was safety, and measures of efficacy included reduction from baseline in primary SEGA volume and corresponding ≥30% or ≥50% response rates.

Results: Of 28 patients enrolled, 24 were continuing treatment at the time of this update. Median age was 11 years (range 3–34 years), median dose was 5.22 mg/m2/day (range 2.0–11.8), and median treatment duration was 45.7 months (range, 4.7–58.5). After 36 (n=23), 42 (n=16), and 48 (n=10) months of everolimus treatment, there was a ≥30% reduction from baseline in primary SEGA volume for 78.3%, 75.0%, and 90% of patients, respectively, and a ≥50% reduction from baseline in primary SEGA volume for 43.5%, 37.5%, and 50.0% of patients, respectively. Patient-reported seizure frequency generally decreased over time. There were no drug-related grade 4 adverse events (AEs); 6 patients had at least 1 drug-related grade 3 AE. No patient discontinued treatment due to an AE.

Conclusions: The results of this 3-year follow-up analysis confirm maintenance of reductions in SEGA volume and no new safety concerns.

Keywords: Brain tumors/oncology, Epilepsy and other paroxysmal disorders, Genetics

8. Effect of the mTOR Inhibitor Everolimus on Angiogenic Biomarkers in Patients with Skin Lesions and Subependymal Giant Cell Astrocytoma (SEGA) Associated with Tuberous Sclerosis Complex (TSC)

Franz DN (Cincinnati, OH), Frost MN, Prestifilippo J, Brechenmacher T, Jozwiak S

Objective: To compare changes in soluble angiogenic biomarkers among patients with different skin lesion response in the EXIST-1 trial (NCT00789828). Previously, this trial demonstrated that everolimus was superior to placebo for reducing SEGA volume (P<0.0001), and in patients who had ≥1 skin lesion at baseline (n=110), a greater proportion of everolimus patients experienced clinical skin lesion response (P=0.0004).

Methods: Patients (median age 9.5 [range, 0.8–26.6] years) received 4.5 mg/m2/day oral everolimus (n=78; target trough, 5–15 ng/mL) or placebo (n=39). Plasma levels of vascular endothelial growth factor (VEGF)-A and -D, placental growth factor (PLGF), soluble VEGF receptor-1 and −2 (sVEGFR1 and sVEGFR2), c-Kit, and collagen type IV (col IV) were measured at baseline and day 1 of weeks 4, 12, 24, 36, and 48.

Results: Similar baseline plasma levels of biomarkers were noted between skin lesion responders and nonresponders. Among everolimus patients, 30 had skin lesion responses and 42 were nonresponders. Regardless of skin lesion response, no change in any biomarker level was seen in placebo patients and no change in PLGF, c-Kit, or sVEGFR1 was detected in everolimus patients. At week 24 in everolimus patients, VEGF-A increased in skin lesion responders and nonresponders by 26% and 43%, respectively, col IV decreased by 32% and 24%, respectively, and sVEGFR2 decreased ∼20% in both responders and nonresponders. In everolimus skin lesion responders, there was a trend toward decreased VEGF-D levels.

Conclusions: While everolimus modulated multiple angiogenic markers, no strong association between change in angiogenic markers and skin lesion response was observed.

Keywords: Brain tumors/oncology, Genetics

9. Exploratory Analyses from the EXIST-1 Trial: The Effect of the mTOR Inhibitor Everolimus on Subependymal Nodule (SEN) and Tuber Volume in Patients with Subependymal Giant Cell Astrocytoma (SEGA) Associated with Tuberous Sclerosis Complex (TSC)

Franz DN (Cincinnati, OH), Prestifilippo J, Cauwel H, Jozwiak S

Objective: To examine the impact of everolimus on SEN and tuber volume in patients with SEGA associated with TSC in the EXIST-1 trial (NCT00789828). This trial previously demonstrated that everolimus was superior to placebo for reducing SEGA volume (P<0.0001).

Methods: Patients (median age 9.5 [range 0.8–26.6] years) received 4.5 mg/m^2/day oral everolimus (n=78; target trough 5–15 ng/mL) or placebo (n=39). Target SENs and tubers (lesions with longest diameter ≥1 cm) were assessed by brain MRI at baseline, at 12, 24, and 48 weeks after randomization, and annually thereafter.

Results: For the subset of patients with SENs and tubers, the median (range) baseline SEN and tuber volumes were 0.88 cm3 (0.10-6.0) and 26.4 cm3 (0.8–158.9), respectively. After 24 and 48 weeks of everolimus treatment, the percentage changes from baseline (range) in the median sums of SEN volumes were −35.4% (−79.0%-121.9%) and −35.3% (−79.9%-23.8%) compared with −12.4% (−45.4%-16.1%) and 6.6% (−19.4%-17.4%) in the placebo arm, respectively. At these same time points, the percentage changes from baseline (range) in the median sums of tuber volumes were −5.5% (−67.5%-46.6%) and 0.07% (−72.3%-59.9%) in the everolimus arm compared with −2.7% (−41.8%-85.2%) and −8.7% (−46.9%-37.3%) in the placebo arm, respectively. Adverse events remained similar to those previously reported for everolimus, mostly grade 1/2.

Conclusions: No clear effect of everolimus on reducing SEN and tuber volume was noted due to the high variability in percentage change observed for both treatment arms.

Keywords: Brain tumors/oncology, Genetics

10. Role of CRABPI in Potentiation of Fenretinide Efficacy in Neuroblastoma

Pu Y (Rochester, NY), Li X, Schor NF

Objective: To test the hypothesis that the effects of p75NTR neurotrophin receptor (p75NTR) on

mitochondrial complex II and the retinoic acid binding protein, CRABPI, play a role in its enhancement of fenretinide sensitivity in neuroblastoma cells.

Methods: p75NTR was transfected into 3T3 fibroblast cells, which normally do not express the protein. The localization and trafficking of p75NTR and protein expression levels, mRNA transcript levels, and function of complex II were assessed. CRABPI protein and mRNA levels were assessed in human neuroblastoma cell lines known to express different amounts of p75NTR. CRABPI levels were also assessed in a human neuroblastoma cell line made to overexpress p75NTR before and after p75NTR knockdown. Finally, CRABPI levels were assessed over time in neuroblastoma cells treated with fenretinide.

Results: Protein and mRNA levels and enzymatic activity of complex II did not change following p75NTR transfection of 3T3 cells. However, CRABPI protein and mRNA levels covaried with p75NTR levels in native and p75NTR-overexpressing neuroblastoma cell lines. Knockdown of p75NTR in overexpressing cells decreased CRABPI expression. CRABPI decreased in both overexpressing and control cells in a time-dependent manner during fenretinide exposure. The activated cleavage product of p75NTR, p75ICD, localized to the nucleus, suggesting it is a transcription factor that influences expression of CRABPI.

Conclusions: p75 did not affect complex II, but its levels correlated with CRABPI protein expression. p75ICD trafficked to the nucleus, where it may affect transcription of CRABPI. CRABPI may serve as an adjunctive therapeutic target to enhance the chemotherapeutic efficacy of fenretinide in neuroblastoma.

Keywords: Brain tumors/oncology, Translational/experimental therapeutics

11. Burnout Syndrome in Pediatric Practice

Al-Youbi RA (Jeddah, KSA), Kan MM

Objective: Burnout is a common work-related syndrome consisting of emotional exhaustion, depersonalization, and diminished feelings of personal accomplishment. Burnout will influence the performance and efficiency of the health care professional and therefore the quality of the provided care. We aim to assess the burnout rates and potential determinants in pediatrics.

Methods: A cross-sectional, descriptive study involving physicians practicing pediatrics in the Jeddah area of Saudi Arabia was conducted utilizing the Maslach Burnout Inventory in addition to questions regarding work-related and lifestyle-related factors.

Results: One hundred and thirty pediatricians (55% females) were included with ages ranging between 25–45 years (mean 30). Most (46%) were consultants, and 54% practiced in a university based setting. Burnout scores were abnormal in 107 (82%) and in 45 (34%) the syndrome was severe. Males were more likely to reach a severe burnout category when compared to females (40% vs 31%, $p=0.012$). Academic pediatrician, working in a university setting, were much more likely to have severe burnout when compared to those working in other hospitals (50% vs 19%, $p=0.0005$). Consultants were also more likely to have severe burnout when compared to residents and assistants (46% vs 27%, $p=0.03$).

Conclusions: At least one third of practicing pediatricians are suffering from burnout syndrome. Specific strategies should be developed and implemented to limit and prevent professional burnout.

Keywords: Case studies/case series

12. Percutaneous Endoscopic Gastrostomy (PEG) Tube Placement in Children with Neurodevelopmental Disabilities: Parent's Perspectives

Alsaggaf AH (Jeddah, KSA), Jan MM, Saadah OI, Alsaggaf HM

Objective: Children with neurodevelopmental disabilities often have serious feeding problems. Placing a percutaneous endoscopic gastrostomy (PEG) tube feeding has a positive impact on growth and quality of life; however the parents frequently resist this decision. We aim to study the attitudes of parents toward PEG tube placement and identify possible correlating and contributing factors to their negative attitudes.

Methods: Consecutive parents of children with neurodevelopmental disabilities were included retrospectively through a single endoscopy unit. A structured 25-item questionnaire was designed to examine their demographics, attitudes, and experience.

Results: 30 families were included with patient's ages of 3–19 years (mean 10.2). Most patients (77%) had severe cerebral palsy. Their PEG tubes were inserted 2–144 months (mean 39) prior to our encounter. Only 43% of the parents felt informed and 73% had negative attitudes toward the procedure which correlated with resistance and delay ($p=0.016$). After the PEG placement, most parents (67%) reported a better than expected experience, correlating with their information levels ($p=0.03$). Most parents (80%) regretted not having the PEG tube placed earlier. Those who were not informed were more likely to have strong regrets when compared to those informed (82% vs 42%, $p=0.008$).

Conclusions: Many parents are not well informed about the PEG procedure, affecting their expectation and experience. Most parents had a better that they expected experience and regretted not having it done earlier. Our findings would hopefully help parents to make the decision earlier.

Keywords: Case studies/case series

13. Evaluation of Somatoform Conditions Seen by a Neurological Consultation Service in a Tertiary Care Pediatric Emergency Room

De Gusmao C (Boston, MA), Guerriero RM, Bernson-Leung M, Davis P, Pier DB, Maski KP, Urion DK, Waugh JL

Background: Somatoform symptoms are frequently the basis for neurologic consultation in the acute care setting. In children, the frequency, severity, and best management practices for these symptoms are unknown.

Objective: To assess the number of neurology consultations in which a somatoform condition is considered, to identify population characteristics and management practices associated with improved clinical outcome.

Methods: Over a 3-month period, patients seen in a tertiary care children's hospital by Neurology residents in which a somatoform condition was suspected were prospectively collected. Conditions documented included conversion, undifferentiated and somatoform disorder NOS, and non-headache pain disorders. Data collected included demographic characteristics, risk factors (psychiatric/medical co-morbidities, social/academic stressors, physical or sexual abuse), and management practices (admission and ER utilization, outpatient referrals). Finally, outcome measures were assessed, including symptom duration, return visits, satisfaction with care provided, and lost days of school and parental work.

Results: Of the 33 subjects analyzed, 58% were female and the mean age was 16 years. 75% had only one or no recognized trigger, 10% had family stressors and 21% had academic stressors. No cases of sexual or physical abuse were identifed.

Conclusions: Pediatric somatoform diagnoses are commonly included in the diferential diagnosis of patients seen in our ER. The final diagnosis proved to be non-organic in 94% of these patients. In the majority, predisposing features are common and ubiquitous, not the extraordinary stressors often assumed to be necessary to provoke somatoform disorders. Patients and families were substantially impacted by these diagnoses, based on days of missed work and school. Increased education for providers and resources for patients with somatoform conditions is needed, particularly in the outpatient setting

Keywords: Case studies/case series

14. Childhood Basilar Artery Occlusion. A Report of 5 Cases and Review of the Literature

Chikkannaiah M (Columbus, OH), Lo WD

Background: Basilar artery occlusion (BAO) has poor outcome in adults; little is known regarding outcomes in children. Whether intra-arterial treatments (IAT) improve adult outcomes is controversial. Safety and efficacy of IAT in children is unknown. We report five cases of BAO and review published cases.

Methods: We estimated NIH stroke score (NIHSS) and modified Rankin score (mRS) of published cases, compared scores between non-IAT and IAT groups, and examined the correlation between NIHSS and mRS.

Results: Of our cases, 4 had good outcomes and one died. Of 63 published cases, 45 had no IAT and 18 had IAT. In the non-IAT group 24 had good outcomes. In the IAT group 13 had good outcomes. There was strong correlation between the NIHSS and the mRS.

Conclusion: Children with BAO have better outcomes than adults. Certain children with BAO may be treated conservatively. A registry for childhood BAO is urgently needed.

Keywords: Case studies/case series

15. Cognitive Impairment Associated with Low Ferritin Responsive to Iron Supplementation

Qubty WF (Rochester, MN), Renaud DL

Objective: Iron deficiency is the most common nutritional deficiency in children. Iron is essential for effective mitochondrial electron transport and neurotransmitter synthesis. Prior studies have shown a correlation between iron storage deficiency and impaired psychomotor development, periodic limb movements of sleep, and breath-holding spells. We review here 3 cases of cognitive impairment improved with iron supplementation.

Methods: We reviewed 3 cases of pediatric patients referred for further evaluation of developmental delay/ cognitive impairment. Extensive testing was negative in these patients except for low ferritin.

Results: The first patient was referred at 14 months of age for gross and fine motor delay, found to have a ferritin of one and hemoglobin of six. He was treated with ferrous sulfate and by 18 months was developmentally normal. The second patient was evaluated at 3 years old for mild global developmental delay and found to have a ferritin of 4. He was treated with ferrous sulfate. Within 1 year he made significant progress and was participating in regular preschool classes. The final patient was seen at 12 years old and had visual and auditory hallucinations, restless legs and depressed mood develop one year prior. Her ferritin was 8 and within one month of her 1st iron sucrose infusion, her psychiatric symptoms were unchanged but cognitive abilities returned to baseline and school performance was improved.

Conclusion: This cohort demonstrated dramatic improvement in cognition once iron stores were repleted, suggesting iron studies should be considered as part of initial investigations of patients with cognitive concerns.

Keywords: Case studies/case series

16. The Utility of Anticonvulsant Levels in Pediatric Patients Presenting to Emergency Room with Seizure : A Retrospective Analysis.

Taravath S (Charleston, WV), Kumar R, Hatfield M

Objective: Despite being on anti-epileptic medication, many Pediatric patients present to Emergency department (ED) with breakthrough seizures. ED work-up for these patients often includes obtaining serum levels of these medications. By means of this research we wish to determine: A) Did serum drug levels return while patient was in ED? B) Were changes made to medication regimen based on these at the time of patient's discharge? C) To analyze if serum level testing of certain medications lead to changes in patient care more often than others. Such as older generation (Valproic acid) vs. Newer one's (Lamotrigine). D) To determine which Pediatric patients benefit most from these tests.

Methods: The proposed retrospective study reviewed the medical records of Pediatric patients with known Epilepsy and currently on anticonvulsants who presented to CAMC women and children ED with breakthrough seizures between January 1, 2007 and January 1, 2012. We examined the results of serum levels. The study included 92 patients, 96 tests were performed for assessment.

Results: Out of the above 59.4% had sub-therapeutic and 12.5% had supra-therapeutic level. 81% of these test results were available during ED admission and 82.3% by the time of hospital discharge. Results for serum levels of "Newer" medications including Lamotrigine, Levitiracitam

and Topiramate were unavailable prior to hospital discharge. For "Older" agents such as Phenytoin, valproic acid, carbamazepine and Phenobarbital the levels were available in time thus significantly associated with changes in medication dosage at discharge. ($p=0.01$)

Conclusions: Serum level results of older medications have the potential to guide treatment changes, while testing of newer ones provides minimal in-hospital benefit due to their extended processing time.

Keywords: Case studies/case series

17. An Under-recognized Cause of Progressive Childhood Ataxia- CACNA1A Mutation: A Case Series

Thakkar KP (Pittsburgh, PA), Vento JM, Goldstein AC

Objective: CACNA1A gene is located on Chromosome19p13 and encodes the alpha1 subunit of P/Q type voltage gated calcium channel. Heterozygous mutations in this gene are known to phenotypically cause autosomal dominant familial hemiplegic migraine and Episodic ataxia type 2. CAG trinucleotide repeats expansion in this gene causes the phenotype of Spinocerebellar Ataxia type6.

Methods: We present a series of pediatric cases that present with progressive cerebellar ataxia along with other associated features such as developmental delay, dysarthria and cerebellar atrophy. One patient had a more severe phenotype with recurrent coma, Prolonged ICU admissions, epilepsy and fever

Results: CACNA1A alterations were reported in each of these patients as a variant of unknown significance. However, based on significant family history, conservation throughout evolution of the amino acid at that position and contributions from PolyPhen/SIFT prediction software, we have concluded that these alterations are likely to be pathogenic and the cause of the described phenotype. Acetazolamide lead to symptomatic improvement in all cases.

Conclusions: CACNA1A gene mutations are not typically considered among the first line causes of Childhood Ataxias, which often causes delay in diagnosis. Considering that symptoms from CACNA1A mutations are known to respond to treatment with Acetazolamide, early diagnosis can end the long diagnostic odyssey for these patients, and offer hope of treatment. Testing for mutations in CACNA1A, especially in the setting of a family history of hemiplegic migraine, should be considered early in the evaluation and can make a huge impact on the families looking after these neurologically affected children.

Keywords: Case studies/case series

18. A Population Based Study of Communication Impairment in Cerebral Palsy

Zhang J (Montreal, QC), Oskoui M, Shevell MI

Aim: To explore factors associated with communication impairments in children with cerebral palsy (CP).

Method: Data was obtained on children born between 1999 and 2008 from the Quebec Cerebral Palsy Registry (REPACQ). Chi-square tests and student t-tests were used to explore associations between communication impairment and clinical factors.

Results: Out of 535 children with CP, 297 were identified to have communication impairments (55.5%). Of these, 96 were unable to communicate verbally (32.3%), 195 had some verbal communication (65.7%) and 6 were unspecified (2.0%). Children who were unable to communicate verbally were significantly more likely to have a more severe motor deficit than children with a milder communication impairment (non-ambulatory GMFCS levels IV-V and poor manual ability MACS levels IV-V, $p<0.001$). These children were also significantly more likely to have spastic quadriplegia or dyskinetic subtypes of cerebral palsy ($p<0.001$), and gray matter injury on neuroimaging ($p=0.002$). Children who were non-verbal were more likely to have associated cognitive impairment ($p<0.001$), cortical visual impairment ($p<0.001$), sensorineural auditory impairment ($p<0.001$), feeding problems ($p<0.001$), history of convulsions ($p<0.001$), neonatal encephalopathy ($p<0.001$), and multisystem involvement at birth ($p<0.001$).

Interpretation: Non-verbal communication impairment is associated with more severe motor deficit, spastic quadriplegic or dyskinetic sub-type of CP, gray matter injury on neuroimaging, and a number of other associated comorbidities. This information allows clinicians to better predict levels communication impairment in children with CP, and to anticipate treatment needs at an earlier stage.

Keywords: Case studies/case series

19. A Prevalence Study of Neurodevelopmental Delays and Autism

Turkdogan D (Istanbul, TR), Eldemir S, Ozyurt O, Yarligan T, Ocal T

Objective: To investigate the prevalence of neurodevelopmental retardation and autism in preschool children in Fatih district of Istanbul Providence

Background: Lack of epidemiological data on the rate of neurodevelopmental delays in Turkish preschool children confines improvement of educational strategies for integrated and special education.

Methods: A cross-sectional and door-to-door study was conducted in 14 regions with the maximum socioeconomic disadvantages. Randomly selected 1195 children aged 3 to 6 years old were assessed by standardized scales including Denver Developmental Screening Test-II (DDST) and Check List for Autism in Toddlers (CHAT).

Results: The prevalence of developmental delay in at least two domains of neurodevelopment was 7.44% and of autism was 1%.

Conclusions: The rates of developmental delay and autism in preschool children are consistent with those of western countries

Keywords: Case studies/case series

20. Behavioral Profiles of Children and Adolescents with Specific Language Impairment and High Functioning Autism

Dy ME (San Diego, CA), Ballantyne AO, Trauner DA

Objective: Specific language impairment (SLI) and autism are two neuro-developmental disorders with language

impairment that rely on clinical features for diagnosis. Although distinct disorders, there are overlapping features that can make correct diagnosis at times challenging. The goal of this study was to determine whether there were behavioral profiles from the Childhood Behavior Checklist (CBCL) that might help to distinguish children with SLI from those with high functioning autism (HFA).

Methods: Parents completed the CBCL for 19 subjects with HFA (mean age 9y9 m + 3y4 m); 86 with SLI (mean age 8y9 m+ 2y11 m); and 223 typically developing participants (CTL) (mean age 8y10 m + 2y10 m).

Results: HFA subjects had significantly higher (more abnormal) T scores on the behavior scales Withdrawn, Thought Problems, and Attention Problems, compared with subjects with SLI and CTLs. A high proportion of HFA children had scores in the clinically "at risk" range for Withdrawn (31.6%), Thought Problems (26%), and Attention Problems (16%) compared to subjects with SLI and CTLs. Language testing revealed significantly poorer language skills in the SLI than the HFA group, suggesting that the behavioral abnormalities could not be explained by language deficits alone.

Conclusions: Children with HFA are much more likely to score in the clinically "at risk" range on subscales Withdrawn, Thought Problems, and Attention Problems of the CBCL than are SLI children. These findings suggest that the CBCL may be useful in distinguishing the likelihood that a child with language delay may have HFA or SLI.

Source of Funding: NINDS #NS022343

Keywords: Case studies/case series

21. Developmental Functioning in Toddlers: Effect of Nutritional Status and Cognitive Stimulation at Home

Thota AS (Chandigarh, India), Malhi P, Bharti B, Menon J

Objective: The present study aims at understanding the effect of nutrition and cognitive stimulation/ training on the child's developmental capabilities in mental and motor spheres.

Methods: Fifteen normal and 15 undernourished (weight for age < -2Z score, as per WHO standards) children in the age group 12months to $2^1/_2$ years were recruited from the outpatient department of a tertiary care Pediatric center in North India. Their developmental functioning was assessed as Mental (MeQ) and Motor (MoQ) quotients using the Developmental assessment scales for Indian infants (DASII, a modification of the Bayley's scale) and compared. The effect of cognitive stimulation at home (STIMQ-T score) on the developmental function was studied.

Results: Mean MeQs in the normal and undernourished groups were 94.49 (SD=5.89) and 83.30 (SD=3.89), with mean difference=11.11 (SE=1.82) and p=14.5) STIMQ-P scores; and their MeQ, MoQ were compared using Mann-Whitney-U-test. MeQs were lower in the Low-STIMQ-P sub-group among normal(P=0.014) and undernourished (P=0.036) children. MoQs were not significantly different (normal: P=0.242; undernourished: P=0.563). STIMQ-P score correlated significantly with MeQ (Normal: r=0.80, p=0.001; Undernourished: r=0.66, p=0.007) values.

Conclusion: Children who were undernourished had poorer developmental quotients, mainly in the motor sector. Mental development of normal as well as undernourished children was significantly influenced by the cognitive stimulation offered at home.

Keywords: Case studies/case series

22. A Comparison of Pediatric and Adult Neuromyelitis Optica (NMO) at a Tertiary Care Center

McGill BE (St. Louis, MO), Ostendorf AP, Alvarez E, Mar SS

Objective: Evaluate clinical characteristics of neuromyelitis optica (NMO) and NMO spectrum disorder (NMOSD) patients.

Methods: Retrospective chart review in academic center.

Results: Fifty-five individuals were identified, including 8 pediatric patients. Twenty-five (53%) adults and 4 (50%) children had NMO. Both adult and pediatric cohorts were primarily women (91% and 88%, respectively) and African American (51% and 63%). Our pediatric cohort presented primarily with concurrent optic neuritis (ON) and transverse myelitis (TM) or demyelinating lesions of the brainstem (63%), whereas these presentations occurred in only 13% of adults. Patients with brainstem lesions presented earlier (median age 24.5[13–37]), which was statistically different from subjects with ON (38[12–63], p=0.010) or TM (50[9–63], p=0.028). NMO-IgG was postive in 75% of children and 81% of adults. Features unique to our pediatric cohort included a presentation of severe orthostatic intolerance out of proportion to hypovolemia in 3 individuals, including postural tachycardia syndrome (POTS) in 2 patients. Behavioral symptoms were prominent in pediatric patients, including pseudobulbar affect and hypersexuality (1 individual each). We identified unique challenges in treating our pediatric population, including relapses related to poor compliance with therapy and two pregnancies.

Conclusion: Pediatric NMO and NMOSD presented more frequently with concurrent ON and TM or brainstem involvement. Children uniquely had a high incidence of orthostatic instability and behavioral symptoms at disease onset. These data suggest that NMO and NMOSD may present differently in children and require separate diagnostic criteria. Poor compliance and risky behaviors present unique challenges in treating pediatric patients with these disorders.

Source of Funding: Dr. Alvarez is supported by the National Multiple Sclerosis society and has recieved speaking honoraria from Teva Neurosciences. Drs. Mar, Ostendorf, and McGill have nothing to disclose.

Keywords: Case studies/case series, Demyelinating disorders

23. Ocular Flutter as a Rare Manifestation of Multiple Sclerosis

Li J (Phoenix, AZ), Martinez-Conde S, Leigh RJ, Donlon S

Objective: Ocular flutter is an eye movement disorder characterized by brief paroxysmal bursts of horizontal saccades

without a saccadic interval. It has been previously hypothesized to be associated with dysfunction at the level of the paramedian pontine reticular formation. Rarely, it can occur as a manifestation of multiple sclerosis.

Methods: We report a case of a 17-year-old girl who presented with oscillopsia and a new onset headache. Her MR brain showed a substantial, but asymptomatic non-enhancing demyelinating lesion over the right parietal region and several smaller bilateral periventricular lesions. However, she did not have any brainstem or cerebellar lesions that could explain her symptoms.

Results: Video-oculography showed her eye movements were indeed consistent with ocular flutter with vergence. She was treated with gabapentin and her symptoms moderately improved.

Conclusions: Despite her CSF results being negative for multiple sclerosis or for an infectious process, it is important to recognize ocular flutter as a "subclinical" presentation of multiple sclerosis or radiologically isolated syndrome.

Keywords: Case studies/case series, Demyelinating disorders, Infections/Neuroimmunology

24. Long-term Outcome of Infantile Gratification Phenomena

Jan MM (Jeddah, KSA), Al Banji MH, Fallatah BA

Objective: Infantile gratification phenomena are self-stimulatory behaviors that are often misdiagnosed as epilepsy. Although the prognosis is thought to be benign, limited long-term follow-up studies exist. This was the objective of our study in addition to exploring the risks of future developmental, behavioral, or neurological abnormalities.

Methods: Series of consecutive infants with gratification phenomena were identified both retrospectively and prospectively over an 8 year period from a single pediatric neurology service. The diagnosis was based on descriptive history, review of videotaped events, lack of neurological or developmental abnormalities, and normal routine electroencephalogram.

Results: Nineteen infants who were followed for 3–11 years (mean 7.1). Their ages ranged between 4–13 months (mean 7) with 79% females. The diagnosis was not reached by the referring physician and 74% were misdiagnosed as epilepsy or movement disorder. The episodes recurred with variable frequency with gradual reduction in number and increase in length of attack-free periods with advancing age. Complete remission was noted in all patients by age 1–3 years (mean 1.9). None of the patients developed epilepsy; however, 4 children (21%) developed features of attention deficit hyperactivity disorders (ADHD) on long-term follow up. In this group, the gratification phenomena appeared at a younger age with higher attack frequency.

Conclusions: Gratification phenomena in infants are benign and self-limited, often spontaneously disappearing by 2 years of age. A correlation with future ADHD was found; however, larger prospective studies are needed to further examine this possible association.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders

25. Epileptic Spasms in Infants with Vitamin B12 Deficiency

Kandula T (Sydney, Australia), Sampaio H

Objective: Cobalamin or Vitamin B12 as a co-factor has a crucial role in DNA synthesis and cellular energy metabolism. Deficiency of cobalamin or its metabolites in infants can have significant deleterious impact on neurological development and rarely presents with seizures. Infantile spasms as a manifestation of epileptic encephalopathy in the setting of cobalamin deficiency have only been reported in a handful of cases. Our aim was to describe the characteristics of a series of patients who presented with epileptic spasms, encephalopathy and concurrent severe cobalamin deficiency at spasm onset.

Methods: A retrospective file review was carried out for each of the three infants. Information was gathered about patient characteristics and developmental status at presentation, seizure semiology, EEG findings, results from other investigations, response to treatment and subsequent developmental progress.

Results: Age range at presentation was 4 to 9 months. Semiology was consistent with symmetrical tonic spasms in all cases and EEG ranged from multifocal epileptiform activity to hypsarrhythmia with variable preservation of background. Developmental delay at commencement of treatment ranged from mild to severe. No other aetiological factor for epileptic spasms was identified in any of the cases. Cobalamin supplementation was undertaken alongside management of seizures in accordance with currently accepted best practice. All patients were seizure free at follow up and demonstrated significant improvement in developmental status.

Conclusion: This might represent a subset of patients with epileptic spasms with a good prognosis if treated promptly. The role of cobalamin in the pathogenesis of spasms requires further research and clarification.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders

26. Surgical Outcome and Prognostic Factors in Children with Medically Intractable Epilepsy (MIE) Caused by Focal Cortical Dysplasia (FCD)

Laoprasert P (Denver, CO), White A, Knupp K, Koh S, Park K, Chapman K, Handler M

Objective: FCD is the most common cause of MIE in children. Epilepsy surgery (ES) is a gold-standard treatment in these patients. Seizure freedom is lower if FCD is the cause of MIE. There is controversy surrounding the PF for SO, especially with respect to FCD type. This study is to report surgical outcome (SO) and prognostic factors (PF) in children with MIE caused by different types of FCD.

Methods: 82 patients with histologically proven FCD were retrospectively reviewed. Patients with FCD who underwent ES for MIE between 2001 and 2008 with ≥ 4 year follow up were included in the study. Data regarding sex, age at seizure onset (ASO), duration of 1st seizure to

surgery (DSS), developmental delay (DD) or mental retardation (MR), presurgical workup, surgery type, completeness of resection (CR - lack of FCD on postoperative MRI and complete resection of epileptogenic zones using intracranial EEG), FCD pathology type and SO were collected. Statistical significance was determined using ordinal logistic regression.

Results: 42 patients were female and 40 were male. Age at surgery ranged from 1 mo to 22 yr (Median 117 mo). Median DSS was 67 mo and follow up was 64 mo. Among 82 patients, 19 had mild malformation of cortical development, 14 had FCD1, 23 had FCD2 and 26 had FCD3. DD or MR was noted in 44, CR in 63, extratemporal FCD in 57 and temporal FCD in 25 patients. MRI showed FCD in 70 and was nonlesional in 12 patients. Engle class 1 surgical outcome was noted in 56 (68.3%), Engle class 2 in 20.7% and Engle class 3 in 11%. The only significant prognostic factor was CR ($p < 0.0001$).

Conclusions: These findings strongly suggest consideration of ES in patients with MIE caused by FCD. CR is the only significant factor for predicting seizure freedom.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders

27. Safety of Transcranial Motor Evoked Potentials in Children and Adolescents with Epilepsy

Wical BS (St Paul, MN), Wical TK, Bawrowski K

Objective: Transcranial electrical stimulation (TES) to obtain motor evoked potentials (MEP) is a safe methodology with few adverse effects. Yet presence of significant epilepsy is often considered a contraindication to TES. To asses safety, we reviewed our series of patients with epilepsy who underwent TES.

Methods: Charts of 490 patients with intra-operative neuromonitoring during spinal or neurosurgical procedures were reviewed. Thirty two patients with significant epilepsy who underwent TES to produce MEP were identified. Patients with a remote history of epilepsy or rare seizures were not included. Data collected included: age, gender, surgical procedure performed, IONM modalities utilized, adequacy of baselines, success of monitoring, changes during monitoring, and complications of monitoring. Seizure frequency and anti-epileptic medications were recorded.

Results: All 32 patients had active epilepsy. Age range was 3–21 years; 15 were male, 18 female. Successful TES producing MEPs throughout the surgical procedure occurred in 27/32 (84.4%) patients. An additional 5/32 (15.6%) patients had MEP via TES but no acceptable baselines were acquired despite multiple attempts to establish them. No patients had any seizures induced by TES; there were no seizures in the immediate post-operative period.

Conclusions: In our group of patients with significant epilepsy, no patient had a seizure despite the use of standard TES/MEP protocols. Epilepsy may not be a contraindication to TES in children if the risk of the monitoring is outweighed by the potential benefit of lowering risk of surgical complications.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders

28. Verapamil as Adjunctive Therapy for Seizures in Dravet Syndrome

Wical BS (St Paul, MN), Wandorf H

Objective: Dravet Syndrome (DS) is characterized by medically intractable epilepsy and requires additional treatment strategies. We present the results of verapamil therapy in 5 children with DS.

Methods: Five children ages 3–18 yr with DS were treated with verapamil as adjunctive therapy for seizures. All have mutations in the SCN1A gene, clinical histories consistent with severe DS, and failed multiple antiepileptic medications. All experienced repetitive generalized tonic clonic seizures (GTCS) and focal seizures with secondary generalization. Normal EKGs were obtained prior to and on therapy. Verapamil was added to existing antiepileptic medications. Doses used were 4–8 mg/kg/d. Patients were monitored for adverse effects and seizure frequency. Due to verapamil's enzyme inhibition, co-medications were reduced if needed.

Results: One child had a trial of verapamil for 6 weeks; it did not improve seizure control, and was rapidly tapered. Four of 5 children given verapamil had a significant reduction in secondarily generalized tonic clonic and GTCS. Range of seizure decrease is to 40 to 80% of baseline. Of responders, effect has been maintained for 29, 21, 4 and 3 mo. No significant adverse effect related to treatment has been identified. One had chronic diarrhea prior to starting verapamil; there is now a mild tendency to constipation. One child has had worsening behavior not clearly related to the verapamil.

Conclusions: In this small series, verapamil provided a clinically important reduction in seizures in 4/5 children with DS. It was well tolerated. Larger studies are needed to assess efficacy.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders

29. Episodic Encephalopathy, Paralysis, Persistent Dysarthria and Ataxia in a Family Is Associated with a Dominantly Inherited Mutation in ATP1A3

Acsádi G (Hartford, CT), Mital S, Newcomb TM, Nelson B, Violet L, Swoboda KJ

Objective: Disease phenotypes associated with mutations in the Na/K-ATPase alpha-3 subunit ATP1A3 (previously described in Rapid Onset Dystonia Parkinsonism [RDP[), have been rapidly expanding since the recent identification of its pathogenic role in Alternating Hemiplegia of Childhood (AHC). We studied a three-generation family of four patients presenting with recurrent episodes of encephalopathy, quadriparesis or hemiparesis, mutism, seizures and subsequent ataxia with speech impairment for mutations in ATP1A3.

Methods: The clinical course, laboratory and neuroimaging studies were determined during separate hospitalizations of two female siblings. Genetic analysis of the ATP1a3 gene was performed by Sanger sequencing in Utah.

Results: The patients were three years old at the initial illness described as possible focal febrile seizure followed by

paresis and mutism. These symptoms have improved over a few weeks with residual ataxia and speech impairment. Blood and CSF studies were negative for infections along with normal metabolic parameters. Multiple brain MRI/MRS studies showed no pathology. Sequencing of CACNA1A (a calcium channel gene) in the older sibling proved negative. However, sequencing of ATP1A3 gene in the proband, and subsequently in the sibling and their mother revealed a hemizygous mutation previously reported in a family with RDP syndrome.

Conclusion: We have identified a known dominant mutation of the ATP1a3 gene in this family suffering from clinically distinct symptoms of recurrent cognitive as well as motor impairments and residual ataxia with dysarthria following recovery. The neurological condition appears to stabilize in adulthood. This unique presentation further expands the phenotypic spectrum associated with mutations in ATP1A3.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Genetics

30. Long-Term Modified Natural History of Glut1 Deficiency Syndrome

Alter AS (New York, NY), Engelstad K, Hinton VJ, Montes J, Pearson TS, Akman CI, De Vivo DC

Objective: The objective of this study was to characterize the long-term natural history of Glut1 Deficiency Syndrome (Glut1 DS), as modified by current standard-of-care treatment.

Methods: Longitudinal outcome measures were collected for 13 patients with confirmed Glut1 DS who were followed for an average of 14.2 years (range = 8.9–23.6 years) at our institution. Longitudinal measures included Columbia Neurological Score (CNS) and neuropsychological test results. The 6-minute walk test (6MWT) was introduced as a new outcome measure, with 8 of 12 patients also completing gait analysis. A parent questionnaire was administered to assess disease manifestations at different periods in the life cycle.

Results: CNS and intelligence test scaled scores did not significantly change over time. Epilepsy was worst in infancy and usually resolved by adulthood. Movement disorders, including paroxysmal exercise-induced dyskinesia (PED), occurred during late childhood or adolescence. There was a trend for symptoms and function to transiently worsen during puberty. %-predicted 6MWT distance and gait velocity correlated well with CNS scores ($p=0.006$ and $p=0.0002$, respectively, Figures 1 and 2). Dystonia was noted to increase during the 6MWT, although there was no evidence of physiological fatigue. Earlier start of the ketogenic diet was associated with better long-term outcomes (Figure 3), but total duration of the ketogenic diet did not correlate with long-term outcomes.

Conclusions: Glut1 DS is a fairly stable disease over time, although the clinical manifestations change throughout neurological development. Early start to the ketogenic diet in infancy appears to be the most important intervention for optimizing long-term outcome.

This study was supported, in part, by the Glut1 Deficiency Foundation, Milestones for Children, and the Colleen Giblin Foundation.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Genetics

31. KCNQ2 Encephalopathy: Electroclinical Presentation and Response to Treatment in Two New Cases

Numis AL (San Francisco, CA), Angriman M, Lewis AJ, Singhal NS, Casara G, Striano P, Cilio MR

Objective: We sought to characterize the electroclinical phenotype associated with the recently described KCNQ2 encephalopathy and the response to treatment in this rare and severe neonatal-onset epileptic encephalopathy.

Methods: We reviewed the medical records of two patients with KCNQ2 encephalopathy diagnosed in the neonatal period. We examined clinical data and video-EEG recordings to describe seizure semiology and EEG features, responses to different AEDs, as well as developmental and seizures outcomes.

Results: The patients presented with seizure onset within the first days of life with multiple seizures per day. Seizure semiology was characterized by stereotyped head and eye deviation with asymmetric, tonic posturing of the arm and leg affecting alternating sides of the body, associated with apnea and desaturation. Myoclonic seizures or tonic spasms were not observed. Ictal EEG demonstrated recruiting focal spikes arising from either hemisphere, followed by focal spikes and waves, and then profound, transient, post-ictal background attenuation or burst-suppression pattern. Interictal EEG demonstrated lack of organization and almost-continuous multifocal epileptiform abnormalities with random attenuations. Both patients failed a number of anti-epileptic agents, including Phenobarbital, Phenytoin, Vigabatrin, Benzodiazepines, Topiramate, Levetiracetam, and the ketogenic diet; and, had seizure freedom shortly after initiation of Carbamazepine or Oxcarbazepine.

Conclusions: Mutations in KCNQ2 can result in both benign and severe epilepsy syndromes. Here, we report he first description of a distinct electroclinical profile of KCNQ2 encephalopathy, disparate from other neonatal epileptic encephalopathies such as Ohtahara syndrome and Early Myoclonic Encephalopathy. We provide evidence of efficacy of Carbamazepine and its derivatives in this disorder.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Genetics

32. Ring Chromosome 20: a Pediatric Potassium Channelopathy Responsive to Treatment with Ezogabine

Walleigh DJ (Philadelphia, PA), Legido A, Valencia I

Objective: Ring chromosome 20 is a genetic disorder characterized by intractable epilepsy, behavioral problems and cognitive deficit. The potassium channel coding gene KCNQ2 is localized at the locus q13.3 on the chromosome 20, the most common site where the ring occurs. Ezogabine is the first potassium channel opener marketed in the USA,

approved in June 2011 by the FDA for adjunctive therapy of partial seizures in adults.

Methods: We report an 8 year old girl with mosaic ring chromosome 20(p13q13.3) and refractory epilepsy, who after being treated with 15 antiepileptic drugs (AEDs) and the ketogenic diet without success, had a remarkable improvement in seizure control with ezogabine.

Results: Her seizures decreased from a baseline of 15–20 per day to 3–4 per day on ezogabine, with up to 2–3 day periods of being seizure free. Prior to ezogabine the patient had never experienced a seizure-free day since diagnosis. She was using clonazepam 1–3 times a day for clusters of seizures before ezogabine compared to none while on it. There were no emergency room visits for over eight months after starting ezogabine compared to 1 to 2 per week before initiating it.

Conclusions: To our knowledge this is the first report using ezogabine to treat pediatric epilepsy. We hypothesize that ring chromosome 20 patients have epilepsy related to dysfunction of potassium channels, and it is a target for treatment with potassium channel openers.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Genetics

33. Functional Movement Disorders in Children with Migraine

Youssef PE (Rochester, MN), Mack KJ

Background: The cause and treatment of functional movement disorders in children is poorly understood, and an association with migraine has not previously been described in the medical literature.

Methods: We reviewed the medical records of children diagnosed in the Pediatric Neurology Clinic at Mayo Clinic Rochester with chronic or episodic migraine since 2006 to determine the proportion with nonorganic movement disorders, as well as the phenomenology, provoking factors and natural history.

Results: Twenty eight patients were identified, representing 5% of our migraine population. Twenty four of the 28 (85.7%) had chronic migraine, with a mean age at headache onset of 13.3 years (range 2–17 years), while 4 (14.3%) had episodic migraine, with a mean age at headache onset of 12.75 years (range 10–15 years). A female predominance was present in both chronic and episodic migraine groups (87% and 75% respectively). Shaking spells or pseudoseizures was the most common phenomenology represented in both cohorts (58.3% and 75% respectively), followed by tremor and functional gait disorders. Severe migraine attacks preceded these nonorganic movements in 70.8% of chronic migraineurs and 100% of episodic migraineurs. The appearance of the movement disorder occurred concomitantly or within six months of headache onset in both populations (70.8% and 75% respectively). When appropriate migraine therapy was instituted and fewer episodes of pain crisis occurred, a significant reduction or resolution of these movements was reported within this population.

Conclusions: Nonorganic movement disorders are observed in 5% of pediatric migraine, and may resolve with improved control of headache pain.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Headache/Migratine

34. A Retrospective Analysis of Paediatric Patients with Medically Unexplained Neurological Symptoms: Epidemiology, Management and Outcomes.

Vidouris M (Edinburgh, UK), Karnth Tallur K

Objective: To study the epidemiology, management and outcome of paediatric medically unexplained neurological symptoms (MUNS).

Methods: This is a retrospective analysis of patients attending the Neurology Department at the Royal Hospital for Sick Children (RHSC) from 2003–2012 and were diagnosed with MUNS.

Results: 35 patients were identified. The predominant symptoms were headaches (13) and visual disturbances (11). There were reports of impaired mobility 31.4%(11/35), effects on education 48.6%(17/35) and sleep disturbance 25.7%(9/35). 77.1%(27/35) were girls; they presented younger (median 11.7years) than boys (median 12.5years). Multiple, repeated investigations were carried out. No positive results were found. 4 MRIs showed incidental findings. Management included referral to mental health services 77.1%(27/35), pharmacological 51.4%(18/35) and non-pharmacological treatment 25.7%(9/35). 77.1% (27/35) improved in an average follow-up of 15.4months. Those that fully recovered 60%(21/35) did so in an average of 10.1 months. 2 deteriorated and 6 remained the same.

Conclusions: Paediatric MUNS is a little researched area. It involves a range of symptoms causing varying levels of impact on daily life. There are complex underlying psychosocial stressors precipitating these symptoms and a multidisciplinary approach is required by paediatricians, psychologists, parents and teachers to minimise the physical and psychological consequences of this condition.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Headache/Migratine, History / Teaching of Child Neurology

35. Abnormal Initial EEG Background is Associated with Electrographic Seizures Among Neonates Treated with Hypothermia: A Multi-Center Study

Glass HC (San Francisco, CA), Wusthoff CJ, Shellhaas RA, Tsuchida TN, Bonifacio SL, Cordiero M, Sullivan J, Abend NS, Chang T

Objective: Electroencephalography (EEG) monitoring is recommended for neonates with encephalopathy (ACNS Guidelines, 2011), however lack of resources may limit its implementation. We aimed to assess factors for seizure risk among neonates treated with hypothermia.

Methods: Three-center study of 90 term neonates treated with hypothermia, and monitored with EEG within the first day of life (onset median 10.7 hrs, range 3.6–22.2 hrs), and continued for >24 hrs (median 93.3hrs, range 24.0–481.2 hrs). A pediatric electroencephalographer at each site reviewed EEGs for seizures and initial background category. Clinical variables were extracted from the medical records.

Results: 43(48%) had seizures, including 9(10%) with status epilepticus (SE). Abnormal initial EEG background classification, but not clinical variables, was strongly associated with seizures (Table, $P<0.00005$).

Conclusion: Despite reports of reduced seizures among neonates treated with hypothermia, they remain common, and are difficult to predict based on clinical features. These results justify the recommendation for EEG monitoring in neonates treated with hypothermia.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Neonatal neurology

36. Neurological Complications of Gastrointestinal Transplantation at a Multidisciplinary Transplant Institute

Angelino AC (Washington, DC), Zecavati N

Objective: To describe the nature of neurological complications in pediatric patients following gastrointestinal transplantation (GT).

Methods: We performed a retrospective chart review of 45 children undergoing GT between 2002 and 2012 to determine post-transplant neurological complications.

Results: Of 45 children with GT, eight children had neurologic complications (17.8%). These included six small bowel, one liver, and one multi-organ transplant. There were five females and three males. The mean age at the time of transplant was 4.12 years. Two patients presented with pre-transplant seizures or a history of developmental delay. Neurologic complications were noted to occur on average 7.1 months following transplantation. These included seizures, headaches, abnormal movements, and mental status changes. The most frequent neurologic complication was seizure (50%). Neurological examination was non-focal in all patients and the most common finding was developmental delay (37.5%). All patients underwent neuroimaging, the majority of whom had magnetic resonance imaging (MRI) of the brain. MRI findings were variable and included posterior reversible leukoencephalopathy (PRES), cortical volume loss, ventricular enlargement, and cystic encephalomalacia secondary to ischemic infarct. Electroencephalography (EEG) was performed in four patients with three being abnormal (75%). The most common abnormalities were abnormal sharps and diffuse slowing. Seizures were treated effectively with Levetiracetam, Clonazepam, and/or Lacosamide. There was one death in this cohort due to multi-organ failure.

Conclusions: The most common neurologic complications in this cohort of pediatric patients following GT include seizures and headaches with developmental delay being prevalent. Early detection and screening of neurological complications may improve long-term outcome.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Neuroimaging

37. Progressive Myoclonic Epilepsy, Motor Neuron Disease, and Dystonia Due to Mutations in ASAH1: the Expanding Phenotype of Farber Disease

Jeong AB (New York, NY), Schuchman EH, Sathe SA, Miles D, Pearson TS

Objective: To describe the clinical, genetic, and biochemical features of a patient with a novel phenotype of Farber disease due to mutations in ASAH1.

Background: Classic Farber disease presents in early infancy, with the clinical triad of hoarse voice, lipogranulomas, and painful joints. It is caused by deficiency of the lysosomal enzyme, acid ceramidase, encoded by ASAH1. A syndrome of spinal muscular atrophy and progressive myoclonic epilepsy (SMA-PME) was recently linked to mutations in the same gene.

Methods: We describe the clinical features of a single patient. ASAH1 mutations were identified with whole-exome sequencing. Acid ceramidase activity was determined in leucocyte lysates using a fluorescence-based assay.

Results: A 14 year-old girl presented with seizures, cognitive decline, weakness, and involuntary movements. Following normal development in infancy and early childhood, cognitive impairment became apparent at age 5 years. She developed myoclonic seizures and involuntary jerky movements at age 9, and generalized tonic-clonic seizures at age 12. Progressive limb weakness appeared soon after her first seizure at age 9. Physical examination revealed hypotonia, symmetrical proximal weakness, hyperreflexia, postural and action myoclonus,, and cervical dystonia. EMG/NCS and muscle biopsy demonstrated neurogenic abnormalities. Whole-exome sequencing revealed novel compound heterozygous missense mutations in ASAH1 (c. 536C>T, c.124A>G). The patient's ceramidase activity was 15% of control, confirming ceramidase deficiency as the cause of her clinical syndrome.

Conclusions: This case expands the phenotypic spectrum of ASAH1 mutations to include dystonia along with SMA-PME, and suggests a particular susceptibility of upper and lower motor neurons to ceramidase deficiency.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Neuromuscular disorders

38. Acute Symptomatic Seizures with Pediatric Stroke Predict Recurrent Remote Seizures

Fox CK (San Francisco, CA), deVeber G, SIPS Investigators

Objective: To determine the frequency and predictors of seizures in pediatric stroke.

Methods: Seizures in Pediatric Stroke investigators prospectively enrolled neonates (birth - 28 days) and children (29 days - 18 years) with arterial ischemic stroke (AIS) or cerebral venous sinus thrombosis (CSVT). Acute symptomatic seizures ($\leq$7 days of stroke onset), remote symptomatic seizures (>7 days post-stroke) and recurrent remote seizures (recurrent unprovoked seizures >14 days post-stroke) were identified by chart review and parental questionnaires 14 days and 4 months after stroke. Time to first seizure was demonstrated by Kaplan-Meier plot. Chi squared analysis was used to determine seizure predictors.

Results: The stroke cohort included 150 participants: 36 neonatal and 114 childhood; 122 AIS and 28 CSVT. Twenty-two neonates (61%, 95% CI 44%, 78%) and 32 children (28%, 95% CI 20%, 36%) had an acute ($\leq$7 days) symptomatic seizure. Most acute seizures were focal

motor (81%), or generalized convulsive (13%). Stroke involving the temporal lobe predicted acute seizure (P=0.01) but gender, AIS, hemorrhage, vascular territory and cortical infarct did not. Follow-up was available for 135 participants at a median of 110 days (interquartile range 95 – 128). Nine (7%, 95% CI 2%, 11%) had at least one remote symptomatic seizure. Five (4%, 95% CI 0.5%, 7%) had recurrent remote seizures, with multiple seizures per month despite anti-convulsant treatment. Acute symptomatic seizures predicted recurrent remote seizures (P=0.04).

Conclusions: Seizures are frequent within the first week of pediatric stroke onset. Nearly one in twenty developed recurrent remote seizures within 4 months of stroke.

Keywords: Case studies/case series, Epilepsy and other paroxysmal disorders, Stroke

39. Using the Autism Diagnostic Interview-Revised (ADI-R) and the Autism Diagnostic Observation Schedule (ADOS) in Diagnosing Autism Spectrum Disorder (ASD) in Children with Down Syndrome (DS)

Bay MJ (Baltimore, MD), Talisa VB, Vaurio RG, Kaufmann WE, Capone GT

Objective: The incidence of ASD is higher in children with DS compared to the general population; however, diagnosing ASD in children with DS is difficult due to co-occurring language and developmental delays. This abstract looks particularly at the agreement between the two gold standard measures of identifying ASD, ADI-R and ADOS, in children with DS.

Methods: We analyzed the sensitivity and specificity of ADI-R and ADOS in diagnosing ASD and agreement between these two diagnostic tools (kappa coefficient). Final ASD diagnostic status was determined by clinical consensus between two independent clinicians according to DSM-IV criteria and their clinical judgment. The cohort (N=53) was from a study that is being conducted at Kennedy Krieger Institute to characterize the specific neurobehavioral profiles of children with DS and ASD.

Results: Twenty-eight out of 53 had final diagnosis of ASD. The sensitivity of ADI-R in identifying ASD was 96.4% (95% CI: 79.8–99.8%) and that of ADOS was 100% (CI: 85.0–100%). The specificity of ADI-R was 72.0% (CI: 50.4–87.1%) and that of ADOS was 73.9% (CI: 51.3–88.9%). If these tests were combined serially, the specificity increased to 92.7%. The agreement rate between ADI-R and ADOS was 84%, with a kappa coefficient of 0.657 (CI: 0.441-0.873).

Conclusions: In a research sample of children with DS, ADI-R and ADOS were highly sensitive in identifying ASD when used independently, but specificity improved when the two were combined. These results have important implications for the use of these tools in future research in DS.

Keywords: Case studies/case series, Genetics

40. An Unbalanced 5;12 Translocation in a Patient with Septo-Optic-Dysplasia

Dhamija, R (Rochester, MN), Waltman LA, Hoppman N, Kirmani S

Introduction: Septo optic dysplasi is a congenital defect of midline and forebrain. The etiology of SOD is considered multifactorial, though familial cases have been reported with mutations in homeobox genes (HESX1, SOX 2, SOX 3). Here we report a patient with septo optic dysplasia and an unbalanced 5;12 translocation.

Case report: An 11-year-old girl with global developmental delay and congenital anomalies was referred for a second opinion. Clinical examination was significant for short stature, abnormal head shape, mid face hypoplasia and dysconjugate eye movements with visual impairment. Brain MRI showed absence of the septum pellucidum and small optic apparatus compatible with SOD. Array comparative genomic hybridization revealed a terminal duplication from 5q35.1 to 5qter and a terminal deletion from 12pter to 12p13.32. FISH studies confirmed maternally inherited unbalanced 5;12 translocation.

Discussion: This translocation lead to duplication of 77 and deletion of 22 genes on chromosome 5 and 12 respectively. Of the genes that are deleted from chromosome 12; three (WNT5B, ERC1, FBXL14) have been reported to be important for brain development. WNT5B encode secreted signaling proteins important for patterning during embryogenesis. The protein encoded by the ERC1 gene is involved in the activation of NF-kB, a transcription factor playing a role in apoptosis and development. Protein encoded by the FBXL14 gene interacts with ubiquitination targets important in development. We propose that haploinsufficiency of these genes might be disrupting the prosencephalon development resulting in the phenotype of septo optic dysplasia. These genes warrant further investigations for their role in prosencephalon development.

Keywords: Case studies/case series, Genetics

41. Neurodevelopmental Diagnoses and Functioning of Children with FMR1 Gene Alleles in the Grey Zone

Jindal AV (Pittsburgh, PA), Kronk R, Filipink R, Noll RB

Objective: We aim to describe the neurodevelopmental phenotypes that can be seen in children with an allele of the FMR1 gene that falls within the grey zone (45–54 CGG repeats).

Methods: Twenty-three children (12 males, 11 females; ages 2–17 years; range 45–52 CGG repeats) with Southern blot and PCR results positive for grey zone allele size were evaluated by parents and teachers using standardized measures of adaptive functioning, behavioral and emotional status.

Results: All participants had at least one neurodevelopmental diagnosis – most common were autism spectrum disorders and ADHD – and multiple co-existing medical and psychiatric conditions at presentation not attributed to a known genetic cause (Table 1). Mean scores for adaptive functioning were in the "extremely low" range for 68.2% of children based on parent evaluations and in the "below average" range for all children based on teacher evaluations. Self-direction, self-care, and community involvement ranked as the lowest functioning skill areas. Mean scores for emotional/behavioral difficulties reached clinically significant

levels for total problem behaviors and internalizing behaviors based on parent reports.

Conclusions: Historically, persons with grey zone alleles were thought to be unaffected from a medical or developmental standpoint. This case series presents a range of neurodevelopmental diagnoses in a population of grey zone allele-carriers. Our findings question whether the functioning of children with grey zone alleles may be affected by the mutation itself and underscore the need for large-scale, population-based epidemiological studies to further investigate the spectrum of functional involvement for children in the grey zone.

Keywords: Case studies/case series, Genetics

42. Heterozygous Deletion of HEPACAM Gene: a Possible Cause of Early Onset Parkinson Disease

Kalsner L (Hartford, CT)

Objective: Dominant mutations in the HEPACAM gene have been associated with several clinical phenotypes including a transient form of Megalencephalic Leukoencephalopathy with Subcortical Cysts (MLC2B). Children with MLC2B typically have a stable to improving course, though little is known of their long term outcome. This is the report of a mother and child with the typical phenotype of MLC2B, both of whom carry a 1.1Mb interstitial deletion within cytogenetic band 11q24.2, which includes the HEPACAM gene. The mother developed early onset Parkinson Disease (PD).

Methods: The child was first evaluated at three years of age for mild developmental delay. His head circumference plotted at the 98th%ile. MRI revealed vacuolization of the white matter in the periventricular regions. His mother developed idiopathic PD at age 40. She had asymmetric resting tremor, cogwheel rigidity and bradykinesia and responded to treatment with levodopa. She required special education services through high school. Her head circumference plotted at the 90th%ile.

Results: The mother and child in this case have findings compatible with MLC2B with cystic leukoencephalopathy in the child and macrocephaly and intellectual disability in both parent and child. The mother developed early onset PD which is known to be caused by dominant mutations at several loci including PARK1 (4q21) and PARK8 (12q12). There are no reports of PD in association with MLC2B. There are, however, no long term studies of patients with heterozygous HEPACAM mutations.

Conclusions: Mutations in or deletions of the HEPACAM gene may be associated with the early onset of Parkinson Disease.

Keywords: Case studies/case series, Genetics

43. Utility of Exome Sequencing in the Evaluation of Neurodevelopmental Disorders

Le Pichon JB (Kansas City, MO), Abdelmoity AT, Soden SE, Smith LD, Modrcin AC, Saunders CJ, Farrow EG, Dinwiddie DL, Miller NA, Atherton AM, Kingsmore S

Objective: Massively parallel next-generation sequencing has made rapid sequencing of the entire coding region of the genome (exome sequencing) possible. Exome sequencing has the potential to diagnose neurodevelopmental diseases more efficiently than sequential gene testing, however research is needed to optimize integration into clinical care. We present our exome-sequencing experience of 72 patients with neurodevelopmental disorders at Children's Mercy Hospital (CMH).

Methods: Seventy-two patients with neurodevelopmental disorders were entered into the exome sequencing study using a research protocol through the Center for Pediatric Genomic Medicine (CPGM) at CMH. Sequencing results were classified as either "definite" for previously reported gene mutations, "probable" for candidate gene mutations with high likelihood of being pathogenic or "negative" if no candidate genes were identified.

Results: The range of disorders varied from severe cognitive impairments with arthrogryposis, to mild cognitive impairment with microcephaly, to Tourette syndrome. Of the 72 patients studied, 25 (35%) were found to have definite gene mutations, 9 (12%) were found to have likely pathogenic mutations in previously unreported genes, 13 (18%) were found to have no clear pathogenic mutations and 13 (35%) are undergoing further analysis.

Conclusions: Exome sequencing is a valuable tool for the evaluation of neurodevelopmental disorders in the pediatric population. We identified likely pathogenic genetic defects in 47% of previously unidentified disorders at a fraction of the cost of traditional sequential testing. Significant challenges remain in the interpretation of the results as exemplified by the 35% of subjects requiring further analysis.

Keywords: Case studies/case series, Genetics

44. A New Phenotypic Presentation of DYT 16: Acute Onset in Infancy and Association with Striatal Necrosis

Lemmon ME (Baltimore, MD), Lavenstein BL, Hamosh A, Singer HS

Objective: Describe the unique presentation of a child with PRKRA mutations and early onset dystonia-parkinsonism (DYT16).

Methods: We report the clinical presentation, imaging findings, and genetic sequencing of a young patient with DYT16.

Results: RS was a healthy and typically developing boy until 13 months of age, when he developed acute hypotonia, bradykinesia, hyperreflexia, and developmental regression in the setting of a febrile illness. He slowly recovered, but by 18 months bradykinesia was accompanied by bilateral upper extremity dystonia. Over the ensuing years, he developed a progressive generalized dystonia, with involvement of the trunk, oromandibular musculature and limbs. An extensive metabolic evaluation was unremarkable, including CSF neurotransmitters and mitochondrial studies. At age 7, MRI revealed bilateral striatal necrosis. Therapeutically, he had a minimal response to levodopa. At age 14, whole exome sequencing revealed 2 mutations, in trans, within the PRKRA gene. The first was c.665C>T (p.P222L), the mutation described in a Brazilian cohort of

patients with DYT16. The second mutation c.637T>C (p.C213R) has not been previously reported.

Conclusions: This case report describes a genetically confirmed case of DYT16, with a novel acute presentation associated with a febrile illness, including hypotonia, bradykinesia, pyramidal signs, and developmental regression. Additionally, after the development of generalized dystonia and bradykinesia, striatal necrosis was present on MRI. This child's early presentation is similar to descriptions of ATP1A3 (rapid-onset dystonia, DYT12) and SLC19A3 (thiamine transporter 2 deficiency) gene mutations. DYT16 should be considered in all patients with early-onset bradykinesia or dystonia appearing after a febrile illness.

Keywords: Case studies/case series, Genetics

45. NDUFA1-Associated Complex I Deficiency Modulates Phenotypic Severity in Autistic Brothers with Pro206Ser Tryptophan Hydroxylase 2 Haploinsufficiency

Trifiletti RR (Ramsey, NJ), Boles R

Objective: Utilize mtDNA and mitonucleome sequencing in two affected brothers to define a new and potentially treatable cause of autism. Use these results to guide rational treatment.

Methods: Case studies. mtDNA deep heteroplasmy analysis on saliva on affected brothers. Mitonucleome analysis (complete sequencing of 1192 genes) including a number of autism candidate genes. Analysis of mitonuleome sequence variants by a multi-stage algorithm (taking into account population frequency, evolutionary conservation, and four different pathogenicity prediction models) isolate three candidate disease genes

Results: mtDNA sequencing with deep heteroplasmy was essentially normal. One of the three candidate genes identified by mitonucleome analysis, TPH2 (tryptophan hydroxylase 2) showed a variant (P206S) previously reported to be associated with bipolar disorder and ADHD in a dominant manner. TPH2 catalyzes the rate limiting step in the biosynthesis of serotonin. One of the two sibs was hemizygous for a polymorphism in NDFUA1(NADH dehydrogenase (ubiquinone) 1 alpha subcomplex 1) predicted to be highly deleterious. This sib also showed marked aggressive behavior, whereas his brother was placid. Both children showed significant cognitive and behavioral improvement on 5-hydroxytryptophan (5-HTP).

Conclusion: We propose that the TPH2(P206S) polymorphism is causally related to the autistic phenotype in these two siblings. The association is novel and potentially treatable. Moreover, we propose that polymorphisms in NDFUA1, and perhaps Complex I in general, can modify the behavioral phenotype in this syndrome. The use of genetic analysis to guide treatment in this particular family is an example of "personalized medicine".

Keywords: Case studies/case series, Genetics

46. Casemapper: A Computational Tool That Facilitates Phenotypic Correlations in Autism Based on Case Studies from the Literature

Srivastava S (Baltimore, MD), Grados MJ

Objective: Autism spectrum disorders (ASDs) have unknown origins. One can gain insight into their pathogenesis by examining genetic syndromes where ASDs are common. Comparative phenotypic analysis can highlight disrupted pathways in ASDs. We designed a tool ("Casemapper") that examines features presented in case reports of individuals with ASD-linked syndromes and determines features occurring more frequently in ASDs.

Methods: Casemapper (https://github.com/sidsrivastava/Casemapper) inputs text files, each corresponding to a different case with information about genotype (e.g., "syndrome: Timothy syndrome"), present features (e.g., "+: ASD, syndactyly"), and absent features (e.g., "-: clinodactyly"). It then creates an internal representation of all features (present or absent) represented collectively by the cases. Finally, it outputs a datafile with a row for each case. Variables exist for study name, syndrome, and each phenotypic feature (possible values: 1 = present, 0 = absent, −1 = not addressed).

Results: For testing, we used Casemapper to analyze 193 cases across 7 disorders associated with ASDs: 16p11 deletion (n = 24), 16p11 duplication (n = 15), 22q13 deletion (n = 70), 2q34 deletion (n = 8), Smith-Lemli-Opitz syndrome (n = 48), ring chromosome 22 (n = 18), Timothy syndrome (n = 10). We imported the generated dataset into Stata and tested the hypothesis that 2,3-toe syndactyly correlates with autistic features. Although the correlation was not significant (p = 0.11), it did demonstrate successful proof of concept.

Conclusions: Casemapper can facilitate comparisons of features associated with ASDs in genetic disorders. Results from Casemapper can raise hypotheses about disrupted signaling pathways in ASDs.

Keywords: Case studies/case series, Genetics

47. Unilateral Cavernomas Caused by Novel CCM2 Mutation Predisposes to Cerebral Abscesses

Misra SN (Houston, TX), Mohila CA, Tran HD, Lotze TE

Objective: To describe the clinical presentation and complications of unilateral hereditary cavernomas secondary to a CCM2 mutation.

Methods: A 4-year-old boy presented with seizures associated with a febrile illness. Contrast enhanced MRI demonstrated a complex vascular malformation with abscesses involving the left hemisphere. Conventional cerebral angiography did not demonstrate any large vessel abnormalities. He subsequently underwent brain biopsy to better characterize the vascular malformation and to find a causative organism for abscesses. Whole exome sequencing was additionally performed to identify a genetic cause for the vascular malformation.

Results: Gross and microscopic pathologic specimens from brain biopsy revealed gliotic brain with abnormal cystic dilated spaces consistent with cavernomas filled with acute and chronic inflammation. Gram positive cocci were identified on gram stain. Whole exome sequencing revealed a novel mutation in the CCM2 gene associated with autosomal dominant cavernomas.

Conclusions: Autosomal dominant cavernomas syndrome may produce unilateral disease in the central nervous system. Whole exome sequencing is emerging as a beneficial tool when interpreted within the clinical context created from a conventional diagnostic workup.

Keywords: Case studies/case series, Genetics, Infections/Neuroimmunology, Neuroimaging

48. Clinical Delineation of Pantothenate Kinase Associated Neurodegeneration

Mishra N (Toronto, ON), Joshi K, Mahmutoglu S, Logan W, Soman T

Objective: To delineate the clinical course, radiological and genetic features of Pantothenate Kinase associated Neurodegeneration (PKAN) in children.

Method: Retrospective longitudinal observational study of patients with genetically proven PKAN who attended neurology clinic from 1995 to 2012.

Results: There were total 7 patients diagnosed genetically with PANK 2 mutation in age range of 3 to 18 years. Four patients had onset before age of 10 years (early onset) and others were in second decade (late onset). Among them 5 had dystonia at presentation among which 4 had generalised dystonia at presentation. Besides these myoclonus , tremor, chorea, ballismus, parkinsonism and pyramidal sign were present in some. Also, four had retinal changes and abnormal ocular movements. Cognitive impairment were seen in 5 patients. Homozygous mutation was seen in two patients who presented at the age of 5 and 7 years and were bed bound within 2 years and required G-Tube feeding within 3 years. Heterozygous mutation were seen in 5 patients among which two became bed bound after 2 years and required G-tube after 4 years of onset and one had novel mutation. Missense mutations were most common. Classical "eye of tiger sign" was seen in 4 patients among but only one had the classical sign at first MRI. Abnormal signal intensity was seen in globus pallidus as well as in substantia nigra and red nucleus in some.

Conclusions: This study describes clinical course of patients diagnosed with PKAN and delineates clinical, genetic and radiologic relationship of this rare disease.

Keywords: Case studies/case series, Genetics, Neuroimaging

49. EEG and MRI Correlates of Neuropsychiatric Manifestations of Mitochondrial Disease: a Case Series

Goldstein AC (Pittsburgh, PA), Asato MR, Bansal L, Zuccoli G

Objective: While mitochondrial disease in children is known to have heterogeneous presenting clinical manifestations, neuropsychiatric manifestations are quite common. In this case series, presenting neuropsychiatric features in children with confirmed mitochondrial disease are reviewed in context of EEG and MRI features.

Methods: Cases from the Mitochondrial Disease Clinic at Children's Hospital with confirmed molecular diagnoses were reviewed. EEG and MRI data were then compared with clinical features.

Results: Two children with POLG presented with severe behavior problems and developmental delay, prior to onset of epilepsy. Two children with MELAS presented with developmental delay and failure to thrive prior to metabolic stroke and status epilepticus. A pair of twins presented with learning disabilities and refractory generalized seizures. Another young girl presented with failure to thrive, hypotonia, epilepsy, progressive behavior problems prior to multiorgan system failure. Common interictal findings included background slowing, disturbance of sleep architecture, and focal epileptiform discharges. MRI findings included global atrophy, abnormal white matter and abnormal MRS.

Conclusions: This series of patients with mitochondrial disease illustrates the diversity of neuropsychiatric manifestations in this population. Early consideration of mitochondrial disease in children presenting with more subtle neuropsychiatric symptoms and systemic features such as failure to thrive and global delay should be considered. From this limited case series, severity of behavioral problems correlates with severity of neurological symptoms and may be considered as a biomarker of overall more severe metabolic disturbance.

Keywords: Case studies/case series, Genetics, Neuroimaging

50. Atypical MRI in a Pediatric Patient with Hereditary Hemorrhagic Telangiectasia

Hughes I (Rochester, NY), Berg MJ

Objective: Hereditary Hemorrhagic Telangiectasia (HHT, also referred as Osler-Weber-Rendu) are genetic disorders leading to the development of abnormal vasculature. Cerebral involvement is found in 2–10% of patients, with usually multiple small, silent arteriovenous malformations (AVMs) in the brain and spine. Cerebral magnetic resonance imaging (MRI) is the most sensitive noninvasive test, although it will fail to detect a significant proportion of AVMs. Here we present a young patient with secondary CNS malformations of the disease.

Methods: A 7 year old young man with history of epistaxis presented with a 6 month progressive history of shortness of breath, and a 1 month history of progressive cyanosis. He was noted to have multiple pulmonary AVMs and cutaneous telangiectasias, suggestive of a diagnosis of HHT. His neurologic examination was normal. He underwent a screening MRI of the brain.

Results: Bilateral T1 hyperintenstities were noted in the bilateral globus pallidi without identified vascular malformations within the brain. Such findings have been described adult patients with HHT, associated with the presence of hepatic AVMs and porto-systemic shunting, leading to hyper-manganesemia. The patient was noted to have elevated managanese levels of serum testing and hepatic vascular malformations were noted on abdominal ultrasound.

Conclusions: T1 basal ganglia hyperintensities have been described in adult HHT patients who have symptomatic parkinsonism presumed secondary to failure of hepatic clearance of heavy metals and elevated serum manganese. Here we describe the youngest asymptomatic patient in the literature with portosystemic shunting and elevated serum manganese levels.

Keywords: Case studies/case series, Genetics, Neuroimaging

51. A Diagnostic Role for Susceptibility-Weighted MRI During Sporadic Hemiplegic Migraine

Fedak EM (Columbus, OH), Zumberge N, Heyer GL

Objective: Hemiplegic migraine is a rare form of migraine with aura that includes motor weakness. Diagnosis during the first episode can be difficult to make and costly, especially with the sporadic form. This case series examines the susceptibility weighted imaging findings during the acute presentation of hemiplegic migraine.

Methods: Our study evaluates the ictal MRI features of four sequential pediatric patients during a first-time, sporadic hemiplegic migraine. Repeat MRI performed after symptom resolution was compared to the ictal neuroimaging in three of the four patients.

Results: Susceptibility-weighted imaging revealed cerebral venous prominence and increased magnetic susceptibility affecting the cerebral hemisphere corresponding with each patient's neurologic impairments. Repeat MRI following migraine recovery demonstrated resolution of all susceptibility abnormalities.

Conclusion: When combined with conventional MRI sequences, SWI has diagnostic value in the acute setting of motor weakness and with clinical features consistent with hemiplegic migraine. The sequence may help to further characterize ictal cerebral blood flow changes during the hemiplegic migraine aura.

Keywords: Case studies/case series, Headache/Migratine, Neuroimaging

52. Sickle Cell Trait and Migraine: an Unusual Cause of Stroke in the Young.

Patterson EW (Lexington, KY), Stewart AM, Smith CD, Robertson WC

Objective: To report a rare complication of sickle cell trait (SCT) and migraine.

Background: Stroke is a complication of sickle cell disease (SCD). Cerebrovascular events occur in up to one third of SCD patients. SCT alone is an uncommon risk factor for stroke especially in the young. SCT may be a significant risk factor if other conditions are present.

Methods: Using Pubmed, the English literature was reviewed with search terms: "stroke in children with sickle cell trait," "migraine in children with sickle cell trait," and "stroke in children with migraine."

Results: A 16-year-old male athlete with history of migraine was admitted with left frontal headache and blurred vision. Examination revealed a right homonymous hemianopsia. Laboratory studies were unremarkable except for hemoglobin electrophoresis which revealed 58% HbA, 38% HbS and <1% fetal Hb. MRI revealed an acute left occipital infarction. The patient was placed on low dose aspirin. Formal visual fields demonstrated a partial right homonymous hemianopsia. The patient's vision improved slightly and he was discharged three days later.

Conclusions: The association of SCT and stroke is rarely reported in children. We found only seven reported cases in patients less than age 18. Children with SCT do not have significantly increased likelihood of stroke without other risk factors such as dehydration, anemia, surgery, or other hemoglobinopathies. Migraine may also increase the possibility of stroke in SCT. We recommend screening for SCT in individuals participating in high intensity sports or vigorous exercise. Patients with SCT should be considered for anti-platelet aggregation therapy.

Keywords: Case studies/case series, Headache/Migratine, Stroke

53. Three Distinct Subtypes of Non-Neoplastic NMDA Receptor Antibody Encephalitis in Children: Why Symptom Presentation May Have a Bearing on Prognosis

DeSena AD (Dallas, TX), Greenberg BM, Graves D

Objective: N-methyl-D-aspartate (NMDA) receptor antibody encephalitis is becoming an increasingly recognized cause of encephalopathy. Various manifestations of this disease include altered mental status, behavior changes, seizures, and movement disorders. We present a case series of NMDA patients grouped according to symptomatic commonalities to demonstrate the differences in response to immunotherapies and prognosis.

Methods: N/A - Case series

Results: In our experience, we have noted 3 distinct subtypes of this disease which appear to have differential responses to immunotherapies as well as varied outcomes. The poorest responders, even to aggressive immunotherapies, are the catatonia persistent type NMDA receptor antibody encephalitis, which has as its hallmark, prolonged periods of severe encephalopathy. Patients with predominantly psychiatric symptoms, which we call the psychiatric predominant NMDA receptor antibody encephalitis, have had excellent responses to plasma exchange and appear to have the least residual deficits at follow-up. Patients with fairly equal representations of periods of altered mental status, behavior problems, and movement disorders appear to have an intermediate prognosis and likely require early aggressive immunotherapy.

Conclusions: In our case series, we discuss representative examples of these clinical subtypes, and we suggest that tracking these subtypes in future cases of NMDA receptor antibody encephalitis might lead to better understanding and better risk stratification with regards to immunotherapy decisions.

Keywords: Case studies/case series, Infections/ Neuroimmunology

54. Anti-CV2/CRMP5-mediated Limbic Encephalitis in a Child

Zhorne LM (Houston, TX), Evankovich KD, Lotze TE, Muscal E

Objective: Anti-CV2/CRMP5 onconeuronal antibody-mediated paraneoplastic neurologic syndromes including limbic encephalitis, chorea, and encephalomyelitis have been well-characterized in the adult literature. They are often found in association with small cell lung cancer and thymoma. A minority of adult patients with anti-CV2/CRMP 5 antibody-mediated neurologic syndromes do not have tumors at diagnosis, but are closely monitored for future

tumor development. To our knowledge, there have been no reported cases in the pediatric literature.

Methods: Case review.

Results: We present a case of an 8-year-old boy with ADHD, mild developmental delay, and a rare chromosomal translocation who developed seropositive anti-CV2/CRMP5-mediated limbic encephalitis manifest as a single new-onset seizure, altered mental status, and global cognitive decline. MRI brain was significant for mild T2 hippocampal hyperintensities. His mental status, expressive language, and school performance improved with a 5 day course of IV solumedrol. However, he required maintenance immunotherapy with monthly IVIG and IV solumedrol for relapsing symptoms of a possible seizure and expressive language regression evident on neurocognitive testing. No underlying tumor has been identified on serial CT scans.

Conclusions: This is the first case report of anti-CV2/CRMP5 mediated limbic encephalitis in the pediatric literature. It highlights the need for a uniform approach to diagnosis and treatment of antibody-mediated limbic encephalitis, as failure to detect such antibodies may lead to inadequate treatment with a protracted or relapsing course. A search for rare onconeuronal antibodies that correlate with specific clinical phenotypes may be of benefit in the early identification and treatment of these conditions in children.

Keywords: Case studies/case series, Infections/Neuroimmunology

55. Neurologic Disease in a Peruvian Neonatal Intensive Care Unit

Medina MP (Lima, Peru), Velásquez PM

Objective: To determine the frequency of neurologic disease in hospitalized newborns and the distribution of most common diseases.

Methods: Observational, descriptive, retrospective study. Pediatric neurology evaluations were revisited for all babies admitted between June 2008 and September 2012.

Results:1626 neonates (11.1% of total hospitalized population) required neurologic evaluation, 803 were VLBW babies. 877 neurologic problems were diagnosed before discharge. 178 cases of intraventricular hemorrhage (20.29% of total neurologic cases) were detected by routine ultrasonography, 29.8% were bilateral. 39.8% IVH cases were severe (III grade IVH or periventricular infarction). IVH was present in 19.7% of VLBW babies and 33.7% of ELBW babies. Periventricular leucomalacia was present in 28/803 VLBW babies (3.48%). Most common problem in term babies was neonatal encephalopathy (190 patients, 21.6% of neurologic disease), 24.7% cases (47 newborns) were definite or probable cases of hypoxic ischemic encephalopathy. CNS malformations were frequent (123 patients, 14% of neurologic diseases), neural tube defects were most common (28/123, 22.7%), as were corpus callosum anomalies (20 cases), holoprosencephaly (15 cases) and Moebius syndrome (16 cases). 49 patients were diagnosed with perinatal trauma, most frequent lesion was brachial plexus injury (30 patients). 41 patients had CNS infections (4.6% of neurologic disease), 31 of them presented acute meningitis. Stroke was diagnosed in 29 patients. 5 patients were admitted for cranial injuries. 25 patients had neonatal seizures for causes not listed above.

Conclusions: Neurologic disease is frequent in hospitalized newborns. Attention must focused on severe, preventable injury and follow up.

Keywords: Case studies/case series, Neonatal neurology

56. Autism Spectrum Disorder in a Term Birth NICU Population

Winkler-Schwartz A (Montreal, QC), Garfinkle J, Shevell MI

Objective: Non-specific perinatal and neonatal risk factors have been shown to be associated with the development of autism spectrum disorder (ASD); however, term at-risk infants, as a distinct population, are underrepresented in the literature. This study examines the incidence and neonatal risk factors for ASD in term neonatal intensive care unit (NICU) survivors.

Methods: Retrospective analysis from a single university-practice database of neonates admitted to the NICU and followed by a single pediatric neurologist. Term infants ($\geq$ 37 weeks), born between 1991 and 2008 with at least two years of follow-up were included. Principle outcomes were: ASD, cerebral palsy (CP), global developmental delay (GDD), and epilepsy.

Results: 180 infants were included from a database of 564 neonates. Twelve (6.6%) developed ASD, 53 (29.4%) CP, 77 (42.7%) GDD and 47 (26.1%) epilepsy. Seventy-one (39.4%) developed no adverse outcomes. Nine patients with ASD (75%) were diagnosed with at least one other adverse outcome. No neonatal or perinatal variables were significantly associated with later ASD.

Conclusions: In term NICU survivors, ASD occurs with a greater incidence than in the general population and often with comorbidities. This highlights the importance of screening NICU survivors for ASD, particularly when comorbidities are present.

Keywords: Case studies/case series, Neonatal neurology

57. Subdural Hemorrhage Associated with Antithrombotic Therapy in Infants with Cerebral Atrophy

Dang L (Ann Arbor, MI), Shavit JA, Singh RK, Joshi SM, Leber SM, Barks JD, Shellhaas RA

Objective: Neonates and infants are treated with antithrombotic therapy such as low molecular-weight heparin (LMWH) for several reasons, including cerebral venous sinus thrombosis (CVST), and deep vein thrombosis (DVT). Anti-thrombotic therapy with LMWH in infants is reported to be safe, because resultant intracranial hemorrhage (ICH) is rare, and in cases with ICH, there is usually no significantly increased morbidity or mortality from the ICH. Anticoagulation in the setting of coexisting diffuse brain injury, such as hypoxic-ischemic injury, has not been well studied.

Methods: Case series of infants with CVST or DVT and comorbid diffuse brain injury that were treated with enoxaparin.

Results: Four infants (ages 1–11 weeks) were studied. Three had CVST and one catheter-associated DVT, treated with LMWH. Each infant subsequently developed subdural hemorrhage (SDH) in the setting of evolving brain atrophy. Two infants had diffuse brain injury from a hypoxic-ischemic insult, and one from severe hypernatremia and dehydration. One infant had multiple congenital abnormalities and progressive brain atrophy of unknown etiology. While three had significant SDH discovered on surveillance imaging with a brain MRI/MR venogram, only one was detected by urgent imaging due to new-onset, refractory, focal seizures. Two required urgent neurosurgical intervention. Developmental outcomes at 4–8 months of age have been unfavorable.

Conclusions: Infants at risk for cerebral atrophy, whether from a diffuse ischemic insult or another cause, are vulnerable to clinically significant SDH when treated with LMWH. Comorbid diffuse brain injury may be a relative contraindication to anticoagulation for small, non-progressive CVST or DVT.

Keywords: Case studies/case series, Neonatal neurology, Neuroimaging

58. Fetal MRI Findings Associated with Aicardi Syndrome

MacLean J (Stanford, CA), Hahn JS, Yeom K

Objective: Aicardi syndrome (AS) is a congenital disorder characterized by the triad of agenesis of the corpus callosum (ACC), infantile spasms, and chorioretinal lacunae. Since the original description on this triad in 1965, numerous other structural anomalies have been found to be associated with AS. The aim of this study was to characterize fetal MRI findings suggestive of a later diagnosis of AS.

Methods: We retrospectively identified five cases referred to our center between 2007 and 2013 with MRI scans concerning for Aicardi syndrome. Features identified on fetal MRI concerning for AS were a female fetus with ACC, plus other structural abnormalities, including colobomas of the optic nerve, abnormalities of neuronal migration, cysts, and asymmetric hemisphere size.

Results: Of the five cases who were suspected of having AS based on fetal magnetic resonance imaging, three were confirmed to have AS postnatally. All three had periventricular heterotopia and frontal lobe dysgenesis on fetal MRI. And all patients with fetally diagnosed coloboma had a postnatal diagnosis of AS. One pregnancy was terminated and the fetus did not have chorioretinal lacunae on autopsy, and one patient did not meet AS criteria, as she did not have chorioretinal lacunae after birth. Neither of these patients had frontal dysplasia or definitive periventricular heterotopia.

Conclusions: Of five fetuses suspected to have AS based on prenatal MRI, three met diagnostic criteria postnatally. In a female fetus with AS, the fetal MRI features most predictive of AS were periventricular heterotopia, frontal dysgenesis, and optic nerve coloboma.

Keywords: Case studies/case series, Neonatal neurology, Neuroimaging

59. Recurrent Encephalopathy Preceding the Diagnosis of X-linked Charcot-Marie-Tooth Disease

Kimbason T (Danville, PA), Anilkumar AC, Bronov O

Objective: To discuss the diagnostic difficulties in children presenting with acute encephalopathy syndrome and to emphasize the need for awareness of early presentation of X-linked Charcot-Marie-Tooth disease (CMT1X)

Methods: A previously healthy boy was evaluated by clinical, laboratory testing, and repeated brain imaging.

Results Patient initially presented at 11 years of age with acute hemiparesis, ataxia, and dysarthria. His family history was significant for peripheral neuropathy in maternal family members. CSF and metabolic testing was normal. Brain MRI showed symmetrical diffusion abnormalities in the white matter. This pattern resolved and recurred at ages of 14 and 17 years. He later developed features of peripheral neuropathy (CMT) including weakness of distal muscles, areflexia, decreased sensations and foot drop. The brain MRIs performed at the time of recurrences revealed symmetric signal alterations with restricted diffusion involving bilateral centrum semiovale and splenium of the corpus callosum and also cerebellar peduncles that were noted during the recent recurrence (Fig 1). Brain MRI findings normalized after 6 months. Genetic testing for hereditary neuropathy revealed mutation in Connexin 32, suggesting a diagnosis of X-linked CMT.

Conclusions: The transient encephalopathic syndrome with focal paresis, dysarthria, and ataxia is an under recognized early presentation of CMT1X and it continues to be clinically challenging due to its rarity. Thus, this case emphasizes the need for awareness among practitioners to consider CMT1X in the differential diagnosis of acute encephalopathy with symmetric cerebral white matter signal alterations with restricted diffusion to avoid unnecessary work-up and the associated costs.

Keywords: Case studies/case series, Neuroimaging, Neuromuscular disorders

60. When GPI fails: Unihemispheric Deep Brain Stimulation in Postnatally Acquired Pediatric Stroke

Marks WA (Fort Worth, TX), Bailey LJ, Reed MA, McManis MH, Pomykal A, Mercer M, Honeycutt JH

Objective: Pallidal stimulation is effective for primary and secondary dystonias. Postnatal strokes are an unusual cause of hemi-dystonia in children, and may result in anatomic disruption of the globus pallidus (GPi). We present our experience with unihemispheric DBS using alternative or multiple stimulation sites.

Methods: Review of 3 patients receiving unihemispheric DBS

Results: Sixty patients with dystonia have undergone primary DBS implant since 2007. Three had unilateral implants due to basal ganglia strokes. Patient 1 had a stroke at age 6 years due to ruptured intracranial aneurysm, with development of severe dystonia and hemiballismic arm winging. After 2 years of pallidal stimulation with little improvement, the GPi lead was relocated and a rescue lead was added to the thalamus. Ballismus resolved and dystonia

has been more manageable. Patient 2 had a stroke at age 4 years due to cardiac embolus. DBS leads were implanted simultaneously into the GPi and subthalamic nucleus (STN). Best response was observed with simultaneous stimulation of both nuclei versus independent stimulation of each site. Patient 3 had a stroke at age 8 years with resultant spastic-dystonic hemiplegia and refractory epilepsy. After undergoing multiple subcortical transections, DBS was placed in the GPI with transient improvement. Magnetoencephalography confirmed appropriate contralateral hemispheric motor representation. Seven months later STN was implanted as a rescue site achieving modest, but sustained, improvement in motor control.

Conclusions: Unilateral disruption of the basal ganglia can results in severe refractory dystonia. Alternative site and dual lead stimulation offers a viable option in unusual cases.

Keywords: Case studies/case series, Neuromuscular disorders, Stroke

61. Recurrent Isolated Optic Neuritis in Children

Lai C (Toronto, ON), Yeh EA, Banwell B

Objective: Although optic neuritis (ON) presenting as a monophasic, isolated event or accompanying multiple sclerosis has been well described, little data on recurrent isolated optic neuritis (RON) in children exists.

Methods: This is a retrospective analysis of prospectively collected data on consecutive patients with recurrent isolated optic neuritis (n=6) attending the pediatric demyelinating disorders clinic at the Hospital for Sick Children between 2003–2013. All patients received a standard visual testing battery and MRI brain scans with contrast. Patients were included if they had more than one ON episode and no evidence of demyelinating lesions of the brain or spinal cord.

Results: Six patients were included in the analysis (M:F 1:1, age range 7.9–14.6 years, median 13.3 years). Median follow up after last episode of ON was 3.0 (range: 0.5–9.3 years). Initial presentation included bilateral ON in 2 and unilateral ON in 4 patients. All patients recovered visual acuity to 20/50 or better in affected eyes, with 4/6 recovering to 20/20 vision. NMO IgG was negative in all patients. MRI studies showed thickening and enhancement in all cases.

Conclusion: Recurrent isolated optic neuritis appears to be a self-limited condition in childhood in most cases. Visual acuity returned to normal in almost all children in this series, although retinal nerve fibre layer thickness was variably affected. Most children experienced recurrence within two years of the initial episode, and only one child continued to have episodes of optic neuritis consistent with chronic relapsing inflammatory optic neuropathy (CRION), which then required prophylactic treatment.

Keywords: Demyelinating disorders

62. Low Levels of Aerobic Exercise Correlate with Fatigue and Relapse Rate in Pediatric MS

Grover S (Toronto, ON), Banwell B, Khan S, Yeh EA

Objective: Fatigue and depression occur in up to three-quarters of children with Multiple Sclerosis (MS). Little is known regarding interventions to alleviate these symptoms in children, but studies suggest benefit from aerobic exercise in adults with MS. We aimed to elucidate the relationship between fatigue, depression, exercise, and disease in this population.

Methods: This was a prospective study of 58 consecutive patients (39: monophasic demyelinating disorders (DD); 19: MS; ages 5–18) at a Pediatric MS Clinic. Pediatric Multidimensional Fatigue Scale, Center for Epidemiological Studies Depression Scale and the Godin Leisure Time Exercise Questionnaire were administered.

Results: Fatigue and depression were significantly higher in the MS group than the DD group (fatigue: 29.7±12.1 vs. 16.9±12.2; depression: 71% vs. 27%,). Level of disability was not significantly different between groups. The DD and MS group participated in exercise with similar frequency (3.7±2.2 vs. 3.5±2.0 activities/week). However, the DD patients participated in more aerobic activities (1.8±1.4 vs. 1.0±1.1, p=0.03). MS patients were more likely to report non-aerobic activities (0.7±0.8 vs. 1.2±0.8, p=0.02). Aerobic exercise negatively correlated with fatigue (r=-0.5, p=0.02). Non-aerobic exercise negatively correlated with annualized relapse rate (ARR) (r=-0.4, p=0.003).

Conclusions: Children with MS were more likely than children with non-relapsing forms of DD to report lower levels of aerobic activity, despite similar levels of disability. Lower levels of aerobic activity correlated with higher levels of fatigue. Given current knowledge suggesting improvement of fatigue and depression with aerobic exercise, future work should focus on increasing participation in aerobic activities in this population.

Sources of Funding: National MS Society, MS Society of Canada, NIH, Jog for the Jake Foundation, Children's Guild Foundation, Dairy Farmers of Canada

Keywords: Demyelinating disorders

63. Pelizaeus Merzbacher Like Disease (PMLD) Related to a Novel GJC2 Promoter Mutation

Vanderver A (Washington, DC), Helman H, Ennis S, Maski K, Soul JS, Caldovic L, Hobson G

Background: Hypomyelinating leukodystrophies are a rare cause of disease of the central nervous system (CNS) characterized by abnormal myelin formation. Pelizaeus-Merzbacher-like disease (PMLD) is an autosomal recessive hypomyelinating leukodystrophy caused by mutations in the gap junction protein gamma 2 gene (GJC2) that encodes a connexin protein. Additionally, the GJC2 promoter region contains a SOX10 transcriptional activation site which allows for SOX10 to play a role in peripheral nervous system (PNS) and CNS myelin formation. A mutation, c.−167A>G, was identified in the putative promoter region in individuals with the phenotype of PMLD, however other mutations have not yet been identified in this region.

Methods: Two patients with unclassified hypomyelinating leukodystrophies were enrolled in IRB-approved biorepositories: the Myelin Disorders Bioregistry Project at Childrens National Medical Center and at Nemours Alfred I. duPont

Hospital for Children. Patient charts were reviewed and negative for other causes of hypomyelinating leukodystrophies. Standard sequencing of the GJC2 gene and its promoter region were performed. In silico analyses using bioinformatics tools modeled the effect of the variant on protein function.

Results: Here we present two PMDL affected individuals with a novel homozygous mutation (c.−170A>G) in the GJC2 SOX10 promoter region, only the second mutation in this region reported to cause PMLD.

Conclusion: This furthers our understanding of underlying causes of PMLD and the role of SOX10 in regulation of GJC2 in CNS and PNS myelin formation. Mutations in the SOX10 activated promoter of GJC2 should be sought as a possible cause of disease in patients with unclassified leukodystrophies.

Keywords: Demyelinating disorders, Genetics

64. Accumulation of Endogenous Retroelements in Aicardi Goutieres Syndrome: a Potential Therapeutic Avenue

Vanderver, A (Washington, DC), Takanokashi A, McNeil N, Caldovic L, Taft R

Background: Aicardi Goutières Syndrome (AGS) is a devastating disorder for which there is no treatment. AGS is a genetic mimicker of viral infections of the brain, with persistent CSF pleocytosis, elevated CSF alpha interferon, CSF neopterin / biopterin and intracranial calcifications. AGS is caused by mutations in a series of genes associated with genome surveillance (TREX1, RNASEH2A/B/C, SAMHD1, ADAR1), which result in the aberrant accumulation of immunogenic nucleic acid structures within the cell. We hypothesized, based on data from a mouse model of AGS, that these accumulated nucleic acids were endogenous retro elements, with important implications for treating this disorder.

Methods: RT-PCR was used to detect the number of sequences of L1 ORF2, the retrotransposon encoded by the LINE-1 retroelement, normalized to nonmobile repetitive DNA sequences in AGS versus control peripheral blood mononuclear cells.

Results: AGS patients had an at least two fold increase of L1 ORF2 versus age matched controls. Calculations performed by 2ΔΔCT.

Conclusion: We show for the first time that there is significant accumulation of a particular transposable element, LINE-1, in human AGS cells. This suggests that the initial step in disease pathogenesis is caused by accumulation of immune-stimulatory retrotransposable elements driven by the LINE-1 encoded reverse transcriptase. Murine AGS data, in which treatment with reverse-transcriptase inhibitors (RTIs) substantially reduced mortality, suggests it may be possible to interrupt the production of these immunostimulatory nucleic acids by targeting host reverse transcription. Widely used and safe RTI therapies may be of significant benefit in reducing disease progression in AGS.

Keywords: Demyelinating disorders, Genetics, Infections/ Neuroimmunology, Translational/experimental therapeutics

65. Efficacy of Hematopoietic Cell Therapy in X-linked Adrenoleukodystrophy: a Multi-Institutional Study (ALD-101)

Raymond GV (Baltimore, MD), Orchard P, Aubourg P, Escolar ML, Kurtzberg J, Paadre S, Balsar J

Objective: The only effective therapy for childhood cerebral adrenoleukodystrophy (CCALD) is hematopoietic cell therapy (HCT), but there is limited outcome information compared to untreated boys. The evaluation of this information has become important because gene therapy uses a similar strategy of autologous transplantation to treat cerebral disease.

Methods: We conducted a retrospective study (ALD-101) to characterize subjects with untreated CCALD; and collect efficacy and safety data from subjects treated with HCT. For both untreated and treated subjects, data was collected on 136 cases (72 untreated/ 65 HCT) from the time of diagnosis until at least 2 years post-diagnosis or until death from 5 centers, 4 in the US and 1 in France. Established measures of neurologic function (NFS) and MRI (Loes) were used in all cases.

Results: At least 1 NFS and MRI (all with gadolinium) were documented in the 65 HCT (100%) In the untreated, 70 of 72 (97%) had at least one NFS score and an MRI study; 30 (42%) with gadolinium. It was shown that enhancement (Gad+) was highly predictive of rapid progression. Overall, 30 untreated had MRI with gadolinium in their course (23 Gad+/7 Gad-) does this refer to a second time point? Above it looks like all 72 had at least one MRI (baseline?). Of the Gad+, 19 had more than one NFS score recorded and the majority showed significant decline in 6–18 months. In the HCT treated cohort there was resolution of enhancement (median time 3.4 months) and stabilization of MRI and NFS. There was no documented cases of resolution of enhancement in the untreated group.

Conclusions: We report here the largest retrospective, multi-institutional study of untreated and treated CCALD, demonstrating that HCT improved all measures and that MRI enhancement is predictive of rapid progression and that it rapidly resolves following HCT. This information will be critical in the evaluation of trials of gene therapy in CCALD.

Keywords: Demyelinating disorders, Genetics, Translational/experimental therapeutics

66. Does Duration of Steroid Treatment Matter in Pediatric Optic Neuritis?

Jayakody HR (Iowa City, IA), Bonthius DJ, Joshi CN

Objective: Optic neuritis is a rare condition in pediatrics. Data extrapolated from the Optic Neuritis Treatment Trial is used in management of pediatric optic neuritis, in the absence of pediatric specific studies. Recent literature promotes a prolonged course of oral steroids to prevent relapse. However, there are no published data to support this view. Patients recently treated in our hospital have received a longer course of steroids, relative to those treated several years ago. We hypothesized that a longer course of steroids results in fewer relapses and better final visual acuity.

Methods: Retrospective analysis was conducted of 26 consecutive patients (age 4.5 to 19) treated for optic neuritis within the past 10 years. Comparison was made using chi square test between groups receiving 2 week steroid treatment (16/26) versus > 2 week steroid treatment (7/26) to analyze rate of relapses, eventual visual acuity, and reported side effects. Three patients were not treated.

Results: There were no significant differences between the 2 groups regarding relapses (7/16 vs 3/7, X2=2.29, p=0.30), side effects (6/16 vs 3/7, X2=0.77, p=0.30), or final visual acuity (> 20/40 in 12/16 vs 5/7, X2=5.88, P=0.20).

Conclusion: For the treatment of pediatric optic neuritis, a prolonged course of steroids did not result in a lower relapse rate, increased side effects, or better visual outcome than the standard two-week treatment. This study was limited by a small number of patients. Further prospective studies are necessary to evaluate the effects of a prolonged course of steroids in pediatric optic neuritis.

Keywords: Demyelinating disorders, Infections/Neuroimmunology

67. Use of the 2010 McDonald Criteria Can Facilitate Early Diagnosis of Pediatric Multiple Sclerosis

Williams MT (Detroit, MI), Tapos DO, Juhász C

Objective: Immune-inflammatory demyelinating disorders are increasingly recognized in children. In young patients who present with a first demyelinating event, diagnosing multiple sclerosis (MS) in a timely manner is essential for initiation of treatment and ultimately for improving long-term prognosis. The goal of this study was to compare the rate of initial MS diagnosis when using the old vs. new McDonald criteria in children diagnosed with MS in our hospital.

Methods: We performed a retrospective study of 25 patients (age: ≤18 years) diagnosed with MS at the Children's Hospital of Michigan from 2005 to early 2013. Both the 2005 and 2010 McDonald criteria were applied based on initial clinical presentation and neuroimaging findings. Demographics were analyzed and compared to previous pediatric MS cohorts.

Results: Age at presentation (mean: 14.6 years), sex ratio (male: female=1:1.5), clinical symptoms and relapse rate were comparable to previous published data, except the high frequency of African-American heritage (64%). Initial MS diagnosis rate applying 2005 McDonald criteria was 32% as compared to 92% for the 2010 criteria (p=0.0003). The mean time after initial symptoms until the 2005 and 2010 McDonald criteria for MS were met was 5.0 and 0.7 months, respectively (p=0.0005).

Conclusions: In our patients with similar demographics to that of previously published cohorts, we found a considerably higher sensitivity for MS diagnosis when using the 2010 McDonald criteria, allowing an earlier initiation of disease-modifying therapy. This suggests that the 2010 McDonald criteria is a more appropriate tool for the timely diagnosis of pediatric MS.

Keywords: Demyelinating disorders, Infections/Neuroimmunology, Neuroimaging

68. PET Imaging of Neuroinflammation in Pediatric MS: A Pilot Study

Kumar A (Detroit, MI), Tapos D, Williams M, Chugani HT, Juhász C

Objective: Increased expression of translocator protein (TSPO, a marker of microglial activation), imaged by positron emission tomography (PET), can detect neuroinflammation, mediated by activated microglia, often in normal-appearing white matter as well as cortex, and correlates with clinical symptoms in adults with multiple sclerosis (MS). In this pilot study, we explored the value of TSPO imaging in pediatric MS.

Methods: PET imaging using the TSPO radiotracer (11)C-[R]-PK11195 was performed after obtaining informed consent in 8 children (age: 10–18 years) with MS associated with typical cerebral MRI findings. The PET images were evaluated by calculating the regional binding potential, based on a simplified reference region model, and the values were compared to a pediatric PET database (Kumar et al., J Neuroinflammation, 2012) to identify brain regions with neuroinflammation.

Results: All but one child showed regions with increased binding on PET, affecting individually variable regions including thalamus (n=4), whose values were also increased bilaterally on the group level; increases were also seen in centrum semiovale (n=2; Figure-A), lentiform nucleus (n=2), frontal (n=3; Figure-B) and parietal cortex (n=2), brainstem (n=2), and cingulate (n=1); some of which were not detected on MRI. Focal areas with increased binding were more restricted than MRI abnormalities. The most severe, multifocal cortical and subcortical increases (Figure-A) were seen in a 17-year-old girl with multiple relapses and progressive MRI changes.

Conclusions: PET imaging of activated microglia can detect cortical and subcortical areas of neuroinflammation in children with MS, and may identify regions with active disease thus complementing clinical MRI.

Keywords: Demyelinating disorders, Neuroimaging

69. Rolandic Epilepsy Seems to have Little Effect on Adult Life: Good News from a Population-Based Study

Camfield CS (Halifax, NS), Camfield PR

Objective: To assess seizure and social outcome in adulthood for children with Rolandic epilepsy.

Method: Cases with medication treated Rolandic epilepsy were identified from the Nova Scotia population-based childhood epilepsy cohort. Epilepsy onset was in 1977-85 and follow up was in 2010-12 with chart review plus structured telephone interview for those aged >21 years.

Results: 41 children developed Rolandic epilepsy (6% of 692 incident epilepsy cases in the cohort). 32 (78%) were contacted at age >21 years. Epilepsy onset averaged 7.7± 2.3 years, follow up 28.8±4.5 years and final age 36.4±4.4 years. All had epilepsy remission and were off AED treatment for 21.2±4.7 years. There were 2 minor injuries from seizures and only one death (from a snowmobile accident). Overall 31% had ≥1 of 6 adverse social outcomes, 6 had 1, 4 had 2 and 3≥3. These were failure to complete high

school (7), pregnancy outside of a stable relationship (3 months (1), poverty (3). Those failing to complete high school were more likely to have parents with low academic achievement ± low income ($p<0.02$). By comparison, rates of ≥1 adverse social outcomes for other epilepsies with normal intelligence from this cohort varied from 75% to 90%.

Conclusions: The long term seizure and social outcome for children with Rolandic Epilepsy is remarkably better than other major epilepsy groupings. We urge that the concept of "benign" be retained.

Keywords: Epilepsy and other paroxysmal disorders

70. What Interventional Measures were Being Adhered to Prior to the AAN Quality Measures?

Clarke, DF (Austin, TX), Jean S, Tindall K, Kane J, Taylor J, LeSure SM, Perkins FF

Objective: 8 Quality measures were recommended by a subcommittee of the AAN in 2011. We reviewed investigative studies (VEEG/EMU, MRI, Neuropsychological evaluation) by our 14 Pediatric Neurology Practice providers (4 epileptologists). 2011 Charts were reviewed and after intervention we are actively reviewing ongoing 2012 and 2013 practice after educational intervention.

Method: Two months of charts were reviewed prior to discussing the AAN quality measures with the group to determine if measures were routinely followed and if the informative discussions about the measures will facilitate a difference in practice. 345 ICD-9 codes were reviewed for May and June of 2011. Other related codes for seizures, convulsions etc. were excluded to limit the possibility of diagnostic ambiguity.

Results: 423 children with epilepsy were reviewed (56 Evaluated in the EMU and Epilepsy Surgery clinic). Patients in the outpatient setting coded as having recurrent seizures were analyzed , 165/367 (45%) of whom 25.8% had failed at least 2 AED's. 23% had tried 1 medicine only, 17.6% two AED's, and 57.6% had tried at least 3 AED's. 21/95 (22%) of those trying at least 3 AED's were not documented as having a prolonged VEEG in the Epilepsy monitoring unit. A further 20/95 (21%) had not been re-evaluated in over 3 years. 10% were documented as receiving MRI's. Only 11.6% received neuropsychology evaluation.

Conclusions: This data from a very active EMU, 350–400/year. This suggests the need for a more protocol driven approach and an urgent need for education, infrastructure and expertise in the field.

Sources of Funding: Dr. Dave Clarke, Lundbeck and Eisai; Dr. Fred Perkins, None; Dr. Jeffrey Kane, None

Keywords: Epilepsy and other paroxysmal disorders

71. Clinical Review of Pimozide in Childhood Tourette's Syndrome

Eremita MJ (Hartford, CT), DiMario FJ

Objective: Tourrete's Syndrome (TS) is a lifelong neurological disorder characterized by involuntary movements and vocalizations. There are several common co-morbidities often associated with TS; Attention Deficit Hyperactivity Disorder (ADHD/ADD), Obsessive-Compulsive Disorder (OCD), Oppositional Defiant Disorder (ODD) and Learning Disabilities (LD). Typical antipsychotics used for treatment include pimozide; however there is limited data on its efficacy and side effects.

Methods: We undertook a retrospective review of all children diagnosed with TS using the diagnostic criteria set out in the DSM IV-TR evaluated from 2001–2011. We categorized their clinical manifestations, co-morbidities and treatment effects with attention to the subset of patients treated with pimozide.

Results: There were 95 subjects with chronic tics of whom 53 (40 boys; mean age 9.7 years) had TS and 10 (19%) were treated with pimozide. Co-morbid symptoms were identified in 81% of the cohort. There were; 66%-ADHD/ADD, 51%-OCD, 34%-ODD and/or behavioral/social/conduct problems, 26%-Anxiety, 25%-LD and/or the requirement of an individualized learning plan and 17%-reported being depressed.

Conclusions: There were 7/10 subjects treated with pimozide who experienced adverse effects; 2-prolonged QTc, 1-dystonic reaction, 5-excess weight gain. However, all remained on the drug with dose modification or additional concomitant treatment due to perceived benefit.

Keywords: Epilepsy and other paroxysmal disorders

72. Electroclinical Features of Epilepsy Following Neonatal Hypoglycaemia

Fong CY (Kuala Lumpur, Malaysia), Harvey AS

Objective: There are few studies of epilepsy following NH and no studies evaluating the epileptology. Studies report the majority of children have occipital epilepsy and good seizure outcome. The aim of this study was to evaluate electroclinical features of epilepsy secondary to neonatal hypoglycaemia (NH).

Method: Retrospective study of children who had seizures beyond infancy after NH. Subjects were identified by searching the EEG database and neurologists' correspondence from 1996–2012 for NH. Clinical details were obtained from medical records. EEGs and MRIs were reviewed.

Results: Eleven patients met inclusion criteria (current age 4–17 yrs). Seizure onset was 4–60 mths. MRI showed gliosis +/- cortical atrophy in the occipital lobe +/- parietal lobe in 11. Seizures were focal in 9 (head / eye version in 4, vomiting in 3, hemiconvulsing in 2), and generalised tonic in 2. Predominant EEG findings included stereotyped occipital or rolandic interictal epileptiform discharges (IEDs) with tangential dipoles on a normal background in 5, polymorphic occipital IEDs or no IEDs on a slow background in 4, and generalised slow spike wave and fast activity in 2. Seizures were infrequent or remitted in 7, and frequent (daily) and refractory in 4.

Conclusion: All patients had an occipital basis for their seizures. Despite the presence of a 'symptomatic' aetiology and lesion, the favourable outcome and stereotyped occipital IEDs suggest an 'idiopathic' mechanism in about half of our cohort. Similar features of idiopathic focal epilepsy are also reported with cerebral palsy.

Keywords: Epilepsy and other paroxysmal disorders

73. Mitochondrial Dysfunction in Children with Epilepsy

Goldenthal M (Philadelphia, PA), Valencia I, Damie S, Fernandez C, Carvalho K, Khurana D, Hardison H, Yorns W, Jethva R Melvin A Legido A

Objective: Mitochondrial (mt) disorders can cause epilepsy, including specific syndromes such as MERRF and MELAS. However, the effects of epilepsy and antiepileptic drugs (AEDs) on mt function are unclear. The objective of this study was to retrospectively assess the incidence of mt respiratory complex (RC) dysfunction in children with epilepsy.

Methods: The following clinical data were gathered: age, gender, presence of chronic static encephalopathy (CSE), epilepsy type, AEDs' number, and epilepsy control. Buccal swabs were used to determine RC-I activity by immunocapture and RC-IV and citrate synthase (CS) activities using microspectrophotometry. RC activity values were normalized relative to CS activity, and expressed as ratios (I/CS and IV/CS).

Results: A total of 58 children, 24 M, 34 F, ages 1–21 years were studied: 33 (57%) had CSE; 27 (46.6%) generalized and 29 (50%) focal epilepsy; AEDs mean number was 1.4 (range 0–3); 41 (70.7%) children had well controlled epilepsy. The frequency of abnormal I/CS and/or IV/CS was significantly higher in patients with CSE (60.6% vs. 20%, $p=0.002$). A significant increased frequency of abnormal I/CS (41.2% vs. 14.6%, $p=0.027$) was seen in patients with uncontrolled epilepsy.

Conclusion: Epilepsy type and AEDs' number did not have an effect on the frequency of RCs dysfunction. Experimental investigations have found that epilepsy decreases mt RC, damages mt, and activates oxidative stress, perpetuating the epileptogenic cycle of high-energy-demand neurons. Our clinical study supports these findings, demonstrating that epilepsy is associated with mt dysfunction, which is worse in patients with underlying CSE or uncontrolled epilepsy.

Keywords: Epilepsy and other paroxysmal disorders

74. Aberrant Neurogenesis in Infantile Spasms and Ohtahara Syndrome: Implications for Cognitive Development

Jansen LA (Charlottesville, VA), Roden WH, Shashipadme A, Siebert JR, Ojemann JG

Objective: Infantile spasms (IS) and Ohtahara syndrome (OS) are early-onset epileptic encephalopathies that may be of structural, metabolic, genetic, or unknown cause. Even when seizures are controlled, developmental outcome is often poor and the incidence of autism is high. Because these syndromes have their onset during a critical period of brain development, we hypothesized that hippocampal and cortical neurogenesis may be affected in children with IS and OS.

Methods: Fluorescence immunohistochemistry studies were performed on formalin-fixed, paraffin-embedded brain sections from infants with IS/OS (2 wks-2 yrs old) and age-matched controls.

Results: In preterm and term control infants high densities of doublecortin (DCX)-immunofluorescent immature neurons were identified in the subgranular zone (SGZ) of the hippocampus, the subventricular zone (SVZ) of the lateral ventricles, and in the cerebral cortex. This was associated with the presence of GFAP-labeled radial glia. DCX labeling dropped off dramatically by 3 months of age in non-epileptic specimens. In contrast, in specimens from children with IS/OS, high densities of DCX-positive neurons were present in the SGZ, SVZ, and cortex through late infancy. These neurons were frequently abnormally distributed and were often found in clusters.

Conclusions: Infantile epileptic encephalopathies are associated with excessive and aberrant hippocampal and cortical neurogenesis. In animal models of epilepsy, these newborn neurons are often abnormally integrated into neuronal circuits and are associated with later cognitive impairments. These findings suggest a potential mechanism for poor developmental outcomes in children with IS/OS despite successful control of their seizures

Sources of Funding: NIH NINDS.

Keywords: Epilepsy and other paroxysmal disorders

75. Telemedicine in Pediatric Epilepsy. Is it Practical?

Joshi CN (Iowa City, IA), Fick T

Objective: Frequent visits to a tertiary care epilepsy centre for pediatric epilepsy patients are a burden to the family in terms of time from work, school and travel costs. Questions related to medication management, side effects and prognosis can be handled through focused examination via a telehealth visit. We sought to assess practicality of telemedicine as adjunct to yearly hospital visits as a safe, secure and acceptable way for delivering patient care.

Methods: Phone survey of 12 patients seen over 1 year using 10 questions. 6 out of 10 questions were related to qualitative measures (information exchange, adequacy of time, privacy concerns, acceptability, and overall satisfaction) and graded on a 5 point Likert scale. Four questions were quantitative related to cost, travel distance and preference for follow up.

Results: 75% of respondents "completely agreed" that they could discuss everything in the telemedicine interview as in the hospital interview. 100% felt that they had enough time to discuss issues without privacy violation.75% of the respondents had saved between $101–300 to travel to the hospital and 16.6% saved between $300–500. 83% of the respondents lived >100 miles from the clinic. All respondents travelled <50 miles to their telemedicine site. 66.6% would prefer their next visit to be a telemedicine visit.

Conclusions: Most patients appreciated greatly the money and time saved due to telemedicine. Insurance remunerated all the patient visits as they would have a hospital visit for a similar level of billing.

Keywords: Epilepsy and other paroxysmal disorders

76. Design and Initial Findings of the National Infantile Spasms Registry of the Pediatric Epilepsy Research Consortium(PERC) - A US Multicenter Initiative to Improve Treatment and Outcomes of Infantile Spasms

Knupp KG (Aurora, CO), Wirrell E, Khan S, Berg A, Pediatric Epilepsy Research Consortium

Objective: There have been few prospective multicenter studies in the US evaluating infantile spasms (IS). The Infantile Spasms Registry of the Pediatric Epilepsy Research Consortium (PERC) brings together 30 US pediatric epilepsy centers with the capacity to identify several hundred children with IS annually for a prospective observational study.

Methods: PERC developed a database that enrolls newly diagnosed IS, age 2 months to 2 years. Data collected includes underlying etiology, development, and initial evaluation (neuroimaging, genetic and metabolic studies) and first treatments used. Follow-up data regarding seizure control, additional seizure types, development, results of subsequent evaluation and additional treatments are assessed after 3 months.

Results: From June 2012 – March 2013, 19 centers have obtained IRB approval. 12 centers with staggered start dates have enrolled 51 patients. Median age at IS onset was 6.5 months (IQR 4.0, 9.8) and 26 (51%) were male. 7/ 51 (14%) had a history of neonatal seizures. 14/51 (27%) had epilepsy prior to onset of IS. 37/45 (82%) of children for whom EEG data were available had hypsarhythmia (voltage $\geq$300 uV with multifocal spikes) or modified hypsarhythmia. A specific cause was identified in 33/48 (69%) of children.

Conclusions: PERC has the capacity to identify a large number of children in the country who are diagnosed IS. This is necessary to facilitate practice-changing research to improve the treatments and outcomes for this devastating disorder. Future randomized trials, other comparative effectiveness studies, and guidelines, are anticipated from this effort. Enrollment of centers into the consortium is open.

Sources of Funding: AES infrastructure grant and PERF

Keywords: Epilepsy and other paroxysmal disorders

77. Clobazam for Treatment of Infantile Spasms

Luke RR (Dallas, TX), Bailey LJ, Malik SI, Hernandez AW, Keator CG, Perry MS

Objective: While several anti-epileptic drugs (AED) are used to treat infantile spasms (IS), their efficacy is variable, with many patients failing to achieve seizure freedom on multiple drugs. Clobazam has demonstrated efficacy as treatment for a wide variety of seizure types. We sought to describe our experience using clobazam in patients with IS.

Methods: We retrospectively reviewed all patients treated with clobazam for IS from a single comprehensive epilepsy center. Patient variables including age at onset, etiology, age at treatment, clobazam dosing, duration of treatment, and response to therapy at initial and last follow-up were recorded. Response was characterized as >50% reduction in IS. As this was a retrospective study, concomitant AEDs were not necessarily maintained at constant dosing.

Results: Twenty-four patients were included and had failed an average of 3.2 AEDs prior to clobazam initiation. Etiology was symptomatic in 17 cases. Eleven patients (46%) reported response at the first follow-up (median 1.54 months, range 0.43-8.95) and 15 (63%) were responders at last follow-up (median 10.6 months, 2.69-31.64). Six (25%) were responders in the absence of other AED changes (median duration of response 15 months, range 3.38-21.57) and 4 (67%) of these patients experienced >90% reduction in IS (mean dose 1.38mg/kg/d, range 0.93-1.98). None of the variables analyzed predicted response to treatment.

Conclusion: Clobazam may be an effective treatment option for patients with IS and should be considered when first-line agents fail. Additional prospective studies of clobazam in patients with IS are warranted.

Drs. Angel Hernandez, Saleem Malikm, and M. Scott Perry receive honoraria from Lundbeck Pharmaceuticals as members of their speakers' bureau and advisory boards.

Keywords: Epilepsy and other paroxysmal disorders

78. Electroretinographic Responses in Epileptic Children Treated With Vigabatrin

Karimzadeh P (Teheran, Iran), Bakhshandeh Bali MK

Objective: Vigabatrin, licensed in many countries as the treatment of pediatric epilepsy. Vigabatrin is an an antiepileptic drug that results in higher gamma-aminobutyrate (GABA) levels in the brain and retina. Vigabatrin-induced visual field defects are usually, asymptomatic and only detectable by perimetry. Perimetry requires good cooperation, and children aged under 10 years cannot do it. Electroretinogram (ERG) response amplitude to full-field 30-Hz flicker shine has been offered to be more specific predictive of visual field defects.

Methods: This study is scheduled to investigate the Vigabatrin associated visual complications in sixty-seven epileptic children taking Vigabatrin using full-field ERG.

Results: Electroretinographic surveys showed normal range parameters despite three months of vigabatrin treatment and just three (4.47%) of children have been visually impaired at the end of six-month treatment. Among these three cases, one patient had persistent ERG abnormality despite Vigabatrin discontinuation.

Conclusions: Our study suggests that Vigabatrin is secure for short term pediatric antiepileptic treatment with few visual impairments which are often reversible.

Keywords: Epilepsy and other paroxysmal disorders

79. Bone Health Screening Practices Amongst Boston Children's Hospital Neurologists in Patients on Anti-Epileptic Medications: A Quality Improvement Project

Patel AA (Boston, MA), Schomer M, Loddenkemper T, Elitt C, Heath C, Heath JL, Julich K, El Achkar M, Spencer K, Hart ES Putman M

Objective: Pediatric epilepsy patients are at risk for low vitamin D levels. Factors potentially related to poor bone health in epilepsy patients include decreased ambulation and sun exposure, as well as the detrimental impact of antiepileptic medications. Studies suggest that neurologists do not routinely screen for bone health when treating epilepsy patients. We surveyed pediatric neurologists at our center on bone health care in pediatric epilepsy patients.

Methods: The objective was to assess care practices amongst pediatric neurologists surrounding bone health in

epilepsy patients, and improve screening by developing a standardized protocol and providing education. To determine baseline self-perceived screening rates of providers, an 11-item survey was administered to the 68 practicing neurologists, including all residents and fellows.

Results: Overall response rate was 48.5%. Providers were requested to estimate overall frequency of bone health screening, graded as 75%. Out of 33 respondents, 67% estimated overall frequency as 75%, all of whom were identified as epilepsy specialists. Based on these results, the following protocol was developed in collaboration with our endocrinology colleagues, and a training module implemented to improve awareness and standardize screening in our center.

Conclusions: At baseline, the majority of pediatric neurologists at BCH did not routinely screen for bone health in pediatric epilepsy patients. Findings prompted us to develop a standardized screening and treatment algorithm in order to improve awareness and patient care. Follow up surveys and chart screening to evaluate effectiveness of implementation intervention are ongoing.

Keywords: Epilepsy and other paroxysmal disorders

80. Efficacy and Safety of Intranasal Midazolam for Seizure Emergencies in Pediatric Patients: A Systematic Review of the Literature

Seinfeld S (Richmond, VA), Pellock JM

Objective: Benzodiazepines are considered effective rescue therapies for seizure emergencies. Rectal diazepam gel is FDA approved; however, for some children an alternative method of administration is required. While a variety of alternative methods have been reported in the literature, intranasal administration of midazolam may offer a convenient and socially acceptable alternative for children. This review summarizes the published results of randomized, prospective, active-comparator controlled, intranasal midazolam (IN-MDZ) studies in the treatment of acute seizure emergencies in pediatric patients.

Methods: A systematic review of IN-MDZ literature was conducted by searching PubMed using the English language filter and the search terms: ((intranasal OR nasal) AND midazolam) AND (seizures OR epilepsy). Search results were reviewed to identify randomized, prospective, active-comparator, efficacy studies that included $\geq$10 pediatric subjects ($\leq$18 years).

Results: Seven studies, which evaluated IN-MDZ in approximately 200 pediatric subjects, were identified. All 7 studies compared IN-MDZ to DZP delivered via either intravenous infusion (IV; n=4) or rectal administration (PR; n=3). Intranasal administration was achieved by spraying (n=2) or dripping (n=5) midazolam IV solution into the nose. All studies demonstrated IN-MDZ (0.2 mg/kg) was as effective as IV- or PR-DZP (0.2 – 0.5 mg/kg) in treating seizure emergencies with a rapid (<5 min) onset of action. Additionally, IN-MDZ and DZP (IV or PR) demonstrated similar safety profiles, with few reports of respiratory depression across all treatments.

Conclusions: As compared with intravenously or rectally administered diazepam, intranasal midazolam was equally effective and demonstrated comparable safety for the treatment of acute seizure emergencies in pediatric patients.

Sources of Funding: Dr. Pellock has been involved in advisory boards and served as consultant to Upsher-Smith Laboratories, Inc.

Keywords: Epilepsy and other paroxysmal disorders

81. Assessment of the Implementation of the Epilepsy Quality Measures in the Commission for Children with Special Health Care Needs (CCSHCN)

Stewart AM (Lexington, KY), Affan M, McKee H, Khan GQ, Baumann R, Bensalem-Owen M

Objective: The purpose of this pilot study was to assess application of the recently developed eight epilepsy quality metrics in the CCSHCN.

Methods: Retrospective review of clinic charts from the CCSHCN between November 2012 and January 2013 identified 81 children with epilepsy; aged 1 to 21 years old (mean age 9.6 years). There were 46 males and 35 females. The measures assessed were: seizure type and frequency, epilepsy etiology or syndrome, electroencephalogram (EEG) and brain imaging, antiepileptic drug side effects, surgery referral, safety counseling, folic acid supplementation and counseling of childbearing potential patients.

Results: The most frequently documented metrics included seizure type and frequency which were addressed in 98.8% of patients, epilepsy etiology or syndrome in 96.3% of cases and EEG reviewed or requested in 97.5% of patients. Brain imaging was reviewed or requested in 79% of the patients. Antiepileptic drug side effects were addressed in 59.3% of cases. Epilepsy surgery evaluation and referral was made for only 3.7% of the 23 patients with drug resistant epilepsy. Documentation regarding safety counseling was found in only 25% of patients. Of the 19 patients with childbearing potential counseling was documented in 40% and folic acid supplementation was addressed in only 33% of these patients.

Conclusion: In this study assessing implementation of the epilepsy quality metrics in the CCSHCN, not a single metric had 100% compliance and four measures had less than 50% compliance. Physician education and use of standardized templates during patients' encounters may help achieve 100% adherence with the core measures.

Keywords: Epilepsy and other paroxysmal disorders

82. Efficacy and Tolerability of Rufinamide in Children Younger than 4 Years with Refractory Epilepsy.

Thome- Souza S (Boston, MA), Ramgopal S, Fernández IS, Bergin AM, Bolton J, Harini C, Libenson M, Olson H, Peters J, Poduri A, Rotenberg A, Takeoka M, Kothare SV, Loddenkemper T

Objective: Rufinamide is FDA approved for treatment of generalized seizures in patients with Lennox-Gastaut syndrome aged $\geq$4 years. We evaluated efficacy and adverse effects of rufinamide in patients with diverse refractory epilepsy syndromes <4 years of age, including children with epileptic spasms.

Methods: We retrospectively reviewed records of children who were treated with rufinamide for refractory epilepsy in

the period from November 2008 to November 2012. We evaluated efficacy, defined as seizure reduction of ≥50%, and adverse effects.

Results: Rufinamide was prescribed in 261 patients, of which 69 (26.4%) were <4 years (29 males, median age 2.4 years, range 0.4-3.9). Median follow-up was 9.3 months (range 1–36.7 months). Seizure semiology included generalized tonic-clonic (16), atypical absence (6), myoclonic (14), clonic (3), tonic (29), atonic (5), focal (15), and unknown (13). Twenty-seven had one, 29 had two, and 13 had three or more seizure types. The responder rate was 49.3% (34/69) overall. Twelve patients became seizure-free and seizure frequency significantly decreased as compared to baseline ($p<0.001$). 15/26 patients (57.7%) with epileptic-spasms and 19/43 patients (44.2%) without epileptic spasms were responders. Adverse events included increased seizures (4), gastrointestinal disturbance (4), cognitive-behavioral changes (4), rash (3), back pain, jaundice and mood changes (1 each). Nine of these patients discontinued treatment due to adverse effects.

Conclusion: We found a good efficacy (57.7%) of rufinamide in younger children. Adverse effects were comparable to those in older children. We did not find different efficacy in children with and without epileptic spasms.

Sources of Funding: Dr. Sigride Thome-Souza is a recipient of the CNPq scholarship (246205/2012-1) from the Brazilian government. Dr. Sriram Ramgopal, Dr.Ann M. Bergin, Dr Jeffrey Bolton, Dr. Chellamani Harini, Dr. Mark Libenson, and Dr. Heather Olson have nothing to disclose. Dr. Iván Sánchez Fernández is supported by a grant for the study of Epileptic Encephalopathies by Fundación Alfonso Martín Escudero. Dr. Loddenkemper serves on the Laboratory Accreditation Board for Long Term (Epilepsy and Intensive Care Unit) Monitoring, on the Council of the American Clinical Neurophysiology Society, on the American Board of Clinical Neurophysiology, as an Associate Editor for Seizure, and performs video electroencephalogram long-term monitoring, electroencephalograms, and other electrophysiological studies at Boston Children's Hospital and bills for these procedures. He receives support from the National Institutes of Health/NINDS, a Career Development Fellowship Award from Harvard Medical School and Boston Children's Hospital, the Program for Quality and Safety at Boston Children's Hospital, the Payer Provider Quality Initiative, The Epilepsy Foundation of America (EF-213583 and EF-213882), the Center for Integration of Medicine and Innovative Technology, the Epilepsy Therapy Project, the Pediatric Epilepsy Research Foundation, and an investigator initiated research grant from Lundbeck. Dr. Jurriaan Peters is supported by National Institutes of Health P20 RFA-NS-12-006 and 1U01NS082320-01 grants, by the World Federation of Neurology Grant-in-Aid Competition, and by a Faculty Development Fellowship from the "Eleanor and Miles Shore 50th Anniversary Fellowship Program for Scholars in Medicine", Boston Children's Hospital, Department of Neurology, 2012–2013. Dr.Alexander Rotenberg is supported by grants from the Department of Defense, NIH NINDS, the Epilepsy Therapy Project, CIMIT, the AlRashed Family Foundation, the Fisher Family Foundation, and the Translational Research Program at Boston Children's Hospital. He serves as Associate Editor at the Journal of Pediatric Neurology. Dr. Masanori Takeoka serves as an editorial board of the Journal of Pediatric Epilepsy, and coinvestigator in Children's Hospital Boston CRP Pilot Grant Award. Dr. Annapurna Poduri is supported by a grant from the National Institute of Neurological Disorders and Stroke (NINDS) (K23NS069784). Dr. Sanjeev Kothare is funded by the following grants: National Institutes of Health: 1 RC1 HL099749-01 (R21), and RFA-HL-09-001, HL-0967561-01A2 (R21), NS076859-01 (R21), NICHD(5U54HD061222), and Investigator Initiated Grant from Eisai Pharma, Inc, to assess safety and efficacy of rufinamide in children, and the Harvard Catalyst to assess cardiorespiratory abnormalities during seizures in children.

Keywords: Epilepsy and other paroxysmal disorders

83. Pediatric Epilepsy Research Consortium (PERC) US Multicenter Study to Improve Treatment and Outcomes of Infantile Spasms: Etiologies and Initial Therapies

Wirrell E (Rochester, MN), Knupp K, Khan S, Berg AT, Pediatric Epilepsy Research Consortium

Objective: To prospectively evaluate the etiology, initial investigations and first treatments used in newly-diagnosed spasms.

Methods: Eighteen US pediatric epilepsy centers enrolled infants with newly diagnosed spasms, both new-onset epilepsy and evolved from other seizure types. Data reviewed included primary etiology, initial evaluations ordered (neuroimaging, genetic and metabolic studies) and initial treatments used.

Results: From 06/12-04/13, 51 infants were enrolled. Median age at seizure onset was 6.5 months (IQR 4.0, 10.0) and 49% were male. An underlying cause was identified in 37/51 (73%) and included malformations of cortical development (MCD) in 7 (13.7%), tuberous sclerosis in 2 (3.9%), other congenital brain anomalies in 5 (9.8%), prior brain injury in 12 (23.5%) (HIE – 4, PVL/IVH – 3, trauma – 3 and stroke – 2), tumor in 2 (3.9%), genetic in 8 (15.7%) and metabolic in 1 (2%). Of those without known etiology, 36% underwent genetic and 64% had metabolic testing. Initial treatment for spasms was recorded in 47 cases, and consisted of ACTH in 47% (19-high-dose, 3-low-dose), oral steroid in 19% (all high dose), vigabatrin in 26% and other in 9%. ACTH/steroids were used in 6/8 with genetic etiologies, 4/9 with MCD/ tuberous sclerosis, 2/4 with other congenital brain anomalies, 8/12 with prior brain injury/tumor, 1/1 with metabolic etiology and 10/13 with unknown etiology.

Conclusions: An underlying etiology for spasms is discovered in nearly three quarters of cases. ACTH or high dose oral steroids are the most commonly used initial therapies and etiology was not significantly correlated with treatment choice.

Sources of Funding: PERC is supported by an AES Infrastructure Award

Keywords: Epilepsy and other paroxysmal disorders

84. Novel SCN2A Mutation in a Proband With Migrating Focal Seizures of Infancy

Dhamija R (Rochester, MN), Wirrell E, Falcao G, Kirmani S, Wong-Kisiel LC

Introduction: Migrating focal seizures of infancy is characterized by seizure onset within 7 months of age, migrating focal motor seizures with multifocal ictal electroencephalography discharges, intractable to conventional antiepileptic drugs and poor prognosis. Reported genetic etiologies include SCN1A and KCNT1 mutations and homozygous deletion of the PLCB1 gene. Here we report a novel SCN2A mutation in a child with this syndrome.

Case report: A 7 week old female infant was admitted to our hospital for management of status epilepticus. She was product of a full term healthy pregnancy. Seizures started around 5 weeks of age and remained medically refractory. Physical examination was significant for encephalopathy, diffuse hypotonia and absence of normal new born reflexes. Head MRI was normal. EEG showed multifocal epileptiform discharges as well as seizures arising from multifocal regions in both cerebral hemispheres. Based on her phenotype a diagnosis of migrating focal seizures of infancy was made. Genomic DNA was isolated from blood and submitted for commercial testing. A novel missense mutation was identified in the SCN2A gene, exon 22 (coding for voltage gated sodium channel type II): c.3977T>A (p.V1326D). Parental testing was negative for the same mutation, thus confirming a de novo change. This mutation affects a highly evolutionarily conserved area of the gene, and replaces hydrophobic nonpolar valine with polar aspartic acid, thus predicted to affect protein function, and presumed pathogenic.

Conclusion: This report expands our knowledge of the genetic basis of migrating focal seizures of infancy to include mutations in SCN2A gene.

Keywords: Epilepsy and other paroxysmal disorders, Genetics

85. Single Otherwise Asymptomatic Mutation Modifies Long-Term Outcome after Mild Perinatal Hypoxia by Resulting Spontaneous Recurrent Seizures without Affecting the Severity of Acute Hypoxic Seizures

Ng Kim CW (Durham, NC), Leonard S, Arehart EJ, Mikati MA

Objective: Whether, otherwise asymptomatic, gene mutations modify the long-term consequences of perinatal hypoxia is often assumed, but remains to be demonstrated. We investigated the hypothesis that an otherwise asymptomatic heterozygous mutation affecting the Kv1.1 voltage-gated channels can modify such consequences.

Methods: Wild type (WT) and Kv1.1 heterozygous (HET) P6 pups were subjected, gradually over 45 min to hypoxia down to 4% for one minute, (2 groups) or were sham manipulated (2 groups). Hippocampal EEG with video recordings were performed to assess acute hypoxic seizures at P6 and spontaneous seizures as adults.

Results: There were no differences in acute hypoxic seizures between HET (n=16) and WT mice (n=13) in either latency to Racine Stage 4 seizures: 1001±133.6 (seconds), 1042±187.4, p=0.85; duration of Stage 4: 131±26.6, 101±29.9, p=0.46; or percent of mice with detected hippocampal seizures: 1/3 and 3/12, p=1.00, Fischer's Exact Test. As adults, the HET-hypoxia group was the only group that developed spontaneous seizures (3/7, compared to 0/7 in WT-Hypoxia group with seizure frequency 0.17 ± 0.073 seizures/day (total of 1255 hours in a long-term monitoring group), 0/5 in HET-Normoxia, and 0/7 in WT-Normoxia, p=0.026).

Conclusions: We established a novel mouse model of mild perinatal hypoxia which demonstrates the long-term additive effects of a gene mutation to those of perinatal hypoxia; and supports the concept that certain gene mutations can predispose to worse outcome and result in epilepsy. This suggests that exome/genome sequencing in humans may identify gene mutations that increase the risk of later epilepsy after perinatal hypoxia.

Keywords: Epilepsy and other paroxysmal disorders, Genetics

86. Whole Exome Sequencing of Patients with Rett-like Features Negative for MECP2 Mutations

Olson HE (Boston, MA), Khwaja O, Poduri A, Kaufmann W

Objective: To identify genetic etiologies in cases with Rett syndrome or with Rett-like features when clinical testing for MECP2 mutations or deletions is negative.

Methods: A cohort of eleven patients with Rett syndrome-like features, four meeting criteria for the disorder, and negative clinical testing for mutations or deletions in MECP2 were recruited by a Rett syndrome specialist to the Core for Neurological Diseases at Boston Children's Hospital. We completed a detailed phenotypic analysis and performed whole exome sequencing.

Results: Using 2010 diagnostic criteria, three patients had classical Rett syndrome and mutations in MECP2 (two frameshift deletions and one pathogenic missense mutation). One patient met criteria for atypical Rett syndrome, with neonatal onset epilepsy including focal seizures and epileptic spasms, and had a frameshift deletion in STXBP1. The remaining patients had Rett-like features but did not meet criteria for Rett syndrome, most often due to lack of regression. One patient with Rett-like features without epilepsy had a missense mutation in FOXG1, and consistent MRI findings. One had a deletion in MECP2. For the remaining five, candidate genes were identified including known epilepsy genes.

Conclusions: Whole exome sequencing is high yield for patients with Rett syndrome or Rett-like features negative for mutations in MECP2, though targeted gene testing may also provide a diagnosis. Genes associated with atypical Rett syndrome, epilepsy, or intellectual disability should be considered in cases not meeting criteria for Rett syndrome or when MECP2 testing is negative. Clinical criteria supportive of classical Rett syndrome correlated well with MECP2 mutations.

Sources of Funding: Funding for whole exome sequencing for this project was provided by a pilot grant from the Gene Partnership ReSeq program, an internal grant from Boston Children's Hospital.

Keywords: Epilepsy and other paroxysmal disorders, Genetics

87. Developmental and Epilepsy Follow-up of Children with Duplications of FOXG1 on 14q12

Seltzer LE (Rochester, NY), Sohnee A, Paciorkowski AR, Bertrand M, Blume HK, Opheim KE, Dobyns WB, Wheless J

Objective: To evaluate the neurodevelopmental and epilepsy outcomes in children with duplications of FOXG1 on 14q12.

Methods: Subjects with duplications of 14q12 that included FOXG1 by clinical chromosomal microarray were identified. Developmental follow-up was obtained using the Vineland Adaptive Behavior Scale and parent report. Data was collected regarding type of epilepsy, treatment, EEG, and neuroimaging.

Results: We report the genomic, developmental, and epilepsy phenotype in 6 children with de novo duplications of 14q12 including FOXG1. Subjects had duplications of varying genomic size, ranging from 3 Mb - 33.9 Mb. One subject had a complex supernumerary marker chromosome resulting from the translocation of the distal long arm of chromosome 6 to the proximal long arm of chromosome 14 resulting in FOXG1 duplication. Five of the 6 subjects developed infantile spasms with ictal electrodecrement and hypsarrhythmia. Four of the five subjects with infantile spasms responded to ACTH with cessation of spasms and normalization of the EEG. One subject with two chromosome 14 duplications has never had a seizure. Long term follow-up developmental data at ages ranging from 1 year – 9 years indicates ongoing cognitive impairment, abnormal expressive language, and repetitive behaviors.

Conclusions: We conclude that duplications of FOXG1 are associated with a neurodevelopmental syndrome that includes autistic features, intellectual disability, and infantile spasms. Infants with smaller 14q12 duplications were non-dysmorphic, with normal brain imaging, and would have previously been categorized in the "cryptogenic" category of infantile spasms. The spasms are often responsive to standard therapy, however long-term developmental outcome demonstrates multiple impairments.

Sources of Funding: K12 NS 066098 (PI Mink) NIH/NINDS Neurological Sciences Academic Development Award

Keywords: Epilepsy and other paroxysmal disorders, Genetics

88. Non-Syndromic Patients with Infantile Spasms and Malformations of Cortical Development: Low Recurrence Risk of Seizures in Siblings

Tiwari VN (Detroit, MI), Kupsky W, Huq AHMM, Chugani HT

Objective: Parents of children with intractable infantile spasms (IS) undergoing epilepsy surgery often ask whether siblings are at risk. Sibling recurrence risk is a measure of familial aggregation of disease, may indicate genetic effect and is useful for genetic counseling. Here, we sought to determine whether non-syndromic patients with IS and malformations of cortical development (MCD) have a family history of seizures, particularly in siblings.

Methods: We selected 29 children with intractable infantile/epileptic spasms who underwent cortical resection (mean age at surgery: 4.4±3.8 years; 12 males, 17 females; age range 0.8–14.9 years). Pathological diagnosis of MCD was confirmed in all patients. Family history (including parents, siblings and close relatives) of seizures was acquired in all patients through neurology chart review/telephonic interview.

Results: Pathological diagnosis of cortical migration disorder (16), cortical dysplasia (9) hemimegalencephaly (1), dysembryoplastic neuroepithelial tumor (1), focal lissencephaly (1) and porencephaly (1) was made in these patients. None of the siblings in any family (total siblings=30) were affected by IS or other types of seizures. The maternal aunt of one patient and mother of another patient had a history of transient childhood seizures.

Conclusions: This retrospective study showed that patients with IS with MCD who underwent resective surgery have negative sibling history for seizures. Although de novo mutation seems to be the most likely cause for this finding, autosomal recessive/oligogenic models or environmental factors cannot be excluded. This small study will provide some reassurance to the families of children with refractory IS but, larger studies are warranted.

Keywords: Epilepsy and other paroxysmal disorders, Genetics

89. Contiguous Deletion Of KCNQ2 And CHRNA4 May Cause a Different Disorder from Benign Familial Neonatal Seizures

Ng YT (Oklahoma City, OK), Pascual FT, Wierenga KJ

Objective: Benign familial neonatal seizures (BFNS) is an autosomal dominant disorder associated with heterozygous mutations of either KCNQ2 or KCNQ3 gene. Most cases have mutations of KCNQ2. The CHRNA4 gene encodes the α4 subunit of neuronal acetylcholine receptors, and its deletion is associated with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE). We report three unrelated individuals with KCNQ2 and CHRNA4 deletion, presenting with neonatal seizures and developmental delay.

Methods: The affected individuals were evaluated for neonatal seizures. Each individual had full neurological work-up and genetic testing. Genetic testing was done using microarray analysis, with two patients diagnosed by 720K Agilent oligoarray and one diagnosed by Reveal SNP array containing 1.9M oligo and 750K SNP probes.

Results: All three patients' seizures started within one week after birth; all required anti-epileptic drugs. Each had normal brain magnetic resonance imaging, and at least two electroencephalograms with either normal or abnormal findings. All were developmentally delayed. All three patients had both KCQN2 and CHRNA4 deletions. None presented with ADNFLE phenotype, associated with CHRNA4 mutation. Our three cases had deletions of 20q13.3 with either 20q13.33 or 20q13.33-qter encompassing the contiguous KCQN2 and CHRNA4 genes.

Conclusions: Microdeletion of 20q13.33 with loss of gene group ARFGAP1, CHRNA4, and KCNQ2 has been associated with cognitive and language deficits, with or without behavior problems or seizures.This study provides evidence that KCNQ2 and CHRNA4 deletion associated with phenotypes different from typical BFNS.

Keywords: Epilepsy and other paroxysmal disorders, Genetics, Neonatal neurology

90. Brain c-fos Expression in Rat Models of Infantile Spasms and Neonatal Status Epilepticus.

Morita K (Tokyo, JP), Akman O, Moshe SL, Galanopoulou AS

Objective: The transcription factor c-fos is used to map brain activity during epileptic seizures in rodents, but very few studies have evaluated its expression during seizures at the first postnatal week. We investigate c-fos expression in infantile spasms (IS) and convulsive status epilepticus (CSE) in postnatal day 4 (PN4) rats.

Methods: We used the multiple-hit rat model of symptomatic IS, induced by right intracerebral doxorubicin and lipopolysaccharide infusions at PN3 male rats (DLP pups, n=3). To induce CSE, intraperitoneal kainic acid (KA) was injected before video-monitoring in 3 PN4 male rats. PN4 DLP and KA-injected rats were perfused after 2 hours of video-monitoring. Controls included 3 PN4 male pups. Coronal brain sections were stained for c-fos.

Results: All 3 DLP rats had spasms, but no brain region was consistently c-fos-labeled. Reduced c-fos labeling of the piriform cortex and inconsistent hippocampal labeling (1/3 rats) were noted in DLP pups. KA injection resulted in CSE in 2 rats but scratching in 1 rat. Increased c-fos labeling compared with controls was noted in the hypothalamus, piriform cortex, and central gray in KA-injected rats, whether they manifested CSE or scratching.

Conclusions: In PN4 pups, DLP spasms involve distinct brain regions than KA-induced CSE. C-fos is not a generic marker of epileptic seizure activity during the first postnatal week. Markers of specific signaling pathways activated during different types of early life seizures could be more sensitive in mapping the operant seizure networks.

Sources of Funding: NINDS, CURE, Autism Speaks, Heffer and Siegel Famillies Foundations.

Keywords: Epilepsy and other paroxysmal disorders, Neonatal neurology

91. Reduced Phenobarbital Use Associated with Prolonged EEG Monitoring Among Neonates with Seizures due to Hypoxic-Ischemic Encephalopathy

Orbach SA (San Franciso, CA), Bonifacio Sl, Kuzniewicz M, Glass HC

Objective: The role of thalamic injury in the development of epilepsy with continuous spike-wave during slow-wave-sleep (CSWS) has been suggested. We studied thalamic abnormalities in patients with CSWS using FDG-PET imaging.

Methods: Thirteen patients (9 females; mean age: 7.7 years) with CSWS (excluding Landau-Kleffner syndrome), who had undergone FDG-PET were studied. Their thalamic glucose metabolism, represented by standardized uptake value normalized to whole brain (NSUV), and its asymmetry [absolute asymmetry index (AAI): |(Right-Left)| *200/(Right+Left)] was calculated. These values were compared with those from 10 normal healthy controls (5 females; mean age: 11.1 years).

Results: Thalamic glucose metabolism was abnormal in 11 patients (85%). Reduced (n=4) or increased (n=1) NSUV was seen in unilateral thalamus in five patients, leading to a significant thalamic asymmetry in these patients (AAI=6–32% (1.9±0.84% in controls); p=0.004). Thalamic NSUV was decreased (n=5) or increased (n=1) bilaterally in 6 children. MRI was abnormal in only one patient, showing right thalamic atrophy, consistent with severely decreased glucose metabolism. Epilepsy surgery (multilobar cortical resections ipsilateral to the side with lower thalamic metabolism) was performed in 6 patients, with class-I outcome seen in 3/4 patients with unilateral and 1/2 patients with bilateral decreased thalamic NSUV.

Conclusions: Thalamic abnormalities, both uni- and bilateral, are seen in a large majority of CSWS patients. FDG-PET is a sensitive and quantifiable modality to detect these changes compared to MRI which is mostly normal. Successful epilepsy surgery is possible in these patients and thalamic metabolic asymmetry may be a biomarker for potential surgical candidates.

Keywords: Epilepsy and other paroxysmal disorders, Neonatal neurology

92. Thalamic Abnormalities in Patients with CSWS – An FDG-PET Study

Agarwal RL (Detroit, MI), Kumar A, Tiwari V, Chugani HT

Objective: The role of thalamic injury in the development of epilepsy with continuous spike-wave during slow-wave-sleep (CSWS) has been suggested. We studied thalamic abnormalities in patients with CSWS using FDG-PET imaging.

Methods: Thirteen patients (9 females; mean age: 7.7 years) with CSWS (excluding Landau-Kleffner syndrome), who had undergone FDG-PET were studied. Their thalamic glucose metabolism, represented by standardized uptake value normalized to whole brain (NSUV), and its asymmetry [absolute asymmetry index (AAI): |(Right-Left)| *200/(Right+Left)] was calculated. These values were compared with those from 10 normal healthy controls (5 females; mean age: 11.1 years).

Results: Thalamic glucose metabolism was abnormal in 11 patients (85%). Reduced (n=4) or increased (n=1) NSUV was seen in unilateral thalamus in five patients, leading to a significant thalamic asymmetry in these patients (AAI=6–32% (1.9±0.84% in controls); p=0.004). Thalamic NSUV was decreased (n=5) or increased (n=1) bilaterally in 6 children. MRI was abnormal in only one patient, showing right thalamic atrophy, consistent with severely decreased glucose metabolism. Epilepsy surgery (multilobar cortical resections ipsilateral to the side with lower thalamic metabolism) was performed in 6 patients, with class-I

outcome seen in 3/4 patients with unilateral and 1/2 patients with bilateral decreased thalamic NSUV.

Conclusions: Thalamic abnormalities, both uni- and bilateral, are seen in a large majority of CSWS patients. FDG-PET is a sensitive and quantifiable modality to detect these changes compared to MRI which is mostly normal. Successful epilepsy surgery is possible in these patients and thalamic metabolic asymmetry may be a biomarker for potential surgical candidates.

Keywords: Epilepsy and other paroxysmal disorders, Neuroimaging

93. A Retrospective Analysis of the Usefulness of Emergent Computed Tomography Scans for Pediatric Patients with Known Epilepsy Presenting to the Emergency Department After an Afebrile Seizure

Cepeda CD (Charleston, WV), Taravath S, Berry SL, Wright J, Thompson S

Objective: Increasing use of medical imaging raises concern about radiation exposure to children and cancer risk later in life. Limited data exists regarding computed tomography (CT) for patients with known seizure disorders presenting to Emergency Department (ED) after afebrile seizures. The American Academy of Neurology (AAN) recommends emergent CT (eCT) for specific patients presenting with seizure, but do not differentiate between initial and chronic seizures. Our purpose is to examine the rate of eCT for patients with known seizure disorder presenting to the ED with afebrile seizure; the patient factors associated with eCT use and clinically significant abnormal findings; the percent of patients demonstrating clinically significant abnormal findings; and the rate of repeat CT scans and percentage of patients with new clinically significant abnormal findings.

Methods: We retrospectively reviewed medical records of pediatric patients with diagnosis of seizure disorder/epilepsy presenting with afebrile seizure to CAMC Women and Children's Hospital ED between 1999–2011. Patients with febrile seizures or new-onset afebrile seizures were excluded.

Results: Ninety-nine children met inclusion criteria. Fourty-four received 53 eCTs during 144 ED visits. Twenty-six of 53 eCTs met AAN guidelines for eCT use. Sixteen of 53 CTs were abnormal (30.2%). Only 1 (6.3%) finding was clinically significant, defined as requiring further intervention/surgery, transfer, or further imaging studies. Of 53 eCTs, 38 (71.7%) were repeat scans; 10 showed new findings (7 new abnormalities, 3 resolution of abnormalities) that were not clinically significant.

Conclusions: Findings on eCT scans occurred at a low frequency, and clinically significant abnormalities were rare.

Keywords: Epilepsy and other paroxysmal disorders, Neuroimaging

94. Hippocampal Formation Activation During a fMRI Language Task in Children with and without Focal Epilepsy

Sepeta LN (Washington, DC), Berl MM, Xu B, Zimmarro LA, Gaillard WD

Objective: We examined if a language task reliably elicited hippocampal formation activation (HF) and whether activation was related to language dominance.

Methods: 16 children with left hemisphere epilepsy (normal MRI; ages 4–12; mean 10.1±2.3) and 32 typically developing controls (TDC) (ages 4–12; 9.1±2.3) underwent 3T EPI BOLD fMRI with an age-level adjusted auditory word definition decision task. Data were analyzed using SPM8; HF region of interest (ROI) was based the Wake Forest PickAtlas. We calculated Laterality Index (LI) for HF and Wernicke's ROI using a bootstrap method (p0.20, Bilateral = $0.20 > LI > -0.20$, Right = $LI < -0.20$.

Results: 21/32 (65%) of TDC and 11/16 (69%) of patients demonstrated HF activation. Mean LI was −0.01± 0.35 (0 Bilateral, 6 Left, 5 Right) for TDC; and −0.01 ± 21 for patients (7 Bilateral, 4 Left, 3 Right): compared to TDC Wernicke's ROI LI, 0.43±0.40 and patient LI, 0.59±32. There were no differences between controls and patients (ANOVA). Of 29 children with Left language dominance HF LI was: 10L; 7R;17B;1R dominant child had L HF; and of 7 with bilateral language HF LI was: 4L; 2R, 1B. There was no correlation between Wernicke's and HF LI (Pearson's).

Conclusions: Children demonstrated bilateral hippocampal activation which was unrelated to language lateralization. Bilateral activation in children indicates less material-specific lateralization of memory function than seen in adults. Developmental differences may explain better memory performance following surgical resection for children compared to adults.

Sources of Funding: Federal funding (WDG, MMB) American Epilepsy Society Post doctoral fellowship award (LNS)

Keywords: Epilepsy and other paroxysmal disorders, Neuroimaging

95. Motor Stereotypies: Pursuing the Underlying Biological Mechanism

Gao SL (Baltimore, MD), French BM, Pletnikov MV, Singer HS

Objective: The goal of this research is to identify the underlying neurochemical mechanism(s) and potential therapeutic treatments for motor stereotypies. Rodent models for stereotypic behaviors (sniffing, chewing, licking, grooming, rearing, and jumping) include drug-induced (amphetamine) and spontaneously appearing movements (deer mouse).

Methods: Study models: 1) Amphetamine (Amp)-induced: Swiss Webster mice (7 weeks old) receive a 5 mg/kg IP dose of Amp 30 minutes prior to IP treatment with either saline or test drug. Activity is quantified post treatment using a 7 point activity scale. 2) Deer mice (2–6 months old) are electronically monitored prior to and following receipt of IP saline or test drug. Test drugs included: N6-cyclopentyladenosine, CPA (adenosine A1 agonist); 2-p-(2-carboxyethyl)phenethylamino-5-n-ethyl carboxamide adenosine, CGS (adenosine A2a agonist); D-serine + amino acid oxidase inhibitor (glutamate agonist); neostigmine (acetylcholinesterase inhibitor); cipoxifen (histamine-3 antagonist); immepip (histamine-3 agonist); 7,8 dihydroxyflavone

(activates TrkB); SCH23390 (D1 antagonist); raclopride (D2 antagonist); and IC87114 (inhibits a phosphoinositide 3-kinase subunit)

Results: Figure 1 shows the results of drug treatment expressed as the mean percent change in behavior at 1 hour as compared to baseline. Responses to medication differed between animal models. In general, drugs that influence dopaminergic neurotransmission, either directly (D1 and D2 antagonists) or indirectly (adenosine receptor and glutamate agonists) appear to reduce behavior. Neostigmine also decreased activity.

Conclusions: Motor stereotypies are reduced by altering neurotransmitter systems, especially dopamine, located within cortico-striatal-thalamo-cortical circuits. Differing responses to test drugs suggests the likelihood of variable underlying mechanisms within animal models. Ongoing efforts are designed to evaluate additional pharmacological agents, long term efficacy, and the site of alteration.

Sources of Funding: Nesbit-McMaster Foundation.

Keywords: Epilepsy and other paroxysmal disorders, Translational/experimental therapeutics

96. Cardiac Risk Factors for Sudden Unexplained Death in Epilepsy (SUDEP) in a Model of Acquired Epilepsy

Lai YC (Houston, TX), Li N, Lawrence W, Wang S, Valderrábano M, Wehrens XHT, Anderson AE

Objective: Sudden unexpected death contributes significantly to mortality in epilepsy. Clinical observation suggests that epilepsy is associated with cardiac manifestations such as resting tachycardia and QTc prolongation. However, the onset of cardiac changes in epilepsy and whether these changes contribute to sudden death remains to be fully investigated. Therefore, we evaluated the onset of cardiac changes and their contribution to sudden death in a model of acquired epilepsy.

Methods: Status epilepticus (SE) was induced in the juvenile rats using pilocarpine (300mg/kg, i.p.). Serial EKG recordings were obtained following SE. HR, PR, QRS and QT intervals were measured. Ex vivo and in vivo electrophysiological studies were performed on age-matched sham and epileptic rats. Electrical pacing was used to induce ventricular tachycardia (VT). Data were analyzed using Student t-test, 2-way ANOVA or Fisher exact test.

Results: The epileptic rats ($n=47$) exhibited decreased survival compared with shams ($n=36$, $p<0.01$). The epileptic rats began to exhibit resting tachycardia and prolonged QTc at 2 mo following SE ($n=20$–21/group, $p<0.01$), coinciding with the appearance of recurrent seizures. The epileptic rats exhibited slower conduction velocity ($n=5$/group, $p<0.05$) and ventricular ectopy ex vivo. Ten of 14 epileptic rats developed reproducible VT whereas 3 of 11 sham had inducible VT in vivo ($p<0.05$).

Conclusions: Early, persistent EKG changes in the epileptic cohort suggest that cardiac changes may parallel the development of epilepsy. Increased VT susceptibility in the epileptic rats may contribute to the decreased life expectancy in this model and represent a potential mechanism for sudden death in epilepsy.

Keywords: Epilepsy and other paroxysmal disorders, Translational/experimental therapeutics

97. Taurine Intervention in Succinic Semialdehyde Dehydrogenase (SSADH) Deficiency

Pearl PL (Washington, DC), Schreiber J, Theodore WH, McCarter R, Wiggs E, Yu Y, He J, Gibson KM,

Objective: Taurine intervention for SSADH is rational due to partial GABA(A&B) receptor agonist effects, rescue in the null mouse from status epilepticus and premature lethality, and a case report.

Methods: Subjects were titrated weekly from 50 to a target 200mg/kg/day, and assessed for safety, tolerability, and adaptive functioning using age-normalized ABAS scales. Selected individuals consented to additional outcome/biomarker studies (neuropsychological testing, CSF GABA/GHB, TMS, flumazenil-PET).

Results: Twenty-five patients (14M/11F, age 0.5–33yrs, mean 11yrs) were recruited. Sixteen unique subjects (8M/8F) provided follow-up data (mean time elapsed 13mo); two re-enrolled after a 3-year hiatus. Three subjects withdrew due to perceived lack of efficacy, and data from one was invalidated due to an error in administering the ABAS. One serious AE occurred (hospitalization for hypersomnia) on 16 grams/day (200mg/kg/day), leading to a dose-lowering paradigm with a maximum dose of 10 grams/D. Results did not show statistically significant improvement in the adaptive domains ($p>0.18$). Eight patients (6M/2F; age range 12–33 yrs) enrolled into the biomarker arm; preliminary neuropsychological results indicate baseline average Full Scale IQ (Wechsler Nonverbal Scale of Ability) of 44.1 (range 34–55), 3.6 SD < mean. Of 6 who returned at 6-month follow-up, 4 completed testing (2M/2F) on therapy; average FS IQ = 43.4 (range 33–51), an insignificant difference.

Conclusions: Adaptive behavior did not improve with taurine. This study provides the first report of formal IQ scores in a series of SSADH patients and baseline CSF, TMS, and PET data for upcoming trials of novel therapeutics including the GABABR antagonist SGS-742.

Sources of Funding: NIH/NINDS RO1 HD58553

Keywords: Epilepsy and other paroxysmal disorders, Translational/experimental therapeutics

98. Effect of Antipsychotic Use on Prevalence of Overweight/Obesity in Fragile X Syndrome

Berry-Kravis E (Chicago, IL), Nelligan M

Objective: To investigate whether use of antipsychotics for irritable behaviors is associated with an increased prevalence of obesity and overweight in individuals with fragile X syndrome (FXS).

Methods: Data including weight, height, age, and medication use at the most recent visit was obtained from patient charts in a large FXS Clinic. Calculated BMIs were categorized as not overweight (<85%ile age/gender BMI), overweight (85%ile age/gender BMI or higher; ≥25 BMI for adults), or obese (95%ile age/gender BMI or higher, ≥30

BMI for adults). Frequency of patients exceeding the overweight and obese cut-offs in groups treated and not treated with antipsychotics was compared with Chi-squared analyses.

Results: Data was available for 221 patients with FXS (62 antipsychotic-treated, 159 not antipsychotic-treated). In the total cohort 114 (51.5%) exceeded the overweight cut-off and 66 (29.9%) were obese. Other medication use was similar in the antipsychotic-treated and non-antipsychotic-treated groups; 45 patients on stimulants were excluded due to known effects on weight (11 (18%) antipsychotic group, 34 (21%) non-antipsychotic group). In the remaining antipsychotic group (N=51, age 19.3±11.1), 36 (70.6%) were at-least overweight and 22 (43.1%) were obese, compared to 59 (47.2%) exceeding the overweight cut-off (p=0.0008) and 33 (26.4%) obese (p=0.0067) in the non-antipsychotic group (N=125, age 16±8.73).

Conclusions: Baseline prevalence of overweight/obesity is high in FXS, and antipsychotic use appears to be associated with further increased risk of exceeding overweight/obesity thresholds, emphasizing the need for alternative effective treatments for severe behaviors in FXS.

Keywords: Genetics

99. Infrared Thermal Analysis and Autonomic Function in Rett Syndrome

Byiers BJ (Minneapolis, MN), Feyma TJ, Symons FJ

Objective: Autonomic dysfunction is frequently mentioned as an issue in clinical descriptions of Rett syndrome [RTT] with concern for autonomic dysfunction. Using infrared thermal imaging we sought to quantify the clinical peripheral symptoms of RTT specific to thermal dysregulation (cold hands/feet) and test for within patient skin temperature asymmetry.

Methods: Infrared thermal images were acquired passively from five patients (mean age = 23.2, range 8–47) with clinical diagnoses of RTT. Images were acquired in field-based settings (regional fund raiser mtg., etc.) using a FLIR T400 IRT camera (still images were recorded at 5 hz, at a resolution of 320x240 pixels, thermal sensitivity = .05° C). Image capture sessions lasted approximately 1 min with consistent measurement sites in all subjects.

Results: Mean hand temp. was 31.4°C (sd = 2.6, range = 27.2–36.6°C). Mean foot temp. was 27.1°C (sd= 5.2,range=23.02–34.49). This differs from same body locations in previous normative studies (hand temp= 29.8+1.8°C; foot temp= 28.6°C +1.5) (1). There were large intra-individual left/right differences in temperature. Four of 5 girls had statistically significant ($p < 0.05$) left/right asymmetries between hands (M diff = 2.74°C, sd = 2.48) and feet (M diff = 2.98°C, sd = 5.11).

Conclusions: Our results replicate one earlier report of distal hypothermia and asymmetries in RTT (2). Although autonomic dysregulation is well recognized in RTT, the majority of the work has focused on breathing abnormalities. Our observed temperature asymmetries, some over 10°C degrees, suggest an avenue of non-invasive clinical data acquisition that might be studied to see if autonomic symptomatology severity.

Keywords: Genetics

100. Unique Neurologic Disorders with Unique Genetic Alterations Revealed by Whole Exome Sequencing (WES)

Clark GD (Houston, TX)

Objective/Methods: Whole exome sequencing (WES) could alter the evaluation of children with unique neurological disorders.

Results: A case of mosaicism of a CASK (X encoded) deleterious de novo mutation in a boy with microcephaly, intellectual disability without seizures or brain malformation was found by WES. Normally, females with similar deleterious mutations in CASK, present with cerebellar and pontine hypoplasia, microcephaly, seizures and intellectual disability. Males with milder missense mutations present with intellectual difficulties, but typically without microcephaly. The mosaicism of a more severe mutation in this male resulted in a phenotype that would not have been linked to this gene were it not for WES. Identical male twins with de novo mutations in EHMT1 resulted in intellectual disability, hypotonia, epilepsy, microcephaly, macroglossia and heart defects; this constellation of features may be seen in 9q deletion syndromes thought to be caused by deletion of EHMT1. However, chromosomal microarray revealed no deletion in 9q. A PTEN mutation was found in a girl with a butterfly vertebra, macrocephaly, hypotonia, mild developmental delay, a heart lesion, and a verrucous skin lesion. Mutations in PTEN have been associated with a number of disorders: VACTERL, Macrocephaly and Autism, and Cowden Syndrome (this child did not fullfill criteria). She is now in a cancer screening program.

Conclusions: All patients reported had extensive, costly evaluations at our institution or others prior to exome sequencing; WES is becoming a cost effective tool in the evaluation of children with unique neurological disorders.

Keywords: Genetics

101. Maternally Acting Gene Alleles (MAGAs) in Autism, a GWAS Study with Meta-analysis

Johnson WG (Piscataway, NJ), Stenroos ES, Buyske S

Objective: MAGAs act in maternal tissues prenatally to alter fetal environment and affect offspring phenotype, independently of whether or not they are inherited by the fetus. From the mother's perspective, MAGAs are genetic factors, producing proteins and perhaps microRNAs or circular RNAs. From the fetus' perspective, MAGAs are environmental factors. We previously carried out the first two maternal analyses of GWAS data for MAGAs using the AGRE dataset and later the AGP dataset. We found genome-wide significant peaks in regions of chromosomes 1 and 3. Here, we carry out a meta-analysis of these two results to identify and characterize additional regions of interest.

Methods: We used the Weinberg log-linear method through a convenient implementation in EMIM. Study-specific results for the two datasets were then meta-analyzed.

Results: In the AGRE dataset, we identified 9 regions of interest; in the AGP dataset we identified 5 regions of interest. In the meta-analysis, we identified 5 new regions of

interest. Thus, we found 19 regions of interest so far, all of maternal origin. Three of these regions contained numerous SNPs in high LD with low p-values. Three of the SNPs with probes with high degrees of Y-homology need to be confirmed with more stringent methods. Two of the regions had been previously implicated in autism, i.e. SHANK2 and CNTN5.

Conclusions: We have now identified 19 regions of interest for MAGAs in autism. We will now study them further by analysis of other datasets and by re-genotyping with more stringent methods and by and imputation.

Keywords: Genetics

102. Distinguishing Autism Spectrum Disorders from Other Developmental Delays Using Blood RNASeq

Letovsky SI (Lexington, MA), Causey ME, Aryee M, Skoletsky J, Proulx C, Sharp FR, Pessah IN, Hansen R, Gregg J Hertz-Picciotto I

Objective: There is an unmet need for objective biomarkers to assist clinicians in the early diagnosis of childhood neurodevelopmental disorders. The aim of this study was to assess whether blood gene expression measured using next generation RNA sequencing (RNASeq) can serve as a biomarker to distinguish children on the autism spectrum from children with other conditions that might present in the same clinical setting.

Methods: The CHARGE (CHildhood Autism Risks from Genetics and the Environment) study recruited children between the ages of 2 and 5, some of whom were diagnosed on the autism spectrum, and others with other developmental delays. Subjects were grouped into autism spectrum disorder (ASD) and other developmental delay (DD) groups to approximate the clinical use case of a secondary screen for autism in children suspected of neurodevelopmental disorders. RNASeq was performed on RNA from 270 blood samples on an Illumina HiSeq 2000. Support vector machine classifiers were trained on a 153 subject training set and assessed on a 117 subject holdout set.

Results: The mean AUC for the holdout set was 65.6 +/- 2.9%; the mean specificity at 90% sensitivity was 25.3, with 95% CI [13.6, 40.6%]. Significantly different gene categories include RNA processing, cell cycle, immune and inflammation-related GO categories.

Conclusions: These results provide evidence that blood gene expression can distinguish between ASD subjects and subjects with other developmental delays. A prospective multicenter clinical study is being conducted to further refine and validate a blood-based assay.

Keywords: Genetic

103. Clinical Exome Sequencing has a High Diagnostic Yield for Syndromic Epilepsy and Identifies Many Rare Disorders.

McKnight D (Gaithersburg, MD), Butler E, Retterer K, Richard G, Haverfield E, Aradhya S

Objective: This study aims to demonstrate that whole exome sequencing is a vital clinical tool in elucidating the genetic basis of syndromic epilepsy.

Methods: We examined results of individuals referred to our laboratory for exome sequencing with a clinical indication of epilepsy. All of these patients were reported to have epilepsy as part of an undetermined syndromic disorder that included additional neurological finding (i.e. encephalopathy, brain abnormalities, developmental delay) and in some patients, the involvement of other non-neurological organ systems. Almost all patients had previous testing that included a karyotype, aCGH, and metabolic analysis and most patients had additional specific diagnostic testing for Prader-Willi, Angelman, Rett, and/or Fragile X syndromes.

Results: We identified a definitive molecular diagnosis in 40% of patients. Mutations were identified in genes that are either common (CDKL5, SCN1A, SLC6A8) or rare (KCNT1, SCARB2) causes of epilepsy. However, approximately half of the positive cases had mutations in genes not commonly associated with epilepsy, i.e. AP4E1-related spastic paraplegia, NK cell deficiency, PLA2G6-associated neurodegeneration, Cantu syndrome, and WDR45-related neurodegeneration with brain iron accumulation.

Conclusions: Our results indicate that epilepsy can be the major clinical indication for a wide variety of neurological disorders that would not typically be considered in the differential diagnosis. Based on our experience, exome sequencing is a high-yield clinical test to identify the molecular diagnosis in individuals with syndromic epilepsy and may broaden the phenotypes associated with many neurological disorders.

Support: GeneDx

Keywords: Genetics

104. Ethnicity and Geographic Distribution of Pediatric Chronic Ataxia in Manitoba, Canada

Salman MS (Winnipeg, MB), Masood S, Azad M, Chodirker BN

Background: Genetic and environmental factors are important determinants of disease distribution. Several disorders associated with ataxia are known to occur more commonly in certain ethnic groups; for example, the disequilibrium syndrome in the Hutterites. The aim of this study was to determine the ethnic and geographic distribution of pediatric patients with chronic ataxia in Manitoba, Canada.

Methods: We identified 184 patients less than 17 years of age with chronic ataxia during 1991–2008 from multiple sources. Their diagnosis, ethnicity and place of residence were determined following a chart review.

Results: Most patients resided in Manitoba (N=177) and the majority in Winnipeg, the provincial capital. Thirty five Aboriginal, 29 Mennonite and 11 Hutterite patients resided in Manitoba. The latter two groups were significantly overrepresented in our cohort. Ataxia telangiectasia, mitochondrial disorders, and non-progressive ataxia of unknown etiology associated with pyramidal tracts signs and developmental delay were significantly more common in Mennonite patients. Four of five patients with neuronal migration disorders associated with chronic ataxia were Aboriginal. Few isolated disorders with chronic ataxia occurred

in the 11 Hutterite patients including a Joubert syndrome related disorder.

Conclusions: Three disorders associated with chronic ataxia were more prevalent than expected in Mennonites in Manitoba. Few rare disorders were more prevalent in the Hutterite and Aboriginal population. Further research is needed to determine the risk factors underlying these variations in prevalence within different ethnic groups. The unique risk factor profiles of each ethnic group need to be considered in health promotion endeavors.

Keywords: Genetics

105. Movement Abnormalities and Associated Neurodevelopmental Challenges in Children with 16p11.2 Deletion or Duplication

Steinman KJ (Seattle, WA), Bernier R, Berry LN, Goin-Kochel RP, Johnson K, Kanne SM, Snow AV, Wallace A, Ramocki MB, Spence SJ, Proud MB, Kessler SK, Marco EJ, Sherr EH, Chung WK, Hanson E, Simons VIP Consortium

Objective: To examine (1) functional motor abilities in children with deletions (del) and duplications (dup) of 16p11.2, recurrent copy-number variants (CNVs) that increase the risk of autism spectrum (ASD) and other neurodevelopmental disorders, and (2) the association of movement deficits with intellectual ability, ASD, hypotonia, and these two CNVs.

Methods: The Movement Assessment Battery for Children – 2 was administered to 74 children with 16p11.2 del or dup from the Simons Variation in Individuals Project. We used one-sample t-tests to compare total standardized scores (MABC-TSS) in del or dup groups to the general population and two-sample t-tests to compare del and dup. Multivariable linear regression models were used to examine the independent associations of MABC-TSS with FSIQ, ASD, hypotonia, and del versus dup.

Results: (see Table) Del and dup groups each exhibited low MABC-TSS compared to norm (z-scores, del: -1.4 [$p<0.001$]; dup: -2.1 [$p<0.001$]; del versus dup: $p<0.001$). Lower MABC-TSS were associated with FSIQ ($p<0.001$) in dup and with ASD ($p<0.001$) and hypotonia ($p=0.006$) in del. When comparing CNVs, FSIQ, ASD, hypotonia, and the presence of 16p11.2 del (versus dup) were all independently associated with lower MABC-TSS (all $p<0.001$).

Conclusions: Children with 16p11.2 del and dup have quantifiable movement deficits associated with multiple independent factors. Differential associations of deficits with physical and cognitive abnormalities (hypotonia, low IQ, ASD) in del versus dup, as well as an independent association of motor deficits with del compared to dup, suggest that different mechanisms may underlie the multifactorial movement challenges in these two phenotypes.

Sources of Funding: This work was supported by the Simons Foundation Autism Research Initiative (SFARI; all authors), Seattle Children's Research Institute, Center for Integrative Brain Research (KJS), and NIH Clinical Research Loan Repayment Program (KJS). EHS owns stock in Chemocentryx & Ingenuity Systems. No other authors have potential conflicts of interest to disclose.

Keywords: Genetics

106. The Effects of Aging on an Autistic-like Mouse Model

Jasien J (Baltimore, MD), Daimon CM, Wang R, Maudsley S, Martin B

Autism spectrum disorders (ASD) are heterogeneous neurodevelopmental disorders characterized by alterations in social functioning and engagement in repetitive or restrictive behaviors. The process of aging in individuals with autism and related neurodevelopmental disorders is not understood, despite the fact that the number of individuals with ASD aged 65 and older is projected to increase by over half a million individuals in the next 20 years. To begin to fill the gap in knowledge about aging in an abnormal central system, we investigated the effects of age on the BTBR T+tf/j mouse, a well characterized and widely used mouse model that displays an ASD-like phenotype. We found that a reduction in social behavior persists into old age in male BTBR T+tf/j mice. Additionally, we found that aged male BTBR T+tf/j mice display a similar phenotype to their younger male BTBR T+tf/j. Since little is known about aging in this mouse model a proteomic analysis (iTRAQ) was utilized to explore significant protein differences in BTBR hippocampus and cortex compared to age-matched wildtype mice; this revealed a significant decrease in brain derived neurotrophic factor and significant increases in multiple synaptic markers (spinophilin). We also observed distinct changes in functional pathways populated by the significantly altered proteins. Taken together, these results contribute to our understanding of the effects of aging on an ASD-like mouse model in behavior, protein changes and functional pathways.

Keywords: Genetics

107. Measuring Disease Progression in Giant Axonal Neuropathy: Implications for Clinical Trial Design

Roth LA (New York, NY), Marra JD, LaMarca NH, Sproule DM

Objective: We hypothesized that the Friedreich Ataxia Rating Scale and the Gross Motor Function Measure would show a significant change over 6 months in subjects with Giant Axonal Neuropathy, reflecting their decline in motor function.

Methods: As part of a broader study of the natural history of Giant Axonal Neuropathy, standardized clinical function assessments were performed twice with a six-month interval. The Friedreich Ataxia Rating Scale was performed on 10 subjects and the Gross Motor Function Measure was performed on 9 subjects. A paired, two-tailed T-test was used to assess the difference in each subject's score.

Results: The Friedreich Ataxia Rating Scale showed a significant change over 6 months of 12.4 ± 11.3 ($p = 0.007$). The Gross Motor Function Measure showed a change over 6 months of -9.9 ± 14.3, which did not meet statistical significance ($p = 0.071$). These changes reflected subjects' decline in motor function on examination and by their own report.

Conclusion: There are no currently approved therapies for Giant Axonal Neuropathy, but a clinical trial of an

adeno-associated virus type 9 vector containing the normal GAN gene is likely to occur in the next year [1]. This study represents the first time that a standardized measurement of clinical function has been validated in Giant Axonal Neuropathy, which can be used to measure therapeutic effect in this upcoming trial. The measurement of a significant change in motor function over a relatively short period of time also improves the feasibility of a potential clinical trial.

Keywords: Genetics, Neuromuscular disorders, Translational/experimental therapeutics

108. Functional Communication Training in Rett Syndrome

Byiers BJ (Minneapolis, MN), Feyma TJ, Symons FJ

Objective: Language and communication are severely compromised in girls and women living with Rett syndrome (RTT), but evidence suggests that intentional communicative acts rarely occur (e.g., Woodyatt & Ozanne, 1997). Functional Communication Training (FCT), involves replacing idiosyncratic or aberrant behaviors (e.g., vocalizations, body movements, problem behavior), that may have acquired functional (i.e., communicative) properties, with more specific responses (e.g., switch pressing) to improve the likelihood of being understood (Carr & Durand, 1985; Keen, Sigafoos, & Woodyatt, 2001).

Methods: Three young girls (5–8 years) with classic RTT and confirmed MECP2 mutations participated. The FCT intervention involved differential reinforcement of the idiosyncratic behavior (e.g., vocalizing) and a functional alternative communicative response (e.g., activating a voice-output switch) in an ABA (reversal) single-subject design with each participant. Repeated direct observation assessed communicative responding (mean inter-observer agreement on 50% of session = 96% [80–100]). Each session consisted of five communication opportunities, and the first response (idiosyncratic behavior, functional alternative response) was counted for each opportunity.

Results: All participants learned to activate the voice-output switch within a single session. During Phase 1, when reinforcement was available for switch-pressing, but not idiosyncratic behavior, switch pressing was the first response attempted on at least 67% of the trials in each session for each participant. The pattern reversed in Phase 2 when reinforcement was only available for vocalizations. All participants resumed switch pressing in the final phase.

Conclusions: The results suggest that girls with RTT are capable of learning novel communicative responses within the context of FCT.

Keywords: Genetics, Translational/experimental therapeutics

109. The Urgency of Newborn Identification and Early Hematopoietic Stem Cell Transplantation in MPS I

Chagnon SL (Pittsburgh, PA), Poe M, Boelens JJ, Escolar ML

Objective: Hurler's syndrome, MPS I, is an autosomal recessive metabolic storage disease characterized by progressive neurological and somatic disease and death in childhood. Hematopoietic stem cell transplantation is the only available treatment for the neurological sequelae. However, it is believed that children who are more than 2 years of age or have an IQ less than 70 do not benefit from transplantation. This study examines the relationship between age at transplant, cognitive function and long term post-transplant outcomes.

Methods: This multicenter study reviewed the developmental trajectory, including motor, cognitive, receptive and expressive language and adaptive behavior, of 83 patients who received hematopoietic stem cell transplantation as compared to norms of typically developing children. As a marker of disease progression the baseline cognitive score was used to create a cognitive ratio of mental age/calendar age. Developmental curves were generated and analyzed in relation to age at transplant as well as baseline evaluations.

Results: Cognitive ratio at the time of transplant was found to be a strong predictor of post-transplant development. While age at transplant is a significant predictor of post-transplant development, it became non-significant once the cognitive ratio was added to the model.

Conclusions: The degree of cognitive impairment at the time of transplantation is a more relevant predictor than age at transplant. These results emphasize the urgency of identifying patients with MPS I before progression of neurological disease via newborn screening, follow up and transplantation before cognitive involvement.

Keywords: Genetics, Translational/experimental therapeutics

110. Post Concussion Headache (PCHA) in Children and Adolescents (C&A)

A. Leubitz (Cleveland, OH), Rothner AD

Objective: To determine the feature of PCHA in C/A. 1.6 – 3.8 million concussions occur annually. Many have PCHA. Details concerning types of HA, duration of symptoms, imaging data, treatment and prognosis are needed.

Methods: We reviewed 67 cases of PCHA seen 2010–2012. Data regarding age, sex, previous concussion, family history of HA, and concussion were collected.

Results: Our 67 patients were from a total of 675 New HA patients seen during the same time. 39 were males, sports were football, hockey, lacrosse and falls. In 28/64 the HA was immediate, in others it started after days or weeks. Types of HA: episodic TTH, chronic daily headache with superimposed migraine. Pure episodic migraine was rare. Imaging was negative in all save 3 who showed abnormalities unrelated to the HA or injury. Concussion symptoms included headache, dizziness, irritability, anxiety, depression, photophobia and memory and concentration impairment. School issues were prominent. This OPD sample demonstrates that HA following head injuries are common. Even mild concussions may result in prolonged HA which interfere with school function. Data regarding management in the first 6 weeks is lacking. If the HA has been present for >6 weeks, education, judicious use of rescue medication, preventive medication, psychosocial support and lifestyle approaches are useful. The prognosis is guarded and many HA last > 1 yr.

Conclusion: Additional prospective date regarding PCHA in C/A is needed. Agreement regarding management of these patients is lacking.

Keywords: Headache/Migratine

111. Risk Factors for the Development of Headache after Traumatic Brain Injury in a Pediatric Subspecialty Clinic Population.

Choe MC (Los Angeles, CA), Fischer JT, Yudovin S, McArthur DL, Asarnow R, Giza CC

Objective: Traumatic brain injury (TBI) is a major pediatric public health problem, with as many as 500,000 children under the age of 15 presenting to emergency departments annually. The most prevalent and debilitating post-traumatic symptom is headache. Post-traumatic headache (PTHA) can lead to poor school performance, disruption in social function, and familial hardships. This study was conducted to further understand the factors that contribute to development of PTHA in a pediatric subspecialty population.

Methods: Data was prospectively collected from individuals 5–22 years of age presenting to clinic with TBI. 172 patients had 6 month follow-up after injury.

Results: 136 patients (119 males, 54 females) had mild injuries and 36 patients had moderate or severe injuries. 2/3 of patients presented with PTHA. PTHA was 5 times more likely amongst those patients with mild injuries. Patients who presented with PTHA were 2.70 times more likely to have had a prior TBI (C.I. 1.35-5.64), and a premorbid history of headache (C.I 1.62-16.00). Patients with PTHA were also 2.21 times more likely to present with comorbid psychiatric or cognitive complaints (C.I. 1.12-4.57). Female patients were almost 4 times more likely to have PTHA (C.I. 1.80-9.90) and more than $2^1/_2$ times more likely to have suffered a mild injury (C.I. 1.06–7.37). Statistical analysis was performed using EpiTools: R Package (v0.5–6).

Conclusions: Careful risk factor assessment may help to identify patients more likely to develop persistent PTHA who would benefit from early pediatric neurology clinic referral and intervention.

Sources of Funding: We acknowledge support from UCLA BIRC, NS05489, HD061504, Morris A. Hazan Friends of Semel Fellowship, Child Neurology Foundation/Winokur Family Foundation, Today's and Tomorrow's Children Fund.

Keywords: Headache/Migratine

112. Management of Migraine in a Tertiary Care Pediatric Emergency Department

Eapen A (Detroit, MI), Agarwal R, Thomas R, Sivaswamy L

Objective: Combination therapy (analgesic and anti-dopaminergic agent, with or without diphenhydramine) has been proposed as "standard of care" for children presenting with migraine to the emergency department (ED). Protocol adherence, and its effects on outcomes have not been well studied.

Methods: A database containing 2,208 headache patients of an academic, urban pediatric ED, from June 2011 to June 2012, was retrospectively analyzed. Patients with migraine fulfilling ICHD-II criteria were selected. Adherence to standardized combination therapy (SCT) was compared across ethnicity, gender, age and severity of headache. The effect of SCT on duration of ED stay and need for hospital admission was assessed.

Results: 158 patients (mean age 13.7 years, 70% female, 67% African-American) were available for analysis. 38.6% of children received SCT with adherence rates lacking variance by gender, ethnicity, age, severity or headache duration prior to ED visit. Admission rates were higher in children who received SCT (31.1%) compared to non-SCT (18.6%). Logistic regression analysis revealed that the main predictors of hospital admission were use of opiates (Odds Ratio=3.7%; 95% CI: .01 to .20), presence of nausea (Odds Ratio=16.8%; 95% CI: .04 to .70), and use of SCT (Odds Ratio=44%; 95% CI: .19 to 1.02).

Conclusions: SCT was not widely utilized in a pediatric ED setting. Further, use of SCT did not positively influence duration of ED stay or the hospital admission rates. Larger studies across pediatric EDs nationwide are required before SCT can be accepted as the best practice parameter.

Keywords: Headache/Migratine

113. Analgesic Overuse Contributes to Chronic Post-Traumatic Headaches in Adolescent Concussion Patients

Heyer GL (Columbus, OH), Idris SA

Objective: Among a cohort of adolescents with chronic post-concussion headaches, we sought to compare signs, symptoms, and outcomes of patients with medication overuse to those without medication overuse.

Methods: A retrospective cohort review was conducted of adolescent concussion patients referred to a pediatric headache clinic for chronic post-traumatic headaches of 3–12 months duration. Concussion symptoms, headache symptoms (pre- and post-concussion), demographic data, and headache outcomes were compared between those with and those without probable medication-overuse headache.

Results: Of 104 adolescent concussion patients referred, 77 had chronic post-traumatic headache of 3–12 months duration. Fifty four of 77 (70.1%) met criteria for probable medication-overuse headache. Patients with medication overuse were more likely to have daily headaches ($p=0.006$), to be female ($p=0.02$), to have nausea ($p<0.001$) and/or throbbing ($p=0.001$) associated with headaches, to have had increased irritability following concussion ($p=0.03$), and to have had a longer interval between injury and neurology evaluation ($p=0.003$). Of the patients with medication overuse, 37 (68.5%) had resolution of headaches or improvements to pre-concussion headache patterns after discontinuing analgesics, 7 (13%) had no change in headaches or worsening of headaches after discontinuing analgesics, and 10 (18.5%) did not discontinue analgesics or were lost to follow up.

Conclusion: Excessive use of analgesics post-concussion may exacerbate or chronify post-traumatic headaches in some adolescents. Analgesics should be minimized or discontinued when headaches continue several weeks following concussion.

Keywords: Headache/Migratine

114. Is Family History of Migraine Obtained from Relatives as Reliable as a Self-Report?

Lateef TM (Washington, DC), Cui L, Nakamurae E, Merikangas KM

Objective: This study evaluated the validity of migraine diagnosis derived from one or more family member reports.

Methods: The study sample consisted of 553 adults (375 female, 178 males), ages 18 through 96 years, who were directly interviewed about their headaches and had at least one family member provide a report on headache history and symptoms for them. The participants were identified through a large community family study of physical and mental health at the National Institute of Mental Health. A direct clinical interview with the relatives was considered the gold standard in our analyses. A validated headache interview based on the ICHD-II criteria was used.

Results: Of the 553 study participants, 396 had migraine with or without aura, 69 had tension type headache, 82 had non-migraine and non-tension type headache and 6 had no headache at all. Overall sensitivity and specificity of detecting migraine using family history report are 38.9% and 89.8% respectively. The positive and negative predictive values of migraine diagnosis provided by family member report are 90.6% and 36.8% respectively. Our results confirm that migraine assessed by family member report largely underestimates the number of affected relatives.

Conclusions: In clinical practice and especially in family studies or genetic research a direct interview of relatives to ascertain migraine may be necessary.

Keywords: Headache/Migratine

115. Inpatient Admission for Intravenous Dihydroergotamine Treatment of Migraine: Is it Worth the Headache?

Nelson GR (Salt Lake City, UT), Bale JF, Kerr LM

Objective: Intravenous dihydroergotamine (DHE) is commonly used to treat intractable migraines in adult and pediatric patients. Although prior reports suggest benefit, the value of DHE therapy in pediatric patients deserves further study. We investigated the cost and efficacy of admitting patients for DHE treatment.

Methods: We performed a retrospective chart review of 145 pediatric admissions from 2001–2010 for intravenous DHE therapy for headache. Data extraction included general demographics, presentation of headache, dosing of DHE, consultations, total costs, and effect on headache severity at discharge and follow-up.

Results: Seventy-four percent of the patients were female. Mean age was 14.9 years. Headache was described as chronic or daily in almost all patients. Eighty-seven percent had a family history of migraine. The average length of stay was 3.7 days, and cost was $7,569/admission. Patients received an average of 8 doses of DHE. On discharge, 68.7% of patients noted improvement from DHE treatment. Follow up visits, recorded for 58.6% of the cohort at a median of 42 days after discharge, indicated that only 26% had sustained headache relief after DHE. Prophylactic medication use at follow-up was not different between the responders and non-responders ($p=0.18$).

Conclusions: Although intravenous DHE is an effective abortive medication for intractable migraine, DHE appears to provide only short-term improvement. Hospital admission is relatively costly with only modest long-term benefit. Further studies are warranted to identify the patient variables associated with a more lasting benefit from DHE.

Keywords: Headache/Migratine

116. Atypical Presentations of Paroxysmal Hemicrania (PH) are Common in Children and Adolescents (C/A)

Jessel S (Cleveland, OH), Rothner AD

Objective: To increase recognition of PH in C/A. Background: PH, is a trigeminal autonomic cephalalgias (TAC). Is Indomethacin responsive. PH: attacks of unilateral, severe, pain (2–30 min), autonomic features and responds to indomethacin. PH in C/A is uncommon. We studied PH in C/A to aid earlier recognition and treatment, prevent exposure to multiple medications.

Methods: Literature review. A retrospective chart review.

Results: Fifteen cases of possible PH were identified. We combined these with 20 in the literature. F/M ratio was 1:1., diagnosis 9.6 years. 10 typical, 25 atypical cases. "Atypical": No response to indomethacin or responsive to other medications, stuttering course, variable autonomic symptoms or spontaneous remission. Seven, no response to indomethacin. Four, duration more than 30 minutes. 3 frequency < 5 attacks per day. 4 pain bilateral. 6 no autonomic features. Typical and atypical cases will be presented.

Conclusion: There is a predominance of "atypical" presentation in C/A. A stuttering course, fewer attacks, periods of remission, variable response to indomethacin and lack of autonomic features are seen. The clinical phenotype may not be fully expressed in C/A, due to immaturity of the C.N.S. in C/A. Suspect PH in any child that presents with daily multiple, unilateral, discrete, short lasting headaches, even if autonomic features are lacking. A trial of indomethacin may be indicated.

Keywords: Headache/Migratine

117. Molecular Maladaptations Underlying Behavioral Deficits in Prenatal Cocaine Exposed Mice

Kabir Z (New York, NY), Katzman A, Rajadhyaksha A, Kosofsky BE

Objective: To identify mechanisms underlying the spontaneous recovery of conditioned fear in adult mice following prenatal cocaine exposure (PCE)

Methods: The prefrontal cortex (PFC), a brain region that receives strong dopaminergic input, shows persistent morphological and functional deficits in PCE animals consistent with cocaine's molecular site of action. Deficits in social development and cognition, processes that are heavily dependent on the PFC, have been reported following PCE, but have not been elucidated at the molecular level.

Results: In adult PCE mice, we identified spontaneous recovery of an extinguished cue-conditioned fear which could be rescued by infusion of recombinant BDNF protein

into the mPFC after extinction learning. We identified a similar behavioral deficit in PCE adult mice that had a single copy of the BDNF Val66Met allele, a SNP in the BDNF gene that alters the synaptic release of BDNF protein. In both studies this was attributed to a decrease in induction of mature BDNF protein in the mPFC during extinction learning. We additionally observed a lack of plasticity of the BDNF gene in the mPFC of PCE animals evident as decreased constitutive binding of the transcription factors, methyl CpG binding protein 2 (MeCP2) and pCREB at the promoters of the BDNF activity-driven exons I and IV, that was unchanged after extinction learning.

Conclusions: These findings extend our knowledge of the neurobiologic impact of PCE on the mPFC of mice, which may lead to improved clinical recognition and treatment of exposed individuals.

Sources of Funding: (supported by K02DA00354, and R01DA017905 to BEK)

Keywords: Headache/Migratine, Translational/experimental therapeutics

118. The Effect of an Intranet Supplement to a Core Curriculum on RITE scores

Urion DK (Boston, MA)

Objective: To study the effect of an intranet-based supplement (wiki) to a didactic curriculum as measured by RITE scores in a Child Neurology Residency.

Methods: The Core Curriculum includes three hourly sessions weekly, and covers the major didactic elements of child neurology in a helical fashion, placing topics proximate to one another based on diagnostic disorders, rather than teaching areas such as anatomy or physiology. Although resident time is covered by NP's for these lectures at the main hospital, residents on away rotations, or post-call, cannot attend. A wiki was developed which includes the slides and video/audio recording and can be accessed via secure log in to a website. This study compares RITE exam results by year cohort over four years with this technology. Cohort scores for all the RITE categories were compared for three groups: 1) those attending the lectures relevant to the topic, 2) those accessing via wiki, and 3) those doing neither.

Results: In all domains, cohorts who attended live lectures consistently performed better than peers, and showed the largest increase in scores over the course of training. Cohorts who accessed the lectures via wiki were a second tier, scoring below the first and showing a smaller increase in scores over training. Cohorts who did neither, presumably studying on their own, were at the lowest tier in all domains, and showed the least growth over training.

Conclusion: An intranet-based supplement can be an effective adjunct in didactic teaching in an hours-constrained environment.

Keywords: History / Teaching of Child Neurology

119. State of Affairs of Current Child Neurology Education during Pediatric Residency: "Upping the Ante"

Goldstein JR (Cleveland, OH), Strosaker R, Nwankwo CC, Wright M, O'Rierdon MA, Bass NE

Objective: Nationally, there is a shortage of pediatric neurologists resulting in an increased need for pediatricians to diagnose and co-manage children with neurological disorders. Pediatricians are from different training backgrounds regarding their education in neurology resulting in variable comfort levels in caring for this patient population. Our goal was to assess pediatricians' comfort level in diagnosing and managing neurological problems and to determine the frequency of reported referral to a neurologist in order to understand which areas of child neurology should be emphasized during training.

Methods: An anonymous survey was distributed to 216 pediatricians from January to March 2011. The 24-item survey consisted of 9 demographic questions; 12 questions rating comfort level and referral practices for 29 neurological problems; and 3 open-ended questions regarding pediatric residency training. Descriptive statistical analyses were performed.

Results: 92 surveys (43% response rate) were returned. >75% pediatricians reported comfort with simple febrile seizures, ADHD, tension headache, migraine, behavioral disorders and developmental delay. Pediatricians reported at least a 50% referral rate for all topics with the exception of simple febrile seizures (16%) and tension headache (45%). Seizures, developmental delay, headache/migraine, ADHD and autism were most frequently cited as topics to emphasize during pediatric residency.

Conclusions: Despite the fact that pediatricians are comfortable evaluating and managing a variety of neurological problems they report referring the majority of diagnoses for evaluation by a pediatric neurologist. Tailoring pediatric resident education in neurology may empower graduates to manage commonly encountered neurological problems with more selective referral to a neurologist.

Keywords: History/Teaching of Child Neurology

120. Risk Factors for Cerebral Palsy in Children with HIV/AIDS in Botswana

Bearden DR (Philadelphia, PA), Monkowane B

Background: Cerebral palsy is common among children with HIV /AIDS in the developing world, but there are no published studies that address potentially preventable risk factors.

Objective: To identify risk factors for cerebral palsy in children with HIV/AIDS compared to uninfected controls.

Methods: We conducted a prospective cohort study with a nested case control component to identify risk factors and outcomes in children with cerebral palsy seen in a pediatrics clinic at a major referral center in Gaborone, Botswana.

Results: Risk factors for cerebral palsy in HIV uninfected children include prematurity, birth asphyxia, and CNS infections. Risk factors for cerebral palsy in children with HIV include CD4 count <200, advanced clinical stage, history of HIV encephalopathy, and history of CNS infections.

Conclusions: Cerebral palsy in children with HIV has distinct risk factors compared to HIV uninfected controls, and is largely acquired postnatally. Risk factors emerge in more advanced HIV disease and may be preventable by earlier initiation of antiretroviral therapy.

Sources of Funding: Dr. Bearden is supported by an NIH T32 Training grant and by a grant from the L. Morton Morley fund of the Philadelphia Foundation. Dr. Bearden has no other disclosures. Dr. Monokwane has no disclosures.

Keywords: Infections/Neuroimmunology

121. Global Health Problem: Meningoencephalitis in Myanmar

Linn K (Yangon, Myanmar), Ko S, Thair C, Mar S

Objective: To identify viral etiology, management and prognosis of the children presenting with features of meningoencephalitis in Myanmar

Methods: Prospective enrollment of children (1m-12 yr) with fever with encephalopathy at Yangon Children's Hospital over 6 months period. Patients with acute bacterial meningitis and tuberculous meningitis were excluded.

Results: Total 41 children (0.2–12 yr, mean 4.6 yr) met the inclusion criteria. The majority were late referral, self-treated with oral antibiotics, without complete immunization. Among them, 31 children had seizure, 15 with meningism, and 9 with movement disorder. High CSF protein with low glucose in 12 children and CSF pleocytosis with lymphocytes predominance in 15 individuals were noted. All were treated with IV cefotaxime, without Acyclovir. Management of status epilepticus (SE) was suboptimal due to poor knowledge and the lack of resources. The essential medications for SE are not available in Myanmar and intravenous diazepam solution is used for per rectal and intravenous route. CSF samples were tested for RNA viruses in Myanmar but no virus was identified. Samples were also sent to Malaysia for DNA viruses as a part of the collaborated research study, but the results are still pending. The complete recovery was noted in 15 patients only. The neurological deficits included hemiparesis (8), aphasia (7) spastic quadriparesis (4), movement disorders including choreoathetosis, dystonia and tremor (8).

Conclusions: The poor prognosis of the children with meningoencephalitis can be attributed to possible new viruses, late referral, substandard medical education and resources. International help is essential to help these children in Myanmar.

Keywords: Infections/Neuroimmunology

122. Interim Efficacy and Safety Analysis of Adjunctive Perampanel in the Adolescent Population From the Extension Phase of 3 Double-Blind, Placebo-Controlled, Phase 3 (Core) Studies in Patients with Refractory Partial-Onset Seizures

Renfroe B (Gulf Breeze, FL), Yang H, Williams B, Huang S, Laurenza A

Objective: To provide additional efficacy and safety data for adjunctive perampanel in adolescents from the extension phase of the core studies.

Methods: The interim analysis included 124/143 adolescents (aged 12–17 years) with refractory partial seizures who completed the core studies and entered the extension. The ongoing extension study included a 16-week blinded conversion, up to 256-week maintenance and 4-week follow-up periods. Placebo and perampanel patients from the core studies were up-titrated to the individual's maximum-tolerated perampanel dose ($\leq$12 mg/day) from 2 mg/day or the last received dose, respectively. Efficacy was analyzed in 13-week intervals from the date of first perampanel dose and compared with pre-perampanel baseline. Efficacy parameters included percent reduction in seizure frequency/28 days and 50% responder rate. Safety parameters were also analyzed.

Results: As of the interim cut-off date (October 2011), 87 patients reached $\geq$1 year of perampanel exposure, and 44 patients reached $\geq$2 years. Most adolescents (93%) reached doses of 10 mg/day or 12 mg/day perampanel. In patients with $\geq$2 years' perampanel exposure), efficacy results are shown in Table 1. Treatment-related treatment-emergent adverse events (AEs) occurring in >5% patients were dizziness (29%), somnolence (23%), aggression (17%), irritability (8%), headache (8%), decreased appetite (7%), convulsion (7%), insomnia (6%), fatigue (6%), and ataxia (6%). Primary reasons for study withdrawal included subject choice (16%), AEs (11%), and inadequate efficacy (10%).

Conclusions: Long-term treatment with perampanel maintained improvements in seizure control compared with baseline in adolescents with refractory partial seizures. Perampanel was well-tolerated and demonstrated a favorable risk/benefit profile.

TABLE 1. Median Decrease in Seizure Frequency and 50% Responder Rate in Adolescents Administered at Least Two Years of Perampanel, Compared with Pre-perampanel Baseline. Data Shown in 13-Week Intervals, Up to 2 Years

	Weeks 1–13[a]	Weeks 14–26	Weeks 27–39	Weeks 40–52	Weeks 53–65	Weeks 66–78	Weeks 79–91	Weeks 92–104
Median decrease in seizure frequency (%)	22.6	31.5	57.2	50.0	53.9	67.3	57.6	61.0
50% responder rate (%)	27.3	40.9	59.1	50.0	52.3	63.6	56.8	56.8

[a]Includes titration from double-blind (core studies for patients randomized to perampanel) or conversion period (extension study for patients previously randomized to placebo).

123. MRI in Retinopathy Negative Cerebral Malaria

Postels DG (East Lansing, MI), Li C, Birbeck GL, Taylor TE, Seydel KB, Kampondeni SD, Potchen MJ

Objective: Our objective was to determine if there were MRI findings associated with the adverse outcomes of mortality or neurologic morbidity in children with retinopathy negative cerebral malaria.

Methods: We reviewed MRI scans performed on a 0.35T magnet in 45 children with retinopathy negative cerebral malaria to describe the neuroimaging findings in this syndrome. Univariate and multivariate analyses were performed to determine if there were MRI findings associated with adverse outcomes.

Results: Three (6.7%) children died and 8/42 (19.1%) of survivors had neurologic sequelae. On univariate analysis, all children who died or had neurologic sequelae had T2 weighted imaging abnormalities in cortical gray matter, almost always (10/11 or 90.9%of the time) associated with cortical DWI abnormalities. Children without cortical DWI abnormalities were extremely likely to survive without neurologic sequelae. White matter abnormalities did not affect the odds of having an adverse outcome. On multivariate analysis, no neuroimaging findings were associated with mortality. Cortical DWI abnormalities, focal cortical changes, cortical T2 signal abnormalities, and increased brain volume were significantly associated with neurologic morbidity in survivors. The highest odds of morbidity occurred in children with cortical DWI abnormalities. Due to small patient numbers these findings must be considered preliminary.

Conclusions: Cortical DWI abnormalities and increased brain volume may be associated with an increased odds of an adverse neurologic outcome in retinopathy negative cerebral malaria survivors. MRI findings in these children may lead to potential therapeutic targets for future clinical trials in children with retinopathy negative cerebral malaria.

Keywords: Infections/Neuroimmunology, Neuroimaging

124. Somatosensory Evoked Responses in Newborns with Hypoxic-Ischemic Encephalopathy Treated with Hypothermia

Garfinkle JS (Montreal, QC), Rosenblatt B, Majnamer A, Sant'anna GM, Wintermark P, Shevell MI

Objective: In the pre-therapeutic hypothermia era, somatosensory evoked responses (SERs) were considered to be an important prognostic adjunct to the neurologic investigation of term infants with hypoxic-ischemic encephalopathy (HIE), with a reported specificity of up to 100%. The objective of this study was to assess if SERs maintain their prognostic value when these infants are treated with hypothermia.

Methods: A cohort of term HIE infants treated with hypothermia was prospectively enrolled between September 2008 and September 2010. SERs were elicited following median nerve stimulation after hypothermia but before discharge from hospital at 37–44 weeks conceptional age; they were defined as normal or abnormal (i.e., delayed or absent SERs). Neurologic outcome was defined as normal or adverse (i.e., cerebral palsy, global developmental delay, and/or epilepsy).

Results: Thirty-seven infants received therapeutic hypothermia during that period and survived the neonatal period; 3 were lost to follow-up. SERs were performed in 26 infants on mean day of life 11 $\pm$ SD 4; they were abnormal in sixteen infants (62%). Mean age at last follow-up was 27 $\pm$ SD 10 months and only four infants (15%) had an adverse outcome. SERs had a sensitivity of 100%, a specificity of 45%, a positive predictive value of 25%, and a negative predictive value of 100%.

Conclusions: The majority of HIE infants treated with hypothermia who had an abnormal SER in the neonatal period had a normal outcome. This suggests that as a prognostic tool, SERs should be interpreted with caution in this population.

Keywords: Neonatal neurology

125. Multi-domain Neurodevelopmental Delays in Multiple Gestation and Singleton Preterm Infants

Jarjour IT (Houston, TX), Sibley AA, Jarjour LK

Objective: Incidence of multiple gestations (MG) in the USA is increasing. Most studies of neurodevelopmental outcome after MG lack control groups. This study compares the prevalence of neurodevelopmental delays in MG and singletons (SG) preterm infants.

Methods: We reviewed the medical records of patients born $<$37 weeks as MG or SG, evaluated at corrected age of 3–36 months in Neonatal Follow-up Clinic between July 2005 and December 2010 using neurological examination and neurodevelopmental assessment (Clinical Linguistic and Auditory Milestone Scale, Cognitive Adaptive Test and Gesell Scales). We defined significant delay as developmental quotient (DQ) $<$70.

Results: MG group had 49 (34 twins, 11 triplets, and 4 quadruplets), SG group had 63 infants, with mean $\pm$ SD for MG vs. SG for corrected age 13 $\pm$ 7.5 vs. 12 $\pm$ 9 months, gestational age 30 $\pm$ 3.4 vs. 29 $\pm$ 4 weeks, and birth weight 1267 $\pm$ 484 vs. 1286 $\pm$ 686 g (NS). Comparing MG vs. SG, prevalence of developmental delays in $\geq$ 1 domain was 42 vs. 69% (P=0.015), receptive language 8 vs. 28% (P=0.03), full scale DQ 10 vs. 24% (P=0.06), total language 16 vs. 30% (P=0.09), expressive language 27 vs. 42% (NS), cognitive adaptive 14 vs. 21% (NS), gross motor 17 vs. 30% (NS). Prevalence of generalized hypotonia was (35 vs. 32%), focal hypotonia (18 vs. 16%), hypertonia (29 vs. 38%), oral motor dysfunction 25 vs. 19% (NS).

Conclusions: Developmental delays are more common in singleton than multiple gestations. The reasons for such difference require further study.

Keywords: Neonatal neurology

126. Persisting Developmental and Functional Sequelae in Adolescents with Congenital Heart Defects who Required Early Open Heart Surgery

Majnemer A (Montreal, QC), Shevell MI, Rohlicek C, Drulinsky D, Maltais D, Lach L, Schmitz N

Objective: This study describes developmental (motor, cognitive, behavioral) and functional outcomes of adolescents with congenital heart defects.

Methods: To date, 37 adolescents who required open heart surgery in infancy were evaluated in a blind fashion using standardized measures of intelligence (Leiter Brief IQ), motor ability (Movement-ABC) and behavior (Strengths and Difficulties Questionnaire). Activity

limitations (communication, socialization, daily living skills, adaptive behavior) were assessed by semi-structured interview of parents using the Vineland Adaptive Behavior Scale.

Results: Participants were assessed at 15.5±1.6 (11.4–18.5) years. Behavior problems were common, particularly emotional symptoms (37.8%) and peer problems (32.4%) with a high impact on more than half of parents reporting. Youth were at-risk (22.9%) or had significant movement difficulty (17.1%). Leiter IQ scores were below 80 in 27%. Activity limitations were experienced by approximately 10% except for communication limitations, which was reported in 22.9%. Age at testing was only correlated with peer problems (r=-.35, p=.036). Scores on most subscales were lower in males, reaching significance for all activity limitation domains, particularly daily living skills (males:88.2±19.4, females:104.1±12.8, p=.006) and adaptive behavior (males:87.9±17.7, females:102.5±13.8, p=.01).

Conclusions: Developmental challenges in behavioral, motor and cognitive domains remain a concern in adolescence in a subset of survivors of infant open heart surgery. Although relatively few experienced limitations in everyday activities, this was more common in males with mean scores 10–15 points lower than females. Ongoing recruitment will enable us to determine the potential influence of sociodemographic factors, type of heart lesion and age at surgery on developmental and functional outcomes.

Sources of Funding: Study funded by the Canadian Institutes of Health Research MOP-102720.

Keywords: Neonatal neurology

127. Chorioamnionitis and Cerebral Palsy: Lessons from a Patient Registry

Shevell AH (Montreal, QC), Benini R, Shevell MI, Oskoui M

Objective: The neuroinflammatory response to prenatal infection has been inconsistently linked to periventricular white matter injury and subsequent neurologic impairment. We aimed to investigate the association between histological chorioamnionitis and maternal and child factors in a cohort of children with cerebral palsy.

Methods: We conducted a retrospective observational study on a cohort of children with cerebral palsy who were identified from a Cerebral Palsy Registry. Factors associated with histological chorioamnionitis were explored.

Results: In 455 children with cerebral palsy, 54 had histologic chorioamnionitis reported on placental pathology (11.9%). These children were born significantly more prematurely (mean 33.0 weeks, SD 6.2, p 0.0003) and at a lower birth weight (mean 2171.9g, SD 1123.3, p 0.004) than the rest of the cohort. Although periventricular white matter injury and spastic diplegic type of cerebral palsy were more often reported in these children on univariate analysis, neuroimaging and cerebral palsy subtype were no longer significant once gestational age was adjusted for. Placentas with chorioamnionitis were also more likely to have a mass above the 90th percentile.

Conclusions: Chorioamnionitis is associated with premature birth with no observed additional effect on cerebral palsy subtype or neuroimaging. The significance of larger placental mass in this population is unclear.

Keywords: Neonatal neurology

128. Neonatal MRI Measures Predict Visual Function in School Age Children Born Preterm

Soul JS (Boston, MA), Moskowitz A, Hansen R, Landers J, Fortuno CR, Fulton A

Objective: Children born preterm frequently sustain cerebral white matter (WM) injury that puts them at high risk for cerebral visual impairment (CVI). We aimed to determine whether quantitative MRI measures of visual structures in newborns predicted cerebral visual function in childhood. Specifically, we hypothesized the DTI measure of visual pathways would predict VEP latency and volumes of visual cerebral regions would predict VEP amplitude.

Methods: Nineteen preterm-born children with term-age brain MRI scans were enrolled in a study to measure visual function at school age (7.1–10.3 years). WM structure was assessed by measuring the fractional anisotropy and apparent diffusion coefficient (ADC) in the optic radiations, and the volume of dorsal visuo-motor and ventral perceptual-visual regions. Visual function at school age was measured by pattern reversal VEP latency and amplitude.

Results: Anisotropy and ADC at term age were both highly predictive of VEP latency at school age; lower anisotropy correlated with longer latency (occipital WM: left rs=−0.87, p < 0.001; right rs=-0.69, p=0.04) and similarly, higher ADC correlated with longer latency (peritrigonal WM: left rs=0.88, p <0.001; right rs=0.83, p=0.01). Smaller parieto-occipital WM volumes at term age predicted lower VEP amplitude at school age (left rs=0.63, p=0.02; right rs=0.88, p<0.001).

Conclusions: These data show that quantitative MRI measures of white matter structure in preterm newborns at term age are strong predictors of visual function at school age. This approach has the potential to identify children at risk of CVI in early infancy, thereby enhancing early intervention to improve long-term educational success.

Sources of Funding: March of Dimes Foundation grant

Keywords: Neonatal neurology

129. Decreased Non-Cystic White Matter Injury in Premature Newborns Over Time

Gano D (San Francisco, CA), Partridge JC, Bonifacio S, Xu D, Ferriero DM, Barkovich AJ, Glass HC

Objective: We have previously shown that cystic WMI decreased over a ten-year period (Hamrick et al., J Pediatr 2004). The purpose of this study was to determine the proportion of infants with MRI-detected non-cystic white matter injury (WMI) over time among a prospective cohort of premature newborns.

Methods: 315 infants born at gestational age (GA) 3 areas of signal abnormality or areas measured >2 mm but 5% of hemisphere affected). WMI was classified as: none/mild, moderate/severe non-cystic, moderate/severe cystic. 46 subjects were excluded from the analysis for moderate/severe cystic WMI (N=7), grade 4 intraventricular hemorrhage (N=22), or poor quality MRI (N=17). The proportion of newborns with non-cystic WMI over time was explored using descriptive statistics and linear regression.

Results: 269 subjects of mean GA 28.2±0.14 weeks and mean birth weight (BW) 1086.9 ± 21.1 grams were included. Subjects were imaged at a mean corrected GA 31.9±0.12 weeks. The proportion of infants with moderate/severe non-cystic WMI decreased over time (Figure 1). Adjusting for GA and BW, birth year was significantly associated with moderate/severe noncystic WMI (P =.002).

Conclusion: The decreased burden of MRI-detected moderate/severe non-cystic WMI over time in our prospective cohort of premature newborns may reflect changes in the practice of neonatal intensive care during this period.

Keywords: Neonatal neurology, Neuroimaging

130. Biometry to Diagnose Inferior Vermian Hypoplasia Prenatally

Jacob FD (Boston, MA), Grant PE, Soul JS

Objective: Inferior vermian hypoplasia (IVH) is a common posterior fossa malformation identified prenatally but criteria for classification and diagnosis are debated. We aimed to determine which biometry measures of the developing cerebellar vermis could define IVH.

Methods: We retrospectively identified fetuses with IVH and normal controls diagnosed by fetal MRI in the Advanced Fetal Care Center database at Boston Children's Hospital for 2003–2012. Cases with other cerebellar anomalies were excluded. Standard biometric measurements, the height, area and ratio of the upper & lower vermis, and the brainstem/tentorium, brainstem/vermis and fastigeal angles were measured.

Results: We reviewed 72 MRI studies in 50 fetuses with IVH; 32 fetuses had isolated IVH, 18 had associated cerebral and/or systemic anomalies, and 32 MRI studies in 28 normal controls. The first MRI was performed at mean gestational age 20+6 (±3+4) weeks. Fetuses with IVH had a significantly larger upper/lower vermis area ratio (1.43±0.32 vs. 1.12±0.13, $p<0.0001$), fourth ventricular size, brainstem/tentorium angle (40.3±10.8 vs. 28.8±6.7, $p<0.0001$), brainstem/vermis angle (32.8±14.4 vs 6.6±3.7, $p<0.0001$), and fastigeal angle (133.1±20.6 vs. 95.6±15.1, $p<0.0001$), compared with controls. There was no difference in other measures of vermis or cerebellar height, area or diameter. There was no significant difference between subjects with isolated IVH vs. those with associated cerebral &/or systemic anomaly.

Conclusions: Normal fetuses cannot be distinguished from those with IVH using standard biometric measures, but more detailed measures including the upper/lower vermis area ratio, brainstem/tentorial, brainstem/vermis and fastigeal angles show significantly differences so can be used to identify IVH prenatally.

Keywords: Neonatal neurology, Neuroimaging

131. The Role of Magnetic Resonance Imaging in Isolated Fetal Cerebral Ventriculomegaly

Kandula T (Sydney, Australia), Clark J, Fahey M, Goergen S

Objective: Antenatal counseling for fetal cerebral ventriculomegaly is guided by the size of the ventricles and the presence and nature of concurrent structural abnormalities. Current available evidence suggests that magnetic resonance imaging (MRI) is indicated when the isolated ventriculomegaly (iVM) on ultrasound is severe (>15 mm), but there is less agreement when iVM is mild or moderate (10–15 mm). Consensus guidelines are limited. Our aim was to report additional findings on MRI in iVM.

Methods: Data was gathered prospectively from all cases referred to a single, tertiary, university affiliated hospital between November 2006 and February 2013. Cases with a tertiary ultrasound that showed VM with no other suspected abnormalities were included. Amniocentesis was offered but not universally taken up.

Results: Of the 60 fetuses included, additional findings were seen on MRI in 5/42 (11.9%) with mild VM, 1/10 with moderate VM (10%) and 4/7 (57.1%) with severe VM. The findings were clinically significant in 3/6 cases with mild or moderate VM compared with 4/4 cases with severe VM. Amniocentesis carried out in three cases was normal. Severity of VM was concordant on ultrasound and MRI in 42/60 cases. The median gestational age at ultrasound was 26 weeks (21–36) and at MRI was 28 weeks (22–37). Median time delay for MRI after ultrasound was 7 days (0–21).

Conclusions: Clinically significant additional findings on MRI were seen in around 6% of cases with mild to moderate iVM. Anomalies commonly missed on ultrasound include agenesis of septum pellucidum/corpus callosum and cortical malformations.

Keywords: Neonatal neurology, Neuroimaging

132. Hypothermia after Rat Pup Hypoxia/Ischemia: Effects on Cytokines, Signaling Molecules and Core/Penumbra Volumes

Xiangpeng Y (Loma Linda, CA), Ghosh N, McFadden B, Tone B, Tian HR, Snyder EY, Obenaus A, Ashwal S

Objective: Hypothermia (HT) is standard of care for neonates with hypoxic ischemic injury (HII). Because of its modest effect, additional translational studies are needed to maximize neuroprotection, specifically when HT is combined with other treatments (e.g., stem cells).

Methods: Unilateral HII (carotid occlusion, 8% O2,) was induced in 10d rat pups and followed by 24 hours of HT (30°C; n=18) or normothermia (NT, 35°C; n=15). MRI, neurological testing (righting reflex) and cytokine/signaling molecule profiles (Luminex/ELISA) were collected pre-HII and at 0, 24, 48, 72 hrs post HII.

Results: Compared to NT, HT pups had less weight loss (33.5%) at 24hr and faster righting reflexes (43%) at 0–48hr post HII. Compared to NT, HT reduced MRI measures of HII including the rat pup severity score (64%) & HII volumes (total lesion, 69%; ischemic core, 79% & penumbra, 63%) between 0–48 hrs. HT reduced expression of inflammatory cytokines (interleukin-1β, $p<0.05$). Interferon-γ, tumor necrosis factor-α and monocyte chemoattractant protein-1 expression were lower in the HT than in the NT group (although not statistically significant) indicating less inflammation in the HT group. Stromal cell-derived factor-1α levels were not modified ($p<0.81$)

suggesting that HT does not affect stem cell signaling molecules. Interestingly, at 72hrs post HII (48hrs post HT) there was an increase in cytokine levels that was associated with increased HII injury volumes and a reduced righting reflex, suggesting a rebound effect. Our data demonstrate that HT reduces inflammatory cytokines without altering stem cell signaling within 0–48hrs post HII, thus increasing the HT treatment window.

Sources of Funding: Supported by NINDS grant
Keywords: Neonatal neurology, Neuroimaging

133. Automated Quantification of Ischemic Core and Penumbra in Neonates with Arterial Ischemic Stroke

Ghosh N (Loma Linda, CA), Obenaus A, Ashwal S

Objective: Neonatal arterial ischemic stroke occurs in about 1/2300 live births and is associated with significant morbidity. MRI has improved our ability to detect neonatal AIS and future treatments will be predicated on determining the degree of irreversibly injured (core) from salvageable (penumbra) tissues using different MRI modalities. In recent translational/human studies we have shown that Hierarchical Region Splitting (HRS), a computational analysis method, can differentiate core from penumbra based on diffusion and T2 weighted imaging (Ghosh et al, J Cereb Blood Flow Metab. 2012; 32:2161).

Methods: HRS recursively partitions the apparent diffusion coefficient (ADC) maps into uniform-diffusivity regions that allows detection of total ischemic lesion volume and allows quantification of ischemic core and penumbra based on subtle ADC variations within the lesion.

Results: Our pilot data from 6 AIS neonates (studied ~3–5 days after birth) showed considerable variations in total lesion and core/penumbral volumes and no emerging correlation between lesion volume and the percentage of tissue that was core/penumbra (i.e., some neonates with large lesions had large penumbral volumes). Ongoing HRS analysis is being concluded on an additional 20 neonates.

Conclusions: We have demonstrated that HRS can quantify ischemic core and penumbra volumes in neonates with AIS. Ongoing work is aimed at determining the relation between time post-injury and the relative core/penumbra volumes as well as the relationships between total lesion volume and the degree of salvageable tissue. Such data are clearly needed for using any therapy to treat neonatal AIS.

Keywords: Neonatal neurology, Neuroimaging, Stroke

134. Reproducibility and Reliability of ABC/2 for Calculating Infarct Volume in Perinatal Arterial Ischemic Stroke

Mirsky DM (Aurora, CO), Stence NV, Bernard TJ, Armstrong-Wells J

Introduction: Counseling and prognostic decisions in perinatal arterial ischemic stroke (PAS) necessitate rapid, accurate estimation of true infarct volume. ABC/2 method is a fast, reproducible way to calculate infarct volume in adult and childhood hemorrhagic stroke, but overestimates infarct volume in adult arterial ischemic stroke. We sought to determine the accuracy and reproducibility of ABC/2 in assessing acute infarct volume in PAS.

Methods: We studied 25 term newborns in our prospective cohort study from 08/01/2000 - 1/01/2012 with: 1) clinical presentation consistent with acute symptomatic PAS; 2) MRI showing infarction in an arterial distribution with an acuity consistent with neurological signs/symptoms. Stroke volume by ABC/2 method and gold standard (manual planimetric) were determined by two blinded pediatric neuroradiologists. Student's t-test and Mann-Whitney U, and linear regression were utilized, with p-value < 0.05 significant.

Results: There was no difference in mean volume between ABC/2 and planimetric method (mean 46cm3 versus 32cm3, respectively, $p = 0.01$), with good correlation ($R2 = 0.84$). ABC/2 overestimated infarct volume by a median false increase (variable ABC/2 volume minus planimetric volume) of 8 cm3, representing a 61 % increase over the gold standard.

Conclusion: ABC/2 is a reproducible tool for clinicians to rapidly calculate PAS volume in the emergent setting. Similar to adult arterial ischemic stroke, ABC/2 overestimates infarct volume compared to the gold standard planimetric volume method. Therefore, caution should be used when relying solely on ABC/2 for counseling. Further studies are warranted to validate ABC/2 calculation with risk assessment and outcomes after PAS.

Sources of Funding: NIH BIRCWH K12 KD HDO57022

Keywords: Neonatal neurology, Neuroimaging, Stroke

135. Understanding Perinatal Stroke: A Study of Risk Factors

Zingariello CD (Falls Church, VA), Nelson KB, Carpenter J, Boortalary T, Kline A, Lateef T

Objective: Cerebral ischemic insults are not uncommon in the perinatal period. Ischemic insults can occur in several forms, including perinatal arterial ischemic stroke (PAIS), watershed infarction (WSI) and diffuse hypoxic ischemic injury (HIE). The etiology of PAIS is not well understood. This study examines risk factors associated with HIE and WSI as compared to PAIS.

Methods: We conducted a retrospective chart review of all neonates admitted to Inova Fairfax Hospital from 2002 through 2012 with a diagnosis of cerebral ischemic insult, based on search terms "infarct", "stroke", "CVA", and "HIE." Infants were characterized as having PAIS, WSI or HIE based on clinical history and supportive imaging. Maternal, perinatal and neonatal risk factors for perinatal ischemic events were evaluated.

Results: Fifty-six patients with cerebral ischemic insults were identified (PAIS 18, WSI 10, and HIE 28). Across the groups, all risk factors were similarly present, except maternal gestational diabetes and large birth weight (≥97th% for age) were more common in the PAIS group, ($P=0.02$ and 0.07 respectively). MTHFR deficiency was found in 60% of infants with PAIS and not in any patients with WSI or HIE ($P=0.06$).

Conclusions: In this preliminary uncontrolled study, mothers of infants with PAIS and the infants themselves,

had more findings potentially related to risk for thrombotic disease, including maternal gestational diabetes, large birth weight, and infant MTHFR deficiency, when compared to WSI and HIE. This experience indicates the need for a controlled investigation of PAIS risk factors in a large study that includes placental findings.

Keywords: Neonatal neurology, Stroke

136. Advanced MR and Spectroscopic Imaging in Adolescents with Chronic Post-Concussive Symptoms Following Sports-Related Concussion

Bartnik-Olson BL (Loma Linda, CA), Grube M, Wang H, Wong V, Holshouser BA, Ashwal S

Objective: There is growing interest in using advanced MRI techniques (diffusion tensor imaging, DTI; perfusion weighted imaging, PWI) to identify and quantify microstructural axonal injury and perfusion abnormalities in adolescents with sports related concussion (SRC). We investigated these changes in a group of post-concussive symptomatic adolescents.

Methods: We studied 13 adolescents (16 ± 4 years) who sustained a SRC (1–24 months before imaging) and 14 controls (1 5± 4 years). Symptoms included headache (persistent or intermittent, n=13), dizziness (n=3), and cognitive (n=6) or behavioral changes (including depression, n=4). DTI and PWI data were acquired on a Siemens Tim Trio 3T scanner. Region of interest DTI (FA, MD, RD) and PWI (CBF, CBV, MTT) analysis was performed.

Results: FA and RD were reduced in the genu of the corpus callosum in SRC subjects compared to controls ($p=0.05$ and $p=0.04$). SRC subjects also showed reduced rCBF ($p=0.03$) and rCBV ($p=0.05$) in the right thalamus and a trend ($p=0.06$) towards reduced rCBF and rCBV in the left thalamus.

Conclusions: Lower callosal FA values have been reported after mild TBI and indicate axonal injury. Elevated RD in this region suggests the presence of myelin damage along with axonal injury. rCBF and rCBV also were reduced in the thalami of SRC subjects and may be due to post-injury vascular disruption or impairment of microvascular responsiveness. Our findings suggest that DTI and PWI reflect different components of the complex injury that occurs after SRC and that both are sensitive indicators of lasting injury in chronically symptomatic athletes.

Keywords: Neuroimaging

137. Fractional Anisotropy and Volumetric Measurements of the Corpus Callosum are Associated with Disease Severity in Niemann-Pick Disease, Type C

Apkarian KL (Baltimore, MD), Jung ES, Yoshida S, Mori S, Baker E, Yanjanin N, Porter FD, Lee R

Objective: Niemann Pick Disease, Type C (NPC1) is a neurodegenerative lysosomal storage disorder. With no cure or effective treatment, biomarkers of severity would be beneficial for prognostication and testing interventions. Diffusion tensor imaging (DTI) has shown microstructural abnormalities in adults with NPC. This is the first study to apply DTI and volumetric analysis to evaluate the corpus callosum (CC) in a pediatric population of NPC patients. We hypothesized that the callosal mean fractional anisotropy (mFA), surface area, volume, and cross-sectional area will negatively correlate with NPC severity score (SS).

Methods: Thirty-nine individuals with NPC1, ages 1 year to 21.9 years (mean=11.1, SD=6.1), each received one MRI scan. SS were obtained by examination and clinical observation. An atlas-based, automated approach was used to measure mFA, surface area, cross-sectional area and volume. For comparative analysis, one midsagittal image was chosen and the CC manually traced to obtain cross-sectional area. Statistical analyses were applied to study the relationships between imaging and clinical severity.

Results: For NPC patients, lower CC mFA, surface area, volume, and cross-sectional area significantly correlate with higher SS. Severity sub-domain analysis showed ambulation, speech, seizures, and incontinence have the strongest relationships with callosal measures. Comparison of atlas-based processing and manual tracing techniques demonstrated validity for the automated method.

Conclusions: For individuals with NPC, the CC measures are correlated with clinical severity. These findings show promise for imaging biomarker discovery in this disorder.

Keywords: Neuroimaging

138. Early Parietal Lobe PET Hypometabolism Predicts Non-Verbal Cognitive Changes in Children with Sturge-Weber Syndrome

Guy WC (Detroit, MI), Kamson DO, Behen ME, Chugani HT, Juhász C

Objective: We evaluated if severity of lobar metabolic abnormalities in children with unilateral SWS, measured during the early disease stage by glucose metabolism positron emission tomography (PET), could predict subsequent changes in verbal and/or non-verbal cognitive function (VIQ/PIQ).

Methods: Seventeen children (mean age: 4 years) with unilateral SWS (9 left-sided) were prospectively evaluated by MRI, glucose metabolism PET and neuropsychology testing. IQ was re-evaluated 12–38 months later (mean: 23 months). Baseline and follow-up IQ, as well as interval IQ changes were correlated with asymmetry indices (AI) of glucose metabolism measured in the four cerebral lobes (frontal, temporal, parietal, occipital) ipsi- and contralateral to brain involvement shown by MRI.

Results: Lobar glucose metabolism AIs did not correlate with baseline or follow-up IQ ($p>0.1$). However, in a subgroup of 13 children (age>30 months), where both baseline and follow-up IQ could be evaluated by WPPSI-III, parietal glucose AI showed a negative correlation with interval PIQ (but not VIQ) changes (Spearman's rho: 0.64, $p=0.02$). This correlation was particularly strong in the youngest patients (age<6, n=10, $r=0.86$, $p=0.002$) and remained significant ($p=0.01$) after controlling for lesion side. Early parietal lobe hypometabolism was associated with a subsequent decline in mean PQ (mean change: −7), while children with no/minimal parietal metabolic asymmetries showed improved PIQ (mean change: +9; $p=0.01$).

Conclusions: These results suggest that severity of early damage in parietal cortex (commonly affected in SWS), as assessed quantitatively by glucose metabolism PET, may predict subsequent non-verbal cognitive changes in children with unilateral brain injury due to SWS.

Sources of Funding: Funding source: NIH grant R01 NS041922

Keywords: Neuroimaging

139. Default Mode Network Development in Early Childhood Using scMRI

Helm L (Salt Lake City, UT), Zielinski BA

Objective: To determine early developmental trends of DMN structure by investigating whole-network scMRI topology in infants and young children.

Methods: We applied scMRI techniques to investigate relationships between covariance maps anchored by four major nodes of the DMN (posterior cingulate, precuneus, anterior medial prefrontal, angular gyrus) in two age- and gender-matched groups (Group 1, 0.9-4.5 yrs (mean 2.4); Group 2, 5.0–7.8 yrs (6.5); $n = 70$). Whole-brain Z-statistic maps ($p<.001$, FWE) of groupwise GM density covariance were derived for each seed and compared qualitatively to provide a broad assessment of DMN development in early childhood.

Results: Z-statistic maps derived from each DMN node comprised distinct structural covariance networks (SCNs) that varied by age. In general, SCN volume increased between Groups 1 and 2. However, topological differences were apparent. Anterior DMN covariance was present in both groups, although to a lesser degree in Group 1. In contrast, posterior regions were largely uncoupled from anterior DMN regions in Group 1. Covariance between DMN seeds and regions within canonical 'executive control' and 'salience' networks was evidenced in both groups, but to a greater degree in Group 2.

Conclusions: Immature DMN structure is apparent by infancy, and early DMN topology includes elements of anterior-posterior progression as well as cross-network covariance with other SCNs. Differences in DMN seed maps support the model of heterogeneous subcomponents comprising the DMN. Relationships of early DMN structure and cross-network covariance are consistent with large-scale network segregation as childhood proceeds, and may have implications in neurodevelopmental disorders.

Sources of Funding: This work was supported by the Primary Children's Medical Center Foundation and NIH CHRCDA 5K12HD001410. We utilized publicly available data from the NIH MRI study of normal brain development, Objective: 2 (http://pediatricmri.nih.gov).

Keywords: Neuroimaging

140. Pediatric TBI: Acute and 1-Year MRS/DTI Findings

Holshouser BH (Loma Linda, CA), Ghosh N, Sun R, Tong KA, Pivonka-Jones J, Rundquist M, Ashwal S

Objective: We present longitudinal MR spectroscopic and DTI findings in children with complicated mild/severe TBI.

Methods: Studies were done (7–15 days & 1 year) with MRI (3D-T1W, 3D-T2W, FLAIR, SWI, DTI-mean FA, ADC, AD, RD) and with 3D MRSI (10 mm slabs-corpus callosum--brain stem). MRSI voxel data were overlaid onto DTI white matter (WM) data to compare DTI parameters to metabolite ratios (NAA/Cr, NAA/Cho, Cho/Cr) for each voxel and region. Neuropsychological evaluations were done (3, 12 months).

Results: We studied 17 TBI (13.2yrs; GCS: 3–15) and 15 controls (11.5 yrs). Initial MRI found decreased NAA/Cr and NAA/Cho ratios in all regions in TBI patients compared to controls. Mean FA values were decreased in corpus callosum (CC), basal ganglia (BG), parieto-occipital and temporal white matter. The mixed model analysis which accounts for age effects, showed a significant recovery of NAA/Cr only in 3 regions - BG ($p=0.01$), temporal gray ($p=0.03$) and thalami ($p=0.01$) and showed no significant longitudinal recovery of DTI metrics compared to controls. The initial NAA ratios and mean FA measurements correlated significantly with IQ and memory deficits evaluated at 12 months after injury.

Conclusions: Early decreases in NAA represent neuronal loss or dysfunction and early FA reductions represent structural white matter injury. At 12 months, MRS showed significant recovery of metabolite ratios only in 3 regions, whereas, no regional DTI metrics recovered. This suggests incomplete metabolic and axonal recovery as the source of cognitive impairment.

Keywords: Neuroimaging

141. Neural Correlates of Visual Statistical Learning in Young Children with Autism Spectrum Disorder (ASD)

Jeste SS (Los Angeles, CA), Freeman SN, Paparella T, Senturak D, Kupelian C, Kirkham N, Johnson SP

Objective: Statistical learning is characterized by detection of regularities in ones environment without an explicit awareness or intention to learn, and it plays a critical role in language and social behavior. A better understanding of statistical learning, therefore, could provide insight into our understanding of pathways to core deficits in autism spectrum disorder (ASD), a neurodevelopmental disorder defined by impairments in social interaction and communication.

Methods: We investigated the electrophysiological correlates of visual statistical learning in young children with autism spectrum disorder, compared to typically developing (TD) age matched controls, using an event related potential shape learning paradigm (modified from Kirkham et al, 2002) and we examined the correlation between visual statistical learning and cognitive and adaptive function.

Results: Compared to TD controls, the ASD group as a whole showed no evidence of learning as defined by N1 (early visual discrimination) and P300 (attention to novelty) components. Upon further analysis, in the ASD group there was a positive correlation between N1 amplitude difference and both full scale IQ ($r=0.298$, $p=0.047$) and non-verbal IQ ($r=0.283$, $p=0.06$), and a positive correlation between P300 amplitude difference and adaptive social function

($r=0.388$, $p=0.012$). Children with ASD and a high nonverbal IQ and high adaptive social function demonstrated a distinctive pattern of learning.

Conclusions: This is the first study to identify electrophysiological markers of visual statistical learning in children with ASD. Through this work we have demonstrated heterogeneity in statistical learning in ASD that maps onto nonverbal cognition and adaptive social function.

Keywords: Neuroimaging

142. The Effect of Learning on an Event-related Potential in Adolescents with Dyslexia

Kraus D (Cincinnati, OH), Horowitz-Kraus T

Objective: Dyslexia is a reading difficulty also accompanied by more generalized learning deficits. Feedback-related negativity (FRN) is an event-related potential that has been linked to learning processes. This study aimed to define the effect of learning in adolescents with dyslexia (DR) as compared to typical readers (TR) by measuring changes in FRN.

Methods: 27 adolescents with dyslexia (16 males, mean age 12.84 ± 0.55 years-old) and 31 age-matched typical readers performed the Wisconsin Card Sorting Test (WCST) while undergoing EEG. We obtained accuracy rates and reaction times and calculated FRN amplitudes in early and late phases of the task.

Results: Typical readers performed better than individuals with dyslexia on the WCST, although both groups showed shorter reaction times in late phases, indicative of a learning process. Differences in average reaction times were significant and increased in late phases (Early phase: 2.33 ± 1.21 sec in DR vs. 1.98 ± 0.59 sec in TR, $p<0.05$; Late phase: 2.19 ± 0.92 sec vs 1.68 ± 0.37sec, $p<0.05$). FRN amplitudes in early phases were significantly lower in dyslexic readers (2.99 ± 4.1 μV in DR vs 6.08 ± 3.72 μV in TR, $p<0.01$), but were essentially equivalent in the late phase (6.39 ± 3.01 μV in DR vs 6.64 ± 4.26 μV in TR).

Conclusions: Both groups demonstrated electrophysiological changes while learning a new task. However, learning patterns were different: during early phases, individuals with dyslexia showed decreased FRN amplitudes. Repetition of the task resulted in a correction of this difference, i.e. the development of a more "typical" FRN response. These results might be of consequence in the development of future remedial programs for dyslexia.

Keywords: Neuroimaging

143. Resting State Alpha Power Differences in Adults with Autism Spectrum Disorders are not Present in Toddlers

Levin AR (Boston, MA), Tager-Flusberg H, Nelson CA

Objective: In 2012, Mathewson et al. demonstrated higher resting-state EEG alpha power in adults with autism spectrum disorders (ASD) than in typically developing (TD) adults, in multiple regions. We evaluated resting-state EEG in toddlers with and without ASD, to determine whether similar findings are seen early in the developmental trajectory of ASD.

Methods: We collected EEG from children at high risk for ASD (HRA) by virtue of having an older sibling with ASD, which increases risk 20-fold, and low risk controls (LRC), who have a typically developing older sibling, at 12, 18, and 36 months of age with a 128 HydroCel Sensor Net System (EGI, Inc) while they were seated on their mother's lap, watching bubbles. The diagnosis of autism was based on an ADOS by a certified examiner at 36 months of age, and confirmed by clinical impression.

Results: Preliminary analyses demonstrate that children who were diagnosed with ASD at 36 months (all from the HRA group) showed no differences in alpha power compared to TD children from either the HRA or LRC groups, in any of the regions previously shown to demonstrate between-group differences in adults (left and right frontal and posterior), at any of the ages tested.

Conclusions: EEG-based differences in the alpha band of the power spectrum seen in ASD versus TD adults are not present in children at or prior to the time when ASD is frequently diagnosed, suggesting that electrophysiological differences between ASD and TD groups change over the course of development.

Sources of Funding: Autism Science Foundation Postdoctoral Fellowship Award (Levin) NIDCD 5R01DC010290-04 (Tager-Flusberg) Simons Foundation (Nelson)

Keywords: Neuroimaging

144. High Frequency Oscillations Serve as a Promising Biomarker of Autism Spectrum Disorders (ASD)

McEvoy K (Los Angeles, CA), Jeste SS

Objective: High frequency oscillations in the gamma range represent local, synchronous cortical activity and have been linked to various cognitive functions, such as language. Given the aberrant local connectivity seen in autism spectrum disorders (ASD), resting state gamma could serve as a biomarker of atypical development.

Methods: We studied resting state oscillations of 26 children with ASD (average age 53 months) and 29 TD controls. EEG was recorded using a 128-electrode Hydrocel Geodesic Sensor Net System (EGI Inc.) and filtered from 1 to 50 Hz. Segments containing blinks, saccades, and muscle movements were analyzed separately from artifact free segments in order to determine their impact on the calculation of gamma. Data were transformed into the frequency domain using a Fast Fourier Transform. Estimates of relative power were calculated for low-gamma (30–50 Hz) activity.

Results: Blinks and saccades significantly reduced relative frontal gamma power. Therefore, all segments with ocular artifact were removed for analysis. A distinctive pattern of gamma power was seen in the ASD group. For instance, relative gamma power was higher in the left central and left posterior regions in the ASD group compared to the TD controls.

Conclusions: Eye movements significantly impact the characterization of high frequency oscillations. Gamma band activity can differentiate children with ASD from TD controls. Higher left tempero-parietal gamma activity may reflect local over-connectivity in cortical regions important

for language processing and learning. Correlations bewteen EEG power and cognitive function will provide more insight into the functional significance of these resting state EEG differences.

Sources of Funding: Kevin McEvoy is supported by an Autism Speaks Weatherstone Fellowship, 2012–2014

Keywords: Neuroimaging

145. Magnetic Resonance Spectroscopy in Predicting Outcomes for Children after Cardiac Transplantation

Pichon P (Loma Linda, CA), Brandt E, Chinnock R, Holshouser BA, Ashwal S

Objective: We performed a retrospective chart review of children undergoing cardiac transplantation (1999- 2011) who had pre-transplantation proton Magnetic Resonance Spectroscopy (MRS).

Methods: MRS was done at a mean age of 7.9 months. Pediatric Cerebral Performance Category Scale (PCPCS) scores were determined on average at 5.3 years post-transplant. N-acetylaspartate (NAA), creatine (Cre), choline (Cho), myo-inositol (Ins), presence of lactate (Lac), and metabolite ratios (NAA/Cre, NAA/Cho, Cho/Cre) were evaluated in the mid-occipital gray matter, basal ganglia and thalami. MRS data were correlated to pertinent clinical data and neurologic outcome (PCPCS, dichotomized as poor: moderate/severe disability, vegetative state, or death; n=7; vs. good: normal, mild disabilities; n=18).

Results: We studied 25 patients (mean age 11.3 months at transplant) and compared their MRS findings to age-matched controls. The presence of lactate and reduced NAA in occipital gray matter or basal ganglia correlated with poor outcomes ($\chi 2$; p=0.016). The presence of lactate correlated with a higher PCPCS score (Pearson; p=0.004) and with poor outcome in the dichotomized PCPCS (Pearson; p=0.014). Seizures pre or post transplantation correlated with a higher PCPCS score (p=0.04) and a poor PCPCS categorized outcome (p=0.02).

Conclusions: Pre-transplant elevated lactate levels signifying altered energy metabolism and reduced N-acetylaspartate levels signifying neuronal loss or dysfunction correlated with poor outcomes for children who had heart transplantation. The presence of pre or post-transplant seizures was a predictor of poor outcome. MRS performed prior to heart transplant may be used with clinical data (e.g., seizures) to determine long term-prognosis.

Keywords: Neuroimaging

146. Reduced Extent and Strength of Resting State Functional Network Connectivity in Pediatric TBI

Pizoli CE (Durham, NC), Englander ZA, Song AW, Schlaggar BL, Pineda JA

Objective: The relationship between structural changes in white matter and the neurobehavioral sequelae after TBI remains unclear; it is theorized that functional network disruption caused by structural network damage plays a key role. We aimed to investigate the integrity of functional networks in children acutely following TBI to test the hypothesis that TBI results in widespread disruption of multiple functional networks.

Methods: Using resting state functional MRI, we studied the integrity of functional networks in children with mild to severe TBI within 1 week of injury. Our cohort consisted of 13 control subjects (mean age 11.3y+/- 2.8), 15 children with mild or moderate TBI (mean age 10.9y+/- 4.4) and 22 children with severe TBI (mean age 9.7y+/- 4.8). Functional networks were identified for the task control, default mode, and sensorimotor networks and the extent and strength of connectivity within and between networks was assessed.

Results: Significant group differences were seen in the spatial extent of intra-network correlations in each of the networks analyzed with reduced correlations noted in those with severe TBI. Likewise, differences in inter-network connectivities showed a significant decrease in the typical anti-correlations seen between the task control and default mode networks in severe TBI subjects. The strength of connectivity within each network was also significantly decreased in the task control and default mode networks across groups with a trend toward reduction in the sensorimotor network.

Conclusions: Our results support the theory that functional networks are acutely disrupted after TBI in children, specifically in those with severe injury.

Sources of Funding: NINDS NSADA K12 awarded to Washington University in St. Louis funded this work.

Keywords: Neuroimaging

147. Abnormal Neural Activity During Spatial Working Memory Performance in Neurofibromatosis Type 1

Rosser T (Los Angeles, CA), Montojo C, Ibrahim A, Jonas R, Enrique N, Silva A, Bearden C

Working memory (WM) deficits have been documented in the NF1 mouse model as well as in NF1 patients and are likely secondary to increased GABAergic inhibition in specific brain regions.

Hypothesis: We hypothesized that NF1 patients would show differential activation patterns compared to controls during performance of a functional MRI (fMRI) spatial WM task.

Methods: An fMRI spatial delayed response task was performed by 24 (16 female, 9 male) NF1 patients (mean age 33 years) and 25 age, gender and scanner-matched controls. Subjects were shown a target array of 1, 3, 5 and 7 black circles. After a variable delay period, they were shown a green circle and asked to indicate whether this circle was in the same position as one of the target circles.

Results: Consistent with previous WM literature, controls exhibited activation of the intraparietal sulcus (IPS) and occipital cortex in a contrast of high versus low WM load (Load5-Load1). In addition to activating IPS and occipital cortex for this contrast, NF1 patients showed activation of the superior frontal sulcus, middle frontal and temporal gyrus, and basal ganglia. In a between-group contrast for high versus low WM load, NF1 patients showed hyperactivation of several regions relative to controls, including

occipital cortex, middle frontal and temporal gyrus, posterior cingulate gyrus and insula.

Conclusion: NF1 patients showed activation of brain regions not typically associated with spatial WM, suggesting neural inefficiency and/or compensatory activity. These findings help elucidate the abnormal cortical networks involved in NF1 cognitive dysfunction.

Keywords: Neuroimaging

148. Volumetric Deep Grey Matter Differences in Pediatric Patients with Dyskinetic vs Spastic CP.

Tillema JM (Rochester, MN), Pouwels PJW, Buizer AI, de Graaf P, Barkhof F, Van Der Knaap MS, Vermeulen RJ

Background: White matter (WM) involvement in patients with spastic cerebral palsy (CP) with periventricular leukomalacia (PVL) has been well described. Smaller studies have described thalamic loss in children with PVL and spastic CP. In dyskinetic CP, no quantitative volumetric studies are available.

Methods: Twenty-one patients with CP (Mean age 9.1±3.9y; M:F=11:10; 14 spastic CP and 7 dyskinetic CP) were compared to 21 age- and gender-matched controls. T1-weighted images (3D-MPRAGE, 1.5T, Siemens) were used to automatically obtain WM, thalamus and putamen volumes, using FSL. Segmentations were reviewed by a neuro-radiologist and corrected for errors. Control and patient groups were analyzed with student t-tests and non-parametric tests were performed between patient subgroups.

Results: Age and gender distribution was not significantly different between patient subgroups. Patients with spastic CP were all ex-premature (mean gestational age 30.5 wk, SD 2.4), dyskinetic patients were born at term. Compared to controls, patients had smaller volumes of WM (480±67 vs. 391±57 cm^3), thalamus (12.7±1.6 vs. 8.0±1.9 cm^3) and putamen (9.0±1.2 vs. 7.1±1.6 cm^3), all with p-values$<$0.001. Subgroup analysis revealed significantly smaller volume of putamen ($p<0.05$) in patients with dyskinetic CP, without differences in WM ($p=0.74$) and thalamus ($p=0.80$). Pearson correlation was significant (corrected for age and gender) between functional motor classification (GMFCS) and thalamic volume ($r=-0.52$; $p<0.05$).

Conclusion: We describe thalamic, putamen and WM volume loss in CP patients compared to controls. Subgroup analysis shows significant lower putamen volumes in dyskinetic patients compared to spastic CP, with similar extent of WM and thalamic volume loss.

Keywords: Neuroimaging

149. Acute and 1-Year Susceptibility-weighted MRI of Hemorrhagic Shearing Injury after Pediatric TBI

Tong KA (Loma Linda, CA), Al-Ramadhani R, Rundquist M, Pivonka-Jones J, Holshouser BA, Ashwal S

Objective: MRI susceptibility-weighted imaging (SWI) accentuates paramagnetic properties of blood products and depicts more hemorrhagic brain lesions after traumatic brain injury (TBI) than conventional MRI. We present initial/1 year SWI data in 17 pediatric TBI patients.

Methods: Hospitalized pediatric patients with moderate/severe TBI (GCS score <13 or intracranial injury on CT scan) underwent MRI acutely (7–17d post TBI) and at 1 year. SWI was analyzed using an off-line post-processing program, "SPIN", to semi-automatically count and measure the volume of lesions. The number/volume of lesions between the initial and one year study were compared and correlated with initial injury and gender.

Results: We studied 17 patients (6–17 yrs;12 males; 13-motor vehicle, motorcycle, ATV or pedestrian accidents; 4 falls).The number of SWI lesions/patient on the initial MRI ranged from 0 to 299.The number/volume of hemorrhages on the acute MRI did not correlate with the initial GCS score. By 1 year, the number (up to 81.3%) and volume (up to 84.5%) of hemorrhages decreased. Surprisingly, 9/17 patients retained more than 50% of the original hemorrhagic volume. We did not observe gender differences in resolution of the number/volume of hemorrhages.

Conclusions: About 50% of moderate/severe TBI patients have persistent SWI hemorrhagic lesions 1 year after injury. There was no association in degree of hemorrhage resolution with gender or initial GCS. Further analysis will determine if there are regional differences in the resolution or persistence of hemorrhages, correlation with other clinical and imaging variables, associations with lesion location or specific neurological/neuropsychological outcomes.

Keywords: Neuroimaging

150. Neurophysiological Correlates of Impaired Statistical Learning in Infants with Tuberous Sclerosis Complex (TSC)

Tye C (London, UK), Nelson CA, Jeste SS

Objective: The ability to extract statistical patterns from visual input is present from early infancy, suggesting that such a learning mechanism may play an important role in cognitive development. Tuberous Sclerosis Complex (TSC) is associated with a variable cognitive profile and a high incidence of intellectual disability. Using event-related potential (ERPs) that can directly measure covert cognitive processes, this study investigated (i) the neurophysiological markers of statistical learning in TSC and (ii) the relationship between neurophysiological and behavioural correlates of TSC.

Methods: A visual statistical learning paradigm was administered to 13 infants with TSC (average age 19 months) and 12 age matched controls, during which ERPs in response to visual stimuli were measured (P1, N1, P3). Following habituation of pairs of coloured shapes, infants were presented with familiar sequences (100%) alternating with novel sequences (10%), with transitional probabilities defining between-stimulus boundaries (33%).

Results: Control infants demonstrated longer latency and greater amplitude for probabilistic compared to expected trials, suggesting discrimination of familiar sequences based on statistical probabilities. In contrast, TSC infants exhibited shorter latency and no amplitude difference for probabilistic compared to expected trials. These neurophysiological

abnormalities correlated with receptive and expressive language ability in the TSC group.

Conclusions: These findings indicate altered statistical learning in TSC from infancy that is associated with cognitive ability. The identification of early and robust risk markers of cognitive function may aid in clinical assessment and specific treatment strategies. Further work examining longitudinal changes in these neurophysiological markers and their relationship with behaviour is warranted.

Keywords: Neuroimaging

151. Lesion Volume and Localization in Acute Ischemic Basal Ganglia Stroke as Predictors of Dystonia

Goldfarb JA (Toronto, ON), Askalan R, Pontigon AM, deVeber G

Objective: Basal ganglia infarction occurs in nearly 50% of children with arterial ischemic stroke (AIS). Delayed onset dystonia develops in 21% of such children. The dystonia can be extremely disabling. Predictors of dystonia in children with basal ganglia AIS are not identified but would guide prognosis and selection for early treatment. The purpose of this study was to examine infarct volume and location within basal ganglia substructures for prediction of dystonia in childhood AIS.

Methods: We conducted a case-control analysis of 32 children with AIS involving basal ganglia, comparing 16 cases with dystonia to 16 control children without dystonia. Utilizing automated planimetry (Analyze 7.0) we calculated infarct volume and analyzed infarct location within deep grey matter substructures. We compared cases to controls with stratified exact conditional logistical regression.

Results: The development of dystonia was associated with an increased number of involved deep grey substructures (p-value=0.0308; OR=2.7; CI=1.1,10.7). Age at stroke, infarct volume, location within caudate head, globus pallidus interna or globus pallidus externa did not predict dystonia (p-value>0.05).

Conclusions: Surprisingly, simple lesion volume and lesioning of any given deep gray matter sub-structure are not predictive of dystonia. Rather, a more complex involvement of multiple deep grey structures puts children with AIS at increased risk for post-stroke dystonia. Additional future study may elucidate dystonia-specific lesion patterns.

Keywords: Neuroimaging, Neuromuscular disorders, Stroke

152. FMRI-navigated Transcranial Magnetic Stimulation over Supplementary Motor Area in Tourette Syndrome

Wu SW (Cincinnati, OH), Maloney T, Dixon SG, Horn P, Vannest J, Huddleston DA, Eaton K, Gilbert DL

Objective: To determine whether an inhibitory repetitive Transcranial Magnetic Stimulation protocol over Supplementary Motor Area (SMA) may reduce tics and motor cortical network activity in Tourette Syndrome (TS).

Methods: Randomized (1:1), double-blind, sham-controlled clinical trial of functional MRI (fMRI) - navigated, 30 Hz Continuous (inhibitory) Theta Burst Stimulation (cTBS) (Magstim® SuperRapid2) at 90% of resting motor threshold over SMA in 12 TS patients ages 10–22 years. Each patient received 8 trains of cTBS over 2 consecutive days. Comorbid ADHD (n=7), OCD (n=8), and stable concurrent medications (n=9) were permitted. Navigation (BrainSight®) utilized each individual's event-related fMRI signal. Primary clinical and cortical outcomes were: 1) Yale Global Tic Severity Scale (YGTSS) at one week; 2) fMRI event-related signal in SMA and Motor Cortex (MC) during a finger-tapping motor task.

Results: Pre-treatment ages (active mean 13.5, SD 3.9; sham mean 15.5, SD 4.0; p=0.4), comorbidities (both 4 of 6), and YGTSS (active mean 27.5, SD 7.4; sham mean 26.8, SD 4.8; p=0.9) were similar. One-week, post-treatment YGTSS did not differ (active mean 23.2, SD 9.8; sham mean 21.7, SD 7.7; p=0.4). Two-day post-treatment fMRI activation during finger tapping decreased significantly in active vs. sham groups for SMA (p=0.02), left MC (p=0.0004), and right MC (p<0.0001). No serious adverse events occurred.

Conclusions: Active, fMRI-navigated cTBS administered in 8 sessions over 2 days induced significant inhibition in the motor network (SMA, bilateral MC) but did not reduce tics. Protocol modifications may be needed to produce clinical benefits.

Sources of Funding: This study was funded by the Tourette Syndrome Association.

Keywords: Neuroimaging, Translational/experimental therapeutics

153. Acoustic Radiation Force Impulse Imaging for the Differentiation of Muscle Tissue Stiffness in Neuromuscular Disorders

Dastgir J (Bethesda, MD), Vuilerot C, Harrison K, Poon A, Donkervoort S, Leach M, Jain M, Meilleur K, Rutkowski A, Mankodi A, Bonnemann C

Objective: Acoustic Radiation Force Impulse (ARFI)-Imaging is an ultrasound-based operator independent elastography method enabling quantitative measurement of tissue stiffness. It involves mechanical excitation of tissue using acoustic pulses to generate localized displacements and result in shear-wave propagation (meters/second). This study aims to evaluate the sensitivity and specificity of ARFI-imaging for muscle tissue stiffness differentiation (fat vs. fibrous tissue) in select muscles of patients without muscle disease vs. those with collagen 6 myopathy (COL6), LAMA2 related muscular dystrophy (LAMA2), or Duchenne muscular dystrophy (DMD).

Methods: Inclusion criteria: 5–18 year old boys and girls without muscle disease and age-matched children diagnosed with COL6, LAMA2, or DMD. All participants underwent B-Mode ultrasound and ARFI imaging at anatomical landmarks for the greatest bulk of select upper and lower extremity muscles.

Results: Data from 85 (20 COL6; 10 DMD, 15 LAMA2, 40 unaffected) children will be available for analysis. Preliminarily, mean averaged velocity of all assessed muscles in unaffected participants was 1.43m/s, in COL6 -

1.21 m/s and in DMD - 1.53 m/s. For muscles assess individually, the most reproducibly distinguishing values were noted in the tibialis anterior muscle with average muscle velocities of 1.55 m/s in unaffected muscle tissue, vs. 1.17m/s in COL6 and 2.29 m/s in DMD.

Conclusions: ARFI can be used as a tool for the non-invasive assessment of muscle stiffness in neuromuscular disorders. Longitudinal data acquisition, validation as an outcome measure, and comparison to MRI data and motor function testing as it relates to this cohort is pending.

Keywords: Neuromuscular disorders

154. Common Data Elements for Muscle Biopsy Reporting

Dastgir J (Bethesda, MD), Rutkowski A, Alvarez R, Cossette S, Yan KE, Hoffmann R, Sewry C Hayashi Y, Moore SA, Goebel HH, Bonnemann C, Lawlor MW

Objective: Physicians commonly utilize the muscle biopsy to assist in the diagnosis of neuromuscular diseases. However, there is no current standard for evaluating or reporting on findings, and the resulting variability can impede accurate diagnoses and limit the utility of the muscle biopsy as a tool for clinical care and research. The National Institutes of Neurological Disorders and Stroke (NINDS) recently launched a Common Data Element (CDE) in order to standardize neuromuscular data collected in clinical reports.

Method: For this study, the authors adapted the NINDS Muscle Biopsy CDE to generate a form for prospective muscle biopsy reporting (CDE-R). This form was used to analyze a set of 49 reports from patients with a range of congenital muscle disorders enrolled in the Congenital Muscular Disease International Registry (CMDIR). Using the CDE-R as a checklist, data were extracted from each report and scored to determine the degree to which the report contained the recommended common data elements.

Results: Analysis of the data highlighted the lack of consistent reporting of key clinical features from the referring physicians to the pathologist and variability in the reporting of a range of pertinent positive and negative findings. However, when using only data extracted to the CDE-R to characterize these biopsies, we found a >80% concordance between the reported diagnosis and the diagnosis determined by a blinded pathologist.

Conclusions: Thus, we propose implementing a combined format for muscle biopsy reporting that consists of the CDE-R and a brief comment that interprets the data in support of a final diagnosis

Keywords: Neuromuscular disorders

155. Variations of Gait Patterns in Pediatric Charcot-Marie-Tooth Disease (CMT)

Acsádi G (Hartford, CT), Õunpuu S, Garibay E, Solomito M, Pierz K

Objective: Inherited peripheral neuropathy, or Charcot-Marie-Tooth disease (CMT), one of the most common pediatric neuromuscular diseases, has variable clinical presentation and progression. Ambulation is a significant quality of life indicator in CMT. The purpose of this retrospective study was to analyze gait patterns in children with CMT. Defining gait pathology based on specific kinematic deficits would allow a better understanding of gait abnormalities and treatment.

Methods: This retrospective study included 33 patients (age=12±4 years; 16 males/17 females; CMT1A: n=11; CMT2A: n=6; CMT2B: n=1; unknown: n=15). All of the patients underwent the following procedures: clinical examination (range of motion/muscle strength), motion analysis (kinematics/kinetics) and foot pressures.

Results: Gait analysis showed three distinct ankle kinematic patterns in terminal stance consistent with ankle plantar flexor weakness, cavus deformity and plantar flexor contracture: a) decreased dorsiflexion, b) normal peak dorsiflexion and c) excessive peak dorsiflexion. All patients showed delayed peak dorsiflexion in stance consistent with the most common impairment of ankle plantar flexor weakness. There were no correlations found between age, date of diagnosis and genetic type of CMT with gait patterns.

Conclusion: A better understanding of gait in pediatric CMT is the first step towards understanding the progression of neuropathy in terms of ambulatory deficits over time. Gait abnormalities in our cohort were related to the impairment at the foot and ankle. A prospective study of the natural history of gait pathology and correlation with other functional measures (e.g. CMTPeds) will be important to understand the disability progression and improve treatments.

Keywords: Neuromuscular disorders

156. Cardiomyopathy in Dystroglycanopathies

Lutz KL (Iowa City, IA), Ng B, Edens E, Reinking B, Stephan C, Mathews KD

Objective: Dystroglycanopathies (DGs) are muscular dystrophies characterized by deficient glycosylation of α-dystroglycan due to mutations in one of 13 known genes. The most commonly affected gene encodes fukutin related protein (FKRP). DGs include a variety of phenotypes including Walker-Warburg syndrome, muscle-eye-brain disease, and limb-girdle muscular dystrophy. All subtypes first manifest in childhood. There is limited description of cardiomyopathy in DGs. Here we describe prevalence and age of onset of cardiomyopathy in a cohort of people with DG in North America.

Methods: Restrospective analysis of all available echocardiogram reports from participants in the Dystroglycanopathy Natural History study at the University of Iowa. Cardiomyopathy was defined as ejection fraction <50%, shortening fraction <22%, or ventricular dilation.

Results: Echocardiogram reports were available for 35 participants. Average follow up was 3 years (0–15.75 years). Ten participants (29%) had cardiomyopathy. Of those with cardiomyopathy, 9 had FKRP mutations and 1 had fukutin mutations. Mean age at first abnormal echocardiogram was 22 years of age (range 3–43 years). We also found that participants homozygous for the common FKRP mutation, c.826C>A, demonstrated cardiomyopathy findings later

than those heterozygous for the mutation (mean 32 years of age vs. 14 years of age, respectively).

Conclusions: These results support screening for cardiomyopathy in people with DGs starting in childhood and consideration of cardioprotective medications in this population.

Keywords: Neuromuscular disorders

157. Pathophysiology of SMA Should Accommodate Weakness and Fatigue: the Diagnostic Value of the Six Minute Walk Test (6MWT)

Montes J (New York, NY), Blumenschine M, Dunaway S, Rao AK, CHiriboga C, De Vivo DC

Objective: The six minute walk test (6MWT) is a preferred end-point in Duchenne/Becker Muscular Dystrophy (DBMD) clinical trials, and used to measure weakness and fatigue in Spinal Muscular Atrophy (SMA). Progression of weakness and fatigue has not been studied.

Methods: Fifty-six patients performed the 6MWT (SMA=25; DBMD=31), ranging from age 4 to 49 years. Longitudinal data was collected in 24 patients (SMA=9; DBMD=15) at 0 and 12 months. 7 DBMD patients also were evaluated at 24 months. Percent-predicted distance was computed from normative values to determine weakness. Fatigue was determined by the decrement in distance from the first to sixth minute. Pearson correlation coefficients and paired sample t-tests evaluated fatigue and weakness.

Results: Weakness, was seen with SMA and DBMD (%-predicted distance=59.2%). Fatigue was prominent only in SMA (21.3%). DBMD patients showed little fatigue (6.1%). Correlation between %-predicted distance and fatigue was significant only in SMA ($R = -0.67$; $p<0.001$). Longitudinally, %-predicted distance was stable in SMA changing only 0.8%. In DBMD %-predicted distance declined over 12 (5.8%) and 24 months (11.8%), while fatigue remained minimal. In SMA, fatigue increased significantly (9.6%; $p=0.042$).

Conclusions: Both SMA and DBMD patients had weakness. Only the SMA group demonstrated fatigue related to weakness. Distance walked declined only in DBMD. In SMA, weakness did not change, but fatigue increased significantly. This discordance between weakness and fatigue implies different pathophysiologies. Recent studies have focused on central and peripheral SMA disturbances and our findings are consistent with these observations. Progressive fatigue appears to be a distinctive clinical signature of SMA.

Keywords: Neuromuscular disorders

158. Expectations and Decision Making in Clinical Trials for Duchenne and Becker Muscular Dystrophy

Peay HL (Richmond, VA), Sheffer H, Tibben A

Objective: Increased community knowledge of and access to clinical trials for Duchenne and Becker muscular dystrophy (DBMD) may amplify adaptive optimism, but also inappropriately high expectations. This study explored parental and clinician motivations and expectations for DBMD clinical trials.

Methods: We interviewed parents of children with DBMD and clinicians participating in clinical trials for DBMD. Interviews were transcribed and coded for thematic analysis.

Results: All parent participants (n=15) hoped for, and most expected, direct benefit to their child. Other motivators were a desire to affect the disease course; that "doing something is better than nothing;" and altruism. Most parents sought a trial and described making their decision before the informed consent (IC). The majority hoped for a cure but recognized this as unrealistic. Parents' reported expectations were inconsistent in different contexts. Some had difficulty differentiating expectations and optimistic hopes. Some reported efforts to temper expectations, or outside factors tempering expectations such as being in a placebo-controlled trial. Many parents described reductions to expectations and hopes over time. Clinicians (n=11) observed that families had unrealistic expectations and were motivated by desperation and hope for benefit more than altruism. They observed that parents' unmet expectations may prove detrimental to their well-being.

Conclusions: This study suggests a need for increased attention on directing expectations, and anticipatory guidance regarding challenges to optimistic hopes. As parents reported decision making before IC, this may be most effective prior to IC. Further studies are needed to identify outcomes of inappropriately high expectations in DBMD clinical trials.

Keywords: Neuromuscular disorders

159. Congenital Myasthenic Syndrome (CMS), Autophagic Myopathy, and Cognitive Dysfunction Caused by Mutations in DPAGT1

Selcen D (Rochester, MN), Shen XM, Li Y, Wiben E, Engel AG

Objective: To identify the underlying genetic defect in two CMS patients with CNS involvement.

Methods: Clinical data, whole exome sequencing, in vitro electrophysiology, muscle histochemistry, immunoblot, electron microscopy, and transferrin isoelectric focusing

Results: Patient 1 is a16-year-old mentally retarded girl with severe generalized CMS since infancy. One of her siblings is also affected and has autistic features. Patient 2 is a 14-year-old girl with mild cognitive deficits and progressive limb-girdle CMS since infancy. Both respond poorly to anti-AChE therapy. Intercostal muscle specimens in both show small tubular aggregates in type 2 fibers, type1 fiber atrophy, and a vacuolar myopathy with autophagic features. Endplate studies reveal that quantal release, postsynaptic response to acetylcholine quanta, and endplate AChR content are reduced to ~50% of normal. Quantitative EM of 65 endplate region s shows hypoplastic endplates, very small nerve terminals, and poorly differentiated postsynaptic regions. Neither patient harbors mutations in currently recognized CMS disease genes but exome sequencing in each identified two heteroallelic mutations in DPAGT1 coding for dolichyl-phosphate N-acetylglucosamine phosphotransferase, an enzyme subserving protein N-glycosylation.

Immunoblots of muscle extracts probed by two different antibodies demonstrates reduced to absent glycosylation of ~70 kDa proteins in Patient 1 but not in Patient 2. Transferrin isoelectric focusing is abnormal in Patient 2 and the affected brother of Patient 1.

Conclusions: (1) DPAGT1 mutations result in both pre- and postsynaptic structural and electrophysiologic abnormalities. (2) Hypoglycosylation of synapse-specific proteins causes defects in motor as well as central synapses.

Sources of Funding: Support: NIH and MDA

Keywords: Neuromuscular disorders

160. Socioeconomic Deprivation in Cerebral Palsy: a Population-Based Study

Oskoui M, Pampalon R, Gamache P, Shevell MI

Aim: To examine the association between area-level socioeconomic deprivation measures and cerebral palsy phenotype including subtype, severity and comorbidities; and to examine the degree to which these associations are mediated by differences in premature birth.

Methods: Population-based data from a provincial cerebral palsy register were used for analysis, using a combined area-based deprivation index as the measure of socioeconomic status.

Results: A socioeconomic gradient was seen in our cohort in both mobility and cognitive impairment, despite a lack of differences in maternal and perinatal factors and underlying imaging findings. This gradient was seen only in children born prematurely and not those born at term.

Conclusion: Contextual socioeconomic factors can impact the disease severity in CP. Further study is warranted to identify potentially modifiable factors that would lead to targeted interventions for vulnerable populations.

Financial Disclosure and funding source: The Registre de la Paralyse Cérébrale de Québec (REPACQ) has been funded by the Réseau de recherche sur le développement, la santé et le bien-être de l'enfant (RSDE) des Fonds de Recherche en Santé du Québec (FRSQ) and NeuroDevNet National Centre of Excellence. No funding sources were involved in the design, analysis or manuscript preparation of this study Conflict of interest: The authors have no conflict of interest to report.

Keywords: Neuromuscular disorders

161. Population Pharmacokinetic Analysis of Oral Baclofen in Pediatric Patients with Cerebral Palsy

He Y (Silver Spring, MD), Brunstrom-Hernandez JE, Thio LL, Lackey S, Gaebler-Spira D, Kuroda MM, Stashinko E, Hoon AH, Vargus-Adams J, Stevenson RD, Lowenhaupt S, McLaughlin JF, Christensen A, Dosa NP, Butler M, Schwabe A, Lopez C, Roge D, Kennedy D, Tilton AH, Krach LE, Lewandowski A, Jusko WJ

Objective: Oral baclofen is used for treatment of spasticity in adults and children with cerebral palsy (CP). Pharmacokinetic (PK) information is lacking in the pediatric population. This study characterizes the PK properties of oral baclofen to support clinical use in children with CP.

Subjects and Methods: Children (2–16 years) with CP were titrated on oral baclofen from 2.5 mg TID to a maximum tolerated dose of up to 20 mg QID. A PK visit typically followed titration of 10 to 12 weeks. Serial R- and S-baclofen plasma concentrations were measured for up to 16 hours in 49 subjects. Population PK modeling was performed using NONMEM 7.

Results: R- and S-baclofen showed essentially identical concentration-time profiles. Both enantiomers exhibited linear and dose/kg-proportional PK and there were no gender differences. A two-compartment model with linear elimination and transit absorption steps adequately described concentration-time profiles of both baclofen enantiomers (see figure). The mean population estimate of apparent clearance (CL/F) was 0.273 L/hr/kg with 33.4% interindividual variability (IIV), and the apparent volume of distribution (Vss/F) was 1.16 L/kg with 43.9% IIV. Delayed absorption was expressed by a mean transit time (MTT) of 0.389 hr with 83.7% IIV. The population PK of oral baclofen shows highly consistent behavior in children with CP, except for variability in the absorption process.

Conclusion: The pharmacokinetics of oral baclofen exhibited dose proportionality and was adequately described by a two-compartment model. Current dosing recommendations apply to children and are not complicated by PK issues.

Keywords: Neuromuscular disorders, Translational/experimental therapeutics

162. Quality of Life One Year after Arterial Ischaemic Stroke in a Population-Based Cohort

Mallick AA (Bristol, UK), Ganesan V, Kirkham FJ, Fallon P, Hedderly T, McShane MA, Parker AP, Wassmer E, Wraige E Amin S Edwards HB O'Callaghan FJ

Objective: To assess the quality of life (QoL) of children after arterial ischaemic stroke (AIS) and analyse factors associated with impaired QoL.

Methods: A population-based cohort of 96 children (aged >28 days to <16 years) residing in southern England with AIS onset between July 2008 and June 2009 were followed-up at one year. QoL was assessed by the Pediatric Quality of Life Inventory (PedsQL). Children were also assessed using the Pediatric Stroke Outcome Measure (PSOM) and the Recurrence and Recovery Questionnaire (RRQ). Cognitive outcome was also assessed using a short form of the Wechsler Intelligence Scale for Children (WISC).

Results: Parental-proxy PedsQL scores were available for 62 children and child self-reported PedsQL scores were available for 34 children. The mean total-scale PedsQL score by parental-proxy was 75.5 (SD 20.2) which was significantly below the UK norm for healthy children (84.6, $p=0.0008$). The mean total-scale PedsQL score by self-report was 83.0 (SD 15.7) which was not significantly different from the UK norm (83.9, $p=0.72$). Increasing total PSOM scores (greater neurological impairment) was associated with lower parental ($p<0.0001$) and self-reported ($p<0.0001$) PedsQL scores. Higher WISC scores were

associated with higher parental ($p=0.005$) and self-reported ($p=0.001$) PedsQL scores. In a multivariate analysis PSOM sensorimotor deficits, female gender, and the presence of recurrent headache were all independently associated with lower parental-proxy PedsQL scores.

Conclusions: Parental-proxy QoL scores are reduced one year after AIS but child self-reported scores are not. The presence of sensorimotor deficits is the most important predictor of reduced QoL.

Keywords: Stroke

163. Maternal High-Fat Diet Influences Neuroprotective Efficacy of Docosahexaenoic Acid in Neonatal Rats

Barks JDE (Ann Arbor, MI), Liu YQ, Shangguan GY, Djuric Z, SIlverstein FS

Objective: Both maternal pre- and post-natal dietary supplementation with the omega-3 fatty acid docosahexaenoic acid (DHA) and acute post-insult DHA injections (2.5 mg/kg) improve outcomes after hypoxic-ischemic brain injury in neonatal rodents. However, prior studies were performed in animals fed a diet (14% fat-derived calories) that does not replicate the dietary fat intake of US women of childbearing age (34% fat-derived calories). We re-assessed DHA neuroprotective efficacy in a translationally relevant metabolic milieu.

Methods: Pregnant Wistar rats received a diet that replicates the typical US fat intake from mid-gestation ["high-fat diet" (HFD)]. Their progeny underwent right carotid artery ligation, followed by 60 min 8% oxygen exposure on postnatal day 7, and subsequent injections of albumin-conjugated DHA (2.5, 5, or 10 mg/kg) or equal amounts of albumin ($n>7$/group/dose). 1h later, pups underwent brief cooling (3h, 30oC) to evaluate interactions between DHA and hypothermia in this metabolic milieu. Sensorimotor (forepaw placement and grip strength) and pathology outcomes were examined 1–3 weeks later.

Results: In contrast with findings in conventionally fed animals (Neonatology, in press), DHA 2.5 mg/kg was ineffective. Treatment with both higher DHA doses, coupled with hypothermia, resulted in near normalization of sensorimotor function measures (ANOVA, $p<0.001$); measures of overall brain damage were unaffected.

Conclusions: Although maternal HFD reduced DHA's neuroprotective potency, post-hypoxia-ischemia DHA treatment at higher doses markedly improved functional recovery. Maternal diet during pregnancy/lactation may exert potent influences on mechanisms of brain injury and repair; this variable must be considered in optimizing pre-clinical studies to evaluate neonatal neuroprotection interventions.

Sources of Funding: NIH R21 AT006636

Keywords: Stroke, Translational/experimental therapeutics

164. Targeting GABAA Receptors for Treatment of Behaviors following Prenatal Cocaine Exposure

Bamford NS (Seattle, WA), Wang W, Bamford IJ, Julyanti M

Objective: Prenatal cocaine exposure (PCE) can produce abnormal behaviors in affected children. Studies in laboratory animals suggest that abnormal dopamine-dependent behaviors following PCE are related to a reduction in GABA interneuron migration, function, and connectivity. We hypothesized that a GABAA receptor antagonist in vivo might treat behaviors and striatal synaptic plasticity following PCE.

Methods: Mice were exposed to cocaine in utero (20 mg/kg, s.c., twice daily from E8–E18). Controls included mice born to saline-treated, pair-fed dams. Pups were fostered to untreated dams at P0 and beginning on P30, mice from each group received daily treatment with the GABAA receptor antagonist picrotoxin (1 mg/kg i.p.) or saline. On P60, mice were subject to behavioral tests or slice electrophysiological recordings in striatal GABA interneurons and striatal output neurons.

Results: PTX reversed abnormal D2 receptor-mediated corticostriatal activity and improved ambulatory responses to repeated amphetamine, while having no untoward effects. Further, while PTX had no effect on hippocampal function, as measured by novel object recognition testing, it enhanced novel object discrimination in PCE mice.

Conclusions: Abnormal GABA interneuron function has been implicated in many neuropsychological disorders and results suggest that aberrant GABAA autoreceptor signaling is necessary and sufficient to cause abnormal DA-dependent behaviors and corticostriatal signaling following PCE. Palliative therapies aimed at ameliorating symptoms observed in children with PCE are lacking and we show that targeted therapy using a GABAA receptor antagonist can safely and effectively treat behaviors and striatal synaptic plasticity that occurs in mice following PCE.

Keywords: Translational/experimental therapeutics

165. Mechanisms of Prefrontal Microcircuit Dysfunction in Animal Models of Autism

Brumback AC (San Francisco, CA), Sohal VS

Objective: Abnormal electrical activity in the autistic brain is thought to result from an imbalance between neuronal excitation and inhibition. One main hypothesis for the proposed imbalance is that there is long-range hypoconnectivity but local hyperconnectivity in cortical microcircuits. Many of the major output neurons of cortex are located in Layer 5 (L5), and our lab recently showed that L5 of medial prefrontal cortex (mPFC) contains at least two distinct subpopulations of pyramidal neurons: Type A cells project subcortically, have prominent hyperpolarization-activated currents (Ih), thick-tufted apical dendrites, and express dopamine D2 receptors, whereas Type B neurons project to the contralateral cortex, have small Ih currents, thin-tufted apical dendrites, and lack D2 receptors. We hypothesize that in autism, the proposed pathological changes do not come about via global changes in the overall level of cortical excitation or inhibition, but rather reflect an imbalance of activity between these two subtypes of cortical pyramidal neurons.

Methods: We performed whole-cell electrophysiological recordings from acute mPFC brain slices of adult mice

exposed to valproate (VPA) or saline at embryonic day 10.5.

Results: Our preliminary data suggest that in the VPA mouse model of autism, there is a defect in action potential generation in Type B mPFC neurons but not in Type A cells.

Conclusions: By elucidating how these cellular alterations relate to synaptic, EEG, and behavioral abnormalities, our studies may lead to new ways of understanding neuronal circuit dysfunction in autism, as well as novel biomarkers and therapies for this prevalent neuropsychiatric disease.

Sources of Funding: Dr. Brumback's research is supported by NIH grant R25NS070680-02S1 from the National Institutes of Neurological Disorders and Stroke under the Research Education (R25) Program for Residents and Fellows in Neurology and Neurosurgery.

Keywords: Translational/experimental therapeutics

166. Absent Premotor Potentials in Children with Primary Motor Stereotypies

Houdayer E (Bethesda, MD), Walthall J, Belluscio B, Vorbach S, Hallett M, Singer HS

Objective: The underlying pathophysiologic mechanism for Complex Motor Stereotypies in children is unknown with hypotheses ranging from an arousal to a motor control disorder. Premotor potentials, representing the activation of cerebral areas involved in the generation of movements, precede and accompany self-initiated voluntary movements. The goal of this study was to compare cerebral activity associated with stereotypies to that seen with voluntary movements in children with primary complex motor stereotypies.

Methods: Electroencephalographic (EEG) activity synchronized with video recording was recorded in 10 children diagnosed with primary motor stereotypies (5 boys/5 girls, ages 7–14 years, onset before age 4) and 7 controls. EEG activity related to stereotypies and self-paced arm movements were analyzed for presence or absence of a Bereitschaftspotential (BP), a steep negativity beginning about one second before the onset of a voluntary movement.

Results: A BP preceded a self-paced requested arm movement in 8 out of 10 children with motor stereotypies and in 6 out of 7 controls. These observed BPs did not differ between groups. In contrast, no BP was identified before the appearance of a complex motor stereotypy.

Conclusions: Unlike voluntary movements, stereotypies are not preceded by a BP. This indicates that premotor areas are not involved in the preparation of these complex movements and suggests that stereotypies are initiated by mechanisms different from voluntary movements. Further studies are required to determine the site of the motor control abnormality within cortico-striatal-thalamo-cortical pathways and to identify whether similar findings would be found in children with secondary stereotypies.

Sources of Funding: This work was supported in part by the: Nesbitt-McMaster Foundation Fyssen Foundation NINDS Intramural Research Program

Keywords: Translational/experimental therapeutics

Late Breaking Abstracts

167. Therapeutic Hypothermia Reduces Progression of Hypoxic Ischemic Brain Damage in the Term-Equivalent (P10) Rat Pup

Pierce L (New York, NY), Patel S, Ciardiello A, Vannucci S, Perlman JM

Objective: Therapeutic hypothermia (TH), when initiated early, is effective for reducing brain injury following intrapartum hypoxia-ischemia (HI). However, protection is incomplete and long-term outcome not well defined. Previous TH studies in rats have used postnatal day(P) 7 rats, representing 32–36 weeks GA. Our objective was to characterize short and longterm effects of TH after HI in a term-equivalent P10 rat.

Methods: 7 litters of P10 rats of both sexes were subjected to unilateral HI (65 min, 8% O_2). Following return to normoxia, pups were randomly assigned to normothermic (N) (35.50C) or TH (30.50C; target rectal temperature of 320C) recovery for 4 hours. Pups were rewarmed and returned to the dam. Damage was evaluated by MRI (7T) at 2 weeks and H&E at 6 weeks. Additional cohort was evaluated at 24 hours for neutrophil infiltration.

Results: Mean rectal temperature of TH pups was 31.60C; 20% did not reach 320C, and N pups = 37.20C. At 24 hrs neutrophils were reduced by TH ($p < 0.005$), T2 images showed significant protection with TH in pups that reached target temperature ($p < 0.05$). At 6 wks, 5/7 TH pups had no damage, 2/7 were mild-moderate vs 7/9 normothermic pups with extensive damage.

Conclusion: TH in the term-equivalent HI rat prevents and/or limits progression of brain damage; an effect that was temperature dependent. TH reduces the early neutrophil response to HI, which may minimize progression by limiting inflammation. TH in the P10 rat offers a more translational paradigm for future studies.

Keywords: Neonatal neurology, Translational/experimental therapeutics

168. Rett Syndrome, MeCP2, Rictor, and Neuronal Size

Narayanan V (Phoenix, AZ), Rangasamy S, Olfers SS, Yin H

The MeCP2 A140V missense mutation causes non-syndromic X-linked mental retardation. We created a mouse model expressing the MeCP2 A140V mutation. Pathological studies in A140V mice show increased cell packing density, and diminished dendritic branching, similar to what is seen in Rett brain tissue. Neuronal size (staining with class III beta tubulin) in the A140V hippocampus is reduced by 25% compared to male wild-type animals. Nuclear size (Lamin B staining) of mutant neurons is reduced by 13% compared to wild-type. There is a similar reduction in soma and nuclear size of cultured hippocampal neurons from mutant male animals. We explored mTOR pathway molecules in MeCP2 A140V mutant mice and found a selective decrease in Rictor protein (component of the mTORC2 complex) in brain homogenates of mutant male animals. Treatment of cultured mutant neurons with IGF-1 (100 ng/

ml for 24 hrs) rescued the neuronal size phenotype. We generated female animals heterozygous for A140V mutation (maternal X) and an X-linked GFP gene (paternal X). In cultures prepared from such female (A140V:X-eGFP) pups, we can distinguish neurons expressing mutant MeCP2 (GFP-) vs. WT MeCP2 (GFP+) in a single coverslip. In such cultures, there is a 25% reduction in soma size of neurons expressing mutant MeCP2 compared to WT. Primary neuronal cultures from female carrier pups were plated in a 96-well format, stained with anti-tubulin, and imaged in a high-throughput high-content system. This is being developed into a high-throughput screen for novel compounds that rescue the neuronal size in mutant neurons, without affecting normal neurons.

Sources of Funding: Supported by a grant from the Barrow Neurological Foundation (VN)

Keywords: Genetics, Translational/experimental therapeutics

169. Aicardi-Goutieres Syndrome (AGS) – Phenotypic Variability and Diagnosis in a Series of Cases Using Whole Exome and RNA Sequencing

Narayanan V (Phoenix, AZ), Szelinger S, Corneveaux JJ, Schrauwen I, Siniard AL, Kurdoglu AA, Malenica I, Ramsey K, Craig DW, Huentelman MJ

AGS is an autosomal recessive disorder, with causal mutations reported in 6 genes (TREX1, RNAseH2A, RNAseH2B, RNAseH2C, SAMHD1, ADAR) to date. Here we describe 3 families with affected children in whom AGS was suspected and causal variations identified by family based whole-exome sequencing. Each study participant was pooled into multiplexed libraries of 6 total samples by TruSeq Exome Enrichment v2 chemistry and sequenced on two lanes of a HiSeq2000 flowcell to a mean target depth of 97±70X. Family 1: a single affected male and parental consanguinity, initial clinical diagnosis of leukodystrophy; conventional testing was negative. Exome sequencing uncovered a homozygous variant in exon 3 of RNASEH2B that is highly conserved, deleterious and never before seen in any public SNP databases. Both parents were identified as carriers. Family 2: a single affected female with normal development; progressive encephalopathy after immunization at 13 months. Exome sequencing uncovered compound heterozygous variants in Exons 2 and 9 of (ADAR1), both highly conserved and deleterious. One of the causal variants is a previously described risk allele for AGS cases. Family 3: two affected boys, the initial clinical diagnosis was acute disseminated encephalomyelitis (ADEM); questioned after the younger sibling developed a subacute encephalopathy. Exome sequencing uncovered deleterious compound heterozygous variants in Exon 2 and 8 of RNASEH2A. AGS may be more prevalent than previously thought and should be considered in cases of acute leukoencephalopathy, following infection or immunization. Whole exome sequencing may be an efficient approach to diagnosis, and discovery of new genes linked to AGS.

Keywords: Demyelinating disorders, Genetics, Infections/Neuroimmunology

170. Can You Fine-tune the Ketogenic Diet?

Selter J (Baltimore, MD), Turner Z, Kossoff EH

Background: Although the ketogenic diet (KD) is effective in approximately 50% of children with refractory epilepsy, some children on the diet are not fully controlled. In these situations, doctors often begin "fine-tuning" the KD.

Methods: A retrospective chart review was performed of 200 children that started the KD at Johns Hopkins Hospital between October 2007 and June 2013. Ten dietary/supplement changes were identified as the most commonly implemented. Medication adjustments were also reviewed. Patient records were reviewed over the entire KD duration up to a maximum of 4 interventions per child. Success was defined as a documentation of >50% seizure reduction after a change.

Results: The majority, 156 (78%), had at least one intervention. A total of 391 distinct and occasionally concurrent interventions occurred, of which 265 were made specifically for seizure control. Overall, there was an 18% chance that any intervention would be successful, but only a 3% chance of resultant seizure freedom. The likelihood of success did not decrease with each subsequent intervention. There was a trend towards medication adjustments being more successful than dietary modifications (24% vs. 15%, $p = 0.08$). Of the dietary intervention s, increasing ratio, carnitine, and MCT oil addition were similar and more likely to help than reducing calories.

Conclusions: These findings suggest that fine-tuning the KD is helpful in approximately 1 in 5, even after 12 months of use. Medication adjustment and dietary modification lead to similar outcomes, therefore both can be tried if the KD is not meeting seizure control expectations.

Keywords: Epilepsy and other paroxysmal disorders

171. Cerebellar Grey Matter and Lobular Measures Correlate with Core Autism Symptoms

Mostofsky S (Baltimore, MD), D'Mello A, Croceti D, Stoodley CJ

Objective: Structural differences in the cerebellum are among the most consistent neuroanatomical findings in autism spectrum disorder (ASD). We investigated grey matter (GM) and volumetric measurements of the cerebellum in ASD children compared to typically-developing (TD) children, and examined the relationship between cerebellar structure and core ASD symptoms.

Methods: Voxel-based morphometry (VBM) was used to compare whole-brain GM in 33 ASD and 33 TD children (mean age 10.6±4.4 years; range 8–13 years). The cerebellar SUIT atlas was used to compute volumetric measurements of individual cerebellar lobules. Correlations were calculated between the autism diagnostic scales and the VBM and volumetric data.

Results: VBM revealed reduced GM in ASD children bilaterally in cerebellar lobule VII (Crus I/II). Reduced GM in right Crus I/II and lobule VIII significantly correlated with poorer scores on the Autism Diagnostic Observation Schedule (ADOS). More impaired scores on the Autism Diagnostic Interview (ADI) Communication subscale correlated with lower GM bilaterally in Crus I/II. The SUIT volumetric analysis revealed larger vermis lobule VIIIA and a trend for smaller

right Crus I in the ASD group. Larger VIIIA was associated with poorer ADI-repetitive behavior scores, and smaller right Crus I correlated with poorer ADOS-Communication+Social and ADI-repetitive behavior scores.

Conclusions: Using two analytic approaches, we showed reduced cerebellar Crus I/II GM in ASD, a region which connects to prefrontal and parietal association areas. Importantly, cerebellar GM volume and lobule volumes significantly correlated with ASD severity, providing further evidence of a role for the cerebellum in ASD etiology.

Keywords: Neuroimaging

172. Exome Sequencing Identifies a Novel SMCHD1 Mutation in Facioscapulohumeral Muscular Dystrophy 2

Kang P (Boston, MA), Mitsuhashi S, Boyden SE, Estrella EA, Jones TI, Rahimov F, Yu TW, Darras BT, Amato AA, Folkerth RD, Jones PL, Kunkel LM

Objective: FSHD2 is a rare form of facioscapulohumeral muscular dystrophy (FSHD) characterized by the absence of a contraction in the D4Z4 macrosatellite repeat region on chromosome 4q35 that is the hallmark of FSHD1. Hypomethylation of this region is common to both subtypes. Recently, mutations in SMCHD1 combined with a permissive 4q35 allele were found to be the cause of FSHD2. The objective of this study was to identify a causative mutation in SMCHD1 in another family with FSHD2.

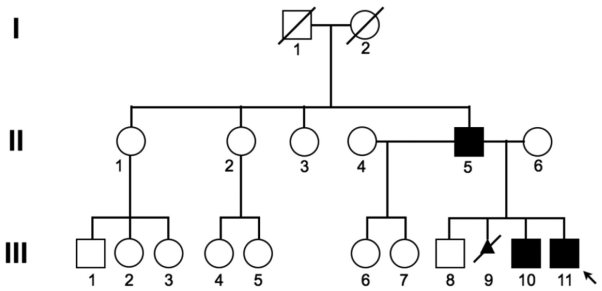
Methods: Linkage analysis, whole exome sequencing, Sanger sequencing, and bisulfite sequencing were performed on DNA samples from members of an autosomal dominant family with a phenotype characteristic of FSHD whose affected individuals did not have deletions in the D4Z4 macrosatellite repeat region. DUX4 expression analysis was performed on RNA that was extracted from the muscle tissue of one affected individual.

Results: Biopsy of biceps brachii in one affected individual demonstrated lobulated fibers and dystrophic changes. We identified a novel p.Lys275del SMCHD1 mutation in this family that alters a highly conserved amino acid in the ATPase domain. Decreased methylation of the 4qA allele was found in the DNA of two affected individuals compared to two unaffected individuals. DUX4 expression was confirmed in the muscle of one affected family member.

Conclusions: Given the clinical presentations, the absence of a deletion in the D4Z4 macrosatellite repeat region, the previous report of SMCHD1 mutations in FSHD2, and our genetic findings, we conclude that the SMCHD1 mutation is the likely cause of the disease in this family.

Keywords: Genetics, Neuromuscular disorders

Sources of Funding: This study was supported by the William Randolph Hearst Fund at Harvard Medical School (SM), Muscular Dystrophy Association (MDA) Research Grant 186796 (PBK), NIH R01 NS080929 (PBK), the Association Française contre les Myopathies grant 15700 (TIJ, PLJ), Muscular Dystrophy Association (MDA) Development Grant 202863 (FR), and the Bernard F. and Alva B. Gimbel Foundation (LMK). Microarray genotyping and Sanger DNA sequencing experiments were performed in the Molecular Genetics Core Facility at Boston Children's Hospital, supported by NIH P30 HD18655 through the Intellectual and Developmental Disabilities Research Center and NIH P50NS40828 through the Neuromuscular Disease Project.



173. Improving on Time Anticonvulsant Administration during the Home-to-Hospital Transition

Jones C (Columbus, OH), Raman VT, DeVries SP, Cole JW, Tobias J

Objective: Children with epilepsy are at increased risk of missing scheduled anticonvulsants during the home to hospital transition.[1,2] Missing anticonvulsants during this transition has been associated with an increased risk for breakthrough seizures and the consequences of seizures.[3] It is a national standard of care that children receive their anticonvulsants even while NPO. We undertook a quality improvement project to improve anticonvulsant administration during the home to hospital transition for children with epilepsy under gong procedures under anesthesia.

Methods: Using the methodology of the Institute for Health Care Improvement we created Key Driver Diagrams and undertook interventions based on these drivers. Major interventions included increasing awareness of the problem, feedback on our successes and failures and education on medications administration and alternatives when children are NPO.

Results: We have increased the percentage of children receiving their anticonvulsants prior to procedures requiring anesthesia from 76% to 88% (p value =0.02). We increased from 23% to 91% (p value= .0001) the number of children who received their anticonvulsant in the hospital prior to their procedure who had not received it at home. (Graph Attached)

Conclusion: Using a team based approach with anesthesiology and neurology will were able to significantly improve anticonvulsant administration for children with epilepsy during the home to hospital transition. Missed anticonvulsant administrations during the home to hospital transition can and should be prevented and we have demonstrated that using accepted quality improvement methodology they can be. Our success can provide guidance for addressing this problem

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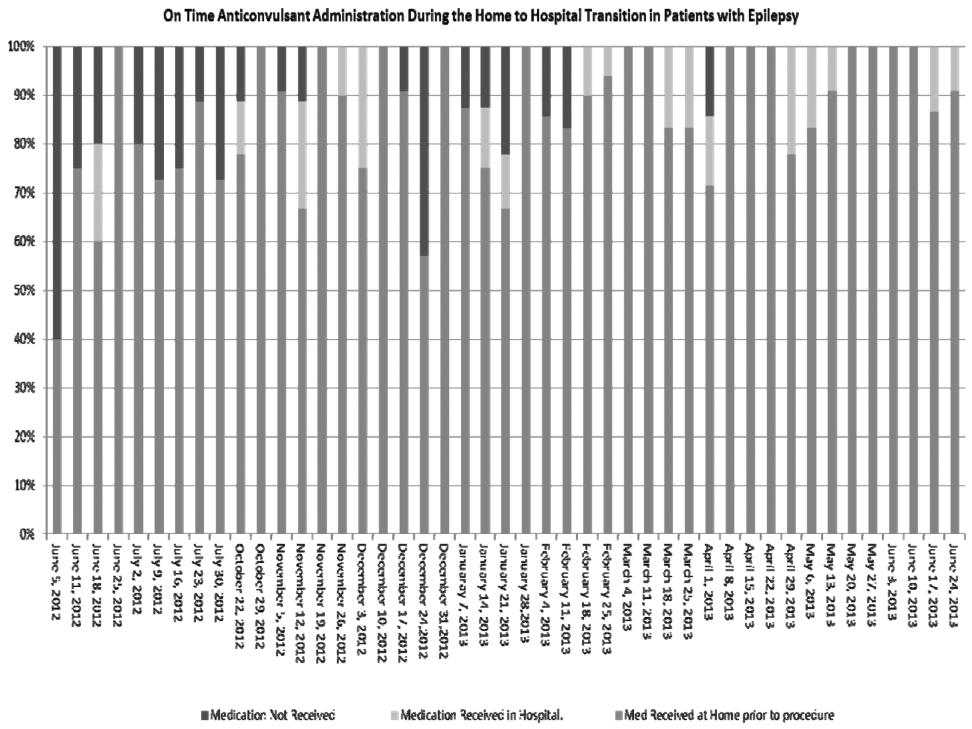

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Keywords: Epilepsy and other paroxysmal disorders, Translational/experimental therapeutics

174. Significant Time Lag from Initial Concerns to Diagnosis of Fragile X in Children

Gabis L (Israel), Hochberg O, Banet-Levi Y, Shilon-Hadass A, Leon O, Shefer S

Objective: Fragile X syndrome (FXS) is the most prevalent known genetically inherited cause for autism and intellectual disability, highly symptomatic in males and occasionally in females, mildly symptomatic in some carriers. Prevalence of carrier state (58–199 CGG repeats) In Israel is 1:120. Presenting symptoms and physical features might be non-specific, hence evaluation, especially in girls, might render different paths until specific genetic diagnosis is made. We assessed lag between presenting symptoms to genetic diagnosis.

Methods: Initial concerns, presenting symptoms, evaluation schedule, current medical needs, comorbid disorders and CGG repeats were acquired through interviews with families.

Preliminary Results: Initial 60 screened patients (13 females), from 40 families revealed that 13 families (20%), had more than one child with FRAX. In less than 20% diagnosis was made below first year. Mean age of first concern- 13.6 months boys, 36.8 months girls, definitive diagnosis made- boys 35.5 months, girls 67 months. Presenting symptoms, raised in 67% by parents and 20% by health care professionals, were motor delay in 48%, language delay in 20%, poor eye contact in 10%, behavioral difficulties in 10% (girls). Only 60% were subsequently referred to specialist while 20% parents were reassured. 84% of multiplex families had another child with FXS before index case diagnosed.

Conclusions: Fragile X syndrome is prevalent and highly symptomatic, however, underdiagnosed and frequently diagnosis is delayed until a second sibling is born with the disorder. In view of research advances and medical needs across ages, increased awareness to early diagnosis in non-specific delays- is warranted.

Keywords: Genetics