

# ANA 2023 Program

## Sunday Poster Sessions

### Cerebrovascular Disease

#### **S100. A Caregiver Approach to Prevention of Aspiration Pneumonia in Stroke Patients at UTHs-Adult Hospital, Lusaka; an Interventional Prospective Study**

**Dickson Munkombwe, MBChB<sup>1</sup>**, Faith Simushi, MBChB<sup>1</sup>, Frighton Mutete, MBChB<sup>2</sup>, Chilando Mulenga, MBChB<sup>2</sup>, Naluca Mwendaweli, MBChB<sup>1</sup>, Deanna Saylor, MD, MHS, Associate Professor of Neurology<sup>3</sup>, Dominique Mortel, MD<sup>4</sup>.

<sup>1</sup>University of Zambia, School of Medicine - Department of Internal Medicine, Lusaka, Zambia, <sup>2</sup>University Teaching Hospitals - Adult Hospital, Department of Internal Medicine, Lusaka, Zambia, <sup>3</sup>Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>4</sup>Department of Neurology, Brown University, Providence, Providence, RI, USA.

#### **S101. A Case of Unprovoked Catastrophic Antiphospholipid Syndrome Who Underwent Venous Thrombectomy**

**Rachael Cella, B.S.<sup>1</sup>**, Zoha Sarwat, B.S.<sup>1</sup>, Shivam Patel, B.S.<sup>1</sup>, Anvesh Balabhadra, MD<sup>1</sup>, Syed Daniyal Asad, MD<sup>2</sup>, Tapan Mehta, MD<sup>2</sup>. <sup>1</sup>University of Connecticut Health Center, Farmington, CT, USA, <sup>2</sup>Hartford Hospital, Hartford, CT, USA.

#### **S103. A Presentation of Anterior Inferior Cerebellar Artery Syndrome in a Young Male with Non-Compaction Cardiomyopathy**

**Neda Jafri, DO**, Savanna Dasgupta, DO, Hermann C. Schumacher, MD. Cooper University Hospital, Philadelphia, PA, USA.

#### **\*S104. A Randomized Controlled Trial of Transcranial Direct Current Stimulation in Subacute Aphasia**

**Melissa D. Stockbridge, Ph.D., CCC-SLP<sup>1</sup>**, Jordan Elm, Ph.D.<sup>2</sup>, Bonnie Breining, Ph.D.<sup>1</sup>, Donna C. Tippet, M.P.H., M.A., CCC-SLP<sup>1</sup>, Rajani Sebastian, Ph.D., CCC-SLP<sup>1</sup>, Christy Cassarly, Ph.D.<sup>2</sup>, Abeba Teklehaimanot, M.S.<sup>2</sup>, Leigh Ann Spell, Ph.D., CCC-SLP<sup>3</sup>, Shannon M. Sheppard, Ph.D., CCC-SLP<sup>4</sup>, Emilia Vitti, CCC-SLP<sup>1</sup>, Kristina Ruch, CCC-SLP<sup>1</sup>, Emily B. Goldberg, CCC-SLP<sup>3</sup>, Catherine Kelly, CCC-SLP<sup>1</sup>, Lynsey M. Keator, Ph.D., CCC-SLP<sup>3</sup>, Julius Fridriksson, Ph.D., CCC-SLP<sup>3</sup>, Argye E. Hillis, M.D., M.A.<sup>1</sup>. <sup>1</sup>Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>Medical University of South Carolina, Charleston, SC, USA, <sup>3</sup>University of South Carolina, Columbia, SC, USA, <sup>4</sup>Chapman University, Orange, CA, USA.

#### **S105. A Review of Paradoxical Brain Emboli Secondary to Intrapulmonary Shunts**

**Kimberly Boldig, DO<sup>1</sup>**, Marwan Shaikh, MD<sup>2</sup>. <sup>1</sup>University of Florida College of Medicine - Jacksonville, Jacksonville, FL, USA, <sup>2</sup>Mayo Clinic, Jacksonville, FL, USA.

#### **\*S106. Absence Of Chordin-Like 1 Prevents Loss of GluA2 and Improves Motor Recovery in a Mouse Model of Stroke**

**Eileen Collyer, PhD**, Bridget R. Boyle, PhD (Candidate), Yolanda Gomez-Galvez, PhD, Lorraine Iacovitti, PhD, Elena Blanco-Suarez, PhD. Thomas Jefferson University, Philadelphia, PA, USA.

#### **\*S107. ANA Futures: Evaluation of the ANA Junior and Early Career Committee 2022 Longitudinal Mentoring Scheme for Medical Students and Neurology Residents**

**Hendrik J. Greve, PhD<sup>1</sup>**, Omar M. Al-Janabi, MD PhD<sup>2</sup>, Eric Landsness, MD PhD<sup>3</sup>, Bhooma Aravamuthan, MD DPhil<sup>3</sup>, Sara J. Stern-Nezer, MD<sup>4</sup>, James A. Giles, MD PhD<sup>5</sup>. <sup>1</sup>Indiana University School of Medicine, Indianapolis, IN, USA, <sup>2</sup>University of Kentucky, Lexington, KY, USA, <sup>3</sup>Washington University School of Medicine, Saint Louis, MO, USA, <sup>4</sup>University of California Irving School of Medicine, Orange, CA, USA, <sup>5</sup>Yale University School of Medicine, New Haven, CT, USA.

#### **\*S108. Analysis of the Plasma Proteome in Early CADASIL Reveals Dysregulations in Angiogenesis**

**Stephen Fitzsimons, PhD<sup>1</sup>**, Jonah Keller, BSc<sup>1</sup>, Hannah Radabaugh, PhD<sup>2</sup>, Ryan Park, BSc<sup>1</sup>, Bradley Oh, BSc<sup>1</sup>, Scott Treiman, BA<sup>2</sup>, Lisa McDonnell, PhD<sup>1</sup>, Luana Moury, MD<sup>1</sup>, Nikolaos Karvelas, MD<sup>1</sup>, Pauline August, PhD<sup>1</sup>, Adam R. Ferguson, MS, PhD<sup>2</sup>, Fanny M. Elahi, MD, PhD<sup>1</sup>. <sup>1</sup>Icahn School of Medicine at Mount Sinai, New York, NY, USA, <sup>2</sup>University of California San Francisco, California, CA, USA.

#### **S109. Anterior Cerebral Artery Aneurysm in a 7-Month-Old Infant, a Case Report**

**Soroush Kakawand, M.D. MSc.<sup>1</sup>**, Dee H Wu, PhD<sup>2</sup>, Anne Tsai, M.D. MSc.<sup>3</sup>, Neil Borden, M.D.<sup>2</sup>, Yang Yuan, PhD<sup>4</sup>, Benjamin Cornwell, M.D.<sup>2</sup>, Rachel Dolan, BSc<sup>5</sup>, Cherie Herren, M.D.<sup>1</sup>. <sup>1</sup>Department of Neurology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA, <sup>2</sup>Department of Radiological Sciences, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA, <sup>3</sup>Department of Pediatric Genetics, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA, <sup>4</sup>Stephenson Biomedical Engineering The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA, <sup>5</sup>School of Medicine, The University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.

**\*S110. Association of Cerebral Blood Flow with Microstructural Injury in Periventricular and Whole Brain White Matter**

**Banafsheh Shakibajahromi, MD/MPH**, Sudipto Dolui, PHD, Christopher Brown, MD/PhD, William Tackett, BS, Pulkrit Khandehwal, PhD, Shokufeh Sadaghiani, MD, Mohammad Taghvaei, MD/MPH, Paul Yushkevich, PHD, David Wolk, MD, John Detre, MD. University of Pennsylvania, Philadelphia, PA, USA.

**S111. Atypical Central Nervous System Vasculopathy with Moyamoya Syndrome Secondary to B Cell Lymphoma**

**Shivam Patel, BS<sup>1</sup>**, Zoha Sarwat, BS<sup>1</sup>, Anvesh Balabhadra, MBBS<sup>2</sup>, Yana Ivashkevich, MD<sup>3</sup>, Karan Tarasaria, MD<sup>3</sup>. <sup>1</sup>University of Connecticut School of Medicine, Farmington, CT, USA, <sup>2</sup>UConn Health, Farmington, CT, USA, <sup>3</sup>Hartford Hospital, Hartford, CT, USA.

**S112. Atypical Presentation of Ischemic Stroke Secondary to HSV-2 Vasculitis**

**Zoha Sarwat, B.S.<sup>1</sup>**, Shivam Patel, B.S.<sup>1</sup>, Anvesh Balabhadra, M.B.B.S.<sup>2</sup>, Danison Emmerson, M.D.<sup>2</sup>, Gaurav Kapoor, M.D.<sup>3</sup>. <sup>1</sup>University of Connecticut School of Medicine, Farmington, CT, USA, <sup>2</sup>University of Connecticut, Farmington, CT, USA, <sup>3</sup>Hartford Healthcare, Hartford, CT, USA.

**\*S114. Cardiac Troponin Patterns and Insula Involvement in Acute Ischemic Stroke**

**Michela Rosso, MD<sup>1</sup>**, Jessica N. Little, MD<sup>1</sup>, Ankita Brahmaroutu, MD, MS<sup>1</sup>, Izabela Marczak, MD<sup>2</sup>, Yohannes Mulatu, MD<sup>2</sup>, Nino Kvantaliani, MD<sup>1</sup>, Srinath Ramaswamy, MD<sup>2</sup>, Steven R. Messé, MD<sup>1</sup>, Brett L. Cucchiara, MD<sup>1</sup>, Steven R. Levine, MD<sup>2</sup>, Scott E. Kasner, MD<sup>1</sup>. <sup>1</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>SUNY Downstate Health Sciences University, Brooklyn, NY, USA.

**S115. Cerebral Blood Flow in Patients with Congestive Heart Failure**

**Sandra Kong, MS<sup>1</sup>**, Emma Gootee, MS<sup>1</sup>, Nicole Williams, MS<sup>2</sup>, Rebecca F. Gottesman, MD<sup>2</sup>, Michelle Johansen, MD<sup>1</sup>. <sup>1</sup>Johns Hopkins, Baltimore, MD, USA, <sup>2</sup>National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA.

**\*S117. Characteristics and In-Hospital Outcomes of Adults with Acute Stroke Presenting with Seizures at the University Teaching Hospital in Lusaka, Zambia**

**Melody T. Asukile, MB.ChB, MMED<sup>1</sup>**, Coolwe Namangala, MB.ChB<sup>2</sup>, Aparna Nutakki, MD<sup>3</sup>, Mulenga Chilando, MB.ChB<sup>1</sup>, Lorraine Chishimba, MB.ChB, MMED<sup>1</sup>, Mashina Chomba, MB.ChB, MMED<sup>1</sup>, Sarah Braun, MD<sup>1</sup>, Musiye Luchembe, MB.ChB<sup>1</sup>, Dominique Mortel, MD<sup>4</sup>, Moses Mataa, MB.ChB<sup>1</sup>, Dickson Munkombwe, MB.ChB<sup>2</sup>, Frighton Mutete, MB.ChB<sup>1</sup>, Naluca Mwendaweli, MB.ChB<sup>1</sup>, Faith Simushi, MB.ChB<sup>2</sup>, Stanley Zimba, MB.ChB, MMED<sup>1</sup>, Mona Bahouth, MD, PhD<sup>3</sup>, Rebecca Gottesman, MD, PhD<sup>3</sup>,

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**S118. Characterization of Anxiety Disorders after Cerebrovascular Accident**

**Timea M. Hodics, M.D.<sup>1</sup>**, Amber Criswell, B.A.<sup>1</sup>, Mario F. Dulay, Ph.D.<sup>2</sup>. <sup>1</sup>Department of Neurology and Eddy Scurlock Stroke Center, Houston Methodist Hospital, Houston, TX, USA, <sup>2</sup>Department of Neurosurgery, Houston Methodist Hospital, Houston, TX, USA.

**\*S119. Defining the Age of Young Ischemic Stroke Using a Data Driven Approach**

**Clare Lambert, MD<sup>1</sup>**, Vida Abedi, MS, PHD<sup>2</sup>, Durgesh Chaudhary, MD<sup>3</sup>, Emily Rieder, MD Candidate<sup>4</sup>, Venkatesh Avula, MS<sup>2</sup>, Wenke Hwang, MA, PHD<sup>5</sup>, Jiang Li, MD PHD<sup>2</sup>, Ramin Zand, MD PHD<sup>3</sup>. <sup>1</sup>Yale New Haven Hospital, New Haven, CT, USA, <sup>2</sup>Department of Molecular and Functional Genomics, Weis Center for Research, Geisinger Health System, Danville, PA, USA, <sup>3</sup>Geisinger Neuroscience Institute, Geisinger Health System, Danville, PA, USA, <sup>4</sup>Geisinger Commonwealth School of Medicine, Scranton, PA, USA, <sup>5</sup>Department of Public Health Sciences, College of Medicine, The Pennsylvania State University, Hershey, PA, USA.

**S120. Determining the Impact of Occupation on the Association between Cardiac Structure and Mortality in Ischemic Stroke Patients**

**Emma Gootee, MS<sup>1</sup>**, Michael Blaha, MD, MPH<sup>1</sup>, Joao AC Lima, MD, MBA<sup>1</sup>, Rebecca F. Gottesman, MD, PhD<sup>2</sup>, Michelle C. Johansen, MD, PhD<sup>1</sup>. <sup>1</sup>The Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA.

**\*S121. Developing STaR Medical Trainees: Knowledge Gains from Three Years of the Stroke, Thrombectomy, and Revascularization (STaR) Nexus Course**

**Emma M. Loebel, MD<sup>1</sup>**, Desiree Markantone, MD<sup>2</sup>, Daniella Sisniega, MD<sup>3</sup>, Laura K. Stein, MD MPH<sup>1</sup>. <sup>1</sup>Icahn School of Medicine at Mount Sinai, New York, NY, USA, <sup>2</sup>Cleveland Clinic, Cleveland, OH, USA, <sup>3</sup>University of Pennsylvania, Philadelphia, PA, USA.

**S122. Diagnosis in the Eye of the Beholder: Isolated Vein of Labbe Thrombosis, a Rare Disease with Textbook Presentation and Non-Contrast CT Scan Findings**

**Ramit Singla, MD<sup>1</sup>**, Sarayu Santhosh, MBBS<sup>2</sup>, Yaimara Hernandez Silva, MD<sup>1</sup>, Vivek Batra, MD<sup>1</sup>, Savdeep Singh, MD<sup>1</sup>, Balaji Krishnaiah, MD<sup>1</sup>, Cheran Elangovan, MD<sup>1</sup>. <sup>1</sup>University of Tennessee Health Science Center, Memphis, TN, USA, <sup>2</sup>Adichunchanagiri Institute of Medical Sciences, B.G. Nagara, India.

# **S123. Discontinuation and Non-Publication of Stroke Clinical Studies: A Cross-Sectional Analysis**

**Ahmed Aljabali, MD<sup>1</sup>**, Ibraheem M. Alkhawaldeh, MD<sup>2</sup>, Mariam Abdelhady, MD<sup>3</sup>, Yomna Goudy, MD<sup>4</sup>, Ahmed Allam, MD<sup>5</sup>, Heba Temraz, MD<sup>6</sup>, Abdullah Hamad, MD<sup>6</sup>, Eman Reda, MD<sup>7</sup>, Amina Arar, MD<sup>8</sup>, Mahmoud Hefnawy, MD<sup>9</sup>, Rehab Diab, MD<sup>10</sup>, Zainab ElBaz, MD<sup>9</sup>, Marwa Abdelazim, MD<sup>9</sup>, Amir Nabil, MD<sup>11</sup>, Yomna Abdalla, MD<sup>9</sup>, Hazem Ghaith, MD<sup>10</sup>, Ahmed Negida, MD, PhD<sup>12</sup>. <sup>1</sup>Jordan University of Science & Technology, Irbid, Jordan, <sup>2</sup>Mutah University, Karak, Jordan, <sup>3</sup>October 6 University, Giza, Egypt, <sup>4</sup>South Valley University, Qena, Egypt, <sup>5</sup>Tanta Medical School, Tanta, Egypt, <sup>6</sup>Menoufia University, Menoufia, Egypt, <sup>7</sup>Cairo University, Cairo, Egypt, <sup>8</sup>University of Algiers, Algiers, Algeria, <sup>9</sup>Zagazig University, Zagazig, Egypt, <sup>10</sup>Al-Azhar University, Cairo, Egypt, <sup>11</sup>Cairo University, Cairo, Egypt, <sup>12</sup>Harvard University, Boston, MA, USA.

# **\*S124. Dynamic and Static Functional Network Connectivity Differentiates Cognitive Impairment in Individuals with CADASIL**

Bradley T. Baker, MS<sup>1</sup>, H. Jeremy Bockholt, MS<sup>1</sup>, Helen Petropoulos, BS<sup>1</sup>, Vince D. Calhoun, PhD<sup>1</sup>, Arvind Caprihan, PhD<sup>2</sup>, Michael D. Geschwind, MD, PhD<sup>3</sup>, David S. Liebeskind, MD<sup>4</sup>, Kevin M. Johnson, PhD<sup>5</sup>, Laura B. Eisenmenger, MD<sup>5</sup>, William H. Adams, PhD<sup>6</sup>, Michael A. Newton, PhD<sup>5</sup>, **Jane S. Paulsen, PhD<sup>5</sup>**. <sup>1</sup>Tri-Institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS), Georgia State University, Georgia Institute of Technology, and Emory University, Atlanta, GA, USA, <sup>2</sup>The Mind Research Network, Albuquerque, NM, USA, <sup>3</sup>University of California, San Francisco, San Francisco, CA, USA, <sup>4</sup>University of California, Los Angeles, Los Angeles, CA, USA, <sup>5</sup>University of Wisconsin-Madison, Madison, WI, USA, <sup>6</sup>Loyola University Chicago, Chicago, IL, USA.

# **\*S125. Greater Albumin Concentration in Serum May Be Protective against Stroke: The Northern Manhattan Study**

**Adomas Bunevicius, MD, PhD<sup>1</sup>**, Hannah Gardener, PhD<sup>2</sup>, Clinton B. Wright, MD, MS<sup>3</sup>, Mitchel SV Elkind, MD, MS<sup>1</sup>, Tatjana Rundek, MD, PhD<sup>2</sup>, Jose Gutierrez, MD, MPH<sup>1</sup>. <sup>1</sup>Department of Neurology, Columbia University, Vagelos College of Physicians and Surgeons, New York, NY, USA, <sup>2</sup>University of Miami Miller School of Medicine, Miami, FL, USA, <sup>3</sup>National Institute of Neurologic Disorders and Stroke, Bethesda, MD, USA.

# **S126. Healthy Eating Index (HEI) and Mortality among Stroke Patients in the US: A Nationwide Study from the National Health and Nutrition Examination Survey (2003-2018)**

**Jinpyo Hong, BS<sup>1</sup>**, Alain Lekoubou, MD, MS<sup>1</sup>, Manuel Bita, BS (Expected 2024)<sup>2</sup>, Djibril Ba, MPH, PhD<sup>1</sup>. <sup>1</sup>Penn State College of Medicine, Hershey, PA, USA, <sup>2</sup>Georgia State University, Atlanta, GA, USA.

# **\*S127. Improving Early Recanalization and Treatment Times with Transition to Tenecteplase at a Single Comprehensive Stroke Center**

**Paulina Przydzial, MD<sup>1</sup>**, Laura Gutierrez Quiceno, MD<sup>1</sup>, Kimberly Hollender, MSN, RN, ACNP-BC, ANVP<sup>1</sup>, Florence Chukwunneke, MSN, RN, AGPCNP-BC, CNRN, NVRN-BC<sup>1</sup>, Adam Ganzman, MSN, RN, ACNP-BC<sup>2</sup>, Ram Gowda, MD<sup>1</sup>, Mirasol Raymond, MD<sup>1</sup>, Deviyani Mehta, MD<sup>1</sup>, Igor Rybinnik, MD<sup>1</sup>, Roger Cheng, MD<sup>1</sup>, Kiwon Lee, MD<sup>1</sup>. <sup>1</sup>Rutgers RWJMS, New Brunswick, NJ, USA, <sup>2</sup>RWJBH, New Brunswick, NJ, USA.

# **\*S128. In-Stent Restenosis and Concomitant Infarction of Stented Area Following Carotid versus Vertebrobasilar Artery Stenting**

**Hamza Maqsood, MD<sup>1</sup>**, Rubiya Ali, MD<sup>2</sup>, Mehak Rashid, MBBS<sup>3</sup>, Alvina Karam, MD<sup>4</sup>, Azouba Gulraiz, MD<sup>5</sup>, Laraib Jumani, MD<sup>6</sup>, Amna Saleem, MBBS<sup>7</sup>, Sohaib Rasool, MD<sup>8</sup>, Uzzam A. Khawaja, MBBS<sup>7</sup>, Imtiaz Nazam, MBBS<sup>9</sup>, Aftab Ahmed, MD<sup>6</sup>. <sup>1</sup>Nishtar Medical University, Multan, Pakistan, <sup>2</sup>Jinnah Sindh Medical University, Karachi, Pakistan, <sup>3</sup>Bahawal Victoria Hospital, Bahawalpur, Pakistan, <sup>4</sup>Khyber Medical University, Peshawar, Pakistan, <sup>5</sup>Merit Health, Hattiesburg, MS, USA, <sup>6</sup>Pakistan Institute of Medical Sciences (PIMS) Hospital, Islamabad, Pakistan, <sup>7</sup>Aga Khan University Hospital, Karachi, Pakistan, <sup>8</sup>Bakhtawar Amin Medical and Dental College, Multan, Pakistan, <sup>9</sup>Sadiq Abbasi Hospital, Bahawalpur, Pakistan.

# **S129. Increased Interstitial Free Water and Disruption of the Blood-Brain Barrier are Independently Associated with Poor Cognitive Performance in Patients with Chronic Cerebrovascular Disease**

**Kyle C. Kern, MD MS<sup>1</sup>**, Clinton B. Wright, MD MS<sup>1</sup>, Rebecca F. Gottesman, MD PhD<sup>1</sup>, Richard Leigh, MD PhD<sup>2</sup>. <sup>1</sup>National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA, <sup>2</sup>Johns Hopkins Medicine, Baltimore, MD, USA.

# **S130. Inpatient Stroke Quality Improvement and Patient Safety Education: A Needs Assessment**

**Mahan Shabrivari, MD**, Anjail Sharrief, M.D, Amanda Jagolino, MD. UT Health Science Center, Houston, TX, USA.

# **S131. Iron Accumulates in Multiple Cell Types in the Brain Following Perinatal Hypoxic Ischemic Brain Injury**

**Joseph Vithayathil, MD, PhD<sup>1</sup>**, Frances E. Jensen, MD<sup>2</sup>, Delia M. Talos, PhD<sup>2</sup>, Joshua L. Dunaief, MD, PhD<sup>2</sup>. <sup>1</sup>Children's Hospital of Philadelphia, Philadelphia, PA, USA, <sup>2</sup>University of Pennsylvania, Philadelphia, PA, USA.

# **\*S132. Is Catheter Ablation Associated with Favorable Cognitive Function over Time? An Analysis from the SAGE-AF Observational Cohort Study**

**Babadar S. Srichawla, DO, MS**, Alexander Hamel, BS, Philip Cook, DO, Rozaleen Aleyadeh, MD, Darleen Lessard,

MS, Edith M. Otabil, BA, Jordy Mehawej, MD, Jane Saczynski, PhD, Majaz Moonis, MD, David D. McManus, MD. University of Massachusetts Chan Medical School, Worcester, MA, USA.

**\*S133. IV Thrombolysis for Central Retinal Artery Occlusion - Experiences from a Comprehensive Stroke Center**

**Christoph Stretz, MD<sup>1</sup>**, Tina Burton, MD<sup>1</sup>, Narendra Kala, MD<sup>1</sup>, Elizabeth Perelstein, MD<sup>1</sup>, Maheen Rana, MD<sup>1</sup>, Liqi Shu, MD<sup>1</sup>, Eric Goldstein, MD<sup>1</sup>, Shadi Yaghi, MD<sup>1</sup>, Karen Furie, MD<sup>1</sup>, Brian Mac Grory, MB BCH BAO<sup>2</sup>. <sup>1</sup>Brown University, Providence, RI, USA, <sup>2</sup>Duke University, Durham, NC, USA.

**S134. Lemierre Syndrome Variant Following a Mild Head Injury and COVID-19 Infection**

**Heidi Hindsley, BSc, PA-C<sup>1</sup>**, Miriam Quinlan, MD, MPh<sup>2</sup>, Rmneek Kaur, DO<sup>2</sup>, Andrew Zaky, MD<sup>2</sup>, Oksana Levchenko, DO<sup>2</sup>, Tamer Abdelhak, MD<sup>2</sup>. <sup>1</sup>Upstate Medical University, Syracuse, NY, USA, <sup>2</sup>Albany Medical College, Albany, NY, USA.

**S135. MELAS Syndrome: Thrombolytics Treatment and Literature Review**

**Papul Chalia, MD**, Nader El Seblani, MD, Alain Zingraff Lekoubou Looti, MD. Hershey Medical Center, Penn State Health, Hershey, PA, USA.

**S136. Multiple Sclerosis 'Surge' or a Variant of 'Sturge'? : An Unusual Case of Sturge Weber Syndrome**

**Varsha Muddasani, MD**, Brooke Devenney, MD, Yan Zhang, MD, PhD, Aparna Prabhu, MD, MRCP. Einstein Jefferson Healthcare Network, Philadelphia, PA, USA.

**\*S137. Neurovascular Imaging Markers of Cognitive Impairment in CADASIL**

H. Jeremy Bockholt, MS<sup>1</sup>, William H. Adams, PhD<sup>2</sup>, Michael D. Geschwind, MD, PhD<sup>3</sup>, Arvind Caprihan, PhD<sup>4</sup>, Kevin M. Johnson, PhD<sup>5</sup>, David S. Liebeskind, MD<sup>6</sup>, Laura B. Eisenmenger, MD<sup>5</sup>, Helen Petropoulos, BS<sup>1</sup>, Jason Hernandez, BS<sup>1</sup>, Jordan Clemens, HS<sup>1</sup>, Vince D. Calhoun, PhD<sup>1</sup>, **Jane S. Paulsen, PhD<sup>5</sup>**. <sup>1</sup>Tri-Institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS), Georgia State University, Georgia Institute of Technology, and Emory University, Atlanta, GA, USA, <sup>2</sup>Loyola University Chicago, Chicago, IL, USA, <sup>3</sup>University of California, San Francisco, San Francisco, CA, USA, <sup>4</sup>The Mind Research Network, Albuquerque, NM, USA, <sup>5</sup>University of Wisconsin-Madison, Madison, WI, USA, <sup>6</sup>University of California, Los Angeles, Los Angeles, CA, USA.

**S138. Overlap Syndrome of Sjogren's and Systemic Sclerosis with Moya Moya Morphology: A Rare Case**

**Varsha Muddasani, MD<sup>1</sup>**, Maria Diaz Rojas, MD<sup>1</sup>, Irene Tan, MD<sup>1</sup>, Annika G. Samuelson, B.S<sup>2</sup>, Samantha C. Okere, BA<sup>2</sup>. <sup>1</sup>Einstein Jefferson Healthcare Network, Philadelphia, PA, USA, <sup>2</sup>Sidney Kimmel Medical College, Philadelphia, PA, USA.

**S139. Oversweetened: Prolonged Treatment-Resistant Hemichorea-Hemiballismus Syndrome Due to Hyperglycemia**

**Philion L. Gatchoff, MD**, Oleksandra Los, MD, Claire Delpirou-Nouh, MD, Joon-Shik Moon, MD, PhD. University of Oklahoma Health Science Center, Oklahoma City, OK, USA.

**S140. Perceptions of a Hybrid Telestroke Hub and Spoke Stroke Support Group**

Shima Bozorgui, MD<sup>1</sup>, Cristy Autry, RN, BSN<sup>2</sup>, Ieshia Deal, AA<sup>1</sup>, Melanie Jagolino, BS<sup>1</sup>, Abigail Betner, MLS<sup>1</sup>, **Amanda Jagolino-Cole, MD<sup>1</sup>**. <sup>1</sup>McGovern Medical School at the University of Texas Health Science Center at Houston, Houston, TX, USA, <sup>2</sup>Citizens Medical Center, Victoria, TX, USA.

**\*S142. Prognostication and Risk Stratification of Hemorrhagic Transformation in Patients with Acute Ischemic Stroke Based on Serum Homocysteine Levels**

**Hamza Maqsood, MD<sup>1</sup>**, Laraib Jumani, MD<sup>2</sup>, Rubiya Ali, MD<sup>3</sup>, Alvina Karam, MD<sup>4</sup>, Sohaib Rasool, MD<sup>5</sup>, Mehak Rashid, MBBS<sup>6</sup>, Azouba Gulraiz, MD<sup>7</sup>, Amna Saleem, MBBS<sup>8</sup>, Uzzam A. Khawaja, MBBS<sup>8</sup>, Aftab Ahmed, MD<sup>2</sup>, Imtiaz Nazam, MBBS<sup>9</sup>. <sup>1</sup>Nishtar Medical University, Multan, Pakistan, <sup>2</sup>Pakistan Institute of Medical Sciences (PIMS) Hospital, Islamabad, Pakistan, <sup>3</sup>Jinnah Sindh Medical University, Karachi, Pakistan, <sup>4</sup>Khyber Medical University, Peshawar, Pakistan, <sup>5</sup>Bakhtawar Amin Medical and Dental College, Multan, Pakistan, <sup>6</sup>Bahawal Victoria Hospital, Bahawalpur, Pakistan, <sup>7</sup>Merit Health, Hattiesburg, MS, USA, <sup>8</sup>Aga Khan University Hospital, Karachi, Pakistan, <sup>9</sup>Sadiq Abbasi Hospital, Bahawalpur, Pakistan.

**\*S143. Proteomic Profiling of Intracranial Atherosclerotic Plaque in the Human Brain**

**Qing Hao, MD, PhD<sup>1</sup>**, Erming Wang, PhD<sup>1</sup>, Ju Wang, PhD<sup>2</sup>, Zhiping Wu, PhD<sup>2</sup>, John F. Crary, MD, PhD<sup>1</sup>, Fanny Elahi, MD, PhD<sup>1</sup>, Bin Zhang, PhD<sup>1</sup>, Junmin Peng, PhD<sup>2</sup>. <sup>1</sup>Icahn School of Medicine at Mount Sinai, New York, NY, USA, <sup>2</sup>St. Jude Children's Research Hospital, Memphis, TN, USA.

**\*S144. Retrospective Study of Multi-Site CADASIL: Implications for Clinical and Research Practice**

**Michael D. Geschwind, MD, PhD<sup>1</sup>**, Jennifer Zitser, MD<sup>1</sup>, Fanny M. Elahi, MD, PhD<sup>2</sup>, Ihab Hajjar, MD<sup>3</sup>, Jose Gutierrez, MD, MPH<sup>4</sup>, Iman Fathali, BA<sup>1</sup>, Daven Crossland,

BA<sup>1</sup>, Michael Terranova, MS<sup>1</sup>, Theresa Driscoll, BA<sup>1</sup>, H. Jeremy Bockholt, MS<sup>5</sup>, Jane S. Paulsen, PhD<sup>6</sup>, Mirjana Djakovic, MSN<sup>7</sup>, Michael J. Schneck, MD<sup>7</sup>, Jose Biller, MD<sup>7</sup>. <sup>1</sup>University of California San Francisco, San Francisco, CA, USA, <sup>2</sup>Icahn School of Medicine at Mount Sinai, New York, NY, USA, <sup>3</sup>The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA, <sup>4</sup>Columbia University Irving Medical Center, New York, NY, USA, <sup>5</sup>Georgia State University, Georgia Institute of Technology, and Emory University, Atlanta, GA, USA, <sup>6</sup>University of Wisconsin-Madison, Madison, WI, USA, <sup>7</sup>Loyola University Chicago, Chicago, IL, USA.

#### **S145. Revolutionizing Stroke Diagnosis: The Role of Artificial Intelligence**

**Harendra Kumar, MBBS<sup>1</sup>**, Jinal Choudhary, MD<sup>2</sup>, Sujan Poudel, MBBS<sup>2</sup>, Nisha Panta, MBBS<sup>3</sup>, Amin Abolfazli, MD<sup>2</sup>, Wilson Cueva, MD<sup>2</sup>. <sup>1</sup>Dow University of Health Sciences, Karachi, Pakistan, <sup>2</sup>Larkin Community Hospital, South Miami, FL, USA, <sup>3</sup>Kathmandu Medical College, Kathmandu, Nepal.

#### **\*S147. Safety and Efficacy of Tenecteplase versus Alteplase for Thrombolysis in Acute Ischemic Stroke at a Single Center Experience**

**Abigail C. Hasan, Masters**, Pouria Moshayedi, MD, Maria Bracamontes, MD, Madiha Aurangzeb, MD, Aldona Chorzepa, BA, Andrew Miele, MA, Kelly Cervellione, MA, Jonathan Robitsek, PhD, Robert Mendelson, MD. Jamaica Hospital, Jamaica, NY, USA.

#### **S148. Safety of Thrombolytics in Acute Stroke with History of Repaired Aortic Dissection: A Case Report**

**Ramit Singla, MD**, Balaji Krishnaiah, MD, Cheran Elangovan, MD. University of Tennessee Health Science Center, Memphis, TN, USA.

#### **\*S149. Serum Neuregulin as a Predictive Biomarker of Severity and In-Patient Outcomes among Young Acute Intracerebral Hemorrhage Patients in Ghana**

**Priscilla Abrati Opere-Addo, MD**, Richard Boateng, MSc, Minas Aikins, MD, Serwaa Asare-Bediako, MD, Fred Stephen Sarfo, MD PhD. Komfo Anokye Teaching Hospital, Kumasi, Ghana.

#### **\*S150. Sex Differences in Treatment Effect in Neuroprotectant Trials for Acute Ischemic Stroke**

**Sabily Reyes-Estevés, MD, PhD**, Donna K. George, MD, Brett L. Cucchiara, MD. Hospital of the University of Pennsylvania, Philadelphia, PA, USA.

#### **\*S151. Susceptibility Vessel Sign as a Predictor of Intracranial Large Vessel Occlusion - A Retrospective, Single Centre Study**

**Aiswarya Raj, MBBS**, Ashraf VV, MBBS, MD, DNB, DM (Neurology), MRCP (SCE-Neurology), Paul Johnny, MBBS,

DNB (Medicine), Paul J. Alapatt, MBBS, MD, DNB, DM (Neurology), MRCP (SCE-neurology), Abdurehman KP, MBBS, MD (General Medicine), DM (Neurology), Sreevidya LK, MBBS, DM (Neurology), Noufal Basheer, MBBS (AIIMS) MCh (Neurosurgery- AIIMS). Aster MIMS, Kozhikode, Kerala, India.

#### **S152. Synergistic Contribution of Blood Pressure and Cerebral White Matter Hyperintensities to the Risk of Major Adverse Brain Events**

**Richa Sharma, MD, MPH**, Guido Falcone, MD, ScD, MPH, Cyprien Rivier, MD, MS, Rachel Forman, MD, Harlan Krumholz, MD, SM, Kevin N. Sheth, MD, Adam de Havenon, MD, MSCI. Yale School of Medicine, New Haven, CT, USA.

#### **\*S153. Systematic Review and Meta-Analysis of Post-Stroke Upper Extremity Home Rehabilitation Clinical Trials**

**Kajol Shah, B.Sc.<sup>1</sup>**, Jiaqiong Xu, Ph.D.<sup>2</sup>, Timea M. Hodics, M.D.<sup>3</sup>. <sup>1</sup>Texas A&M University College of Medicine ENMED, Houston, TX, USA, <sup>2</sup>Center for Health Data Science and Analytics, Houston Methodist Research Institute, Houston, TX, USA, <sup>3</sup>Department of Neurology and Eddy Scurlock Stroke Center, Houston Methodist Hospital, Houston, TX, USA.

#### **S154. Takotsubo Cardiomyopathy in Patients with Acute Ischemic Stroke: A Case Series**

**Jessica N. Little, MD, PhD**, Brett L. Cucchiara, MD, Scott E. Kasner, MD, Michela Rosso, MD. University of Pennsylvania, Philadelphia, PA, USA.

#### **\*S155. The Association between Hepatic Fibrosis Due to Non-Alcoholic Fatty Liver Disease and Post-Stroke Depression in Patients after Ischemic Stroke**

**Hamza Maqsood, MD<sup>1</sup>**, Shifa Younus, MBBS<sup>1</sup>, Mehak Rashid, MBBS<sup>2</sup>, Laraib Jumani, MD<sup>3</sup>, Azouba Gulraiz, MD<sup>4</sup>, Sohaib Rasool, MD<sup>5</sup>, Uzzam A. Khawaja, MBBS<sup>6</sup>, Amna Saleem, MBBS<sup>6</sup>, Aftab Ahmed, MD<sup>3</sup>, Sadiq Naveed, MD, MPH, DFAACAP<sup>7</sup>. <sup>1</sup>Nishtar Medical University, Multan, Pakistan, <sup>2</sup>Bahawal Victoria Hospital, Bahawalpur, Pakistan, <sup>3</sup>Pakistan Institute of Medical Sciences (PIMS) Hospital, Islamabad, Pakistan, <sup>4</sup>Merit Health, Hattiesburg, MS, USA, <sup>5</sup>Bakhtawar Amin Medical and Dental College, Multan, Pakistan, <sup>6</sup>Aga Khan University Hospital, Karachi, Pakistan, <sup>7</sup>Eastern Connecticut Health Network, Manchester, CT, USA.

#### **\*S156. Thrombolytic Therapy for Central Retinal Artery Occlusion: A Systematic Review and Individual Participant Level Meta-Analysis**

**Shima Shahjouei, MD, MPH<sup>1</sup>**, Reza Bavarsad Shahripour, MD<sup>2</sup>, Oana Dumitrascu, MD, MSc<sup>3</sup>. <sup>1</sup>Barrow Neurological Institute, Phoenix, AZ, USA, <sup>2</sup>Loma Linda University, Loma Linda, CA, USA, <sup>3</sup>Mayo Clinic, Scottsdale, AZ, USA.

**S157. To See or Not to See: Anton Babinski Syndrome Secondary to Posterior Reversible Encephalopathy Syndrome along with Alprazolam and Tramadol Withdrawal**

**Soroush Kakawand, M.D. MSc., Raman Singh, M.D., Hamza Ahmed, M.D., Ahmad Al-Auwad, M.D.** Department of Neurology, University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.

**S158. Transient Ischemic Event Secondary to Extrinsic Compression of the Cervical Internal Carotid Artery by the Lateral Process of C1 Vertebrae: A Case Report**

**Nasser Abdelall, B.Med.Sc, M.D.<sup>1</sup>, Warren Spinner, DO<sup>2</sup>, Stefan Franco, Bachelor's in Biology<sup>2</sup>.** <sup>1</sup>LSU HSC, New Orleans, LA, USA, <sup>2</sup>North Suffolk Neurology, Long Island, NY, USA.

**S159. Traveling Tumor: Papillary Fibroelastoma as an Unusual Etiology of Cardioembolic Stroke**

**Ragha Sakuru, MD, Chandra Mannyam, MD, Sameer Sharma, MD.** UMMC, Jackson, MS, USA.

**S160. Unraveling the Earliest Phases of Vascular Cognitive Impairment and Dementia Using CADASIL**

**Michael D. Geschwind, MD, PhD<sup>1</sup>, Jose Biller, MD<sup>2</sup>, Jamie L. Elliot, MD, PhD<sup>3</sup>, Suman Jayadev, MD<sup>4</sup>, Stephen Salloway, MD, MS<sup>5</sup>, Jose Gutierrez, MD, MPH<sup>6</sup>, Sudha Seshadri, MD, DM<sup>7</sup>, Jennifer J. Majersik, MD, MS<sup>8</sup>, Karen D. Orjuela, MD, MS<sup>9</sup>, David S. Liebeskind, MD<sup>10</sup>, Helmi L. Lutsep, MD<sup>11</sup>, Ihab Hajjar, MD<sup>12</sup>, Fanny M. Elahi, MD, PhD<sup>13</sup>, Iman Fathali, BA<sup>1</sup>, H. Jeremy Bockholt, MS<sup>14</sup>, Jane S. Paulsen, PhD<sup>3</sup>.** <sup>1</sup>University of California San Francisco, San Francisco, CA, USA, <sup>2</sup>Loyola University Chicago, Chicago, IL, USA, <sup>3</sup>University of Wisconsin-Madison, Madison, WI, USA, <sup>4</sup>University of Washington, Seattle, WA, USA, <sup>5</sup>Butler Hospital and Brown University, Providence, RI, USA, <sup>6</sup>Columbia University Irving Medical Center, New York, NY, USA, <sup>7</sup>The University of Texas Health Science Center at San Antonio, San Antonio, TX, USA, <sup>8</sup>University of Utah, Salt Lake City, UT, USA, <sup>9</sup>University of Colorado Anschutz Medical Campus, Aurora, CO, USA, <sup>10</sup>University of California Los Angeles, Los Angeles, CA, USA, <sup>11</sup>Oregon Health & Science University, Portland, OR, USA, <sup>12</sup>The University of Texas Southwestern Medical Center, Dallas, TX, USA, <sup>13</sup>Icahn School of Medicine at Mount Sinai, New York, NY, USA, <sup>14</sup>Georgia State University, Georgia Institute of Technology, and Emory University, Atlanta, GA, USA.

**S161. Use of IV Thrombolytics to Treat Ischemic Stroke in a Patient with an Acute Myocardial Infarction and Intra-Aortic Balloon Pump**

**Akash Chakravartty, MD, Meaghan Puckett, MD, Tamra Ranasinghe, MD.** Wake Forest Baptist Medical Center, Winston Salem, NC, USA.

**\*S162. Validation of the Modified Rankin Scale for Stroke Clinical Research in Zambia**

**Lorraine Chishimba, MMED<sup>1</sup>, Dominique Mortel, MD<sup>2</sup>, Sarah Braun, MD<sup>1</sup>, Melody Asukile, MMED<sup>1</sup>, Mashina Chomba, MMED<sup>1</sup>, Mulenga Chilando, STP<sup>1</sup>, Moses Mataa, MMED<sup>1</sup>, Dickson Munkombwe, MMED<sup>1</sup>, Frighton Mutete, STP<sup>1</sup>, Naluca Mwendaweli, MMED<sup>1</sup>, Faith Simushi, MMED<sup>1</sup>, Stanley Zimba, MMED<sup>1</sup>, Rebecca Gottesman, MD<sup>2</sup>, Deanna Saylor, MD<sup>2</sup>, Mona Bahouth, MD, PhD<sup>2</sup>.** <sup>1</sup>University Teaching Hospital - Adult Hospitals, Lusaka, Zambia, <sup>2</sup>Johns Hopkins, Baltimore, MD, USA.

**\*S163. Work Smarter Not Harder- Improving Overall Efficiency on Stroke Service through Epic Handoff Tool**

**Rani Priyanka Vasireddy, MBBS, MHA, Jessica Lee, MD.** University of Kentucky, Lexington, KY, USA.

**K-S100. Arginase-1 Microglia and Efferocytosis after Murine Neonatal Brain Hypoxia-Ischemia**

**Jana Mike, MD/PhD, Emin Maltepe, MD, PhD, Donna Ferriero, MD,MS.** University of California San Francisco, San Francisco, CA, USA.

**K-S101. Astrocyte TLR4 Signaling Mediates Astrogliosis Following Focal Cerebral Ischemia**

**Bolanle Famakin, MD, Sireesh Kumar Teertam, PhD, Babyosimi Fadiran, n/a, Ronan Couch, BS.** University of Wisconsin School of Medicine and Public Health, Madison, WI, USA.

**K-S102. Targeting Microglial NF-kB to Improve Neurologic Outcomes after Aneurysmal Subarachnoid Hemorrhage**

**Meizi Liu, MD, Keshav Jayaraman, BA, Gregory J. Zipfel, MD, Umeshkumar Athiraman, MD.** Washington University in Saint Louis, Saint Louis, MO, USA.

**LB-S100. A Case of Reversible Cerebral Vasoconstriction Syndrome in a Young Female**

**Jacob Tremoulis, M.S., OMS-III<sup>1</sup>, Ben Petrykowski, OMS-III<sup>1</sup>, Timothy Ohlemacher, PA-C<sup>2</sup>, Hannah Lyons, M.S., OMS-III<sup>1</sup>, Nathaniel Quinn, MD<sup>2</sup>.** <sup>1</sup>Ohio University Heritage College of Osteopathic Medicine, Dublin, OH, USA, <sup>2</sup>Mercy Health - St. Rita's Medical Center, Lima, OH, USA.

**LB-S101. Cerebral Venous Thrombosis as Subarachnoid Hemorrhage, a Case Report**

**Paulina Henriquez-Rojas, MD, Shruthi Harish, MD, Yan Zhang, MD, PhD, Saman Zafar, MD.** Einstein Medical Center Philadelphia, Philadelphia, PA, USA.

**\*LB-S129. A Structured-Textual Machine Learning Model to Classify Penumbra-Core Mismatch among Patients Presenting with Acute Ischemic Stroke from Large-Vessel Occlusion**

**Shaun Kohli, Sc.B, Benjamin Kummer, MD.** Icahn School of Medicine at Mt. Sinai, New York, NY, USA.

# Headache and Pain

## S164. A Rare Presentation of Migraine in an Adolescent Male

**Sarah Oveisitork, BS<sup>1</sup>**, Zachary S. Gulergun, MD<sup>2</sup>. <sup>1</sup>St. George's University School of Medicine, True Blue, Grenada, <sup>2</sup>Northwestern University Feinberg School of Medicine, Chicago, IL, USA.

## \*S166. Altered Functional Connectivity of the Thalamus and Salience Network in Patients with Cluster Headache

**Enchao Qiu, M.D. & Ph.D.<sup>1</sup>**, Xinbo Xing, M.D.<sup>2</sup>, Hsiangkuo Yuan, M.D. & Ph.D.<sup>1</sup>. <sup>1</sup>Jefferson Headache Center, Philadelphia, PA, USA, <sup>2</sup>The Fourth Medical Center of Chinese PLA General Hospital, Beijing, China.

## S167. Central Sensitization is the Main Mechanism Underlying Chronic Pain in Patients with Persistent Post-Concussive Syndrome

**Christopher File, BSA**, Alejandro Villasante-Tezanos, Ph.D., Sean Pappolla, Assoc. Sci., Ahmed Harazeen, M.D., Remi Nader, M.D., Xiang Fang, M.D., Miguel Pappolla, M.D. Ph.D. University of Texas Medical Branch, Galveston, TX, USA.

## \*S168. Developing and Delivering a Migraine Disparities and Diagnosis Undergraduate Medical Educational Program to Underrepresented in Medicine Medical Student Members of the Student National Medical Association

**Larry Charleston, IV, MD, MSc, FAHS**. Michigan State University College of Human Medicine, East Lansing, MI, USA.

## \*S169. Feasibility and Acceptability of Remote-Delivered Mindfulness-Based Cognitive Therapy (MBCT) for Patients with Migraine and Depressive Symptoms

**Elizabeth Seng, Ph.D.<sup>1</sup>**, Jacob Hill, N.D., M.S.<sup>2</sup>, Annie Kate Reeder, M.A.<sup>1</sup>, Pallavi Visvanathan, Ph.D.<sup>3</sup>, Rebecca E. Wells, M.D., MPH<sup>4</sup>, Richard B. Lipton, M.D.<sup>5</sup>, Mia Minen, M.D.<sup>2</sup>, Jodi Scharf, B.A.<sup>2</sup>, Amanda Shallcross, N.D., MPH<sup>6</sup>. <sup>1</sup>Ferkauf Graduate School of Psychology, Yeshiva University, Bronx, NY, USA, <sup>2</sup>NYU Langone, New York, NY, USA, <sup>3</sup>Manhattan Center for Mindfulness-Based Cognitive Behavioral Therapy, New York, NY, USA, <sup>4</sup>Wake Forest School of Medicine, Winston Salem, NC, USA, <sup>5</sup>Albert Einstein College of Medicine, Bronx, NY, USA, <sup>6</sup>The Cleveland Clinic, Cleveland, OH, USA.

## \*S170. Headache-Related Stigma in Adults Experiencing High-Frequency Headache/Migraine and High Acute Medication Use: Results of the Harris Poll Migraine Report Card Survey

Dawn C. Buse, PhD<sup>1</sup>, Roger Cady, MD, FAHS<sup>2</sup>, Amaal J. Starling, MD<sup>3</sup>, Meghan Buzby, MBA<sup>4</sup>, Charlie Spinale,

BA<sup>5</sup>, Kathy Steinberg, BS<sup>5</sup>, **Sandeep Sharma, MD, DrPH<sup>6</sup>**, Steven Kymes, PhD<sup>6</sup>. <sup>1</sup>Department of Neurology, Albert Einstein College of Medicine, Bronx, NY, USA, <sup>2</sup>RK Consults, Ozark, MO, USA, <sup>3</sup>Mayo Clinic Arizona, Scottsdale, AZ, USA, <sup>4</sup>Coalition for Headache and Migraine Patients (CHAMP), San Rafael, CA, USA, <sup>5</sup>The Harris Poll, New York, NY, USA, <sup>6</sup>Lundbeck LLC, Deerfield, IL, USA.

**\*S171. Health Concerns and Treatment Perspectives among US Adults with Current versus Previous High-Frequency Headache/Migraine and Acute Medication Overuse: The Harris Poll Migraine Report Card Survey**  
Amaal J. Starling, MD<sup>1</sup>, Roger Cady, MD, FAHS<sup>2</sup>, Dawn C. Buse, PhD<sup>3</sup>, Meghan Buzby, MBA<sup>4</sup>, Charlie Spinale, BA<sup>5</sup>, Kathy Steinberg, BS<sup>5</sup>, **Sandeep Sharma, MD, DrPH<sup>6</sup>**, Steven Kymes, PhD<sup>6</sup>. <sup>1</sup>Mayo Clinic Arizona, Scottsdale, AZ, USA, <sup>2</sup>RK Consults, Ozark, MO, USA, <sup>3</sup>Albert Einstein College of Medicine, Bronx, NY, USA, <sup>4</sup>Coalition for Headache and Migraine Patients (CHAMP), San Rafael, CA, USA, <sup>5</sup>The Harris Poll, New York City, NY, USA, <sup>6</sup>Lundbeck LLC, Deerfield, IL, USA.

## S172. Inflammatory and Cell Adhesion Biomarkers are Associated with Distal Sensory Polyneuropathy in People with HIV

**Mohammasobhan Sheikh Andalibi, M.D.**, Scott L. Letendre, M.D., Bin Tang, Ph.D., Ronald J. Ellis, M.D., Ph.D. University of California, San Diego, San Diego, CA, USA.

## S173. Migraine Abortive Therapy for Severe Hyperemesis Gravidarum, a Case Report

**Soroush Kakawand, M.D. MSc.**, David Lee Gordon, M.D., FAAN, FANA, FAHA. Department of Neurology University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.

## S174. Recurrent, Severe Coital Headaches Associated with Bilateral Carotid Artery Aneurysms

**Emma Martinez-Arellano, B.S.**, George Ishac, B.S., B.A., M.S., Hannah Lu, B.S.A., Ruiqing L. Sun, M.D., PhD. University of Texas Medical Branch, Galveston, TX, USA.

## \*S175. Targeting the Photoreceptor Basis of Light Aversive Behavior in Mice

**Eric A. Kaiser, MD/PhD**, Audrey Cavanah, BS, Geoffrey K. Aguirre, MD, PhD, Frances E. Jensen, MD. University of Pennsylvania, Philadelphia, PA, USA.

## S176. Weight Loss Medications in the Setting of Chronic Migraine

**Nicole Rigler, BA<sup>1</sup>**, Austin Du, BS<sup>1</sup>, Nina Riggins, MD PhD<sup>2</sup>. <sup>1</sup>University of California San Diego School of Medicine, La Jolla, CA, USA, <sup>2</sup>University of California San Diego



Headache Center, Department of Neurosciences, La Jolla, CA, USA.

### **K-S103. Measuring Descending Pain Modulation with Offset Analgesia and Onset Hyperalgesia in Patients with Chronic Musculoskeletal Pain**

**Benedict Alter, MD, PhD**, Maya Maurer, BS, Theodore Huppert, PhD, Ajay Wasan, MD, MSc. University of Pittsburgh, Pittsburgh, PA, USA.

### **K-S104. Time It Right! The Application of Circadian Medicine Interventions for the Management of Migraine**

**Yohannes W. Woldeamanuel, MD<sup>1</sup>**, Oxana Palesh, PhD, MPH<sup>2</sup>, Robert P. Cowan, MD<sup>1</sup>. <sup>1</sup>Stanford University School of Medicine, Stanford, CA, USA, <sup>2</sup>Virginia Commonwealth University, Richmond, VA, USA.

### **LB-S102. Alleviation of Burning Mouth Syndrome Pain through Retronasal Olfaction**

**Shrenik Shah, MD<sup>1</sup>**, Aneetinder Somal, MD<sup>1</sup>, Alan R. Hirsch, MD<sup>2</sup>. <sup>1</sup>Windsor University School of Medicine, Cayon, Saint Kitts and Nevis, <sup>2</sup>Smell and Taste Treatment and Research Foundation, Des Plaines, IL, USA.

### **LB-S103. Chronic Neuropathic Pain: PTPRD Phosphatase Inhibitors Provide Novel Therapeutic Approaches**

**George R. Uhl, MD PhD**. University of Maryland School of Medicine/VA Maryland Healthcare System, Baltimore, MD, USA.

### **\*LB-S104. Psychological Resilience in People with Primary Headache Disorders: A Systematic Review and Meta-Analysis**

**Kevin Pacheco-Barrios, MD, MSc, MPH<sup>1,2</sup>**, Alba Navarro-Flores, MD, MSc<sup>3</sup>, Bizu Gelaye, PhD<sup>1</sup>. <sup>1</sup>Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA, USA, <sup>2</sup>Neuromodulation Center and Center for Clinical Research Learning, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, <sup>3</sup>International Max Planck Research School for Neurosciences, Georg-August The University of Göttingen, Göttingen, Germany.

### **\*LB-S105. Randomized Controlled Trial of a Smartphone-Based Preventive Migraine Self-Management Program in the Emergency Department Setting: A Promising Teachable Moment**

**Mia T. Minen, MD, MPH<sup>1</sup>**, Elizabeth Seng, PhD<sup>2</sup>, Benjamin W. Friedman, MD<sup>3</sup>, Alexis George, BA<sup>1</sup>, Kristina Fanning, PhD<sup>4</sup>, Ryan Bostic, BS<sup>4</sup>, Scott W. Powers, PhD<sup>5</sup>, Richard B. Lipton, MD<sup>3</sup>. <sup>1</sup>Department of Neurology, NYU Langone Health, New York, NY, USA, <sup>2</sup>Ferkauf Graduate School of Psychology, Yeshiva University, Bronx, NY, USA,

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## **Health Services and Health Equity Research**

### **\*S177. Barriers to Publishing Scholarship: A Cross-Sectional Study on Physician Residents and Fellows in Neurology**

**Keng Lam, MD<sup>1</sup>**, Kary Calderon, B.S.<sup>2</sup>, Jung G. Kim, MPH, PhD<sup>2</sup>. <sup>1</sup>MD Anderson Cancer Center, Houston, TX, USA, <sup>2</sup>Kaiser Permanente Bernard J. Tyson School of Medicine, Los Angeles, CA, USA.

### **\*S178. Community-Driven Brain Health Workshop Series in Historically Marginalized Communities: A Novel Approach to Brain Health Promotion and Education**

**Christine Zizzi, MPA<sup>1</sup>**, Charles White, BA<sup>2</sup>, Christine Annis, BS<sup>2</sup>, Heidi Schwarz, MD<sup>1</sup>, Robert Holloway, MD, MPH<sup>2</sup>, Phyllis Jackson, RN<sup>1</sup>, Katherine Webster, NP<sup>2</sup>. <sup>1</sup>University of Rochester Medical Center, Center for Health + Technology (CHeT), Rochester, NY, USA, <sup>2</sup>University of Rochester Medical Center, Department of Neurology, Rochester, NY, USA.

### **S179. Comorbid Psychiatric Disorders are Associated with Lesser Use of Mechanical Thrombectomy in Patients with Ischemic Stroke**

**Alsu Zagorulkov, M.D.<sup>1</sup>**, Pavel Sinyagovskiy, M.D.<sup>2</sup>. <sup>1</sup>Foresight Mental Health, Decatur, GA, USA, <sup>2</sup>Yuma Regional Medical Center, Yuma, AZ, USA.

### **S180. Development of a National, Clinically-Focused, Virtual Journal Club in Neurology**

**Melissa R. Briones, MD<sup>1</sup>**, Adeel S. Zubair, MD<sup>2</sup>, Nadine Housri, MD<sup>3</sup>. <sup>1</sup>Loyola University Medical Center, Maywood, IL, USA, <sup>2</sup>Yale Department of Medicine, Section of Neurology, New Haven, CT, USA, <sup>3</sup>Yale School of Medicine, Department of Therapeutic Radiology, New Haven, CT, USA.

### **\*S182. Disparities in Access to and Experience with Technology and Teleconferencing in MCI Subjects**

**Abhinav Bhamidipati, BS<sup>1</sup>**, Manasa Mula, BS<sup>1</sup>, Elena Park, BS<sup>2</sup>, Asha Chandaka, BS<sup>1</sup>, Jennifer Morris, MS<sup>2</sup>, Alicia Lozano, MS<sup>3</sup>, Stephen Moelter, PhD<sup>4</sup>, Luigi Chi, MD<sup>5</sup>, Cindy Cheng, MD<sup>6</sup>, Eric M. Davis, MD<sup>7</sup>, Alexandra Hanlon, PhD<sup>3</sup>, David Wolk, MD<sup>2</sup>, Kathy Richards, PhD<sup>8</sup>,



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**S183. Effectiveness of a Short Brochure-Based Educational Intervention on the Clinical Applications of Alzheimer's Disease Biomarkers in Cognitively Healthy Older Adults**

**Emma Casey, MSPH<sup>1</sup>**, Katherine Sanders, MPH<sup>2</sup>, James J. Lah, MD, PhD<sup>3</sup>. <sup>1</sup>Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA, USA, <sup>2</sup>Personalized Brain Health Initiative, Emory Healthy Brain Study, Goizueta Institute, Emory University, Atlanta, GA, USA, <sup>3</sup>Department of Neurology, School of Medicine, Emory University, Atlanta, GA, USA.

**S184. Evaluating Current Perception, Cultural Beliefs, and Associated Social Stigma of Autism Spectrum Disorder in Uganda. Insights from an Educational Intervention Study**

**Franziska Hoche, MD<sup>1</sup>**, Pamela Tiiti, M.S.<sup>2</sup>, Ann M. Neumeyer, MD<sup>1</sup>, Shelley R. Waite, MD<sup>1</sup>, Caesar A. Odama, PhD, cand.<sup>3</sup>, Juliet Nakalule, Ph.D.<sup>3</sup>. <sup>1</sup>Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, <sup>2</sup>Tunaweza Children's Center, Kampala, Uganda, <sup>3</sup>Kyambogo University, Kampala, Uganda.

**\*S185. Evidence-Based Implementation of Free Phenytoin and Free Valproate Therapeutic Drug Monitoring to Reduce Costs and Improve Patient Care at the University of Texas Medical Branch**

**Hannah Lu, BSA**, George Ishac, BS, MS, Emma Martinez-Arellano, BS, Ruiqing Sun, MD, PhD. University of Texas Medical Branch, Galveston, TX, USA.

**S187. Free Neurology Community Clinic: Characteristics, Trends, and Needs**

**Ashley V. Madera, MD**, Trevor Hawkins, MD. University of Colorado, Aurora, CO, USA.

**\*S188. From Resident to Chair: Gender Disparities in Child Neurology Pipeline**

**Keamogetswe Rakolle, BS<sup>1</sup>**, Megan Darrell, BA<sup>2</sup>, Mill Etienne, MD, MPH<sup>3</sup>. <sup>1</sup>St. George's University Keith B. Taylor, Newcastle, United Kingdom, <sup>2</sup>Albert Einstein College of Medicine, Bronx, NY, USA, <sup>3</sup>New York Medical College, Valhalla, NY, USA.

**\*S189. Implementation of an Interactive Neuroradiology Curriculum for Neurology Residents: Interim Results**

**Dan Tong Jia, MD**, Jasmine May, MD, PhD, Tulsi Malavia, MD, Karan Dixit, MD. Northwestern University, Chicago, IL, USA.

**\*S190. Improving Communication Barriers among Patients with Limited English Proficiency and Neurological Illness**

**Sarika R. Bharil, BS<sup>1</sup>**, Margarita Velasco, MS<sup>2</sup>, Deena Haque, BS<sup>3</sup>, Altaf Saadi, MD, MSc<sup>2</sup>. <sup>1</sup>Harvard T.H. Chan School of Public Health, Boston, MA, USA, <sup>2</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>3</sup>Brown University, Providence, RI, USA.

**\*S191. Journey from Junior Resident to Senior Resident: Neurology Residents' Perspective of Meaningful Transformative Experiences**

**Annika Daya, MPH<sup>1</sup>**, Ema V. Karakoleva, BS<sup>1</sup>, John Cavendish, MD, PhD<sup>2</sup>, Max R. Lowden, MD, MEd<sup>2</sup>. <sup>1</sup>Penn State College of Medicine, Hershey, PA, USA, <sup>2</sup>Penn State Health Medical Center, Hershey, PA, USA.

**S192. Penn Multiple Sclerosis and Related Disorders Center's Approach towards Addressing Disparities in Care in Resident Clinic**

Erin Kim, BA, Lane Camryn, BS, Kristin McCabe, MSN, RN, CNRN, Stephanie Gandelman, MD, Noellie Rivera-Torres, MD, Mihir Kakara, MD, Rachel Brandstadter, MD, Chris Perrone, MD, Matthew Schindler, MD, PhD, Jennifer Orthmann-Murphy, MD, PhD, Clyde Markowitz, MD, Joseph Berger, MD, Amit Bar-Or, MD, Erin Perrone, BSN, RN, MSCN, Alison Noon, BSN, RN, Dawn Johnson, BSN, RN, MSCN, Angelica Carmolingo, BA, Ryan Fuller, PharmD, Kerry Lenzi, PharmD, Janice Lee, PharmD, Julie Mozes, BA, MBA, Lee Leibowitz, BS, MBA, Caitlin Pileggi, BSN, MSN, Meghan Garabedian, BSN, MSN, Sara Zeccardi, BSN, MSN, Nora Sekella, BA, MSW, Rohini Samudralwar, MD, Laura Stein, MD, Ray Price, MD, **Dina Jacobs, MD**. Perelman School of Medicine at the Hospital of the University of Pennsylvania, Philadelphia, PA, USA.

**S193. Promoting Research in Graduate Medical Education: A Longitudinal Integrated Research Track Designed for Neurology Residents**

**Max Lowden, M.D., MEd**, Rae Bacharach, DO. Pennsylvania State University, Hershey, PA, USA.

**\*S194. Recruiting and Retaining a Diverse Child Neurology Workforce: Disparities in Child Neurology Residency Programs from 2011 to 2022**

**Keamogetswe Rakolle, BS<sup>1</sup>**, Megan Darrell, BA<sup>2</sup>, Mill Etienne, MD, MPH<sup>3</sup>. <sup>1</sup>St. George's University Keith B. Taylor,

Newcastle, United Kingdom, <sup>2</sup>Albert Einstein College of Medicine, Bronx, NY, USA, <sup>3</sup>New York Medical College, Valhalla, NY, USA.

**\*S195. Recruiting and Retaining a Diverse Neurology Workforce: The Pipeline from 2011 to 2022**

**George Ghaly, BA**, Mill Etienne, MD, MPH. New York Medical College, Valhalla, NY, USA.

**\*S196. Retrospective Assessment of Equitable Inclusion of Subjects in the National Institute of Neurological Disorders and Stroke Clinical Studies**

**Manabel Zabid, BS**, Gina Norato, MS, Sandy Martin, MS, Lauren Reoma, MD. NINDS, Bethesda, MD, USA.

**S197. Social and Health Characteristics, and Racial/Ethnic Disparities among Community-Dwelling Adults with Intellectual and Developmental Disabilities: National Data from 2004-2018**

**Mibir Kakara, M.D.** University of Pennsylvania, Philadelphia, PA, USA.

**\*S198. Telemedicine Use before and during the COVID-19 Pandemic among People with Neurological Disorders: A Cross-Sectional Study Using US Commercial Claims Data**

**Anisha M. Patel, PhD<sup>1</sup>**, Robert Schuldt, PhD<sup>1</sup>, Denise M. Boudreau, PhD<sup>1</sup>, Nikki Win, PhD<sup>1</sup>, Bryan R. Cobb, PhD<sup>1</sup>, Marisa McGinley, DO<sup>2</sup>. <sup>1</sup>Genentech, Inc., South San Francisco, CA, USA, <sup>2</sup>Cleveland Clinic, Cleveland, OH, USA.

**S199. The Current State of Feedback: A Mixed-Method Analysis of Medical Student Feedback in Neurology Clerkships**

**Adam M. Karp, MD**, Matthew Swan, MD, Laura K. Stein, MD, MPH, Michael Fara, MD. Icahn School of Medicine at Mount Sinai, New York, NY, USA.

**\*S200. The VA National TeleNeurology Program (NTNP): Targeting Rural Veterans to Provide Equitable Access to Specialty Care**

**Steven Schreiber, MD<sup>1</sup>**, Aditi Narechania, MD<sup>2</sup>, Heidi Watson, RN<sup>1</sup>, Grace Bastin, BS<sup>3</sup>, Joanne Daggy, PhD<sup>4</sup>, Laura Myers, PhD<sup>3</sup>, Stanley Taylor, MS<sup>3</sup>, Holly Martin, MPH<sup>3</sup>, Linda Williams, MD<sup>3</sup>, Jayne Wilkinson, MD<sup>1</sup>. <sup>1</sup>Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, USA, <sup>2</sup>Jesse Brown VA Medical Center, Chicago, IL, USA, <sup>3</sup>Quality Enhancement Research Initiative Team, Roudebush VA Medical Center, Indianapolis, IN, USA, <sup>4</sup>Dept of Biostatistics, Indiana Univ Sch of Medicine, Indianapolis, IN, USA.

**S201. Thymectomy in Myasthenia Gravis: Enhancement or Expense?**

**Shaweta Khosa, M.B.B.S.<sup>1</sup>**, Gurveer Singh Khosa, M.B.B.S.<sup>2</sup>, Namrata Shetty, B.S.<sup>3</sup>, Robert Freundlich, M.D.<sup>1</sup>, Shri Kant

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**S202. To Neuro or Not to Neuro; That is the Question: A Focus on Women Neurologists Leaving Our Work Force**

**Aparna M. Prabhu, MD, MRCP**. Einstein Medical Center, Philadelphia, PA, USA.

**K-S105. Clinician and Patient Stakeholder Perspectives on Cognitive Rehabilitation Interventions for Asylum Seekers and Refugees**

**Altaf Saadi, MD, MSc<sup>1</sup>**, Margarita Velasco, MA<sup>2</sup>, Nusrath Jahan, MD<sup>3</sup>, Ana-Maria Vranceanu, PhD<sup>1</sup>, Margarita Alegria, PhD<sup>1</sup>. <sup>1</sup>Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA, <sup>2</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>3</sup>Tufts School of Medicine, Boston, MA, USA.

**\*LB-S106. Case-Based Didactic Curriculum in Neurology Residency Continuity Clinic**

**Jose Montes-Rivera, MD**. UConn Health, Farmington, CT, USA.

**LB-S107. Medical Student Interest in Neurology at a Historically Black College & University (HBCU)**

**Britney Pitter, BS Neuroscience**, John Degraft Hanson, B.S. Biology, Minnie Mitchell, BS Biology, Erica Sutton, MD FACS, Uma Menon, MD, MBA (Healthcare), FACNS, FAES, FAAN, FANA. Morehouse School of Medicine, Atlanta, GA, USA.

**\*LB-S108. National Epilepsy Learning Healthcare Registry Uncovers Disparities in Care and Outcomes for LGBTQ Community**

**Lidia Moura, MD, PhD, MPH<sup>1</sup>**, Julianne Brooks, MPH<sup>2</sup>, Maria A. Donabue, MD<sup>2</sup>, Aya ElHassan, .<sup>2</sup>, Sahar Zafar, MD, MSc<sup>1</sup>, Nick Abend, MD<sup>3</sup>, William Trescher, MD<sup>4</sup>, Jacob Pellinen, MD<sup>5</sup>, Deepa Sirsi, MD<sup>6</sup>, David Ficker, MD<sup>7</sup>, Shawna W. Benard, MD<sup>8</sup>, Shawna W. Benard, MD<sup>8</sup>, Jeffrey Buchhalter, MD, PhD<sup>9</sup>, Kathleen Farrell, MD<sup>9</sup>, Brandy Fureman, PhD<sup>9</sup>. <sup>1</sup>Harvard Medical School | MGH, Boston, MA, USA, <sup>2</sup>MGH, Boston, MA, USA, <sup>3</sup>Children's Hospital of Philadelphia, Philadelphia, PA, USA, <sup>4</sup>Penn State Health Milton S. Hershey Medical Center, Hershey, PA, USA, <sup>5</sup>University of Colorado Denver School, Aurora, CO, USA, <sup>6</sup>UT Southwestern Medical Center, Dallas, TX, USA, <sup>7</sup>UC Health, Cincinnati, OH, USA, <sup>8</sup>Keck School of Medicine of USC, Los Angeles, CA, USA, <sup>9</sup>Epilepsy Foundation, Bowie, MD, USA.

# Movement Disorders

## \*S203. A Genome-Wide CRISPR Interference Screen Reveals Genetic Modifiers of Lysosomal Glucocerebrosidase Activity

**Georgia Minakaki, PhD<sup>1</sup>**, Nathaniel Safren, PhD<sup>1</sup>, Niccolò E. Mencacci, MD, PhD<sup>2</sup>, Dimitri Krainc, MD, PhD<sup>2</sup>. <sup>1</sup>Ken and Ruth Davee Department of Neurology, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA, <sup>2</sup>Ken and Ruth Davee Department of Neurology and Simpson Querrey Center for Neurogenetics, Northwestern University, Feinberg School of Medicine, Chicago, IL, USA.

## \*S204. A Minimal Clinically Important Difference for UHDRS® Total Maximal Chorea Score as a Measure of Chorea Severity in Huntington Disease

**Erin Furr Stimming, MD<sup>1</sup>**, Daniel O. Claassen, MD<sup>2</sup>, Elise Kayson, MS, RN, ANP<sup>3</sup>, Jody Goldstein, BS<sup>3</sup>, Hui Zhang, PhD<sup>4</sup>, Olga Klepitskaya, MD<sup>4</sup>, Grace Liang, MD<sup>4</sup>, Dietrich Haubenberger, MD<sup>4</sup>. <sup>1</sup>The University of Texas Health Science Center at Houston, McGovern Medical School, Houston, TX, USA, <sup>2</sup>Vanderbilt University Medical Center, Nashville, TN, USA, <sup>3</sup>Huntington Study Group®, Rochester, NY, USA, <sup>4</sup>Neurocrine Biosciences, Inc., San Diego, CA, USA.

## S205. Adolescent Onset Ataxia Neuropathy Spectrum Disorder with a G737R POLG Variant

**John Rafferty, BS**, Prashant Natteru, MD, Annie Killoran, MD, MSc. University of Iowa Hospitals and Clinics Department of Neurology, Iowa City, IA, USA.

## S206. An Atypical Presentation of Tardive Dyskinesia in an Adolescent Patient with Complex Neuropsychiatric History: A Case Report

**Zachary Roccaforte, BS**, Parnaz Daghighi, BA, J. Chase Findley, MD, Cristian Zeni, MD PhD. McGovern Medical School, The University of Texas Health Science Center at Houston, Houston, TX, USA.

## \*S207. ATN<sub>PD</sub> Framework Using Biofluid Markers Predicts Cognitive Decline in Early Parkinson's Disease

**Katheryn AQ Cousins, PhD<sup>1</sup>**, David J. Irwin, MD<sup>1</sup>, Thomas F. Tropea, DO<sup>1</sup>, Emma Rhodes, PhD<sup>1</sup>, Jeffrey S. Phillips, PhD<sup>1</sup>, Alice S. Chen-Plotkin, MD<sup>1</sup>, Michael C. Brumm, MS<sup>2</sup>, Christopher S. Coffey, PhD<sup>2</sup>, Ju Hee Kang, PhD<sup>3</sup>, Tanya Simuni, MD<sup>4</sup>, Tatiana Foroud, PhD<sup>5</sup>, Arthur W. Toga, PhD<sup>6</sup>, Caroline M. Tanner, MD, PhD<sup>7</sup>, Karl Kiebert, MD, MPH<sup>8</sup>, Brit Mollenhauer, MD<sup>9</sup>, Douglas R. Galasko, MD<sup>10</sup>, Samantha Hutten, PhD<sup>11</sup>, Daniel Weintraub, MD<sup>1</sup>, Andrew Siderowf, MD<sup>1</sup>, Kenneth Marek, MD<sup>12</sup>, Gwendlyn Kollmorgen, PhD<sup>13</sup>, Kathleen L. Poston, MD, MS<sup>14</sup>, Leslie M. Shaw, PhD<sup>1</sup>. <sup>1</sup>University of

Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>University of Iowa, Iowa City, IA, USA, <sup>3</sup>Inha University, Incheon, Korea, Republic of, <sup>4</sup>Northwestern University, Chicago, IL, USA, <sup>5</sup>Indiana University, Indianapolis, IN, USA, <sup>6</sup>University of Southern California, Los Angeles, CA, USA, <sup>7</sup>University of California San Francisco, San Francisco, CA, USA, <sup>8</sup>University of Rochester Medical Center, Rochester, NY, USA, <sup>9</sup>University Medical Center, Göttingen, Göttingen, Germany, <sup>10</sup>University of California San Diego, San Diego, PA, USA, <sup>11</sup>The Michael J. Fox Foundation, New York, NY, USA, <sup>12</sup>Institute for Neurodegenerative Disorders, New Haven, CT, USA, <sup>13</sup>Roche Diagnostics GmbH, Penzberg, Germany, <sup>14</sup>Stanford University, Palo Alto, CA, USA.

## \*S210. Cropland Density and Risk of Parkinson Disease in Medicare Beneficiaries

**Brittany Krzyzanowski, PhD**, Brad A. Racette, MD. Barrow Neurological Institute, Phoenix, AZ, USA.

## \*S211. Differential Diagnoses for Patients Presenting to a Multi-Disciplinary Normal Pressure Hydrocephalus Clinic

**Kathryn Sine, BS<sup>1</sup>**, Saud Alhusaini, MD, PhD<sup>1</sup>, Prarthana Prakash, MD<sup>1</sup>, Laura E. Korthauer, PhD<sup>2</sup>, Seth A. Margolis, PhD<sup>2</sup>, Nicole Rawnley, DPT, NCS<sup>3</sup>, Elizabeth Breen, DPT<sup>3</sup>, Athar Malik, MD, PhD<sup>4</sup>, Konstantina Svokos, DO, MS<sup>4</sup>, Jennifer Davis, PhD<sup>2</sup>, Petra Klinge, MD, PhD<sup>4</sup>, Umer Akbar, MD<sup>1</sup>. <sup>1</sup>Department of Neurology, Alpert Medical School of Brown University, Providence, RI, USA, <sup>2</sup>Department of Psychiatry & Human Behavior, Alpert Medical School of Brown University, Providence, RI, USA, <sup>3</sup>Rehabilitation Services, Rhode Island Hospital, Providence, RI, USA, <sup>4</sup>Neurosurgery Department, Alpert Medical School of Brown University, Providence, RI, USA.

## S212. Disturbances of Basal Ganglia and Cerebellar Bioenergetics in Patients with X-linked Dystonia-Parkinsonism and Heterozygous TAF1 Insertion Carriers

**Jannik Prasuhn, M.D.<sup>1</sup>**, Julia Henkel, M.D.<sup>1</sup>, Ana Westenberger, Ph.D.<sup>2</sup>, Jan Uter, M.D.<sup>1</sup>, Raymond L. Rosales, M.D.<sup>3</sup>, Christine Klein, M.D.<sup>2</sup>, Julia Steinhardt, Ph.D.<sup>1</sup>, Cid C. Diesta, M.D.<sup>4</sup>, Norbert Brüggemann, M.D.<sup>1</sup>. <sup>1</sup>Dpt. of Neurology, University Medical Center Schleswig-Holstein, Lübeck, Germany, <sup>2</sup>Institute of Neurogenetics, University of Lübeck, Lübeck, Germany, <sup>3</sup>University of Santo Tomas, Manila, Philippines, <sup>4</sup>Asian Hospital and Medical Center, Filinvest Corporate City, Alabang, Muntinlupa City, Lübeck, Philippines.

## \*S213. Dopaminergic Neuronal Cell Therapy for Parkinson's Disease: Results from a Phase 1 Study of Bemdaneprocel

**Claire Henchcliffe, MD, PhD<sup>1</sup>**, Harini Sarva, MD<sup>2</sup>, Andres Lozano, MD, PhD, FRCSC, FRSC, FCAHS<sup>3</sup>,

Alfonso Fasano, MD, PhD<sup>3</sup>, Suneil Kalia, MD, PhD<sup>3</sup>, Cameron Brennan, MD, FAANS<sup>4</sup>, Kenneth Yu, MD, MBBS, PhD, FRCS<sup>4</sup>, Marcus Yountz, MD<sup>5</sup>, Ahmed Enayetallah, MD, PhD<sup>6</sup>, Marcus Yountz, MD<sup>6</sup>, Antoine Lampron, PhD<sup>6</sup>, Viviane Tabar, MD<sup>4</sup>. <sup>1</sup>University of California - Irvine, Irvine, CA, USA, <sup>2</sup>Weill Cornell - Medical Center, New York, NY, USA, <sup>3</sup>University Health Network, Toronto, ON, Canada, <sup>4</sup>Memorial Sloan Kettering Cancer Center, New York, NY, USA, <sup>5</sup>Bluerock Therapeutics, Boston, MA, USA, <sup>6</sup>Bluerock Therapeutics, Cambridge, MA, USA.

**\*S214. Early Changes in  $\alpha$ -Synuclein Membrane-Binding in the Central and Enteric Nervous System in Parkinson's Disease**

Virginia Gao, MD, PhD<sup>1</sup>, Juan Briano, BA<sup>2</sup>, Lauren Komer, BA<sup>2</sup>, Carl Crawford, MD<sup>2</sup>, Claire Henchcliffe, MD DPhil<sup>3</sup>, Andrea Lee, MD<sup>4</sup>, Jacqueline Burré, PhD<sup>2</sup>. <sup>1</sup>Weill Cornell and Columbia, New York, NY, USA, <sup>2</sup>Weill Cornell, New York, NY, USA, <sup>3</sup>University of California Irvine, Irvine, CA, USA, <sup>4</sup>University of Kansas Medical Center, Kansas City, KS, USA.

**S215. Early Onset Parkinson's Disease Patients with Rem Behavioral Disorder and Constipation Show Poor Performance on the Mental Rotation Task**

Joyeta Razzaque, MD<sup>1</sup>, Bryan Mullen, BS<sup>1</sup>, Khoi Le, MS<sup>1</sup>, Megha P. Subramanian, BS<sup>2</sup>, Chase Dougherty, MD<sup>2</sup>, Samyuktha Ravi, MS<sup>2</sup>, Daymond Wagner, MS<sup>2</sup>, Keshav Iyer, BS<sup>2</sup>, Thyagarajan Subramanian, MD, MBA<sup>1</sup>, Kala Venkiteswaran, PhD<sup>1</sup>, Huriyyah Chaudhry, BSc<sup>1</sup>, Paul Eslinger, PhD<sup>2</sup>. <sup>1</sup>The University of Toledo, Toledo, OH, USA, <sup>2</sup>Penn State College of Medicine, Hershey, PA, USA.

**\*S216. Elucidating the Retromer-Mediated Neuroprotective Mechanisms in Parkinson's Disease**

Michele Persico, MD, Tracy Shi Zhang Fang, MD, PhD, Carli Tucci, Bachelors of Science Candidate, David Keith Simon, MD, PhD, Simona Carmen Eleuteri, PhD. Beth Israel Deaconess Medical Center, Boston, MA, USA.

**S217. Evaluation of  $\alpha$ -Synuclein in Blood CNS-Originating Extracellular Vesicles for Parkinsonian Disorders: Systematic Review and Meta-Analysis**

Hash Brown Taba, MS, Shomik Ati, MS. University of California Los Angeles, Los Angeles, CA, USA.

**\*S218. Extensibility of Machine Learning Models for Remote Monitoring of Parkinson's Disease Motor Symptoms across Geography and Disease Severity**

King Chung Ho, PhD<sup>1</sup>, Maximilien Burq, PhD<sup>1</sup>, Erin Rainaldi, MS<sup>1</sup>, Chen Chen, PhD<sup>1</sup>, Genko Oyama, MD, PhD<sup>2</sup>, Yoshihiko Furusawa, MD, PhD<sup>3</sup>, Nobutaka Hattori, MD,

PhD<sup>2</sup>, William J. Marks, Jr., MD<sup>1</sup>, Ritu Kapur, PhD<sup>1</sup>. <sup>1</sup>Verily Life Science, San Francisco, CA, USA, <sup>2</sup>Juntendo University Faculty of Medicine, Tokyo, Japan, <sup>3</sup>Takeda Pharmaceutical Company Limited, Tokyo, Japan.

**\*S219. Feasibility of Neurofilament Light Chain as a Blood-Based Biomarker for Screening across Neurological Diseases**

Briana Cameron, PhD<sup>1</sup>, Anisha M. Patel, PhD<sup>1</sup>, Bryan R. Cobb, PhD<sup>1</sup>, Ivonne Suridjan, PhD<sup>2</sup>, Nikki Win, PhD<sup>1</sup>. <sup>1</sup>Genentech, Inc., South San Francisco, CA, USA, <sup>2</sup>Roche Diagnostics International Ltd, Rotkreuz, Switzerland.

**\*S221. Guanidine Hydrazone (2a): A Novel Disease-Modifying Treatment for Parkinson's Disease**

Michele Persico, MD, Tracy Shi Zhang Fang, MD, PhD, Simona Carmen Eleuteri, PhD, David Keith Simon, MD, PhD. Beth Israel Deaconess Medical Center, Harvard Medical School, Boston, MA, USA.

**\*S222. Higher Plasma Concentrations of Peripheral Inflammatory Markers in Parkinson's Disease Linked to Cognitive Impairment and Worse Clinical Outcomes**

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**\*S223. Human Astrocyte Lipid Trafficking Dysregulation in Parkinson's Disease**

Aboud Tabanis, M.D.<sup>1</sup>, Megh Patel, B.S.<sup>1</sup>, Samira Aghlari-Fotovat, B.S.<sup>2</sup>, Thao Nguyen, Ph. D.<sup>1</sup>, Robert Krencik, Ph. D.<sup>1</sup>. <sup>1</sup>Center for Neuroregeneration, Houston Methodist Research Institute, Houston, TX, USA, <sup>2</sup>Department of Bioengineering, Rice University, Houston, TX, USA.

**S224. Late-Onset Wilson's Disease in an Elderly Woman with Unusual Natural History: A Case Report**

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**\*S225. Limitations in Biomarker Discovery Efforts for Prodromal Huntington's Disease**

Alex Pinto, MS<sup>1</sup>, Maria Rudrud, HS<sup>1</sup>, William H. Adams, PhD<sup>2</sup>, Michael A. Newton, PhD<sup>1</sup>, H. Jeremy Bockholt, MS<sup>3</sup>, Kathleen M. Shannon, MD<sup>1</sup>, **Jane S. Paulsen, PhD<sup>1</sup>**.  
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**\*S226. Lower Doses of Tofacitinib Extend Survival in ALS Mice**

**Benjamin Murdock, Ph.D.** University of Michigan, Ann Arbor, MI, USA.

**\*S227. Measurement of Systemic Phospho-Tau, Ab, NfL and GFAP in Patients with Essential Tremor and Parkinson's Disease after MR-Guided High Intensity Focused Ultrasounds**

**Nil Saez Calveras, MD**, Barbara Stopschinski, MD, Marc Diamond, MD, Bhavya Shah, MD. University of Texas Southwestern, Dallas, TX, USA.

**\*S228. Movement Disorders in Adults with X-linked Adrenoleukodystrophy**

**Natalie Grant, BA**, Melanie Leigh Supnet, MD, Lizbeth De la Rosa, BS, Xena Al Qahtani, MBBS, Christopher Stephen, MBCHB, Catherine Becker, MSN, RN, Nutan Sharma, MD, PhD, Florian Eichler, MD. Massachusetts General Hospital, Boston, MA, USA.

**S229. Myelin Lipid Composition of Sciatic Nerves in a HNPP Mouse Model**

**Sebastian Pernal, M.S.**, Bo Hu, Ph.D., Jun Li, M.D., Ph.D. Houston Methodist Research Institute, Houston, TX, USA.

**\*S230. Neuroanatomical Origin of Anxiety in Cervical Dystonia: Are the Basal Ganglia the Culprit?**

**Abhimanyu Mahajan, MD, MHS**, Travis Stoub, PhD, Glenn Stebbins, PhD, David A. Gonzalez, PhD, Dana Sugar, MD, Gabrielle Gray, BS, Tila WarnerRosen, BA, Caroline Pylpyuk, N/A, Mandy Yu, BS, Cynthia Comella, MD. Rush University Medical Center, Chicago, IL, USA.

**\*S231. Nicotinamide Riboside Supplementation for Early Parkinson's Disease: Clinical Benefit Correlates with a Distinct Resting State Network**

**János Barbero, MD/PhD Candidate<sup>1</sup>**, An Vo, PhD<sup>1</sup>, Yilong Ma, PhD<sup>1</sup>, Shichun Peng, PhD<sup>1</sup>, Brage Brakedal, MD, PhD

Fellow<sup>2</sup>, Christian Dölle, Dr.-Ing<sup>2</sup>, Vivian Skjeie, BS<sup>2</sup>, Charalampos Tzoulis, MD, PhD<sup>2</sup>, David Eidelberg, MD<sup>1</sup>.

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**S232. Online Self Report of Problems and Functional Consequences in Huntington Disease: Feasibility and Informativeness**

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**S233. Palingenetic Delusional Movement Disorder as Part of Kandinsky-Clerambault Syndrome**

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**S234. Pathophysiology and Radiological Features of Hemichorea Hemiballismus Syndrome: A Literature Review**

**Juan F. Ortiz, MD<sup>1</sup>**, Alex S. Aguirre, MD<sup>2</sup>, Ricardo A. Vivanco, MD<sup>3</sup>, John Fiallos, MD<sup>4</sup>, Gabriela Garofalo, Medical Student<sup>5</sup>, Olga M. Astudillo, MD<sup>6</sup>, Walter E. Insuasti, MD<sup>7</sup>. <sup>1</sup>Corewell Health/Michigan State University, Grand Rapids, MI, USA, <sup>2</sup>Universidad San Francisco de Quito, Quito, Ecuador, <sup>3</sup>Universidad Católica de Santiago de Guayaquil, Guayaquil, Ecuador, <sup>4</sup>Universidad de Guayaquil, Guayaquil, Ecuador, <sup>5</sup>Universidad Central del Ecuador, Quito, Ecuador, <sup>6</sup>Universidad de Cuenca, Cuenca, Ecuador, <sup>7</sup>Larkin Community Hospital, Miami, FL, USA.

**\*S235. Quantifying the Value of Multimodal MRI in Outcomes Prediction for STN DBS in PD**

**John R. Younce, M.D.<sup>1</sup>**, Scott A. Norris, M.D.<sup>2</sup>, Joel S. Perlmuter, M.D.<sup>2</sup>. <sup>1</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>2</sup>Washington University in St Louis, St Louis, MO, USA.

**\*S236. Racial and Ethnic Differences in Suicidal Ideation in North American Patients with Huntington's Disease: Analysis Using the Enroll-HD Dataset**

**Adys Mendizabal, MD, MS**, Susan Perlman, MD, Yvette Bordelon, MD/PhD. UCLA, Los Angeles, CA, USA.

**\*S237. Remote Monitoring of Physical Activity for Tracking Disease Progression in Friedreich Ataxia**

**David Lynch, MD PHD<sup>1</sup>**, McKenzie Wells, MS<sup>1</sup>, Ram Kinker Mishra, PhD<sup>2</sup>, Ana Enriquez, BS<sup>2</sup>, Ashkan Vaziri, PhD<sup>2</sup>. <sup>1</sup>Children's Hospital of Philadelphia, Philadelphia, PA, USA, <sup>2</sup>Biosensics, Newton, MA, USA.

**\*S238. Remote UHDRS Motor Exam Using Machine Learning**

*H. Jeremy Bockholt, MS<sup>1</sup>, Kathleen M. Shannon, MD<sup>2</sup>, Michael A. Newton, PhD<sup>2</sup>, William H. Adams, PhD<sup>3</sup>, Vince D. Calhoun, PhD<sup>1</sup>, Jane S. Paulsen, PhD<sup>2</sup>.* <sup>1</sup>Tri-Institutional Center for Translational Research in Neuroimaging and Data Science (TReNDS), Georgia State University, Georgia Institute of Technology, and Emory University, Atlanta, GA, USA, <sup>2</sup>University of Wisconsin-Madison, Madison, WI, USA, <sup>3</sup>Loyola University Chicago, Chicago, IL, USA.

**\*S240. Sex Differences for Clinical Correlates of Lewy Body Pathology, Alzheimer Disease Pathology and Substantia Nigra Neuron Loss in Lewy Body Dementia**

*Ece Bayram, MD, PhD, Irene Litvan, MD.* University of California San Diego, La Jolla, CA, USA.

**S241. Spastic Ataxia 4 Due to mtPAP Deficiency, Case Presentation and Literature Review**

*Austin Clanton, MD, Ramsha Bhutta, MD, Faiza Butt, MD.* University of Oklahoma Health Sciences Center, Oklahoma City, OK, USA.

**\*S242. Statewide Burdens of Parkinson's Disease across the United States between 1990-2019: A Systematic and Comparative Benchmarking Study**

*Hassan Chaudhry, MD<sup>1</sup>, Hardik Dineshbhai Desai, MBBS<sup>2</sup>, Vishrant Amin, MBBS<sup>3</sup>, Juhi R. Patel, MBBS<sup>3</sup>, Nadia Hossain, MBBS<sup>4</sup>.* <sup>1</sup>Medical University of Lublin, Lublin, Poland, <sup>2</sup>Gujarat Adani Institute of Medical Sciences, Bhuj, India, <sup>3</sup>GMERS Medical College, Valsad, India, <sup>4</sup>Dhaka Medical College, Dhaka, Bangladesh.

**\*S243. T1 MRI Reveals Differential Hippocampal Atrophy in Lewy Body Disorders with and without Alzheimer's Copathology**

*Jesse Cohen, MD, Jeffrey Phillips, PhD, Sandhitsu Das, PhD, Emma Rhodes, PhD, Katheryn Cousins, PhD, Paul Yushkevich, PhD, David Wolk, MD, Daniel Weintraub, MD, David Irwin, MD, Corey McMillan, PhD.* University of Pennsylvania, Philadelphia, PA, USA.

**\*S244. Tandem Gait Step-Width Increases More Rapidly In More Severely Affected Patients With Parkinson's Disease**

*Jennie Burns, BS, Lakshmi Pillai, MS, Reid Landes, PhD, Tuhin Virmani, MD, PhD.* University of Arkansas for Medical Sciences, Little Rock, AR, USA.

**\*S245. Tau Maturation in Clinicopathological Spectrum of Lewy Body and Alzheimer's Disease**

*Sanaz Arezoumandan, MD, Katheryn A.Q. Cousins, PhD, Daniel Ohm, PhD, Makayla Lowe, MS, Jeffrey S. Phillips,*

*PhD, Corey McMillan, PhD, Andrew D. Siderowf, MD, Alice Chen-Plotkin, MD, Andres Deik, MD, MEd, Meredith Spindler, MD, Thomas Tropea, DO, Daniel Weintraub, MD, David Wolk, MD, Murray Grossman, MD, Edward Lee, MD, PhD, David Irwin, MD.* University of Pennsylvania, Philadelphia, PA, USA.

**\*S246. The Adaptive Immune System is Not Necessary for  $\alpha$ -Synuclein Pathology Formation or Dopaminergic Neuron Loss after  $\alpha$ -Synuclein Pre-Formed Fibril Injection**

*Esteban Luna, MD/PHD.* University of Pennsylvania, Philadelphia, PA, USA.

**S247. The Effect of Deep Brain Stimulation on the Sequence Effect in Speech in Parkinson's Disease**

*Goun Je, MD-PhD<sup>1</sup>, Kevin B. Wilkins, PhD<sup>1</sup>, Jillian A. Melbourne, BS<sup>1</sup>, Helen M. Bronte-Stewart, MD, MSE<sup>2</sup>.* <sup>1</sup>Department of Neurology and Neurological Sciences, Stanford University School of Medicine, Stanford, CA, USA, <sup>2</sup>Department of Neurology and Neurological Sciences, Department of Neurosurgery, Stanford University School of Medicine, Stanford, CA, USA.

**\*S248. Therapeutic Suppression of Tubulin alpha 4a Rescues HABC Leukodystrophy in Mice**

*Sunetra Sase, PhD<sup>1</sup>, Julia Hacker, MS<sup>1</sup>, Prabhat Napit, PhD<sup>1</sup>, Asako Takanohashi, PhD DVM<sup>1</sup>, Quasar Padiath, MBBS PhD<sup>2</sup>, Eric Marsh, MD PhD<sup>1</sup>, Adeline Vanderver, MD<sup>1</sup>.* <sup>1</sup>Children's Hospital of Philadelphia, Philadelphia, PA, USA, <sup>2</sup>University of Pittsburgh, Pittsburgh, PA, USA.

**\*S251. Understanding How GBA Mutations Influence Parkinson's Disease Progression**

*Arnav Khera, BS<sup>1</sup>, Sarah Fish, BA, BAS<sup>1</sup>, Raja Estes, BS<sup>2</sup>, Selina Yu, BS<sup>1</sup>, Leo Pallanck, BS, PhD<sup>3</sup>, Jessica Young, BS, MA, PhD<sup>4</sup>, Marie Davis, BS, MD, PhD<sup>1</sup>.* <sup>1</sup>VA Puget Sound, Seattle, WA, USA, <sup>2</sup>VA Puget Sound Health Care System, Seattle, WA, USA, <sup>3</sup>Department of Genome Sciences, University of Washington, Seattle, WA, USA, <sup>4</sup>Institute for Stem Cell Regenerative Medicine, University of Washington, Seattle, WA, USA.

**\*S254. Variability between Patient and Caregiver QUIP-RS Scores before and after Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease**

*Asra Askari, MD, Xiru Lyu, MS, Parag Patil, MD, PhD, Kelvin Chou, MD.* University of Michigan, Ann Arbor, MI, USA.

**\*S256. White Matter Lesion Characteristics of Patients with Multiple Sclerosis and Parkinsonism**

*Yiwen Shi, MD<sup>1</sup>, Sachin Gadani, MD, PhD<sup>2</sup>, Kelly A. Mills, MD, MHS<sup>2</sup>.* <sup>1</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>Johns Hopkins Hospital, Baltimore, MD, USA.

**K-S106. In Humans, Striato-Pallido-Thalamic Projections are Largely Segregated by Their Origin in Either the Striosome or Matrix Compartments**

*Adrian T. Funk, BA<sup>1</sup>, Asim AO Hassan, MA<sup>1</sup>, Norbert Brüggemann, MD<sup>2</sup>, Nutan Sharma, MD/PhD<sup>3</sup>, Hans C. Breiter, MD<sup>4</sup>, Anne J. Blood, PhD<sup>3</sup>, Jeff L. Waugh, MD/PhD<sup>1</sup>. <sup>1</sup>University of Texas Southwestern, Dallas, TX, USA, <sup>2</sup>University of Luebeck, Luebeck, Germany, <sup>3</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>4</sup>University of Cincinnati, Cincinnati, OH, USA.*

**K-S107. Quantifying the Value of Multimodal MRI in Outcomes Prediction for STN DBS in PD**

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**\*LB-S109. Genetic Factors and Clinical Heterogeneity of Parkinson's Disease: Genome-Wide Association Study on PD Subtypes**

*Jaroslav Dulski, MD PhD<sup>1</sup>, Ryan J. Uitti, MD<sup>1</sup>, Alexandra Beasley, MS<sup>1</sup>, Dena Hernandez, PhD<sup>2</sup>, Vijay Ramanan, MD PhD<sup>3</sup>, Elliot Cahn, MS<sup>3</sup>, Yingxue Ren, PhD<sup>1</sup>, Patrick Johnson, MS<sup>1</sup>, Zachary Quicksall, MS<sup>1</sup>, Zbigniew Wszolek, MD<sup>1</sup>, Owen Ross, PhD<sup>1</sup>, Michael Heckman, MS<sup>1</sup>. <sup>1</sup>Mayo Clinic Florida, Jacksonville, FL, USA, <sup>2</sup>National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA, <sup>3</sup>Mayo Clinic Florida, Rochester, MN, USA.*

**\*LB-S110. Paired Deep Brain Stimuli Elicit Short-Term Facilitation in Globus Pallidus Interna and Subthalamic Nucleus**

*Harrison Walker, MD, Cameron Gordon, BA, Mohammad Awad, MS, Sarah Brinkerhoff, MS, Christopher Gonzalez, MS, Arie Nakhmani, PhD, Joseph Olson, PhD, Nicole Bentley, MD, Marshall Holland, MD, Bart Guthrie, MD. University of Alabama at Birmingham, Birmingham, AL, USA.*

**\*LB-S111. Plasma-Derived Alpha-Synuclein Strains Distinguish Parkinson's Disease from Dementia with Lewy Bodies**

*George T. Kannarkat, MD, PhD<sup>1</sup>, Rebecca Zack, BS<sup>1</sup>, R Tyler Skrinak, BS<sup>1</sup>, James F. Morley, MD, PhD<sup>1,2</sup>, Roseanne Davila-Rivera, BS<sup>1</sup>, Sanaz Arezoumandan, MD<sup>1</sup>, Katherine Dorfman, BS<sup>1</sup>, Kelvin Luk, PhD<sup>1</sup>, Daniel Weintraub, MD<sup>1,2</sup>, Thomas F. Tropea, MD<sup>1</sup>, Edward B. Lee, MD, PhD<sup>1</sup>, Virginia M-Y Lee, PhD<sup>1</sup>, David Irwin, MD<sup>1</sup>, Rizwan S. Akhtar, MD, PhD<sup>3</sup>, Alice Chen-Plotkin, MD<sup>1</sup>. <sup>1</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>Corporal Michael J. Crescenz VA Medical Center, Philadelphia, PA, USA, <sup>3</sup>Northwestern University Feinberg School of Medicine, Chicago, IL, USA.*

**\*LB-S112. Prediction of Phenoconversion Time in REM Sleep Behavior Disorder (RBD) with Brain Metabolic Network and Dopaminergic Imaging: A Longitudinal Study**

*Chris C. Tang, MD, PhD<sup>1</sup>, Katharina Schindlbeck, MD<sup>1</sup>, Yoshikazu Nakano, MD<sup>1</sup>, Martin Niethammer, MD, PhD<sup>1</sup>, Vijay Dhawan, PhD<sup>1</sup>, Kathleen Poston, MD, MSc<sup>2</sup>, David Eidelberg, MD<sup>1</sup>. <sup>1</sup>Feinstein Institutes for Medical Research, Manhasset, NY, USA, <sup>2</sup>Stanford School of Medicine, Stanford, CA, USA.*

**\*LB-S113. Social Determinants of Health and Health-Related Quality of Life in Individuals with Isolated Dystonia**

*Caroline Nelson, BA, Chris Stephen, MBCHB, Nutan Sharma, MD, PhD, Marisela Dy-Hollins, MD. Massachusetts General Hospital, Boston, MA, USA.*

## Neurodegeneration and Cell Death

**\*S276. Age-Dependent Changes in Perineuronal Nets and Associated Parvalbumin Interneurons in the 5xFAD Amyloidosis Mouse Model**

*Ruth S. Nelson, BS (2023), Claudia Espinosa-Garcia, PhD, Prateek Kumar, PhD, Sruti Rayaprolu, PhD, Hailian Xiao, BS, Srikant Rangaraju, MBBS, MS. Emory University, Atlanta, GA, USA.*

**S277. An Overview of Peripheral Nervous System Aging Findings in Human and Animal Studies**

*Shaweta Khosa, M.B.B.S.<sup>1</sup>, Gurveer Singh Khosa, M.B.B.S.<sup>2</sup>, Namrata Shetty, B.S.<sup>3</sup>, Robert Freundlich, M.D.<sup>4</sup>, Shri Kant Mishra, M.D.<sup>5</sup>. <sup>1</sup>VA Greater Los Angeles Health Care, Los Angeles, CA, USA, <sup>2</sup>Adesh Institute of Medical Sciences & Research, Bathinda, India, <sup>3</sup>University of California San Francisco, San Francisco, CA, USA, <sup>4</sup>Olive View-UCLA Medical Center, Sylmar, CA, USA, <sup>5</sup>Keck School of Medicine of USC, Los Angeles, CA, USA.*

**\*S278. Brain Tau and  $\alpha$ -Synuclein Seeding Activity Correlates with Pathological Disease Stage and Precedes Neurofibrillary Tangle and Lewy Body Formation**

*David G. Coughlin, MD MTR<sup>1</sup>, Denis Smirnov, MD PhD<sup>1</sup>, Yongya Kim, BSc<sup>1</sup>, Matteo Manca, PhD<sup>2</sup>, Danielle F. Browne, BSc<sup>2</sup>, Hannah H. Zamore, AB<sup>2</sup>, Mikayla L. Huntley, BSc<sup>2</sup>, Olivia R. Thomas, BA<sup>2</sup>, Douglas Galasko, MD<sup>1</sup>, Annie Hiniker, MD PhD<sup>1</sup>, Allison Kraus, PhD<sup>2</sup>. <sup>1</sup>University of California San Diego, La Jolla, CA, USA, <sup>2</sup>Case Western Reserve University, Cleveland, OH, USA.*



**\*S279. Developing a Scalable HiPSC-Based Model for Characterizing Genetic Modifiers of Synucleinopathies**  
**Xinyuan Wang, MD, PhD**, Ping Xu, MS, Sumaiya Nazeen, PhD, Erinc Hallacli, PhD, Dina Zielinski, PhD, Isabel Lam, PhD, Vikram Khurana, MD, PhD. Brigham and Women's Hospital and Harvard Medical School, Boston, MA, USA.

**\*S280. Development of a Rigorous Approach for Retrospective Natural History Studies in Rare Neurologic Diseases**

**Anjana Sevagamoorthy, MBBS, MPH**, Francesco Gavazzi, M.D., Ph.D., Omar Sherbini, MPH, Ariel Vincent, B.S., Russel D'Aiello, M.S., Isabella Barcelos, M.D., Nicholson Modesti, B.S., Sylvia Mutua, B.A., Emily Yu, B.A., Gabrielle M. Sudilovsky, B.A., Jacqueline A. Erler, B.A., Sarah Woidill, M.S., Kayla Muirhead, M.S., LCGC, Johanna L. Schmidt, MPH, MGC, LCGC, Amy Pizzino, M.S., LCGC, Justine Shults, Ph.D., Adeline Vanderver, M.D., Laura Adang, M.D., Ph.D., MSTR. Children's Hospital of Philadelphia, Philadelphia, PA, USA.

**\*S281. Diffusion Tensor Imaging of the Corpus Callosum as an Early Disease Marker in Adrenoleukodystrophy**

**Elizabeth I. Pierpont, PhD<sup>1</sup>**, Rene Labounek, PhD<sup>1</sup>, Monica T. Bondy, B.S.<sup>1</sup>, Amy Paulson, B.A.<sup>1</sup>, Bryon A. Mueller, PhD<sup>2</sup>, Jeffrey R. Wozniak, PhD<sup>1</sup>, William B. Dobyns, MD<sup>1</sup>, Ashish O. Gupta, MD<sup>1</sup>, Troy C. Lund, MD, PhD<sup>1</sup>, Paul J. Orchard, MD<sup>1</sup>, David Nascene, MD<sup>1</sup>, Igor Nestratil, MD, PhD<sup>1</sup>.  
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**\*S282. Experimental Confirmation of PI3KR1 Gene Mutation as a Cause of ALS-Like Syndrome Associated with Primary Immunodeficiency**

**Farinaz Safavi, MD, PhD<sup>1</sup>**, Brice Calco, BSc<sup>1</sup>, Joe Steiner, PhD<sup>2</sup>, Lisa Henderson, PhD<sup>2</sup>, Suk See DeRavin, MD, PhD<sup>1</sup>, Gulbu Uzel, MD<sup>1</sup>, Christa S. Zerbe, MD<sup>1</sup>, Luigi D. Notarangelo, MD<sup>1</sup>, Steven M. Holland, MD<sup>1</sup>, Avindra Nath, MD<sup>3</sup>. <sup>1</sup>NIAID, NIH, Bethesda, MD, USA, <sup>2</sup>NINDS, NIH, Bethesda, MD, USA.

**\*S283. Inhibition of Multifunctional MIF Protein Prevents Inflammatory- and Parthanatic- Mediated Neurodegeneration in the Context of Multiple Sclerosis**

**Jackson W. Mace, B.S.**, Sachin Gadani, M.D., Ph.D., Danny Galleguillos, Ph.D., Matthew Smith, M.S., Thomas Garton, B.S., Marjan Gharagozloo, Ph.D., Valina L. Dawson, Ph.D., Ted M. Dawson, M.D., Ph.D., Peter A. Calabresi, M.D. Johns Hopkins University School of Medicine, Baltimore, MD, USA.

**\*S284. Investigating the Impact of  $\gamma$ -Secretase Modulator BPN15606 on a Mouse Model of Down Syndrome**

**Xu-Qiao Chen, Ph.D.<sup>1</sup>**, Mariko Sawa, Ph.D.<sup>1</sup>, Ann Becker, BA<sup>1</sup>, Ricardo Albay, Ph.D.<sup>1</sup>, Dmitry Karachentsev, Ph.D.<sup>1</sup>,

Amanda J. Roberts, Ph.D.<sup>2</sup>, Kevin D. Ryneerson, Ph.D.<sup>1</sup>, Rudolph E. Tanzi, Ph.D.<sup>3</sup>, William C. Mobley, Ph.D.; M.D.<sup>1</sup>.  
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**S285. Neuroprotective Impact of Ashwagandha (Withania Somnifera) on Titanium Dioxide Nanoparticle-Induced Neurotoxicity in the Frontal Cortex and Cerebellum in Male Rats: An Experimental Animal Study**

**Ahmed Aljabali, MD<sup>1</sup>**, Ibraheem Alkhawaldeh, MD<sup>2</sup>, Eman Mohammed, MD<sup>2</sup>, Fardous Karawya, MD, PhD<sup>2</sup>, Anas Satari, MD<sup>2</sup>, Sarya Swed, MD<sup>3</sup>. <sup>1</sup>Jordan University of Science & Technology, Irbid, Jordan, <sup>2</sup>Mutah University, Karak, Jordan, <sup>3</sup>Aleppo University, Aleppo, Syrian Arab Republic.

**\*S288. Seizures Exacerbate Cognitive Deficits and Excitatory: Inhibitory Imbalance in Alzheimer's Disease**

**Aaron Barbour, Ph.D.** University of Pennsylvania, Philadelphia, PA, USA.

**\*S289. Transdifferentiation: A Novel Tool for Disease Modeling and Translational Applications in Alzheimer's Disease**

**Ching-Chieh Chou, PhD<sup>1</sup>**, Ryan Vest, PhD<sup>1</sup>, Miguel A. Prado, PhD<sup>2</sup>, Joshua Wilson-Grady, PhD<sup>3</sup>, Joao A. Paulo, PhD<sup>3</sup>, Yohei Shibuya, PhD<sup>1</sup>, Patricia Moran-Losada, PhD<sup>1</sup>, Ting-Ting Lee, PhD<sup>1</sup>, Jian Luo, PhD<sup>4</sup>, Steven P. Gygi, PhD<sup>3</sup>, Jeffery W. Kelly, PhD<sup>5</sup>, Daniel P. Finley, PhD<sup>3</sup>, Marius Wernig, MD<sup>1</sup>, Tony Wyss-Coray, PhD<sup>1</sup>, Judith Frydman, PhD<sup>1</sup>. <sup>1</sup>Stanford University, Stanford, CA, USA, <sup>2</sup>Instituto de Investigación Sanitaria del Principado de Asturias, Oviedo, Spain, <sup>3</sup>Harvard Medical School, Boston, MA, USA, <sup>4</sup>Palo Alto Veterans Institute for Research, Inc., Palo Alto, CA, USA, <sup>5</sup>The Scripps Research Institute, La Jolla, CA, USA.

**K-S108. Amyloid Beta Fibrils Induce Microglial Biosynthesis of Heparan Sulfate Proteoglycans Leading to Increased Tau Phagocytosis and Seeding**

**Brandon B. Holmes, MD PhD<sup>1</sup>**, Yun Zhang, MS<sup>1</sup>, Martin Kampmann, PhD<sup>1</sup>, Jaeda Coutinho-Budd, PhD<sup>2</sup>, Jim A. Wells, PhD<sup>1</sup>. <sup>1</sup>UCSF, San Francisco, CA, USA, <sup>2</sup>University of Virginia, Charlottesville, VA, USA.

**K-S109. Diffusion Tensor Imaging of the Corpus Callosum as an Early Disease Marker in Adrenoleukodystrophy**

**Elizabeth I. Pierpont, PhD**, Rene Labounek, PhD, Monica Bondy, BS, Amy Paulson, MS, Bryon Mueller, PhD, Jeffrey Wozniak, PhD, William Dobyns, MD, Ashish Gupta, MD, Troy Lund, MD, PhD, Paul Orchard, MD, David Nascene, MD, Igor Nestratil, MD, PhD. University of Minnesota Medical School, Minneapolis, MN, USA.

**\*LB-S117. A CRISPR Library Approach to Identify Microglial Genes That Regulate Uptake and Endolysosomal Trafficking of Aggregated Alpha-Synuclein**  
*Yun Chen, BS<sup>1</sup>, Yongjoon Shin, BS<sup>1</sup>, Yuhua Amelia Li, BS (anticipated 2024)<sup>1</sup>, Bruno A. Benitez, MD<sup>2</sup>, Albert A. (Gus) Davis, MD, PhD<sup>1</sup>. <sup>1</sup>Washington University School of Medicine, St Louis, MO, USA, <sup>2</sup>Beth Israel Deaconess Medical Center, Boston, MA, USA.*

**LB-S118. Exploring the Utility of ChatGPT in Enhancing Diagnostic Discussions in Neurodegenerative Disorders**  
*Shunsuke Koga, M.D., Ph.D., Nicholas B. Martin, BS, Dennis W. Dickson, MD. Mayo Clinic, Jacksonville, FL, USA.*

**\*LB-S119. Human iPSC-Derived Neurons Reveal Mechanisms of Selective Neuronal Vulnerability in TBCK Encephaloneuronopathy**  
*Marco Flores-Mendez, PhD<sup>1</sup>, Jesus A. Tintos-Hernandez, PhD<sup>1</sup>, Leonardo Ramos-Rodriguez, BS<sup>2</sup>, Miosotis Alicea-Delgado, BS<sup>2</sup>, Xilma R. Ortiz-Gonzalez, MD, PhD<sup>3</sup>. <sup>1</sup>Children's Hospital of Philadelphia, Philadelphia, PA, USA, <sup>2</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>3</sup>University of Pennsylvania, Children's Hospital of Philadelphia, Philadelphia, PA, USA.*

**\*LB-S120. Poly-GA Pathology Affects Oxidative Stress Response Pathways in an AAV-Based Organotypic Brain Slice Model of C9-ALS/FTD**  
*Feilin Liu, MD<sup>1</sup>, Dmytro Moderer, PhD<sup>1</sup>, Sara Vettleson-Trutza, .<sup>1</sup>, Anh M. Ly, .<sup>1</sup>, Michelle Salemi, .<sup>2</sup>, Chih-Wei Tsai, .<sup>1</sup>, Brett S. Phinney, PhD<sup>2</sup>, Dennis W. Dickson, MD<sup>1</sup>, Wilfried Rossoll, PhD<sup>1</sup>. <sup>1</sup>Mayo Clinic, Jacksonville, FL, USA, <sup>2</sup>University of California at Davis, Davis, CA, USA.*

**LB-S121. Undercover COP (CO Poisoning) Carbon Monoxide Poisoning - Under-Diagnosed "Refractory Psychosis"**  
*Amber R. Hughes, BS BA<sup>1</sup>, Spencer Brown, MPH<sup>1</sup>, Rajiv K. Midha, MS<sup>1</sup>, Kamil Dar, MBBS<sup>2</sup>, Jordan J. Ghassemian, MD<sup>2</sup>. <sup>1</sup>St. George's University, St. George, Grenada, <sup>2</sup>Elmhurst Hospital Center, Mount Sinai Services, Queens, NY, USA.*

## Neurodevelopment

**S291. Atypical Presentation of Vasovagal Episodes in Chiari Malformation Type 1**  
*G. Peter Gliebus, M.D.<sup>1</sup>, Benjamin Rahmani, MS<sup>3</sup>, Kenneth Liebman, M.D.<sup>1</sup>, Jennifer Ross, Ph.D.<sup>1</sup>. <sup>1</sup>Drexel University COM / Global Neurosciences Institute, Philadelphia, PA, USA, <sup>2</sup>Drexel University COM, Philadelphia, PA, USA.*

**S292. Blood-Brain Barrier Function Associates with Brain Iron Dynamics along Developmental Trajectory: A Combined Quantitative Magnetic Resonance Imaging Study during Childhood**  
*Yuto Uchida, MD, PhD<sup>1</sup>, Hirohito Kan, PhD<sup>2</sup>, Gen Furukawa, MD<sup>3</sup>, Kengo Onda, MD<sup>1</sup>, Keita Sakurai, MD, PhD<sup>4</sup>, Koji Takada, MD, PhD<sup>5</sup>, Noriyuki Matsukawa, MD, PhD<sup>6</sup>, Kenichi Oishi, MD, PhD<sup>1</sup>. <sup>1</sup>Johns Hopkins University, Baltimore, MD, USA, <sup>2</sup>Nagoya University Graduate School of Medicine, Nagoya, Japan, <sup>3</sup>Fujita Health University School of Medicine, Toyoake, Japan, <sup>4</sup>National Center for Geriatrics and Gerontology, Obu, Japan, <sup>5</sup>Toyokawa City Hospital, Toyokawa, Japan, <sup>6</sup>Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan.*

**\*S293. Clinical Outcomes in Aicardi Goutières Syndrome: A Natural History Study**  
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**S294. Development of a Disease-Specific Scale for Multiple Sulfatase Deficiency**  
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**\*S295. Early Disruption of Epigenetic and Transcriptomic Organization after Prenatal Hypoxia Predicts Persistent Functional Deficits in Glutamatergic Neurons**  
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**\*S296. Gross Motor Function in Pediatric Onset TUBB4A-Related Leukodystrophy: GMFM-88 Performance and Validation of GMFC-MLD Use**  
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## S297. In Vitro Modeling of Human Neuron Development for Studying Prenatal Hypoxia Effects on Brain Development and Function

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## \*S298. Mapping Function Prior to Diagnosis is Essential in Metachromatic Leukodystrophy

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## \*S299. Measurement of Gross Motor Function in Pelizaeus-Merzbacher Disease (PMD)

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## S301. Severe Congenital Brain Malformations in a Patient with Preserved Neurologic Function

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## K-S112. The Role of FOS and the BAF Complex in Neuronal Activity-Dependent Chromatin Remodeling and Gene Expression

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## \*LB-S122. Effects of Microglia Depletion on Brain Lesion Size and Developmental Milestones after Hypoxia-Ischemia in Male and Female C57Bl/6J Mice

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# Neurogenetics and Gene Therapy

## \*S302. Cross-Sectional and Longitudinal Functional Abilities of Individuals with Beta-Propeller Protein-Associated Neurodegeneration (BPAN)

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#### **S304. Genetic Testing Trends in Adult Neurology: Increasing Access and Evolving Yield**

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#### **\*S305. Genotype-Phenotype Discordance in Siblings with Aicardi Goutières Syndrome**

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#### **\*S306. Identification of Dysregulated Genes in SCA7 Mouse Model through Transcriptome Analysis**

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#### **\*S307. Identification of Unique Peripheral Monocyte Phenotypes in CSF1R-Related Leukoencephalopathies**

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#### **\*S308. Improved Survival, Strength, Weight, and Neuroinflammation in a Mouse Model of Sporadic ALS after Novel AAV-Mediated Delivery of RNAi Targeting Atxn2**

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#### **S309. N-of-1 Use of Moberg CNS Monitor in an Inborn Error of Metabolism**

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#### **\*S310. Patient-Reported Outcome Measures Describe Impact of Disease in TUBB4A-Related Leukodystrophy**

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#### **\*S311. Potential Treatment for CMT2S Caused by IGHMBP2 Cryptic Splice Variant, with ASO Based Therapeutic**

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#### **\*S312. The Natural History of Variable Subtypes in Pediatric-Onset TUBB4A-Related Disorders**

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**\*S313. Time-to-Event Measures by Electronic Medical Record Extraction in a Multisite Leukodystrophy Population**

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**K-S113. Differential Post-Translational Sulfatase Activation Correlates with Disease Severity in Multiple Sulfatase Deficiency**

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**K-S114 . Improved Survival, Strength, And Neuroinflammation In A Mouse Model Of Sporadic ALS After Novel AAV-mediated Delivery Of RNAi TargetingAtxn2**

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**K-S115. Increased Degradation of FMRP Contributes to Neuronal Hyperexcitability in Tuberous Sclerosis Complex**

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**K-S116. Loss of O-glycosylation via Neuronal Galnt2 Knock-Out in Mice Recapitulates GALNT2-CDG Patient Seizure Phenotype**

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**K-S117. Reversal of C9orf72 Mutation-Induced Transcriptional Dysregulation and Pathology in Cultured Human Neurons by Allele-Specific Excision**

Aradhana Sachdev, BA<sup>1</sup>, Kamaljit Gill, BA<sup>2</sup>, Maria Scaff, BS<sup>2</sup>, Alisha Birk, BS<sup>2</sup>, Olubankole Aladesuyi Arongundade, PhD<sup>2</sup>, Kathleen Keough, PhD<sup>1</sup>, Bruce Conklin, MD<sup>1</sup>, **Claire Clelland, PhD, MD, MPhil<sup>2</sup>**. <sup>1</sup>Gladstone Institutes, San Francisco, CA, USA, <sup>2</sup>UCSF Weill Institute of Neurosciences, San Francisco, CA, USA.

# LB-S123. Reversal of C9orf72 Mutation-Induced Transcriptional Dysregulation and Pathology in Cultured Human Neurons by Allele-Specific Excision

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## Neuroinflammation and Neuroinfection

### S314. A Patient with CLIPPERS Initially Diagnosed as Parkinson's Disease and Responding Well to Cyclophosphamide

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### \*S315. A Progressive Multifocal Leukoencephalopathy (PML) Risk Genetic Test to Identify At-Risk Patients on PML-Linked Disease-Modifying Therapies (DMTs)

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### S316. A Rare Case of Wernicke's Encephalopathy Presenting as Idiopathic Intracranial Hypertension

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### S317. Autoimmune Glial Fibrillary Acidic Protein (GFAP) Astrocytopathy Causing an Eosinophilic Meningoencephalomyelitis

**Mallory C. Lowe, MD**, Kelli M. Money, MD, PhD, Cara Wilson, MD, Elizabeth Matthews, MD, Daniel M. Pastula, MD, Amanda L. Piquet, MD. University of Colorado, Aurora, CO, USA.

### S318. Central Nervous System Chagas Disease in an AIDS Patient: Differential Diagnosis of a Space-Occupying Lesion

**Karina Wigodski, MD<sup>1</sup>**, Paloma Becker, MD<sup>1</sup>, Walter Feuerhake, MD<sup>2</sup>, Milena Chiappe, MD<sup>2</sup>. <sup>1</sup>Universidad de los Andes, Santiago, Chile, <sup>2</sup>Clínica Santa María, Santiago, Chile.

### \*S319. Cortical Microglia Heterogeneity in Remyelination and Aging

**Hannah K. Loo, BS/BA**, Teshawn Johnson, BS, Joseph Gallegos, BS, Jennifer Orthmann-Murphy, MD/PhD. University of Pennsylvania, Philadelphia, PA, USA.

### S320. COVID-19 Induced Chemosensory Deficits Concurrent with Peripheral Neuropathy

**Youbong Hu, MD**, Alan R. Hirsch, MD. Smell and Taste Treatment and Research Foundation, Chicago, IL, USA.

### S323. Epidemiological Analysis of Lyme Meningitis among Adults within the United States

**Shaheen Sombans, MBBS<sup>1</sup>**, Kamleshun Ramphul, MD<sup>2</sup>, Fiifi Duodu, FWACP<sup>3</sup>, Maya Gabel, MD<sup>4</sup>, Prince Kwabla Peki-Boateng, MBBS<sup>3</sup>, Balkiranjit Kaur Dhillon, MBBS<sup>5</sup>, Babel Agbinko-Djobalar, MD<sup>3</sup>, Ewuradjo Ayirebi-Acquah, MBBS<sup>6</sup>, Patrick Deladem Peki-Boateng, MBChB<sup>7</sup>, Hemamalini Sakthivel, MD<sup>8</sup>. <sup>1</sup>Bharati Vidyapeeth deemed Medical University, Pune, India, <sup>2</sup>Independent Researcher, Triolet, Mauritius, <sup>3</sup>Korle-bu Teaching Hospital, Accra, Ghana, <sup>4</sup>University of Miami - Jackson Memorial Hospital, Miami, FL, USA, <sup>5</sup>Independent Researcher, Brampton, ON, Canada, <sup>6</sup>Lekma Hospital, Accra, Ghana, <sup>7</sup>Kwame Nkrumah University of Science and Technology, Kumasi, Ghana, <sup>8</sup>Interfaith Medical Centre, Brooklyn, NY, USA.

### S324. Horner's Syndrome: A Rare Clinical Presentation of Giant Cell Arteritis

**Emily Barr, BS**, Justine Levesque, BS, Randy Dunston, MD, MBA, Tamra Ranasinghe, MD. Wake Forest School of Medicine, Winston-Salem, NC, USA.

### S325. Identification of Mycoplasma Hominis Infection in Neurosurgical Wound by 16S Ribosomal RNA Nanopore Metagenomic Sequencing Study

**Seolah Lee, MD<sup>1</sup>**, Yoonhyuk Jang, MD<sup>1</sup>, Han-Sang Lee, MD<sup>1</sup>, Seon-Jae Ahn, MD<sup>1</sup>, Yongnoo Kim, MD<sup>1</sup>, Yong-Won Shin, MD<sup>2</sup>, Jangsup Moon, MD<sup>3</sup>, Kon Chu, MD<sup>1</sup>. <sup>1</sup>Department of Neurology, Seoul National University Hospital, Seoul, Korea, Republic of, <sup>2</sup>Department of Neurosurgery, Seoul National University Hospital, Seoul, Korea, Republic of, <sup>3</sup>Department of Genomic Medicine, Seoul National University Hospital, Seoul, Korea, Republic of.

### \*S326. Long Term High-Fat Feeding: Connecting Metabolism, Cognitive Impairment, and Altered Microglial Morphology

Sarah Elzinga, Ph.D.<sup>1</sup>, Mohamed Noureldein, Ph.D.<sup>1</sup>, Kai Guo, Ph.D.<sup>2</sup>, Dae Gyu Jang, Ph.D.<sup>1</sup>, John Hayes, B.S.<sup>1</sup>, Rosemary Henn, Ph.D.<sup>1</sup>, Ian Webber-Davis, B.S.<sup>1</sup>, Faye Mendelson, B.S.<sup>1</sup>, Rachel Parent, B.S.<sup>1</sup>, Diana Rigan, B.S.<sup>1</sup>, Ali Turfah, M.A.<sup>1</sup>, Lili Zhao, Ph.D.<sup>1</sup>, Geoffrey Murphy, Ph.D.<sup>1</sup>, Junguk Hur, Ph.D.<sup>2</sup>, **Eva Feldman, M.D., Ph.D.<sup>1</sup>**. <sup>1</sup>University of Michigan, Ann Arbor, MI, USA, <sup>2</sup>University of North Dakota, Grand Forks, ND, USA.

### S327. Neurosarcoidosis Presenting with Recurrent Strokes Due to Large Artery Vasculitis

**Paneeni Lohana, DO**, Justin Thorson, MD, Cheryl Bushnell, MD, Tamra Ranasinghe, MD. Wake Forest Baptist Medical Center, Winston Salem, NC, USA.

### S328. Neurosyphilis: A Great Mimicker

**Papul Chalia, MD**, Michelle Calmet, MD, Timothy Q. Lequang, MS, Mansoureh Mamarabadi, MD. Penn State Health, Hershey Medical Center, Hershey, PA, USA.

### S329. Not All Lower Back Pain is Sciatica, a Case of Meningitis Secondary to Septic Emboli from Infective Endocarditis

**Jashank Parwani, MBBS**, Zachary Meili, MD, Andrew Beckman, MD. Temple University, Philadelphia, PA, USA.

### \*S330. Smell Recovery in Post-Acute Sequelae of COVID (PASC) - Drug Repurposing of Baricitinib

**Sasha Mukhija, MD**, Alexander Chung, BS, Colin Magdamo, BA, Mark Albers, MD, PhD. Harvard Medical School, Boston, MA, USA.

### \*S332. The Racial and Ethnic Disparities in Clinical Outcomes in Patients with Encephalitis

**Rajesh K. Gupta, MD, MS**, Sienna L. Wu, BS, Laya Rao, BS, Rodrigo Hasbun, MD, MPH. UTHealth, Houston, TX, USA.

### S333. Unilateral High Sciatic Neuropathy Associated with Severe COVID-19

**Karina Wigodski, MD<sup>1</sup>**, Jacqueline Hirschey, MD<sup>2</sup>, Nicholas E. Sasso, MAT<sup>2</sup>, Jose Biller, MD<sup>2</sup>. <sup>1</sup>Universidad de los Andes, Santiago, Chile, <sup>2</sup>Loyola University Chicago Stritch School of Medicine, Maywood, IL, USA.

### K-S118. Brain Capillary Obstruction by Leukocytes is Ameliorated by Integrin Blockade in an Immunocompetent Mouse Model of CAR T Cell Neurotoxicity

**Juliane Gust, MD PhD**, Lila Faulhaber, BS, Lina Park, BS, Annie Tsai, BS, Andy Shih, PhD. Seattle Children's, Seattle, WA, USA.

### K-S119. Satellite Microglia Have a Role in Regulation of Neuronal Excitability and Change in Response to Injury

Alicia Feichtenbiner, BS, Ryan O'Boyle, BS, Karinn Sytsma, BS, Christopher Ransom, MD, PhD, **Amber Nolan, MD, PhD**. University of Washington, Seattle, WA, USA.

### \*LB-S125. High Dimensional Analysis on Mechanism of Action of Siponimod

**Lawrence Steinman, MD**, Peggy P. Ho, PhD. Stanford University, Stanford, CA, USA.

### \*LB-S126. Pregnancy Outcomes among Multiple Sclerosis Patients on Disease Modifying Drugs: A Systematic Review and Meta-Analysis

**Erum I. Khan, MBBS<sup>1</sup>**, Shitiz Sriwastava, MD<sup>2</sup>. <sup>1</sup>B.J. Medical College, Ahmedabad, India, <sup>2</sup>U T Houston, Houston, TX, USA.

### LB-S128. Neurosyphilis Presenting with Abducens Nerve Palsy

**Juan M. Martinez, Jr., BS**, Erika Salarda, MD, Khalid E. Khalid, MD. University of Texas Health Science Center at Houston McGovern Medical School, Houston, TX, USA.

## Neuro-oncology

### S257. A Case of Diffuse Large B Cell Lymphoma Presenting with Neurolymphomatosis and Leptomeningeal Disease

**Catherine Boldig, DO**, Grace Johnson, BS, Lauren Fragapane, MD, Rebecca Hurst, MD. University of South Florida, Tampa, FL, USA.

### S260. An Incidental Finding of a Dysembryoplastic Neuroepithelial Tumor

**Mauricio X. Perez Davila, MD<sup>1</sup>**, Marcelo Montero, MD<sup>2</sup>, Ricardo A. Vivanco, MD<sup>3</sup>, Alex S. Aguirre, MD<sup>4</sup>. <sup>1</sup>Yale University, New Haven, CT, USA, <sup>2</sup>Universidad de las Americas, Quito, Ecuador, <sup>3</sup>Universidad Catolica Santiago de Guayaquil, Guayaquil, Ecuador, <sup>4</sup>Universidad San Francisco de Quito, Quito, Ecuador.

### \*S261. Baroreflex Dysfunction after Neck Irradiation and Chemotherapy for Tonsillar Cancer

**Nicholas E. Sasso, MAT<sup>d</sup>**, Karina Wigodski, MD<sup>2</sup>, Zachary Pardieck, MD<sup>1</sup>, Jose Biller, MD<sup>1</sup>. <sup>1</sup>Loyola University Chicago Stritch School of Medicine, Maywood, IL, USA, <sup>2</sup>Universidad de los Andes, Santiago, Chile.

### S262. Disparities among Astrocytoma Clinical Trials between 1996 - 2022

**Angelique Boyer, B.S, M.S**, Mill Etienne, MD, MPH, Maya Pandit, MPH, Patrick J. Crockin, B.S, Peter Lenchur, B.A, Zachary Abbate, B.S, M.S, Hilla Katz-Lichtenstein, B.A, Emma Bloom, B.A, Ann Mercurio, M.S, Melanie Vassallo, B.S, M.S, Dalynah Maldonado, M.S, Matea Mezic, B.A. New York Medical College, Valhalla, NY, USA.

### \*S263. Integration of Neuroimaging, Patient-Reported Outcomes, and Genetics in IDH-Mutant Gliomas

**Ankush Bhatia, MD<sup>1</sup>**, William Adams, PhD<sup>2</sup>, Antonio Dono, MD<sup>3</sup>, Yoshua Esquenazi, MD<sup>3</sup>, Kristen Clemons, B.S.<sup>3</sup>, Mahua Dey, MD<sup>1</sup>, Robert Young, MD<sup>4</sup>, Ingo Mellinghoff, MD<sup>4</sup>, Stephen Sands, MD<sup>4</sup>, Jane S. Paulsen, PhD<sup>1</sup>. <sup>1</sup>University of Wisconsin School of Medicine and Public Health, Madison, WI, USA, <sup>2</sup>Loyola University Chicago Health Sciences Division, Chicago, IL, USA, <sup>3</sup>University of Texas Health Science Center at Houston, Houston, TX, USA, <sup>4</sup>Memorial Sloan Kettering Cancer Center, New York City, NY, USA.



**S264. Large Frontal Meningioma Presenting with 10 Months of Major Depressive Disorder, Headache, and Catatonic Symptoms**

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**\*S265. Receipt of Guideline Concordant-Care for Neurofibromatosis 1 (NF1) in the United States: A National Survey of NF1 Patients and Caregivers**

**Vanessa L. Merker, PhD<sup>1</sup>**, Yidan Ma, BS<sup>2</sup>, Lori Chibnik, PhD<sup>2</sup>, Nicole J. Ullrich, MD, PhD<sup>3</sup>, Kaleb Yohay, MD<sup>4</sup>, Heather B. Radtke, MS, CGC<sup>5</sup>, Scott R. Plotkin, MD, PhD<sup>1</sup>, Justin T. Jordan, MD, MPH<sup>1</sup>. <sup>1</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>2</sup>Harvard T.H. Chan School of Public Health, Boston, MA, USA, <sup>3</sup>Boston Children's Hospital, Boston, MA, USA, <sup>4</sup>NYU Langone Medical Center, New York, NY, USA, <sup>5</sup>Children's Tumor Foundation, New York, NY, USA.

**S266. Risk of Intraparenchymal Metastasis from Castration-Resistant Prostate Carcinoma via Hematogenous Spread: A Rare Case Presentation**

**William H. Roberts, BS<sup>1</sup>**, Sami Belakhlef, MD<sup>2</sup>, Jacey Salley, NP<sup>3</sup>, Gerald C. Wallace, IV, MD<sup>3</sup>. <sup>1</sup>Medical College of Georgia, Augusta, GA, USA, <sup>2</sup>Augusta University Medical Center, Augusta, GA, USA, <sup>3</sup>Georgia Cancer Center, Augusta, GA, USA.

**S267. Soft Tissue Metastasis in a Patient with Glioblastoma**

**Mauricio X. Perez-Davila, MD<sup>1</sup>**, Carlos Vindel Zuñiga, MD<sup>2</sup>, Joachim Baehring, MD<sup>1</sup>. <sup>1</sup>Yale University, New Haven, CT, USA, <sup>2</sup>Universidad Catolica Santiago de Guayaquil, Guayaquil, Ecuador.

**\*S268. The Natural History of Neurolymphomatosis**

**Elizabeth Xu, Student<sup>1</sup>**, Quan Ho, BS<sup>2</sup>, Ashley Liu, Student<sup>2</sup>, Shiva Gautam, PhD<sup>3</sup>, Eric T. Wong, MD<sup>4</sup>. <sup>1</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>Boston University, Boston, MA, USA, <sup>3</sup>University of Florida, Gainesville, FL, USA, <sup>4</sup>Brown University, Providence, RI, USA.

## Neuro-ophthalmology and Neurovestibular Disease

**S269. A Case of Opsoclonus Secondary to Increased Intracranial Pressure**

**Rui Tang, MA**, Michael Boes, DO, Salvador Cruz-Flores, MD, MPH. Texas Tech University Health Sciences Center El Paso, El Paso, TX, USA.

**S270. A Patient with Takayasu Arteritis Developing Multiorgan Failure Including Multiple Strokes and Bilateral Optic Neuropathy**

**Rajesh K. Gupta, MD**, Laya Rao, BS. UT Health, Houston, TX, USA.

**S271. Diagnostic Challenge: A Case of Leptomenigeal Carcinomatosis Causing Severe Optic Neuropathy**

**Malya Sabu, MD**, Rohini Samudralwar, MD. University of Pennsylvania, Philadelphia, PA, USA.

**\*S272. Feasibility and Usability of a Smartphone Eye-Tracking Application ("Eyephone") for Self-Recording of Eye Movements in ALS Patients**

**Pouya B. Bastani, MD<sup>1</sup>**, Ali S. Saber Tehrani, MD<sup>1</sup>, Shervin Badibian, MD<sup>2</sup>, David Rastall, DO, PhD<sup>1</sup>, Nathan Farrell, BS<sup>1</sup>, T. Maxwell Parker, BS<sup>1</sup>, Jorge Otero-Millan, PhD<sup>3</sup>, Hector Rieiro, PhD<sup>1</sup>, Ahmed Hassoon, MD<sup>4</sup>, David E. Newman-Toker, MD, PhD<sup>1</sup>, Lora L. Clawson, MSN, CRNP<sup>1</sup>, Alpa Uchil, MSN, MPH, CRNP<sup>1</sup>, Steven R. Zeiler, MD, PhD<sup>1</sup>. <sup>1</sup>Department of Neurology, Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>2</sup>Department of Neurology, Cleveland Clinic, Cleveland, OH, USA, <sup>3</sup>Herbert Wertheim School of Optometry and Vision Science, University of California, Berkeley, Berkeley, CA, USA, <sup>4</sup>Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA.

**\*S274. Neuroadaptability to Multifocal Intraocular Lens after Cataract Extraction: Pilot Evidence of an Association with Cognition**

**Victoria S. Pelak, MD**, Michael Taravella, MD, Jennifer Patnaik, PhD, Nathan Grove, PhD Pending. University of Colorado School of Medicine, Aurora, CO, USA.

**S275. When Clinical Symptoms Don't Match Imaging: A Case Report of WEBINO Syndrome**

**Ramit Singla, MD**, Mohammad Alzayadneh, MD, Ra'ed Alkhaddash, MD, Balaji Krishnaiah, MD, Cheran Elangovan, MD. University of Tennessee Health Science Center, Memphis, TN, USA.

**\*LB-S116. Estrogen-Induced IL-1 $\beta$  Mediates Retinal Ganglion Cell Loss in Murine Optic Glioma**

**Yunshuo Tang, MD, PhD**, Ngan Wagoner, BS, Jit Chatterjee, PhD, David H. Gutmann, MD, PhD. Washington University in Saint Louis, Saint Louis, MO, USA.

## Neurorecovery and Neuroplasticity

**S334. Atypical Frey's Syndrome: A Case Report**

**Nasser A. Abdelall, B.Med.Sc, M.D.<sup>1</sup>**, Warren Spinner, DO<sup>2</sup>, Stefan Franco, Bachelor's in Biology<sup>2</sup>. <sup>1</sup>LSU HSC, New

Orleans, LA, USA, <sup>2</sup>North Suffolk Neurology, Long Island, NY, USA.

**S335. Potential Effects of Untreated Moderate-to-Severe Sleep-Related Breathing Disorders on the Number of Silent Episodes of Autonomic Dysreflexia during Sleep in People with Spinal Cord Injury**

**Julio C. Furlan, MD, LLB, MBA, MSc, PhD, FRCPC, FAAN<sup>1</sup>**, Eldon Loh, MD, FRCPC<sup>2</sup>, Mark I. Boulos, BSc, MSc, MD, FRCPC<sup>3</sup>. <sup>1</sup>KITE Research Institute, University Health Network; University of Toronto, Toronto, ON, Canada, <sup>2</sup>Lawson Health Research Institute; Western University, London, ON, Canada, <sup>3</sup>Sunnybrook Health Sciences Centre; University of Toronto, Toronto, ON, Canada.

**S336. The Effects of Race/Ethnicity on Epidemiology, Survival and Neurological Outcomes Following Acute Traumatic Spinal Cord Injury**

**Julio C. Furlan, MD, LLB, MBA, MSc, PhD, FRCPC, FAAN.** KITE Research Institute, University Health Network; University of Toronto, Toronto, ON, Canada.

**\*LB-S127. Neural Correlates of Phantom Motor Execution: A Systematic Review and Functional Neuroimaging Meta-Analysis**

**Kevin Pacheco-Barrios, MD, MSc, MPH<sup>1,2</sup>**, Robin Heemels, BSc<sup>1,3</sup>, Felipe Fregni, MD, MPH, PhD<sup>1</sup>. <sup>1</sup>Neuromodulation Center and Center for Clinical Research Learning, Spaulding Rehabilitation Hospital and Massachusetts General Hospital, Harvard Medical School, Cambridge, MA, USA, <sup>2</sup>Unidad de Investigación para la Generación y Síntesis de Evidencias en Salud, Universidad San Ignacio de Loyola, Lima, Peru, <sup>3</sup>Movement Control and Neuroplasticity Research Group, Department of Movement Sciences, Group Biomedical Sciences, KU Leuven, Heverlee, Belgium.

## Sleep Disorders and Circadian Rhythms

**\*S337. Actigraphy-Determined Physical Activity in Older Adults with MCI and Sleep Apnea: Correlation with Self-Reported Sleepiness**

**Riya Solanky, BS<sup>1</sup>**, Elena Park, BS<sup>2</sup>, Jani Coni, BS<sup>3</sup>, Cassidy Reandeau, BS<sup>3</sup>, James Virtucio, BS<sup>3</sup>, KerCheng Chen, BA<sup>4</sup>, Alicia Lozano, MS<sup>5</sup>, Cynthia Cheng, MD/PhD<sup>6</sup>, Luqi Chi, MD<sup>7</sup>, Eric Davis, MD<sup>8</sup>, David Wolk, MD<sup>2</sup>, Kathy Richards, PhD<sup>9</sup>, Nalaka Gooneratne, MD<sup>2</sup>. <sup>1</sup>Drexel University College of Medicine, Philadelphia, PA, USA, <sup>2</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>3</sup>Drexel University, Philadelphia, PA, USA, <sup>4</sup>Downstate Health Sciences University, Brooklyn, NY, USA, <sup>5</sup>Virginia Tech, Roanoke, VA, USA, <sup>6</sup>Thomas Jefferson University, Philadelphia, PA, USA, <sup>7</sup>Washington University,

St. Louis, MO, USA, <sup>8</sup>University of Virginia, Charlottesville, VA, USA, <sup>9</sup>University of Texas, Austin, TX, USA.

**\*S338. COVID-19 Disrupts Sleep Architecture by Reducing N3 Stage Sleep**

**Sung Ji, MD, PhD, Payal Patel, MD.** University of Washington, Department of Neurology, Seattle, WA, USA.

**S339. Differential Cortical Network Engagement during States of Un / Consciousness in Humans**

**Rina Zelman, Ph.D.<sup>1</sup>**, Angelique C. Paulk, Ph.D.<sup>1</sup>, Fangyun Tian, Ph.D.<sup>1</sup>, Gustavo A. Balanza Villegas, M.D.<sup>1</sup>, Jaquelin Dezha Peralta, B.Eng.<sup>1</sup>, G. Rees Cosgrove, M.D.<sup>2</sup>, R. Mark Richardson, M.D., Ph.D.<sup>1</sup>, Ziv Williams, M.D.<sup>1</sup>, Darin D. Dougherty, M.D.<sup>1</sup>, Patrick L. Purdon, Ph.D.<sup>1</sup>, Sydney S. Cash, M.D., Ph.D.<sup>1</sup>. <sup>1</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>2</sup>Brigham and Women's Hospital, Boston, MA, USA.

**\*S340. Dose Titration and Tolerability of Once-Nightly Sodium Oxybate: Interim Data from RESTORE**

**Asim Roy, MD<sup>1</sup>**, Brian Abaluck, MD<sup>2</sup>, Thomas Stern, MD<sup>3</sup>, Clete A. Kushida, MD<sup>4</sup>, Jordan Dubow, MD<sup>5</sup>, Jennifer Gudeman, PharmD<sup>5</sup>. <sup>1</sup>Ohio Sleep Medicine and Neuroscience Institute, Dublin, OH, USA, <sup>2</sup>Private Practice, Malvern, PA, USA, <sup>3</sup>Advanced Respiratory and Sleep Medicine, PLLC, Huntersville, NC, USA, <sup>4</sup>Stanford University Medical Center, Redwood City, CA, USA, <sup>5</sup>Avadel Pharmaceuticals, Chesterfield, MO, USA.

**\*S341. Effect of Continuous Positive Airway Pressure (CPAP) Treatment on Hippocampal Volume in Patients with Obstructive Sleep Apnea (OSA)**

**Manasa Mula, BS<sup>1</sup>**, Alex Mathew, BS<sup>2</sup>, Sandhitsu Das, PhD<sup>2</sup>, Ilya M. Nasrallah, MD/PhD<sup>2</sup>, Tammie Benzinger, MD/PhD<sup>3</sup>, Robert Nick Bryan, MD/PhD<sup>2</sup>, John A. Detre, MD<sup>2</sup>, David A. Wolk, MD<sup>2</sup>, Alexandra Hanlon, PhD<sup>4</sup>, Alicia Lozano, MS<sup>4</sup>, Stephen T. Moelter, PhD<sup>5</sup>, Luqi Chi, MD<sup>3</sup>, Eric Davis, MD<sup>6</sup>, Cynthia Cheng, MD/PhD<sup>7</sup>, Abhinav Bhamidipati, BS<sup>1</sup>, Nalaka Gooneratne, MD<sup>2</sup>, Kathy Richards, PhD<sup>8</sup>. <sup>1</sup>Drexel University, Philadelphia, PA, USA, <sup>2</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>3</sup>Washington University, St. Louis, MO, USA, <sup>4</sup>Virginia Tech, Roanoke, VA, USA, <sup>5</sup>Saint Joseph's University, Philadelphia, PA, USA, <sup>6</sup>University of Virginia School of Medicine, Charlottesville, VA, USA, <sup>7</sup>Thomas Jefferson University, Philadelphia, PA, USA, <sup>8</sup>The University of Texas, Austin, TX, USA.

**\*S342. Light Exposure before Bedtime in Pregnancy is Associated with a Higher Risk of Gestational Diabetes**

**Minjee Kim, MD<sup>1</sup>**, Francesca L. Facco, MD, MS<sup>2</sup>, Rosemary I. Braun, PhD<sup>1</sup>, Michael S. Wolf, PhD, MPH<sup>1</sup>,

William A. Grobman, MD, MBA<sup>3</sup>, Phyllis C. Zee, MD, PhD<sup>1</sup>, Kathryn J. Reid, PhD<sup>1</sup>. <sup>1</sup>Northwestern University Feinberg School of Medicine, Chicago, IL, USA, <sup>2</sup>University of Pittsburgh School of Medicine, Pittsburgh, PA, USA, <sup>3</sup>The Ohio State University College of Medicine, Columbus, OH, USA.

**\*S343. Long-Term Safety of Once-Nightly Sodium Oxybate for Narcolepsy: RESTORE Study Interim Analysis of Data**

**Thomas Stern, MD<sup>1</sup>**, Asim Roy, MD<sup>2</sup>, Colin M. Shapiro, PhD<sup>3</sup>, John Harsh, PhD<sup>4</sup>, Akinyemi O. Ajayi, MD<sup>5</sup>, Sally Ibrahim, MD<sup>6</sup>, Jordan Dubow, MD<sup>7</sup>, Jennifer Gudeman, PharmD<sup>7</sup>. <sup>1</sup>Advanced Respiratory and Sleep Medicine, PLLC, Huntersville, NC, USA, <sup>2</sup>Ohio Sleep Medicine and Neuroscience Institute, Dublin, OH, USA, <sup>3</sup>University of Toronto, Toronto, ON, Canada, <sup>4</sup>Colorado Sleep Institute, Boulder, CO, USA, <sup>5</sup>Florida Pediatric Research Institute, Winter Park, FL, USA, <sup>6</sup>University Hospitals Cleveland Medical Center, Cleveland, OH, USA, <sup>7</sup>Avadel Pharmaceuticals, Chesterfield, MO, USA.

**S345. Patient Preference and Nocturnal Experience with Oxybate Treatment for Narcolepsy: Interim Analysis of Data from RESTORE**

**Asim Roy, MD<sup>1</sup>**, John Harsh, PhD<sup>2</sup>, Akinyemi O. Ajayi, MD<sup>3</sup>, Thomas Stern, MD<sup>4</sup>, Jordan Dubow, MD<sup>5</sup>, Jennifer Gudeman, PharmD<sup>5</sup>. <sup>1</sup>Ohio Sleep Medicine and Neuroscience Institute, Dublin, OH, USA, <sup>2</sup>Colorado Sleep Institute, Boulder, CO, USA, <sup>3</sup>Florida Pediatric Research Institute, Winter Park, FL, USA, <sup>4</sup>Advanced Respiratory and Sleep Medicine, PLLC, Huntersville, NC, USA, <sup>5</sup>Avadel Pharmaceuticals, Chesterfield, MO, USA.

**S346. Sleep Insufficiency, Circadian Rhythms, and Metabolomics: The Connection to Metabolic Sleep Disorders**

**Katherine L. Russell, MSPH<sup>1</sup>**, Hillary R. Rodman, Ph.D.<sup>2</sup>, Victoria M. Pak, PhD, MS, MTR<sup>2</sup>. <sup>1</sup>UNTHSC TCOM, Fort Worth, TX, USA, <sup>2</sup>Emory University, Atlanta, GA, USA.

**\*S347. The Dual Orexin Receptor Antagonist Lemborexant Induces Microglial Phagocytosis and Reduces Amyloid Plaque Deposition in APP/PS1 Mice**

Ashish Sharma, PhD<sup>1</sup>, Chanung Wang, PhD<sup>1</sup>, Jocelyn Cheng, PhD<sup>2</sup>, Garth E. Ringheim, PhD<sup>2</sup>, Ken Hatanaka, PhD<sup>3</sup>, Margaret Moline, PhD<sup>2</sup>, **Erik S. Musiek, MD, PhD<sup>1</sup>**. <sup>1</sup>Washington University School of Medicine, St. Louis, MO, USA, <sup>2</sup>Eisai Inc., Nutley, NJ, USA, <sup>3</sup>Eisai Co. Ltd., Tokyo, Japan.

**\*S348. The Impact of CPAP Therapy for 4 Months for Management of SRBDs on Psychosocial Outcomes in Individuals with Chronic Spinal Cord Injury: A Mixed-Methods Study**

**Julio C. Furlan, MD, LLB, MBA, MSc, PhD, FRCPC, FAAN<sup>1</sup>**, Sander L. Hitzig, DEC, BA, MA, PhD<sup>2</sup>, Mark I. Boulos, BSc, MSc, MD, FRCPC<sup>3</sup>. <sup>1</sup>KITE Research Institute, University Health Network; University of Toronto, Toronto, ON, Canada, <sup>2</sup>St. John's Rehab Research Program, Sunnybrook Research Institute, Toronto, ON, Canada, <sup>3</sup>Sunnybrook Health Sciences Centre; University of Toronto, Toronto, ON, Canada.

**S349. Understanding Narcolepsy Treatments from the Patient's Perspective: A Survey of People Living with Narcolepsy**

**Luis Ortiz, MD<sup>1</sup>**, Anne Marie Morse, MD<sup>2</sup>, Lois Krahn, MD<sup>3</sup>, Maggie Lavender, FNP<sup>4</sup>, Matthew Horsnell, BS<sup>5</sup>, Dianna Cronin, BS<sup>6</sup>, Beth Schneider, BA<sup>6</sup>, Jennifer Gudeman, PharmD<sup>7</sup>. <sup>1</sup>Johns Hopkins All Children's Hospital, St. Petersburg, FL, USA, <sup>2</sup>Geisinger Commonwealth School of Medicine, Geisinger Medical Center, Janet Weis Children's Hospital, Danville, PA, USA, <sup>3</sup>Mayo Clinic, Phoenix, AZ, USA, <sup>4</sup>Comprehensive Sleep Medicine Associates, Houston, TN, USA, <sup>5</sup>Patient Author, Project Sleep's Rising Voices of Narcolepsy, Los Angeles, CA, USA, <sup>6</sup>MyHealthTeam, San Francisco, CA, USA, <sup>7</sup>Avadel Pharmaceuticals, Chesterfield, MO, USA.

**K-S120. Local Changes in Sleep Oscillations after Stroke**

**Eric C. Landsness, MD PhD**, Hanyang Miao, BS, Wei Chen, BS, Michelle Tang, BS, Spencer Blackwood, BS, Jonah Padawer-Curry, BS, Joe Culver, PhD, Adam Q. Bauer, PhD, Jin Moo Lee, MD PhD. Washington University - St. Louis, Saint Louis, MO, USA.

## Monday Poster Sessions

### Autoimmune Neurology & MS

**\*M100. <sup>18</sup>F-Fluorodeoxyglucose-Positron Emission Tomography Findings in Neuromyelitis Optica Spectrum Disorder and Myelin Oligodendrocyte Glycoprotein Antibody Associated Disease**

**Gelareh Ahmadi, MD, PhD, FRACP, Postdoctoral Fellow**, Eleni Vasileiou, MD, Postdoctoral Fellow, Paula Barreras, MD, Neuroimmunology Clinical Fellow, Samantha Roman, BS, MD, Neuroimmunology Clinical Fellow, Elias Sotirchos, MD, Assistant Professor of Neurology. Johns Hopkins, Baltimore, MD, USA.

**\*M101. A 90-Year-Old Woman with NMDA Encephalitis Who Was Initially Diagnosed to Have Parkinson Disease**

**Rajesh K. Gupta, MD**, Sienna Wu, BS. UTHHealth, Houston, TX, USA.

**M103. A Case of Multiple Autoantibody-Related Treatment-Refractory Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) and Cerebellar Dysfunction Overlap Syndrome**

**Anza Zahid, MBBS, MD<sup>1</sup>**, Akhil Shivaprasad, MD<sup>1</sup>, Mujtaba Saeed, MD<sup>2</sup>, Bing Liao, MD, MSc<sup>3</sup>. <sup>1</sup>Houston Methodist Hospital, Neurological Institute, Houston, TX, USA, <sup>2</sup>Houston Methodist Hospital, Department of Imaging, Houston, TX, USA, <sup>3</sup>Houston Methodist Hospital, Neurological Institute, Department of Neuromuscular Diseases, Houston, TX, USA.

**M104. A Rare Case of Co-Existing Dermatomyositis and Myasthenia Gravis**

**Sumeyye Kus, MD**, Matthew Imperioli, MD, Hamza Coban, MD. University of Connecticut School of Medicine, Farmington, CT, USA.

**M105. A Rare Presentation of Neurosarcoidosis as Thoracic Radiculopathy in a Patient with Ankylosing Spondylitis**

**Rajesh K. Gupta, MD, MS**, Manish M. Bhojwani, BS. UTHHealth, Houston, TX, USA.

**M106. AMAN Presenting with Myeloradiculitis**

**Phillion Gatchoff, MD**, Mohammad Hussein, MD, Estevao Ribeiro, MD, Ahmad Al-Awwad, MD. University of Oklahoma Health Science Center, Oklahoma City, OK, USA.

**M107. An Immunosuppressed Marathoner with Headaches and Fevers Progressing to Coma**

**Ilana Green, MD**, Sam Horng, MD, PhD, Neha Dangayach, MD. Icahn School of Medicine at Mount Sinai, New York, NY, USA.

**M110. Autism-Like Presentation of Pediatric Autoimmune Encephalitis, Completely Recovered after Immunotherapy**

**Yongmoo Kim, MD<sup>1</sup>**, Yoonhyuk Jang, MD<sup>1</sup>, Seolah Lee, MD<sup>1</sup>, Han Sang Lee, MD<sup>1</sup>, Seon-Jae Ahn, MD<sup>1</sup>, Yong-Won Shin, MD<sup>2</sup>, Jangsup Moon, MD<sup>3</sup>, Kon Chu, MD<sup>1</sup>. <sup>1</sup>Department of Neurology, Seoul National University Hospital, Seoul, Korea, Republic of, <sup>2</sup>Department of Neurosurgery, Seoul National University Hospital, Seoul, Korea, Republic of, <sup>3</sup>Department of Genomic Medicine, Seoul National University Hospital, Seoul, Korea, Republic of.

**\*M111. Autoimmune Brainstem Encephalitis: Serological and Clinical Associations, and Predictors of Outcome**

**Michael Gilligan, MB BCh BAO**. Mayo Clinic, Rochester, MN, USA.

**\*M112. Biomarkers of Inflammation and Neuronal and Glial Injury in Leucine-Rich Glioma Inactivated-1 (LGI1) Autoimmune Encephalitis**

**Tyler L. Borko, BS**, Sarah Bausano, BS, Christopher Mizenko, BS, Kelli M. Money, MD, PhD, Ryan M. Kammeyer, MD, MSE, Alanna Ritchie, BS, Sean Selva, BS, Stefan Sillau, PhD, Gregory Owens, PhD, Timothy L. Vollmer, MD, Kavita V. Nair, PhD, Jeffrey L. Bennett, MD, PhD, Amanda L. Piquet, MD. University of Colorado, Aurora, CO, USA.

**M114. Botulinum Toxin Could Be Helpful as an Adjunct Therapy in Stiff Person Syndrome**

**Samantha Roman, MD**, Elena Taylor, BS, Scott Newsome, DO, Emile Moukheiber, MD. Johns Hopkins University Department of Neurology, Baltimore, MD, USA.

**M115. Chronic Progressive Presentation in a Case of Neuromyelitis Optica Spectrum Disorder**

**Narges Rabimi, MD**. Einstein Health, Philadelphia, PA, USA.

**M117. Diencephalon Involvement as a Presenting Feature of Neuromyelitis Optica Spectrum Disorder in a Teenager**

**Shikhar Khurana, MD<sup>1</sup>**, Sushma Helagalli Paramashivaiah, MBBS<sup>1</sup>, Salma Suhana, MD<sup>2</sup>, Aparna M. Prabhu, MD, MRCP<sup>1</sup>. <sup>1</sup>Einstein Medical Center, Philadelphia, PA, USA, <sup>2</sup>Yenepoya University, Mangalore, India.

**\*M118. Dimethyl Fumarate Modulates Brain Oxidative Stress Immunodeficiency Virus (SIV)-Infected Rhesus Macaques: Potential Repurposing for HIV Neuroprotection**

**Adam Adelsberg, B.S.<sup>1</sup>**, Yoelvis Garcia-Mesa, PhD<sup>2</sup>, Halvor Juul, PhD<sup>1</sup>, He Xu, PhD<sup>1</sup>, Dennis L. Kolson, MD, PhD<sup>1</sup>. <sup>1</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>Case Western Reserve University, Cleveland, OH, USA.

**M119. Do TNF $\alpha$ , IL-1 $\alpha$ , and C1q Promote Cortical Oligodendrocyte Regeneration after Demyelination?**

**Joseph T. Gallegos, PhD Candidate**, Hannah Loo, PhD Candidate, Jennifer L. Orthmann-Murphy, MD PhD. University of Pennsylvania, Philadelphia, PA, USA.

# **M120. EEG Findings in Patients with Encephalitis of Autoimmune and Infectious Causes**

**Shirin Jamal Omid, MD, Rajesh Gupta, MD, Rodrigo Hasbun, MD.** UTHSC at Houston, Houston, TX, USA.

# **\*M121. Exosome Connexin43-Truncated Isoforms and Bound RNAs Distinctively Associated with Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder**

**Jun-ichi Kira, M.D., Ph.D.<sup>1</sup>**, Guzailiayi Maimaitijiang, M.D., Ph.D.<sup>1</sup>, Ayako Sakoda, M.D., Ph.D.<sup>2</sup>, Katsuhisa Masaki, M.D., Ph.D.<sup>3</sup>, Mitsuru Watanabe, M.D., Ph.D.<sup>3</sup>, Satoshi Nagata, M.D.<sup>3</sup>, Ezgi Ozdemir, M.D.<sup>3</sup>, Ryo Yamasaki, M.D., Ph.D.<sup>3</sup>, Noriko Isobe, M.D., Ph.D.<sup>3</sup>, Xu Zhang, M.D., Ph.D.<sup>1</sup>, Tomohiro Imamura, M.D., Ph.D.<sup>4</sup>, Yuri Nakamura, M.D., Ph.D.<sup>2</sup>. <sup>1</sup>Translational Neuroscience Center, International University of Health and Welfare, Okawa, Japan, <sup>2</sup>Department of Neurology, Brain and Nerve Center, Fukuoka Central Hospital, Fukuoka, Japan, <sup>3</sup>Department of Neurology, Neurological Institute, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan, <sup>4</sup>School of Pharmacy at Fukuoka, International University of Health and Welfare, Okawa, Japan.

# **\*M122. Experience and Outcomes of an Online Mindfulness-Based Stress Reduction (MBSR) Pilot Program for People with Multiple Sclerosis**

**Nivethitha Manohar, MPH<sup>1</sup>**, Jackson Cabot, NA<sup>2</sup>, Nicole Delcourt, RN<sup>3</sup>, Jeanne Ann Whittington, NA<sup>3</sup>, Brant Oliver, PhD, MS, MPH, FNP-BC, PMHNP-BC<sup>4</sup>. <sup>1</sup>Paul L. Foster School of Medicine, Texas Tech University Health Science Center, El Paso, TX, USA, <sup>2</sup>University of New Hampshire, Durham, NH, USA, <sup>3</sup>Multiple Sclerosis Specialty Care Program, Concord Hospital, Concord, NH, USA, <sup>4</sup>The Dartmouth Institute, Dartmouth College; Geisel School of Medicine at Dartmouth; The Value Institute, Dartmouth Health, Lebanon, NH, USA.

# **\*M124. International Panel Criteria for the Diagnosis of MOG-Antibody Associated Disease**

**Brenda Banwell, MD<sup>1</sup>**, Giulia Fadda, MD<sup>2</sup>, Jeffery Bennett, MD, PhD<sup>3</sup>, Romain Marignier, MD, PhD<sup>4</sup>, Ho Jin Kim, MD, PhD<sup>5</sup>, Fabienne Brilot, PhD<sup>6</sup>, Eoin Flanagan, MB, BCh<sup>7</sup>, Sudarshini Ramanathan, MD, PhD<sup>8</sup>, Patrick Waters, PhD<sup>9</sup>, Silvia Tenenbaum, MD<sup>10</sup>, Jennifer Graves, MD, PhD<sup>11</sup>, Tanuja Chitnis, MD, PhD<sup>12</sup>, Cheryl Hemingway, MBChB, PhD<sup>13</sup>, Rinze Neuteboom, MD<sup>14</sup>, Lekha Pandit, MD<sup>15</sup>, Markus Reindl, PhD<sup>16</sup>, Douglas Sato, MD, PhD<sup>17</sup>, Kevin Rostasy, MD<sup>18</sup>, Friedemann Paul, MD<sup>19</sup>, Sean Pittock, MD<sup>7</sup>, Kazuo Fukihara, MD<sup>20</sup>, Jacqueline Palace, MD<sup>21</sup>. <sup>1</sup>Children's Hospital of Philadelphia, Philadelphia, PA, USA, <sup>2</sup>Ottawa Research Institute, Ottawa, ON, Canada, <sup>3</sup>University of Colorado School of Medicine, Colorado, CO, USA, <sup>4</sup>Hôpital Neurologique Pierre Wertheimer, Hospices Civils de Lyon, Lyon, France, <sup>5</sup>Department of Neurology, Research Institute and Hospital of National Cancer Center, Goyang, Korea, Democratic People's Republic of, <sup>6</sup>School of Medical Sciences,

Faculty of Medicine and Health, University of Sydney, Sydney, Australia, <sup>7</sup>Mayo Clinic, Rochester, MN, USA, <sup>8</sup>Sydney Medical School, Faculty of Medicine and Health, University of Sydney, Sydney, Australia, <sup>9</sup>University of Oxford, Oxford, United Kingdom, <sup>10</sup>Department of Neurology, National Paediatric Hospital Dr. J. P. Garrahan, Ciudad de Buenos Aires, Argentina, <sup>11</sup>University of California San Diego, San Diego, CA, USA, <sup>12</sup>Harvard University, Boston, MA, USA, <sup>13</sup>Great Ormond Street, London, United Kingdom, <sup>14</sup>Erasmus MC University Medical Center, Rotterdam, Netherlands, <sup>15</sup>Nitte University, Mangalore, India, <sup>16</sup>Medical University of Innsbruck, Innsbruck, Austria, <sup>17</sup>Pontifical Catholic University of Rio Grande do Sul, Porto Alegre, Brazil, <sup>18</sup>Witten/Herdecke University, Datteln, Germany, <sup>19</sup>Humboldt-Universität zu Berlin and Berlin Institute of Health, Berlin, Germany, <sup>20</sup>Southern TOHOKU Research Institute for Neuroscience, Koriyama, Japan, <sup>21</sup>Oxford University, Oxford, United Kingdom.

# **M126. Investigations of Synaptic Signaling Targets of Human Anti-NMDAR Antibodies**

Yuyoung Joo, PhD<sup>1</sup>, Weiliang Huang, PhD<sup>2</sup>, Scott K. Dessain, MD, PhD<sup>3</sup>, Maureen Kane, PhD<sup>2</sup>, **David R. Benavides, MD, PhD<sup>1</sup>**. <sup>1</sup>University of Maryland School of Medicine, Baltimore, MD, USA, <sup>2</sup>University of Maryland School of Pharmacy, Baltimore, MD, USA, <sup>3</sup>Lankenau Institute for Medical Research, Wynnewood, PA, USA.

# **M127. Late Onset Rasmussen Encephalitis - Age is Just a Number!**

Prashant Natteru, MBBS, **Arshaq Saleem, BS**, Christine Gill, MD. University of Iowa Hospitals & Clinics, Iowa City, IA, USA.

# **\*M128. Longitudinal FDG-PET/CT Changes in People with Stiff Person Syndrome Spectrum Disorders**

**Samantha Roman, MD**, Scott Newsome, DO. Johns Hopkins University Department of Neurology, Baltimore, MD, USA.

# **\*M129. Mendelian Randomization of Inflammatory Markers to Show Their Causal Role in Multiple Sclerosis Pathophysiology**

**Sara Seyedroudbari, B.A.<sup>1</sup>**, Pranav Sharma, B.A.<sup>1</sup>, Troy Desai, MD<sup>2</sup>. <sup>1</sup>Drexel University College of Medicine, Philadelphia, PA, USA, <sup>2</sup>Allegheny Multiple Sclerosis Treatment Center, Allegheny General Hospital, Allegheny Health Network, Philadelphia, PA, USA.

# **\*M130. Misdiagnosis of Atypical Presentations of Multiple Sclerosis: Lessons from the Penn White Matter Disorders Adult Neurogenetics Clinic**

**Leah Zuroff, MD, MS**, Jennifer Orthmann-Murphy, MD, PhD. Hospital of the University of Pennsylvania, Philadelphia, PA, USA.

**\*M131. Neurological Autoimmunity in Patients with Non-Pulmonary Neuroendocrine Tumors: Clinical Manifestations and Neural Autoantibody Profiles**

**Georgios Mangioris, MD**, Thorvardur R. Halfdanarson, MD, Vanda A. Lennon, MD, Divyanshu Dubey, MD, Eoin P. Flanagan, MD, Andrew McKeon, MD, Sean J. Pittock, MD, Anastasia Zekeridou, MD, PhD. Mayo Clinic, Rochester, MN, USA.

**M132. New Diagnosis of Multiple Sclerosis after Moderna COVID-19 mRNA Vaccination**

**Hannah Lu, BSA**, George Ishac, BS, Emma Martinez-Arellano, BS, Muhammad Ansari, MD, Manmeet Kaur, MD, Ruiqing Sun, MD, PhD, Ruiqing Sun, MD, PhD. University of Texas Medical Branch, Galveston, TX, USA.

**M133. One is Bad, Two is Worse: A Case of Double Antibody Positive Encephalitis as a Harbinger of Malignancy**

**Karandeep S. Bhatti, MBBS**, Robert Sharkus, DO, Richa Thakkar, DO, Olga R. Thon, MD, Jesse M. Thon, MD. Cooper University Hospital, Camden, NJ, USA.

**M134. Patient Reported Outcome Measures in Autoimmune Encephalitis**

**Deja Leadley, BS**, Eric Engebretson, BS, Stefan Sillau, PhD, Brooke Valdez, BA, Tyler L. Borko, BS, Sarah Bausano, BS, Kelli M. Money, MD, PhD, Enrique Alvarez, MD, PhD, John R. Corboy, MD, Timothy L. Vollmer, MD, Amanda L. Piquet, MD. University of Colorado, Aurora, CO, USA.

**\*M135. Povetacicept (ALPN-303), a Potent Dual BAFF/APRIL Antagonist, for the Treatment of Myasthenia Gravis (MG) and Other Antibody-Related Neurological Diseases**

**Stacey R. Dillon, PhD<sup>1</sup>**, Rupert Davies, PhD<sup>1</sup>, Jason D. Lickliter, PhD<sup>2</sup>, Kristi McLendon, MD<sup>3</sup>, Kristi Manjarrez, BS<sup>1</sup>, Alina Smith, BS<sup>1</sup>, Lori Blanchfield, PhD<sup>1</sup>, Russell J. Sanderson, PhD<sup>1</sup>, Allison Chunyk, MS<sup>1</sup>, Tiffany Blair, PhD<sup>1</sup>, Amanda Enstrom, PhD<sup>1</sup>, Hany Zayed, PhD<sup>1</sup>, Alessandra Consonni, PhD<sup>4</sup>, Martina Miglietti, MSc<sup>4</sup>, Elena Rinaldi, MSc<sup>4</sup>, Fulvio Baggi, MSc<sup>4</sup>, Renato Mantegazza, MD<sup>4</sup>, Katherine E. Lewis, PhD<sup>1</sup>, Stanford Peng, MD, PhD<sup>1</sup>. <sup>1</sup>Alpine Immune Sciences, Inc., Seattle, WA, USA, <sup>2</sup>Nucleus Network, Melbourne, Australia, <sup>3</sup>Nucleus Network, Brisbane, Australia, <sup>4</sup>Fondazione IRCCS Istituto Neurologico Carlo Besta, Milan, Italy.

**M138. Rare Case of Transverse Myelitis Related to Myelin Oligodendrocyte Glycoprotein Associated Disease**

**Shaweta Khosa, M.B.B.S.<sup>1</sup>**, Sanjay Anandram, M.D.<sup>2</sup>, Rupinder Singh Buttar, M.D.<sup>2</sup>, Gurveer Singh Khosa, M.B.B.S.<sup>3</sup>, Shri K. Mishra, M.D.<sup>1</sup>. <sup>1</sup>Olive View-UCLA Medical Center, Sylmar, CA, USA, <sup>2</sup>Rochester General

Hospital, Rochester, NY, USA, <sup>3</sup>Adesh Institute of Medical Sciences & Research, Bathinda, India.

**\*M139. Stiff-Person Syndrome (SPS) with Very High GAD-Titers Triggered by COVID-19-Booster in 2 Neurologically Asymptomatic GAD-Positive Patients with Diabetes Mellitus Type 1 (DM1)**

**Gema Giler, MD**, Marinos C. Dalakas, MD. Thomas Jefferson University, Philadelphia, PA, USA.

**M140. Stroke in a Young Adult: Immunomodulation Responsive Bilateral Supraclinoid Carotid Artery Vasculitis Secondary to Systemic Lupus Erythematosus**

**Sneha Lingam, MD**, Jacob M. Stout, MD, Amy K. Guzik, MD, Tamra I.J. Ranasinghe, MD. Atrium Health Wake Forest Baptist, Winston-Salem, NC, USA.

**M141. The Effect of Ocrelizumab on Balo's Tumefactive Lesion: A Case Report**

**Muhammad Faraz Raghbi, MD**, Fen Bao, MS, Sophia Tessema, MD, Emily Pelc, MSc, Adam Lazar, MSc, Carla Santiago Martinez, MS, Jacob Rube, MD, Evanthea Bernitsas, MD. Wayne State University, Detroit, MI, USA.

**\*M142. The Innate Immune Regulator Nlrp1 Limits Inflammatory Neurodegeneration in the Visual Pathway in Experimental Autoimmune Encephalomyelitis**

**Alexander J. Gill, MD, PhD**, Thomas Garton, B.S., Matthew Smith, M.S., Marjan Gharagozloo, PhD, Peter Calabresi, MD. Johns Hopkins University, School of Medicine, Baltimore, MD, USA.

**M144. The Societal Costs of Metachromatic Leukodystrophy (MLD) in the United States and Potential Benefits of Disease-Modifying Therapy**

**Karen Bean, MSc<sup>1</sup>**, Beckley Miller, MSc<sup>2</sup>, Kenneth Howie, BSc<sup>3</sup>, Markus Walz, BSc<sup>3</sup>, Christopher Fields, BSc<sup>4</sup>, Ivar Jensen, BSc<sup>2</sup>, Rebecca Dean, MSc<sup>2</sup>, Francis Pang, MSc<sup>1</sup>. <sup>1</sup>Orchard Therapeutics, London, United Kingdom, <sup>2</sup>Precision Health Economics and Outcomes Research, Boston, MA, USA, <sup>3</sup>Magnolia Innovation, Hoboken, NJ, USA, <sup>4</sup>Orchard Therapeutics, Boston, MA, USA.

**M145. Two Cases of Neurosarcoidosis Presenting with Sexual Dysfunction: One with Anejaculation and Another of Erectile Dysfunction**

**Rajesh K. Gupta, MD**. UT Health, Houston, TX, USA.

**\*M146. Unusual CNS Manifestations of COVID-19: A Case Series**

**Osman Ozel, MD**, Bing Liao, MD, MSc. Houston Methodist Hospital, Houston, TX, USA.

**\*M147. Utility of Protein Microarrays for Detection of Classified & Novel Antibodies in Autoimmune Neurological Disease**

**Nisa Vorasoot, MD,** Connie E. Lesnick, MS, Eoin P. Flanagan, MD, Michael Gilligan, MB, BCh, Sean J. Pittock, MD, Binxia Yang, PhD, Anastasia Zekeridou, MD, PhD, Divyanshu Dubey, MD, John R. Mills, PhD, Andrew McKeon, MD. Mayo Clinic, Rochester, MN, USA.

**\*M148. Validation of the 2023 International MOGAD Panel Proposed Criteria: An Institutional Cohort**  
**Malak Alaboudi, MD.** Case Western Reserve University School of Medicine - University Hospitals Cleveland Medical Center, Cleveland, OH, USA.

**M149. Voltage Gated Calcium Channel Antibodies Associated Peripheral Neuropathy**  
**Shaweta Khosa, M.D.<sup>1</sup>,** Venkat Srikar Lavu, M.B.B.S.<sup>2</sup>, Bhavesh Trikamji, M.D.<sup>3</sup>, Shrikant Mishra, M.D.<sup>4</sup>. <sup>1</sup>Sepulveda VA Medical Center, Los Angeles, CA, USA, <sup>2</sup>Osmania Medical College, Hyderabad, India, <sup>3</sup>University of California, Riverside, CA, USA, <sup>4</sup>Keck School of Medicine USC, Los Angeles, CA, USA.

**M150. When It's Not MS: Rediagnosing Recurrent ADEM in an Adult**  
**Caroline Nall, Bachelor of Arts,** Chandra Mannyam, MD, Muhammad Bhatti, MD, Mary Willis, MD. University of Mississippi Medical Center, Jackson, MS, USA.

**K-M100. Disrupted Cerebral Metabolism in Multiple Sclerosis**  
**Matthew R. Brier, MD PhD,** Bradley Judge, BS, Chunwei Ying, PhD, Hongyu An, PhD, Anne Cross, MD, Tammie Benzinger, MD PhD, Manu Goyal, MD. Washington University in St. Louis, St. Louis, MO, USA.

**K-M101. Investigations of Synaptic Signaling Targets of Human Anti-NMDAR Antibodies**  
Yuyoung Joo, PhD<sup>1</sup>, Weiliang Huang, PhD<sup>2</sup>, Scott K. Dessain, MD, PhD<sup>3</sup>, Maureen Kane, PhD<sup>2</sup>, **David R. Benavides, MD, PhD<sup>1</sup>.** <sup>1</sup>University of Maryland School of Medicine, Baltimore, MD, USA, <sup>2</sup>University of Maryland School of Pharmacy, Baltimore, MD, USA, <sup>3</sup>Lankenau Institute for Medical Research, Wynnewood, PA, USA.

**K-M102. Longitudinal Clinical Evaluation of Paramagnetic Rim Lesions in Multiple Sclerosis**  
**Christopher C Hemond, MD<sup>1</sup>,** Sathish K. Dundamadappa, MD<sup>1</sup>, Mugdha Deshpande, BS<sup>1</sup>, Jonggyu Baek, PhD<sup>1</sup>, Robert H. Brown, Jr., MD PhD<sup>1</sup>, Daniel S. Reich, MD PhD<sup>2</sup>. <sup>1</sup>University of Massachusetts, Worcester, MA, USA, <sup>2</sup>National

*Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD, USA.*

**K-M103. The PKC Modulator Bryostatin-1 Augments Remyelination through Therapeutic Targeting of CNS Innate Immunity**  
**Michael D. Kornberg, MD, PhD.** Johns Hopkins, Baltimore, MD, USA.

## Autoimmune Neurology & MX

**LB-M100. Demographics and Clinical Characteristics of Possible Autoimmune Encephalitis with GAD 65-Antibody**  
**Sara E. Benitez, M.D.,** Timea Hodics, M.D., Joseph Masdeu, M.D. PhD, Eugene Lai, M.D. PhD, Steve Fung, M.D., Osman Ozel, M.D., Maya Ramy, B.A., M.S. Houston Methodist Hospital, Houston, TX, USA.

**\*LB-M101. Hemicord White Matter Enhancement and the Croissant Sign in Spondylotic Myelopathies**  
**Xiaoyang Li, MD,** Anastasia Zekeridou, MD, PhD, Michel Toledano, MD, Eoin P. Flanagan, MB.BCh. Mayo Clinic, Rochester, MN, USA.

## Behavioral Neurology and Dementia

**\*M151. A Phase 1, First-in-Human, Randomized, Double-Blind, Placebo-Controlled, Single- and Multiple-Ascending Intravenous Dose Study of VGL101, a Novel TREM2 Agonist, in Healthy Volunteers (HVs)**  
**Andreas Meier, MD, PhD<sup>1</sup>,** Spyros Papapetropoulos, MD, PhD<sup>2</sup>, Andrew Marsh, BS<sup>2</sup>, Kelly Neelon, PhD<sup>1</sup>, Evan Thackaberry, PhD<sup>1</sup>, David Stiles, PhD<sup>1</sup>, Ryan O'Mara, BS<sup>1</sup>, Raj Rajagovindan, PhD<sup>1</sup>. <sup>1</sup>Vigil Neuroscience, Inc., Watertown, MA, USA, <sup>2</sup>Formerly Vigil Neuroscience, Inc., Watertown, MA, USA.

**\*M152. Advanced Cerebral Adrenoleukodystrophy: Hope for a Vulnerable Cohort**  
**Yedda Li, MD, PhD,** Florian S. Eichler, MD. Massachusetts General Hospital, Boston, MA, USA.

**\*M153. Alterations in Basal Ganglia Connectivity in Individuals with Primary Progressive Aphasia**  
**Daniel Seog, BA,** Jordan Behn, MS, Elena Barbieri, PhD, Emily Rogalski, PhD, Marsel Mesulam, MD, Bornha Bonakdarpour, MD. Northwestern University Feinberg School of Medicine, Chicago, IL, USA.



**\*M154. Are Psychotic-Spectrum Disorders with Comorbid Anxiety and Depression Predisposing Factors for Parkinson's Disease**

**Anna Shvartsur, MD<sup>1</sup>**, Kelli Peterman, MPH<sup>2</sup>, Matthew E. Hirschrift, MD, MPH<sup>3</sup>, Nirmala D. Ramalingam, MPP<sup>4</sup>.  
<sup>1</sup>Kaiser Permanente Medical Center, Psychiatry Residency Program, Oakland, CA, USA, <sup>2</sup>Kaiser Permanente Northern California, Division of Research, Oakland, CA, USA, <sup>3</sup>Kaiser Permanente Northern California, Division of Research; The Permanente Medical Group, Kaiser Permanente Oakland, Department of Psychiatry; University of California, San Francisco, Department of Psychiatry and Behavioral Sciences, Oakland, CA, USA, <sup>4</sup>Kaiser Permanente Oakland Medical Center, Graduate Medical Education, Division of Research, Oakland, CA, USA.

**\*M155. Association between Retinal Microvascular Changes and Late Brain Amyloid Deposition: The ARIC-PET Study**

**Marco Egle, Ph.D.<sup>1</sup>**, Jennifer A. Deal, Ph.D.<sup>2</sup>, Keenan A. Walker, Ph.D.<sup>3</sup>, Dean F. Wong, M.D., Ph.D.<sup>4</sup>, A. Richey Sharet, M.D., DrPH<sup>2</sup>, Rebecca F. Gottesman, M.D., Ph.D.<sup>1</sup>. <sup>1</sup>NINDS, Bethesda, MD, USA, <sup>2</sup>Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>3</sup>National Institute on Aging, Baltimore, MD, USA, <sup>4</sup>Washington University School of Medicine, St. Louis, MN, USA.

**M156. Association of Birth Weight and Preterm Birth with PET-Amyloid Burden: The Atherosclerosis Risk in Communities (ARIC) PET Study**

**Olivia M. Emanuel, BA<sup>1</sup>**, Mark Lee, PhD<sup>2</sup>, Pamela L. Lutsey, PhD<sup>3</sup>, Kevin Sullivan, PhD, MPH<sup>4</sup>, Renée Groechel, PhD<sup>1</sup>, Marco Egle, PhD<sup>1</sup>, Thomas Mosley, PhD<sup>5</sup>, Andrea L.C. Schneider, MD, PhD<sup>6</sup>, Dean Wong, MD, PhD<sup>7</sup>, Rebecca F. Gottesman, MD, PhD<sup>1</sup>. <sup>1</sup>National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA, <sup>2</sup>Minnesota Department of Health, St. Paul, MN, USA, <sup>3</sup>Division of Epidemiology & Community Health, University of Minnesota School of Public Health, Minneapolis, MN, USA, <sup>4</sup>The MIND Center, University of Mississippi Medical Center, Jackson, MS, USA, <sup>5</sup>Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA, <sup>6</sup>University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA, <sup>7</sup>Department of Radiology, Washington University, St. Louis, MO, USA.

**M157. Autozoanthroposopometamorphopsia: Transformation to Equine Countenance**

**Babak Moradi, Medical Student<sup>1</sup>**, Fathima Shaik, Medical Student<sup>1</sup>, Alan R. Hirsch, MD<sup>2</sup>. <sup>1</sup>Aureus University School of Medicine, Oranjestad, Aruba, <sup>2</sup>Smell & Taste Treatment and Research Foundation, Chicago, IL, USA.

**\*M159. Brain Insulin Signaling is Associated with Late-Life Cognitive Decline**

**Han Tong, MBBS, PhD<sup>1</sup>**, Ana W. Capuano, PhD<sup>1</sup>, Rexford S. Ahima, MD, PhD<sup>2</sup>, Steven E. Arnold, MD<sup>3</sup>, Zoe Arvanitakis, MD, MS, EMBA<sup>1</sup>. <sup>1</sup>Rush Alzheimer's Disease Center, Rush University Medical Center, Chicago, IL, USA, <sup>2</sup>Division of Diabetes, Endocrinology and Metabolism, Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>3</sup>Interdisciplinary Brain Center, Massachusetts General Hospital, Harvard Medical School, Boston, MA, USA.

**M160. Can Antiepileptic Help Recovery in Opioid-Associated Amnesic Syndrome? A Case Report**

**Ola Al Shagi, MD, Estevo Ribeiro, MD, Claire Delpirou Nouh, MD, Ahmad Al Awwad, MD.** University of Oklahoma Health Sciences Center Department of Neurology, Oklahoma City, OK, USA.

**M161. Cannabis Induced Obsessive Compulsive Disorder**

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**M162. Clinical Phenotype of Posterior Cortical Atrophy Progressing to Corticobasal Syndrome: A Case Report**

**Kaancan Deniz, MD, Prashant A. Natteru, MD, Christopher L. Groth, MD.** University of Iowa, Iowa City, IA, USA.

**M163. Creutzfeldt-Jakob Disease Presenting as Psychiatric Disorder: Case Presentation and Systematic Review**

**Brendan Huang, MD<sup>1</sup>**, Neeva Shafian, BS<sup>2</sup>, Paul J. Masi, MD<sup>1</sup>, Marc L. Gordon, MD<sup>1</sup>, Ana M. Franceschi, MD/PhD<sup>3</sup>, Luca Giliberto, MD/PhD<sup>4</sup>. <sup>1</sup>Northwell Health System, Manhasset, NY, USA, <sup>2</sup>Donald and Barbara Zucker School of Medicine, Hempstead, NY, USA, <sup>3</sup>Lenox Hill Hospital, New York City, NY, USA, <sup>4</sup>Feinstein Institutes for Medical Research, Manhasset, NY, USA.

**M164. Dementia and the Gut: Is There a Gut Immune Imbalance? Can We Intervene?**

**Ereny Demian, MD<sup>1</sup>**, Yosef Tobi, Graduate Student - BS<sup>2</sup>, Papul Chalia, MD<sup>1</sup>, Fadi Antaki, MD<sup>3</sup>, Harvinder Talwar, PhD<sup>3</sup>, Michael Lawson, PhD<sup>4</sup>, Benita McVicker, PhD<sup>5</sup>, Martin Tobi, MD<sup>6</sup>. <sup>1</sup>Penn State Health. Hershey Medical Center, Hershey, PA, USA, <sup>2</sup>Memorial Sloan Kettering Cancer Center, New York, NY, USA, <sup>3</sup>John D Dingell VA Medical Center, Detroit, MI, USA, <sup>4</sup>University of California at Sacramento, Sacramento, CA, USA, <sup>5</sup>University of Nebraska Medical Center, Omaha, Omaha, NE, USA, <sup>6</sup>John D Dingell VA Medical Center, Detroit, Detroit, MI, USA.

**M165. Dementia with Lewy Bodies Presenting with Coexisting TDP-43 and Tau Proteinopathy without Beta-Amyloid Pathology**

**Kaancan Deniz, MD<sup>1</sup>**, Ramasamy Thangavel, PhD<sup>2</sup>, Marco Hefli, MD<sup>1</sup>, Qiang Zhang, MD<sup>1</sup>, Georgina M. Aldridge, MD PhD<sup>1</sup>. <sup>1</sup>University of Iowa Hospitals and Clinics, Iowa City, IA, USA, <sup>2</sup>University of Iowa, Iowa City, IA, USA.

**\*M166. Depression Associates with Cognitive Impairment and Rates of Decline in African Americans**

**Christian Lachner, M.D.**, Emily C. Craver, M.S., John A. Lucas, Ph.D., Tanis J. Ferman, Ph.D., Neill R. Graff-Radford, M.D., Gregory S. Day, M.D. Mayo Clinic, Jacksonville, FL, USA.

**M167. Development of a Novel Mouse Model of Neonatal Hypoxic Ischemic Encephalopathy**

**Bailey Collins, BS<sup>1</sup>**, Elise Lemanski, BS<sup>2</sup>, Sayera Muqarram, MBBS<sup>1</sup>, Elizabeth Wright-Jin, MD, PhD<sup>1</sup>. <sup>1</sup>Nemours Children's Hospital, Wilmington, DE, USA, <sup>2</sup>University of Delaware, Newark, DE, USA.

**\*M168. Differential ATN Networks of Cerebrospinal Fluid and Neuroimaging Biomarkers and Their Prediction of Cognition between Self-Reported Black and Non-Hispanic White Individuals**

**Samuele Bonomi, MD<sup>1</sup>**, Ruijin Lu, PhD<sup>2</sup>, Suzanne Schindler, MD, PhD<sup>1</sup>, David Wolk, MD<sup>3</sup>, James J. Lah, MD, PhD<sup>4</sup>, Reisa A. Sperling, MD<sup>5</sup>, Allan I. Levey, MD, PhD<sup>4</sup>, Leslie M. Shaw, PhD<sup>6</sup>, John C. Morris, MD<sup>7</sup>, Tammie L.S. Benzinger, MD, PhD<sup>8</sup>, Quoc Bui, MD<sup>2</sup>, Chengjie Xiong, PhD<sup>2</sup>. <sup>1</sup>Department of Neurology, Washington University School of Medicine, St. Louis, MO, USA, <sup>2</sup>Division of Biostatistics, Washington University School of Medicine, St. Louis, MO, USA, <sup>3</sup>Department of Neurology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA, <sup>4</sup>Department of Neurology, Emory University School of Medicine, Atlanta, GA, USA, <sup>5</sup>Department of Neurology, Center for Alzheimer Research and Treatment, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA, <sup>6</sup>Department of Pathology and Laboratory Medicine, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, USA, <sup>7</sup>Knight Alzheimer Disease Research Center, Washington University School of Medicine, St. Louis, MO, USA, <sup>8</sup>Department of Radiology, Washington University School of Medicine, St. Louis, MO, USA.

**\*M169. Dysfunction of the Neuroglial Lactate Shuttle in Metabolic Syndrome Contributing to Cognitive and Memory Impairment**

**Mohamed Noureldein, PhD**, Sarah Elzinga, PhD, John Hayes, BS, Diana Rigan, BS, Samuel Teener, BS, Eva Feldman, MD, PhD. University of Michigan, Ann Arbor, MI, USA.

**\*M170. Expanding the Diagnostic Applications of Cerebrospinal Fluid Biomarkers in Patients with Rapidly Progressive Dementia**

Lindsey A. Kuchenbecker, BSc<sup>1</sup>, Philip W. Tipton, MD<sup>1</sup>, Yuka A. Martens, PhD<sup>1</sup>, Matthew R. Brier, MD PhD<sup>2</sup>, Nihal Satyadev, MD<sup>1</sup>, S. Richard Dunham, MD<sup>2</sup>, Evelyn B. Lazar, MD<sup>3</sup>, Maxwell V. Dacquel, BSc<sup>1</sup>, Guojun Bu, PhD<sup>1</sup>, Michael D. Geschwind, MD PhD<sup>4</sup>, John C. Morris, MD<sup>2</sup>, Suzanne E. Schindler, MD PhD<sup>2</sup>, Anne M. Fagan, PhD<sup>2</sup>, Neill R. Graff-Radford, MD<sup>1</sup>, **Gregory S. Day, MD MSc MSCI<sup>1</sup>**. <sup>1</sup>Mayo Clinic in Florida, Jacksonville, FL, USA, <sup>2</sup>Washington University School of Medicine, Saint Louis, MO, USA, <sup>3</sup>Hackensack Meridian Health, Perth Amboy, NJ, USA, <sup>4</sup>University of California San Francisco, San Francisco, CA, USA.

**M171. Exploring Cognitive Functioning and Health Literacy in Patients with Familial Hypercholesterolemia**

**Aishwarya Ganesb, MBBS<sup>1</sup>**, Moon Fai Chan, PhD<sup>1</sup>, Sangeetha Mahadevan, BA<sup>1</sup>, Siham Al Shamli, <sup>-2</sup>, Khalid Al-Waili, MD<sup>1</sup>, Suad Al-Mukhaini, BS<sup>1</sup>, Khalid Al-Rasadi, MD<sup>1</sup>, Samir Al-Adawi, PhD<sup>1</sup>. <sup>1</sup>Sultan Qaboos University, Muscat, Oman, <sup>2</sup>Ibri Hospital, Al Dhahira, Oman.

**M172. Exploring Divergences between the Experiences and Future Perceptions of People with Dementia and Their Care Partners**

**Maayra I. Butt, MS**, Jasmine A. Silvestri, MPH, Catherine L. Auriemma, MD, MS, Julia McMillan, BS, Tamar Klaiman, PhD, MPH, Melanie Bhatti, MEd. University of Pennsylvania, Philadelphia, PA, USA.

**\*M174. General and Biomarker Cerebrospinal Fluid Findings in Prion Disease and Other Rapidly Progressive Dementias**

Alyssa J. Baird, B.S., M.D., Kolette Cho, B.S., Michael Terranova, B.S., M.S., Theresa Driscoll, B.S., Megan Casey, B.A., Kelly O'Leary, BSN, RN, Kendra Benisano, BA, MPEN, MS, Katherine Wong, MD, Sven Forner, BA, Guoyu Zhou, MD, PhD, **Michael D. Geschwind, MD, PhD**. UCSF Memory and Aging Center, San Francisco, CA, USA.

**\*M175. Generation of Position Correlated Cells in Primary Sensory Cortices Requires Bottom-Up Inputs**

**Dhruba Banerjee, PhD**, Zaneta Navratilova, PhD, Jordan Zhang, BA, Bruce McNaughton, PhD, Sunil Gandhi, PhD. University of California, Irvine, Irvine, CA, USA.

**\*M176. Handedness in Alzheimer's Disease: A Systematic Review and Future Directions**

Giorgio Guido, MS<sup>1</sup>, Alberto Bonato, MS<sup>2</sup>, **Samuele Bonomi, MD<sup>3</sup>**, Simone Franceschini, MS<sup>4</sup>, John C. Morris, MD<sup>5</sup>. <sup>1</sup>University of Catania, Catania, Italy, <sup>2</sup>University of Padua, Padua, Italy, <sup>3</sup>Department of Neurology, Washington University in St. Louis, St. Louis, MO, USA, <sup>4</sup>University of Chieti, Chieti,

Italy, <sup>5</sup>Knight Alzheimer Disease Research Center, Washington University School of Medicine, St. Louis, MO, USA.

**\*M177. Immune Modulating Mechanisms of Human Neural Stem Cell Transplantation in a Transgenic Alzheimer's Disease Mouse Model**

Kevin S. Chen, MD, **Mohamed H. Noureldein, PhD**, Lisa M. McGinley, PhD, John M. Hayes, BS, Diana M. Rigan, BS, Jacquelin F. Kwentus, BS, Shayna N. Mason, BS, Faye E. Mendelson, BS, Masha G. Savellieff, PhD, Eva L. Feldman, MD PhD. University of Michigan, Ann Arbor, MI, USA.

**\*M178. Improving Early Recognition of Potentially Treatment-Responsive Causes of Rapidly Progressive Dementia**

Nihal Satyadev, MD MPH<sup>1</sup>, Philip W. Tipton, MD<sup>1</sup>, Yuka Martens, PhD<sup>1</sup>, S. Richard Dunham, MD<sup>2</sup>, Michael D. Geschwind, MD PhD FANA<sup>3</sup>, John C. Morris, MD<sup>2</sup>, Matthew R. Brier, MD PhD<sup>2</sup>, Neill R. Graff-Radford, MD<sup>1</sup>, **Gregory S. Day, MD MSc MSC<sup>1</sup>**. <sup>1</sup>Mayo Clinic in Florida, Jacksonville, FL, USA, <sup>2</sup>Washington University School of Medicine, Saint Louis, MO, USA, <sup>3</sup>University of California San Francisco, San Francisco, CA, USA.

**\*M179. Influences of Demographic Factors on the Digital Clock and Recall (DCR) and the Mini Mental Status Examination (MMSE)**

**Ali Jannati, MD, PhD<sup>1</sup>**, Joyce Gomes-Osman, PT, PhD<sup>1</sup>, Russell Banks, CCC-SLP, PhD<sup>1</sup>, Claudio Toro-Serey, PhD<sup>1</sup>, Connor Higgins, MSc<sup>1</sup>, Shirley Fecteau, PhD<sup>2</sup>, Marissa Ciesla, PhD<sup>1</sup>, Sean Tobbyne, PhD<sup>1</sup>, John Showalter, MD<sup>1</sup>, Alvaro Pascual-Leone, MD, PhD<sup>3</sup>. <sup>1</sup>Linus Health, Boston, MA, USA, <sup>2</sup>Université Laval, Quebec City, QC, Canada, <sup>3</sup>Hebrew SeniorLife, Harvard Medical School, Boston, MA, USA.

**M180. Innate Lymphoid Cells as Novel Prognostic Biomarkers for VCID**

Sahar Emami Naeini, MD, Evila L. Salles, Ph D, Bidhan Bhandari, DDS, Hesamoldin Khodadadi-Chamgordani, MD, PhD, David C. Hess, MD, Lei P. Wang, Ph D, **Askiel Bruno, MD, MS**, Babak Baban, Ph D. Augusta University, Augusta, GA, USA.

**M181. Integrated Spatial Genomics Reveals Cell-Type Specific Responses and Interactions in Human Alzheimer's Disease Brain Tissue Environments**

**Anthony Linares, MD PhD<sup>1</sup>**, Jina Yun, BA<sup>2</sup>, Lynn Fang, MS<sup>2</sup>, John Allman, PhD<sup>2</sup>, Barbara Wold, PhD<sup>2</sup>, Long Cai, PhD<sup>2</sup>. <sup>1</sup>UCLA, Los Angeles, CA, USA, <sup>2</sup>Caltech, Pasadena, CA, USA.

**\*M183. Metabolic Dysregulation in Probable Alzheimer's Disease**

**Christopher L. Reading, PhD<sup>1</sup>**, Clarence Ahlem, N/A<sup>1</sup>, Joseph M. Palumbo, MD, LFAPA, MACPsych<sup>1</sup>, Marcia A. Testa, PhD, MPhil, MPH<sup>2</sup>, Donald C. Simonson, MD, MPH, ScD, MBA<sup>3</sup>. <sup>1</sup>BioVie Inc, Carson City, NV, USA, <sup>2</sup>Department of Biostatistics, Harvard T.H. Chan School of Public Health, Boston, MA, USA, <sup>3</sup>Division of Endocrinology, Diabetes, and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

**M184. Misdiagnosis of Early-Onset Dementia and Dementia-Plus Syndromes**

**Yedda Li, MD, PhD**, Florian S. Eichler, MD. Massachusetts General Hospital, Boston, MA, USA.

**M186. MRI Perfusion and Structural Markers of Pathologic Burden in Frontotemporal Lobar Degeneration Due to Tau**

**Christopher A. Olm, MA**, Claire S. Peterson, BS, David J. Irwin, MD, Edward B. Lee, MD, PhD, John Q. Trojanowski, MD, PhD, Lauren Massimo, PhD, CRNP, John A. Detre, MD, Corey T. McMillan, PhD, James C. Gee, PhD, Murray Grossman, MD. University of Pennsylvania, Philadelphia, PA, USA.

**\*M188. Polygenic Burden of Expanded Short Tandem Repeats Promotes Risk for Alzheimer's Disease**

**Michael Guo, MD, PhD**, Wan-Ping Lee, PhD, Badri Vardarajan, PhD, Gerard Schellenberg, PhD, Jennifer Phillips-Cremens, PhD. University of Pennsylvania, Philadelphia, PA, USA.

**\*M189. Predicting Emotional and Behavioral Complications of Hemorrhagic Stroke**

**Daniel Talmasov, MD<sup>1</sup>**, Sean Kelly, MD PhD<sup>2</sup>, Sarah Ecker, BS<sup>2</sup>, Anlys Olivera, MD PhD<sup>2</sup>, Aaron Lord, MD<sup>2</sup>, Lindsey Gurin, MD<sup>2</sup>, Koto Ishida, MD<sup>2</sup>, Kara Melmed, MD<sup>2</sup>, Jose Torres, MD<sup>2</sup>, Barry Czeisler, MD<sup>2</sup>, Cen Zhang, MD<sup>2</sup>, Jennifer Frontera, MD<sup>2</sup>, Ariane Lewis, MD<sup>2</sup>. <sup>1</sup>Columbia University, New York City, NY, USA, <sup>2</sup>NYU School of Medicine, New York City, NY, USA.

**M190. Prevalence and Predictors of Cognitive Impairment in Nonalcoholic Fatty Liver Disease**

**Neal S. Parikh, MD, MS**, Farah Wahbeh, -, Christopher Tapia, BS, Mallory Ianelli, RN, Abhishek Jaywant, PhD, Hooman Kamel, MD, MS, Sonal Kumar, MD, MPH, Costantino Iadecola, MD. Weill Cornell Medicine, New York, NY, USA.

**\*M191. Pyramidal Neurodegeneration is Linked to Select Cytoarchitecture and Cognitive Impairment in Behavioral Variant Frontotemporal Dementia with Tau or TDP-43 Pathology**

**Daniel T. Ohm, PhD**, Alejandra Bahena, BS, Sanaz Arezoumandan, MD, Kathryn A.Q. Cousins, PhD, Jeffrey Phillips, PhD, Noah Capp, BS, Winifred Trotman, MS, Emily Xie, BS, David Wolk, MD, Corey McMillan, PhD, Edward Lee, MD, PhD, Murray Grossman, MD, David Irwin, MD. University of Pennsylvania, Philadelphia, PA, USA.

**M192. Racial Disparities in Alzheimer's Disease and Related Dementias (ADRD): The Association between Early Life Adversity and ADRD**

**Deborah Rose, MD<sup>1</sup>**, Catherine Gervais, BA<sup>2</sup>, Shakthi Unnithan, MS<sup>2</sup>, Hussein Al-Khalidi, PhD<sup>2</sup>, Andy Liu, MD<sup>1</sup>. <sup>1</sup>Duke University Medical Center, Durham, NC, USA, <sup>2</sup>Duke University, Durham, NC, USA.

**M193. Rapidly Progressive Dementia (RPD) in the Setting of Depression**

**Estevao Ribeiro, MD**, Philion Gatchoff, MD, Claire Delpirou Noub, MD, Danny Samkutty, MD, Nidhiben Anadani, MD. University of Oklahoma Health Sciences Center Department of Neurology, Oklahoma City, OK, USA.

**M194. Revisiting the Wood Criteria for Frontotemporal Degeneration Pedigree Classification: 10 Years Later**

**Laynie Dratch, ScM, CGC**, Vivianna M. Van Deerlin, MD, PhD, EunRan Suh, PhD, Alyson Hally, BS, Murray Grossman, MDCM, EdD, David J. Irwin, MD, Lauren Massimo, PhD, CRNP, Sara Manning, MD, MS, Corey T. McMillan, PhD. University of Pennsylvania, Philadelphia, PA, USA.

**M195. Saccadic Eye Movement Variability and Scattered Patterns in Children with Autism Spectrum Disorder**

**Blake S. Lockard, BS<sup>1</sup>**, Gesulla Cavanaugh, PhD, MS, MPH<sup>2</sup>, Nurit Sheinberg, PhD<sup>3</sup>, Leanne Boucher, PhD<sup>3</sup>, Vanessa Johnson, PhD<sup>1</sup>, Mark Epstein, MD<sup>4</sup>. <sup>1</sup>Nova Southeastern University Dr. Kiran C. Patel College of Allopathic Medicine, Davie, FL, USA, <sup>2</sup>Nova Southeastern University Ron and Kathy Assaf College of Nursing, Davie, FL, USA, <sup>3</sup>Nova Southeastern University College of Psychology, Davie, FL, USA, <sup>4</sup>Nicklaus Children's Hospital, Weston, FL, USA.

**M196. Scaled Event Based Modeling to Elucidate Alzheimer's Disease Progression Dynamics**

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**\*M197. Seizures Increase Microglial Proliferation in Alzheimer's Disease**

**Delia M. Talos, MD**, Xiaofan Li, MS, Sarah Gourmaud, PhD, Aaron Barbour, PhD, David J. Irwin, MD, PhD, Frances E. Jensen, MD. University of Pennsylvania, Philadelphia, PA, USA.

**\*M198. Sex Differences and Microglial Response in a Novel Mouse Model of Hypoxic Ischemic Encephalopathy**

**Jordan Case, Bachelor of Science**. Nemours Children's Health, Wilmington, DE, USA.

**\*M199. Shared and Disparate Transcriptomic Signatures Associated with Cortical Atrophy Change in Genetic Behavioral Variant Frontotemporal Degeneration**

**Ting Shen, PhD<sup>1</sup>**, Jacob W. Vogel, PhD<sup>2</sup>, Vivianna M Van Deerlin, MD, PhD<sup>3</sup>, Laynie Dratch, ScM<sup>1</sup>, Edward B. Lee, MD, PhD<sup>3</sup>, Jeffrey S. Phillips, PhD<sup>1</sup>, Murray Grossman, MD, EdD<sup>1</sup>, Lauren Massimo, PhD, CRNP<sup>1</sup>, David J. Irwin, MD<sup>1</sup>, Corey T. McMillan, PhD<sup>1</sup>. <sup>1</sup>Frontotemporal Degeneration Center, Department of Neurology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>Department of Clinical Sciences, SciLifeLab, Lund University, Lund, Sweden, <sup>3</sup>Center for Neurodegenerative Disease Research, Department of Pathology and Laboratory Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA.

**\*M200. Soluble Amyloid Precursor Protein-β Turnover is Slower Than Soluble Amyloid Precursor Protein-α Turnover in Humans Irrespective of Age or Amyloid Status**

**Justyna A. Dobrowolska Zakaria, PhD<sup>1</sup>**, Randall J. Bateman, MD<sup>2</sup>, Bruce W. Patterson, PhD<sup>3</sup>, Robert Vassar, PhD<sup>1</sup>. <sup>1</sup>Neurology, Northwestern University, Chicago, IL, USA, <sup>2</sup>Neurology, Washington University in St. Louis, St. Louis, MO, USA, <sup>3</sup>Medicine, Washington University in St. Louis, St. Louis, MO, USA.

**M201. Structural Analysis of the Basal Ganglia Using Ex Vivo 7T MRI Can Differentiate Frontotemporal Lobar Degeneration with TDP-43 vs Tau Accumulation**

**Rebecca L. Williamson, MD, PhD**, Pulkit Khandelwal, MS, Sandhitsu R. Das, PhD, Gabor Mizsei, MS, Karthik Prabhakaran, MS, Ranjit Ittyerah, MS, David A. Wolk, MD, John A. Detre, MD, Paul Yushkevich, PhD, Edward B. Lee, MD, PhD, James Gee, PhD, Murray Grossman, MDCM, EdD, Corey T. McMillan, PhD, M. Dylan Tisdall, PhD, David J. Irwin, MD. University of Pennsylvania, Philadelphia, PA, USA.

**\*M202. The Digital Clock and Recall Predict the Functional Activity Level in Older Adults**

**Joyce Gomes-Osman, PT, PhD<sup>1</sup>**, Ali Jannati, MD, PhD<sup>1</sup>, Russel Banks, PhD<sup>1</sup>, Claudio Toro-Serey, PhD<sup>1</sup>, Connor Higgins, MSc<sup>1</sup>, Shirley Fecteau, PhD<sup>2</sup>, Marissa Ciesla, PhD<sup>1</sup>, David Libon, PhD<sup>3</sup>, Rod Swenson, PhD<sup>4</sup>, Sean Tobyne, PhD<sup>1</sup>, John Showalter, MD<sup>1</sup>, Alvaro Pascual-Leone, MD, PhD<sup>5</sup>.

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**M203. Tracking Longitudinal Change in Presymptomatic Genetic Prion Disease**

Guoyu Zhou, MD, PhD<sup>1</sup>, Theresa Driscoll, BS<sup>1</sup>, Kolette Cho, BS<sup>1</sup>, Michael Terranova, BS, MS<sup>1</sup>, Kendra Benisaro, MPEN, MS<sup>1</sup>, Kelly L. O'Leary, BSN, RN<sup>1</sup>, Stacy Metcalf, PhD<sup>1</sup>, Aili Golubjatnikov, BSN, MS, RN<sup>1</sup>, Ralf D. Reilmann, MD, PhD<sup>2</sup>, Robin Schubert, M.Sc.<sup>2</sup>, Amy Litvin, NP<sup>1</sup>, Katherine S. Wong, MD<sup>1</sup>, **Michael D. Geschwind, MD, PhD<sup>1</sup>**. <sup>1</sup>UCSF Memory and Aging Center, San Francisco, CA, USA, <sup>2</sup>George Huntington Institute, Muenster, Germany.

**\*M204. Transcriptional Changes in Microglia in a Noninvasive Mouse Model of Neonatal Hypoxic Ischemic Encephalopathy**

**Elise Lemanski, BS<sup>1</sup>**, Bailey Collins, BA<sup>1</sup>, Elizabeth Wright-Jin, MD PhD<sup>2</sup>. <sup>1</sup>University of Delaware, Newark, DE, USA, <sup>2</sup>Nemours Children's Hospital, Wilmington, DE, USA.

**M205. Volumetric Analysis of Hippocampal Subregions and Subfields in Left and Right Predominant Semantic Dementia**

**Arenn F. Carlos, MD**, Stephen D. Weigand, MSc, Rene L. Utianski, PhD, Joseph R. Duffy, PhD, Heather M. Clark, PhD, Mary M. Machulda, PhD, Nha Trang Thu Pham, BSc, Christopher G. Schwarz, PhD, Clifford R. Jack, MD, Jennifer L. Whitwell, PhD, Keith A. Josephs, MD, MST, MSc. Mayo Clinic, Rochester, MN, USA.

**K-M104. Disease Associated Changes in Neuronal-Glia Interactions Implicates Neuroimmune Inhibition in Tau Dementias**

Xia Han, PhD, **Jessica E. Rexach, MD PhD**. UCLA, Los Angeles, CA, USA.

**LB-M102. Bibliometric Analysis of the 100 Most Cited Kluver-Bucy Research Articles**

**Cynthia Janku, B.S.<sup>1</sup>**, Priya V. Engel, MPH<sup>1</sup>, Kisan Patel, M.S.<sup>1</sup>, Elias Giraldo, M.D.<sup>1,2</sup>. <sup>1</sup>California University of Science and Medicine, School of Medicine, Colton, CA, USA, <sup>2</sup>California University of Science and Medicine, Department of Neurology, Colton, CA, USA.

**\*LB-M103. Clinicopathologic Features of a Novel Star-Like Transactive Response DNA-Binding Protein 43 (TDP-43) Pathology in the Oldest Old**

**Arenn F. Carlos, MD<sup>1</sup>**, Shunsuke Koga, MD, PhD<sup>2</sup>, Rodolfo G. Gatto, MD, PhD<sup>1</sup>, Nha Trang Thu Pham, BSc<sup>1</sup>, Irene Sintini, PhD<sup>1</sup>, Mary M. Machulda, PhD<sup>1</sup>, Clifford R. Jack, MD<sup>1</sup>, Val J. Lowe, MD<sup>1</sup>, Jennifer L. Whitwell, PhD<sup>1</sup>, Leonard Petrucelli, PhD<sup>1</sup>, R. Ross Reichard, MD<sup>1</sup>, Ronald C. Petersen, MD, PhD<sup>1</sup>, Dennis W. Dickson, MD<sup>1</sup>, Keith A. Josephs, MD, MST, MSc<sup>1</sup>, Keith A. Josephs, MD, MST, MSc<sup>1</sup>. <sup>1</sup>Mayo Clinic, Rochester, MN, USA, <sup>2</sup>Mayo Clinic, Jacksonville, FL, USA.

**LB-M104. Differential Diagnosis and Alzheimer's Disease: Can CART and CHAID Analysis Improve Diagnostic Accuracy and Decrease Barriers to Care**

**Jakob Thorn, MS**, Jessica Harvey, MA MS. Mercer University, Atlanta, GA, USA.

**LB-M105. Disease Associated Changes in Neuronal-Glia Interactions Implicates Neuroimmune Inhibition in Tau Dementias**

Xia Han, PhD<sup>1</sup>, Conor Webb, BA<sup>1</sup>, William Seeley, MD<sup>2</sup>, Daniel Geschwind, MD PhD<sup>1</sup>, **Jessica E. Rexach, MD PhD<sup>1</sup>**. <sup>1</sup>University of California, Los Angeles (UCLA), Los Angeles, CA, USA, <sup>2</sup>University of California, San Francisco (UCSF), San Francisco, CA, USA.

**LB-M106. Ignite: A Phase 2 Proof-of-Concept Study of VGL101 in Patients with Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia**

Jeffery Gelfand, MD, MAS<sup>1</sup>, Andreas Meier, MD<sup>2</sup>, Raj Rajagovindan, PhD<sup>2</sup>, David Stiles, PhD<sup>2</sup>, Benjamin Matys, BA<sup>2</sup>, Spyros Papapetropoulos, MD, PhD<sup>3</sup>, **Zbigniew Wszolek, MD<sup>4</sup>**. <sup>1</sup>UCSF, San Francisco, CA, USA, <sup>2</sup>Vigil Neurosciences, Inc., Watertown, MA, USA, <sup>3</sup>Vigil Neurosciences, Inc. (formerly), Watertown, MA, USA, <sup>4</sup>Mayo Clinic, Jacksonville, FL, USA.

**LB-M107. Mephitical Olfactory Hallucinations from Delusions of Demonic Possession**

**Aneetinder Somal, MD<sup>1</sup>**, Shrenik Shah, MD<sup>1</sup>, Alan R. Hirsch, MD<sup>2</sup>. <sup>1</sup>Windsor University School of Medicine, Cayon, Saint Kitts and Nevis, <sup>2</sup>Smell and Taste Treatment and Research Foundation, Des Plaines, IL, USA.

**\*LB-M108. Neuropathological Validation of Monoamine Oxidase-B (MAO-B) as PET Imaging Biomarker of Reactive Astroglia in Alzheimer's Disease**

**Methasit Jaisa-aad, MD<sup>1,2</sup>**, Clara Muñoz-Castro, PhD<sup>1,2</sup>, Molly A. Healey, BA<sup>1</sup>, Bradley T. Hyman, MD PhD<sup>1,2</sup>, Alberto Serrano-Pozo, MD, PhD<sup>1,2</sup>. <sup>1</sup>Department of Neurology,

Massachusetts General Hospital, Boston, MA, USA, <sup>2</sup>Harvard Medical School, Boston, MA, USA.

### **LB-M109. Predicting Differences in Open-Ended Decision Making between Healthy Controls and Individuals with Dementia**

Zhihao Zhang, Ph.D.<sup>1</sup>, Winston Chiong, MD, PhD<sup>2</sup>, Ming Hsu, Ph.D.<sup>3</sup>, **Andrew Kayser, MD, PhD<sup>2</sup>**. <sup>1</sup>University of Virginia, Darden School of Business, Charlottesville, VA, USA, <sup>2</sup>University of California San Francisco, San Francisco, CA, USA, <sup>3</sup>University of California Berkeley, Berkeley, CA, USA.

## **Epilepsy**

### **\*M206. Activity-Dependent Ectopic Action Potentials in Regular Spiking Neurons of the Mouse Neocortex**

**Styliani Sapantzi, Undergraduate Student**, Yizhen S. Zhang, BS, Savannah R. Doelfel, BS, Alice Lin, BS, Barry W. Connors, PhD, Brian B. Theyel, MD PhD. Brown University, Providence, RI, USA.

### **M207. Alpha 3 Ganglionic Acetylcholine Receptor Antibody- Associated Seizure Disorder**

**Shaweta Khosa, M.B.B.S.<sup>1</sup>**, Sanjay Anandram, M.D.<sup>2</sup>, Gurveer Singh Khosa, M.B.B.S.<sup>3</sup>, Rupinder Singh Buttar, M.D.<sup>4</sup>, Shri K. Mishra, M.D.<sup>5</sup>. <sup>1</sup>Olive View-UCLA Medical Center, Sylmar, CA, USA, <sup>2</sup>Rochester General Hospital, ROCHESTER, NY, USA, <sup>3</sup>Adesh Institute of Medical Sciences & Research, Bathinda, India, <sup>4</sup>Rochester General Hospital, Rochester, NY, USA, <sup>5</sup>Keck School of Medicine of USC, Los Angeles, CA, USA.

### **M208. An Unusually Late Case of Myoclonic Epilepsy with Ragged-Red Fibers (MERRF) Syndrome**

**Ariana Barreau, BS<sup>1</sup>**, McLean Nasrallah, MD, PhD<sup>2</sup>, Taneeta Ganguly, MD<sup>2</sup>, Fadi Mikhail, MD<sup>3</sup>. <sup>1</sup>Carle Illinois College of Medicine, University of Illinois Urbana-Champaign, Urbana, IL, USA, <sup>2</sup>Hospital of the University of Pennsylvania, Philadelphia, PA, USA, <sup>3</sup>Carle Foundation Hospital, Urbana, IL, USA.

### **M209. Association between Catamenial Epilepsy and Seizure Frequency during Pregnancy**

**Emma Osterhaus, BS<sup>1</sup>**, Jacqueline French, MD<sup>2</sup>, Rishabh Jain, B. Tech, MS<sup>1</sup>, Nikhil Khongbantabam, BS<sup>1</sup>, Page Pennell, MD<sup>1</sup>. <sup>1</sup>University of Pittsburgh, Pittsburgh, PA, USA, <sup>2</sup>New York University, New York, NY, USA.

### **\*M210. Association between Structural Brain MRI Abnormalities and Epilepsy in Older Adults**

**James J. Gugger, MD, PharmD<sup>1</sup>**, Alexa E. Walter, PhD<sup>1</sup>, Ramon Diaz-Arrastia, MD, PhD<sup>1</sup>, Juebin Huang, MD<sup>2</sup>, Robert

Reid, PhD<sup>3</sup>, Anna M. Kucharska-Newton, PhD, MPH<sup>4</sup>, Rebecca F. Gottesman, MD, PhD<sup>5</sup>, Andrea LC Schneider, MD, PhD<sup>1</sup>, Emily L. Johnson, MD<sup>6</sup>. <sup>1</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>University of Mississippi Medical Center, Jackson, MS, USA, <sup>3</sup>Mayo Clinic, Rochester, MN, USA, <sup>4</sup>University of Kentucky, Lexington, KY, USA, <sup>5</sup>National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA, <sup>6</sup>Johns Hopkins University, Baltimore, MD, USA.

### **M211. Disparities in Outcomes of 57310 People with Epilepsy Admitted for COVID-19 in the United States**

**Maya Gabel, MD<sup>1</sup>**, Prince Kwabla Pekyi-Boateng, MBBS<sup>2</sup>, Fiifi Duodu, FWACP<sup>2</sup>, Shaheen Sombans, MD<sup>3</sup>, Kamleshun Ramphul, MD<sup>4</sup>, Smith Kofi Frimpong, MD<sup>5</sup>, Ewuradjoa Ayirebi-Acquah, MBBS<sup>6</sup>, Babel Agbinko-Djobalar, MBChB<sup>2</sup>, Patrick Deladem Pekyi-Boateng, MBChB<sup>7</sup>, Nadia Isabelle Wuni, MBBS<sup>8</sup>, George Selali Blewusi, MD<sup>9</sup>, Balkiranjit Kaur Dhillon, MBBS<sup>10</sup>, Hemamalini Sakthivel, MD<sup>11</sup>. <sup>1</sup>University of Miami - Jackson Memorial Hospital, Miami, FL, USA, <sup>2</sup>Korle-bu Teaching Hospital, Accra, Ghana, <sup>3</sup>Bharati Vidyapeeth deemed Medical University, Hyderabad, India, <sup>4</sup>Independent Researcher, Triolet, Mauritius, <sup>5</sup>Philadelphia College of Medicine, Philadelphia, PA, USA, <sup>6</sup>Lekma Hospital, Accra, Ghana, <sup>7</sup>Kwame Nkrumah University of Science and Technology, Kumasi, Ghana, <sup>8</sup>Greater Accra Regional Hospital, Accra, Ghana, <sup>9</sup>Achimota Hospital, Accra, Ghana, <sup>10</sup>Independent Researcher, Brampton, ON, Canada, <sup>11</sup>Interfaith Medical Centre, Brooklyn, NY, USA.

### **M212. Effect of Vagus Nerve Stimulator (VNS) Signal Frequency on Vocal Cord Function: Case Report**

**Ruchi Dhyani, MD**, Sandra Stinnett, MD, Jacob Kaufman, PA-C, Alexandra Urban, MD, Thandar Aung, MD. University of Pittsburgh Medical Center, Pittsburgh, PA, USA.

### **M213. Exploring Interdisciplinary Cross-Talk and Gap of Knowledge for Catamenial Epilepsy in Puerto Rico**

**Gladys Flores, MD (2nd year), BS**, Gabriela Betances, MD (2nd year), BS. University of Puerto Rico School of Medicine, San Juan, PR, USA.

### **M214. Gelastic Seizures as a Presentation of NMDA Encephalitis**

**Pooneh Memar Ardestani, MD, PhD**, Jessica Genkil, MD, Sahil Naik, MD, Naraharsetty Anita Rau, MD, Narges Rahimi, MD, Maria Diaz Rojas, MD, Aparna Prabhu, MD, Saman Zafar, MD. Einstein Medical Center, Philadelphia, PA, USA.

### **\*M215. Health-Related Quality of Life in Transgender Individuals with Epilepsy**

Karina Tassiopoulos, MS<sup>1</sup>, Ernesto Gonzalez-Giraldo, MD<sup>2</sup>, Esther Bui, MD<sup>3</sup>, **Emily Johnson, MD<sup>4</sup>**. <sup>1</sup>Western University, London, ON, Canada, <sup>2</sup>University of California San Francisco,

San Francisco, CA, USA, <sup>3</sup>University of Toronto, Toronto, ON, Canada, <sup>4</sup>Johns Hopkins School of Medicine, Baltimore, MD, USA.

**\*M216. How Well Can Machine Learning Predict Late Seizures after Intracerebral Hemorrhages? Evidence from Real-World Data**

**Alain Lekoubou, MD, MS**, Justin Petucci, PhD, Avinsh Katoch, IT Project manager, Vasant Honavar, PhD. Pennsylvania State University, Hershey, PA, USA.

**\*M217. Human Cerebral Organoids with PIDD1 Mutations Implicate AKT-mTOR Pathway Hypoactivity in Lissencephaly**

**Ce Zhang, PhD**, Dan Liang, PhD, Tukiet Lam, PhD, Anand Narayanan, PhD, Murat Gunel, MD, Kaya Bilguvar, MD PhD, Angeliki Louvi, PhD. Yale University School of Medicine, New Haven, CT, USA.

**\*M218. Increased Degradation of FMRP Contributes to Neuronal Hyperexcitability in Tuberous Sclerosis Complex**

**Kellen Winden, MD PhD**, Truc Pham, BS, Nicole Teaney, BS, Juan Ruiz, BS, Ryan Chen, BS, Cidi Chen, PhD, Mustafa Sabin, MD PhD. Boston Children's Hospital, Boston, MA, USA.

**\*M219. Knowledge Translation of the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) Study: A Survey of Healthcare Providers (HCPs) and Reproductive-Aged People with Epilepsy (RPWE)**

**Laura Kirkpatrick, MD<sup>1</sup>**, Irena Bellinski, RN, MPH<sup>2</sup>, Elizabeth E. Gerard, MD<sup>2</sup>, Kimford J. Meador, MD<sup>3</sup>, Thomas F. McElrath, MD, PhD<sup>4</sup>, Alison M. Pack, MD<sup>5</sup>, Page B. Pennell, MD<sup>1</sup>. <sup>1</sup>University of Pittsburgh, Pittsburgh, PA, USA, <sup>2</sup>Northwestern University, Chicago, IL, USA, <sup>3</sup>Stanford University, Palo Alto, CA, USA, <sup>4</sup>Harvard University / Brigham and Women's Hospital, Boston, MA, USA, <sup>5</sup>Columbia University, New York, NY, USA.

**M221. Over the Counter (OTC) Supplements May Exacerbate Pre-Existing Neurological Abnormalities and Incite Neurological Episodes**

**Ayesha Asghar, MS<sup>3</sup>, Taikchan Lildar, MD**, Anil Kapoor, MD. Flushing Hospital Medical Center, Flushing, NY, USA.

**\*M222. Peripheral T Cell Clonal Expansion as a Proxy for Intractable Epilepsy and Brain Atrophy**

**Yong-Won Shin, MD<sup>1</sup>**, Han Sang Lee, MD<sup>2</sup>, Seon-Jae Ahn, MD<sup>2</sup>, Yoonhyuk Jang, MD<sup>2</sup>, Seolah Lee, MD<sup>2</sup>, Yongmoo Kim, MD<sup>2</sup>, Soon-Tae Lee, MD<sup>2</sup>, Jangsup Moon, MD<sup>2</sup>, Kon Chu,

MD<sup>2</sup>, Sang Kun Lee, MD<sup>2</sup>. <sup>1</sup>Department of Neurosurgery, Seoul National University Hospital, Seoul, Korea, Republic of, <sup>2</sup>Department of Neurology, Seoul National University Hospital, Seoul, Korea, Republic of.

**M223. Predicting Serum Concentration of Lacosamide: Effects of CYP2C19 Genetic Polymorphisms and Possible Correlation with Saliva Concentration**

**Seon-Jae Ahn, MD<sup>1</sup>**, Yoonhyuk Jang, MD<sup>1</sup>, Yongmoo Kim, MD<sup>1</sup>, Seolah Lee, MD<sup>1</sup>, Han-Sang Lee, MD<sup>1</sup>, Yong-Won Shin, MD<sup>2</sup>, Kyung-Il Park, MD<sup>1</sup>, Keun-Hwa Jung, MD<sup>1</sup>, Soon-Tae Lee, MD<sup>1</sup>, Jangsup Moon, MD<sup>3</sup>, Sang Kun Lee, MD<sup>1</sup>, Kon Chu, MD<sup>1</sup>. <sup>1</sup>Department of Neurology, Seoul National University Hospital, Seoul, Korea, Republic of, <sup>2</sup>Department of Neurosurgery, Seoul National University Hospital, Seoul, Korea, Republic of, <sup>3</sup>Department of Genomic Medicine, Seoul National University Hospital, Seoul, Korea, Republic of.

**\*M224. Somatic Variants Activating Ras-MAPK Signaling Cause a Spectrum of Focal Lesions Associated with Mesial Temporal Lobe Epilepsy**

**Sattar Khoshkboo, MD<sup>1</sup>**, Yilan Wang, BS<sup>2</sup>, Yasmine Chahine, BS<sup>2</sup>, August Yue Huang, PhD<sup>2</sup>, Stephanie M. Robert, MD, PhD<sup>3</sup>, Emre Kiziltug, BS<sup>3</sup>, Eyiyeemisi C. Damisah, MD<sup>3</sup>, Carol Nelson-Williams, MS<sup>3</sup>, Guangya Zhu, PhD<sup>4</sup>, Wenna Kong, BS<sup>4</sup>, Edward Stronge, BS<sup>5</sup>, H. Westley Phillips, MD<sup>1</sup>, Brian H. Chhouk, BS<sup>2</sup>, Sara Bizzotto, PhD<sup>6</sup>, Thiuni N. Adikari, BMS<sup>7</sup>, Zimeng Ye, MS<sup>7</sup>, Tom Witkowski, BSc<sup>7</sup>, Nadine Lee, HSD<sup>2</sup>, Julie Lokan, MBBS<sup>8</sup>, Ingrid Scheffer, MBBS, PhD<sup>9</sup>, Sam Berkovic, MBBS<sup>8</sup>, Michael Hildebrand, PhD<sup>7</sup>, Edward Yang, MD, PhD<sup>2</sup>, Ingmar Blümcke, MD<sup>10</sup>, Sanda Alexandrescu, MD<sup>2</sup>, Anita Huttner, MD<sup>3</sup>, Erin L. Heinzen, PharmD, PhD<sup>11</sup>, Jidong Zhu, PhD<sup>4</sup>, Annapurna Poduri, MD, MPH<sup>2</sup>, Nihal DeLanerolle, DPil, DSc<sup>3</sup>, Dennis Spencer, MD<sup>3</sup>, Eunjung Alice Lee, PhD<sup>2</sup>, Kristopher T. Kahle, MD, PhD<sup>12</sup>, Christopher A. Walsh, MD, PhD<sup>2</sup>. <sup>1</sup>Brigham and Women's Hospital, Boston, MA, USA, <sup>2</sup>Boston Children's Hospital, Boston, MA, USA, <sup>3</sup>Yale School of Medicine, New Haven, CT, USA, <sup>4</sup>Shanghai Institute of Organic Chemistry, Shanghai, China, <sup>5</sup>Boston Children's Hospital, Boston, MA, USA, <sup>6</sup>Sorbonne University, Paris Brain Institute, Paris, France, <sup>7</sup>University of Melbourne, Heidelberg, Australia, <sup>8</sup>Austin Health, Heidelberg, Australia, <sup>9</sup>Royal Children's Hospital, Parkville, Australia, <sup>10</sup>University Hospitals Erlangen, Erlangen, Germany, <sup>11</sup>University of North Carolina, Chapel Hill, NC, USA, <sup>12</sup>Massachusetts General Hospital, Boston, MA, USA.

**\*M225. Synaptic Changes in a Distinct Population of Hippocampal Neurons Activated by Early Life Seizures**

**Bo Xing, MD PhD**, **Eunjoo Lancaster, MD PhD**, Aaron Barbour, PhD, Xiaofan Li, MS, Marcus Handy, BA, Delia Talos, MD, Frances E. Jensen, MD FACP. University of Pennsylvania, Philadelphia, PA, USA.



# **M226. The Effect of Anti-Seizure Medications on Lipid Values in Adults with Epilepsy**

Ashley Muller, B.S., Luisa A. Diaz-Arias, M.D., Mackenzie C. Cervenka, M.D., **Tanya J. W. McDonald, MD, PhD**. Johns Hopkins University, Baltimore, MD, USA.

# **\*M227. The Effect of Deep Brain Stimulation (DBS) on Cognitive, Psychiatric and Quality of Life Outcomes in Drug-Resistant Epilepsy**

**Dale Tager, MD MBA<sup>1</sup>**, Jimmy C. Yang, MD<sup>1</sup>, Katrina Munoz, MD<sup>1</sup>, Abdulrahman Alhwaki, MD<sup>1</sup>, David W. Loring, PhD<sup>1</sup>, Ekaterina Staikova, PhD<sup>1</sup>, Cady Block, PhD<sup>1</sup>, Leonardo Bonilha, MD PhD<sup>1</sup>, Jon T. Willie, MD PhD<sup>2</sup>, Robert E. Gross, MD PhD<sup>1</sup>, Daniel L. Drane, PhD MA MS<sup>1</sup>, Ioannis Karakis, MD PhD MSc<sup>1</sup>. <sup>1</sup>Emory University School of Medicine, Atlanta, GA, USA, <sup>2</sup>Washington University School of Medicine, St. Louis, MO, USA.

# **\*M228. The Ketogenic Diet in DEPDC5-Related Epilepsies: Clinical and Preclinical Observations**

**Nishtha Gupta, BS<sup>1</sup>**, Yini Liang, BS<sup>2</sup>, Karenn Groff, BS<sup>2</sup>, Maria Osipovich, BS<sup>2</sup>, Mustafa Sahin, MD, PhD<sup>2</sup>, Christopher Yuskaitis, MD, PhD<sup>2</sup>. <sup>1</sup>Drexel University College of Medicine, Philadelphia, PA, USA, <sup>2</sup>Boston Children's Hospital, Boston, MA, USA.

# **\*M229. Therapeutic Range of Topiramate: A Lower Dose of Topiramate is Enough for an Anti-Seizure Effect**

**Seolah Lee, MD<sup>1</sup>**, Yoonhyuk Jang, MD<sup>1</sup>, Han-Sang Lee, MD<sup>1</sup>, Seon-Jae Ahn, MD<sup>1</sup>, Yongmoo Kim, MD<sup>1</sup>, Yong-Won Shin, MD<sup>2</sup>, Jangsup Moon, MD<sup>3</sup>, Kyung-Il Park, MD<sup>1</sup>, Soon-Tae Lee, MD<sup>1</sup>, Ki-Young Jung, MD<sup>1</sup>, Kon Chu, MD<sup>1</sup>, Sang Kun Lee, MD<sup>1</sup>. <sup>1</sup>Department of Neurology, Seoul National University Hospital, Seoul, Korea, Republic of, <sup>2</sup>Department of Neurosurgery, Seoul National University Hospital, Seoul, Korea, Republic of, <sup>3</sup>Department of Genomic Medicine, Seoul National University Hospital, Seoul, Korea, Republic of.

# **M230. Vagal Nerve Stimulator Induced Artifact on Electroencephalogram**

**Saniya Pervin, MBBS**, Julie Youssefi, MD, Sally Mathias, MD. University of Kentucky, Lexington, KY, USA.

# **K-M105. An Unsupervised Learning Approach for Discovering Pathological High-Frequency Oscillations**

**Hiroki Nariai, MD, PhD, MS**, Yipeng Zhang, MS, Lawrence Liu, MS, Atsuro Daida, MD, PhD, Shingo Oana, MD, PhD, Tonmoy Monsoor, MS, Jacqueline P. Ngo, MD, Shaun A. Hussain, shussain@mednet.ucla.edu, Raman Sankar, MD, PhD, Aria Fallah, MD, MS, Richard J. Staba, PhD, Jerome Engel, Jr., MD, PhD, William Speier, IV, PhD, Vwani Roychowdhury, PhD. UCLA, Los Angeles, CA, USA.

# **K-M106. Characterizing Sleep Architecture and Its Effects on Cognition in New-Onset Temporal Lobe Epilepsy**

**Temitayo Oyegbile-Chidi, MD, PhD**. University of California Davis, Sacramento, CA, USA.

# **K-M107. Frequency-Responsive Ectopic Action Potentials in Neocortical Regular Spiking Neurons**

**Brian Theyel, MD, PhD**, Yizhen Zhang, BSc, Styliani Sapantzi, HS, Barry Connors, PhD. Brown University, Providence, RI, USA.

# **K-M108. Homeostatic Sleep Need Increases Seizure Risk**

**Vishnu A. Cuddapah, MD, PhD<sup>1</sup>**, Amita Sehgal, PhD<sup>2</sup>. <sup>1</sup>Children's Hospital of Philadelphia, Philadelphia, PA, USA, <sup>2</sup>University of Pennsylvania, Philadelphia, PA, USA.

# **K-M109. Predicting Post-Ischemic Stroke Epilepsy Using Quantitative Markers and Competing Risk Covariates**

**Jennifer A. Kim, MD-PhD**, Yilun Chen, MA. Yale School of Medicine, New Haven, CT, USA.

# **K-M110. Repetitive Transcranial Magnetic Stimulation Modulates Brain Connectivity in Children with Self-Limited Epilepsy with Centrotemporal Spikes**

**Fiona M. Baumer, MD, MS**, Xiwei She, PhD, Kerry Nix, BS, Kerry Nix, BS, Wendy Qi, BS. Stanford University School of Medicine, Palo Alto, CA, USA.

# **K-M111. Zebrafish Models of Genetic and Chemical Seizures: Opportunities and Challenges**

**Christopher M. McGraw, MD, PhD<sup>1</sup>**, Cristina Baker, BA<sup>2</sup>, Barbara Robens, PhD<sup>2</sup>, Guoqi Zhang, MD<sup>2</sup>, Christopher M. Lacoursiere, MA<sup>2</sup>, Annapurna Poduri, MD, MPH<sup>3</sup>. <sup>1</sup>Mass General Hospital, Boston Childrens Hospital, Harvard Medical School, Boston, MA, USA, <sup>2</sup>Boston Childrens Hospital, Boston, MA, USA, <sup>3</sup>Boston Childrens Hospital, Harvard Medical School, Boston, MA, USA.

# **LB-M112. Cenobamate in the Treatment of Medically Refractory Seizures: A Single-Center Experience**

**Christopher Saouda, MD<sup>1</sup>**, Yamane Makke, MD<sup>1</sup>, Mohamad Z. Koubeissi, MD<sup>2</sup>. <sup>1</sup>George Washington University, Washington, DC, USA, <sup>2</sup>George Washington University, Chevy Chase, MD, USA.

# **\*LB-M113. Inducible Genetically-Encoded Voltage Indicator for Non-Invasive Functional Analysis of Human Stem Cell-Derived Neurons**

**Scott K. Adney, M.D., Ph.D.**, Christopher H. Thompson, Ph.D., Jean-Marc L. DeKeyser, M.S., Nora F. Ghabra, M.S., Alfred L. George, Jr., M.D. Northwestern University Feinberg School of Medicine, Chicago, IL, USA.

# Global Neurology

## \*M231. A Phase 3 Clinical Trial of Leriglitazone with Adaptive Placebo-Controlled Treatment Duration in Adults with Cerebral

### Adrenoleukodystrophy

**Ali Fatemi, MD<sup>1</sup>**, Wolfgang Köhler, MD<sup>2</sup>, Florian Eichler, MD<sup>3</sup>, Fanny Mochel, MD<sup>4</sup>, Reza Sadjadi, MD<sup>3</sup>, Troy Lund, MD<sup>5</sup>, Jacinda Sampson, MD<sup>6</sup>, Hans Shuhaiber, MD<sup>7</sup>, Hernan Amartino, MD<sup>8</sup>, Paulo Sgobbi, MD<sup>9</sup>, Martin Kappler, PhD<sup>10</sup>, Richard Kay, PhD<sup>11</sup>, Guillem Pina, MSc<sup>12</sup>, Arun Mistry, MD<sup>12</sup>, María Pascual, PhD<sup>12</sup>, Silvia Pascual, MSc<sup>12</sup>, Marc Martinell, PhD<sup>12</sup>. <sup>1</sup>Kennedy Krieger Institute, Baltimore, MD, USA, <sup>2</sup>University of Leipzig Medical Center, Leipzig, Germany, <sup>3</sup>Massachusetts General Hospital, Boston, MA, USA, <sup>4</sup>Sorbonne Pitié-Salpêtrière Hospital, Paris, France, <sup>5</sup>University of Minnesota, Minneapolis, MN, USA, <sup>6</sup>Stanford University, Stanford, CA, USA, <sup>7</sup>University of Florida, Gainesville, FL, USA, <sup>8</sup>Austral University Hospital, Buenos Aires, Argentina, <sup>9</sup>The Federal University of São Paulo, São Paulo, Brazil, <sup>10</sup>Cytel Inc., Waltham, MA, USA, <sup>11</sup>RK Statistics, Bakewell, United Kingdom, <sup>12</sup>Minoryx Therapeutics SL, Barcelona, Spain.

## \*M232. Acute Neurological Inflammatory Diseases in Colombia during the COVID-19 Pandemic: A Multi-Center Observational Study

**Susana C. Dominguez-Penuela, MD<sup>1</sup>**, Martha Moyano, MSc<sup>2</sup>, David O. Acero-Garcés, MD<sup>2</sup>, Reydmir Lopez, MD<sup>3</sup>, Jose M. Enciso, MD<sup>2</sup>, Jenny P. Garzon, MD<sup>4</sup>, Jose E. Vargas-Manotas, MD<sup>5</sup>, Jorge A. Jimenez-Arango, MD<sup>3</sup>, Guillermo Gonzalez-Manrique, MD<sup>6</sup>, Jairo F. Lizarazo-Nino, MD<sup>7</sup>, Daniela Zuluaga-Lotero, MD<sup>2</sup>, Maria F. Ramos, MD<sup>7</sup>, Julie Benavides-Melo, MSc<sup>8</sup>, Katherine V. Claros-Ortiz, MD<sup>9</sup>, Christian A. Rojas-Ceron, MD<sup>10</sup>, Juan P. Rojas, MD<sup>11</sup>, Gustavo Ramos, MD<sup>12</sup>, Mario Llanos, MD<sup>12</sup>, Catalina Vallejo, MD<sup>13</sup>, Jonathan Urrego, MD<sup>14</sup>, Beatriz Parra-Patino, PhD<sup>2</sup>, Lyda Osorio-Amaya, MD PhD<sup>2</sup>, Carlos A. Pardo-Villamizar, MD<sup>1</sup>. <sup>1</sup>Johns Hopkins University, Baltimore, MD, USA, <sup>2</sup>Universidad del Valle, Cali, Colombia, <sup>3</sup>Clinica Leon XIII, Medellin, Colombia, <sup>4</sup>Hospital Internacional de Colombia, Bucaramanga, Colombia, <sup>5</sup>Universidad Simon Bolivar, Barranquilla, Colombia, <sup>6</sup>Universidad Surcolombia, Neiva, Colombia, <sup>7</sup>Hospital Universitario Erasmo Meoz, Cucuta, Colombia, <sup>8</sup>Universidad Cooperativa de Colombia, Pasto, Colombia, <sup>9</sup>Hospital Universitario de Neiva, Neiva, Colombia, <sup>10</sup>Centro Medico Imbanaco, Cali, Colombia, <sup>11</sup>Hospital Infantil Club Noel, Cali, Colombia, <sup>12</sup>Clinica Rey David, Cali, Colombia, <sup>13</sup>Hospital Universitario Departamental de Nariño, Pasto, Colombia, <sup>14</sup>Hospital Universitario del Valle, Cali, Colombia.

## \*M233. Anatomically Interpretable Brain Age Prediction in Alzheimer's Disease Using Graph Neural Networks

**Saurabh Sibag, PhD<sup>1</sup>**, Gonzalo Mateos, PhD<sup>2</sup>, Alejandro Ribeiro, PhD<sup>1</sup>, Corey T. McMillan, PhD<sup>1</sup>. <sup>1</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>University of Rochester, Rochester, NY, USA.

## M234. Assessing the Effectiveness of Instagram in Teaching Functional Neuroanatomy to Medical Students

**Ibrahim Laswi, MS-IV**, Malik Mushannen, MD, Ameer Raoof, MBChB, PhD. Weill Cornell Medicine-Qatar, Doha, Qatar.

## \*M235. Current Practice for Continuous EEG Monitoring in the Critically Ill Patient: A Latin American Survey

**Clio Rubinos, MD, MS<sup>1</sup>**, Jorge Carrizosa, MD<sup>2</sup>, Daniel Godoy, MD<sup>3</sup>. <sup>1</sup>University of North Carolina, Chapel Hill, NC, USA, <sup>2</sup>University Hospital Santa Fe Foundation, Bogota, Colombia, <sup>3</sup>Sanatorio Pasteur, Catamarca, Argentina.

## M238. Metabolic Syndrome-Associated Microbiota Disrupts Fatty Acid Receptors Leading to Peripheral Neuropathy

**Mohamed Noureldein, PhD**, Samuel Teener, BS, Diana Rigan, BS, Andrew Carter, BS, Eva Feldman, MD, PhD. University of Michigan, Ann Arbor, MI, USA.

## M239. Neural Wave: The Brain Dynamic Neural Equation, Patterns and Alert by Artificial Intelligence to Predict Seizures on Epileptic Patients

Julio Andres Florez Realpe, Medical Doctor, Physicist, MS Physics in Progress. Alip Corporation, Pasto, Colombia.

## M240. Neurologic Sequelae Following Ebola Virus Disease in a Liberian Pediatric Population

**Hanalise V. Huff, MD, MPH<sup>1</sup>**, B. Jeanne Billioux, MD<sup>1</sup>, Cavan Reilly, PhD<sup>2</sup>, Collin Van Ryn, MS<sup>2</sup>, Helen Tarfe-Burnette, PA<sup>3</sup>, David Bearden, MD<sup>4</sup>. <sup>1</sup>National Institute of Health, Bethesda, MD, USA, <sup>2</sup>University of Minnesota, Minneapolis, MN, USA, <sup>3</sup>John F. Kennedy Medical Center, Monrovia, Liberia, <sup>4</sup>University of Rochester Medical Center, Rochester, NY, USA.

## \*M241. Patient Knowledge of Epilepsy and Seizure Safety in Lusaka, Zambia

**Alexa King, MD<sup>1</sup>**, Melody Asukile, BScHB, MB.ChB, MMED, FC Neurol<sup>2</sup>, Elizabeth E. Gerard, MD<sup>1</sup>, Deanna Saylor, MD, MHS<sup>3</sup>. <sup>1</sup>Northwestern, Chicago, IL, USA, <sup>2</sup>The University Teaching Hospital, Lusaka, Zambia, <sup>3</sup>Johns Hopkins, Baltimore, MD, USA.

**\*M242. Prediabetes Disrupts Lactate Trafficking in Peripheral Nerves: A Novel Mechanistic Target?**

Stephanie Eid, PhD, John Hayes, BS, Diana Rigan, BS, Crystal Pacut, BS, Pongrat Jaisil, MS, Andrew Carter, BS, **Eva Feldman, MD, PhD**. University of Michigan, Ann Arbor, MI, USA.

**\*M243. Relationships between Cortical Excitability, Segregation of Functional Networks, and Concentrations of Plasma pTau181 in Healthy Middle-Aged Individuals**

**Ruben Perellón-Alfonso, MSc<sup>1</sup>**, Kilian Abellana-Pérez, PhD<sup>2</sup>, María Cabello-Toscano, MSc<sup>1</sup>, Gabriele Cattaneo, PhD<sup>2</sup>, María Redondo-Camós, PhD<sup>2</sup>, Selma Delgado-Gallen, MSc<sup>2</sup>, Goreti España-Irla, PhD<sup>3</sup>, Indre Pileckyte, MSc<sup>4</sup>, Javier Solana Sánchez, PhD<sup>2</sup>, Henrik Zetterberg, MD, PhD<sup>5</sup>, Josep M. Tormos, MD, PhD<sup>6</sup>, Alvaro Pascual-Leone, MD, PhD<sup>7</sup>, David Bartrés-Faz, PhD<sup>1</sup>. <sup>1</sup>Faculty of Medicine and Health Sciences, and Institute of Neurosciences, University of Barcelona, Barcelona, Spain, <sup>2</sup>Institut Guttmann, Institut Universitari de Neurorehabilitació adscrit a la UAB, Badalona, Barcelona, Spain, <sup>3</sup>Department of Psychology Center for Cognitive and Brain Health Northeastern University, Boston, MA, USA, <sup>4</sup>Center for Brain and Cognition, Pompeu Fabra University, Barcelona, Spain, <sup>5</sup>Department of Psychiatry and Neurochemistry, Institute of Neuroscience & Physiology, the Sahlgrenska Academy at the University of Gothenburg, Mölndal, Sweden, <sup>6</sup>Centro de Investigación Translacional San Alberto Magno - Facultad Ciencias de la Salud - Universidad Católica de Valencia, Valencia, Spain, <sup>7</sup>Hinda and Arthur Marcus Institute for Aging Research and Deanna and Sidney Wolk Center for Memory Health, Hebrew SeniorLife, Boston, MA, USA.

**M244. The Utility of the Anatomage Virtual Dissection Table and Osirix in Creating Clinical Anatomy and Radiology Learning Modules on Brain Lesions**

**Ibrahim Laswi, MS-IV**, Zuhair Sadiq, MD, Shehroz Rana, MS-IV, Ameer Raoof, MBChB, PhD. Weill Cornell Medicine-Qatar, Doha, Qatar.

**M245. Thoracic Disc Herniation and Syrinx Formation: The Anatomic Connection**

**Katherine L. Russell, MSPH**. University of North Texas Health Science Center, TCOM, Fort Worth, TX, USA.

**M246. Two Case Reports of Movement Disorder in Adolescents from Ghana with Psychiatric Manifestation: Juvenile Huntington's (Westphal Variant) and Sydenham Chorea**

Fifi Duodu, FWACP<sup>1</sup>, **Prince Kwabla Peki-Boateng, MBBS<sup>1</sup>**, Maya Gabel, MD<sup>2</sup>, Prince Twumasi Ankrh, MD<sup>3</sup>, Shaheen Sombans, MD<sup>4</sup>, Kamleshun Ramphul, MD<sup>5</sup>, Babbal Agbinko-Djobalar, MBChB<sup>1</sup>, Nana Boakye Agyeman Badu, MBChB<sup>1</sup>, David Brodie-Mends Brodie-Mends, FWACP<sup>1</sup>, Kodwo Nkrumah, FWACP<sup>1</sup>, Albert Akpalu,

FWACP<sup>1</sup>, Patrick Adjei, FWACP, PhD<sup>1</sup>. <sup>1</sup>Korle-bu Teaching Hospital, Accra, Ghana, <sup>2</sup>University of Miami - Jackson Memorial Hospital, Miami, FL, USA, <sup>3</sup>Ghana Health Service, Accra, Ghana, <sup>4</sup>Bharati Vidyapeeth deemed Medical University, Hyderabad, India, <sup>5</sup>Independent Researcher, Triolet, Mauritius.

**\*M247. Understanding the Spectrum of SCA1, SCA2, SCA3, and SCA6: Self-Reported Functional Status and Quality of Life**

Lauren C. Seeberger, MD<sup>1</sup>, Melissa Wolfe Beiner, MD<sup>2</sup>, Michele Potashman, PhD<sup>2</sup>, Anne Neumann, RN, BSN<sup>2</sup>, Tanya Z. Fischer, MD, PhD<sup>2</sup>, Skyler Jackson, BA<sup>3</sup>, Austin R. Letcher, MS<sup>3</sup>, Patti A. Engel, BSN<sup>3</sup>, Lauren Moore, PhD<sup>4</sup>, Julie Greenfield, PhD<sup>5</sup>, Giovanni Ristori, MD<sup>6</sup>, **Laura Heller, PharmD<sup>2</sup>**. <sup>1</sup>Charleston Area Medical Center Institute for Academic Medicine and West Virginia University Department of Neurology, Charleston, WV, USA, <sup>2</sup>Biohaven Pharmaceuticals, Inc., New Haven, CT, USA, <sup>3</sup>Engage Health, Inc., Eagan, MN, USA, <sup>4</sup>National Ataxia Foundation, Minneapolis, MN, USA, <sup>5</sup>Ataxia UK, London, United Kingdom, <sup>6</sup>Department of Neurosciences, Mental Health and Sensory Organs, Sant'Andrea Hospital, Sapienza University of Rome and Neuroimmunology Unit, IRCCS Fondazione Santa Lucia, Rome, Italy.

**K-M112. Distal Symmetric Polyneuropathy Prevalence and Predictors in Urban and Rural Zambia: A Population-Based, Cross-Sectional Household Survey**

**Michelle Kvalsund, DO<sup>1,2</sup>**, Musambo Kapapa, MS<sup>3</sup>, Stanley Zimba, MBChB<sup>2</sup>, Gamaliel Misago, MBChB<sup>4</sup>, Lorraine Chishimba, MBChB<sup>2</sup>, Mashina Chomba, MBChB<sup>2</sup>, Melody Asukile, MBChB<sup>2,5</sup>, Joseph Gardiner, PhD<sup>6</sup>, David N. Herrmann, MBBCh<sup>1</sup>, Gretchen Birbeck, MD<sup>1,7</sup>. <sup>1</sup>University of Rochester Medical Center, Rochester, NY, USA, <sup>2</sup>University of Zambia School of Medicine, Lusaka, Zambia, <sup>3</sup>University of Zambia School of Health Sciences, Lusaka, Zambia, <sup>4</sup>Chikankata Mission Hospital, Chikankata, Zambia, <sup>5</sup>University of Cape Town Neuroscience Institute, Cape Town, South Africa, <sup>6</sup>Michigan State University, East Lansing, MI, USA, <sup>7</sup>University Teaching Hospital Neurology Research Office, Lusaka, Zambia.

**K-M113. Longitudinal Cognitive Outcomes in Children with HIV in Zambia**

**David Bearden, MD MSCE**, Gauri Patil, MD, Gretchen Birbeck, MD MPH. University of Rochester, Rochester, NY, USA.

**\*LB-M114. Association between Migraine Diagnosis and Low Psychological Resilience among Teenage Mothers in Peru: The Role of Adverse Childhood Experiences and Postpartum Mental Health**

**Kevin Pacheco-Barrios, MD, MSc, MPH<sup>1,2</sup>**, Diana Juvinao-Quintero, PhD<sup>1</sup>, Bizu Gelaye, PhD<sup>1,3</sup>. <sup>1</sup>Department of

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## Neurocritical Care and Traumatic Brain Injury

### M249. A Novel Treatment to Reduce Secondary Damage in Traumatic Brain Injury

**Siyuan C. Liu, MD, PhD**, Ryan Bertossi, BS, Tammy McGuire, BS, Chian-Yu Peng, PhD, John A. Kessler, MD. Northwestern University, Chicago, IL, USA.

**\*M250. A Rare Case Report of CHANTER Syndrome**  
**Abdurrahman Roussi, BS**, Kajol Navinchandra Patel, DO, Caleb James Lee, MD, Mustapha Ezzeddine, MD, Tamra Ranasinghe, MD. Wake Forest School of Medicine, Winston Salem, NC, USA.

### M251. An Explanation of the Vascular and Functional Anatomy of Thoracic Spinal Cord Ischemia and Its Clinical Presentation in the Setting of Radicular Artery Occlusion

**Rachel Thomas, MD, PhD<sup>1</sup>**, Daniel DePietro, MD<sup>2</sup>, Shreya Mehta, BA, BSE<sup>1</sup>, Michael L. McGarvey, MD<sup>1</sup>. <sup>1</sup>Department of Neurology, University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>Department of Interventional Radiology, University of Pennsylvania, Philadelphia, PA, USA.

### \*M252. Associations of Head Injury with Risk of Injurious Falls: Results from the Atherosclerosis Risk in Communities (ARIC) Study

**Katherine J. Hunzinger, PhD<sup>1</sup>**, Connor A. Law, BS<sup>1</sup>, Holly Elsder, MD, PhD<sup>1</sup>, Alexa E. Walter, PhD<sup>1</sup>, B. Gwen Windham, MD, MHS<sup>2</sup>, Priya Palta, PhD<sup>3</sup>, Stephen P. Juraschek, MD, PhD<sup>4</sup>, Caitlin Hicks, MD, MHS<sup>5</sup>, Rebecca F. Gottesman, MD, PhD<sup>6</sup>, Andrea LC Schneider, MD, PhD<sup>1</sup>. <sup>1</sup>University of Pennsylvania-Perelman School of Medicine, Philadelphia, PA, USA, <sup>2</sup>University of Mississippi Medical Center, Jackson, MS, USA, <sup>3</sup>University of North Carolina Chapel Hill, Chapel Hill, NC, USA, <sup>4</sup>Beth Israel Deaconess Medical Center, Boston, MA, USA, <sup>5</sup>Johns Hopkins University School of Medicine, Baltimore, MD, USA, <sup>6</sup>National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA.

### \*M253. Beyond the Injury: The Impact of Traumatic Brain Injury on Quality of Life and Life Satisfaction

**Sara K. Heide, BS**, Rasheed Hosein-Woodley, BA, Jason A. Morency, BS, James Williams, BA, Mill Etienne, MD,

MPH. New York Medical College, Valhalla, NY, USA.

### M256. Delayed Diagnosis of HIV and Cerebral Toxoplasmosis Resulting in Massive Cerebral Edema and Brain Death

**Paul B. Lee, MD MS<sup>1</sup>**, Vishakh C. Keri, MBBS DM<sup>2</sup>, Lea Monday, MD PharmD<sup>2</sup>, Arun Sherma, MD<sup>1</sup>. <sup>1</sup>Department of Neurology, Division of Neurotrauma/Neurocritical Care – Detroit Medical Center/Wayne State University, Detroit, MI, USA, <sup>2</sup>Department of Infectious Disease – Wayne State University, Detroit, MI, USA.

### M257. Discontinuation and Non-Publication of Traumatic Brain Injuries Clinical Studies: A Cross-Sectional Analysis

**Ahmed Aljabali, MD<sup>1</sup>**, Ibraheem M. Alkhawaldeh, MD<sup>2</sup>, Mariam Hady, MD<sup>3</sup>, Dina Essam, MD<sup>4</sup>, Yomna Goudy, MD<sup>5</sup>, Ahmed Allam, MD<sup>6</sup>, Khaled Albakri, MD<sup>7</sup>, Nada Ibrahim, MD<sup>8</sup>, Marwa Kabeel, MD<sup>9</sup>, Rehab Diab, MD<sup>10</sup>, Marwa Abdelazim, MD<sup>4</sup>, Esraa Zedan, MD<sup>11</sup>, Noha Yasen, Applied Medical Sciences BSc<sup>12</sup>, Maged Elsayed, MD<sup>4</sup>, Hazem Ghaith, MD<sup>13</sup>, Ahmed Negida, MD, PhD<sup>14</sup>. <sup>1</sup>Jordan University of Science & Technology, Irbid, Jordan, <sup>2</sup>Mutah University, Karak, Jordan, <sup>3</sup>October 6 University, Giza, Egypt, <sup>4</sup>Zagazig University, Zagazig, Egypt, <sup>5</sup>South Valley University, Qena, Egypt, <sup>6</sup>Tanta University, Tanta, Egypt, <sup>7</sup>The Hashemite University, Zarqa, Jordan, <sup>8</sup>Ain Shams University, Cairo, Egypt, <sup>9</sup>Kafr Elsheikh University, Kafr El Sheikh, Egypt, <sup>10</sup>Al-Azhar University, Cairo, Jordan, <sup>11</sup>Alazhar University, Cairo, Egypt, <sup>12</sup>Misr University for Science and Technology, Giza, Egypt, <sup>13</sup>Al-Azhar University, Cairo, Egypt, <sup>14</sup>Harvard University, Boston, MA, USA.

### \*M258. Eye-Tracking to Optimize a Digital Goals-of-Care Decision Aid for Patients with Severe Acute Brain Injury

**Shravan Sivakumar, MBBS<sup>1</sup>**, Doaa Alrefae, MS<sup>2</sup>, Lidan Zhang, MS<sup>3</sup>, Camarlin Franco, BS<sup>1</sup>, Connie Ge, BS<sup>1</sup>, Shazeb Meraj, BS<sup>1</sup>, Bengisu Tulu, PhD<sup>4</sup>, Soussan Djamshbi, PhD<sup>2</sup>, Susanne Muehlschlegel, MD, MPH<sup>5</sup>. <sup>1</sup>Department of Neurology, University of Massachusetts Chan Medical School, Worcester, MA, USA, <sup>2</sup>User Experience and Decision Making (UXDM) Laboratory, Worcester Polytechnic Institute, Worcester, MA, USA, <sup>3</sup>User Experience and Decision Making (UXDM) Laboratory, Worcester Polytechnic Institute, Worcester, MA, Worcester, MA, USA, <sup>4</sup>The WPI Business School, Worcester Polytechnic Institute, Worcester, MA, USA, <sup>5</sup>Departments of Neurology, Anesthesiology/Critical Care and Surgery, University of Massachusetts Chan Medical School, Worcester, MA, USA.

### \*M259. Head Injury and Incident Ischemic Stroke in Community-Dwelling Adults

**Holly Elser, MD, PhD<sup>1</sup>**, Laura W. Pappalardo, MD, PhD, PharmD<sup>1</sup>, Rebecca F. Gottesman, MD, PhD<sup>2</sup>, Josef Coresh, MD, PhD<sup>3</sup>, Ramon Diaz-Arrastia, MD, PhD<sup>4</sup>, Thomas

H. Mosley, MD<sup>5</sup>, Silvia Koton, MD<sup>6</sup>, Andrea L.C. Schneider, MD, PhD<sup>4</sup>. <sup>1</sup>Hospital of the University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>National Institute of Neurological Disorders and Stroke, Bethesda, MD, USA, <sup>3</sup>Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>4</sup>University of Pennsylvania Perelman School of Medicine, Philadelphia, PA, USA, <sup>5</sup>University of Mississippi Medical Center, Jackson, MS, USA, <sup>6</sup>School of Health Professions, Tel Aviv University, Tel Aviv, Israel.

**\*M260. Loss of Sarm1 Attenuates Functional Deficit Severity and Pathological pTDP-43 and pTau Accumulation in a Murine Repetitive Traumatic Brain Injury Model**

**Elif O. Dogan, MD**, James Bouley, BA, Daryl A. Bosco, PhD, Nils Henninger, MD, PhD. Umass Chan Medical School, Worcester, MA, USA.

**\*M262. Relation of Hypertension and Elevated Body Mass Index to Duration of Symptoms Following Concussion**

**Daniel N. de Souza, B.S.**, Sara Hyman, B.S., B.A., Mitchell Jarmol, B.S., Scott Grossman, M.D., Laura Balcer, M.D., MSCE. New York University Grossman School of Medicine, New York, NY, USA.

**M263. The Recovery of Consciousness via Evidence-Based Medicine and Research (RECOVER) Program: An Innovative Paradigm for Advancing Neuroprognostication**

**David Fischer, MD**, Benjamin S. Abella, MD, MPhil, Geoffrey D. Bass, MD, MBA, Jeremy Charles, MD, Stephen Hampton, MD, Catherine V. Kulick-Soper, MD, Matthew T. Mendlik, MD, PhD, Oscar J.L. Mitchell, MD, Aliza M. Narva, JD, RN, William Pino, PT, DPT, Morgan Sikandar, LCSW, Saurabh R. Sinha, MD, PhD, Genna J. Waldman, MD, Jeffrey B. Ware, MD, Joshua Levine, MD. University of Pennsylvania, Philadelphia, PA, USA.

**M264. Thyrotoxic Periodic Paralysis Triggered by COVID-19 in Undiagnosed Graves Disease: A Case Report Highlighting Risks Associated with Potassium Overcorrection**

**Tom J. Pisano, MD PhD**, Brandon Merical, MD, Zehui Wang, MD, Joshua Levine, MD. University of Pennsylvania, Philadelphia, PA, USA.

**\*M265. Trends in Traumatic Brain Injury Mortality in the United States: 1999-2019**

**Noor F. Shaik, MD, PhD**, Connor Law, BS, Holly Elser, MD, PhD, Andrea L.C. Schneider, MD, PhD. University of Pennsylvania, Philadelphia, PA, USA.

**K-M114. Association of Dexmedetomidine Utilization with Clinical Outcomes Following Moderate-Severe Traumatic Brain Injury**

Sunny Yang Liu, BA, Margot Kelly-Hedrick, MBE, Tetsu Ohnuma, MD, PhD, Jordan Komisarow, MD, PhD, **Vijay Krishnamoorthy, MD, PhD**. Duke University, Durham, NC, USA.

**K-M115. Biomarkers Associated with Progression of Intracranial Hemorrhage in the Prehospital TXA for TBI Trial**

**H. E. Hinson, MD, MCR<sup>1</sup>**, Peter Li, MD<sup>2</sup>, Toshinori Fukada, MD<sup>2</sup>, Jeffrey M. Pollock, MD<sup>2</sup>, Martin Schreiber, MD<sup>2</sup>, Susan Rowell, MD, MBA<sup>3</sup>. <sup>1</sup>UCSF, San Francisco, CA, USA, <sup>2</sup>OHSU, Portland, OR, USA, <sup>3</sup>University of Chicago, Chicago, IL, USA.

**K-M116. Head Injury and Cognitive Change over 30 Years**

**Andrea L.C. Schneider, MD PhD<sup>1</sup>**, James R. Pike, MBA<sup>2</sup>, Holly C. Elser, MD PhD<sup>1</sup>, Josef Coresh, MD PhD<sup>2</sup>, Thomas H. Mosley, PhD<sup>3</sup>, Ramon Diaz-Arrastia, MD PhD<sup>1</sup>, Rebecca F. Gottesman, MD PhD<sup>4</sup>. <sup>1</sup>University of Pennsylvania, Philadelphia, PA, USA, <sup>2</sup>Johns Hopkins University, Baltimore, MD, USA, <sup>3</sup>University of Mississippi, Jackson, MS, USA, <sup>4</sup>NINDS, Bethesda, MD, USA.

**K-M117. Symptomatic Baroreflex Abnormalities Following Concussion**

**Melissa Cortez, DO**, Ryan Pelo, BS, Peter Fino, PhD, Lee Dibble, PhD, KC Brennan, MD. University of Utah, Salt Lake City, UT, USA.

**K-M118. Systemic Metabolic Alterations after Aneurysmal Subarachnoid Hemorrhage**

**Aaron M. Gusdon, MD<sup>1</sup>**, Jude PJ Savarraj, PhD<sup>1</sup>, Hua Chen, BS<sup>1</sup>, Neeraj Badjatia, MD, MS<sup>2</sup>, Huimahn A. Choi, MD, MS<sup>1</sup>. <sup>1</sup>University of Texas Health Science Center, Houston, TX, USA, <sup>2</sup>University of Maryland, Baltimore, MD, USA.

**LB-M115. Cocaine Intoxication Resulting in an Atypical Stroke**

**Amber R. Hughes, BS BA<sup>1</sup>**, Karim Makhoul, MD<sup>2</sup>, Spencer Brown, MPH<sup>1</sup>. <sup>1</sup>St. George's University, St. George, Grenada, <sup>2</sup>Queens Hospital Center, Mount Sinai Services, Queens, NY, USA.

**\*LB-M116. Enhanced In Vivo Blood Brain Barrier Transcytosis of Macromolecular Cargo Using an Engineered pH-Sensitive Mouse Transferrin Receptor Binding Nanobody**  
*David L. Brody, MD PhD. USUHS, Bethesda, MD, USA.*

## Neuromuscular Disease

**M267. A Brief Report on Juvenile ALS in the National ALS Registry: 2010 - 2018**

*Jaime Raymond, MPH, Jasmine Berry, MPH, Paul Mehta, MD, Theodore Larson, MS, Kevin Horton, DrPH, MSPH. CDC/ATSDR, Atlanta, GA, USA.*

**M268. A Case of Anti-Neurofascin Autoantibody Positive Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) Concurrent with Angioimmunoblastic T-cell Lymphoma**

*Brandon Wei, MD, Bing Liao, MD. Houston Methodist Hospital, Houston, TX, USA.*

**M269. A Case of Anti-NXP2 Dermatomyositis without Histopathological Evidence of Myopathy**

*Mehmet C. Kadipasaoglu, MD, PhD, Bing Liao, MD. Houston Methodist Hospital, Houston, TX, USA.*

**M270. A Case of Thrombocytopenic COVID-19 and Miller Fisher Syndrome on a Concurrent Chronic Immune Neuropathy**

*Lisle Blackburn, MD, Umair Hamid, MD, Janaki Tokala, MD, Gregory Blume, MD. University of Illinois COM Peoria, Peoria, IL, USA.*

**M271. A Case Report of Systemic Lupus Erythematosus Presenting as Isolated Mononeuritis Multiplex**

*Mia Andreoli, BA, Cecilia Hollenhorst, MD, Tulsi Malavia, MD, Jasmine May, MD, Shubadra Priyadarshini, MD, Arjun Seth, MD, Karan Dixit, MD. Northwestern University, Chicago, IL, USA.*

**M272. Acute Motor Sensory Axonal Neuropathy with IgM Antibodies Against NS65**

*Lamees Alzyoud, M.D., Ajitesh Ojha, M.D. University of Pittsburgh Medical Center, Pittsburgh, PA, USA.*

**M273. AL Amyloid Neuropathy Clinical and Electrophysiological Characteristics**

*Sara Benítez, M.D., Sheetal Shroff, M.D. Houston Methodist Hospital, Houston, TX, USA.*

**M274. Algal Blooms and Amyotrophic Lateral Sclerosis: A Systematic Review**

*Surya Suresh, MBBS<sup>1</sup>, Akshara Sudhakaran Lissy, MBBS<sup>2</sup>, Sandra James, MBBS<sup>1</sup>, Neena Viswanathan, MD<sup>3</sup>. <sup>1</sup>Thanjavur Medical College, Thanjavur, India, <sup>2</sup>T.D. Medical College, Alappuzha, India, <sup>3</sup>University of South Florida, Tampa, FL, USA.*

**\*M275. Anti-RGMA Antibody Restores the Neuronal Actin Barrier against Disease-Implicated Protein and Prevents Neurodegeneration in an Animal Model of ALS**

*Mikito Shimizu, MD, PhD<sup>1</sup>, Naoyuki Shiraishi, MD<sup>1</sup>, Satoru Tada, MD, PhD<sup>1</sup>, Tsutomu Sasaki, MD, PhD<sup>1</sup>, Goichi Beck, MD, PhD<sup>1</sup>, Seiichi Nagano, MD, PhD<sup>1</sup>, Makoto Kinoshita, MD, PhD<sup>1</sup>, Hisae Sumi, MD, PhD<sup>2</sup>, Tomoyuki Sugimoto, PhD<sup>3</sup>, Toru Koda, MD, PhD<sup>1</sup>, Teruyuki Ishikura, MD, PhD<sup>2</sup>, Yasuko Sugiyama, MD<sup>1</sup>, Keigo Kihara, MD<sup>1</sup>, Minami Kanakura, Master's degree<sup>4</sup>, Tsuneo Nakajima, MD, PhD<sup>1</sup>, Shuko Takeda, MD, PhD<sup>1</sup>, Toshihide Yamashita, MD, PhD<sup>1</sup>, Tatsusada Okuno, MD, PhD<sup>1</sup>, Hideki Mochizuki, MD, PhD<sup>1</sup>. <sup>1</sup>Osaka University Graduate School of Medicine, Osaka, Japan, <sup>2</sup>Higashiosaka City Medical Center, Osaka, Japan, <sup>3</sup>Shiga University, Shiga, Japan, <sup>4</sup>Osaka University, Osaka, Japan.*

**M276. Association between Urinary Metals and Amyotrophic Lateral Sclerosis (ALS) Survival**

*Dae-Gyu Jang, PhD, Samuel Teener, BS, Hasan Farid, MS, Caroline Piecuch, BS, Eva Fedman, MD, PhD, Stephen Goutman, MD, MS. University of Michigan, Ann Arbor, MI, USA.*

**M277. Atypical Guillain-Barre Syndrome (GBS) Preceding High-Grade Burkitt Lymphoma with Central Nervous System (CNS) Involvement: A Case Report**

*Jason Gandhi, MD, Romil Singh, MBBS, MD, Hassan Abdullah Shakeel, MBBS, MD, Thomas Scott, MD. Allegheny General Hospital, Pittsburgh, PA, USA.*

**M278. Atypical Presentation of Chronic Inflammatory Demyelinating Polyneuropathy**

*Michelle Calmet, MD, Papul Chalia, MD, James Grogan, MD, Mansoureh Mamarabadi, MD. Penn State Health, Hershey, PA, USA.*

**\*M279. Baseline Data from a Phase 2 Clinical Trial of Repeated Intrathecal Autologous Adipose-Derived MSCs in ALS**

*Nathan P. Staff, MD, PhD<sup>1</sup>, Bjorn Oskarsson, MD<sup>2</sup>, Iryna Muzyka, MD<sup>3</sup>, Nicolas N. Madigan, MBCh, PhD<sup>1</sup>, Daniel Figdore, BS<sup>1</sup>, Michelle Turner, BS<sup>1</sup>, Lisa Thuro, BS<sup>2</sup>, Thomas Osgood, BS<sup>3</sup>, Pranathi Madde, BS<sup>1</sup>, Michael Deeds, BS<sup>1</sup>, Timothy Wiltshire, PhD<sup>1</sup>, Alicia Algeciras-Schimmich, PhD<sup>1</sup>, Jay Mandrekar, PhD<sup>1</sup>, Allan Dietz, PhD<sup>1</sup>, Anthony*

Windebank, MD<sup>1</sup>. <sup>1</sup>Mayo Clinic, Rochester, MN, USA, <sup>2</sup>Mayo Clinic, Jacksonville, FL, USA, <sup>3</sup>Mayo Clinic, Scottsdale, AZ, USA.

**\*M280. Cardiolipin Nanoparticles as Therapeutic Molecules for Providing Neuroprotection by Improving Mitochondrial Function in FTD/ALS**

**Mukesh Gautam, PhD**, Angela M. Ahrens, BS, Jacquelyn E. Trujillo, BS, Colby S. Thaxton, MD PhD, Pembe Hande Ozdinler, PhD. Northwestern University, Chicago, IL, USA.

**M281. Case of Guillain-Barré Syndrome in Patient Receiving Checkpoint Inhibitor Therapy**

**Anthony Ghobrial, MD<sup>1</sup>**, Daniel Diehl, MD<sup>2</sup>, Sandeep Rana, MD<sup>2</sup>. <sup>1</sup>Drexel University College of Medicine, Philadelphia, PA, USA, <sup>2</sup>Allegheny Health Network, Allegheny General Hospital, Pittsburgh, PA, USA.

**M282. Case Study: Botulism in Short Gut Syndrome**

**Savanna Dasgupta, DO**, Arthur Gribachov, MD, Michael Gallagher, MD, Yunis Mayasi, MD. Cooper University Hospital, Camden, NJ, USA.

**\*M283. Clingen's Neurological Disorders Clinical Domain Working Group: Advancing Gene-Disease Relationships through a Rigorous Validation Process**

**Kumari Latchman, DO<sup>1</sup>**, Courtney Thaxton, PhD<sup>2</sup>, Meredith Weaver, PhD<sup>3</sup>, Raquel Fernandez, BS<sup>3</sup>, Marwa Elnagheeb, MPH<sup>2</sup>, Hailey Segall, MSc<sup>2</sup>, Matthew Harms, MD<sup>4</sup>, Claudia Testa, MD PhD<sup>2</sup>, Stephan Zuchner, MD PhD<sup>1</sup>. <sup>1</sup>University of Miami Miller School of Medicine Department of Genetics, Miami, FL, USA, <sup>2</sup>University of North Carolina at Chapel Hill, Chapel Hill, NC, USA, <sup>3</sup>American College of Medical Genetics and Genomics, Bethesda, MD, USA, <sup>4</sup>Columbia University, New York, NY, USA.

**M284. Clinical Implications of Specific Autoantibodies in Chronic Inflammatory Neuropathies**

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**M285. Comparison of Diagnostic Efficacy of Electrophysiology and Magnetic Resonance Neurography in Patients with Nontraumatic Ulnar Mononeuropathy**

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**\*M286. Congenital Myasthenic Syndrome with Dual Loss-of-Function Variants in the  $\alpha$  Subunit of Acetylcholine Receptor**

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**\*M287. Early B Cell Tolerance Defects in Anti-Neurofascin-155-Mediated Autoimmune Nodopathy**

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**M288. Evaluation of Length of In Hospital Stay and Treatment Based Complications in Patients Hospitalized Due to Exacerbation of Myasthenia Gravis**

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**M291. Higher Glycemic Index Diet is Associated with Slower Disease Progression in Amyotrophic Lateral Sclerosis**

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University, New York, NY, USA, <sup>5</sup>Department of Epidemiology, Mailman School of Public Health, New York, NY, USA.

## **M292. Lifesaving Treatments for Spinal Muscular Atrophy: Global Access and Availability**

**Victor D. Armengol, MD<sup>1</sup>**, Basil T. Darras, MD<sup>2</sup>, Ahmad A. Abulaban, MBBS<sup>3</sup>, Ali Alshehri, MBBS<sup>4</sup>, Nina Barišić, MD, PhD<sup>5</sup>, Tawfeg Ben-Omran, MD, MBChB<sup>6</sup>, Günther Bernert, MD<sup>7</sup>, Claudia Castiglioni, MD<sup>8</sup>, Yin-Hsiu Chien, MD, PhD<sup>9</sup>, Michelle A. Farrar, MBBS, PhD<sup>10</sup>, Gwendoline Kandawasvika, MBChB, MMed, MPhil, PhD<sup>11</sup>, Satish Khadilkar, MD, DM, DNBE<sup>12</sup>, Jean K. Mah, MD, MSc<sup>13</sup>, Chiara Marini-Bettolo, MD, PhD<sup>14</sup>, Damjan Osredkar, MD, PhD<sup>15</sup>, Gerald Pfeffer, MD, PhD<sup>13</sup>, Flavia Piazzon, MD, PhD<sup>16</sup>, Inmaculada Pitarch Castellano, MD<sup>17</sup>, Susana Quijano-Roy, MD, PhD<sup>18</sup>, Kayoko Saito, MD<sup>19</sup>, Jin-Hong Shin, MD, PhD<sup>20</sup>, Juan F. Vázquez-Costa, MD, PhD<sup>21</sup>, Maggie C. Walter, MD, MA<sup>22</sup>, Jithangi Wanigasinghe, MD<sup>23</sup>, Hui Xiong, MD<sup>24</sup>, Robert C. Griggs, MD<sup>25</sup>, Bhaskar Roy, MBBS, MBioMedSci, MHS<sup>1</sup>. <sup>1</sup>Yale School of Medicine, New Haven, CT, USA, <sup>2</sup>Boston Children's Hospital, Boston, MA, USA, <sup>3</sup>King Abdullah International Medical Research Center, Riyadh, Saudi Arabia, <sup>4</sup>King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia, <sup>5</sup>University of Zagreb Medical School, Zagreb, Croatia, <sup>6</sup>Sidra Medicine and Hamad Medical Corporation, Doha, Qatar, <sup>7</sup>Klinik Favoriten, Vienna, Austria, <sup>8</sup>Clinica Meds, Santiago, Chile, <sup>9</sup>National Taiwan University Hospital, Taipei, Taiwan, <sup>10</sup>Sydney Children's Hospital, Sydney, Australia, <sup>11</sup>University of Zimbabwe, Harare, Zimbabwe, <sup>12</sup>Bombay Hospital and Medical Research Centre, Mumbai, India, <sup>13</sup>University of Calgary Cumming School of Medicine, Calgary, AB, Canada, <sup>14</sup>John Walton Muscular Dystrophy Research Centre, Newcastle upon Tyne, United Kingdom, <sup>15</sup>University Children's Hospital Ljubljana, Ljubljana, Slovenia, <sup>16</sup>University of São Paulo, São Paulo, Brazil, <sup>17</sup>Hospital Universitari i Politècnic La Fe, Valencia, Spain, <sup>18</sup>Raymond Poincaré University Hospital, Garches, France, <sup>19</sup>Tokyo Women's Medical University, Tokyo, Japan, <sup>20</sup>Pusan National University Yangsan Hospital, Yangsan, Korea, Republic of, <sup>21</sup>Universitat de València, Valencia, Spain, <sup>22</sup>Ludwig-Maximilians-University of Munich, Munich, Germany, <sup>23</sup>University of Colombo, Colombo, Sri Lanka, <sup>24</sup>Peking University First Hospital, Beijing, China, <sup>25</sup>University of Rochester Medical Center, Rochester, NY, USA.

## **\*M293. Long-Term Outcomes of Offspring of Mothers with Fetal Acetylcholine Receptor Antibodies**

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**\*M294. Long-Term Safety, Tolerability, and Efficacy of Subcutaneous Efgartigimod PH20 in Patients with Generalized Myasthenia Gravis: Interim Results of the ADAPT-SC+ Study**

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**\*M296. Monitoring and Prognostication of Dysferlinopathy Based on Novel Biomarkers: Myostatin and Follistatin**

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**M297. National Trends in the Utilization of Thymectomy for Myasthenia Gravis**

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**\*M299. NMD670, a Novel First-in-Class Skeletal Muscle CIC-1 Inhibitor, Improves Symptoms of Myasthenia Gravis: A Randomized, Single-Dose, Double-Blind, Placebo-Controlled, Study**

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**\*M300. PET Imaging of Neuroinflammation in ALS Patients Using <sup>18</sup>F-OP-801, a Novel Nanoimaging Agent**

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**M301. Phase 3b Extension Study to Evaluate the Efficacy and Safety of 2 Dosing Regimens of Oral Edaravone in Patients with Amyotrophic Lateral Sclerosis**

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### **M302. Predictors of Longer Mechanical Ventilator Use among Amyotrophic Lateral Sclerosis Patients**

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### **M303. Prognostication of Disease Severity and Mortality in Patients with Amyotrophic Lateral Sclerosis Based on Peak Expiratory Flow Measurements by Household Peak Flow Meter**

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### **M304. RAD23 Enhances the Degradation of Proteins That Cause Familial Amyotrophic Lateral Sclerosis (ALS)**

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### **M305. Ravulizumab-Responsive Seronegative Myasthenia Gravis**

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### **\*M306. Results from First-in-Human Study of VRG50635, a Pikfyve Inhibitor for Treatment of ALS, in Healthy Adult Volunteers**

Lars Smits, MD<sup>1</sup>, Philip Kremer, MD<sup>1</sup>, Jules Heuberger, Ph.D.<sup>1</sup>, Sujata Sankar, Ph.D.<sup>2</sup>, Payal Nanavati, MS<sup>2</sup>, Bruce Morimoto,

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### **M307. SARM 1 Deficiency Attenuates Peripheral Neuropathy in Diabetic Mice**

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### **\*M308. Schmidt-Lanterman Incisure and Adherens Junction Defects in CMT1A and HNPP Myelin**

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### **M311. The Importance of Offering Exome or Genome Sequencing in Adult Neuromuscular Clinics**

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### **M312. The Notorious Drg: A Delayed Diagnosis of Dorsal Root Ganglionopathy**

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### **\*M313. The OMA1-DELE1 Mitochondrial Integrated Stress Response is Activated by Diverse Mitochondrial Stressors to Promote Growth and Survival in Mitochondrial Myopathy**

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### **M314. Treatment of Canomab with Rituximab: A Systematic Review**

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**M315. Two Cases of Monomelic Amyotrophy (Hirayama Disease) in Young Caucasian Males**

**Maya Ramy, MS**, Osman Ozel, MD, Syed Gillani, MD, Sheetal Shroff, MD. Houston Methodist Hospital, Houston, TX, USA.

**M316. Unilateral Abdominal Wall Hernia Secondary to Thoracic Disc Herniation: A Case Report**

**Bao Nguyen, MD**, Darrick Alaimo, MD. Darrick J. Alaimo MD, LLC, Rochester, NY, USA.

**\*M317. Using Unsupervised Machine Learning to Identify Phenotypic Clusters of Small Fiber Neuropathy**

**Peyton Murin, MD<sup>1</sup>**, Stefanie Geisler, MD<sup>2</sup>. <sup>1</sup>Saint Louis University, St. Louis, MO, USA, <sup>2</sup>Washington University in Saint Louis, St. Louis, MO, USA.

**K-M119. Higher Glycemic Index Diet is Associated with Slower Disease Progression in Amyotrophic Lateral Sclerosis**

**Ikjae Lee, MD<sup>1</sup>**, Hiroshi Mitumoto, MD<sup>1</sup>, Seonjoo Lee, PhD<sup>2</sup>, Edward Kasarskis, MD PhD<sup>3</sup>, Michael Rosenbaum, MD<sup>1</sup>, Pam Factor-Litvak, PhD<sup>2</sup>, Jeri W. Nieves, PhD<sup>2</sup>. <sup>1</sup>Columbia University Irving Medical Center, New York, NY, USA, <sup>2</sup>Columbia University, New York, NY, USA, <sup>3</sup>University of Kentucky, Lexington, KY, USA.

**K-M120. Pathogenicity of Novel KIF5A Disease Causative Variants**

**Jonathan R. Brent, MD/PhD**, Oliver Sterling-Angus, B.S., Han-Xiang Deng, MD/PhD. Northwestern University, Chicago, IL, USA.

**K-M121. Predictors of Undiagnosed Peripheral Neuropathy in a Predominantly Low-Income, Black U.S. Primary Care Population**

**Melissa A. Elafros, MD PhD<sup>1</sup>**, Alexandra Brown, MPH<sup>1</sup>, Huda Marcus, MD MS<sup>2,3</sup>, Thair Dawood, MD<sup>2,3</sup>, Ghassan I. Bachuwa, MD MHS MS<sup>2,3</sup>, Mousumi Banerjee, PhD<sup>1</sup>, Peter J. Winch, MD MPH<sup>4</sup>, Michelle P. Kvalsund, DO MS<sup>5,6</sup>, Eva L. Feldman, MD MPH<sup>1</sup>, Brian C. Callaghan, MD MS<sup>1</sup>, Lesli E. Skolarus, MD MS<sup>7</sup>. <sup>1</sup>University of Michigan, Ann Arbor, MI, USA, <sup>2</sup>Hurley Medical Center, Flint, MI, USA, <sup>3</sup>Michigan State University, East Lansing, MI, USA, <sup>4</sup>Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA, <sup>5</sup>University of Rochester, Rochester, NY, USA, <sup>6</sup>University of Zambia, Lusaka, Zambia, <sup>7</sup>Northwestern University, Chicago, IL, USA.

**\*LB-M118. Alternative Polyadenylation in the Pathogenesis of Amyotrophic Lateral Sclerosis**

**Sebastian Michels, MD**, Frederick J. Arnold, PhD, Ya Cui, PhD, Michael R. Colwin, BS, Wei Li, PhD, Albert R. La Spada, MD, PhD. University of California, Irvine, Irvine, CA, USA.

**LB-M119. Descriptive Analysis of 12 Patients with Anti-Plexin-D1 Seropositive Small Fiber Neuropathy**

**Ivana Massabki, B.Arts Sc.<sup>1</sup>**, Peyton Murin, M.D.<sup>2</sup>, Jafar Kafaie, M.D.<sup>2</sup>. <sup>1</sup>Saint Louis University School of Medicine, St Louis, MO, USA, <sup>2</sup>Saint Louis University Department of Neurology, St Louis, MO, USA.

**\*LB-M120. Inclusion Body Myositis is a TDP-43 Proteinopathy with Nuclear Pore Disruption**

Chiseko Ikenaga, MD PhD, Andrew Wilson, MS, Phil Wong, PhD, **Thomas Lloyd, MD PhD**. Johns Hopkins University School of Medicine, Baltimore, MD, USA.

## Autoimmune Neurology & MS

### \*M100. <sup>18</sup>F-Fluorodeoxyglucose-Positron Emission Tomography Findings in Neuromyelitis Optica Spectrum Disorder and Myelin Oligodendrocyte Glycoprotein Antibody Associated Disease

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**Background:** Neuromyelitis optica spectrum disorder (NMOSD) and myelin oligodendrocyte glycoprotein antibody associated disease (MOGAD) are rare inflammatory diseases of the central nervous system (CNS). Reports regarding findings of <sup>18</sup>F-Fluorodeoxyglucose-positron emission tomography (<sup>18</sup>FDG-PET) in NMOSD and MOGAD are limited. **Objective:** To report <sup>18</sup>FDG-PET findings in people with NMOSD and MOGAD and assess clinical relevance and associations with disease characteristics. **Methods:** This was a retrospective, single-center cohort study of people with NMOSD or MOGAD who underwent <sup>18</sup>FDG-PET at Johns Hopkins Hospital after onset of their neurological condition. The main indication for obtaining FDG-PET imaging in these cases was to assess for underlying neoplasia, due to concern for paraneoplastic syndrome. All participants underwent whole body <sup>18</sup>FDG-PET imaging (including brain) except for one patient who only underwent imaging from the skull base to mid-thighs. **Result:** We identified 42 NMOSD and 10 MOGAD patients who underwent FDG-PET imaging. Twenty-seven NMOSD and 6 MOGAD patients were within 1 month of an acute attack at the time of the FDG-PET scan. Hypermetabolic changes were observed corresponding to the site of the attack in 7 attacks (3 myelitis, 3 optic neuritis and 1 brainstem). Remote to the site of involvement, one patient had CNS hypermetabolic changes and 6 patients had CNS hypometabolic changes, including in anatomically relevant areas to the site of attack (e.g., bilateral visual cortex hypometabolism in patients with optic neuritis). Abnormalities outside of the CNS were identified in 25 patients, but the vast majority were deemed incidental and irrelevant to the patient's presentation. Only one NMOSD patient was diagnosed with breast cancer that was detected on the FDG-PET scan and confirmed by subsequent biopsy. **Conclusion:** Our study describes findings observed on FDG-PET imaging in people with NMOSD and MOGAD. We observed hypermetabolic activity associated with inflammatory lesions in a significant proportion of cases, as well as hypometabolism in areas remote to the site of involvement, possibly due to a diaschisis phenomenon. Importantly, the diagnostic yield for detection of a malignancy (the main indication for FDG-PET scan) was relatively

low, with only one participant being identified as having cancer on the basis of the FDG-PET findings.

### M101. A 90-Year-Old Woman with NMDA Encephalitis Who Was Initially Diagnosed to Have Parkinson Disease

**Rajesh K. Gupta, MD, Sienna Wu, BS. UTHealth, Houston, TX, USA.**

**Introduction:** Diagnosing autoimmune encephalitis is challenging, and patients can go undiagnosed for several years, however, timely diagnosis can change the clinical course and avoid disability. **Objective:** To report a patient of advanced age with autoimmune encephalitis who went undiagnosed for almost 5 years leading to significant disability. **Case Report:** A 92-year-old woman with a past medical history of basal cell carcinoma, hiatal hernia, and recurrent pancreatitis presented to an outside facility 5 years ago with an episode of subacute onset vertigo, nystagmus, voice change, and gait imbalance. Almost a year after onset, the patient has the progression of weakness involving the other leg and start using a walker. Two years later, she became wheelchair-bound and developed dysphagia requiring PEG tube placement. Her initial exam was reported significant for limited eye movements, rigidity, and generalized weakness. Later she became non-verbal. MR imaging showed generalized atrophy of the brain. CSF findings were unremarkable except for mildly elevated protein. The patient was diagnosed with a neurodegenerative process of unclear nature. There was minimal to no improvement with Sinemet and other dopaminergic agonists. During the consultation at our institution, the patient's daughter reported that the patient had initially complained of her left leg not following her commands and developed visual neglect. Given the suspicion of autoimmune encephalitis, an autoimmune encephalitis panel was performed that was positive for the NMDA antibody. The patient responded well to high-dose IV steroids and had improvement in extraocular movements, neck and arm strength, dysphagia, and verbal output. Maintenance IVIG treatment led to continued improvement in her symptoms including breathing. **Conclusion:** This case report highlights the importance of early diagnosis and treatment of autoimmune encephalitis even in patients with advanced age.

### M103. A Case of Multiple Autoantibody-Related Treatment-Refractory Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) and Cerebellar Dysfunction Overlap Syndrome

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**Objectives:** To discuss a rare case of multiple autoantibody-related, treatment-refractory Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) and cerebellar dysfunction overlap syndrome. **Background:** CIDP and cerebellar dysfunction are disabling diseases with pathophysiological

heterogeneity. Autoantibodies targeting various antigens in peripheral and central nervous system have been identified. Patients may present with complex neurological syndromes related to multiple autoantibodies, posing challenges to prompt diagnosis and effective treatment. **Case Report:** A 70-year-old male with past medical history of hypertension and mitral valve prolapse presented to the neuromuscular clinic with subacute onset left foot drop and left leg numbness. Initial electromyography and nerve conduction studies (EMG/NCS) showed mild sensory motor axonal neuropathy. In the next two months, his condition worsened with progressive leg weakness, sensory loss, and gait instability, along with new onset difficulty swallowing and slurred speech. Neurological exam revealed proximal and distal lower extremity weakness, asymmetric sensory deficits, areflexia, dysarthria, dysphagia, dysmetria and cerebellar ataxia. Cerebral spinal fluid studies revealed elevated Q-albumin ratio, IgG, and myelin basic protein concentrations. Serum autoantibody tests revealed significantly elevated IgG anti-GQ1b antibody, anti-P/Q and N type calcium channel antibody and anti-GAD 65 antibody titers. EMG/NCS showed worsened findings suggestive of demyelinating sensorimotor polyradiculoneuropathy. CT thorax, abdomen and pelvis was unremarkable for malignancy. Treatment with intravenous immunoglobulin (IVIg) was partially effective resulting in improvement of leg weakness. Therapeutic plasma exchange and corticosteroids worsened his dysmetria and ataxia. Rituximab was initiated, which led to marked improvement in dysarthria and dysphagia. Patient continued to have upper extremity dysmetria and gait impairment requiring a rolling walker to assist ambulation. **Conclusion:** Neurological manifestations of autoantibodies targeting peripheral and central nervous system are complex. Antibody testing should be utilized in appropriate clinical scenarios to improve diagnosis promptness and outcome.

#### **M104. A Rare Case of Co-Existing Dermatomyositis and Myasthenia Gravis**

**Sumeyye Kus, MD, Matthew Imperoli, MD, Hamza Coban, MD.** University of Connecticut School of Medicine, Farmington, CT, USA.

Myasthenia gravis (MG) is an autoimmune neuromuscular junction disorder characterized by fluctuating proximal muscle weakness as well as ocular, bulbar and respiratory muscle involvement. Dermatomyositis (DM) is another autoimmune disease with inflammatory myositis and manifests with proximal muscle weakness. Although rare, the co-occurrence of these two conditions has been reported. In this case presentation, we describe a patient with DM and MG who responded favorably to steroid and intravenous immunoglobulin (IVIg). A 79-year-old Caucasian male developed subacute onset, fatigable, progressive proximal weakness. He later developed dysphagia and diplopia but no significant ptosis. Over several weeks, he developed dysphagia and dyspnea. The examination showed no rash but fatigable weakness in neck muscles as well as proximal muscles in both upper and lower extremities with some intrinsic muscle atrophy in his hands bilaterally without distal weakness. The initial workup

revealed elevated ESR, CRP, and CK levels. There was no thymoma or any sign of malignancy on initial computed tomography of chest, abdomen, pelvis. Bedside EMG showed irritable, proximal myopathy, 3-hertz repetitive stimulation test was inconclusive. Subsequently, muscle biopsy was done. Due to concern for MG and DM, he was started on a 3-day course of high dose IV steroids, then oral prednisone taper. He had improvement in his symptoms and was discharged home with pending work up. However, he returned with worsening dysphagia and persistent proximal weakness. In the meantime, the acetylcholine receptor binding and blocking antibodies returned significantly elevated and a muscle biopsy was consistent with dermatomyositis. The myositis panel showed a positive Nxp2 antibody as well. Whole body PET scan was negative for malignancy. Patient was further treated with IVIG in addition to prednisone which resulted in an improvement of his muscle strength and dysphagia improved. Prednisone was tapered down to 5 mg daily overtime, and azathioprine was started for long-term adjunctive therapy. Myasthenia Gravis and Dermatomyositis are separate entities but can present with overlapping symptoms, however, both conditions can rarely co-exist as in our case. Our patient responded favorably to a combination of steroids and IVIG. This case highlights the importance of recognizing the coexistence of MG and DM as it may have implications for treatment and management including malignancy screening. Further research is needed to determine the optimal treatment approach for patients who suffer from both MG and DM though fortunately both disorder response to many of the same immunotherapies.

#### **M105. A Rare Presentation of Neurosarcoidosis as Thoracic Radiculopathy in a Patient with Ankylosing Spondylitis**

**Rajesh K. Gupta, MD, MS, Manish M. Bhojwani, BS.** UTHealth, Houston, TX, USA.

**Background:** Neurosarcoidosis (NS) can have a myriad of presentations, however, a presentation with thoracic radiculopathy is exceedingly rare. Here we report a man in his 60 with ankylosing spondylitis who presented with severe weight loss and thoracic rib cage pain. **Case Report:** A Caucasian man in his late 60s, with diabetes and + HLA-B27 inflammatory Spondyloarthritis, complained to his rheumatologist of pain over the left rib cage of 3 months and a patchy area of numbness and almost 60 pounds of weight loss over two years. CT chest showed a spiculated lesion in the right upper lobe, which on biopsy showed well-differentiated adenocarcinoma and non-caseating granulomas consistent with the diagnosis of pulmonary sarcoidosis. He did not have any pulmonary symptoms including chest pain, hemoptysis, cough or shortness of breath. He presented to neurology with progressive worsening of pain over the left rib cage. On neurological exam, he was found to have length-dependent diminished sensation, mild distal lower limb weakness and absent lower extremity reflexes. EMG test was suggestive of a length-dependent polyneuropathy that was attributed to diabetes polyneuropathy. His left thoracic pain was believed to be from thoracic radiculopathy given unremarkable work up including an MRIs

of the thoracic and lumbar spine. **Conclusion:** NS can present as isolated thoracic radiculopathy and can be the only presenting symptom of sarcoidosis at times.

#### **M106. AMAN Presenting with Myeloradiculitis**

**Philion Gatchoff, MD, Mohammad Hussein, MD, Estevo Ribeiro, MD, Ahmad Al-Awwad, MD.** University of Oklahoma Health Science Center, Oklahoma City, OK, USA.

**Background:** Acute Motor Axonal Neuropathy (AMAN) is a variant of Guillain-Barré syndrome characterized by peripheral motor axonal degeneration due to antibody-mediated neuronal membrane damage usually following immune insult with symptoms of symmetrical flaccid progressive paralysis with areflexia. Previously described cases of AMAN show bilateral cauda equina enhancement sparing the conus medullaris. Here, we describe a patient who presented with initial concern for transverse myelitis or spinal cord tumor affecting the T12 spinal level and was subsequently found to have AMAN confirmed on EEG with atypical enhancement. **Objective:** To describe an atypical case of AMAN presenting with myeloradiculitis at the level of conus medullaris and cauda equina. **Results:** 31-year-old man without significant medical history presenting with 10-day history of progressive ascending bilateral leg weakness and numbness without recent infection or vaccination. Neurological exam showed symmetric progressive lower extremity distal weakness with absent Achilles reflexes and high-steppage gait. MRI T-spine w/wo showed cord swelling with intramedullary enhancement at the level of T12 extending into the nerve roots and through the cauda equina. MRI brain and C-spine were without abnormal enhancement in the brain, optic nerves or cervical spine. CSF analysis demonstrated elevated protein and no oligoclonal bands. PET scan was negative for malignancy. The patient was empirically started on IVIG and methylprednisolone 1 gram daily for 5 days for transverse myelitis. Extensive serum and CSF workup for other causes of myelopathy including rheumatologic, infectious, and nutritional etiologies were unremarkable. Delayed NCS revealed low amplitude CMAP with relatively normal motor nerve conduction velocities and no evidence of conduction block in bilateral lower extremities and normal sensory studies confirming AMAN. He had mild improvement in strength after treatment and was discharged home with a walker. At one month follow up, his weakness had markedly improved and was approaching baseline. Repeat MRI revealed resolution of conus medullaris expansion and enhancement and partial improvement in cauda equina enhancement. **Conclusions:** Myeloradiculitis as a presenting symptom is usually caused by infectious, inflammatory, or neoplastic causes. We report this case to highlight this previously undescribed presentation of AMAN.

#### **M107. An Immunosuppressed Marathoner with Headaches and Fevers Progressing to Coma**

**Ilana Green, MD, Sam Horng, MD, PhD, Neha Dangayach, MD.** Icahn School of Medicine at Mount Sinai, New York, NY, USA.

**Presentation:** A 42-year-old marathoner with a past medical history of multiple sclerosis and seronegative rheumatoid

arthritis (on ocrelizumab and methotrexate) presented with worsening fever, headache, and vomiting. Her headache felt like “a terrible pressure” as if her head were “going to explode” that gradually increased over 48 hours. She had associated neck pain and stiffness without photophobia or phonophobia. She reported horizontal binocular diplopia, peri-orbital tenderness, and a sensation of pressure behind her eyes. She was treated for mild sinus congestion and generalized malaise with doxycycline and levofloxacin two weeks prior, but felt well enough to complete a 5K a week prior to presentation. **Exam:** Her initial physical exam was notable for tender frontal and ethmoid sinuses, and neck pain with movement with normal range of motion, as well as multiple cranial neuropathies and corticospinal tract signs. She was admitted to the inpatient neurology service for further workup, and over the course of 36 hours, developed a rapidly progressive bulbar palsy requiring intubation and transfer to the neurological intensive care unit. **Workup and Differential Diagnosis:** Her CSF studies were significant for a neutrophilic pleocytosis, elevated protein, and positive enterovirus PCR. Her MRI brain was significant for T2/FLAIR hyperintensity spanning from her medulla through her midbrain. Differential diagnosis focused on brainstem meningoencephalitis with consideration of infectious, autoimmune and paraneoplastic etiologies. **Outcome and Discussion:** The timeline of her prodromal respiratory symptoms and subsequent development of neurological symptoms in the setting of her immunosuppressive regimen were consistent with the aggressive immuno-pathogenesis of EV-A71 with CNS involvement (Garzo-Caldas, Neurology, 2017; Lee, Korean J Pediatr, 2016). There are no approved therapies for enterovirus rhombencephalitis, though there are reports of improvement with intravenous immunoglobulin (IVIG) (Wagner, Int J Infect Dis, 2021). The rationale behind the use of IVIG is to provide neutralizing antibodies and attenuate cytokine production. We treated our patient with a course of IVIG given a favorable risk-benefit balance in the setting of rapid progression to respiratory failure and coma. Our patient experienced a slow but significant and ongoing clinical recovery. At 12 weeks she was discharged home from acute rehab with mild dysarthria, scanning speech, and a slight truncal ataxia. At 11 months, she completed the New York City Marathon.

#### **M110. Autism-Like Presentation of Pediatric Autoimmune Encephalitis, Completely Recovered after Immunotherapy**

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**Introduction:** Autism, a developmental disability characterized by atypical social skills, repetitive behaviors, and challenges with communication, has been defined by a set of

autistic traits, rather than a specific molecular basis. Due to the ambiguity of the definition, the prevalence of autism has grown more than fivefold in recent decades and the difference between the autism patient group and the normal control group has decreased. Here, we present a case of a young patient with autism-like symptoms who completely recovered by immunotherapy. **Case:** A 15-year-old female was admitted to a psychiatry hospital for visual hallucination, disorganized speech, and behavior developed one month ago. At age four, she faced difficulty in interacting with peers, which could be a major criterion for autism spectrum disorder. Her language function was not enough for her age and her intelligence was retarded. But unlike cases of autism spectrum disorder, interest restriction or repetitive behaviors were not prominent. As one of the accompanying symptoms was staring into space suggesting absence seizure, she was transferred to the neurology department. On bedside examination, language comprehension was impaired but otherwise, no focal neurologic deficit was seen. The cerebrospinal fluid showed a normal white blood cell count of  $1/\text{mm}^3$  and mildly elevated protein of  $52.0\text{mg/dL}$ . Brain magnetic resonance imaging was normal, and all autoantibody test was negative. However, in cancer screening, a  $3.5\text{cm}$  enhancing mass in the liver was found, suggesting focal nodular hyperplasia or adenoma. We decided on empirical immunotherapy for this patient because she could be diagnosed with probable autoimmune encephalitis. With the sequential immunotherapy, she fully recovered to a modified Rankin Scale score of 0 and a Clinical Assessment Scale for Autoimmune encephalitis score of 0 and joined a social workspace as a bakery staff. **Discussion:** This case implies that autism-like features might be presented as key symptoms of pediatric autoimmune encephalitis. Accordingly, young patients with autism-like symptoms should be examined and explored enough, for they could have a reversible treatment option. Since this is just one case that showed an effect of immune suppression in autism-like social behavior, this diagnostic and therapeutic approach should not be applied to all autism patients. A meticulous setup of criteria for the autism subcategory and a well-designed randomized study should redefine a novel disease category and will provide a better option to resolve the disability of the under-diagnosed patient population.

**M111. Autoimmune Brainstem Encephalitis: Serological and Clinical Associations, and Predictors of Outcome**  
**Michael Gilligan, MB BCh BAO.** Mayo Clinic, Rochester, MN, USA.

**Introduction:** Autoimmune brainstem encephalitis is increasingly recognized. We describe the demographic, serologic and clinical features of autoimmune brainstem encephalitis. **Methods:** Medical records of patients receiving autoimmune brainstem encephalitis diagnoses at Mayo Clinic, Minnesota (January 1<sup>st</sup> 2006-December 31<sup>st</sup> 2022) were reviewed, and patient subgroups compared. **Results:** Fifty-seven patients (36 male) were included. The median symptom-onset age was 49 years (range, 2-75). Symptom onset was subacute ( $< 3$  months) in 72%. Presenting features were  $\geq 1$ : diplopia (75%), ataxia (72%), vestibulocochlear symptoms (63%),

dysarthria (54%), dysphagia (46%), sleep disorders (23%), facial weakness (14%), nausea/vomiting (12%) and trigeminal symptoms (7%). Altered mental status was uncommon (7%). An encephalitis-pertinent neural antibody biomarker was detected in serum or CSF in 75%. These were KLHL-11 (14 patients), ANNA-2 (anti-Ri, 6), IgLON5 (5), Ma2 (3), ANNA-1 (anti-Hu, 3), MOG (3), high-titer ( $\geq 20$  nmol/L) GAD-65 (3), neurochondrin (2), glycine receptor (2), AGNA-1 (SOX-1, 1), and aquaporin-4 (1). A cancer was identified in 53% of patients: testicular or extratesticular germ cell (12 patients), small cell carcinoma (4), breast adenocarcinoma (4), head/neck squamous cell carcinoma (2), Merkel cell carcinoma (1), gynecologic adenocarcinoma (2), other (5). Male sex was strongly associated with KLHL-11 autoimmunity (14/14 versus 22/43;  $p < 0.001$ ) whereas female sex was associated with ANNA-2 (5/6 versus 16/51;  $p = 0.02$ ). Paraneoplastic cases were older at onset (median age 53 versus 43;  $p = 0.01$ ). Although vestibulocochlear symptoms were common in the entire cohort (36/57), hearing loss was specifically associated with KLHL-11 autoimmunity (7/14 versus 3/43;  $p = 0.001$ ). All patients with IgLON-5 autoimmunity had insidious onset (5/5 versus 11/52;  $p = 0.001$ ) and had sleep disorders (5/5 versus 8/52;  $p < 0.001$ ). Patients with MOGAD were young at symptom onset (median onset-age, 3 years, versus 49 for the entire cohort). Among paraneoplastic brainstem encephalitis cases, testicular germ cell tumors strongly associated with KLHL-11 autoimmunity (8/9 versus 4/21;  $p < 0.001$ ) whereas breast adenocarcinoma uniquely associated with ANNA-2 autoimmunity. Factors associated with poor outcome (mRS  $> 2$ ) were: presence of ataxia (28/33 versus 13/24;  $p = 0.02$ ), inflammatory CSF (pleocytosis, raised IgG index, CSF-exclusive oligoclonal bands; 21/33 versus 7/24;  $p = 0.02$ ) and the presence of brainstem/cerebellar lesion on MRI (23/33 versus 5/24;  $p < 0.001$ ). **Conclusions:** Antibody biomarkers in autoimmune brainstem encephalitis are predictive of some phenotypic and cancer-risk differences. Over half of cases are paraneoplastic. Co-existent ataxia and inflammatory-appearing MRI and CSF are associated with worse outcome.

**M112. Biomarkers of Inflammation and Neuronal and Glial Injury in Leucine-Rich Glioma Inactivated-1 (LGI1) Autoimmune Encephalitis**

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**Objective:** Compare the concentrations of plasma-based biomarkers obtained from leucine-rich glioma inactivated 1 (LGI1) autoimmune encephalitis (AIE) patients to non-inflammatory controls (HC). **Background:** Markers of neuronal and glial injury have been adapted for monitoring disease activity and injury in individuals with neurodegenerative and neuroinflammatory disorders. There are currently no biomarkers that inform on disease activity, prognosis, and treatment in LGI1-AIE. **Design/Methods:** Plasma concentrations

of neurofilament light (NFL), glial fibrillary acidic protein (GFAP), chemokine ligand 13 (CXCL-13), and cytokine levels (INF $\gamma$ , IL-1B, IL-4, IL-5, IL-6, IL-8, IL-10, IL-12p70, IL-22 and TNF $\alpha$ ) in LGI1-AIE and HCs (mostly headache) using Quanterix SIMOA were longitudinally evaluated and correlated with clinical outcome measures using mixed model regression. **Results:** Thirteen LGI1-AIE patients (mean age 63.7, 69.2% male), eight of whom have longitudinal collections, and eleven HCs (mean age 44.6, 54.5% male) were analyzed. Cross-sectional analysis of 48 samples of LGI1-AIE shows a geometric mean plasma concentrations of NFL, GFAP, and UCH-L1 were elevated in LGI1-AIE patients compared to HCs (n=48 LGI1; 11 HC): NFL (10.0 v. 478 pg/ml,  $p = 0.0019$ ), GFAP (77.58 v. 30.31 pg/ml,  $p < 0.0001$ ), UCH-L1 (10.30 v. 2.95 pg/mL,  $p = 0.0082$ ). Plasma tau levels were not different (2.69 v. 2.84 pg/mL,  $p = 0.74$ ). In the LGI1-AIE patients longitudinally, NFL, GFAP, and UCH-L1 decreased, while tau increased, in the 3-year period following disease initiation. Geometric mean CXCL13 (39.90 pg/mL) levels in LGI1-AIE decreased 39.2% per year of disease duration ( $p = 0.010$ ). LGI1-AIE hIL1B (0.05 pg/mL), hIL6 (1.24 pg/mL), and hIL10 (0.84 pg/mL) trended higher compared to hIL1B (0.027 pg/mL,  $p = 0.067$ ), hIL6 (0.55 pg/mL,  $p = 0.064$ ), and hIL10 (0.38 pg/mL,  $p = 0.012$ ) levels in HC. Additional analysis on LGI1-AIE patients is ongoing including evaluation of time-of-flight mass cytometry (CyTOF) to evaluate B cell activation. **Conclusions:** Preliminary results show plasma NFL, GFAP, UCHL-1, CXCL-13, hIL1B, hIL6, and hIL10 levels are elevated in LGI1-AIE at the time of their disease onset and decrease with treatment.

#### M114. Botulinum Toxin Could Be Helpful as an Adjunct Therapy in Stiff Person Syndrome

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**Background:** Stiff person syndrome (SPS) is a disabling immune-mediated disorder that most commonly causes progressive rigidity and painful spasms. Botulinum toxin (BoNT) has anecdotally improved symptoms in people with SPS, though evidence is scarce regarding efficacy, patterns of muscle groups targeted, and whether certain patient or disease characteristics correlate with response to therapy. **Objective:** To characterize the distribution, number and frequency of muscles injected, dosages used, and clinical response to BoNT in people with SPS. **Methods:** We conducted a retrospective analysis of seropositive SPS patients who received 3 or more BoNT treatments by a single injector (EM) at Johns Hopkins between August 2018 and January 2023. The following was recorded and compared between visits 1 and 3: muscles injected, BoNT brand, units per muscle, patient-reported response to treatment (Likert scale 1-5; higher=better response), time to effect, side effects, systemic therapies used, and timed 25-foot walk. **Results:** Twenty SPS patients (19 anti-GAD-65, 1 amphiphysin) were included, with mean age  $50.7 \pm 8.3$  years. The majority were female (65%), white (70%), and on immune therapies (95%). All

patients were on other symptomatic treatments at the time of BoNT treatments. Common patterns of injected muscles included cranio-cervical, thoracic/back, hip/pelvis, and distal lower extremity muscle groups, with median total doses injected being 257.5 units (IQR 188.8-300.0) at visit 1 and 447.5 units (IQR 292.5-600.0) at visit 3. Muscles were selected based on patient-specific phenomenological presentation. Doses up to 795 units were used without adverse effects. Nineteen patients reported improvement in stiffness and/or spasms after the first injection with effect lasting a median of 9 weeks. Median patient-reported Likert rating after the first visit was 4 (IQR 3.5-4.5) and after the third visit was 5 (IQR 4.5-5). Median change in timed 25-foot walk between visits 1 and 3 was -0.54 seconds (IQR -2.87-1.10). Other symptomatic therapy use decreased in 4 patients and increased in 10 patients. Three patients reported transiently increased spasms for 1 week following injections, which improved with repeated injections, but overall injections were well-tolerated. **Conclusions:** Based on this qualitative retrospective study, BoNT may be an effective adjunctive symptomatic therapy for people with SPS with targeted muscle selection based on specific phenomenology. However, randomized placebo-controlled trials are required to establish class I evidence for use of BoNT in SPS.

#### M115. Chronic Progressive Presentation in a Case of Neuromyelitis Optica Spectrum Disorder

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A 65-year-old woman who presented with several years of progressive balance and gait disturbance. The symptoms initially started in her 40s (in the late 1990s). She was placed on interferon-beta-1a for a few years but subsequently discontinued it. She had progressive weakness in legs more than arms in her disease course and has been ambulating with walker. She had no history of optic neuritis. She presented first to our clinic in 2019. Her initial MRI of the brain in 2013 demonstrated extensive regions of non-enhancing T2 prolongation within the supratentorial, infratentorial brain and brainstem. The lesions demonstrated an increase in signal intensity and extent with repeat MRI in 2019. She had no intrinsic spinal cord lesions. OCT showed bilateral optic nerve thinning. In our workup, for evaluation of white matter disorder, her Hepatitis B, C, HIV, Syphilis, Lyme, Hypercoagulability panel, MOG, SSa and SSb, ANA, ANCA, lactic acid, urine organic acids, plasma amino acids, very long chain fatty acids, lysosomal enzymes were all unremarkable. On genetic testing, she was found to have a few variants of unclear significance. Her serum aquaporin-4 IgG antibody was positive by CBA ( $>1:2560$ ) and the diagnosis of Neuromyelitis-Optica-Spectrum-Disorder (NMOSD) was made. She started on Eculizumab in 2020 but developed post infusion syndrome and was given a drug holiday in January 2021. She was switched to Inebilizumab in May 2021 and her symptoms have stabilized. MRI neuro imaging has also remained stable. Discussion: NMOSD is a CNS autoimmune disorder that primarily presents acutely with myelitis, optic neuritis, area postrema syndrome or other CNS presentations. Antibody against



AQP4 in the serum, by cell-based-assay is a highly specific diagnostic biomarker. In a paper by Wingerchuk(2007) there is a report of secondary progression in less than 2% of NMOSD patients as opposed to patients with multiple sclerosis where about a third could be at risk of secondary progression. Progression is predicted typically by spinal cord lesions which our patient did not have. Our hypothesis is that her white matter lesions in the brain progressed due to delayed diagnosis and resulted in a progressive course. Her atypical presentation with progression from the start resulted in delayed diagnosis. This case underlines the importance of considering unusual presentations of NMOSD in the differential diagnosis of white matter disease so that there is an opportunity for early intervention and treatment.

**M117. Diencephalon Involvement as a Presenting Feature of Neuromyelitis Optica Spectrum Disorder in a Teenager**  
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**Background:** Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory demyelinating disorder, characterized by the presence of IgG antibodies to aquaporin-4 (AQP4) dominant water channel found mainly in the blood-brain barrier. NMOSD typically presents with involvement of spinal cord, optic nerve, area postrema but can also involve other areas such as brainstem, diencephalon and cerebral hemispheres. Although hypothalamic lesions are observed infrequently in patients with AQP4 antibodies, the presentation remains wide and hence poses a diagnostic challenge clinically. **Case Report:** We report a case of a 16-year-old female who presented with hypersomnolence for a month. She experienced cataplexic attacks multiple times a day, causing her to sleep for over 10 hours daily leading to initial suspicion of narcolepsy. She also had noted loss of appetite and weight loss. She then had difficulty walking in the week prior to presentation. CNS examination revealed weakness in all limbs and diminished deep-tendon-reflexes bilaterally. She was also noted to have hyperthermia and heart-rate fluctuations with labs showing low serum cortisol and TSH. MRI-brain affirmed hypothalamic rim enhancement and T2 hyperintensities in the peri-ependymal area. MRI of the cervical spine showed longitudinally extensive lesion characteristic for NMOSD. Visual Evoked Potential showed prolonged latency in bilateral optic nerves. Chest-X-ray did not reveal hilar lymphadenopathy. CSF analysis showed lymphocytic pleocytosis. Serum autoimmune workup disclosed strongly positive serum anti-NMO-IgG-antibodies. She was diagnosed with NMOSD presenting with diencephalic syndrome and started on IV methylprednisolone pulse therapy. She had minimal improvement with subsequent development of new right lower limb paralysis. She underwent plasmapheresis which resulted in a drastic improvement in her weakness and sensorium. She was initiated on a disease-modifying agent while undergoing physiotherapy but was lost to follow-up. **Discussion:** NMOSD can less commonly involve other areas of the brain, including brainstem and cerebrum, including the hypothalamic involvement. Our patient presented

with narcolepsy like features, autonomic dysfunction, hypopituitarism, weight loss from bilateral hypothalamic lesions and leg weakness from concomitant transverse myelitis as the first presentation of NMOSD. Other differential diagnoses include Sarcoidosis and midline Germinomas especially in this young patient. Testing for Serum AQP4 antibodies by cell based assay is highly specific and should be utilized early in the diagnostic work up. Combination of IV steroids with Plasma exchange results in improved outcomes when compared to either individual treatment.

**M118. Dimethyl Fumarate Modulates Brain Oxidative Stress Immunodeficiency Virus (SIV)-Infected Rhesus Macaques: Potential Repurposing for HIV Neuroprotection**

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**Introduction:** Dimethyl fumarate (DMF) is an antioxidant/anti-inflammatory drug approved for multiple sclerosis treatment. DMF's active in vivo metabolite, monomethyl fumarate (MMF), has high brain penetration. We used the rhesus macaque simian immunodeficiency virus (SIV) infection model of HIV/AIDS to determine the neuroprotective potential of DMF. We hypothesized that DMF induces brain antioxidant enzyme expression and reduces oxidative stress and neuroinflammation in SIV-infection. **Methods:** We studied twelve macaques; each was immunologically depleted of CD8+ T lymphocytes to accelerate immune deficiency and AIDS pathogenesis. Ten animals were infected with SIV and six received oral DMF from day 7 prior to SIV infection and to day of necropsy (terminal AIDS, up to 111 days). Levels of SIV expression and neurofilament light chain (NFL) were quantified in plasma and cerebrospinal fluid. Protein expression was analyzed in 11 brain regions by Western blot. Quantitative immunohistochemistry determined the levels of protein and DNA oxidation, expression of antioxidant enzymes, expression of the lipid peroxidation enzyme, lysophosphatidylcholine acyltransferase 3 (LPCAT3), and neuroinflammation markers. Optical redox imaging (ORI) of fixed tissue slices quantified oxidized flavoproteins containing flavin adenine dinucleotide (Fp) and reduced nicotinamide adenine dinucleotide (NADH). **Results:** DMF treatment associated with i) increased expression of antioxidant enzymes; ii) reduced protein and DNA oxidation; iii) a more reduced redox state; and iv) increased LPCAT3 enzyme expression. No effects on neuroinflammatory markers, neuronal markers, SIV replication levels, or small intestine macrophage numbers were observed. No adverse effects on blood hematological counts were observed. Independent of DMF treatment, ORI analysis indicated higher metabolic activity in gray matter vs white matter in all brain regions examined (frontal cortex, brain stem, parietal cortex, thalamus, caudate nucleus). Moreover, DMF treatment associated with a reduced redox state (reduced oxidative stress) in both gray and white matter of the frontal cortex, consistent with reduced protein and DNA oxidation results.

**Conclusions:** In SIV-infected immune deficient rhesus macaques, the dimethyl fumarate (DMF) effects of increasing brain antioxidant enzyme expression and reducing oxidation of protein and DNA, without altering inflammatory responses, inducing brain injury, or altering SIV infection levels suggests that DMF can safely limit CNS oxidative stress in HIV-infected individuals. DMF treatment may have protective effects in different brain regions regardless of the level of regional metabolic activity. We propose that DMF could serve as an adjunct to anti-retroviral therapy (ART) for neuroprotection against HIV-associated brain injury.

#### M119. Do TNF $\alpha$ , IL-1 $\alpha$ , and C1q Promote Cortical Oligodendrocyte Regeneration after Demyelination?

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Multiple sclerosis is a chronic inflammatory disorder characterized by loss of oligodendrocytes and myelin in the CNS. There are no treatments that promote oligodendrocyte regeneration and lesion repair - an unmet clinical need. We recently discovered that oligodendrocyte replacement is inefficient in deep cortical regions following cortical demyelination, and that astrocytes persistently upregulate GFAP in the same regions (Orthmann-Murphy *et al.* 2020). We therefore hypothesized that deep cortical reactive astrocytes impair oligodendrocyte regeneration in the cortex. Previous studies found that TNF $\alpha$ , IL-1 $\alpha$ , and C1q ("TIC") induce a specific type of reactive astrocyte that releases substances toxic to oligodendrocytes *in vitro* (Liddelaw *et al.* 2017). In this study, we test whether genetic ablation of TIC molecules prevents persistent deep cortical reactive astrocyte upregulation of GFAP and improves oligodendrocyte regeneration after cuprizone-induced demyelination. **Methods:** Adult WT, or transgenic mice lacking TIC (TIC-KO mice) were placed on a diet supplemented with 0.2% cuprizone (or sham) for a period of 4 weeks to induce demyelination, followed by up to 5 weeks of recovery (remyelination). To determine changes in astrocyte or oligodendrocyte cell density or reactive marker expression, I performed both *in situ* mRNA labeling and immunolabeling for astrocytes (*Gfap*, *Aldh1l1*, or *Slc1a3* RNA; GFAP protein) and TIC-induced astrocytes (*C3* RNA), and oligodendrocytes (ASPA protein) within the somatosensory cortex. I compared relative expression of markers in superficial (0 - 250  $\mu$ m), middle (250-500  $\mu$ m) and deep cortical regions (500-750  $\mu$ m). **Findings:** In a preliminary analysis, I found that cortical reactive astrocytes upregulate *C3* RNA after cuprizone treatment, in WT, but not TIC-KO, mice. WT and TIC-KO mice have similar GFAP expression dynamics, and GFAP upregulation in deep cortical regions is still observed in TIC-KO mice. In TIC-KO mice, cuprizone-treatment induces oligodendrocyte loss to levels similar to WT. Unexpectedly, at 5 weeks of recovery, TIC-KO mice have significantly fewer oligodendrocytes than WT mice. **Conclusions:** These findings suggest that TIC-induced reactive astrocytes are generated in the cortex following cuprizone-induced demyelination in WT, but not TIC-KO, mice. Unexpectedly, the absence of TIC did not

alter persistent upregulation of GFAP in deep cortical reactive astrocytes and worsened oligodendrocyte regeneration. This suggests that TIC molecules may promote cortical oligodendrocyte regeneration in our model. Future experiments will determine whether TIC (or one of its components) mediates oligodendrocyte regeneration indirectly through reactive astrocytes or directly on the oligodendrocyte lineage.

#### M120. EEG Findings in Patients with Encephalitis of Autoimmune and Infectious Causes

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**Objective:** To characterize EEG findings in patients with encephalitis. **Methods/Design:** All patients with a final diagnosis of encephalitis admitted in university hospitals affiliated with UTH at Houston, admitted in years 2005-2020 were included in this study. Definite antibody positive cases of autoimmune encephalitis (AE) and definite infectious encephalitis (IE) cases that had EEGs were followed. Then we abstracted EEG data during admission of these groups. Clinical data were gathered from patients' EMR. **Results:** 350 patients, 34.8% women, were enrolled, mean age 46.5 years old. Etiology was autoimmune with positive antibodies or biopsy in 9.7%, infectious in 28.5%, and unknown in 61.8%. For 143 patients EEG was performed, 43 were monitored with continuous long-term EEG (cEEG); out of which, 3 belonged to AE group and only one to AI. Routine EEGs consisted 90.6% and 98.2% of EEGs in the AE and AI respectively. Half of records were abnormal in AE and 76% in AI. Status Epilepticus happened in 2.3% of AE patients, and did not occur in AI group. Seizure incidence was similar in both groups. Periodic pattern and epileptiform discharges were noted in 2.3% and 5.8% of AE patients, vs 9.0% and 6% in AI group. Focal slowing was noted in 9.3% and 14.2% of records in AE and AI groups respectively. **Discussion:** In our cohort, EEG findings are not significantly different in Ab-positive AE and infectious encephalitis. More patients in AE group needed cEEG than the IE group. Obtaining cEEG in encephalitis patients who are admitted with a cognitive decline or seizures is important in short-term and long-term treatment planning. As an example, patients with seizures on EEG, even if subclinical, should have follow up with epilepsy clinic.

#### M121. Exosome Connexin43-Truncated Isoforms and Bound RNAs Distinctively Associated with Multiple Sclerosis and Neuromyelitis Optica Spectrum Disorder

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Fukuoka, International University of Health and Welfare, Okawa, Japan.

**Objective:** Astroglial connexin (Cx)43 forming gap junction channels is lost in acute multiple sclerosis (MS) and neuro-myelitis optica spectrum disorder (NMOSD) lesions but increased in chronic MS lesions. Experimental autoimmune encephalomyelitis (EAE) showed similar Cx43 alterations to MS. *GJA1* coding Cx43 (43k) produces truncated isoforms (29k/26k/11k) without channel function, which bind and transmit RNA, upon stress. 43k and truncated isoforms are expressed in glial exosomes (Exs). We aimed to characterize Ex-changes associated with MS and NMOSD. **Methods:** Serum Exs extracted by precipitation from 48 MS [34 relapsing remitting MS, 14 secondary progressive MS (SPMS)], 35 NMOSD (aquaporin 4-IgG-positive in 27), 20 other inflammatory neurologic diseases (OIND), and 17 healthy controls (HC) were subjected to quantitative western blots for CD63 (Ex marker) and Cx43. Ex RNA was determined by next generation sequencing in the selected cases. Serum Exs from wild type (WT) and astroglia-specific *Cx43*-inducible conditional knockout (*Cx43* icKO: *Cx43<sup>fl/fl</sup>;GLAST<sup>CreERT2</sup>*) mice were also studied. **Results:** Ex CD63, 43k and 26k did not significantly differ among the subjects. 29k was higher in MS than NMOSD, OIND, and HC ( $p<0.001$ ), and higher in NMOSD than OIND and HC ( $p<0.01$ ). 11k was less in NMOSD than MS and HC ( $p<0.0001$ ). In MS, 29k was highest in SPMS; SP>remission>relapse>HC ( $p<0.001$ ) while in NMOSD, 29k was increased at relapse compared with HC ( $p<0.01$ ) but decreased in remission. Compared with HC, SPMS showed significantly up-regulated Ex miR301a, miR324, miR21, miR191, let-7e, let-7d, let-7f-1 and let-7f-2 but NMOSD had no changes. By contrast, Ex long intergenic non-coding RNA (lincRNA)01482, 01858, 01560, 02288, 01814, 01840, 0082, and 02071, which act as miR sponges blocking miR's functions, were significantly up-regulated in NMOSD but not in SPMS compared with HC. WT mice showed increase of Ex *GJA1*-29k upon EAE compared with the pre-immunized state; more pronounced in chronic than acute phase. By contrast, *Cx43* icKO mice showed attenuated acute and chronic EAE compared with WT mice, and had no and attenuated increase of 29k at acute and chronic phases, respectively. Splenic regulatory T cells and IL10 production were significantly greater in *Cx43* icKO than WT mice upon EAE. **Conclusion:** Increased circulating Ex *GJA1*-29k, partly derived from astroglia, is associated with SPMS and NMOSD relapse reflecting progressive astrogliosis and acute astrocytopathy, respectively, and may propagate distinct pro-inflammatory messages between MS and NMOSD via bound miRs/lincRNAs.

## M122. Experience and Outcomes of an Online Mindfulness-Based Stress Reduction (MBSR) Pilot Program for People with Multiple Sclerosis

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**Background:** Multiple Sclerosis (MS) impacts an individual's quality of life due to physical and cognitive impairment leading to fatigue, depression, and anxiety. Mindfulness-Based Stress Reduction (MBSR) is an 8-week evidence-based approach that helps individuals reduce stress and improve well-being by increasing self-awareness. Concord Hospital is a community hospital in the Northeastern US that began offering an online MBSR course designed for people with MS. Few studies have investigated the effects of MBSR on the MS population, and the outcomes of participating in MBSR online.

**Objective:** To investigate the feasibility, acceptability, utility, and pre-/post-outcomes of MBSR on MS patients enrolled in a pilot online MBSR program **Methods:** We used a pre-post design to follow 8 prospective cohorts of 5-15 adults with MS enrolled in the online MBSR pilot at Concord Hospital. The program was conducted over Zoom, and an interactive online HIPAA-compliant platform was used to collect Patient Reported Outcomes (PROs) through pre- and post-program surveys: PHQ-9; PROMIS Cognitive Function (short form); PROMIS Fatigue-MS (short form); and Wasson Health Confidence (2-item). Paired t-tests were used to assess for a significant difference in pre- vs post-program mean survey scores. A post-program feedback survey was also collected to qualitatively evaluate participant experience. This study was approved as a minimal-risk research study by the Concord Hospital IRB. **Results:** Seventy-seven people with MS participated across the cohorts (2021-2023) with a program completion rate of 81%. Pre- and post-program survey completion rates were 73% and 53%, respectively. Mean scores of PHQ9 pre- vs post-program show significant improvement in depressive symptoms (6.9 vs 4.6,  $p=0.01$ ). Likewise, mean PROMIS Cognitive Function scores pre- vs post-program show a significant increase in cognitive function (16.7 vs 22.4,  $p<0.01$ ). Mean PROMIS Fatigue scores pre- vs post-program show a significant decrease in fatigue (59.3 vs 55.3,  $p<0.05$ ), and mean Wasson Health Confidence scores pre- vs post-program show a significant increase in health confidence (13.6 vs 15.3,  $p<0.01$ ). Post-program feedback surveys revealed perceived feasibility, acceptability, and utility of the online MBSR program. **Conclusion:** The online MBSR pilot demonstrated feasibility, acceptability, and utility amongst participants. Analyses of PRO measures show statistically significant improvement in depressive symptoms, cognitive function, self-confidence, and fatigue following program participation. Online MBSR has the potential to improve patient well-being and should be considered in addition to standard medical treatments for MS.

## M124. International Panel Criteria for the Diagnosis of MOG-Antibody Associated Disease

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**Background:** The development of cell-based assays (CBAs) for the detection of antibodies to myelin oligodendrocyte glycoprotein (MOG) has enabled identification of pediatric and adult patients with monophasic or relapsing CNS demyelination with clinical features, therapeutic responses and outcomes distinct from multiple sclerosis (MS) and aquaporin-4-seropositive neuromyelitis optica spectrum disorder (NMOSD). **Aim:** To propose international consensus criteria for the diagnosis of MOG-antibody associated disease (MOGAD). **Methods:** An international panel of 23 pediatric and adult neurologists, neuroimmunologists, and researchers from 13 countries was convened. Between March 2020 and June 2022 and over the course of 70 one-hour virtual meetings, the panel conducted a review of 378 unique manuscripts relative to the features of MOGAD and applied a structured consensus process to define a set of criteria for MOGAD diagnosis. Comprehensive tabular comparisons of the clinical and MRI features of the optic nerve, spinal cord and brain involvement in MOGAD, MS and AQP4-seropositive NMOSD, a detailed delineation of other differential diagnoses, and a diagrammatic representation of MOG-IgG assay methodologies were also created. **Results:** The proposed criteria include (A) presentation with a core clinical attack (acute disseminated encephalomyelitis, optic neuritis, myelitis, cerebral cortical encephalitis, cerebral, brainstem or cerebellar presentations); (B) presence of MOG-IgG detected using a live or fixed CBA either with a titer that is clearly positive ( $\geq$  twice doubling dilution of lab cut-off or

$\geq 1:100$ ) or low positive (above cut-off but  $<$  twice doubling dilution or  $\geq 1:10$  but  $< 1:100$ ); (C) If low positive (above cut-off but  $<$  twice doubling dilution or  $> 1:20$  but  $< 1:100$ ), non-titered or if only CSF MOG-IgG was detected then presence of defined, supportive clinical or MRI features are required; and (D) exclusion of a better diagnosis (including MS). Criteria are applicable across the age span. **Conclusions:** The international panel MOGAD criteria will aid in the diagnosis of MOGAD in children and adults and will foster consistency in patients selected for enrolment in MOGAD cohorts and clinical trials. Future studies are needed to validate the criteria performance in a real world setting.

## M126. Investigations of Synaptic Signaling Targets of Human Anti-NMDAR Antibodies

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The most common form of autoimmune encephalitis is associated with antibodies that target N-methyl-D-aspartic acid (NMDA) receptors. NMDARs are glutamate receptors that govern cellular mechanisms of learning and memory, including synaptic long-term potentiation (LTP), through induction of post-synaptic signaling cascades and regulation of synaptic protein synthesis. In anti-NMDAR encephalitis, antibody binding to the obligate GluN1 subunit of NMDARs leads to crosslinking and internalization of NMDARs. The molecular mechanisms that lead to the diverse neuropsychiatric symptoms associated with anti-NMDAR encephalitis remain incompletely defined but are hypothesized to involve synaptic dysfunction. We previously demonstrated that human GluN1 monoclonal antibodies (GluN1 hMAbs) rapidly localize to and regulate synaptic NMDAR function at native synapses of primary neurons. Here, we sought to explore signaling targets of GluN1 hMAbs in primary neurons using biochemistry and subcellular fractionation. We utilized unbiased quantitative phosphoproteomics to evaluate signaling pathways in membrane fractions from primary cortical neurons. GluN1 hMAbs altered global membrane protein phosphorylation states associated with numerous biological processes relevant to neuronal structure and function. These data suggest that NMDAR antibodies alter neuronal signaling networks. In separate experiments, we defined activity-dependent regulation of local RNA content in the postsynaptic density (PSD) fractions of primary neurons. Pharmacological manipulation of autophagy resulted in local synaptic RNA regulation. Thus, autophagy may contribute to synaptic plasticity via regulation of local RNA metabolism. These results raise the question of whether the effects of GluN1 hMAbs impact synaptic protein homeostasis involving autophagy and local RNA metabolism at the PSD. Future studies will investigate the regulation of autophagy and RNA metabolism in the underlying pathophysiology of anti-NMDAR encephalitis. These studies may

contribute to the identification of potential therapeutic targets for novel therapies for patients with anti-NMDAR encephalitis and disorders involving antibodies targeting cell surface antigens.

#### **M127. Late Onset Rasmussen Encephalitis - Age is Just a Number!**

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**Background:** Rasmussen Encephalitis (RE) is a chronic, inflammatory neurological disorder that is characterized by progressive unilateral hemispheric atrophy resulting in refractory epilepsy, EPC, neurocognitive decline and focal neurologic deficits. The underlying pathophysiology is believed to be immune-mediated. RE classically has an onset before age 6; however late-onset RE (LoRE) has been described in about 10% of all cases. We describe here a case of LoRE in a 52-year-old male. **Case Presentation:** Patient was hospitalized after being found down, encephalopathic and incontinent of stool after a suspected seizure. MRI brain showed T2/FLAIR hyperintensity in the right temporo-parieto-occipital region with associated gyriform enhancement. Work-up for neoplastic and inflammatory conditions was unremarkable. Initial concern was for malignancy; however, repeat MRIs at 5 and 12 months showed resolution of the gyriform enhancement with persistent T2/FLAIR hyperintensities and progressive atrophy in the right temporo-parieto-occipital region, suggestive of an inflammatory process. Serial neurological exams revealed no focal neurologic deficits. Neuropsychological assessment identified deficits in spatial processing, nonverbal reasoning, and memory, consistent with right hemispheric dysfunction. These results in conjunction with suspected seizure and unihemispheric atrophy raised concern for LoRE though were not sufficient to fulfill RE diagnostic criteria. Therefore, brain biopsy was performed that revealed CD8+ T-cell predominant infiltration with microglial activation, reactive astrocytosis and focal neuronal loss, satisfying the histological aspect of the Part -B diagnostic criteria of RE. **Discussion:** Classical RE is characterized by three phases: a *prodromal* phase with intermediate frequency of focal seizures and minimal neurologic deficits, an *acute phase* with more frequent seizures, hemispheric atrophy with cortical deficits, and a *residual* phase with fewer seizures, severe neurologic deficits and marked hemiatrophy. Compared to classical RE, symptoms in LoRE evolve more slowly with delayed onset of neurocognitive deficits, as was the case with our patient. Given the slower evolution and delayed deficits, early diagnosis of LoRE is challenging; however, most will ultimately fulfill part B of the childhood-onset RE diagnostic criteria. Available evidence suggests that patients with LoRE have a better response to immunomodulatory therapy; however, long-term outcomes are variable. **Conclusion:** LoRE is a rare, often severe neurological disorder with a variable presentation than classical RE. Early diagnosis and treatment are essential to improve outcomes. Unfortunately, the slow evolution and delayed onset of deficits in LoRE often preclude early diagnosis using childhood-onset RE diagnostic criteria, highlighting the need for revised, LoRE specific criteria.

#### **M128. Longitudinal FDG-PET/CT Changes in People with Stiff Person Syndrome Spectrum Disorders**

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**Background:** Stiff person spectrum disorders (SPSDs) are immune-mediated processes that include multiple clinical phenotypes. SPDs are typically associated with autoantibodies against glutamate acid decarboxylase 65 (anti-GAD65), amphiphysin, and/or glycine receptor (anti-GlyR), and are rarely paraneoplastic in origin. A fluorodeoxyglucose positron emission tomography ( $^{18}\text{F}$ FDG-PET/CT) scan is frequently obtained as part of the malignancy work-up in patients with SPDs, and abnormal metabolic activity unrelated to malignancy has been shown to occur in both the brain and skeletal muscles of patients with SPD. However, it is unclear if such findings persist or change over time. **Objective:** To describe changes in  $^{18}\text{F}$ FDG-PET/CT findings in the brain and muscles of individuals with SPDs longitudinally. **Methods:** A retrospective study was performed of patients with SPDs who were seen at Johns Hopkins SPS Center from 2009 to March 2023, with at least two  $^{18}\text{F}$ FDG-PET/CT scans of the brain and body. Qualitative data was extracted from clinical radiology reports and semi-quantitative data was extracted for dedicated brain  $^{18}\text{F}$ FDG-PET/CT scans using NeuroQ<sup>TM</sup>, a commercially-available software program that calculates Z-scores of 47 brain regions of interest compared to healthy controls. Patient clinical characteristics, including serology, clinical presentation, physical exam findings, and immune and systemic therapies will be described along with  $^{18}\text{F}$ FDG-PET/CT results at two or more time points. **Results:** Fifteen patients were included with a mean age  $51.3 \pm 15.9$  years at time of SPD symptom onset. Nine (60.0%) were female, 8 (53.3%) were Caucasian and all had one or more autoantibodies detected on serology (12 anti-GAD65, 4 anti-GlyR, 1 anti-amphiphysin). Phenotypes included SPS-plus (8), classic SPS (5), predominant cerebellar ataxia (1), and progressive encephalomyelitis with rigidity and myoclonus (1). Median duration from symptom onset to initial  $^{18}\text{F}$ FDG-PET/CT was 1.03 years (IQR 1.34-2.11), and median time between first and second  $^{18}\text{F}$ FDG-PET/CT was 1.04 years (IQR 0.56-1.46). **Conclusions:** We will present qualitative and semi-quantitative  $^{18}\text{F}$ FDG-PET/CT data for patients with SPD to determine how brain and skeletal muscle metabolism changes over time. For any changes in metabolism observed over time, we will do further analyses to determine if any clinical characteristics, including therapies utilized, correlate with  $^{18}\text{F}$ FDG-PET/CT findings.

#### **M129. Mendelian Randomization of Inflammatory Markers to Show Their Causal Role in Multiple Sclerosis Pathophysiology**

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**Intro:** While observational studies can be limited by sample size and confounding variables, Mendelian Randomization (MR) is an analytic tool that uses genetic variation as a natural experiment to investigate causal relationships between exposures and outcomes in observational data. Our study explores the association between well-known serum inflammatory markers and Multiple Sclerosis (MS). Observational studies have revealed associations between several serum markers and MS, but there is little known about causal relationships. We aim to elucidate the causal association between MS and inflammatory markers using 2 sample MR. **Methods:** We developed genetic instruments for 134 inflammatory markers by mapping them to a genome wide association study (GWAS) that included 47,429 subjects with MS and 68,374 controls. Our inflammatory markers were selected based on literature studies of common serum inflammatory biomarkers in a variety of disease processes, as well as availability of data that could be used for genetic instruments. We employed Wald ratio and inverse-variance weighted MR. Weighted median and weighted mode methods were used for sensitivity analyses. **Results:** We found that 7 inflammatory markers were nominally associated with MS ( $p < 0.05$ ). After applying a false discovery rate ( $FDR < 0.05$ ), an analytic tool for multiple experiments that identifies significant results while maintaining a low false positive rate, we found that 2 markers remained significant and were positively associated with MS ( $p < 0.05$ ): IL-6 and TLR-4. **Discussion:** Multiple studies have shown that serum levels of IL-6 are elevated in patients with MS, and our results show that this relationship is indeed causal. Regarding TLR-4, the literature does not agree on its importance in MS pathophysiology, yet our results showing causation suggest there is more to be understood about TLR-4. Observational studies have shown that d-dimer, homocysteine, hs-CRP, IFN- $\gamma$ , and TNF- $\alpha$  are positively correlated with MS pathophysiology; our results show no causative relationship. IL-17 and ESR have also shown correlational significance but were not included in our study, highlighting the need for further investigation using genetic instruments. **Conclusion:** This study highlights IL-6 and TLR-4 as causal inflammatory markers in MS pathophysiology. Additionally, we reveal key differences between observational and genetic studies. As many patients with MS still do not have a robust response to current treatments, MR may help to augment our understanding of the disease process and guide future therapies.

#### **M130. Misdiagnosis of Atypical Presentations of Multiple Sclerosis: Lessons from the Penn White Matter Disorders Adult Neurogenetics Clinic**

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**Background:** Misdiagnosis of multiple sclerosis (MS) can result in negative neurologic outcomes and patient experience. Adult-onset inherited leukoencephalopathies (iLE) can present similarly to MS. Due to the rarity and heterogeneous presentation of iLE, and inconsistent access to genetic testing, iLEs are typically not considered in the MS differential

diagnosis. **Objective:** To determine the rate of iLE diagnoses in patients with white matter disease and some clinical MS features, who were referred for neurogenetics evaluation. **Methods:** We considered patients to have 'atypical MS' if they reported an MS diagnosis or were given an MS diagnosis code (G35 ICD-10) and were referred for neurogenetics evaluation to Penn between 2015-2022. Charts were retrospectively reviewed to determine whether patients met 2017 McDonald Criteria for relapsing-remitting MS (RRMS) or primary progressive MS (PPMS) based on available clinical, laboratory, and radiographic data. Genetic testing data was also collected. **Results:** Twenty-nine patients had a presumed diagnosis of RRMS and 32 patients were diagnosed with PPMS. In a preliminary retrospective evaluation, only ~35% (21/61) patients met diagnostic criteria for MS. There was insufficient data to assess diagnostic criteria in 6 patients. Oligoclonal bands were present in the spinal fluid in ~83% of patients meeting diagnostic criteria (15/18) and ~22% of those not meeting criteria (5/23). Genetic testing included: panel testing (N=41), whole exome with reflex mitochondrial sequencing (N=20), clinical (N=11) and research (N=3) whole genome sequencing. Genetic testing was non-diagnostic in most cases. Genetic disorders were identified in 5 patients, and include CADASIL, CARASIL, KIF1A Disorder, Spastic Paraplegia Type 7, and MERRF-like syndrome. Over 40% of 'atypical MS' patients (25/61) were ultimately given an alternative diagnosis after further diagnostic evaluation, including undifferentiated myelopathy or neuromyelitis optica. **Conclusions and Future Directions:** Misdiagnosis was high in a cohort of patients with presumed atypical MS. Genetic testing to-date yielded a diagnosis in only 5 cases, but more than half of patients have not yet had whole exome or genome sequencing. The iLEs identified included inherited vascular disorders, hereditary spastic paraplegia and mitochondrial disorders, as well as a neurodevelopmental disorder (KIF1A). We will next determine which clinical features of the 'atypical MS' cohort align with diagnosis of genetic or acquired disorders. We will continue to pursue whole exome or genome sequencing in cases where this was not already done.

#### **M131. Neurological Autoimmunity in Patients with Non-Pulmonary Neuroendocrine Tumors: Clinical Manifestations and Neural Autoantibody Profiles**

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**Objective:** To describe the clinical phenotypes and neural antibody profiles of patients with paraneoplastic neurological syndromes (PNS) associated with neuroendocrine tumors (NETs), other than small-cell lung cancer. **Background:** PNS are manifestations of anti-tumor immune responses. Neural autoantibodies detected in the patient's serum or CSF are indicative of the onconeural antigens expressed by the underlying neoplasm. PNS are well-described in the context of small-cell lung cancer but not in other NETs. **Methods:**

We retrospectively identified patients evaluated at Mayo Clinic with a histopathologically-confirmed NETs (excluding lung), neurological manifestations compatible with PNS within five years of cancer diagnosis and neural antibody testing performed at the Mayo Clinic Neuroimmunology Laboratory (1/2008-02/2023). Poor outcome was defined as mRS score  $\geq 3$  at last follow-up, or at least requiring bilateral gait assistance. Dichotomous variables were compared with Fisher's exact test. **Results:** Of 34 identified patients, 44% were female and median age was 68 years at PNS onset (range, 31-85). Patients had NETs of pancreas and other gastrointestinal tract, Merkel cell, prostate, uterus, bladder and of unknown primary. Fifty-three percent had neurological symptoms prior to cancer diagnosis (median 7 months; range, 0-59); PNS followed ICI administration in five. Movement disorders were the most common neurological manifestation (13; cerebellar ataxia, 11) followed by dysautonomia (9), peripheral neuropathy (7), myopathy (4), neuromuscular junction disorder (myasthenia gravis, 3; Lambert-Eaton myasthenic syndrome, 1), cranial neuropathy (4), encephalitis (4) and myelopathy (2). Five patients exhibited both peripheral and central nervous system manifestations. The cancer was extensive at diagnosis in 79% of patients. Fifty-three percent had at least one neural antibody identified (18 patients). Commonest specificities were voltage-gated calcium channel (P/Q-type, 7; N-type, 2), muscle-type acetylcholine receptor (3), anti-neuronal nuclear antibody-type 1 (3) and neuronal intermediate filament (2). Half of 28 patients who received immunosuppressive therapy improved, with 10 having minimal residual symptoms or none. Overall, 15 patients (47%) had unfavorable neurologic outcomes. **Conclusions:** NET-associated PNS are often multifocal; half of the patients respond favorably to immunosuppressant treatment. Neural autoantibody profiles are similar to those found with small-cell lung cancer. The increasing use of immune checkpoint inhibitors (ICI) as first line therapy for NETs raises the likelihood of autoimmune complications in the future.

#### **M132. New Diagnosis of Multiple Sclerosis after Moderna COVID-19 mRNA Vaccination**

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**Background:** Very few reports of new-onset multiple sclerosis (MS) in patients following vaccination with an mRNA COVID-19 vaccine have been published with a majority of these cases reporting likelihood of pre-existing subclinical inflammatory central nervous system (CNS) disease or family history of neurologic or autoimmune conditions prior to vaccination. We present a rare case of new-onset MS in the absence of pre-existing CNS disease after COVID-19 vaccination. **Case Presentation:** A 31-year-old woman with no significant past medical history or family medical history presented to clinic with numbness/tingling over her left-sided mouth and tongue and loss of taste over her left side tongue. Around 2-3 weeks after receiving the first dose of Moderna mRNA COVID -19 vaccine, she began experiencing

headache, difficulty swallowing, blurry vision, left sided mouth numbness and left arm numbness/weakness. Her symptoms gradually improved in the following three months. However, 5 days after receiving her second dose of Moderna vaccine, her symptoms relapsed. She began having difficulty swallowing, left-sided facial numbness/tingling and loss of taste on the left side of the tongue. She was seen in the emergency room for suspicion of bell's palsy. Brain MRI demonstrated numerous supratentorial and infratentorial T2/FLAIR hyperintense lesions, some with contrast enhancement. Cervical/thoracic (C/T) spine MRI showed T2/FLAIR hyperintense lesions in the C/T spinal cord. The cerebral spinal fluid study revealed increased IgG index and oligoclonal bands. Clinical presentation, imaging, and laboratory findings supported the diagnosis of remitting and relapsing MS. She received solumedrol 1000 mg IV daily for 5 days and then she was started on ocrelizumab infusion treatment. Her symptoms had resolved at one month follow-up. Repeat brain and C/T MRI 5 months later demonstrated decreased number and size of lesions in brain and less conspicuous demyelinating plaques in the spine. **Conclusion:** We report an uncommon case of new diagnosis of MS after Moderna COVID-19 mRNA vaccination. There is a temporal relationship between receiving the vaccine and the clinical manifestation of MS. Although association does not always imply causation and vaccination is still the preferred modality to combat the virus, understanding the timing and prevalence of adverse events will help with recognition of this condition after COVID-19 vaccination.

#### **M133. One is Bad, Two is Worse: A Case of Double Antibody Positive Encephalitis as a Harbinger of Malignancy**

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**Objective:** To describe a case report of double antibody positive encephalitis leading to the diagnosis of an underlying malignancy as the paraneoplastic source. **Introduction:** Auto-immune encephalitis are a heterogeneous group of disorders mediated by antibodies against either cell surface antigens, synaptic proteins, or intracellular proteins [1]. An underlying tumor or infection can trigger the immunological response leading to antibody generation, or it may be spontaneous. The co-existence of two distinct positive antibodies in the same patient is rare, and the literature is limited [2]. **Case Report:** We present a 74-year-old woman with history of remote breast and colon cancer (both in remission) who was admitted for progressive short-term memory loss and behavioral changes over 4-6 weeks. Exam findings with impaired visuospatial and executive function as well as delayed recall. MRI brain with contrast demonstrated non-enhancing T2 hyperintensities in the right medial temporal lobe and hippocampus. Lumbar puncture showed a mild CSF lymphocytic pleocytosis (96% lymphocytes, WBC 16/uL) and mildly elevated protein (69 mg/dL), with normal glucose and cytology. CT chest, abdomen, and pelvis (CT C/A/P) showed no evidence of malignancy. The patient was treated with three days

of high-dose steroids (IV solumedrol 1000 mg), followed by an oral steroid taper for suspected autoimmune limbic encephalitis. Serum and CSF autoimmune and paraneoplastic panels were pending upon discharge. Exam with improvement in delayed recall after the completion of high dose steroids. After discharge, her serum autoimmune panel resulted positive for anti-contactin-associated protein-like 2 (CASPR2) antibodies and anti-Hu antibodies (titer: 167 SI, ref <11 SI). Given the presence of two distinct autoimmune antibodies, suspicion was for an underlying malignancy as the cause of a robust immune response producing more than one antibody, rather than a primary autoimmune cause with a single pathogenic antibody. For this reason, a PET scan was ordered despite the negative CT C/A/P, which showed foci of hypermetabolism in the cervix and right inguinal lymph node. Biopsy of the cervix lesion was consistent with vaginal small cell carcinoma. **Conclusion:** While the diagnosis of autoimmune encephalitis should lead to a work-up of underlying malignancy, the co-existence of two distinct autoantibodies should raise a higher suspicion for a paraneoplastic condition eliciting a broader immune response to an underlying tumor; and should prompt a more thorough investigation for an underlying malignancy. **References:** 1) Dalmau J. *N Engl J Med.* 2018 2) Gu Y. *Front Immunol.* 2019

#### M134. Patient Reported Outcome Measures in Autoimmune Encephalitis

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**Objective:** Assess patient reported outcome measures (PROs) in autoimmune encephalitis (AE). **Background:** Objective measures of cognition do not always fully capture the patient's experience of disease symptoms, treatment side effects, functioning and wellbeing. The assessment of PROs may lead to better understanding of AE patients' perception of their ongoing disability and disease. **Methods:** Patients were consented and enrolled into the autoimmune neurological disease registry at the University of Colorado and followed prospectively with longitudinal collection of clinical and cognitive outcome measures and PROs. Surveys completed include the functional assessment of chronic illness therapy-fatigue (FACIT-F) and NeuroQOL for measures of depression, anxiety, sleep disturbance and cognitive function. These surveys were emailed to patients for them to complete remotely every 3 months. Differences between antibody-positive and negative patients were tested with chi-square/Fisher's exact association test for categorical outcomes and with two-sample T-tests for continuous and scale outcomes. **Results:** We cross-sectionally analyzed PRO survey results from 14 patients with a diagnosis of autoimmune encephalitis, including 6 antibody-positive patients (43%) (3 LGI1, 2 glycine receptor [GlyR] and 1 unclassified [UNCA]) and 8 seronegative patients (57%). 71% of survey responders were female with a mean age of 53 years old. Five patients (36%) were not currently on immune therapy, while

9 (64%) were actively receiving treatment. Employment status was surveyed: 3 patients (21%) returned to work full time, 2 (21%) returned part time and 9 (64%) were not currently working (3 were disabled while 6 considered themselves retired but not disabled). For those who were working or disabled, 6 (67%) reported that their neurological illness was a direct cause to cutting back on work hours. While our sample size was small, we did see differences among the antibody-positive and seronegative AE groups. Antibody-positive patients were statistically significantly older on average ( $p < 0.01$ ), more likely to be currently receiving immunotherapy ( $p < 0.05$ ), had higher mean FACIT emotional wellbeing scores ( $p < 0.05$ ), had lower mean scores for NeuroQOL depression and anxiety ( $p < 0.05$ ), and trended towards higher mean cognitive scores ( $p < 0.10$ ). No differences were appreciated with sleep scores. Analysis of 3- and 6-month longitudinal data is ongoing. **Conclusion:** Traditional outcome measures fail to represent the full impact of disease and treatment in AE, and the identification of meaningful PROs may provide a useful tool for ongoing assessment of patient-perceived neurological disability.

#### M135. Povetacicept (ALPN-303), a Potent Dual BAFF/APRIL Antagonist, for the Treatment of Myasthenia Gravis (MG) and Other Antibody-Related Neurological Diseases

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**Objective:** To evaluate povetacicept for pharmacodynamics (PD) and efficacy in a murine experimental autoimmune myasthenia gravis (EAMG) model, and for safety, tolerability, pharmacokinetics (PK), and PD in adult healthy volunteers (HV). **Background:** Povetacicept is an Fc fusion protein of an engineered TACI domain which mediates significantly more potent dual inhibition of APRIL and BAFF than WT TACI-Fc (e.g., telitacicept), which has shown promise in the treatment of MG and other antibody-related neurological diseases. **Design/Methods:** Mice were immunized with acetylcholine receptor (AChR) and treated after disease onset with 200 µg povetacicept or molar-matched doses of Fc control or WT TACI-Fc (telitacicept), twice weekly for 7 total injections. HV were studied in single ascending dose cohorts of intravenous (IV) or subcutaneous (SC) povetacicept or placebo (NCT05034484). Safety, PK, circulating immunoglobulins (Ig), and circulating leukocyte populations were assessed. **Results:** Povetacicept-treated EAMG mice demonstrated significantly lower clinical disease scores over time and at termination than controls. Serum anti-AChR IgG antibody



levels were significantly lower ( $p < 0.05$ ) in the povetacept group vs. both the Fc control and telitacept groups. In adult HV, povetacept has been well tolerated in all cohorts evaluated as single IV or SC doses of up to 960 mg. It exhibits dose-related PK and its expected PD effects, including reductions in circulating Ig and antibody-secreting cells, appear greater than those reported for WT TACI-Fc molecules in HV. To date, there have been no imbalances of infections between placebo and povetacept groups, no serious adverse events, no infusion-related or injection site reactions other than grade 1 injection-site pain, and no adverse trends in safety laboratories. **Conclusions:** Povetacept demonstrates promising efficacy in a preclinical EAMG model, and to date has demonstrated acceptable safety and tolerability and exhibits expected PK and PD effects in adult HV. Future studies of povetacept in MG and other autoantibody-related neurological diseases are therefore strongly supported.

**M138. Rare Case of Transverse Myelitis Related to Myelin Oligodendrocyte Glycoprotein Associated Disease**  
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**Objective:** To describe a rare case of Myelin oligodendrocyte glycoprotein associated disease. **Background:** Myelin oligodendrocyte glycoprotein associated disease (MOGAD) is a rare immune-mediated demyelinating disorder characterized by presence of pathogenic antibodies against Myelinoligodendrocyte glycoprotein (MOG). **Design/Methods:** 17-year-old male with medical history of Lennox-Gastaut syndrome and global developmental delays presented with chief complaint of difficulty ambulating and fever. **Results:** Patient was nonverbal at baseline and unable to follow commands. CT cervical spine was unremarkable. Patient could not get MRI spine due to a vagal nerve stimulator. MRI of the head was unremarkable. Lumbar puncture showed elevated protein and lymphocytic pleocytosis. Patient required intubation for airway protection. Extensive workup revealed negative anti-SSA/SSB Ab, ANCA, Lyme Ab, Q4 Ab, paraneoplastic Ab, HIV testing, normal B12 and a negative meningitis encephalitis panel. EEG showed no seizure activity. Initially GBS was suspected based on acute presentation, as patient recently received hepatitis A vaccine. But clinical exam was notable for brisk/hyperreflexia of lower extremities with clonus, strongly suggestive of a myelopathic process. Patient received plasmapheresis therapy and IV SoluMedrol without any significant improvement. Work up eventually showed positive MOG-IgG on CSF panel. Subsequent MRI of orbit and head did not show any demyelinating lesions. He was switched to IVIG followed by slow prednisone taper for suspected transverse myelitis related to MOGAD. Patient was eventually extubated and noted to have improvement in his symptoms.

**Conclusions:** MOGAD can be easily missed as clinical picture can be similar for patients with multiple sclerosis, neuromyelitis optica spectrum disorder (NMOSD), transverse myelitis (TM), acute demyelinating encephalomyelitis (ADEM). Clinicians should be aware of MOGAD and send testing for MOG antibodies when suspected. This case also highlights the importance of good neurological examination. Presence of vagal nerve stimulator prohibited MRI spinal imaging in our case, nonetheless, clinical exam was strongly suggestive of a myelopathy and not a peripheral neuropathy.

### **M139. Stiff-Person Syndrome (SPS) with Very High GAD-Titers Triggered by COVID-19-Booster in 2 Neurologically Asymptomatic GAD-Positive Patients with Diabetes Mellitus Type 1 (DM1)**

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SPS is an autoimmune disease characterized by stiffness in agonist and antagonist muscles, hyperexcitability, muscle spasms and very high GAD antibody titers directed against linear GAD epitopes (Dalakas 2001). Patients with DM1 have low GAD antibody titers directed against conformational epitopes and up to 25% of them develop SPS. What triggers SPS in some DM1 patients is unknown. We report 2 neurologically asymptomatic DM1 patients with documented low GAD-antibody titers, who developed SPS soon after the COVID booster with very high anti-GAD titers. *Patient #1* is a 51-year-old man with relatively well-controlled DM1 associated with low-titer GAD antibodies, being stable on insulin for 30 years. Three weeks after receiving the Covid-19 Pfizer booster started to experience stiffness in the abdominal muscles with radiation around the back, followed by leg stiffness and muscle spasms. When examined 6 months later, he exhibited prominent leg stiffness with hung-up knee reflex, stiff gait and stiffness to palpation in the thoracolumbar region, all typical for SPS. GAD-65-antibody titers were now very high, above 250 (normal  $< 5$  IU/ml); before the vaccine, his GAD titers were 10.6 ( $< 1.0$  U/mL). *Patient #2* is a 53-year-old woman with DM1 and elevated GAD antibodies (10 times above normal). Her diabetes was well controlled not requiring insulin. Patient was physically active without limitations enjoying dancing activities two times per week. Within minutes after the Covid-19 Pfizer booster, she experienced tingling sensation throughout her body but within months her symptoms had steadily progressed to uncomfortable stiffness and muscle spasms in legs and arms with tightness of the abdominal and back muscles that have significantly compromised her dancing ability. When examined, she exhibited stiffness in the thoracolumbar paraspinal and abdominal muscles with a hung-up reflex on the right knee. GAD-antibody titers were now extremely high 1,015.3 (0.0-5.0 U/mL). Although COVID-vaccines can rarely trigger autoimmunities and various non-specific symptomatology, our two cases demonstrate the first manifestation of SPS, temporally connected to COVID-vaccine booster, confirmed clinically and immunologically. Because COVID boosters induce a coordinated humoral and cell-

mediated immune response, they have likely triggered a strong B cell activation that increased GAD-65 antibody production and the development of SPS autoimmunity. It remains however unclear if the vaccine has also changed the GAD-epitope specificity from conformational, as seen in DM1, to linear as connected with SPS

#### **M140. Stroke in a Young Adult: Immunomodulation Responsive Bilateral Supraclinoid Carotid Artery Vasculitis Secondary to Systemic Lupus Erythematosus**

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**Background:** Stroke is prevalent in 3-20% of patients with systemic lupus erythematosus (SLE) and accounts for 15% of mortality. CNS vasculitis secondary to SLE is extremely rare and mainly affects the small vessels per histopathologic studies. The pathophysiology is thought to be secondary to immune complex deposition triggering perivascular inflammation, endothelial proliferation, and hyalinization. There is a paucity of data on CNS vasculitis in SLE, especially involving cerebral large vessels. **Case Presentation:** A 20-year-old female, with a history of SLE diagnosed 12 years prior (on hydroxychloroquine and mycophenolate), lupus nephritis, and Budd-Chiari, presented as a transfer from an outside hospital for stroke workup. On arrival she was afebrile with BP 132/88 and HR 82. On exam, she had mild to moderate receptive aphasia with right arm and leg weakness. MRI demonstrated bilateral MCA/ACA and MCA/PCA watershed infarcts. Cerebral angiogram revealed bilateral supraclinoid ICA stenosis (right 79%, left 61%), without distal medium and small vessel irregularity or beading to suggest a diffuse vasculitic process. Lumbar puncture demonstrated 15 WBCs, protein 41, and glucose 45 in her CSF. Serum studies demonstrated elevated ESR 85 and normal C-reactive protein. Her infectious work up and urine drug screen were negative. Transesophageal echocardiogram was negative for Libman-Sacks endocarditis. Hypercoagulability workup demonstrated positive DNA double stranded antibody with elevated titers 1:80, borderline low protein C, and negative antiphospholipid antibody, beta-2-glycoprotein, and lupus inhibitor. Rheumatology was consulted, and although it was atypical for lupus vasculitis to involve cerebral large vessels, the patient was treated with pulse dose IV methylprednisolone followed by oral prednisone with prolonged taper. Further, she was started on warfarin with a heparin bridge. CT angiography at two years demonstrated significant improvement versus almost complete resolution of bilateral supraclinoid ICA stenosis. The patient continues to do well neurologically with a modified Rankin score of 1. **Conclusion:** Given the high mortality and morbidity associated with SLE vasculitis, it is of great importance for providers to be aware of this disease. Diagnosis of SLE vasculitis can be challenging due to similar radiographic appearance seen with moyamoya, intracranial atherosclerosis, or reversible cerebral vasoconstriction syndrome. We suggest early initiation of immunomodulatory therapy including high-dose steroids if vasculitis is suspected in patients with SLE who present with an ischemic stroke.

#### **M141. The Effect of Ocrelizumab on Balo's Tumefactive Lesion: A Case Report**

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**Introduction:** Balo's concentric sclerosis (BCS) is a rare subtype of multiple sclerosis characterized by large tumefactive lesions (TL) consisting of alternating zones of demyelinated and myelinated white matter. BCS presents with headaches, aphasia, cognitive or behavioral dysfunction, and seizures. Magnetization transfer ratio (MTR), fractional anisotropy (FA) and mean diffusivity (MD) are the most commonly used advanced brain imaging parameters to study the effect of a disease modifying therapy (DMT). Ocrelizumab is an FDA-approved DMT for relapsing- remitting multiple sclerosis (RRMS). There are no reports that examine the effect of ocrelizumab on MTR, FA and MD on BCS lesions. We report a patient diagnosed with BCS, receiving ocrelizumab, and provide a comparison in of the lesion volume, T1-gadolinium lesion volume, MTR, FA, and MD at baseline, 6- and 12-month follow-up. **Case Presentation:** A 40-year-old woman presented with new onset of right-hand weakness, slurred speech, and urinary frequency and urgency, and was treated with intravenous steroids and recovered. Paraclinical tests were supportive of demyelinating etiology. The MRI scan of the brain demonstrated an enhancing tumefactive left frontoparietal lesion. The patient received her induction therapy with ocrelizumab and a 6-month maintenance therapy followed by a repeat MRI showing a significant reduction in the size of the left lesion. The patient then completed a 12-month infusion and MRI scan of the brain at month 12 showed no significant changes. She has been clinically stable since her baseline MRI scan. **Results:** There was a reduction in Balo's lesion volume on FLAIR imaging observed in our patient from baseline (23.925 mL) to 12-month follow-up (2.391 mL), with the largest decrease from baseline to 6-month follow-up (3.650 mL). There was no T1-gadolinium enhancement seen at month 6 and 12. The MTR of the lesion did not change significantly (baseline= 50.9%, 6-month= 49.9%, 12-month=50.1%) but the FA increased from 0.188 (at baseline) to 0.304 (at 6 months), while the 12-month follow-up FA was 0.297. We also noted a reduction in MD from baseline ( $1.333 \times 10^{-3} \text{ mm}^2/\text{s}$ ) to 6-month follow-up ( $1.037 \times 10^{-3} \text{ mm}^2/\text{s}$ ), while the 12-month follow-up MD was  $1.086 \times 10^{-3} \text{ mm}^2/\text{s}$ . **Conclusion:** Our results demonstrate for the first time a direct effect of ocrelizumab on BCS lesions. To validate our findings, more observations are needed in a larger group of BCS patients.

#### **M142. The Innate Immune Regulator Nlr1 Limits Inflammatory Neurodegeneration in the Visual Pathway in Experimental Autoimmune Encephalomyelitis**

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Smoldering low-level inflammation within the central nervous system (CNS) due to reactive glia is one potential source of chronic demyelination and neurodegeneration in progressive multiple sclerosis (MS). There is a critical need for the identification of novel adjunctive therapeutic strategies that target these inflammatory glia and prevent downstream neurodegeneration in MS. Nucleotide-binding, leucine-rich repeat containing X1 (NLRX1) is an innate immune sensor that negatively regulates several pro-inflammatory signaling cascades including nuclear factor- $\kappa$ B. We have recently shown that neurotoxic astrocytes and microglia are prevalent in the optic nerve and retina and are associated with retinal ganglion cell (RGC) loss in mice with experimental autoimmune encephalomyelitis (EAE), a model of inflammatory demyelination. In the current study, we used several EAE models to determine the ability of NLRX1 to limit visual pathway inflammation and neurodegeneration. In active EAE induced by myelin oligodendrocyte glycoprotein (MOG)<sub>35-55</sub>-immunization, Nlr1<sup>-/-</sup> mice had similar EAE clinical scores but more severe loss of retinal Brn3a<sup>+</sup> RGCs at day 42 post-immunization (42 PID) compared to wild-type EAE mice (1699 vs. 2097 RGC/mm<sup>2</sup>,  $p = 0.02$ ). A similar enhanced loss of RGCs was observed in Nlr1<sup>-/-</sup> opticospinal encephalomyelitis (OSE) mice, a spontaneous EAE model in which mice have both CD4<sup>+</sup> T-lymphocytes expressing a transgenic T-cell receptor recognizing MOG<sub>35-55</sub> peptide ("2D2") and B-lymphocytes that produce antibodies with MOG-specific heavy-chains. To assess the role of NLRX1 in the innate immune compartment in EAE visual pathway inflammation, we adoptively transferred T-cells from 2D2 mice into Rag<sup>-/-</sup> and Nlr1<sup>-/-</sup>Rag<sup>-/-</sup> mice. We found atypical EAE cerebellar symptoms and more severe optic neuritis associated with increased optic nerve infiltration by T-cells and myeloid cells in Nlr1<sup>-/-</sup>Rag<sup>-/-</sup> mice compared to Rag<sup>-/-</sup> mice. A novel CNS-penetrant NLRX1 activating compound, LABP-66, has recently been developed. To assess whether activation of NLRX1 could ameliorate RGC loss in EAE, we treated wild-type MOG<sub>35-55</sub>-immunized mice after EAE symptom onset with oral LABP-66. Compared to vehicle-treated mice, LABP-66 treated mice had significantly higher RGC density at 42 PID (2418 vs. 1997 RGCs/mm<sup>2</sup>,  $p = .02$ ). These findings suggest that loss of NLRX1 within the innate immune compartment exacerbates inflammation and neurodegeneration within the visual pathway in multiple models of CNS autoimmunity. Moreover LABP-66 limited RGC loss even when initiated after the development of EAE clinical symptoms, suggesting pharmacologic NLRX1 activators have the potential to limit inflammatory neurodegeneration in chronic CNS inflammatory diseases including MS.

#### **M144. The Societal Costs of Metachromatic Leukodystrophy (MLD) in the United States and Potential Benefits of Disease-Modifying Therapy**

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MLD is an ultra-rare neurodegenerative disease leading to motor and cognitive decline and premature death. At present, US patients with early-onset MLD have no disease modifying treatment options and have very poor survival outcomes and neurological decline, with progressive loss of motor and cognitive abilities, spasticity, seizures, feeding difficulties, typically culminating in a decerebrated state or death before adolescence. Due to the debilitating nature of early-onset MLD, parents are often forced to give up work to care for their affected children. The aim of this study was to determine the lost family income due to caring for early-onset MLD patients, and productivity gains associated with potential disease-modifying treatment from a US perspective. US specific data from a cross-national MLD caregiver survey were used to inform changes in employment status together with lost family income derived from the mean annual salaries and number of working days in the US in 2022. Future productivity gains were calculated using the Human Capital Approach. Due to lack of employment data in MLD patients, published data from cerebral palsy and Down's syndrome were utilised as proxies to estimate the impact of motor and cognitive dysfunction on employment, alongside expected earnings based on the US education levels of achievement. A 3.0% discount rate was used to adjust productivity gains and lost family income for time preference. The results demonstrate there are significant productivity gains for patients treated with disease-modifying therapy compared to untreated. Further it was established that significant family income is lost through non-treatment, particularly in the later stages of MLD. In conclusion, these results demonstrate the positive impact of disease-modifying therapy in reducing the societal costs of MLD.

#### **M145. Two Cases of Neurosarcoidosis Presenting with Sexual Dysfunction: One with Anejaculation and Another of Erectile Dysfunction**

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**Introduction:** Neurosarcoidosis (NS) can have myriad presentations and hypogonadism can be a presenting symptom of NS when this involves the pituitary gland. Here we report two cases of neurosarcoidosis presenting with sexual dysfunction.

**Case Reports: Patient 1:** An African American man in early 40s presented with a few months' history of erectile dysfunction. During his work-up, he was found to have panhypopituitarism. He developed diplopia, headache, and incoordination and an MRI brain showed basal ganglia lesion and reduced size of the pituitary gland. CSF showed lymphocytic pleocytosis with elevated protein. He had dramatic improvement with IV steroids. Three years later, he had progression and developed left-sided weakness and numbness. Repeat MRI showed an enlarged pituitary gland, which was biopsied and showed noncaseating granuloma. He was started on Infliximab and has been stable over the last 2 years. **Patient 2:** An African American man in his early 40s presented to reproductive medicine for infertility evaluation. He complained about his inability to ejaculate. MRI of the brain showed a sellar mass that was extending into the suprasellar

cistern and impinging on the optic chiasm. Hormonal studies showed adrenal insufficiency, hypothyroidism and hypogonadotropic hypogonadism. Pituitary adenoma biopsy showed noncaseating granulomas. He was started on hydroxychloroquine and has been doing well. **Conclusion:** Neurosarcoidosis should be in given consideration when a patient presents with infertility and if there is suspicion of pituitary involvement given hypogonadotropic hypogonadism.

#### M146. Unusual CNS Manifestations of COVID-19: A

##### Case Series

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**Objective:** The objective of this study is to report a case series of COVID-19-related CNS complications, specifically 3 cases of longitudinally extensive transverse myelitis (LETM) and 2 instances of bilateral corticospinal (BCS) tractopathy. **Background:** Various neurological complications have been identified in relation to COVID-19. However, LETM and BCS tractopathy are rare CNS complications that require better clinical characterization as early recognition, and intervention can prevent further damage to the CNS. This study aims to add to the existing literature by reporting a case series of these complications. **Cases:** The transverse myelitis cases presented with progressively worsening bilateral lower extremity (BLE) sensory and motor deficits followed by bowel and bladder incontinence. All cases started within 2-3 weeks of COVID-19 exposure and were associated with initial clinical and neuroimaging progression within the first few weeks of symptom onset despite immunosuppressive treatment. In two cases, spinal cord MRIs were negative initially and later repeat imaging showed abnormalities. One case had a relapse confirmed with imaging after initial improvement. All patients showed incomplete but significant improvement at follow-up with immunosuppressive therapy. All cases required immunomodulatory treatment at their follow-up visits. The BCS tractopathy cases presented with progressive weakness in BLE. All cases had a more remote exposure at ~2-3 months. One case was superimposed with GBS. These cases also improved with immunosuppressive therapy, but the clinical benefits were modest. No relapses were seen. **Conclusions:** COVID-associated LETM and BCS tractopathy appear to be inflammatory in nature, as they are associated with contrast-enhancing lesions on MRI and are responsive to immunosuppression. The differences in disease onset suggest a different immune mechanism at play. This study highlights the possibility of unremarkable initial imaging and progression in clinical and imaging findings, as well as relapses, despite the initial treatment in LETM. Therefore, long-term immunosuppression and close follow-up may be necessary for these patients. In addition, the central and peripheral nervous systems can be concurrently involved.

#### M147. Utility of Protein Microarrays for Detection of Classified & Novel Antibodies in Autoimmune Neurological Disease

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**Background:** In Mayo Clinic's Neuroimmunology Laboratory, neural antibodies are detected using a tissue-based indirect immunofluorescence assay (IFA), but the process of characterizing and validating novel antibodies is time-consuming. We report our early experience of detecting known positives using protein arrays, and also 4 patients, who had novel, recently reported IgGs detected. **Methods:** The arrays were evaluated (81% human proteome coverage) using a variety of known positive samples (17 serum, 14 CSF). Patients' samples with novel neural antibodies were reflexed from IFA to arrays. Cell-based (CBA) or line-blot was used for confirmation assays. **Results:** Control positive samples known to be reactive with linear epitopes of intracellular antigens (e.g., ANNA-1 [anti-Hu]) were readily identified by arrays in 20/21 samples. In contrast, 10 positive controls known to be enriched with antibodies against cell surface protein conformational epitopes (e.g., GluN1 subunit of NMDA-R) were indistinguishable from the background signal. Three antibodies, previously characterized by other investigators (but unclassified in our laboratory), were unmasked in 4 patients using arrays (July-December 2022): Neurexin-3 $\alpha$ , 1 patient; regulator of gene protein signaling 8 (RGS8), 1; and seizure-related homolog like 2 (SEZ6L2), 2. Patient 1 presented with subacute onset of seizures, emotional lability, and cognitive impairment. Brain MRI was unremarkable. EEG recorded myoclonic seizures. CSF revealed 27 white blood cells/ $\mu$ L, lymphocyte predominant. Protein microarray testing of serum and CSF disclosed reactivity with neurexin-3 $\alpha$  (2<sup>nd</sup> highest-ranked neural antigen). Neurexin-3 $\alpha$  CBA was positive in both. Patient 2 presented with a rapidly progressive cerebellar syndrome. Neurological examination revealed a severe pancerebellar syndrome. Brain MRI revealed mild cerebellar atrophy and bland CSF. Protein microarray testing of CSF disclosed reactivity with RGS8 (highest-ranked neural antigen). RGS8-specific line blot was positive. Patient 3 presented with rapid-onset cerebellar ataxia and autonomic dysfunction. CSF revealed lymphocytic pleocytosis of 26/ $\mu$ L and elevated protein of 103 mg/dL. MRI of the brain revealed generalized atrophy. Patient 4 had a rapidly progressive cerebellar syndrome over 15 months and became walker dependent. CSF findings were normal. Brain MRI demonstrated mild diffuse cerebellar volume loss. Protein microarray testing of serum (both patients 3 and 4) and CSF (patient 3) disclosed SEZ6L2. **Conclusions:** Individualized autoimmune neurological diagnoses may be accelerated using protein arrays. They are optimal for the detection of intracellular antigen-reactive antibodies, though certain cell surface-directed antibodies (neurexin-3 $\alpha$  and SEZ6L2) may also be detected.

#### M148. Validation of the 2023 International MOGAD Panel Proposed Criteria: An Institutional Cohort

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**Background:** Myelin oligodendrocyte glycoprotein antibody-associated disease (MOGAD) is a recently defined demyelinating disorder with a rapidly evolving clinical spectrum.

Recently, consensus criteria have been proposed to help with disease diagnosis (Banwell et al., The Lancet, 2023). However, validation of the proposed criteria in real-life MOGAD patients is lacking. In this study, we applied the proposed criteria to a cohort of MOG antibody-positive patients. **Methods:** A retrospective study was conducted at a tertiary neuroimmunology clinic from 2018 to 2023. Patients who had at least one core clinical feature of MOGAD and positive serum MOG antibody by cell-based assay were included. Demographics and clinical data were recorded and analyzed. Cases were divided into definite MOGAD, questionable MOGAD, and false-positive MOGAD as determined by the treating neuroimmunology and/or neuro-ophthalmology specialists prior to applying the new MOGAD criteria. **Results:** A total of 27 patients were included, of which 20 (74%) were female, the average age of the sample was 44 +/- 15 years. High titer ( $\geq 1:100$ ) was found in 11 patients (40.7%) and low titer ( $< 1:100$ ) in 12 (44.4%). A total of 22 (81.5%) met the 2023 MOGAD criteria. As determined by expert opinion; 18 (66.7%) were identified as definitive MOGAD, 6 (22.2%) as false-positive MOGAD, and 3 (11.1%) as questionable MOGAD. All 18 patients identified by clinicians as definite MOGAD met the new 2023 criteria. Of the 9 patients with questionable MOGAD or false-positive MOG antibody, four patients met the 2023 MOGAD criteria. Those four patients had the following final diagnoses: pseudotumor cerebri, paraneoplastic retinopathy and bevacizumab-induced anterior ischemic optic neuropathy, CNS vasculitis, and primary progressive MS with relapses. Compared to clinician assessment, applying the 2023 MOGAD criteria to our institutional cohort yielded a sensitivity of 100%, a specificity of 55.5%, a positive predictive value of 81.5%, and a negative predictive value of 100%. **Conclusion:** These findings suggest that the 2023 MOGAD criteria are highly sensitive for detection of definite MOGAD but has modest specificity. A number of MOGAD mimickers can resemble the core clinical events of MOGAD and share similar supportive clinical and MRI features. Clinicians should practice caution when evaluating patients with low titer MOG antibody even if they meet the additional supportive features proposed by the 2023 criteria. Further studies are needed to evaluate the 2023 criteria in larger cohorts and in the pediatric population.

#### M149. Voltage Gated Calcium Channel Antibodies Associated Peripheral Neuropathy

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**Objective:** To describe a rare case of voltage gated calcium channel antibodies associated with peripheral neuropathy. **Background:** Voltage gated calcium channel (VGCC) antibodies are usually seen in Lambert-Eaton myasthenic syndrome (LEMS). They are also reported in patients with other autoimmune neurological disorders such as cerebellar ataxia,

and dysautonomia. We describe a rare case of VGCC associated peripheral neuropathy. **Design/Methods:** A 32-year-old woman with no significant past medical history presented with painful paresthesia involving bilateral extremities of 9 months duration. Symptoms began in bilateral hands followed by lower extremities the following month. There was no associated weakness, stiffness, fatigability, oculo-bulbar abnormalities, or symptoms of dysautonomia. **Results:** Neurological examination was unremarkable with intact motor strength, sensation, and reflexes. Laboratory testing including HbA1c, TSH, Immunofixation, ANA, ESR, SSA/SSB, dsDNA, ganglioside panel, B12, MMA, Copper, ceruloplasmin, CK, and myositis panel were unremarkable. Interestingly, paraneoplastic panel revealed significantly elevated VGCC antibody titers when tested twice. EMG was found to be unremarkable including slow repetitive nerve stimulation and post-exercise potentiation. Imaging of the brain and whole spine was unremarkable. CT chest revealed solitary pulmonary nodule, which was concluded to be benign based on PET-CT. The patient was started on intravenous immunoglobulins with adequate resolution of symptoms. **Conclusions:** VGCC autoantibodies are typically associated with paraneoplastic LEMS but can be seen in about 2% of neurological patients without neoplasia. The VGCC is not only limited to the presynaptic nerve terminals but can also be seen on sensory nerves and autonomic nerves. We would like to highlight the manifestation of peripheral neuropathy in individuals with non-paraneoplastic VGCC antibodies.

#### M150. When It's Not MS: Rediagnosing Recurrent ADEM in an Adult

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**Background:** Misdiagnosis of multiple sclerosis (MS) is common. An unusual clinical presentation with breakthrough disease on highly effective therapies warrants reconsideration of an established diagnosis. Myelin oligodendrocyte glycoprotein associated disorder (MOGAD) is an increasingly recognized MS mimic with diverse presentations including acute disseminated encephalomyelitis (ADEM). **Methods:** Case report and review of the literature **Results:** A 37-year-old male with HIV and a diagnosis of MS was referred for treatment recommendations after relapses and progression on interferon beta-1a, natalizumab, and ocrelizumab. His initial event was ADEM with prolonged hospitalization and incomplete recovery. Episodes of severe symptoms (blurry vision, double vision, dysarthria, and gait ataxia) were steroid responsive though there was a progressive cognitive impairment, dysarthria, and ataxia. Retrospective review of images revealed multifocal, large, and poorly demarcated areas of T2 hyperintensity with contrast enhancement involving both cerebral hemispheres, brainstem, and cerebellum during relapses. The signal changes and contrast enhancement resolved with high dose steroids for each event. Serum MOG antibody was positive with at 1:1000. **Conclusion:** We describe a case of recurrent ADEM initially diagnosed as MS. Revisiting the diagnosis in the setting of unusual features

or lack of expected response to treatments may lead to an alternative diagnosis and targeted treatments.

### **K-M100. Disrupted Cerebral Metabolism in Multiple Sclerosis**

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Multiple sclerosis (MS) is an inflammatory and degenerative disease of the central nervous system. Neurodegeneration begins early in MS and may be exacerbated by metabolic stress. MS is hypothesized to disrupt cerebral metabolism due to 1) demyelination which precludes saltatory conduction and increases the metabolic cost of ionic gradients, 2) inefficiencies in reactively produced mitochondria, 3) metabolic costs of remyelination, and 4) metabolic costs of infiltrative immune cells. The extent to which metabolic abnormalities are present in early relapsing MS is unknown. This study assessed the cerebral metabolic rate of glucose ( $CMR_{glc}$ ), cerebral blood flow (CBF), and cerebral oxygen extraction fraction (OEF) in 20 recently diagnosed relapsing MS (RMS) patients prior to initiation of disease modifying therapy, five non-relapsing MS (NRMS) patients with at least 10-year disease duration, and twelve healthy control participants.  $CMR_{glc}$  was measured by Patlak analysis of dynamic fluorodeoxyglucose positron emission tomography, and CBF and OEF were measured by arterial spin labeling and oxygen sensitive magnetic resonance imaging, respectively. These metabolic parameters were estimated in non-lesional white matter (WM), gray matter (GM), and WM lesions (WML) using symmetric geometric transfer matrix partial volume correction. In non-lesional WM, RMS ( $t=2.14$ ,  $p=0.044$ ) and NRMS ( $t=2.47$ ,  $p=0.022$ ) patients had higher  $CMR_{glc}$  than controls. No differences in non-lesional WM CBF were observed and OEF was mildly increased in the NRMS patients only ( $t=2.06$ ,  $p=0.048$ ). Increased  $CMR_{glc}$  absent significant changes in oxygen metabolism indicates increased aerobic glycolysis. No significant effects were seen in GM. In MS patients, WMLs demonstrate decreased  $CMR_{glc}$  ( $t=4.18$ ,  $p<0.001$ ) and CBF ( $t=2.81$ ,  $p=0.0064$ ) but increased OEF ( $t=2.93$ ,  $p=0.0046$ ) compared to non-lesional WM. Increased OEF combined with decreased CBF can indicate relative ischemia, but changes in cerebral metabolic rate of oxygen ( $CMR_{O_2}$ ) depend on both CBF and OEF. We calculated the WML to non-lesional WM ratio for  $CMR_{glc}$  and  $CMR_{O_2}$  and found that whereas  $CMR_{glc}$  was decreased in WMLs by 27%,  $CMR_{O_2}$  was only reduced by about 4%. This suggests a decrease in glycolytic metabolism in WMLs, in contrast to non-lesional WM where glycolysis is increased. These findings suggest that cerebral metabolic stress is present early and late in MS, including in non-lesional WM. Future work will investigate the effect of treatment on metabolic stress and associations with disease severity.

### **K-M101. Investigations of Synaptic Signaling Targets of Human Anti-NMDAR Antibodies**

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The most common form of autoimmune encephalitis is associated with antibodies that target N-methyl-D-aspartic acid (NMDA) receptors. NMDARs are glutamate receptors that govern cellular mechanisms of learning and memory, including synaptic long-term potentiation (LTP), through induction of post-synaptic signaling cascades and regulation of synaptic protein synthesis. In anti-NMDAR encephalitis, antibody binding to the obligate GluN1 subunit of NMDARs leads to crosslinking and internalization of NMDARs. The molecular mechanisms that lead to the diverse neuropsychiatric symptoms associated with anti-NMDAR encephalitis remain incompletely defined but are hypothesized to involve synaptic dysfunction. We previously demonstrated that human GluN1 monoclonal antibodies (GluN1 hMAbs) rapidly localize to and regulate synaptic NMDAR function at native synapses of primary neurons. Here, we sought to explore signaling targets of GluN1 hMAbs in primary neurons using biochemistry and subcellular fractionation. We utilized unbiased quantitative phosphoproteomics to evaluate signaling pathways in membrane fractions from primary cortical neurons. GluN1 hMAbs altered global membrane protein phosphorylation states associated with numerous biological processes relevant to neuronal structure and function. These data suggest that NMDAR antibodies alter neuronal signaling networks. In separate experiments, we defined activity-dependent regulation of local RNA content in the postsynaptic density (PSD) fractions of primary neurons. Pharmacological manipulation of autophagy resulted in local synaptic RNA regulation. Thus, autophagy may contribute to synaptic plasticity via regulation of local RNA metabolism. These results raise the question of whether the effects of GluN1 hMAbs impact synaptic protein homeostasis involving autophagy and local RNA metabolism at the PSD. Future studies will investigate the regulation of autophagy and RNA metabolism in the underlying pathophysiology of anti-NMDAR encephalitis. These studies may contribute to the identification of potential therapeutic targets for novel therapies for patients with anti-NMDAR encephalitis and disorders involving antibodies targeting cell surface antigens.

### **K-M102. Longitudinal Clinical Evaluation of Paramagnetic Rim Lesions in Multiple Sclerosis**

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Paramagnetic rim lesions (PRLs) are an MRI biomarker of some chronic active lesions in multiple sclerosis (MS). Longitudinal evolution of these lesions, as well as differential treatment effects, remain poorly characterized. Here we aimed to

evaluate longitudinal PRL imaging characteristics including resolution or fading, as well as clinical associations and relationships with concurrent disease-modifying therapy (DMT) regimens. We retrospectively identified MS patients (all forms) from our observational cohort with MRI follow-up of  $\geq 2$  years using a standardized acquisition protocol, and assessed baseline MRI scans for PRL as determined using filtered-phase susceptibility imaging from a clinical manufacturer protocol at 3T (GE SWAN). PRL were identified as hypointense paramagnetic rims at the edge of FLAIR lesions; confluent lesions were included when sub-lesions could be identified from superstructure. All available longitudinal images were coregistered with uniform phase contrast settings, and PRL were extracted and blindly evaluated for qualitative change including “fading” or resolution. A mixed-effects multivariable logistic regression model was used to evaluate baseline predictors of fading/resolution including age, follow-up duration, and concurrent DMT(s), controlling for subject-specific repeated measures. DMTs were statistically modeled as percentage of the observation period with time-on-treatment. Baseline and longitudinal clinical associations were determined using multivariable regression. 238 patients met overall inclusion criteria, 84 of whom (35%; age  $45.0 \pm 11.5$ , 72% female, 83% relapsing) had  $\geq 1$  baseline PRL, with median follow-up of 3.5 years. We identified 202 baseline PRL (median 2, range 1-13). Over follow-up, 9 PRL resolved (4%), 50 faded (25%), and 122 exhibited no change; 20 evolved in other ways (fragmentation, diffuse paramagnetic change, or enlargement). DMTs received for at least 1/3 of the observation period were 36 (43%) B-cell depletion, 10 (12%) fumarate, 8 (10%) alemtuzumab, and 5 (6%) each for teriflunomide, mycophenolate, and glatiramer. Our regression model adjusted for age, observation time, and subject-specific repeated measures did not show any consistent associations with age, follow-up period, or medication on fading/resolution of PRL (all  $p > 0.05$ ). Baseline number of PRL was associated with baseline lower deep gray volumes, higher choroid plexus volumes, and greater central brain atrophy (all adjusted for age, sex, lesion volume,  $p \leq 0.01$ ). In conclusion, we observed that 29% of PRL qualitatively fade/resolve over a 3.5 year follow-up; filtered-phase longitudinal PRL assessments were both feasible and rapid. PRL were associated with greater pathological baseline MRI-based volume loss, but PRL fading/resolution was not associated with age, DMT, or observation time after accounting for within-subject correlation, suggesting the need for targeted therapies to hasten resolution of CAL.

### **K-M103. The PKC Modulator Bryostatin-1 Augments Remyelination through Therapeutic Targeting of CNS Innate Immunity**

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In multiple sclerosis (MS), microglia and macrophages within the central nervous system (CNS) determine the balance between demyelination, neurodegeneration, and myelin repair. Phagocytic and regenerative functions of these CNS innate immune cells support remyelination, whereas chronic and maladaptive

inflammatory activation promotes lesion expansion and disability, particularly in progressive forms of MS. No currently approved drugs convincingly target microglia and macrophages within the CNS, contributing to the critical lack of therapies promoting remyelination and slowing progression in MS. Here, we found that the protein kinase C (PKC) modulating drug bryostatin-1 (bryo-1), a CNS-penetrant compound with an established human safety profile, produces a shift in microglia and CNS macrophage transcriptional programs from pro-inflammatory to regenerative phenotypes, both *in vitro* and *in vivo*. Treatment of microglia with bryo-1 prevented the activation of neurotoxic astrocytes while stimulating scavenger pathways, phagocytosis, and secretion of factors that promote oligodendrocyte differentiation. In line with these findings, systemic treatment with bryo-1 augmented remyelination following focal demyelinating injury *in vivo*. Our results demonstrate the potential of bryo-1 and related PKC modulators as myelin regenerative and neuroprotective agents in MS and other neurologic diseases through therapeutic targeting of microglia and CNS macrophages.

### **Autoimmune Neurology & MX**

#### **LB-M100. Demographics and Clinical Characteristics of Possible Autoimmune Encephalitis with GAD**

##### **65-Antibody**

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**Objective:** Glutamic acid decarboxylase 65 (GAD 65) is a neuronal intracellular antigen. Antibodies to GAD 65 are associated with stiff person syndrome, cerebellar ataxia, and epilepsy. Anti-GAD 65 antibodies have also been implicated in autoimmune encephalitis. The objective of this study is to report demographic and clinical characteristics of patients with a positive GAD 65 antibody in the serum or CSF with possible autoimmune encephalitis. **Methods:** Retrospective chart review of patients at Houston Methodist Hospital with GAD 65 positive antibodies and possible autoimmune encephalitis. **Results:** There were 33 patients in our cohort (ages 21-78) with most patients presenting in their 60s or 70s (45%). About half (51%) of the patients were female. Most patients were Caucasian (70%), then African American (12%), and Asian (0.1%). 5 patients (15%) identified as Hispanic or Latino. 1 patient had type 1 DM and 8 patients (24%) had concurrent type 2 DM. 2 patients (0.1%) had Hashimoto's thyroiditis. 13 patients (39%) presented with confusion and 11 patients (33%) presented with cognitive impairment. 6 patients (18%) presented with psychiatric manifestations, including hallucinations, delusions or paranoia. 5 patients (15%) presented with seizures. 12 (36%) of the patients presented with acute symptoms within 2-3 days. Many of the patients (23, 70%) had a positive serum GAD65 titer of  $< 0.2$  nmol/L with only 2 (0.1%) patients having a titer greater than 4. 6 (18%) of the patients had a positive GAD 65 CSF titer. The CSF titer ranged from 0.6-999 IU/ml. 14 (48%) of the 29 patients that had an interpretable MRI showed anterior cingulate, insula, amygdala/hippocampus or lateral temporal

cortex high FLAIR signal or less frequently caudate/putamen, cerebellar or brainstem changes. 11 patients (33%) met Graus' diagnostic criteria for possible autoimmune encephalitis. 21 (64%) patients received steroids, 20 (61%) received IVIG, and 26 (79%) received PLEX. 2 (0.1%) patients received second-line treatment with Rituximab. 15 patients (45%) were functionally independent with MRS 1-2 and 2 patients (0.1%) were deceased in our cohort. **Conclusion:** In our cohort, a minority of those with positive serum or CSF GAD 65 antibody titers had a likely autoimmune etiology for their symptoms. Clinical presentations included altered mental status, psychiatric symptoms, and seizures. Anti-GAD 65 antibody disease should be considered in the differential diagnosis of those presentations, particularly when occurring acutely in patients in their 60s or 70s.

#### **LB-M101. Hemicord White Matter Enhancement and the Croissant Sign in Spondylotic Myelopathies**

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**Background:** Gadolinium enhancement occurs in 7% of patients with cervical spondylotic myelopathies, and its presence often leads to misdiagnosis as tumors or inflammation. A flat pancake-like sagittal enhancement pattern (width $\geq$ height) with axial circumferential white matter enhancement is characteristic of spondylotic myelopathies. However, unilateral enhancement has not been reported. **Aim:** To report a novel unilateral spinal cord gadolinium enhancement pattern accompanying cervical spondylotic myelopathies that may help reduce misdiagnosis and allow earlier treatment. **Methods:** We searched our Mayo Clinic database of spondylotic myelopathies with enhancement from January 1<sup>st</sup>, 1996 to May 1<sup>st</sup>, 2023 and included patients fulfilling the following criteria: 1) Clinical myelopathy due to cervical spondylosis; 2) Presence of unilateral spinal cord gadolinium enhancement that involves the white matter and spares the gray matter on axial images, resembling a "croissant". **Results:** We found 16/111 (14%) patients from our database of spondylotic myelopathies with enhancement had unilateral hemicord (right, 8; left, 8) enhancement, resembling a "croissant". The median age was 52 years (range 24-74 years) and 75% were male. The onset was either insidious (n=12) or subacute (n=4). The myelopathy was asymmetric in 12 (6 had Brown-Sequard syndrome localizing to the side of enhancement) and symmetric in 4. The reverse Lhermitte's phenomenon with shooting sensation radiating down the spine or into the extremities with neck extension was noted in 4 (25%). The MRIs were performed prior to surgical decompression in 12 patients. Notably, the compression was often worse on the opposite side of the unilateral enhancement (contralateral, 5; middle, 4; ipsilateral, 3). In those with sufficient follow-up data available, the enhancement could take up to a few years to resolve after decompression surgery. **Conclusions:** Unilateral spinal cord enhancement on the axial post-gadolinium images involves the white matter and spares the gray matter, resembling a "croissant". The presence of this enhancement pattern should raise suspicion for spondylotic myelopathies.

#### **Behavioral Neurology and Dementia**

#### **M151. A Phase 1, First-in-Human, Randomized, Double-Blind, Placebo-Controlled, Single- and Multiple-Ascending Intravenous Dose Study of VGL101, a Novel TREM2 Agonist, in Healthy Volunteers (HVs)**

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**Background:** VGL101 is a fully human monoclonal antibody TREM2 agonist in development to treat adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP), a rare, progressive, debilitating neurodegenerative disorder caused by *CSF1R* mutations. TREM2 receptors are expressed on brain microglia and critical to microglial function. VGL101 activation of TREM2 was designed to enhance function of microglia and regulation of neural repair mechanisms, compensating for CSF1R-driven deficits and slowing ALSP disease progression. This study evaluated safety, tolerability, pharmacokinetics, and pharmacodynamics after single- (SAD) and multiple-ascending dose (MAD) VGL101 administration. **Methods:** HVs (N $\approx$ 125) received placebo or VGL101 at 1-60mg/kg (SAD) or 10-60mg/kg (MAD). Safety assessments included adverse events (AEs), vital signs, electrocardiograms, and clinical laboratory evaluations. Assessments for cohorts with cerebrospinal fluid (CSF) collection (3, 10, 20, 40, 60mg/kg SAD; 10, 20, 40mg/kg MAD) included VGL101 serum and CSF pharmacokinetics and CSF-soluble TREM2 (sTREM2) and CSF1R (sCSF1R) pharmacodynamics. **Results:** VGL101 safety for 1-40mg/kg SAD cohorts and complete data for the 20mg/kg MAD cohorts were previously presented. Most AEs were mild and resolved without intervention. No serious AEs or investigational product-related clinically meaningful vital sign, electrocardiogram, or laboratory abnormalities were reported. VGL101 demonstrated approximately dose-proportional peripheral pharmacokinetics supportive of monthly dosing. Durable sTREM2 and sCSF1R effects were observed, demonstrating VGL101-associated target engagement and microglial activation. New safety and target engagement findings for additional cohorts (10, 30, 40, and 60mg/kg) will be presented. **Conclusions:** VGL101 demonstrates favorable safety and pharmacokinetics and confirms CNS target engagement, supporting further clinical development in ALSP.

#### **M152. Advanced Cerebral Adrenoleukodystrophy: Hope for a Vulnerable Cohort**

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**Introduction:** X-linked adrenoleukodystrophy (X-ALD) is a neurodegenerative disorder arising from mutations in the *ABCD1* gene that presents with a broad spectrum of phenotypes varying in severity and age of onset. Cerebral X-ALD (cALD) is the most devastating form of the disease that affects boys and men of all ages, manifesting as a rapidly



progressive neurological decline culminating in death. The Loes score is the gold-standard quantification of radiological cALD disease progression calculated from brain magnetic resonance imaging (bMRI) findings. Patients with Loes score >9 are considered to have advanced cALD. While many patients with mild cALD are treated with hematopoietic stem cell transplantation (HSCT) or lentiviral gene therapy, many patients with advanced cALD only receive supportive care. Thus, there is a great need for research targeting this vulnerable cohort. **Methods:** To compare the treatment and prognosis of advanced cALD in boys and men, we conducted a retrospective analysis of advanced cALD patients (Loes score >9) who were seen at a single leukodystrophy center between 2006 and 2022. **Results:** Using the criteria delineated above, we identified a cohort of 43 patients with advanced cALD, comprising 30 pediatric boys (median age: 8 years, range: 5-18 years) and 13 adult men (median age: 37 years, range: 23-62 years). In the pediatric subgroup, 12/30 patients (40%) received treatment in the form of HSCT (10 patients) or lentiviral gene therapy (two patients). In the adult subgroup, however, only 2/13 patients (15%) received treatment in the form of HSCT. In total, 5/30 boys (16.7%) and 10/13 men (76.9%) died before the end of the study ( $p=0.0003$ , Fisher's Exact Test). Among the patients who died, there was no significant difference in median survival after first abnormal bMRI: 22.2 months for boys and 27.2 months for men ( $p=0.306$ , Log-rank test). In contrast, survival analysis regardless of mortality revealed a dramatically higher median survival time after first abnormal bMRI in boys (>170 months) compared to men (27.3 months) ( $p=0.0008$ , Log-rank test). **Conclusion:** Untreated advanced cALD is fatal among boys and men alike. However, the increased availability of treatment in the pediatric population likely contributed to the dramatically decreased mortality and increased survival time in this subset of patients. These data show that advanced cALD is, in fact, amenable to treatment. By expanding the availability of existing therapies and by developing new therapies, we can significantly improve the prognosis of this devastating disease in all advanced cALD patients.

#### M153. Alterations in Basal Ganglia Connectivity in Individuals with Primary Progressive Aphasia

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**Background:** Primary progressive aphasia (PPA) is a syndrome of progressive language decline due to Alzheimer's disease (AD) or frontotemporal degeneration (FTLD). Many studies investigating pathophysiology of PPA have focused on changes in cortical connectivity (Bonakdarpour et al., 2019). There is also evidence of basal ganglia (BG) involvement in both AD (Hamasaki et al., 2019) and FTLD-Tau (Ljubenkov and Miller, 2016), and atrophy in BG structures in PPA (Mandelli et al. 2016). However, changes in BG connectivity and potential differences between PPA-AD and PPA-FTLD have not been well studied. The goal of this

project was to investigate alterations in BG connectivity in PPA; to determine whether there is a difference between PPA-AD and PPA-FTLD; and to understand how alterations in BG connectivity affect aphasic symptoms. **Methods:** Twenty-six PPA-AD, 16 PPA-FTLD, and 31 controls, all right-handed, were enrolled. Diagnosis of pathologies were made by either autopsy or *in vivo* biomarkers (spinal fluid, or amyloid PET). Resting state functional magnetic resonance images were preprocessed via DPARSF-A v4.3. Basal ganglia regions of interest (ROIs) were selected from the WFU-Pick-Atlas (caudate, putamen, globus pallidus [GP]). Connectivity between BG ROIs and the rest of the brain for PPA-AD and PPA-FTLD was separately compared to the controls using two-sample t-tests thresholded at cluster-based family wise error corrected  $p$  value (FWEc) < 0.05 using CONN toolbox. Correlations between resting state functional connectivity (RSFC), grammar, repetition, naming, and word comprehension were conducted in CONN toolbox. **Results:** Whole-brain voxel-wise RSFC of left caudate, putamen, and (GP) ROIs showed significant decreased connectivity in the corresponding regions for both PPA-AD and PPA-FTLD groups compared to controls (left > right). PPA-AD/PPA-FTLD comparison showed no difference in BG connectivity. There was a positive correlation between each BG RSFC and grammar with most significant association in the left putamen. There was no correlation between BG RSFC and other aphasic symptoms. **Discussion:** We found a left dominant decrease in resting BG connectivity for both PPA-AD and PPA-FTLD groups as shown in previous volumetric studies. Contrary to our expectation, there was no difference between RSFC of BG structures in PPA-AD and PPA-FTLD. The positive correlation between grammar and BG RSFC, especially left putamen, is in line with a recent report (Barbieri et al, 2023) showing a correlation between left putamenal volume and grammar. These findings suggest an important role for left putamen in agrammatism in PPA.

#### M154. Are Psychotic-Spectrum Disorders with Comorbid Anxiety and Depression Predisposing Factors for Parkinson's Disease

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**Background:** Multiple studies have demonstrated associations among anxiety and depression and later development of Parkinson's disease (PD); fewer have examined associations between psychotic-spectrum disorders and later development of PD. **Objective:** This study assesses the prevalence of psychotic-spectrum disorders with and without depression

and anxiety preceding a PD diagnosis in a community-based setting. Further characterization of risk factors for development of PD is important for understanding other possible underlying mechanisms of PD and mental illness as well as improving risk stratification. **Methods:** This is a retrospective, case-control study of Kaiser Permanente Northern California members aged  $\geq 60$ . Cases were identified by PD diagnosis and controls were identified in a 3:1 ratio by ambulatory encounter, from January 1, 2015–December 31, 2020, matched by sex, age, admission date, and encounter facility. Mental health conditions were identified by diagnosis code up to 5 years prior to matched case index date. Conditional logistic regression was conducted to assess associations between mental health conditions and PD. **Results:** Among 13,998 patients, the odds of PD were 76% (95% CI 1.39–2.22) higher among members with psychotic-spectrum diagnoses. Among those diagnosed with a psychotic spectrum disorder ( $N=327$ ), an additional diagnosis of anxiety was associated with 166% [95% CI 1.35–5.25] higher odds of PD. **Conclusions:** Awareness of patients' psychiatric conditions, including psychotic-spectrum disorders, especially when paired with anxiety, may be helpful for stratifying individuals who may be more susceptible to later development of PD.

#### **M155. Association between Retinal Microvascular Changes and Late Brain Amyloid Deposition: The ARIC-PET Study**

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**Objective:** Cortical amyloid burden may be preceded, likely by years, by alterations in the small cerebral vessels. The retinal microvasculature is both anatomically and physiologically similar to the small vessels in the brain and has been associated with incident clinical stroke and radiological markers of cerebral small vessel disease. This study assessed the mid- and late-life independent retinal microvascular contributions to greater amyloid burden in adults without dementia in late life. **Methods:** 285 participants without dementia from the ARIC-PET (Atherosclerosis Risk in Communities-Positron Emission Tomography) study with a valid retinal measure were included. Four single retinal signs, namely retinopathy, arteriovenous nicking, focal arterial narrowing and generalized arterial narrowing, and a newly created composite retinal measure which summarizes the presence of all four retinal signs into a single score, (unweighted sum of the 4 retinal signs; range 0–3) were evaluated cross-sectionally with florbetapir PET, where greater amyloid burden was defined as a global cortical standardized uptake value ratio (SUVR)  $> 1.2$ . Using logistic regression models, the associations between mid- and late-life retinal signs and greater late-life amyloid burden were tested adjusting for age, sex, education, APOE-4 status, and race in model 1 and further accounting

for diabetes and hypertension in model 2. **Results:** Neither retinopathy nor any other single retinal signs in midlife or late life were associated with greater late-life amyloid burden in individuals without dementia. A high retinal composite score in late life, indicating a higher burden of retinal abnormalities, was however associated with greater amyloid burden when adjusting for demographic and genetic confounders ( $OR$  (95%  $CI$ ) = 3.58 (1.09, 14.2) but not when further accounting for the vascular risk factors ( $OR$  (95%  $CI$ ) = 3.02 (0.88, 12.3). **Interpretation:** A composite retinal score accounting for multiple retinal vascular abnormalities may serve as a risk indicator for greater amyloid burden in the general population. Well-powered future studies with a greater number of participants with retinopathy and other microvascular signs are needed to test these findings and to reevaluate the role of retinal microvascular signs on amyloid burden above and beyond vascular risk factors.

#### **M156. Association of Birth Weight and Preterm Birth with PET-Amyloid Burden: The Atherosclerosis Risk in Communities (ARIC) PET Study**

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**Introduction:** Early life factors, such as birth weight (BW), may have long-term health consequences, but the importance of these factors with dementia risk or its etiology is poorly understood. Existing studies are largely limited to retrospective surveys in homogenous populations. Having previously described associations between low BW and dementia risk, our objective was to examine the association of BW with PET-amyloid burden, a marker of Alzheimer's pathology. We hypothesized that participants with lower BW will have greater odds of elevated amyloid burden on PET than participants with normal BW, in the community-based ARIC cohort. **Methods:** Of 346 ARIC-PET participants at ARIC visit 5 (2011–2013; all dementia-free), 310 had non-missing BW and covariate data (mean age 76, 56% female, 40% Black). Participants were asked their BW category (low ( $< 5.5$  lbs.), medium/normal (5.5–9.0 lbs.), or high ( $> 9.0$  lbs.)), and if they were born premature (yes/no) through standard interviews at Visit 4 (1996–1998). Amyloid burden was assessed with florbetapir PET within one year after visit 5. Elevated amyloid burden was defined as standardized uptake value ratio (SUVR)  $> 1.2$  in the global cortex. Associations between BW and prematurity, each, with elevated SUVR were investigated using separate logistic

regression models adjusted for demographics, education, APOEε4 genotype, and vascular risk factors. **Results:** Most participants (N=270/310; 87%) reported medium BW, 17 (5.5%) reported low BW and 23 (7.4%) reported high BW. Participants with low BW had a 72% (adjusted OR 0.28, 95% CI 0.08, 0.93) lower odds of elevated SUVR compared to those with medium BW, with no difference in high BW vs medium BW participants (adjusted OR 0.98, 95% CI 0.39, 2.49)). The odds of elevated SUVR were also lower (adjusted OR 0.16; 95% CI 0.03, 0.90) in premature participants (vs not premature). A higher proportion of Black participants with normal BW had elevated amyloid (65%) than did whites (45%) (p=0.001). All Black participants (n=2) with low BW had elevated SUVR compared to only 13% (2/15) of Whites with low BW (p=0.044). **Discussion:** In this cohort without dementia, individuals with low BW and/or premature birth were less likely to have elevated global SUVR. This unexpected relationship may reflect selection bias, whereby individuals with low BW who survive to old age are more robust and less likely to experience amyloid burden than their cohort peers with normal BW.

#### **M157. Autozoanthroprosopometamorphopsia: Transformation to Equine Countenance**

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**Introduction:** As part of Alice in Wonderland Syndrome, prosopometamorphopsia, visual distortion of faces has been noted (Lanska, 2013), as a variant of this, conversion of human to that of animal face, Zoanthroprosopometamorphopsia (Blom, 2020). While perception of one's face transforming into an animal's face, autozoanthroprosopometamorphopsia has been noted (Blom, 2021), having one's own face transform into a horse's face has not been described. **Methods/Case Study:** A 37-year-old female, with past history of schizoaffective disorder, bipolar subtype presented with the perception that her face was elongating into a horse's snout. She described turning into a "black horse with a rainbow mane". She perceived she was wearing horse blinders, felt she was pulling a carriage as if in Cinderella, she could talk to other horses, felt compelled to "neigh". **Results:** Abnormalities in Neurological Examination: Hyperverbal, grandiose with expansive affect, poor insight and judgment. Cranial Nerve (CN) examination: CN I: Alcohol Sniff Test: 8 (Hyposmia). Motor Examination: Mild left pronator drift. Cerebellar Examination: Finger to nose dysmetria bilaterally. Reflexes: 3+ bilateral upper extremities. Absent in both lower extremities. Bilateral positive Hoffman reflexes. Magnetic Resonance Imaging /Magnetic Resonance Angiography of brain with infusion: Normal. **Discussion:** Alice in Wonderland Syndrome pathology is found at the temporoparietal occipital carrefour, the region where both visual and somatosensory information are combined and processed to produce the internal and external representation of self (Mastria, 2016). Prosopometamorphopsia has been postulated to be due to pathophysiology of the occipital face area, fusiform face area, and splenium of corpus callosum (Blom

2021). Zoanthroprosopometamorphopsia, has been posited to be due to dysfunction in the ventral occipito-temporal cortex (Blom, 1998). While autozoanthroprosopometamorphopsia localization has been inconclusive (Blom, 2020), hemi-autoprosopometamorphopsia has been described with lesions between the left retro-splenium and cingulate gyrus (Imai, 1995). It is possible that facial self-perception is impacted by dysfunction of areas involved for facial identification: the fusiform gyrus, occipital lobe face area, and superior temporal sulcus face area (Blom, 2021). Superimposed internalization and recognition may also demonstrate greater involvement of bilateral frontal lobes. In the current case, equine delusion superseded pure facial transformation. This may be more appropriately defined as a form of clinical zoanthropy, an equine variant of lycanthropy, where there is a delusion of transforming into a horse, as opposed to just the face into a horse face (Blom, 2021). In those who present with delusions beyond countenance, an evaluation for neuroanatomic pathology may be revealing.

#### **M159. Brain Insulin Signaling is Associated with Late-Life Cognitive Decline**

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**Background:** In a previous study (Arvanitakis et al., Annals of Neurology, 2020), we showed that higher levels of insulin signaling markers in postmortem human brain were associated with lower levels of cognitive function proximate to death. However, our prior cross-sectional analyses did not address whether brain insulin signaling markers are related to changes in cognitive function over time. **Objective:** To examine the association between postmortem brain insulin signaling and late-life cognitive decline in older adults with or without diabetes who came to autopsy. **Methods:** We studied 150 individuals (mean age at death = 87 years, 48% females), 75 with diabetes matched to 75 without diabetes on age, sex, and education, from the Religious Orders Study, a community-based, clinical-pathologic cohort of Catholic nuns, priests, and brothers from across the United States. Participants underwent annual clinical evaluations including neuropsychological testing (using 19 individual tests) and postmortem brain autopsy. We measured levels of insulin signaling markers in the postmortem prefrontal cortex using enzyme-linked immunosorbent assay and immunohistochemistry, and then conducted linear mixed-effect regression analyses (adjusted for age, sex, and education) to examine the associations of brain insulin signaling markers with longitudinally assessed late-life cognition (outcomes of composite scores of global cognition and five different cognitive domains). **Results:** We found that higher levels of serine/threonine-protein kinase (AKT1) phosphorylation (pT<sup>308</sup>AKT1/total AKT1) in the brain were associated with

lower baseline levels of global cognition (estimate=-0.251,  $p=0.005$ ), and of several cognitive domains, specifically episodic memory (estimate=-0.344,  $p=0.002$ ) and working memory (estimate=-0.203,  $p=0.003$ ), in keeping with our prior cross-sectional findings. In the same series of mixed effect models, higher levels of brain  $pT^{308}AKT1$ /total  $AKT1$  were associated with a faster decline in measures of global cognition (estimate=-0.023,  $p=0.030$ ), and of episodic memory (estimate=-0.024,  $p=0.032$ ), working memory (estimate=-0.018,  $p=0.012$ ), and visuospatial abilities (estimate=-0.013,  $p=0.027$ ). Brain insulin receptor substrate-1 (IRS1) phosphorylation ( $pS^{307}IRS1$ /total IRS1) was not associated with the level or decline in global cognition and most cognitive domains, except for perceptual speed (level effect: estimate=0.233,  $p=0.008$ ; decline effect: estimate=0.020,  $p=0.020$ ). The density of  $pS^{616}IRS1$ -stained cells in the brain was not associated with the level or decline in global cognition or cognitive domains. **Conclusions:** These findings suggest that postmortem brain insulin signaling is associated with late-life cognitive decline. AKT phosphorylation is associated with decline in global cognition and memory in particular, whereas IRS1 phosphorylation is associated with decline in perceptual speed.

#### **M160. Can Antiepileptic Help Recovery in Opioid-Associated Amnesic Syndrome? A Case Report**

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**Objective:** To report a case of Opioid-Associated Amnesic Syndrome (OAS) in a patient previously treated with antiepileptics. **Background:** OAS is manifested by a new onset persistent anterograde amnesia lasting longer than 24 hours and with characteristic MRI bilateral diffuse hippocampi diffusion restriction. Pathophysiology is unclear, but a drug-induced hippocampal excitotoxicity by direct neurotoxic effect leading to cytotoxic edema is suspected, possibly exacerbated by concomitant hypoxemia. Antiepileptics have been considered with some potential to reduce the hyperexcitability. **Method/Design:** Case report **Result:** A 19-year-old man with chronic depression and multiple suicide attempts as well as an unspecified seizure disorder on levetiracetam 500mg BID, and taking alprazolam for insomnia, was found unconscious and in respiratory distress for an unknown period of time requiring intubation. Patient had pinpoint pupils and history confirmed polysubstance use including oxycodone, fentanyl and IV heroin 3 days prior. Patient received 12mg of naloxone, and improved rapidly with supportive care, allowing extubation 3 days after admission. MRI brain revealed the typical bilateral hippocampi diffusion restriction seen in OAS. Initial MoCA after extubation was 9/30 with severe anterograde amnesia, but also affecting extra amnesic domains. A week later, MoCA score had improved to 22/30 with persistent severe anterograde amnesia. At 3 months follow up, family reported mild memory improvement, still preventing work but patient able to resume some hobbies. At 6 months, follow up MRI brain showed resolution of hippocampal

signal abnormalities, and patient reported resolution of memory impairment to PCP, however he was lost to follow up with neurology and neuropsychology clinic. **Conclusion:** OAS syndrome is a devastating diagnosis with typically severe anterograde amnesia and uncertain recovery. Identification of protective factors is warranted. Antiepileptics may have some degree of protective effects which may have been the case in our patient. Longer follow up and more research in this field is needed to further confirm this hypothesis.

#### **M161. Cannabis Induced Obsessive Compulsive Disorder**

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**Introduction:** Precipitation of OCD from cannabis use has not been described. **Case Study:** A 21 year male presented with anxiety and depression intermixed with mania and multiple past hospitalisations starting at age 12 for similar complaints. While he denied use of hallucinogenic or psychotropic substances, he described using cannabis edibles to help him “feel stable”, using 2 grams of cannabis every day since his early teenage years. For 3 months, he had intensified his use of cannabis, through smoking and oral ingestion, once every hour all day long. Since then he finds it difficult to control his own thoughts and gets repetitive unpleasant thoughts beyond his control. He noted obsessing about his girlfriend being disloyal. He began compulsions of checking her cell phone multiple times on a daily basis and started checking door locks three times to make sure they were locked. These obsessive thoughts and compulsions only started after he substantially increased use of marijuana in the last 3 months. Despite the absence of any anxiolytic, antidepressant or neuroleptic treatments, his OCD symptoms have completely resolved since discontinuing marijuana. **Results:** Speech is hyperverbal, pressured and rapid paced. Mood appears manic. There are free floating anxieties. Thought processes appear tangential and circumstantial. National Institute on Drug Abuse for Alcohol, Smoking and Substance Involvement Screening Test (National Institute on Drug Abuse, 2012): positive for cannabis. Cannabis Use Disorder Identification Test-Revised: 26 (possible cannabis use disorder) (Adamson, 2010). Marijuana Problem Scale: 24 (severe functional impairment due to cannabis over the past month) (Stephens, 2000). Obsessive Compulsive Inventory - Revised: difficulty in controlling his own thoughts and feeling upset by unpleasant thoughts that come to his mind against his will (Foa, 2002). Urine drug screen: positive for cannabis. **Discussion:** OCD is hypothesised to be generated from the pre-frontal cortex (orbitofrontal and anterior cingulate cortices), basal ganglia and thalamus (Bokor, 2014). Cannabis impacts upon the olfactory bulb, hippocampus, basal ganglia and cerebellum via the CB1 subtype of cannabinoid receptors encoded by the CNR1 gene (Dhein, 2022). Through cannabis disinhibition of these overlapping brain areas involved in generation of OCD, the patient's OCD symptoms may have been exacerbated. It is possible that the cannabis could have been contaminated with hallucinogens, insecticides, heavy

metals including copper, nickel, or lead as reported in 21% of samples (Evans, 2020). Query as to cannabis use in precipitating OCD may be worthwhile.

#### **M162. Clinical Phenotype of Posterior Cortical Atrophy Progressing to Corticobasal Syndrome: A Case Report**

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Corticobasal syndrome (CBS) is a clinical phenotype most commonly attributed to corticobasal degeneration (CBD) but has also been described in Alzheimer's Disease (AD), progressive supranuclear palsy, Pick's disease, frontotemporal lobar degeneration with TDP-43 inclusions, dementia with lewy bodies (DLB), and Creutzfeldt Jacob disease. On the other hand, posterior cortical atrophy (PCA) is a clinico-radiological syndrome most commonly associated with AD, but also noted with DLB and CBD. Even though PCA and CBS are two distinct neurodegenerative disorders, there may be some commonalities between them. Nearly 20% of patients with PCA also have features of CBS, such as asymmetric motor symptoms and apraxia. This co-occurrence of PCA and CBS may reflect underlying shared neuropathology, including the accumulation of abnormal proteins such as tau and amyloid-beta in the affected brain regions. Additionally, genetic factors such as mutations in the MAPT gene have been associated with both PCA and CBS. We describe a patient who presented with PCA as the primary clinical phenotype that eventually evolved to PCA-CBS spectrum. 73-year-old woman presented to our movement disorder clinic after being referred from Ophthalmology for "visual agnosia" and blurry vision ongoing for 3 years. She was reportedly diagnosed with Parkinson's disease a year ago. She needed assistance with activities of daily living and self-care. Exam was notable for asymmetric right predominant parkinsonism, ideomotor apraxia, and limited vertical ocular motility. A formal neuropsychological evaluation confirmed the ideomotor apraxia, optic ataxia, prosopagnosia, simultagnosia, finger agnosia, and left/right disorientation. Anterograde memory, word-finding, attention, and executive functioning were impaired as well. MRI brain was striking for significant atrophy in the parieto-occipital regions consistent with posterior cortical atrophy. Her initial clinical phenotype was PCA based on visual symptoms which eventually evolved into CBS as documented by the asymmetric extrapyramidal signs and global cognitive deficits. Given the clinical and neuropathological overlap between PCA and CBS, accurate diagnosis of these conditions can be challenging, especially in patients with atypical presentations. We hereby present a case that fits both disease categories and proposes a concept of PCA-CBS sharing the same clinical spectrum. Further research should focus on pathological hallmarks of PCA and CBS especially when they co-occur clinically to better define symptom-pathology correlation.

#### **M163. Creutzfeldt-Jakob Disease Presenting as Psychiatric Disorder: Case Presentation and Systematic Review**

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**Background:** Creutzfeldt-Jakob disease (CJD) is a spongiform encephalopathy caused by misfolded prion proteins. Due to variability in presentation, the diagnosis may be missed in lieu of various psychiatric disorders. Our study reviews psychiatric mimics for CJD, and the workup used to establish the correct diagnosis. **Case Presentation:** A 54-year-old male with past medical history of traumatic brain injury and major depressive disorder presented with chest pain. During the course of hospital stay, he was found to be increasingly aggressive, and behaved out of character. He was involuntarily admitted to the inpatient psychiatric unit. Further review of clinical history revealed that the patient was diagnosed with cognitive impairment and depression a year ago. Patient was agitated, poorly redirectable, and had unstable gait on neurological examination. MRI brain demonstrated restricted diffusion along the parieto-occipital and temporal regions (L>R) and also in the subcortical structures, including the basal ganglia and thalami, with accompanying subtle FLAIR hyperintense signal abnormality in these regions, deemed as artifact at the time. Repeat MRI brain demonstrated persistent findings. Cerebrospinal fluid 14-3-3 and RT-QuIC samples were positive, suggestive of CJD. **Methods:** Literature review was conducted on PubMed to identify CJD cases initially diagnosed with psychiatric disorder. Search terms included "CJD" or "Creutzfeldt-Jakob disease" with three common psychiatric diagnoses, "Depression," "Psychosis," and "Mania." Exclusion criteria included articles not written in English, unrelated neurological pathology, and cases that did not involve an initial psychiatric diagnosis. **Results:** Thirty-five articles met our inclusion criteria representing 45 total patients. 35 patients were identified through the Boolean search "CJD" OR "Creutzfeldt-Jacob Disease" OR "Creutzfeldt-Jacob Disease" AND "Depression." To confirm diagnosis, 89% of cases used MRI, 91% used EEG, 77% used CSF analysis (including protein 14-3-3 and tau), 6% used FDG-PET imaging, and 26% used CT scans. Nine patients were identified through the search "CJD" OR "Creutzfeldt-Jacob Disease" OR "Creutzfeldt-Jacob Disease" AND "Psychosis." To confirm diagnosis, 89% of cases used MRI, 78% used EEG, 67% used CSF analysis, and 33% used CT. One patient was found through the search "CJD" OR "Creutzfeldt-Jacob Disease" OR "Creutzfeldt-Jacob Disease" AND "Mania." MRI, EEG, and CSF analysis were used for diagnosis. **Conclusion:** CJD commonly presents as a psychiatric mimic. Prompt imaging and CSF studies can be used to arrive at the correct diagnosis.

#### **M164. Dementia and the Gut: Is There a Gut Immune Imbalance? Can We Intervene?**

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Sacramento, Sacramento, CA, USA, <sup>5</sup>University of Nebraska Medical Center, Omaha, Omaha, NE, USA, <sup>6</sup>John D Dingell VA Medical Center, Detroit, Detroit, MI, USA.

**Introduction:** The global burden of dementia is staggering. In 2019 dementia ranked 7<sup>th</sup> as a cause of death and the 4<sup>th</sup> in individuals over 70 years of age. The incidence is likely to increase with the increasing proportion of the world's aging population. Since gut microbiota have been implicated, we studied factors that might impact the microbiome and immune system in a cohort of dementia patients. **Methods:** During the follow-up of patients with increased risk of colorectal cancer (CRC), we found 53 patients with a diagnosis of dementia therefore we compared the dementia group against a control group of 2,203. Expression of Paneth cell marker p87 was used as a surrogate for Paneth cell activity determined by ELISA of regional colonic mucosal colonoscopy pinch biopsies. The stance of the innate immune system was scored by the ratio (FERAD) of ferritin: fecal p87 (OD-background). Other parameters such as underlying disease and basic clinical functional tests was obtained from the VHA computerized patient record system (CPRS). Written informed consent was taken at enrollment in accordance with IRB procedures. **Results:** In dementia (53) patients age of  $67 \pm 11$ . The Ferad ratio is 90%, ferritin level of 147. P87 expression in the ascending colon is  $0.77 \pm 0.016$ , transverse colon is  $0.075 \pm 0.026$ , sigmoid colon is  $0.064 \pm 0.036$ . Control (2114) patients age of  $61 \pm 12$ . The Ferad ratio is 33%, ferritin level of 250. Comparing both groups is statistically significant of  $P < .004$ . P87 expression in the ascending colon is  $0.189 \pm 0.248$ , transverse colon is  $0.277 \pm 0.41$ , sigmoid colon is  $0.151 \pm 0.036$ . **Conclusions:** According to the study, we observed that fecal microbiota of dementia patients differ from that of the general population. In the dementia group, the Paneth cell p87 expression is less in the ascending through the sigmoid colon suggesting less modulation effect perhaps explaining the observed difference in the microbiota. In addition, the kidney function is better and ferritin levels are lower which may decrease oxidative stress in dementia patients. The FERAD ratio (ferritin: fecal p87), which is the marker of the innate immune system, was significant with  $P < .004$  in the dementia group compared to the control group. Therefore, implying the importance of the innate immune system in the dementia patients. These significant results can shed some light on early intervention in modulating or reversing early dementia by intervening on the p87 expression.

#### **M165. Dementia with Lewy Bodies Presenting with Coexisting TDP-43 and Tau Proteinopathy without Beta-Amyloid Pathology**

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A 71 year-old ambidextrous man presented to a neurology clinic initially with action tremor, followed by cognitive changes within a couple months. Several years prior to

presentation he had developed social withdrawal, anxiety and apathy, and had been acting out his dreams for multiple years. Within 1 year of motor symptom onset, he developed micrographia, drooling, hypophonia and hypomimia. Initial cognitive changes predominantly involved executive dysfunction such as fixing household equipment. Throughout his course, he developed severe orthostatic hypotension which was difficult to control due to extreme swings of blood pressure. He also suffered from significant delirium and fluctuations which dramatically improved after initiation of acetylcholinesterase inhibitors. His exam 3 years before his death showed bradykinesia, bilateral resting hand tremor and cogwheel rigidity. Neuropsychological evaluation indicated significant cognitive impairments within dementia range; mainly dysfunctions within executive, visual-spatial domains and motor processing speed, with some evidence for mild amnesic symptoms. Brain MRI indicated mild diffuse brain atrophy and mild symmetric hippocampal atrophy. Autopsy revealed substantial neocortical, limbic and brainstem Lewy bodies, involving the substantia nigra, locus coeruleus and diffuse neocortical regions including prefrontal cortex. There were also tau and TDP-43 positive inclusions within the hippocampus, despite absence of  $\beta$ -amyloid deposition. Mild amnesic symptoms and hippocampal atrophy in the setting of Lewy Body Dementia might suggest co-morbid Alzheimer's disease. Instead, our patient was found to have early evidence of limbic associated TDP-43 encephalopathy (LATE) and primary age-related tauopathy (PART), either of which might could contribute to these symptoms. We used this mixed-pathology case to dual stain with p-synuclein, TDP-43, and phospho-tau to determine the co-occurrence and distribution of mixed pathologies across multiple brain regions. Further research into the contribution and interaction between co-morbid pathologies is imperative, given the high incidence of mixed dementias. Detailed investigation of individual cases may provide hypotheses for symptoms that do not currently have a clear underlying etiology, such as fluctuations, anxiety and social withdrawal.

#### **M166. Depression Associates with Cognitive Impairment and Rates of Decline in African Americans**

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**Objectives:** To evaluate the frequency of modifiable dementia risk factors and their associations with cognitive impairment and rate of decline in a diverse cohort. **Background:** African Americans (AA) comprise 12% of the United States population  $\geq 65$  years-old but 19% of patients with dementia. Modifiable dementia risk factors may contribute to 40% of dementia risk and are overrepresented in AA yet their contributions to disparate dementia risk are unknown. **Methods:** The frequency of modifiable dementia risk factors and their associations with cognitive impairment and rate of decline were evaluated in AA ( $n=261$ ) and non-Hispanic White (nHW;  $n=193$ ) participants who completed  $\geq 2$  research visits in studies of aging and memory at the Mayo Clinic

Alzheimer Disease Research Center in Jacksonville, Florida. Modifiable dementia risk factors and their associations with cognitive impairment (global Clinical Dementia Rating® [CDR]  $\geq 0.5$ ), and rates of decline in impaired participants (measured using the CDR Sum-of-Boxes) were compared in AA and nHW, while controlling for demographics, APOE $\epsilon 4$  status, and Area Deprivation Index. **Results:** Hypertension, hypercholesterolemia, obesity, and diabetes were common in both groups and overrepresented in AA participants but did not associate with cognitive impairment. Depression was associated with increased odds of cognitive impairment in AA (OR: 3.10, 95%CI: 1.52-6.30) and nHW participants (OR: 3.46, 95%CI: 1.14-10.48). Furthermore, depression was uniquely associated with an increased rate of cognitive decline in AA participants ( $\beta$ : 1.55, 95%CI: 0.50-2.60;  $p=0.004$ ), who were less likely to report antidepressant medication use (40/45, 89%) compared to nHW participants (21/44, 48%;  $p<0.001$ ). **Interpretation:** Depression was associated with cognitive impairment in AA and nHW participants but with an increased rate of cognitive decline only in AA participants who were less likely to report antidepressant medication use. Optimizing depression screening and treatment in AA communities may improve cognitive trajectories and outcomes in this population.

#### **M167. Development of a Novel Mouse Model of Neonatal Hypoxic Ischemic Encephalopathy**

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Neonatal hypoxic ischemic encephalopathy (HIE) is a brain injury caused by a variety of underlying factors that culminate in insufficient oxygenation of the neonatal brain during birth. HIE can result in devastating and life-long disability in affected infants and there is a critical need to understand the basic mechanisms of disease to develop effective therapeutics. The current standard mouse model of HIE is the Rice-Vannucci model, which utilizes a unilateral carotid artery ligation followed by prolonged moderate hypoxia. This model results in a large hemispheric ischemic injury, which is uncharacteristic of the injury pattern seen in humans affected by this injury. Furthermore, maternal or placental factors cannot be modeled adequately by the Rice-Vannucci model because all manipulations are done postnatally. For these reasons, we developed a novel mouse model of HIE that combines prenatal maternal immune activation (MIA) with deep hypoxia at term equivalence. We found pups subjected to MIA exhibited delayed motor skills (hindlimb splay and spontaneous locomotion) that did not persist to adulthood. However, pups subjected to the combined HIE model (MIA + hypoxia) had persistent motor coordination defects (rotarod) in adulthood. These mice also displayed maladaptive responses to anxiety testing (open field test) and social deficits (three chamber social behavioral tests). This novel non-invasive mouse model of neonatal HIE allows investigation of the pathophysiology and neuroimmune effects of HIE caused by a wider variety of perinatal factors and produces a

diverse range of cognitive, behavioral, and social deficits, similar to that seen in humans who suffer HIE at birth.

#### **M168. Differential ATN Networks of Cerebrospinal Fluid and Neuroimaging Biomarkers and Their Prediction of Cognition between Self-Reported Black and Non-Hispanic White Individuals**

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**Background:** Biomarkers of Alzheimer's disease (AD), including cerebrospinal fluid (CSF), amyloid PET, and MRI imaging measures, have been reported to vary between self-reported Black/African American and Non-Hispanic White individuals. It is unknown whether different racialized groups have differences in the network of connections between AD biomarkers, or in the prediction of cognition by these biomarkers.

**Method:** The Study of Race to Understand Alzheimer Biomarkers (SORTOUT-AB) centrally re-processed CSF samples and imaging scans collected at four AD Research Centers/studies: Washington University, University of Pennsylvania, Emory University, and the Harvard Aging Brain Study. Data included CSF measures for 286 Black and 2,080 White participants, amyloid PET for 157 Black and 936 White participants, tau PET for 67 Black and 492 White participants, and structural MRI for 322 Black and 1,530 White participants. Spearman correlations between biomarkers and cognitive measures were estimated within each racial group, then compared between groups, adjusting for age, sex, APOE  $\epsilon 4$  carrier status, cognitive status, years of education, and medical comorbidities.

**Results:** CSF A $\beta$ 42 was positively correlated with both total tau and p-tau181 in Black but not White participants. CSF A $\beta$ 42/40 was negatively correlated with total tau and p-tau181 in both racial groups, but at a smaller magnitude in Black individuals. CSF A $\beta$ 40 was positively associated with p-tau181 in both racial groups, but at a larger magnitude in Black individuals. CSF neurofilament light (NfL) was correlated with all other CSF biomarkers in both racial groups and did not vary by race. CSF A $\beta$ 42, A $\beta$ 42/40, and p-tau181 had stronger correlations with global cognition and memory in White than

Black participants. No racial differences were found in correlations between different imaging biomarkers, or in correlations between imaging biomarkers and cognition. Amyloid PET Centiloid was negatively correlated with CSF A $\beta$ 42 and A $\beta$ 42/40 in White but not Black individuals. **Conclusion:** Relationships between CSF and imaging biomarkers, and between AD biomarkers and cognitive measures, differed between Black and White groups. This suggests that AD biomarkers may not have consistent meanings across racialized groups. Use of biomarkers in designing/analyzing AD prevention and treatment trials must appropriately address racial differences.

#### **M169. Dysfunction of the Neuroglial Lactate Shuttle in Metabolic Syndrome Contributing to Cognitive and Memory Impairment**

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The metabolic syndrome (MetS) affects 1 in 3 adults in the United States. MetS leads to serious neurological complications including dementia. Glia in the brain provide metabolic support for neurons and their axons by shuttling energy substrates, such as lactate through monocarboxylate transporters (MCTs). Herein, we hypothesize that MetS alters MCT expression leading to neurodegeneration in the CNS causing cognitive and memory impairment. Young (5-week old) and old (12-month old) male mice were fed either standard diet (SD, 10% fat) or high fat diet (HFD, 60% fat) for 12 weeks followed by a full assessment of metabolic parameters, cognitive function, and MCT expression levels. Complimentary *in vitro* work in cultured human oligodendrocytes further characterized MCT-mediated lactate trafficking. Both young and old mice on HFD gained more weight and had higher blood glucose and fat mass compared to SD controls. Old HFD mice performed poorly in puzzle box and social recognition tests, reflecting impaired cognition. Interestingly, oligodendrocyte MCT1 protein expression was upregulated in young HFD mice and downregulated in old HFD mice compared to their SD counterparts. Immunohistochemistry of brain sections show co-localization of MCT1 protein expression in mature oligodendrocytes. *In vitro*, human oligodendrocytes treated with 150  $\mu$ M palmitate to mimic MetS showed downregulation of MCT1 protein expression after 24h. Collectively, these results indicate that MetS impairs MCT-mediated lactate transport in glial cells providing a novel mechanism underlying MetS-associated neurodegeneration in CNS and PNS.

#### **M170. Expanding the Diagnostic Applications of Cerebrospinal Fluid Biomarkers in Patients with Rapidly Progressive Dementia**

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**Objectives:** Apply established and emerging cerebrospinal fluid (CSF) biomarkers to improve diagnostic accuracy in patients with rapidly progressive dementia (RPD). **Background:** The causes of RPD are heterogeneous, including neurodegenerative, vascular, and autoimmune/inflammatory diseases. Overlap in presenting symptoms and signs, results of cognitive testing, and findings on brain imaging and other common diagnostic tests confounds the etiologic diagnosis, contributing to diagnostic delays, missed opportunities for treatment, and poorer outcomes in patients with RPD. New tools and approaches are needed to improve diagnostic accuracy, with particular emphasis on improving early recognition of patients with potentially treatable causes of RPD. **Methods:** Established and emerging biomarkers of Alzheimer disease neuropathology (A $\beta$ 42/40, ptau181, ptau231), neuroaxonal and neuronal injury (neurofilament light [NfL], VILIP-1, total tau), neuroinflammation (YKL-40, sTREM2, GFAP, MCP-1), and synaptic dysfunction (SNAP-25, neurogranin) were measured in CSF obtained at presentation from 78 prospectively accrued patients with RPD due to neurodegenerative (n=35), vascular (n=9), and autoimmune/inflammatory (n=34) diseases, and 72 age- and sex-similar cognitively normal individuals (controls). Causes of RPD were further classified as potentially treatment responsive or nonresponsive. Biomarker levels were compared across etiologic diagnoses and by treatment responsiveness, referencing control values. Analyses were adjusted for age (ANCOVA). **Results:** Alzheimer disease biomarkers (low A $\beta$ 42/40 and elevated ptau181 and ptau231) were associated with neurodegenerative causes of RPD (ANCOVA, p=0.02 p=0.30, p=0.15), while high NfL (p=0.61), low VILIP-1 (p=0.009), and elevated markers of inflammation (sTREM2, p=0.009; YKL-40, p<0.001) identified patients with autoimmune/inflammatory diseases. MCP-1 levels were highest in patients with vascular causes of RPD (p=0.08). 44 patients (56.4%) had potentially treatment responsive causes of RPD. Treatment responsiveness was associated with higher levels of CSF A $\beta$ 42/40 (p=0.003), NfL (p<0.001), sTREM2 (p<0.001) and YKL-40 (p<0.001), and lower levels of ptau181 and ptau231 (p<0.001, p<0.001) and VILIP-1 (p<0.001). **Interpretation:** Selected CSF biomarkers at presentation associated with etiologic diagnoses and treatment responsiveness in patients with neurodegenerative, vascular, and autoimmune/inflammatory causes of RPD. Biomarker panels may be adapted to improve diagnosis and early recognition of patients with treatment responsive causes of RPD.

**M171. Exploring Cognitive Functioning and Health Literacy in Patients with Familial Hypercholesterolemia**  
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**Background:** Familial Hypercholesterolemia (FH) is a genetic disorder characterized by high cholesterol levels. Cholesterol dyshomeostasis is being increasingly recognized as a cause or risk factor for many neurological conditions. There is evidence suggesting that FH is associated with cognitive impairment (CI), and that long-term statin therapy is a potential protective factor against CI in patients with FH. Health literacy (HL), an individual's comprehension of their own health, is an important predictor of outcomes for chronic medical conditions like FH, that require long-term treatment. **Objectives:** (1) To examine the cognitive status of patients with FH and compare the outcomes with a control group; (2) Assess the associations between cognitive domains and HL in FH patients. **Methodology:** Genetically confirmed FH patients attending the lipid clinic at a major tertiary care center in Oman (study group) were compared with matched healthy volunteers (control group). A sociodemographic survey and indices of intellectual status and cognitive functioning were administered to both groups, assessing: (i) current reasoning ability (Raven's Progressive Matrices); (ii) attention and concentration (Digit Span); (iii) verbal learning and memory (California Verbal Learning Test), and (iv) executive functioning (Verbal Fluency Test, Trail Making Test). Univariate analysis was utilized to compare the outcomes of the two groups. The study group was also administered the 3-item Health Literacy questionnaire, and associations between cognitive functioning and HL were examined by univariate analysis. **Results:** A total of 52 FH patients participated in this study, with a mean participant age of 37.2±9.2 years and a sex distribution of 27 males (51.9%) and 25 females (48.1%). FH patients exhibited poorer performance on the indices of current reasoning ability ( $t = 2.37$ ,  $p = 0.02$ ), attention and concentration ( $t = 3.94$ ,  $p < 0.001$ ), verbal learning and memory ( $t = 4.52$ ,  $p < 0.001$ ), and one of the two executive functioning tests ( $t = 4.23$ ,  $p < 0.001$ ). However, the FH patients scored higher than the healthy control group on another index of executive functioning: the Trail Making Test ( $t = 11.45$ ,  $p < 0.001$ ). Lower performance on the attention and concentration domain significantly correlated with low HL status ( $U = 186.00$ ,  $p = 0.017$ ). **Conclusion:** FH was found to affect several cognitive domains, with impaired attention and concentration associated with inadequate HL. This knowledge is expected to help physicians counsel FH patients about their condition, and the importance of adhering to medication and family screening.

#### M172. Exploring Divergences between the Experiences and Future Perceptions of People with Dementia and Their Care Partners

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**Background:** Family care partner engagement in clinical decision making becomes increasingly pertinent if dementia severity progresses and cognitive capacity declines. Care partners are frequently called upon by care teams to communicate on behalf

of persons with dementia (PWD) and to make preference-sensitive decisions on their behalf. There is an underlying assumption that care partners know and can communicate the preferences of PWD. However, research regarding areas of divergence between PWD and care partner perspectives and priorities has been limited. **Methods:** In this qualitative study exploring stakeholder perspectives on living with dementia and planning for the future, we conducted semi-structured, individual interviews among persons with mild cognitive impairment or mild dementia and their family care partners. Interviews were audio-recorded and transcribed. Deidentified transcripts were reviewed by the research team independently and during weekly consensus meetings to identify relevant themes. Qualitative coding was conducted in Atlas.ti (Version 23.1.1.0) utilizing inductive thematic analysis. This analysis focused on the emergence of divergence between the stated experiences and perceptions of PWD and their care partners. Sample size was determined by thematic saturation within each sub-group. **Results:** Thematic saturation was reached after interviewing 12 patient-care partner dyads. Analysis identified divergence between PWD and their care partners in two key areas: 1) lived experiences and 2) the patient's future hopes and worries. Lived experiences encompassed situations in which PWD tended to describe less daily impact of dementia on themselves or their family. This contrasted with care partners who believed the PWD was heavily impacted by their disease and perceived the PWD to be suffering existentially to a greater degree than the PWD reported themselves. When considering hopes and worries, PWD often expressed adopting a "day-to-day" outlook, some indicating this was to avoid thinking about the future. Care partners believed that patient hopes and worries centered around family, maintaining independence, and disease progression. Despite the observed discrepancies between expressed hopes and worries, care partners generally felt confident that they were accurately communicating the patient's priorities. **Conclusion:** The perspectives of PWD and their care partners may diverge substantially even when patients are able to communicate. This raises important questions about how clinicians should approach shared decision-making and goals of care when a patient's ability to communicate becomes limited. Future research should consider methods to improve shared understanding of patient priorities and concerns.

#### M174. General and Biomarker Cerebrospinal Fluid Findings in Prion Disease and Other Rapidly Progressive Dementias

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**Background:** Rapidly progressive dementias (RPDs)—conditions in which patients progress from normal cognition or function in <2 years but typically over weeks to months—have many possible etiologies, including prion disease. Diagnosis can be difficult but better understanding of cerebrospinal fluid (CSF) findings should improve diagnosis. Here we

analyze the spectrum of basic and biomarker CSF findings in our RPD cohort. **Methods:** Retrospective cohort study of patients with RPD referred to the University of California San Francisco (UCSF) Memory and Aging Center (MAC) and evaluated in person or through medical record review. Sporadic CJD (sCJD) cases were included if they met definite sCJD criteria, met UCSF symptom criteria for sCJD and had a brain MRI and/or EEG (periodic sharp wave complexes) indicative of sCJD (probable sCJD). Genetic prion cases had *PRNP* mutations and were symptomatic at the time of data collection. Non-prion RPD (npRPD) cases met strict inclusion criteria. Data were extracted from our MAC RPD database. Statistical analyses were performed in R-studio. **Results:** The cohort included: sCJD (n = 591), npRPD (n = 271), familial CJD (fCJD, n = 42), Gerstmann-Sträussler-Scheinker syndrome (GSS, n = 22), and Fatal Familial Insomnia (FFI, n = 4) for whom we had documented CSF data in the RPD database. 22% of the sCJD and 28% of npRPD cohort had elevated CSF total protein. CSF glucose of the sCJD cohort was slightly higher than npRPD (median (IQR): 66.0 (12) vs. 63.0 (13),  $p=0.0016$ ). Surprisingly, ~5% of the sCJD cohort had leukocytosis (>5 WBCs; 17% of npRPD), ~5% had elevated IgG index (>0.7 mg/dl; 14.3% of npRPD) and ~5.0% had elevated OCBs (>1; 16.7% of npRPD). The sensitivity, specificity, and AUC of sCJD vs. npRPD for t-tau (sCJD n=224; npRPD n=101) was 78.1%, 87.1% and 89.5%; for NSE (sCJD, n=161; npRPD, n=85) was 66.5%, 90.6% and 86.1%; for 14-3-3 (sCJD, n=283; npRPD, n=114) was 64.0, 85.1%, and 74.6%; and for RT-QuIC (sCJD, n=98; npRPD, n=17) was 85.7%, 94.1%, and 89.9%. For a subcohort with RT-QuIC, 14-3-3, and t-tau available from the same CSF sample (sCJD, n=94; npRPD, n=15), t-tau had the highest AUC, 93.2. **Conclusion:** sCJD cases can have abnormal inflammatory markers and elevated protein. t-tau has high diagnostic accuracy, although not as specific as RT-QuIC, but might be used in conjunction with MRI and in place of 14-3-3 to diagnose prion disease.

#### M175. Generation of Position Correlated Cells in Primary Sensory Cortices Requires Bottom-Up Inputs

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Interactions between the hippocampus and neocortex form the basis of memory encoding and recall. The conditions necessary for hippocampal influence on cortical circuits are not well understood, however. Recent studies have found position-correlated cells (PCCs) in the neocortex, which fire sequentially as mice run down real or virtual track environments. Notably, PCC firing fields are similar to hippocampal place fields, require a functional CA1 to form, but, once formed, survive subsequent hippocampal damage. PCCs are a ubiquitous feature of the neocortex and have been found in visual, somatosensory, olfactory, and auditory cortices. But when recording in each of these areas, experimenters have ensured modality-matched sensory cues were available to the animal (i.e. tactile cues when recording in somatosensory

cortex). In this study, we test whether hippocampal signals can drive PCCs in the absence of bottom-up signals by recording from multiple sensory regions simultaneously while animals run in a uni-modal environment. We first used widefield calcium imaging to delineate retrosplenial (RSC), primary visual (V1), and primary somatosensory cortex (S1) based on responses to bottom-up visual and tactile stimulation under light anesthesia. Then we used a two photon mesoscope to record hundreds of cells within these three cortical regions simultaneously, as mice ran through a visual virtual reality environment with no discriminative somatosensory cues. We found cells had organized into PCC sequences in RSC and V1 but were notably absent in S1. Decoding errors were twice as high in S1, comparable to levels expected in hippocampus lesioned animals based on previous studies. S1 fields were clustered around the reward sites, the only portion of the track with a distinctive tactile stimulus. Therefore, top-down hippocampal inputs alone appear insufficient to drive PCC expression in primary sensory cortices without concurrent bottom-up signals potentiating those cells. In contrast, association areas (e.g. RSC) that receive direct hippocampal stimulation express PCCs regardless of the stimulus modality. These results provide evidence that memory consolidation in the neocortex is directed towards the same regions involved in the initial memory formation.

#### M176. Handedness in Alzheimer's Disease: A Systematic Review and Future Directions

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**Background:** Among humans 85-90% are right-handed while only 10-15% are left-handed. Handedness has been a topic of scientific interest for approximately 50 years. Many false and misleading ideas have dominated this field with a still limited amount of research into the association with clinical disorders like Alzheimer's disease (AD). **Objective:** To summarize available evidence on the association of handedness with AD and to provide direction for future research. **Methods:** In this systematic review performed in accordance with PRISMA guidelines, PubMed, Embase and Cochrane Library databases were searched for medical studies regarding the association of handedness and AD. Inclusion criteria were: (1) English language articles published in peer-reviewed journals, (2) including human participants (3) with a diagnosis of AD and (4) assessed for handedness. The ROBINS-I tool and the New Castle Ottawa scale were used for certainty and quality of evidence assessment respectively. **Results:** Eleven articles published between 1984 and 2020 and including a total of 2137 subjects were analyzed. Six were case-control studies, four were cohort studies and 1 was a cross-sectional study. Case-control studies show that left-handedness is not a statistically significant risk factor for

AD. Three studies assessed the role of handedness as a determinant of disease course by measuring cognitive decline in AD patients. However, due to heterogeneity in handedness assessment methods the role of handedness in AD prognosis is not clear. Non-right handedness was found to be more prevalent in early-onset AD patients (EOAD), compared to those with late-onset disease (LOAD). Only two studies measured the strength of handedness using the Edinburgh Handedness Inventory (EHI). Limitations of the current studies include: handedness assessment heterogeneity; collapse of left and mixed handers in a single non-right handedness category; small and non-sex balanced sample design. **Conclusion:** Evidence suggests that left-handedness is not a risk factor for AD as a whole, however a higher number of non-right handers is present in the early-onset patient population, arising the concern that left-handedness may be a risk factor for EOAD. These findings, together with the limitations evidenced by this study, highlight the need for further research to address this concern and to distinguish between left and mixed or shifted handedness in future studies. Recommended strategies and tools to accurately assess handedness for this purpose are presented.

#### **M177. Immune Modulating Mechanisms of Human Neural Stem Cell Transplantation in a Transgenic Alzheimer's Disease Mouse Model**

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**Background:** Many pathways are implicated in pathogenesis of Alzheimer's disease (AD). Stem cells are a promising strategy to simultaneously correct multiple pathways; however, therapeutic mechanisms of stem cells are not well described. Here, we used spatial transcriptomics to quantitate gene expression following intracranial transplantation of human neural stem cells (hNSCs) in a mouse model of AD. **Method:** The 5XFAD mouse model was utilized. An hNSC cell line (HK532-IGF1, Palisade Bio) was transplanted into fimbria fornix of the hippocampus (6 total injections, 180,000-600,000 total cells). Spatial memory was assessed by Morris water maze. Amyloid plaques were assessed by immunofluorescence and ELISA. Hemibrains were submitted for spatial transcriptomics (Visium, 10X Genomics) and significant differentially expressed genes (DEGs) were identified ( $p < 0.05$ ). Pathway enrichment was performed using the Kyoto Encyclopedia of Genes and Genomes (KEGG), and ligand-receptor interaction analysis (CellChat) network analysis examined communication between cell populations. **Result:** hNSC transplantation restored learning curves of 5XFAD mice in Morris water maze testing, mimicking performance of wild-type animals. However, there were no changes in amyloid-beta burden. Spatial transcriptomics elucidated non-amyloid-mediated hNSC therapeutic mechanisms. In hippocampal subregions, we discovered 1061 DEGs that were upregulated in 5XFAD animals but were in turn normalized upon hNSC treatment. KEGG pathway

analysis of these DEGs revealed significant impact on protein processing ("ubiquitin mediated proteolysis", "protein export", and "proteosome"), "long-term potentiation," and "metabolic pathways." A previously published subset of plaque induced genes were normalized upon hNSC transplantation, particularly within microglia. A reduction in stage 1 and stage 2 disease associated microglia (DAM) was seen, without affecting homeostatic microglia populations. CellChat showed hNSCs interacted particularly with glia (astrocytes, oligodendrocytes, and microglia, including stage 1 and stage 2 DAM) along many pathways. Pathologic signaling between hippocampus and DAM upregulated in the 5XFAD model was again normalized upon hNSC transplantation. **Conclusions:** Transplantation of hNSCs rescued memory in 5XFAD mice. No change in amyloid plaque burden was noted, but spatial transcriptomics revealed many genes dysregulated in 5XFAD that were normalized with hNSC transplantation, particularly within hippocampus. hNSCs interacted with and normalized populations of stage 1 and stage 2 DAM. Our results suggest that hNSCs exert beneficial effects in part by modulating microglia-mediated neuroinflammation in AD.

#### **M178. Improving Early Recognition of Potentially Treatment-Responsive Causes of Rapidly Progressive Dementia**

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**Objectives:** To improve the timely recognition of patients with treatment-responsive causes of rapidly progressive dementia (RPD). **Background:** The term RPD encompasses patients who progress from first symptom to dementia in less than one year or to complete incapacitation within two years. Although RPD is often associated with fatal neurodegenerative diseases, including Alzheimer disease or Creutzfeldt-Jakob disease, treatable forms of RPD are increasingly recognized. Early recognition of patients with potentially treatment-responsive causes of RPD is critical to minimize morbidity and optimize outcomes. **Methods:** Patients with suspected RPD were enrolled between February 2016 and August 2022 in a prospective observational study of RPD and followed for two years or until death. Etiologic diagnoses were independently assigned by two neurologists and causes of RPD classified as treatment-responsive or nonresponsive, referencing the clinical literature. Disease progression was objectively measured using the Clinical Dementia Rating<sup>®</sup> Sum-of-Box scores. Clinical and paraclinical features associated with treatment responsiveness were assessed using multivariable logistic regression. Results of multivariable analyses informed development of a practical and accessible clinical criteria to improve recognition of patients with potentially treatable causes of RPD. **Results:** 87/155 patients (56.1%) had a potentially treatment-responsive cause of RPD, including

autoimmune/inflammatory disease (n=52, 59.8%), vasculitis (n=13, 14.9%), primary psychiatric disease (n=4, 4.6%), or nutritional deficiency (n=4, 4.6%). Seizures (OR: 10.49, 95% CI: 3.07-35.79), Tumor (disease-associated; OR: 12.86, 95% CI: 2.11-78.3), Age <50-years (OR: 6.41, 95%CI: 1.49-27.61), MRI suggestive of autoimmune encephalitis (OR: 23.47, 95%CI: 2.33-236.67), Mania (OR: 21.57, 95% CI: 2.04-227.92), Movement abnormalities (OR: 5.27, 95% CI: 1.89, 14.97), and Pleocytosis ( $\geq 10$  cells/ $\mu$ L of CSF; OR: 30.30, 95%CI: 5.54, 165.65) at presentation were independently associated with treatment-responsive causes of RPD (c-statistic = 0.91, 95%CI: 0.86-0.95;  $p < 0.001$ ). Detection of any “STAM<sub>3</sub>P” feature at presentation captured 83/87 cases of treatment-responsive RPD (sensitivity = 95%, specificity = 63%, positive predictive value = 77%, negative predictive value = 92%). The presence of  $\geq 3$  of these features had a positive predictive value of 100%. **Interpretation:** Treatment-responsive causes of RPD were common in our series. The detection of selected features reliably identified patients with potentially treatment-responsive causes of RPD early in the symptomatic course. Adaptation of the STAM<sub>3</sub>P screening score in clinical practice may minimize diagnostic delays and missed opportunities for treatment in patients with RPD.

#### **M179. Influences of Demographic Factors on the Digital Clock and Recall (DCR) and the Mini Mental Status Examination (MMSE)**

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**Introduction:** With disease-modifying treatments for Alzheimer's disease on the horizon, digital cognitive assessments (DCAs) can enable more widespread cognitive screening and help identify suitable candidates for treatments. DCAs such as Linus Health's DCR™, consisting of the DCTclock™ and a 3-word delayed recall, are useful because they are brief and sensitive, are easily administered by non-physicians, are scored automatically, and fit into clinical workflow in primary care. However, to successfully deploy the DCR in diverse settings, we set out to assess the influences of demographic factors such as race/ethnicity and education on DCR results and compare them against traditional paper-based cognitive assessments such as the MMSE. **Methods:** 770 participants (age range 60-85; age mean $\pm$ SD = 71.7 $\pm$ 6.8; 57.7% female; 12.3% African-American; 9.1% Hispanic; 1.0% Asian; years of education mean $\pm$ SD = 15.5 $\pm$ 2.7; primary-language English) were classified as cognitively unimpaired (n=386), having mild cognitive impairment (n=271), or having Alzheimer's disease-related dementia (n=113) based on clinical diagnosis or neuropsychological testing. We evaluated the influences of race (White vs. Non-White), ethnicity (Hispanic vs. Not Hispanic), and education on standardized MMSE and DCR

scores. We also defined a 'minority at-risk' (MAR) status (1=at-risk) for Non-White and/or Hispanic individuals with lower education ( $\leq 15$  yrs). **Results:** The MMSE score was significantly higher among Not-Hispanic than Hispanic individuals ( $t=2.14$ ,  $p=0.03$ ), whereas the DCR score was comparable between the two groups ( $t=0.35$ ,  $p=0.73$ ). MMSE score was also significantly higher in individuals with higher education than those with lower education ( $t=5.06$ ,  $p<0.001$ ), whereas the DCR score was comparable between the two groups ( $t=0.92$ ,  $p=0.36$ ). Both MMSE and DCR scores were higher in White individuals than in Non-White individuals ( $t$ 's $>5.03$ ,  $p$ 's $<0.001$ ). A multivariate regression among 406 individuals found MAR status (present in 79 individuals) predicted lower MMSE ( $\beta=-0.89$ ,  $p<0.001$ ) and DCR ( $\beta=-0.59$ ,  $p<0.001$ ) scores, but a post-estimation Wald test found MAR influence was significantly smaller on DCR than on MMSE,  $F(1,404)=5.53$ ,  $p=0.019$ . **Conclusions:** The DCR is less influenced than the MMSE by ethnicity and level of education. The results indicate an advantage of DCR for reducing the demographic influences affecting traditional paper-based cognitive assessments such as the MMSE.

#### **M180. Innate Lymphoid Cells as Novel Prognostic Biomarkers for VCID**

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**Introduction:** Second only to Alzheimer disease, vascular cognitive impairment and dementia (VCID) is a major cause of dementia. Structurally, VCID causes multifocal ischemic brain injury. Functionally, it compromises patients' quality of life and places great mental, physical and financial burdens on patients, families and society. With the world population aging and incidence of strokes increasing, number of VCID is expected to rise. Despite proven treatments for vascular disorders, there are no specific therapies proven effective for VCID. To develop novel effective therapies, an important task is to understand the pathophysiology underlying ischemic brain injury in VCID. Neural inflammation plays an important role in VCID. Especially, its implication in development of cognitive impairments from vascular disorders to remain unclear. Innate lymphoid cells (ILCs) are newly discovered immune cells that are counterparts of T cells that secrete effector cytokines and regulate the functions of other innate and adaptive immune cells. ILCs carry out some unique functions and share some tasks with T cells. Their role in cardiovascular diseases and stroke are yet to be fully elucidated. **Purpose:** To investigate, for the first time, whether relatively newly discovered ILCs may be a mechanistic link by which remote ischemic conditioning (RIC) may regulate the immune system in patients at risk for VCID. **Materials and Methods:** Patients with transient ischemic attack or subcortical stroke (n=30) were randomly divided into two groups. One group was “Sham” where RIC consisted of subthreshold arm compressions. The second group was subjected to active RIC, four cycles of bilateral arm compressions. Blood samples were collected at multiple time points

(at least 4 samples/subject), pre/post treatment/sham. Flow cytometry assessed ILCs function. **Results:** There was a substantial pre and post treatment difference in the frequency and polarization of ILCs. Active RIC treatment induced alterations in subclasses of ILCs compared to sham. **Conclusion:** Alterations in ILCs profile may be used as innovative diagnostic and prognostic biomarker in patients at risk for VCID. Given the central role of ILCs in the initiation, development and regulation of inflammatory responses, these novel findings propose a new Bio-target for RIC in the treatment of VCID.

### M181. Integrated Spatial Genomics Reveals Cell-Type Specific Responses and Interactions in Human Alzheimer's Disease Brain Tissue Environments

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Alzheimer's disease (AD) is characterized by amyloid plaques and neurofibrillary tangles, but the molecular changes in distinct cell types and their association with AD neuropathology remain unclear. Here, we applied spatial genomics tools to image 1,373 genes and five protein markers in the same brain slices from three individuals with AD and two aged controls. First, we observed gene expression changes in AD brains that influenced cell type organization and transcriptional spatial domains. Second, we mapped the relationship of cell types with AD neuropathology to identify microglia responses to plaques and stress responses linked to neurofibrillary tangle burden. Third, we identified changes in cell-to-cell interactions and ligand-receptor crosstalk. We focused on the blood-brain barrier to highlight candidate interactions that include microglia-vascular signaling and oligodendrocyte precursor-vascular interactions. Lastly, we built an interactive viewer as a resource for the exploration of the multi-omic spatial data sets. This study demonstrates the application of high-resolution spatial genomics on AD samples, revealing features of single-cell expression states and signaling in native human AD brain tissue environments.

### M183. Metabolic Dysregulation in Probable Alzheimer's Disease

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**Background:** Insulin resistance (IR), type 2 diabetes (T2D), and chronic inflammation increase the risk of developing mild cognitive impairment and Alzheimer's disease (AD). **Objectives:** We report here baseline data from a multicenter, randomized, placebo-controlled Phase 3 study (NCT04669028) in patients with mild to moderate AD evaluating the effects of NE3107, an oral, small molecule and a blood-brain barrier-permeable, anti-inflammatory, insulin sensitizer that binds extracellular signal-regulated kinase.

**Methods:** Inclusion criteria were diagnosis and progression of AD, supportive brain scan and Hachinski scale to exclude vascular dementia, Clinical Dementia Rating (CDR) score of 1-2, and Mini Mental State Exam (MMSE) score of 14-24. Primary outcomes will evaluate changes in cognition and function from baseline to 30 weeks. Secondary outcomes include changes in neuropsychological deficits, functional performance, and regulation of glycemia. **Results:** Amyloid beta (A $\beta$ )-positive subjects were older and had worse MMSE scores, AD Assessment Scale-Cognitive Subscale (ADAS-Cog12) scores, and AD Composite Scores than A $\beta$ -negative patients but had less evidence of inflammation (lower C-reactive protein) and less IR (lower fasting glucose, less impaired fasting glycemia and T2D, lower fasting insulin and Homeostatic Model Assessment Index (HOMA2-IR), and less hypertension). Metabolic dysregulation (elevated complement component C1q, increased continuous glucose monitoring mean and mean amplitude of glycemic excursions, increased cholesterol, triglycerides, and waist-hip ratio) was also observed independent of A $\beta$  and apolipoprotein E  $\epsilon$ 4 status. **Conclusion:** Our findings suggest that inflammation and IR may contribute to AD even in the absence of classical risk markers for AD.

### M184. Misdiagnosis of Early-Onset Dementia and Dementia-Plus Syndromes

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**Introduction:** Early-onset dementia presents a diagnostic challenge due to its broad differential. Misdiagnoses occur frequently and are especially detrimental for patients who have treatable conditions. **Case Study:** A 44-year-old woman presented with a two-year history of emotional dysregulation and lapses in judgment. Over time, she also developed mouth-smacking movements as well as difficulties with verbal expression, planning, and memory. Both biological parents were over 70 years old and healthy. On neurological exam, she had difficulty following complex commands but no other abnormalities. Basic labs, inflammatory markers, infectious studies, and metabolic studies were all unremarkable. Magnetic resonance imaging of the brain showed white matter changes with frontal predominance and corresponding anterior corpus callosal thinning. Fluorodeoxyglucose-positron emission tomography of the brain showed hypometabolism in the frontal lobes. She was diagnosed with frontotemporal dementia. Due to her fulminant disease course, she was referred to a subspecialty clinic. Repeat exam was significant for difficulty naming the president, inability to calculate serial sevens, diminished facial expression, and reduced arm swing with right fist clenching on gait testing. She underwent genetic testing that revealed compound heterozygosity in the *CSF1R* gene. The maternally inherited c.1924 C>T mutation was likely pathogenic, while the paternally inherited c.1885 G>T mutation was of unclear clinical significance. Neither mutation had been previously reported. The patient was diagnosed with adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP). ALSP is a monogenic primary microgliopathy with autosomal dominant inheritance

that presents as a dementia-plus syndrome with extrapyramidal signs and symptoms. **Discussion:** Many adult-onset inherited neurometabolic disorders present as early-onset dementia. Here, an ALSP patient was initially misdiagnosed with frontotemporal dementia. Interestingly, both parents were asymptomatic, likely due to the incomplete penetrance of the dominant ALSP phenotype. Incomplete penetrance and variable expressivity are common confounders of family history for inherited neurometabolic disorders. On literature review, other ALSP patients have been misdiagnosed with multiple sclerosis, Parkinson/Parkinson-plus syndromes, Alzheimer, and vascular dementia, among others. Misdiagnoses often carry the modifier “atypical.” Due to recent advances in clinical research, therapies exist for many adult-onset neurometabolic disorders, but they must be administered early in the disease course for maximal efficacy. Thus, accurate early diagnosis is the key to providing patients with access to effective therapies before the treatment window closes. We propose the need for increased provider education on dementia-plus syndromes to increase pattern recognition, facilitate early genetic testing, and accelerate referral to subspecialty clinics for timely treatment of treatable conditions.

#### **M186. MRI Perfusion and Structural Markers of Pathologic Burden in Frontotemporal Lobar Degeneration Due to Tau**

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**Introduction:** Regional cerebral blood flow (CBF) changes quantified using arterial spin labeling (ASL) are altered in frontotemporal lobar degeneration as well as other neurodegenerative disorders, but the relationship between ASL CBF and pathologic burden has not been assessed. We hypothesized that ASL CBF acquired antemortem in patients with FTLT due to tau (FTLT-tau) would reflect FTLT-tau pathologic burden measured at autopsy. **Methods:** Data from twenty-one participants with FTLT-tau (N=10 women, mean[SD] age 67.9[7.56] years) confirmed at autopsy along with 25 controls without central nervous system disease (N=15 women, age 64.7[7.53]) were assessed. All participants had ASL and T1-weighted images collected antemortem. ASL was processed to generate three estimates of CBF: Bayesian Inference for Arterial Spin Labeling (BASIL), BASIL with partial volume correction (PVC), and algebraic CBF calculation using ASL white paper recommendations. T1-weighted images were processed to generate estimates of regional gray matter (GM) volumes. Digital quantification of pathologic burden was performed to find the percent area occupied (%AO) of pathologic FTLT-tau at autopsy. %AO was scaled using min-max normalization for each FTLT-tau subtype (progressive supranuclear palsy N=11, Pick's disease N=5, corticobasal degeneration N=4, tauopathy unclassifiable N=1) to account for differences in morphometry of different inclusions. The natural log of these values was

then taken to improve normality of the data distribution. Regional CBF and GM volumes were related to  $\ln(\text{normalized}(\%AO))$  using linear mixed effects models. Strength of model fits of imaging measures to pathologic burden were compared. CBF in FTLT-tau and controls were compared in each region of interest sampled at autopsy, with results considered significant at  $p < 0.05$  after Bonferroni correction. **Results:** As compared with controls, FTLT-tau patients displayed hypoperfusion in anterior cingulate cortex and angular gyrus with all image processing strategies, but BASIL and BASIL+PVC additionally showed hypoperfusion in orbitofrontal, middle frontal, and superior temporal regions. Regional CBF estimates from patients were significantly associated with pathologic burden in regions sampled at autopsy for algebraic CBF ( $\beta = -1.01$ ,  $t = -3.54$ ), BASIL ( $\beta = -1.07$ ,  $t = -4.80$ ), and BASIL+PVC ( $\beta = -1.19$ ,  $t = -5.04$ ; all  $p < 0.005$ ). Models including both GM volumes and CBF estimates provided significantly better fits to pathologic burden data than single modality models (all  $p < 0.05$ , Bonferroni-corrected). **Conclusions:** CBF changes are associated with pathologic burden in FTLT-tau. Multimodal MRI models produce better fits to pathologic burden data than unimodal models.

#### **M188. Polygenic Burden of Expanded Short Tandem Repeats Promotes Risk for Alzheimer's Disease**

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Studies of the genetics of Alzheimer's disease (AD) have focused on single nucleotide variants and short insertions/deletions. However, despite studies in hundreds of thousands of individuals, the majority of the genetic risk for AD has yet to be identified, suggesting that there is substantial genetic risk conferred by other forms of genetic variation. The impact of complex forms of genetic variation such as the ~1 million short tandem repeats (STRs; 2-6 base pair repeat sequence tracts) in the genome on AD risk has not been explored. As these STRs are known to cause over 30 neurologic diseases, it is important to ascertain whether they may also be implicated in AD risk. Here, we repurposed whole genome sequencing (WGS) data of blood-derived DNA to genotype the lengths of 321,402 polymorphic STR tracts in 1213 neuropathologically confirmed AD cases and 1080 cognitively normal control individuals. We identified five STRs whose lengths are robustly associated with risk of AD at false discovery rate  $< 0.05$ , including one association near the *APOE* gene as well as several other genes with important neuronal functions. We next applied an outlier detection method to identify individuals carrying expansions for each STR. Strikingly, we find that individuals with AD carry a 1.30-fold increased number of expanded STRs compared to individuals without AD. Among the expanded STRs, we find 1294 STRs that are recurrently expanded in individuals with AD, but not control individuals. These recurrently expanded STRs in individuals with AD are enriched near gene regulatory regions implicated in neuronal pathways. Together, these

results demonstrate that a polygenic burden of expanded STRs near genes involved in neuronal function promote incident risk of AD.

#### **M189. Predicting Emotional and Behavioral Complications of Hemorrhagic Stroke**

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**Introduction:** Emotional and behavioral dyscontrol (EBD), a constellation of symptoms comprised of emotional lability, irritability, and pseudobulbar affect, is an important neuropsychiatric sequela of stroke leading to patient/caregiver distress and potential complications to hospitalization and rehabilitation. Existing studies of neuropsychiatric sequelae of stroke are heavily weighted towards ischemic stroke populations; little is known about risk factors for EBD following hemorrhagic stroke. **Design/Methods:** We conducted a prospective cohort study of 156 patients hospitalized for non-traumatic hemorrhagic stroke between January 2015 and February 2021, aiming to identify risk factors associated with EBD development. Patients or caregivers were interviewed at 3 and 12 months post-hospitalization using the Neuro-QOL EBD inventory. Univariate and multivariable analyses identified risk factors linked to the development of EBD after hemorrhagic stroke. **Results:** The incidence of post-stroke EBD was 21% (15 of 72 patients) at 3 months and 26% (10 of 38 patients) at 12 months following hemorrhagic stroke. Patients with intracerebral hemorrhage (ICH) were significantly more likely than patients with subarachnoid hemorrhage (SAH) to experience EBD at 3 months (30% vs 4%; OR 10.2;  $p=0.007$ ). Admission Glasgow Coma Scale (GCS), National Institutes of Health Stroke Scale (NIHSS), and Acute Physiology and Chronic Health Evaluation II (APACHE-II) scores were also significantly associated with EBD at 3 months ( $p<0.05$ ) on univariate analysis. Multivariable analysis identified bleed type (ICH) and poor admission GCS as predictors of EBD at 3-months ( $p<0.05$ ) in a logistic regression model. The presence of EBD at 3 months was associated with poor functional outcomes at 12 months as measured by a modified Rankin score of 1-2 ( $p=0.0254$ ; Fisher exact test). **Conclusion:** Patients with intracerebral hemorrhage and low GCS at admission are at increased risk of developing EBD following hemorrhagic stroke. This population may benefit from proactive neuropsychiatric and behavioral interventions.

#### **M190. Prevalence and Predictors of Cognitive Impairment in Nonalcoholic Fatty Liver Disease**

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**Background:** Data regarding cognitive impairment in non-alcoholic fatty liver disease (NAFLD) are limited. We assessed the prevalence and nature of cognitive deficits in NAFLD and assessed whether liver fibrosis, an important determinant of outcomes in NAFLD, is associated with worse cognitive performance. **Methods:** We performed a prospective cross-sectional study embedded in the Innovative Center for Health and Nutrition in Gastroenterology (ICHANGE) program, a multidisciplinary NAFLD clinic. Between 2020 and 2022, we recruited participants with NAFLD from ICHANGE, which excludes people with chronic liver disease from other causes. We excluded patients with clinically apparent cirrhosis. Participants underwent liver fibrosis assessment with transient elastography (FibroScan<sup>®</sup>) and the following assessments: Cognitive Change Index, Eight-item Informant Interview to Differentiate Aging and Dementia Questionnaire (AD8), Montreal Cognitive Assessment (MoCA), EncephalApp minimal hepatic encephalopathy test. Additionally, we administered a limited NIH Toolbox battery: Flanker Inhibitory Control and Attention Test, Pattern Comparison Test, and Auditory Verbal Learning Test. We summarized cognitive data using standard descriptive statistics. We used multivariable linear regression models to examine the association between liver fibrosis and cognitive outcome measures, while adjusting for demographics, education, cardiometabolic comorbidities, and alcohol use. **Results:** We included 69 participants with mean age 50 (SD, 14) years; 62% were women. The median liver stiffness was 5 (IQR, 4-7) kilopascals, and 17 (25%) had liver fibrosis, defined as  $\geq 7.0$  kilopascals. Cognitive deficits were common in people with NAFLD; 28 (41%) had subjective cognitive impairment, 9 (13%) had an AD8  $\geq 2$ , 22 (32%) had MoCA  $< 26$ , and 8 (12%) had encephalopathy based on the EncephalApp test. In adjusted models, people with liver fibrosis did not have worse scores on screening tests: Cognitive Change Index ( $\beta=1.04$ ; 95% CI, -5.60-7.67;  $P=0.75$ ), AD8 ( $\beta=0.72$ ; 95% CI, -0.19-1.62;  $P=0.12$ ), MoCA ( $\beta=-1.04$ ; 95% CI, -2.69-0.61;  $P=0.21$ ), and EncephalApp hepatic encephalopathy test ( $\beta=-6.61$ ; 95% CI, -29.5-16.3;  $P=0.56$ ). With regards to the NIH Toolbox battery, liver fibrosis was associated with significantly worse performance on the Flanker Inhibitory Control and Attention Task ( $\beta=-0.38$ ; 95% CI, -0.66, -0.10;  $P=0.01$ ), but not with performance on Pattern Comparison ( $\beta=0.33$ ; 95% CI, -4.84-5.50;  $P=0.90$ ) or Verbal Learning ( $\beta=0.87$ ; 95% CI, -2.63-4.38;  $P=0.62$ ). **Conclusions:** Cognitive deficits are common in people with NAFLD, among whom liver fibrosis was associated with worse inhibitory control and attention. Further research is required in larger cohorts to enrich our understanding of the liver-brain axis.

#### **M191. Pyramidal Neurodegeneration is Linked to Select Cytoarchitecture and Cognitive Impairment in Behavioral Variant Frontotemporal Dementia with Tau or TDP-43 Pathology**

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**Background:** The behavioral variant of frontotemporal dementia (bvFTD) is primarily caused by either tauopathies (bvFTD-tau) or TDP-43 (bvFTD-TDP) proteinopathies. Frontal cortices are often the earliest sites of degeneration in bvFTD, and previous studies suggest bvFTD-tau and bvFTD-TDP share similar patterns of pyramidal neurodegeneration in infragranular layers of agranular cortices. However, neurodegeneration in other cortical layers in more laminated (dysgranular-to-granular) cytoarchitecture in bvFTD remain poorly understood. We recently reported that infragranular layers throughout agranular-to-granular regions accumulate more protein inclusions in bvFTD-tau than bvFTD-TDP. Thus, the current study tested the hypothesis that pyramidal neurodegeneration is greater in more laminated regions of bvFTD-tau than bvFTD-TDP and relates to frontal-mediated cognitive impairment. **Methods:** In 49 bvFTD-TDP, 28 bvFTD-tau, and 33 cognitively normal (CN) participants, we examined 11 subregions of anterior cingulate, medial orbitofrontal, and mid-frontal cortices representing a cytoarchitectonic gradation of agranular-to-dysgranular-to-granular cortex (i.e., Brodmann areas 33, 24, 32, 14, 11, 46). We immunostained 6 $\mu$ m-thick serial sections of each region using antibodies to total (NeuN) and pyramidal (SMI-32) neurons, and digitally quantified immunoreactivity of each antibody per subregion. We z-scored measures in bvFTD using the CN group, producing neurodegeneration metrics analyzed in linear mixed-effect models adjusted for demographics and biological variables. Exploratory analyses compared region-specific neurodegeneration to letter fluency performance (an executive functioning test) available within five years from symptom-onset (n=23). **Results:** While total (NeuN) neurodegeneration in each type of cortex was similar between bvFTD-TDP and bvFTD-tau, pyramidal (SMI-32) neurodegeneration in granular cortex (not agranular or dysgranular cortex) was greater in bvFTD-tau than bvFTD-TDP (beta=-0.946, SE=0.306, p=0.003). Pyramidal neurodegeneration progressively worsened across the agranular-to-granular arrangement of six Brodmann areas sampled in bvFTD-TDP (beta=-0.104, SE=0.032, p=0.001) and bvFTD-tau (beta=-0.191, SE=0.04, p<0.001). Executive dysfunction worsened with greater pyramidal neurodegeneration in dysgranular/granular cortex (beta=0.105, SE=0.044, p=0.042), not agranular cortex (p=0.449). **Conclusions:** In clinically similar bvFTD participants, we find greater pyramidal neurodegeneration in more laminated (granular) cytoarchitecture that is more prominent in bvFTD-tau than bvFTD-TDP. Furthermore, selective pyramidal neurodegeneration in more laminated cytoarchitecture may differentially contribute to early executive dysfunction characteristic of bvFTD, suggesting tauopathies may have a clinically relevant and distinctive neurodegenerative pattern in the bvFTD spectrum.

## M192. Racial Disparities in Alzheimer's Disease and Related Dementias (ADRD): The Association between Early Life Adversity and ADRD

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**Background:** Adverse childhood experiences (ACEs) are an important public health concern that predict neuroanatomical changes in development such as decreased prefrontal cortex and hippocampal volumes, and can lead to poor health outcomes in adulthood, including cognitive impairment. Alzheimer's Disease and related dementias (ADRD) are the seventh leading cause of death in the United States (US). AD and vascular contributions to cognitive impairment and dementia (VCID), in particular, disproportionately affect racial and ethnic minoritized (REM) individuals. Research demonstrates that some of the mechanisms underlying these racial disparities may include differences in exposure to specific types of ACEs (i.e. parental remarriage and/or death). A significant ACE burden can lead to disruption of the hypothalamic-pituitary adrenal (HPA) axis, our fight-or-flight response system to environmental threats and stressors. Growing evidence has shown an association between ACEs and the development of cognitive impairment in older adulthood, including ADRD. We do not know, however, how ACEs-related HPA-axis dysregulation inflammatory biomarkers are correlated to ADRD outcomes (cognitive measures, diagnoses, and biomarkers) in a nationally representative, diverse cohort of individuals. **Methods:** A preliminary study is being conducted to evaluate the associations between early life adversity (measured retrospectively through surveys) and ADRD in several cohorts, including the Minority Aging in Research Study (MARS) from the Rush University Alzheimer's Disease Research Center, the Stress and Resilience in Dementia (STRIDE) cohort from the University of Wisconsin, the Wake Forest ADRC cohort, and the Duke University Medical Center clinics using DEDUCE, an on-line query system in MaestroCare, Duke University Hospital's electronic medical record system. Statistical analyses will be performed using R software. **Results:** Preliminary results demonstrate in the MARS cohort that ACEs are protective against cognitive decline in African Americans. Analyses are ongoing to examine the associations between ACEs, biological stress markers, and cognitive measures. The Wake Forest ADRC, STRIDE, and Duke DEDUCE data are currently being transferred. **Conclusion:** Validation of ACEs as independent risk factors for and contributors to racial disparities in ADRD will offer new clinical screening modalities for specific ACEs that are tightly linked to an ADRD diagnosis, and public policy insights to address a history of ACEs in patients with ADRD. This is especially for those REM individuals who have historically had a delayed or missed diagnosis and have been disproportionately impacted by ADRD.



### M193. Rapidly Progressive Dementia (RPD) in the Setting of Depression

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**Objective:** RPD requires urgent evaluation and a systematic approach for timely evaluation of treatable causes. We report a case of RPD secondary to malnutrition and multivitamin deficiencies initially masked by depression. **Background:** RPD, defined as decline in one or more cognitive domains with functional impairment in less than 1 to 2 years, typically raises concern for Creutzfeldt-Jakob disease though assessment should be made for non-prion causes including toxic-metabolic, infectious, autoimmune, paraneoplastic or neurodegenerative. Identifying treatable causes is critical as delay in management may result in persistent cognitive sequelae. Depression can mimic dementia as well as lead to decreased appetite and cause vitamin deficiencies and cognitive decline. **Methods:** Case report **Results:** 57-year-old woman with rheumatoid arthritis off disease modifying therapy for 2 years, depression and GERD was admitted for pneumonia, with neurology consulted for RPD which progressed over an 8 month period. Patient's sister had bipolar disorder and mother had a history of unspecified dementia and passed away 2 years prior and the patient had been taking antidepressants since. Family reported behavioral changes with episodes of disinhibition and impulsive expenses, irritability, then withdrawal and decreased appetite in the last 3 months with secondary 20 lbs involuntary weight loss, as well as short term memory loss and concern for visual hallucinations and restlessness, though living independently until the past month. Initial MoCA was 17/30. There was no history of alcohol or drug use. Psychiatry initially consulted and adjusted the antidepressants. She was also started empirically on high dose thiamine in view of encephalopathy and intermittent conjugate vertical nystagmus. MRI brain showed trace pachymeningeal enhancement along the left frontoparietal convexity. EEG was negative for epileptiform discharges. Full body CT imaging didn't suggest active malignancy. CSF, urinary and blood samples sent for extensive infectious, autoimmune, paraneoplastic, endocrine, neurodegenerative and other metabolic disorders were unrevealing. Folic acid was low (<2.0 ng/L), as well as thiamine (< 20 nmol/L) and vitamin B6 (2.2 microg/L), with normal B12, B3 and nicotinamide. Vitamin repletion lead to rapid cognitive improvement. **Conclusion:** Depression may mimic or mask cognitive impairment, while associated anorexia may trigger vitamin deficiencies which can present as RPD. Timely and extensive initial work up is key for proper identification of treatable causes of RPD, and avoidance of longterm neuropsychological sequelae. High dose thiamine should be initiated empirically before B1 levels result. Wernicke encephalopathy may co-occur with other etiologies which should also be investigated based on the clinical context.

### M194. Revisiting the Wood Criteria for Frontotemporal Degeneration Pedigree Classification: 10 Years Later

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Previously, the Penn Frontotemporal Degeneration (FTD) Center developed and validated family history criteria to stratify FTD pedigrees by likelihood of identifying a genetic etiology (Wood, *JAMA Neurol.*, 2013). Pedigrees were classified as high-risk, medium-risk, low-risk, apparent sporadic, or unknown significance, and genetic testing for the three most common genes that cause FTD (*C9orf72*, *MAPT*, and *GRN*) was completed to assess detection rate of genetic carriers for each category. Given advances in FTD genetics over the last ten years, the current study aims to cross-validate this pedigree classification criteria in a novel cohort and determine the extent to which consideration of additional pathogenic variants increases the diagnostic yield. First, we sought to understand whether updated family history information altered findings in the initially reported cohort (n=306; 15.4% (47/306) overall, 64.1% (25/39) high, 29% (9/31) medium, 10.9% (5/46) low, 1.1% (1/91) apparent sporadic, 7.1% (7/99) unknown significance). Reclassification of pedigrees led to higher yield for the high-risk group (65%, 26/40) and lowered yield for other categories (24.2% (8/33) medium, 10.6% (5/47) low, 1% (1/96) apparent sporadic, 7.8% (7/90) unknown significance). Next, we evaluated whether genetic analysis beyond the three most common genes would alter yields in the initial cohort. This broader analysis identified five additional carriers in the high-risk group and one in the low-risk group (17.3% overall, 77.5% high, 12.8% low). Finally, we applied the Wood criteria to a novel cohort of pedigrees of probands with FTD-spectrum disorders (n=303). Probands underwent exome sequencing or panel testing for genes related to neurodegenerative conditions. When exclusively causal variants in *C9orf72*, *GRN*, and *MAPT* were included, yields were 23.4% (71/303) overall, 70.9% (39/55) in the high-risk group, 28.9% (13/45) in medium-risk, 11.8% (6/51) in low-risk, 5.2% (4/77) in apparent sporadic, and 12% (9/75) in unknown significance. Inclusion of results from broader sequencing identified two additional genetic carriers in the high-risk group (74.5%) and therefore also increased the overall cohort yield (24.1%). These results reiterate the importance of gathering a detailed neurologic family history in genetic risk assessment for FTD. Given the increasing availability of gene-specific clinical trials, we suggest that using this cross-validated pedigree classification criteria provides an accurate first step in determining the likelihood of a genetic diagnosis. Genetic counseling and testing should be routinely offered in the clinical setting for all patients with FTD, regardless of risk stratification.

### M195. Saccadic Eye Movement Variability and Scattered Patterns in Children with Autism Spectrum Disorder

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**Background:** Children diagnosed with autism spectrum disorder (ASD) generally have executive functioning and social attention deficits that hinder their ability to focus and maintain attention. Previous studies have shown that individuals with ASD can have shorter fixation times due to saccade interruption. Saccade abnormalities have also been associated with midbrain, cerebellar, and neurodegenerative disorders, while neuropathology of ASD has been shown to affect the cerebellum, limbic system, and cortex. Since saccades can be helpful in guiding the diagnosis of hyperkinetic and hypokinetic neurodegenerative disorders, we investigated whether saccades and fixation can be a valid predictor for differentiating between children with ASD and neurotypical children. **Methods:** M-CHAT scores and eye tracking data for neurotypical children (n=10) and children with ASD (n=6) are included in this report. Eye-tracking data were collected using Tobii Pro Nano, facial expressions were captured with a computer mounted camera, while Tobii Pro Lab and IBM SPSS V 27.1 were used for data analysis. Saccades ratio was obtained for each participant and linear regression was conducted to assess the predictability of group using M-CHAT scores and saccades ratio as predictor variables. **Results:** Saccades ratio averaged  $.389 \pm .156$  for the ASD group and  $.173 \pm .052$  for the control group. Independent t-test for saccades ratio showed significant differences  $t = 4.1, p < .001$  between groups. M-CHAT scores averaged  $14 \pm 2.53$  for the ASD group and  $1.90 \pm .568$  for the control group. Independent t-test for M-CHAT score showed significant group differences  $t = 14.84, p = .002$ . Results from the regression analysis indicate that the model was significant,  $F = 108.371, p < .001$ , with 93.5% of the variance explained by the model. Further, examination of facial expressions and eye-movement visuals from Tobii Pro Lab revealed that children with ASD had more scattered eye-movement patterns, with random fixations on background and irrelevant objects on the screen. **Conclusion:** The results suggest that eye-tracking measures have the potential to reveal neurological differences between children with ASD and neurotypical children. Ongoing research with larger sample size will provide more robust evidence for saccade and fixation abnormalities to support alternative screening for ASD.

#### **M196. Scaled Event Based Modeling to Elucidate Alzheimer's Disease Progression Dynamics**

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**Introduction:** It is widely believed that identifying and targeting at-risk individuals during the asymptomatic phase of Alzheimer's Disease (AD) may be a more effective strategy to delay or prevent the onset of AD and related dementias. Hence, there are two associated challenges - 1) better characterization of dynamic biomarker changes that occur in the AD disease spectrum, including its functionally asymptomatic phase and; 2) using dynamic biomarker changes to identify

at-risk individuals that may benefit from early disease-modifying therapies. **Methods:** The Event Based Model (EBM) is a probabilistic model which attempts to answer the above posed challenges. It hypothesizes disease progression to emerge from a sequence of biomarker abnormalities and uses this sequence to stage individual subjects from their biomarker measurements. A great strength of the EBM model is that it utilizes cross-sectional data instead of being reliant on sparse longitudinal measurements. However, a previous shortcoming was EBM's lack of scalability for high-dimensional biomarkers. We addressed this challenge to extend EBM to hundreds of biomarkers via a recently published algorithm called the scaled event based model (sEBM). Here we apply sEBM to peptide assay data to infer the sequence of peptide abnormalities which best explain progression across the AD spectrum. **Results:** The sEBM model identifies the most likely sequence of peptide abnormalities which explain cross-sectional cohort biomarker changes. sEBM places individuals into multiple different disease stages based on their increased risk of progression to symptomatic AD. Results illustrate cognitively normal controls and symptomatic AD patients predominantly occupy opposite ends of the progression spectrum, whereas the non-symptomatic patients primarily occupy intermediate stages. The assigned stage is strongly correlated with the pathological burden of amyloid- $\beta$  and tau. However, other less known dynamic patterns were also elucidated. The sEBM inferred biomarker order was overlaid on the peptides' functional roles. Presented results illustrate the dynamic order of dysfunction corresponding to sugar metabolism, synaptic function, systemic function, etc. to clinical disease progression. **Conclusion:** Scaled Event Based Modeling (sEBM) successfully characterized changes related to disease progression during the asymptomatic stage of AD using peptides measured from cerebrospinal fluid. sEBM is an innovative algorithm that has potential applications in staging patients at risk of converting to symptomatic AD using high-dimensional, multimodal biomarkers measured in cross-sectional patient cohorts.

#### **M197. Seizures Increase Microglial Proliferation in Alzheimer's Disease**

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Recent studies demonstrate a negative impact of epilepsy on Alzheimer's disease (AD) progression. Besides beta-amyloid and tau, AD is characterized by early changes in microglial function. Microglial activation can contribute to AD pathogenesis by releasing inflammatory mediators and reactive oxygen species leading to beta-amyloid production and accumulation. To begin to elucidate whether there is a causal link between hyperexcitability and microglial proliferation in AD, we used the 5XFAD mice, containing five AD-linked mutations, and AD patient samples, with the hypothesis that seizure-induced inflammation may play a pivotal role in promoting neurodegeneration. The 5XFAD and wild type (WT) mice were subjected to pentylenetetrazol (PTZ)

kindling at a pre-symptomatic stage (age 3-3.5 months) and were sacrificed three months later for brain tissue analysis (n=9-19/ group). Post-mortem temporal and frontal cortex samples from 10 control subjects and 19 AD patients (9 with seizure history and 10 without known seizures) were obtained from the Penn Center for Neurodegenerative Disease Research (CNDP). Quantitative Iba-1 immunohistochemistry was employed to examine regional microglial densities. We found increased Iba-1 coverage in the hippocampus ( $p<0.0001$ ) and cortex ( $p<0.05$ ) of 5XFAD mice relative to WT mice, with kindling further elevating Iba-1 expression within the 5XFAD group ( $p<0.01$  for the hippocampus and  $p<0.001$  for the cortex). However, kindling did not affect Iba-1 expression in WT mice. Increased microglial densities were also observed in brain tissue from AD patients, both in the temporal lobe ( $p<0.0001$ ) and frontal lobe ( $p<0.01$ ) cortex, and to a greater extent in tissue from patients with a clinical history of epilepsy and AD ( $p<0.05$  and  $p<0.001$ , respectively). Our data suggest that in AD, microglia proliferation is augmented by seizures, providing novel insight into the mechanisms leading to accelerated disease progression in AD with comorbid epilepsy. Intervention specifically targeting microglia activation and neuroinflammation may have high therapeutic potential for diseases modification in AD patients with epilepsy. **Supported By:** National Institute of Neurological Disorders and Stroke R21NS105437 (FEJ) and R01NS101156 (DMT), and National Institute on Aging R01-AG077692 (FEJ, DMT).

#### **M198. Sex Differences and Microglial Response in a Novel Mouse Model of Hypoxic Ischemic Encephalopathy**

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Hypoxic ischemic encephalopathy (HIE), a neurological deficit caused by a lack of blood flow and oxygen to the brain, is the leading cause of cerebral palsy in babies born at full term. HIE is particularly harmful to boys, who have a higher mortality rate and increased risk of blindness, deafness, learning disorders, and motor deficits compared with girls. Microglia mediate the immune response to brain injury such as HIE and also play a role in sex-specific brain development. Despite improvements in care for neonates with neonatal encephalopathy, many neonates go untreated or do not respond to therapeutic hypothermia. Consequently, there is a pressing need to understand the pathophysiology of this brain injury and the microglial response. Existing mouse models poorly recapitulate the injury seen in humans with HIE; therefore, we sought to develop an improved mouse model of HIE utilizing maternal exposure to systemic inflammation via lipopolysaccharide injection and subsequent hypoxia in pups postnatally. Histological evaluation of microglial density in the hippocampus, corpus callosum, and pons of mice treated in this model reveals significant interactions of sex, hypoxia, and LPS conditions. Maternal LPS exposure reduces microglial density, and subsequent hypoxia exposure attenuates this reduction in females, and not males. Continued histological and transcriptional evaluation of the immune response to

injury in this novel mouse model will further our understanding of the pathophysiologic mechanisms of brain injury in neonates who suffer these injuries with the goal of identifying neurotherapeutics to improve outcomes.

#### **M199. Shared and Disparate Transcriptomic Signatures Associated with Cortical Atrophy Change in Genetic Behavioral Variant Frontotemporal Degeneration**

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**Background:** Cortical atrophy is a common manifestation in behavioral variant frontotemporal degeneration (bvFTD), which is thought to be driven by distinct underlying biology across different forms of genetic bvFTD. This study aimed to employ an integrative imaging transcriptomics approach to uncover the shared and disparate transcriptomic signatures associated with cortical thickness changes in bvFTD with pathogenic variants in *C9orf72*, *GRN*, and *MAPT*. **Method:** Cortical thickness data was extracted from 117 apparently sporadic bvFTD patients, 32 *C9orf72*-bvFTD, 11 *GRN*-bvFTD, and 13 *MAPT*-bvFTD cases. Cortical thickness differences were computed between genetic and apparently sporadic bvFTD patients. Normative gene expression profiles were extracted from the Allen Human Brain Atlas. We utilized a partial least squares regression model to rank all genes by their correlation between gene expression and cortical thickness differences in each genetic form of bvFTD. Subsequently, we conducted gene set enrichment analysis to uncover the underlying biological processes associated with top-ranked genes. **Result:** Relative to the apparently sporadic bvFTD, individuals with *C9orf72*-bvFTD had decreased cortical thickness in the prefrontal and temporal cortex, those with *MAPT*-bvFTD exhibited decreased cortical thickness in the frontal operculum insula, temporal and somatomotor cortex, and those with *GRN*-bvFTD had more widespread cortical atrophy. For each genetic form of bvFTD, we identified sets of genes that were either positively or negatively associated with cortical thickness differences. Enrichment analysis revealed that genes associated with cortical atrophy in *GRN*-bvFTD were involved in neural-related biological processes including synaptic pathways, neuronal communication and development. These *GRN*-bvFTD negatively associated genes were enriched in different types of neurons, whereas the positively associated genes were mainly enriched in glial cells. The genes positively associated with cortical atrophy in *MAPT*-bvFTD were involved in synaptic pathways and were preferentially expressed in neurons, while the negatively associated genes were involved in immune-related pathways within the nervous system. Furthermore, the gene sets associated with each genetic form of bvFTD were

enriched in differentially expressed genes related to TDP-43 and tau pathologies. **Conclusion:** Spatial distribution of cortical structural change in each genetic form of bvFTD might be modulated by the expression of genes that were involved in shared and disparate functional pathways, coupled with different cellular signatures. Identification of shared and disparate transcriptomic signatures will contribute to further understanding of potential genetic basis of heterogeneity for different genetic forms of bvFTD.

#### **M200. Soluble Amyloid Precursor Protein- $\beta$ Turnover is Slower Than Soluble Amyloid Precursor Protein- $\alpha$ Turnover in Humans Irrespective of Age or Amyloid Status**

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The amyloid hypothesis posits that increased production and/or decreased clearance of amyloid-beta ( $A\beta$ ) will lead to higher order amyloid structures that initiate a cascade of events, culminating in neuronal death manifesting as Alzheimer's disease (AD). Sequential cleavage of Amyloid Precursor Protein (APP) generates  $A\beta$ . APP may be processed in one of at least two pathways, initially being cleaved by either  $\alpha$ - or  $\beta$ -secretase.  $\beta$ -secretase cleavage of APP releases sAPP $\beta$  and subsequent  $\gamma$ -secretase cleavage produces  $A\beta$ .  $A\beta$  formation is precluded if  $\alpha$ -secretase cleaves APP, producing sAPP $\alpha$ . Investigating proteolytic processing of APP in the living human can inform about the complex nature of a protein from which the central hallmark of AD derives. We measured sAPP $\beta$  and sAPP $\alpha$  turnover in human cerebrospinal fluid (CSF) through stable isotope labeling kinetics/immunoprecipitation/liquid chromatography-tandem mass spectrometry methods in AD and control subjects who had undergone [ $U$ - $^{13}C_6$ ]-leucine labeling and hourly CSF collection over 36h. A model consisting of 5 independent arms, one each for sAPP $\alpha$ , sAPP $\beta$  and  $A\beta$ 38,  $A\beta$ 40,  $A\beta$ 42 (historical data), was used to fit the data. Each arm consists of a single compartment (cpt) with a variable fractional turnover rate (FTR), a time delay of variable length that consists of 5 sub-cpts, and a variable scaling factor. FCR refers to the fractional turnover/clearance rate for the protein in the whole system. Production Rate (PR) was calculated as a product of FCR and absolute concentration. Both sAPP $\alpha$  and sAPP $\beta$  turnover significantly slower than  $A\beta$  in all subjects. sAPP $\alpha$  turns over faster than sAPP $\beta$  in subjects. sAPP $\alpha$  PR was significantly faster than sAPP $\beta$  PR ( $73 \pm 19.2$  vs.  $35.7 \pm 8.85$  ng/mL/h, respectively). The delay time was shorter for sAPP $\alpha$  than for sAPP $\beta$  ( $10.3 \pm 1.7$  vs.  $11.8 \pm 1.8$  h, respectively). The FTR for sAPP $\alpha$  was faster than sAPP $\beta$  ( $0.044 \pm 0.01$  vs.  $0.041 \pm 0.007$  pools/h, respectively). The clearance rate of sAPP $\alpha$  was faster than sAPP $\beta$  ( $0.030 \pm 0.005$  vs.  $0.027 \pm 0.004$  pools/h, respectively). There were no differences due to gender in any of the parameters. Additionally there was no amyloid effect, except for a slightly slower clearance of sAPP $\beta$  in the Amyloid [+] group. The physiological differences between kinetic measures of

sAPP $\alpha$  and sAPP $\beta$  may be at least partially attributed to differential location of APP cleavage by  $\alpha$ - or  $\beta$ -secretase within the cell and the variable trafficking of these proteins once they have been released from the membrane.

#### **M201. Structural Analysis of the Basal Ganglia Using Ex Vivo 7T MRI Can Differentiate Frontotemporal Lobar Degeneration with TDP-43 vs Tau Accumulation**

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**Objective:** Ex vivo 7T MRI can identify macrostructural changes in the basal ganglia that reflect underlying neuropathology, and can be used to differentiate between proteinopathies causing clinical frontotemporal lobar dementia syndromes (FTD). **Background:** Accurate prediction of underlying neuropathology based on clinical phenotype poses a significant challenge to the development of therapeutics in FTD; Frontotemporal lobar degeneration (FTLD) due to TDP-43 (FTLD-TDP) vs tau (FTLD-Tau) can be clinically indistinguishable during life. Ex vivo 7T MRI allows ultra-high resolution imaging of structure and is particularly sensitive to iron, which accumulates in activated glia in the cortex of FTLD but is understudied in the basal ganglia. **Methods:** A cohort of patients with clinical FTD underwent autopsy in which one hemisphere was taken for neuropathologic analysis, while the contralateral hemisphere was imaged at 160  $\mu$ m isotropic resolution with a T2\*w gradient-echo sequence using a whole-body 7T scanner (MAGNETOM Terra, Siemens Healthineers, Erlangen, Germany). MRI images were systematically reviewed, blinded to neuropathologic diagnosis to identify radiographic features of the basal ganglia which were altered in structure and/or intensity compared to control hemispheres. We identified 2 structural features of interest and developed a 4 point ordinal scale (i.e. none, mild, moderate severe) for the loss of normal morphological boundaries in globus pallidus (GP) and subthalamic nucleus (STN). **Results:** FTLD-TDP43 group trended towards diminished STN morphology and relative preservation of GP compared with FTLD-Tau on ex vivo 7T2\*w MRI. Overall, a ratio of change in morphological boundary of GP to STN was significantly different between the two groups (mean  $\pm$  SEM:  $0.93 \pm 0.13$  for FTLD-TDP-43 vs  $1.44 \pm 0.12$  for FTLD-tau). **Conclusion:** Ultra-high resolution ex vivo 7T MRI reveals loss of structural integrity of the GP with preserved STN morphology at a radiographic level in brains with accumulation of tau compared to TDP43, which may aid in more accurate diagnosis of FTLD neuropathology in vivo.

#### **M202. The Digital Clock and Recall Predict the Functional Activity Level in Older Adults**

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**Introduction:** Dementia is characterized by progressive impairment in multiple cognitive domains compromising ability to perform everyday activities. The Linus Health Digital Clock and Recall (DCR™), consisting of DCTclock™ and a 3-word delayed recall, employs AI-enabled analyses of drawing process and acoustic measures to evaluate memory, executive function, visuospatial abilities, and motor functions. We evaluated whether the DCR predicted functional status, measured by the functional abilities questionnaire (FAQ) reported by an informant, in older individuals with statuses ranging from cognitively unimpaired to mild cognitive impairment (MCI) and Alzheimer's disease-related dementia (ADRD). **Methods:** We studied 770 participants from a multisite study (age mean±SD = 71.7±6.8; 57.7% female; years of education mean±SD = 15.5±2.7; primary language English), classified as cognitively unimpaired (n=386), MCI (n=271), or ARDR (n=113). We also conducted logistic regressions to estimate adjusted risk ratio (ARR) for having an FAQ score ≥6 (clinically relevant functional deficits) in individuals with DCR score = 0-1 (Red) vs. 4-5 (Green) and DCR score = 0 vs. 5, controlling for age, sex, and education. We conducted three linear and LASSO regressions with FAQ score as dependent variable and standardized DCR score or DCTclock composite scales as predictors, controlling for age, sex, and education. **Results:** The DCR score significantly predicted FAQ score ( $\beta=-1.45$ ,  $p<0.001$ , adjusted- $R^2=0.14$ ). Individuals with DCR score=0 were seven times more likely [ARR=7.04 (95% CI 3.92-12.63)] to have an FAQ score ≥6 than those with a DCR score=5. Individuals with a Red DCR score were almost five times more likely [ARR=4.92 (95% CI 3.00-8.10)] to have an FAQ score ≥6 than those with a Green DCR score. In the LASSO regression model, the composite scale most predictive of the FAQ score ( $|\beta| \geq 0.05$ ) was Information Processing in the Copy Clock ( $\beta=-1.149$ ), followed by Spatial Reasoning ( $\beta=-0.078$ ) and Information Processing ( $\beta=-0.050$ ), both in the Command Clock. **Conclusion:** DCR performance predicts functional independence level as measured by the FAQ. Our results indicate that in a single task that can be completed in primary-care settings in <3 min, the DCR may provide insights into both cognitive and individual functional impairment, thus, enabling the differentiation between MCI and dementia.

### M203. Tracking Longitudinal Change in Presymptomatic Genetic Prion Disease

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Memory and Aging Center, San Francisco, CA, USA, <sup>2</sup>George Huntington Institute, Muenster, Germany.

**Goal:** Identify potential biomarkers for future treatment trials in the presymptomatic phase of genetic prion disease (gPrD).

**Background:** Due to their rapidity, by the time patients with gPrD become symptomatic, the disease often has progressed too far for any potential treatments to have benefit. Thus, development of early detection methods is vital. Approximately 15% of human prion diseases (PrDs) are genetic in origin, caused by mutations in the prion protein gene (*PRNP*). Because a simple genetic test can identify mutation carriers from gPrD families before symptom onset (presymptomatic), this group is an ideal target for therapeutic trials to delay disease or prevent onset. To prepare for upcoming trials, we need biomarkers of the earliest changes prior to clinical symptom onset. **Methods:** Our preliminary data suggested that such biological changes can be measured in Presymptomatic gPrDs. Without formal funding, we followed participants in an ad hoc manner (less than annually) for more than 15 years and evaluated ~110 participants. After obtaining NIH R56/R01 funding in 9/2018, we have followed asymptomatic carrier and non-carrier controls approximately annually in a more systematic manner using a standardized assessment battery over a ~2-day visit. **Results:** Approximately 143 gPrD participants from 54 families had research visits from 2008-2023, including 50 presymptomatic gPrD participants being seen through our NIH grant, "Tracking longitudinal change in presymptomatic genetic prion disease," period. These 50 participants are from 29 families representing 6 of the more common *PRNP* mutations. 70% of these 50 participants are mutation carriers, 30% non-carriers. Thus far, 26/50 participants have had serial research visits, 18 of whom also had at least one visit prior to the NIH funding period. These 50 participants had a total of 92 visits conducted prior to and during the grant period with the following collection rates: 3T NIC MRI, 96%; neuropsychological testing, 97%; CSF, 80%; blood for DNA, 100%; plasma collection, 91%; serum collection, 72% (began 2018); RNA collection 99%, genetic counseling, 75%; detailed history and neurological exam, 99%; complete battery of informant measures, 60%; quantitative motor testing (qMotor), 78%; OCTs, 86%; and skin biopsies, 21% (began 2022). Recruitment continues. **Conclusion:** Long-term observational studies in presymptomatic gPrD are feasible. Serial evaluations are continuing, and we expect we will identify potential biomarkers of change over the course of presymptomatic gPrD. Information collected in this study will be important for developing clinical trials in presymptomatic gPrD.

### M204. Transcriptional Changes in Microglia in a Noninvasive Mouse Model of Neonatal Hypoxic Ischemic Encephalopathy

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Neonatal hypoxic ischemic encephalopathy (HIE) is caused by insufficient oxygen delivery to the neonatal brain and occurs in an estimated 1.5 per 1000 live births. The resulting brain injury can have many long-lasting effects including

motor deficits, cerebral palsy, cognitive deficits, and developmental delays. Therapeutic hypothermia is the only effective therapy for infants with HIE; however, it has a narrow window of efficacy of six hours following birth. When cooling is not initiated within the required timeframe, or in infants where therapeutic hypothermia is not effective, there are no other effective therapies available. This demonstrates the critical need for additional therapeutics that can work in conjunction with therapeutic hypothermia to mitigate brain injury and reduce the occurrence of lifelong disabilities. We propose that the neuroimmune response following HIE which contributes to secondary neuronal death is a promising target for therapeutic development. Microglia are the first responders to damage in the brain, and are important for the clearance of debris immediately following injury. However, if chronically activated they can also contribute to increased brain damage through maladaptive phagocytosis and cytokine production. Microglia can establish transcriptionally distinct subpopulations that are disease dependent, and next generation sequencing of microglia has provided significant insight into the function of microglia in a variety of disease states. We have conducted bulk RNA-seq on isolated myeloid cells (CD11b+) in our model of HIE from the brains of experimental mice collected 8 days following hypoxia exposure (P14). We found 215 significant differentially expressed genes in HIE exposed mice vs. control mice. These include downregulation of genes important in multiple signaling pathways including NMDA receptors, CaMKII, protein kinase C, and adenylate cyclase, and upregulation of genes involved in cytokine signaling and retinoid metabolism. We are validating these results by qRT-PCR, cytokine arrays, and IHC to determine the regional specificity of transcriptional changes in brain areas related to motor and cognitive deficits in HIE, including the striatum, hippocampus, and cortex. This research reveals the molecular response of microglia to HIE and may be leveraged for the development of future therapeutics.

#### **M205. Volumetric Analysis of Hippocampal Subregions and Subfields in Left and Right Predominant Semantic Dementia**

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**Background:** Semantic dementia(SMD) is characterized by progressive conceptual knowledge loss attributable to degeneration of the anterior temporal lobe. Two variants exist based on pattern of involvement: left-predominant variant(lpSMD) associated with verbal knowledge impairment and right-predominant variant(rpSMD) associated with behavioral changes and non-verbal knowledge loss, including prosopagnosia. The hippocampus participates in semantic memory preservation and is also affected in SMD. We aimed to assess relative volume loss of hippocampal subregions/subfields in SMD compared to controls and determine

whether subregion/subfield volumes differ between lpSMD and rpSMD. **Methods:** Thirty-three SMD and 15 controls from the Neurodegenerative Research Group who had completed 3T volumetric MRI and [<sup>18</sup>F]-fluorodeoxyglucose-PET scans were included. Participants were classified as lpSMD or rpSMD based on temporal lobe hypometabolism. Volumetric analysis of hippocampal subregions(head, body, tail) and subfields(parasubiculum, presubiculum, subiculum, CA1, CA3, CA4, dentate gyrus, molecular layer, hippocampal-amygdaloid transition area[HATA], fimbria) were performed using FreeSurfer7. Subfield volumes were measured separately from the head and body. We fit linear mixed effects models using log-transformed subregion and subfield volumes as the dependent variables; age, sex, total intracranial volume, hemisphere and a group-by-hemisphere interaction as fixed effects; and subfield nested within hemisphere as a random effect. **Results:** Twenty-five participants(76%) were lpSMD, 8(24%) rpSMD. At the subregion level, lpSMD showed ~17%-24% smaller head, body, and tail volumes of the dominant(predominantly involved) hemisphere than controls, while volumes of the non-dominant(sparged) hemisphere were similar. RpSMD showed ~22%-30% smaller volumes of all dominant hemisphere subregions, but only the head of the non-dominant hemisphere was 8% smaller than controls. Comparison of lpSMD and rpSMD dominant hemispheres showed no differences in subregion volumes. At the subfield level, the dominant hemisphere of lpSMD showed ~12-36% smaller volumes across all subfields than controls, while the non-dominant hemisphere had ~13%-15% less volumes of the parasubiculum, presubiculum(head and body), subiculum(head), and HATA. RpSMD showed ~22%-51% volume reductions across all dominant hemisphere subfields *versus* controls, with the non-dominant hemisphere also showing ~14%-25% smaller volumes of the parasubiculum, presubiculum, CA3, CA4, dentate gyrus, and HATA(all from head) and fimbria(body). Comparison of dominant hemispheres showed 29% and 25% smaller volumes of the parasubiculum and fimbria, respectively, in rpSMD than lpSMD; comparison of non-dominant hemispheres showed 14%-20% less volumes of CA1(body), CA3(head and body), CA4(head), dentate gyrus(head) and HATA in rpSMD. **Conclusion:** All hippocampal subregion/subfield volumes are affected in SMD, with specific subregion/subfield volumes being more affected in both dominant and non-dominant hemispheres in rpSMD than lpSMD.

#### **K-M104. Disease Associated Changes in Neuronal-Glia Interactions Implicates Neuroimmune Inhibition in Tau Dementias**

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Tau related dementias affect more than 55.2 million<sup>1</sup> people worldwide and are uniformly incurable. In various tau-related dementias, including Alzheimer's disease, Frontotemporal dementia with tau pathology, and Progressive Supranuclear palsy, the accumulation of abnormal tau protein can selectively affect different brain regions and specific populations of

neurons and glia cells. Tau mediated pathogenesis is still not fully elucidated, and tauopathies are still untreatable. Understanding the causal mechanisms governing selective vulnerability of neuron and glia cells across these disorders holds the potential to unveil new therapeutic strategies and identify drug targets. Emerging evidence and genetics implicate noncell autonomous mechanism of cellular vulnerability in dementia, including potential neuronal-glia and glial-glia interaction. Determining the mechanisms that regulate cell-cell interactions, which undergo changes in diseased brain regions experiencing selective vulnerability, offers a unique perspective to uncover disease mechanisms. Therefore, we combined data from single cell chromatin accessibility and RNA sequencing across various disorders and brain regions with variable vulnerability to tau pathology. This allowed us to map disorder-specific cell-cell interactions and link them to their gene regulatory drivers at the chromatin level. Our studies have uncovered multiple shared and disorder-specific changes in neuronal-glia receptor interaction pairs, revealing unexpected implications of inhibitory neuroimmune signaling in the accumulation of pathological disease states in disease tissue, in addition to disease specific changes in interactions involved in myeloid cell recruitment and cell migrations.

#### LB-M102. Bibliometric Analysis of the 100 Most Cited Kluver-Bucy Research Articles

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**Objective:** Kluver-Bucy Syndrome (KBS) is a rare neuropsychiatric disorder characterized by hyperorality, hypersexuality, bulimia, visual agnosia, and amnesia due to lesions affecting bilateral temporal lobes. It is attributed to a multitude of causes, including stroke, herpes simplex encephalitis, Alzheimer's Disease, and head trauma. Current treatments for KBS include symptomatic management with neuropsychiatric medications. The bibliometric analysis was done to reflect the relevance and understanding of KBS in recent literature.

**Methods:** The SCOPUS database was utilized to search for all articles with the terms "Kluver-Bucy" and "Kluver Bucy" from January 1, 1955 (the first available articles from the search) to February 1, 2023. The parameters included in this analysis were article title, citation numbers, citations per year, authors, institutions, publishing journals, country of origin, Source Normalized Impact per Paper, and Scopus CiteScore.

**Results:** Since 1937, when Kluver-Bucy Syndrome was first defined, the publications on KBS have steadily increased, with up to six publications a year in 2002. The most common institutions were SUNY Upstate Medical University, VA Medical Center, and the State University of New York (SUNY) System. Seven of these papers were published in Neurology. Almost 75% of the articles were published in journals of medicine and neuroscience. **Conclusions:** This is the first bibliometric analysis to evaluate the most influential publications about Kluver-Bucy Syndrome. A majority of the research is case-based and there is a dearth of clinical trials to

identify the exact pathophysiology and physiotherapy management, possibly owing to the rarity of the disease. Our research suggests that there may be significant overlap between Sanfilippo syndrome and KBS, suggesting that refined guidelines for establishing diagnosis may be required for children. Our study could bring a renewed interest in this field and lead to additional research focused on understanding the pathophysiology of KBS in order to promote the development of novel diagnostics and treatment.

#### LB-M103. Clinicopathologic Features of a Novel Star-Like Transactive Response DNA-Binding Protein 43 (TDP-43) Pathology in the Oldest Old

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**Background:** TDP-43 pathology in frontotemporal lobar degeneration (FTLD) and Alzheimer's disease (AD) is categorized based on the morphologic characteristics and pattern of distribution of inclusions. Types A-E exist in FTLD, while type- $\alpha$  (reminiscent of FTLD-TDP Type A) and type- $\beta$  (tau neurofibrillary tangle-associated TDP-43) are seen in AD. Here we describe the clinical, imaging, and pathologic features of a novel TDP-43 inclusion found in the oldest old.

**Methods:** Amygdala slides of 131 cases with varying ages at death and AD neuropathologic changes (ADNC) were screened for TDP-43 pathology using anti-phospho-TDP-43 antibodies. Seven cases (5%) showed atypical TDP-43 inclusions not previously described and could hence not be typed. Clinical and neuroimaging findings were abstracted, and additional immunohistochemistry (IHC) techniques were performed to assess distribution, TDP-43 species, cellular localization, and colocalization with tau. **Results:** Three males and four females showed star-like TDP-43-positive inclusions in the medial (subpial) amygdala and less in basolateral white matter or subependymal areas. All had died at an extremely old age (median: 99.8 years [IQR: 93.5, 101.4]) from non-neurological disorders and after a prolonged agonal period. Only one was a carrier of the apolipoprotein E  $\epsilon 4$  allele. None had dementia prior to death: four were cognitively normal and three were diagnosed with amnesic mild cognitive impairment in their 90s. MRI scans from five cases showed generalized atrophy, most marked in the temporal lobe, and leukoaraiosis. Three had fluorodeoxyglucose-PET scans, with one showing focal progressive left medial temporal hypometabolism. Pathologically, the star-like TDP-43 inclusions were only observed in the amygdala. The hippocampus only showed TDP-43-positive thin neurites in the fimbria and subiculum, while the frontal lobe was free of all types of TDP-43 inclusions. Star-like inclusions were also detected (albeit less) using antibodies against N- and C-terminal TDP-43. Double-labeling IHC confirmed the

cellular localization of TDP-43 within astrocytes. Additionally, aging-related tau astrogliopathy was found in all cases and double-labeling IHC revealed colocalization of TDP-43 and tau within the star-like lesions. None of the seven cases had high ADNC; instead, one had low ADNC, three had intermediate ADNC, and three had primary age-related tauopathy. Six cases had argyrophilic grains disease, four had brainstem/transitional Lewy body disease, and all had varying degrees of cerebrovascular pathology. **Conclusions:** We identified a novel TDP-43 pathology with star-like morphology associated with very old age (superaging), with a relatively homogeneous clinicopathologic picture, possibly representing a novel, true aging-related TDP-43 pathology.

#### **LB-M104. Differential Diagnosis and Alzheimer's Disease: Can CART and CHAID Analysis Improve Diagnostic Accuracy and Decrease Barriers to Care**

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Estimates of adults in the U.S. living with Mild Cognitive Impairment (MCI) are as high as 22 percent (N. Campbell, Clinics in Geriatric Medicine, 2013). Approximately 12 percent of individuals with diagnoses of MCI will develop dementia from an Alzheimer's Disease (AD) pathology (S. H. Tariq, The American Journal of Geriatric Psychiatry, 2006). Using data obtained in 2019, the Alzheimer's Association and Centers for Disease Control and Prevention (CDC) report there are an estimated 5.8 million adults over the age of 60 with Alzheimer's Disease, making it the most prevalent etiology associated with MCI and dementia. With current population trends showing an unprecedented percentage of Americans turning 65 in the next decade, the prevalence of AD is expected to increase dramatically. Such an increase poses a significant threat to an already overwhelmed healthcare system, a reality made more apparent when considering multiple studies of community samples have suggested that, worldwide, nearly 67 percent of individuals living with dementia are undiagnosed (L. Lang, *BMJ Open*, 2017). While standardized neuropsychological assessment is the preferred method for classification of dementia, true neuropsychological testing can often prove inaccessible (American Psychiatric Association, 2013). The results of a survey-based study, conducted by J. Sweet et al. (The Clinical Neuropsychologist, 2021), showed that average wait times for neuropsychological evaluations are as high as 60 days for institution-based practitioners. Lack of insurance, providers, financial resources, battery-length, and inflexible scheduling exacerbate this inaccessibility. Considerable work must be done to examine diagnostic practices and remove barriers when feasible. The current study addresses accessibility issues related to battery length by using supervised learning analysis (decision tree-based algorithms) to evaluate the predictive value of specific tests. Similar work has been previously conducted at the level of gross cognitive domains (S. Belleville, Neuropsychology review, 2017). The current project uses data collected by the BIOCARD study (by Johns Hopkins University) to understand the predictive nature of individual neuropsychological tests and specific combinations thereof, in

the diagnosis of AD. Such data-driven analysis would provide direct information regarding the possibility of shortening traditional battery length, while improving diagnostic integrity therein. Shorter, optimized batteries would allow for administration by an increased number and type of provider. Results from predictive analyses may provide guidance designing standardized, specific batteries that would aid in differentiation of similar dementia etiologies.

#### **LB-M105. Disease Associated Changes in Neuronal-Glia Interactions Implicates Neuroimmune Inhibition in Tau Dementias**

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Tau related dementias affect more than 55.2 million people worldwide and are uniformly incurable. In various tau-related dementias, including Alzheimer's disease, Frontotemporal dementia with tau pathology, and Progressive Supranuclear palsy, the accumulation of abnormal tau protein can selectively affect different brain regions and specific populations of neurons and glia cells. Tau mediated pathogenesis is still not fully elucidated, and tauopathies are still untreatable. Understanding the causal mechanisms governing selective vulnerability of neuron and glia cells across these disorders holds the potential to unveil new therapeutic strategies and identify drug targets. Emerging evidence and genetics implicate noncell autonomous mechanism of cellular vulnerability in dementia, including potential neuronal-glial and glial-glial interaction. Determining the mechanisms that regulate cell-cell interactions, which undergo changes in diseased brain regions experiencing selective vulnerability, offers a unique perspective to uncover disease mechanisms. Therefore, we combined data from single cell chromatin accessibility and RNA sequencing across various disorders and brain regions with variable vulnerability to tau pathology. This allowed us to map disorder-specific cell-cell interactions and link them to their gene regulatory drivers at the chromatin level. Our studies have uncovered multiple shared and disorder-specific changes in neuronal-glial receptor interaction pairs, revealing unexpected implications of inhibitory neuroimmune signaling in the accumulation of pathological disease states in disease tissue, in addition to disease specific changes in interactions involved in myeloid cell recruitment and cell migrations.

#### **LB-M106. Ignite: A Phase 2 Proof-of-Concept Study of VGL101 in Patients with Adult-Onset Leukoencephalopathy with Axonal Spheroids and Pigmented Glia**

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**Background:** Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) is a rare, inherited, autosomal-dominant, progressive, neurodegenerative disorder caused by loss-of-function mutations in the colony-stimulating factor 1 receptor (CSF1R) gene. It is characterized by rapid progression of cognitive dysfunction, neuropsychiatric symptoms, and motor impairment. Adults typically present symptoms in their forties and have a life expectancy of 6 to 7 years thereafter. Prevalence is estimated to be ~10% of adult onset leukodystrophies. Currently, there are no approved treatments available, thus representing a significant unmet medical need. VGL101 is a fully human monoclonal antibody TREM2 agonist in development for the treatment of ALSP. TREM2 and CSF1R are cell-surface receptors expressed on microglia. Their signaling pathways converge intracellularly and are critical to microglial function. VGL101-mediated activation of TREM2 is designed to enhance function of microglia and regulation of neural repair mechanisms, compensating for CSF1R-driven deficits with the potential for slowing ALSP disease progression. Data from the ongoing Phase 1 study in healthy volunteers suggests a safe and well-tolerated safety profile, confirmed CNS target engagement and pharmacological activity, supporting further clinical development in ALSP. Here, we describe the Phase 2 study of VGL101 in ALSP. **Methods:** Ignite (NCT05677659), the first ever interventional study in ALSP, is an open-label, multicenter study that aims to evaluate safety, tolerability, and proof-of-concept of VGL101 in patients with ALSP. The on-going study will enroll approximately 15 adult ALSP patients with confirmed CSF1R gene mutation, MRI findings consistent with ALSP, with 2 or more clinical signs and symptoms, such as cognitive impairment or psychiatric symptoms, pyramidal or extrapyramidal signs on neurological examination, and/or seizures. Participants will receive VGL101 20 mg/kg IV every 4 weeks for 1 year. The primary outcome measure is safety and tolerability of VGL101. Secondary outcome measures include the effects of VGL101 on target engagement and the following disease-related biomarkers 24 weeks after treatment: volumetric MRI, ALSP severity score based on MRI, neurofilament light chain (NfL) in CSF and blood and soluble CSF1R in CSF. Exploratory outcome measures include evaluation of VGL101 effects on biomarkers after 1 year of treatment. **Conclusion:** Individuals with ALSP experience rapid disease progression with significant morbidity and mortality due to lack of treatment options. The Phase 2 Ignite study aims to provide insights into safety, tolerability, and proof-of-concept of VGL101 for the treatment of patients with ALSP; enrollment continues.

#### LB-M107. Mephitical Olfactory Hallucinations from Delusions of Demonic Possession

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**Introduction:** A specific subtype of schizophrenia, Kandinsky Clerambault Syndrome, characterized by delusion of

being possessed, has also been associated with olfactory hallucinations (Lavretsky, H 1998; Gedeveni, 2022). However, the mephitical nature of such hallucinations has not heretofore been described. **Methods:** Case study: This 24 year old right handed single male, presented with perception that the devil went into his body, controlling his actions. The demon forced his hand to hit the coffee table, so hard that it broke the table, and despite his best efforts to resist, he could not control his own body. He attempted to get the spirit out of him, but he could not. Concomitant with these events was a perception of the aroma of rotten eggs in both nostrils. He never had experienced these aromas or haptic sensations before. This odor only occurred when the devil possessed him. He had no perception of hallucinated smells prior to this. The rotten egg smell was in both nostrils with 10/10 in the severity with 10 being most severe. It lasted for a few hours along with haptic sensations with the devil grabbing him. There were no phantageusias. By the time the ambulance had arrived, bringing the patient to the hospital, the demon had left his body. **Results:** Abnormalities on physical examination: Neurological Examination: Mental Status Examination: Immediate recall . Digit span: 7 digits forwards and 2 digits backwards Recent Recall: None of three objects in three minutes and 2 with reinforcement. Proverbs not tested because he only completed 9th grade. Unable to do calculations. Cranial Nerve (CN) examination: CN I: Alcohol Sniff Test: 2 (anosmia). Motor Examination: Tone: 1+ bilateral cogwheel rigidity in both upper extremities. Drift testing with bilateral cerebellar spooning. Cerebellar Examination: Finger to nose dysmetria both upper extremities. Sensory Examination: Rydel-Seiffer Vibratory Sense Evaluation: 8 both upper extremities and 5 both lower extremities. Reflexes: 3+ Brachioradialis bilaterally. Magnetic resonance imaging of the brain with and without infusion: normal. **Discussion:** There are myriad reasons why such miasmic hallucinations may manifest in Kandinsky-Clerambault syndrome. This could represent a neighborhood effect. In schizophrenia, there is pathology involving the piriform cortex, orbitofrontal cortex and insula (Purdon, 1998). These same regions are associated with olfactory processing suggesting common neuroanatomic pathology ( Doty and Hawkes, 2015 ; Mohr, 2001).

#### LB-M108. Neuropathological Validation of Monoamine Oxidase-B (MAO-B) as PET Imaging Biomarker of Reactive Astroglia in Alzheimer's Disease

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**Background:** Reactive astroglia accompanies the two neuropathological hallmarks of Alzheimer's disease (AD)—Aβ plaques and phospho-tau neurofibrillary tangles—and parallels neurodegeneration. Thus, there is growing interest in developing imaging and fluid biomarkers of reactive astroglia for diagnosis and prognostication of AD and related dementias. Monoamine oxidase-B (MAO-B) is

emerging as a target for PET imaging radiotracers of reactive astrogliosis. However, a thorough characterization of MAO-B expression in postmortem control and AD brains is lacking. Also, the *MAOB* rs1799836 SNP genotype may impact MAO-B enzymatic activity yet its effect on MAO-B brain expression level is not well studied. **Objectives:** We sought to: (1) Identify the primary cell type(s) expressing MAO-B in control and AD brains; (2) Quantify MAO-B immunoreactivity in multiple brain regions of control and AD donors as a proxy for PET radiotracer uptake; (3) Correlate MAO-B levels with local burden of AD neuropathological changes, reactive glia, and cortical atrophy; (4) Determine the *MAOB* rs1799836 SNP genotype impact on MAO-B expression level. **METHODS:** We evaluated the colocalization of MAO-B with cell-type specific markers via double fluorescent immunohistochemistry and confocal microscopy. We performed a postmortem quantitative immunohistochemical analysis of MAO-B, AD neuropathological changes (A $\beta$  plaques and phospho-tau), reactive glia (GFAP+ astrocytes and CD68+ microglia), and cortical thickness in multiple brain regions (temporal, frontal, occipital, cerebellum) of control and AD donors (total n=52). *MAOB* rs1799836 SNP was genotyped in cerebellar DNA via Taqman assay. **Results:** We found that (1) MAO-B is mainly expressed by perivascular astrocytes in the normal cortex and white matter and significantly upregulated by both cortical reactive astrocytes and white matter astrocytes in AD brains; (2) MAO-B is uniformly elevated in AD *vs.* control astrocytes across the temporal, frontal, and occipital cortex and white matter, but is unchanged in cerebellum, which has the lowest expression of all four regions; (3) Within the temporal association neocortex, cortical MAO-B expression levels are independently associated with local measures of reactive gliosis, phospho-tau, and cortical atrophy, but not with A $\beta$  plaque burden; (4) MAO-B expression is not affected by the *MAOB* rs1799836 SNP genotype. **Conclusion:** MAO-B is primarily expressed by cortical and white matter astrocytes and significantly upregulated in AD *vs.* control brains, except in cerebellum. Given its low expression levels, cerebellar cortex is an optimal reference region for radiotracer uptake quantification. Our study validates ongoing efforts to develop MAO-B-based PET radiotracers to image reactive astrogliosis.

#### LB-M109. Predicting Differences in Open-Ended Decision Making between Healthy Controls and Individuals with Dementia

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Impaired decision-making, particularly for open-ended choices, is a disabling early feature of Alzheimer's disease (AD) and behavioral-variant frontotemporal dementia (bvFTD). However, no models currently account for mechanisms of open-ended decision making even in controls, and our understanding of the classes of decision errors remains limited. Moreover, potentially protective metacognitive processes that

monitor decision-making have not been assessed. Here we develop a computational model and associated task to evaluate value-based, open-ended choice. In individual trials, subjects make an open-ended choice (OPEN: e.g. "Please choose your favorite fruit") and complete a short fluency task ("Name as many fruits as you can") in counterbalanced order. Subjects then indicate whether they believe they failed to retrieve a more highly-valued option (metacognitive question) before completing a menu-based version of the task (MENU: "Please choose your favorite fruit from the following list"). We evaluate multiple classes of decision errors including option-based decision errors (OBDE) resulting from failures to retrieve a more preferred option, assessed by choice switches from OPEN to MENU; and value-based decision errors (VBDE), assessed by temporal stability of MENU. We correlate the degree of insight with error frequency. Based upon an associative model of semantic retrieval combined with a logit choice function, we hypothesize that OBDE occur from items of high retrieval accessibility to low. Additionally, switch frequency should correlate with insight. In a large online sample (N=500+), regression models confirm that OBDE occurred from higher to lower accessibility items ( $p < 0.005$ ) and could be predicted by insight into choice quality ( $p < 0.01$ ). Importantly, an incentivized task version demonstrated that OBDE had a tangible, deleterious cost to subjects (\$3.81 relative to a \$50 baseline;  $p < 0.01$ ). We also recruited individuals with AD (n=13), bvFTD (n=13), and age-matched healthy controls (HC; n=16) for in-person testing. Consistent with predictions, both AD and bvFTD subjects switched more often than HC ( $p < 0.05$ ). While bvFTD patients showed greater fluency than did AD patients ( $p < 0.05$ ), both groups showed lower category fluency than HC ( $p < 0.05$ ). Across individuals matched for dementia severity (target CDR $\leq 1$ ), category fluency was significantly and inversely associated with OBDE ( $r = -0.51$ ,  $p < 0.001$ ). Lastly, both bvFTD and AD made more VBDE than controls ( $p < 0.05$ ). These data demonstrate that open-ended decision-making can be quantitatively studied, and they suggest that retrieval failures contribute significantly to open-ended decision-making impairments.

#### Cerebrovascular Disease

##### S100. A Caregiver Approach to Prevention of Aspiration Pneumonia in Stroke Patients at UTHs-Adult Hospital, Lusaka; an Interventional Prospective Study

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Aspiration pneumonia causes the highest attributable mortality of all post-stroke medical complications. A study at the

University Teaching Hospital-Adult Hospital (UTH-AH) found 11% of adults with stroke developed aspiration pneumonia with a mortality rate of 93%(Atadzhanov M, The Open General & Internal Medicine Journal, 2012). This study evaluated the effectiveness of a brief caregiver intervention in preventing aspiration pneumonia amongst adults with stroke admitted to the neurology service at UTH-AH. This study was embedded in a prospective observational study of consenting adults admitted to UTH-AH with stroke. The author conducted a five-10-minute individual teaching session with bedside caregivers of consenting consecutive participants on aspiration pneumonia, its risks, and techniques for its prevention (e.g. feeding position, head of bed elevation, oral care) using a two-page pictorial handout. Participants were assessed daily for the first 10-days of their admission for seven clinical signs of aspiration pneumonia (fever, tachypnea, hypoxia, cough, rhonchi on examination, witnessed aspiration event, clinical team initiation of empiric antibiotics for aspiration pneumonia) as well as chest x-ray findings of pneumonia and leukocytosis. Participants meeting more than four indicators were defined as having aspiration pneumonia. Rates were compared between the intervention and non-intervention cohort. Out of 398 participants, females comprised 51% (n=204), mean age was 57  $\pm$  16 years, and half had ischemic strokes. No differences in demographic or clinical characteristics were observed between the intervention (n=142) and non-intervention (n=256) groups. Aspiration pneumonia occurred in 10% (n=256) of the non-intervention group and four percent (n=five) of the intervention group (p=0.02). The majority of caregivers self-reported high levels of confidence in using the intervention and attempted to implement the strategies taught to them. A brief caregiver educational intervention was effective in preventing aspiration pneumonia among adults with stroke at UTH-AH and represents a feasible, cost-effective and generalizable intervention that could markedly improve post-stroke outcomes in similar resource-limited settings.

#### **S101. A Case of Unprovoked Catastrophic Antiphospholipid Syndrome Who Underwent Venous Thrombectomy**

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**Background:** Catastrophic antiphospholipid syndrome (CAPS) is a rare, life-threatening variant of antiphospholipid syndrome (APS) associated with high morbidity and mortality. Widespread intravascular thrombosis affects three or more different organ systems due to the presence of pathologic prothrombotic autoantibodies. It develops over a short period of time, putting patients at high risk of multiorgan ischemia & failure. **Case Presentation:** A 74-year-old male with reported past medical history of provoked DVT secondary to cellulitis without subsequent anticoagulation presented with right-sided weakness and altered mental status. He suddenly became unresponsive warranting emergent intubation.

Examination showed left-sided facial droop, slurred speech, right upper & right lower extremity weakness. CT head revealed a large left parietal intraparenchymal hemorrhage. CTA did not show any abnormalities. CT venogram demonstrated extensive dural venous sinus thrombosis involving the superior sagittal, right transverse and sigmoid sinuses as well as the right internal jugular vein. CTA of the chest showed bilateral distal subsegmental pulmonary emboli. Low-dose heparin infusion was initiated followed by venous thrombectomy requiring 8 passes given extensive thrombus burden. However, follow-up MR venograms showed re-occlusion of the superior sagittal sinus, torcula, right transverse, and right sigmoid sinuses. Venous duplex ultrasound showed extensive bilateral lower extremity DVTs. Hypercoagulable panel was positive for lupus anticoagulant. One week later, a repeat CT head revealed stable ICH. Patient had a prolonged ICU stay complicated by ventilator-associated pneumonia, *clostridium difficile* infection, and severe dysphagia requiring PEG tube placement. He was discharged on warfarin for anticoagulation and transferred to India via air ambulance. **Conclusion:** This syndrome can be difficult to identify as CAPS can demonstrate overlapping characteristics with other microangiopathic disorders. We highlight an atypical patient profile for CAPS lacking traditional risk factors. It is important to consider testing for antiphospholipid antibodies when an individual presents with extensive multisystem thrombosis, regardless of patient age or other characteristics.

#### **S103. A Presentation of Anterior Inferior Cerebellar Artery Syndrome in a Young Male with Non-Compaction Cardiomyopathy**

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**Introduction/Background:** Left ventricular non-compaction cardiomyopathy (LVNC) is a rare genetic disorder in which the myocardium does not develop properly resulting in deep recess formation of the myocardial walls. These recesses are thought to allow thrombus formation because of sluggish blood flow. LVNC is considered an etiology for stroke in young patients. Anterior inferior cerebellar artery (AICA) infarcts are rare compromising only 1% of cerebellar infarcts. AICA infarcts usually present with vertigo, hearing loss, facial weakness, ipsilateral facial sensory loss, contralateral sensory loss, Horner syndrome, or ataxia. AICA infarcts are usually due to local atherosclerotic disease of the vertebrobasilar circulation, but cardiac embolization has been reported in rare cases. We present a patient with a right AICA stroke associated with LVNC. **Case Report:** A 47-year-old male with hypertension, tobacco dependence presented to the hospital with ear pain/fullness, right sided hearing loss, dizziness, dysarthria, right facial hypesthesia, left hemibody hypesthesia, and right hemiataxia. Initial CT head exhibited an area of hypodensity in right middle cerebellar peduncle, and CTA head/neck was without evidence of occlusion, stenosis, or extracranial/intracranial atherosclerotic disease. MRI brain without contrast showed an acute infarct in the right middle

cerebellar peduncle and right high pons. He underwent a full stroke workup, including Hemoglobin A1c (6.5%), LDL (100), and a transthoracic echocardiogram which showed newly reduced LVEF of 45% and with prominent LV trabeculations. Cardiac MR, recommended by cardiology, displayed evidence of left ventricular non-compaction. We started the patient on systemic anticoagulation with apixaban for secondary stroke prevention to reduce the risk of embolization from thrombi formed in LVNC. **Summary/Conclusion:** Left ventricular non-compaction cardiomyopathy is rare genetic disorder that may lead to cerebral embolization, like in our case. Patients with a cryptogenic stroke may benefit from a cardiac MRI for detection of LVNC.

#### S104. A Randomized Controlled Trial of Transcranial Direct Current Stimulation in Subacute Aphasia

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**Introduction & Aims:** Transcranial direct current stimulation (tDCS) is a promising adjunct to language therapy for post-stroke aphasia, which has demonstrated efficacy in the chronic phase of recovery. No prior study has compared tDCS at different periods of recovery. This was a single-center, randomized, double-blind, sham-controlled efficacy trial with the primary objective to examine whether anodal tDCS augmented language therapy to improve outcomes in subacute aphasia. The primary outcome was improvement on a 175-item picture naming test from pre-treatment to one week following treatment. Secondary outcomes were improvements in discourse and overall quality of life. **Methods:** Right-handed English speakers with aphasia <3 months after left hemisphere ischemic stroke were included, unless they had prior neurological or psychiatric disease or injury or were taking certain medications (34 excluded; final sample = 58). Participants were randomized 1:1, controlling for age and aphasia type and severity, to receive 20 minutes of tDCS (1 mA) or sham-tDCS during 15 45-minute sessions of naming treatment. Participants were assessed 1-, 5-, and 20-weeks after the final treatment session. The trial was registered on ClinicalTrials.gov NCT02674490. **Results:** Baseline characteristics were similar between the tDCS (N=30) and sham (N=28) groups in age, education, sex, and time since stroke onset. In modified intent-to-treat analysis (including only those who participated in at least one treatment session), the adjusted mean change from baseline to 1-week post treatment in picture naming was 22.3 items (95%CI 13.5, 31.2) for tDCS and 18.5 (9.6, 27.4) for sham and was not significantly different. The mean difference was nearly identical to

that observed in the chronic phase (Fridriksson et al., JAMA Neurol, 2018). However, variability in the subacute phase was higher. Individuals who received tDCS demonstrated evidence of greater improvements in discourse. They provided more content when describing a picture at all timepoints, which reached significance 5-weeks post-therapy. Their descriptions also were more efficient, resulting in significant differences 5- and 20-weeks post-treatment, when efficiency in the sham group decreased. Quality of life was not impacted by tDCS. Similar rates of adverse events were reported regardless of condition. **Conclusion:** tDCS did not improve recovery of picture naming but did improve recovery of discourse long-term. Discourse skills are a critical reflection of real-world communication, underscoring the importance of these findings to patients. Future research should examine tDCS in a larger sample of people with subacute aphasia.

#### S105. A Review of Paradoxical Brain Emboli Secondary to Intrapulmonary Shunts

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Paradoxical emboli originate in the venous system and travel through an intracardiac or pulmonary fistula, enter arterial circulation and cause ischemia. Rarely, paradoxical emboli can travel through a pulmonary arteriovenous malformation (PAVM) and cause stroke. This clinical association is rarely recognized in the clinical setting. Most often, cryptogenic stroke workup consists of electrocardiogram (ECG) to evaluate for atrial fibrillation and transesophageal echocardiogram (TEE) to evaluate for patent foramen ovale (PFO). However, when these workups are unrevealing, further assessment for PAVM with pulmonary angiography may be useful. PAVMs may be considered congenital or acquired. Congenital PAVMs are often associated with hereditary hemorrhagic telangiectasia (HHT), an autosomal dominant vascular dysplasia that affects genes important for blood vessel development and repair (Tellapuri, The International Journal of Cardiovascular Imaging, 2019). Acquired PAVMs may occur with schistosomiasis, cirrhosis, metastatic carcinoma, or pregnancy (Prager, The Annals of Thoracic Surgery, 1983). The correlation of intrapulmonary shunt and transient ischemic attack (TIA) or stroke is increasingly reported in literature. Patients with history of stroke or TIA have been found to have greater incidence of PAVMs than non-stroke patient counterparts (16% versus 9.7%, p<0.01) (Abushora, Journal of the American Society of Echocardiography, 2013). One study reported that 70% of patients with PAVMs had neurologic complications at the time of diagnosis (Faughnan, Chest, 2000). Timely treatment is essential to prevent complications. Treatment of PAVMs consists of embolization. Previously, PAVMs 3mm or larger were targeted for endovascular coiling (White, Radiology, 1988). However, now it is recognized that PAVMs of any size may result in neurologic complication and warrant treatment (Shovlin, Thorax, 2008). We present three institutional cases of patients who presented with stroke or TIA. Following extensive workup for cryptogenic stroke, the patients were found to have

intrapulmonary shunts secondary to PAVMs. A review of literature identified 42 publications with 381 cases reporting PAVM as the etiology for stroke or TIA. Patients ranged in age from 19 to 74 years old and 231 cases were related to HHT. Two cases reported treatment with aspirin or therapeutic anticoagulation. Three cases reported surgical treatment and the rest were treated via embolization. Although PAVMs remain a rare cause of stroke, having greater awareness and understanding of the relationship between these diseases may allow prompt treatment to decrease the morbidity and mortality associated with stroke and prevent future episodes.

### **S106. Absence Of Chordin-Like 1 Prevents Loss of GluA2 and Improves Motor Recovery in a Mouse Model of Stroke**

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Ischemic stroke is a condition caused by a sudden obstruction of blood flow resulting in reduced glucose and oxygen to an area of the brain. After a stroke, the tissue in the injury core sustains permanent damage while the surrounding area, known as peri-infarct, is associated with plastic changes leading to spontaneous functional recovery. In response to stroke neurons lose GluA2-containing AMPA receptors (GluA2-AMPA), which are  $\text{Ca}^{2+}$ -impermeable, a phenomenon that is linked to excessive  $\text{Ca}^{2+}$  influx to neurons and apoptotic cell death. Understanding the mechanisms that underlie these GluA2-AMPA alterations after an ischemic stroke is crucial to develop new neuroprotective and neurorestorative strategies. Astrocytes, non-neuronal cells in the central nervous system, play important roles in synaptic plasticity regulation via secreted proteins. Chordin-like 1 (Chrdl1) is one of these astrocyte-secreted proteins that regulates synaptic maturation and plasticity via GluA2-AMPA, and we found that ischemic strokes promote upregulation of Chrdl1 in peri-infarct astrocytes. In this study we used molecular, imaging, and behavioral techniques to evaluate the potential of Chrdl1 to regulate GluA2-AMPA synaptic content and functional recovery after a photothrombotic ischemic stroke in both male and female mice. We demonstrate that absence of Chrdl1 promotes a permissive environment for recovery by preventing stroke-driven alterations of GluA2, reducing apoptotic cell death and promoting faster motor recovery, with subtle differences between males and females. Overall, these results suggest that synapse-regulating astrocyte-secreted proteins such as Chrdl1 have therapeutic potential to aid functional recovery after an ischemic injury.

**S107. ANA Futures: Evaluation of the ANA Junior and Early Career Committee 2022 Longitudinal Mentoring Scheme for Medical Students and Neurology Residents**  
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**Introduction:** A mission of the ANA is to advance members' careers to improve neurologic health for all, guided by community growth and cohesion. The Junior and Early Career Membership Subcommittee is tasked with the acquisition and retention of medical students and neurology residents as ANA members. In 2022, the subcommittee developed ANA Futures, a mentorship scheme for a cohort of students and residents. The goal of the scheme was to introduce the cohort to the ANA via providing longitudinal engagement in their academic development in line with ANA guiding principles.

**Method:** From 90 applications, we selected a cohort of 16 third-year medical students applying to residency in the 2022-23 season, and 15 neurology residents comprising eleven PGY1s and four PGY3s. We conducted three virtual mentoring sessions with ANA expert mentors for each cohort throughout the year, and a final session at the ANA Annual Meeting. Student sessions included bespoke support in applying to neurology residency with sessions covering career pathways in neurology, personal statement feedback and mock residency interviews. Resident sessions focused on developing academic career skills including sessions on project planning, academic networking and effective science communication. A final in-person networking session was held at the 2022 Annual Meeting. We maintained engagement between sessions via a Slack communications board. Feedback was obtained after each session. **Results:** In terms of overall satisfaction with ANA Futures, 98% would recommend the program to a peer. Across all sessions, 83% of participants reported they developed knowledge and skills in line with planned learning objectives. In qualitative analysis of survey responses, we noted that both cohorts valued the individualized feedback made possible via virtual mentoring sessions, particularly when connected with senior ANA faculty. Improvements for future cohorts included developing subgroups for junior and senior residents given the different career priorities of PGY1 and PGY3 residents. Longitudinal data regarding retention of ANA membership and further engagement of the 2022 cohort with the ANA will be available by the time of the Annual Meeting. **Conclusion:** The ANA Futures scheme was successful in engaging a cohort of medical students and residents with the mission of the ANA and with a career in academic neurology. Future years will build on this feedback with the goal to establish a mutually sustaining cohort of junior ANA members.

### **S108. Analysis of the Plasma Proteome in Early CADASIL Reveals Dysregulations in Angiogenesis**

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**Background:** Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), is a genetic form of Vascular Cognitive Impairment and Dementia (VCID) caused by mutations in *NOTCH3*. There are currently no therapies for CADASIL. A better molecular understanding of CADASIL could help to advance therapeutic developments for this disease and for the more common sporadic forms of VCID, which are difficult to detect and model. Here, we analyzed the plasma proteome of patients with early CADASIL to understand the molecular pathways dysregulated prior to the onset of severe symptoms. **Methods:** We collected plasma from patients with CADASIL (n=25), enrolled in VascBrain, our longitudinal study of genetic and sporadic VCID. We selected age/sex matched controls (n=28) from the UCSF Memory and Aging Center biobank. Plasma samples were analyzed using aptamer-based technology via the SomaScan Assay (version 4.1) from Somalogic. Pathway analysis (IPA and PANTHER) and correlation analysis was performed. **Results:** 439 proteins were significantly upregulated in the CADASIL group while 98 were significantly downregulated (Fold change cut off +/- 1.2, uncorrected p<0.05). Several proteins previously shown to be altered in brain tissue from patients with CADASIL, including *NOTCH3*, *BGN* and *COL6A1*, were differentially expressed in the plasma. *In silico* pathway analysis on the 537 differentially expressed proteins (DEPs) showed that angiogenesis and VEGF signaling were among the pathways predicted to be activated. Fibrotic and inflammatory pathways were also predicted to be activated. Intersection of plasma proteomics with a publicly available dataset of blood vessel proteomics from patients with CADASIL (Zellner *et al.* 2018) identified 15 overlapping DEPs. Upstream regulators, *LONP1* and *TNFA*, were predicted to be dysregulated. Critically, in plasma, 64% of DEPs correlated with Jagged1 (*JAG1*) in the CADASIL cohort only. *JAG1*, a known ligand of *NOTCH3* and a pro-angiogenic regulator, correlated with the angiogenic regulators, *EDIL3* and *SHMT2*, and other proteins associated with angiogenesis including *FLT4*, *WNT5B* and *GRB2*. Intersection with existing single cell seqRNA analysis on healthy blood vessels (Winkler *et al.* 2022) showed that many of the DEPs were also highly expressed in smooth muscle cells (SMCs) and correlated also with *JAG1* expression. **Conclusion:** This study found that CADASIL plasma is reflective of known disease pathology. In addition, this study identified dysregulations in angiogenesis associated proteins alongside proteins related to fibrosis and inflammation, in early-stage CADASIL. The angiogenic activity, potentially driven by *JAG1*-related SMC dysfunction, may provide insights into therapeutically treating disease progression.

### S109. Anterior Cerebral Artery Aneurysm in a 7-Month-Old Infant, a Case Report

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**Introduction:** Intracranial aneurysm in infancy is a rare phenomenon. The incidence of paediatric aneurysms is ~1-2%. Although mostly idiopathic, other causes must be considered, including trauma, infection, or genetic causes. **Case/Method:** 7-month-old boy, twin gestation, uncomplicated delivery at 38 weeks, with no significant past medical history, presented with lethargy and emesis following three days of fever, cough, and congestion. He had a ruptured ACA aneurysm and underwent surgical clipping with favourable outcome. He had hydrocephalus on admission requiring an eventual ventriculoperitoneal shunt. Patient was followed for several years, and on subsequent imaging, additional aneurysms were seen with no evidence of bleed. The patient recovered well. There was no history of trauma, intracranial infection, or relevant family history. Patient underwent genetic testing including *PKD1*, *PKD2*, *TSC1*, *TSC2*, *VHL*, *TGFBR1*, *TGFBR2*, *SMAD3*, *SMAD4*, *SLC2A10*, *SK1*, *MYH11*, *MED12*, *GDF2*, *FBN1*, *FLNA*, *ENG*, *COL3A1*, *COL5A1*, *COL5A2*, *CBS*, *BMPRI1A*, *ACVRL1*, *ACTA2*. This study did not reveal any mutations within these genes. Whole exome sequencing (WES) showed variants of unknown significance in 2 genes (*SLC19A2* (variant P.G172D) and *STIM1* (variant P.E61G)), which were believed to be clinically unrelated to his aneurysm. **Discussion:** There is no consensus on the exact underlying mechanism of idiopathic paediatric aneurysms; however, genetic susceptibility may play a role. In our case, the WES reported variants of unknown significance. New reports implicate these variants in several disease states. *SLC24A3* gene has been identified to play a role in intracellular calcium homeostasis and actin cytoskeleton development. A variant in the family of *SLC* gene, *SLC19A2*, has been reported to contribute to the development of Thiamine-responsive megaloblastic anaemia (TRMA) was identified, with possible role in destabilizing the aneurysm. Variants previously categorized as “variants of unknown significance” are increasingly recognized as potential disease contributors. We suggest that a Deletion/Duplication analysis or an SNP array may be beneficial to elucidate the underlying cause of aneurysm. Saccular aneurysms most often occur at the bifurcation of the internal carotid artery or one of its immediate branches. There is a higher concentration of internal elastic membrane fenestration in these bifurcations, with the damage to internal elastic lamella as the initiating factor in aneurysm formation. Early diagnosis of paediatric aneurysms is essential as the mortality is ~40% due to increased bleeding and delayed diagnosis compared to adults. **Conclusion:** The infantile cerebral aneurysm is a rare phenomenon and distinct from adults. Intrinsic factors, including genetic mutations, should be considered when an idiopathic aneurysm is suspected.

### S110. Association of Cerebral Blood Flow with Microstructural Injury in Periventricular and Whole Brain White Matter

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**Background:** Periventricular white matter (PVWM), perfused exclusively by small arteries, has the lowest cerebral blood flow (CBF) in the brain and a high load of white matter hyperintensities (WMH) in aging and dementia. Accordingly, PVWM tissue may be particularly sensitive to hypoperfusion and white matter injury. We evaluated the association of CBF and microstructural white matter integrity measured by DTI metrics in normal-appearing periventricular white matter (NAPVWM) and normal-appearing white matter (NAWM) as a whole. **Methods:** Multimodal MRI data from N=168 subjects in the Penn Alzheimer's Disease Research Center were analyzed. We categorized participants into 3 groups: cognitively normal (CN) adults, mild cognitive impairment (MCI), and dementia (including Alzheimer's disease (AD) and non-AD) based on consensus designation. WMH lesion masks were obtained from FLAIR MRI to calculate total WMH volume and to exclude WMH voxels from WM and PVWM regions. Mean values for ASL-derived CBF and DTI metrics (fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD)) were extracted in NAWM and NAPVWM through an established CBF-based PVWM mask. We used multiple linear regression to assess the association of CBF and group as independent variables with each DTI metric as the dependent variable in regions of interest (ROIs) considering age, sex, and WMH volume as the covariates. We selected the models with the highest  $R^2$  to show the strongest associations in each region. **Results:** 168 subjects, including 124 CN, and 28 MCI and 16 dementia subjects were included. The mean (SD) age was 68(15) with 55% females. In NAWM, the multivariate model with the highest  $R^2$  (0.542) suggested that CBF was significantly associated with MD (Beta=-0.206,  $P=0.001$ ) whereas in NAPVWM, CBF was significantly associated with RD in the model with the highest  $R^2$  (0.641) (Beta= -0.212,  $P<0.001$ ). In both models, group differences (CN> MCI> dementia) were associated with MD in NAWM (Beta=0.212,  $p<0.001$ ) and RD in NAPVWM (Beta=0.224,  $P<0.001$ ). **Conclusion:** Lower CBF is correlated with DTI evidence of microstructural injury in both NAWM and NAPVWM and across clinical phenotypes. The finding of lower CBF with higher RD in the NAPVWM suggests that hypoperfusion in this region might be primarily associated with myelin injury.

### S111. Atypical Central Nervous System Vasculopathy with Moyamoya Syndrome Secondary to B Cell Lymphoma

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**Background:** Workup of CNS vasculopathy remains challenging given atypical clinical presentations and multiple etiologies including potential infectious, rheumatologic, and neoplastic causes. **Case Presentation:** A 54-year-old lady with history of hypertension initially presented with left extremity weakness in 2019. MRI Brain with and without contrast at that time revealed hyperintense FLAIR lesions in the left periventricular white matter, bilateral thalami and left brainstem, without post contrast enhancement. She was prescribed oral steroids with presumed demyelinating disease resulting in interval improvement of her white matter disease. In 2023, she then presented with acute onset of right sided gaze deviation, complete left facial palsy, left hemiparesis, expressive aphasia, mild dysarthria. Repeat MRI of brain demonstrated DWI lesions suggestive of acute infarcts in the right and left MCA territories with persistent confluent periventricular, subcortical, and midbrain white matter signal abnormality and associated contrast enhancing lesions in the midbrain. Diagnostic cerebral angiogram revealed a multifocal vasculopathy predominantly involving terminal ICA and proximal MCA branches suggestive of a moyamoya pattern. CSF analysis showed elevated protein of 182. Serological work-up revealed an ESR of 36 and CRP of 13; anti-MOG and AQP4 Ab were negative. CT chest/abdomen/pelvis was unrevealing. The patient received 3-days of IV methylprednisolone and was discharged on aspirin. Follow up brain MRI showed improvement of T2 signal abnormalities previously identified and no worsening white matter disease. About 3 weeks later, the patient was re-admitted with worsening episodes of aphasia and developed some dysphagia. CTA re-demonstrated moyamoya pattern bilaterally. MRI demonstrated worsening multifocal parenchymal enhancement in bilateral posterior internal capsules and cerebral peduncles, and new areas of enhancement within right frontoparietal lobe, high frontal lobes, anterior corpus callosum, and left occipital lobe. Repeat lumbar puncture showed protein of 78. She completed 5 days of IV methylprednisolone and later transitioned to oral steroids. She subsequently underwent brain biopsy that showed perivascular inflammation and sparse neoplastic cells, consistent with B-Cell non-Hodgkin lymphoma confirmed with immunohistochemistry staining. PET-CT was performed which demonstrated focal intense increased metabolism at the gastroduodenal junction. GI biopsies obtained via endoscopy were negative for malignancy. She also underwent a bone marrow biopsy, which was unremarkable. She was later started on chemotherapy for treatment of B cell lymphoma. **Conclusion:** The patient's steroid responsive white matter lesions, CSF protein elevation, angiographic findings suggestive of moyamoya syndrome, and biopsy findings provided confirmatory evidence for B-cell non-Hodgkin's lymphoma.

### S112. Atypical Presentation of Ischemic Stroke Secondary to HSV-2 Vasculitis

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**Background:** CNS infection is a well-known cause of cerebrovascular complications, including both ischemic and hemorrhagic strokes. However, stroke work-up in the infectious setting can be challenging, especially with atypical presentations. We present a rare case of ischemic stroke secondary to HSV-2 vasculitis in an adult patient. **Case Presentation:** An 80 year old female presented as an activated stroke code due to altered mental status and abnormal MRI. Notable medical history included bilateral subdural hematoma and bilateral subarachnoid hemorrhage post-fall one month prior, pulmonary Mycobacterium avium complex infection, paroxysmal atrial fibrillation not on anticoagulation, and hypertension. MRI demonstrated subacute bilateral infarcts, left more than right, in the occipital regions. Basilar leptomeningeal enhancement was likely indicative of meningitis. CT angiogram showed reduced caliber fetal posterior cerebral arteries (PCAs). Lumbar puncture revealed increased nucleated cells in the CSF of 104 with lymphocytic pleocytosis, elevated protein of 393 mg/dl, and hypoglycorrhachia of 36 mg/dl. Meningitis/encephalitis panel was positive for HSV-2. Patient's physical exam declined from being awake, alert, able to follow simple commands to being lethargic and minimally responsive. Repeat MRI demonstrated a new acute ischemic stroke in the left thalamus and posterior limb of the left internal capsule. MRA showed even further narrowing of bilateral PCAs, and now new narrowing of the bilateral middle cerebral arteries and bilateral distal anterior cerebral arteries. EEG demonstrated moderate encephalopathy with no clear epileptiform discharges. This clinical presentation, CSF findings, and vessel imaging together raised a concern for HSV-2 vasculitis in addition to meningitis. Patient was started on and completed a 3-week course of acyclovir with no significant improvement in her mental status. She also completed a 5-day course of IV solumedrol. Unfortunately, the patient continued to decline and became apneic, eventually passing away. **Conclusion:** In summary, HSV-2 has been implicated as a rare cause of ischemic strokes in adults. Consensus on the diagnostic approaches for HSV encephalitis and meningitis has made earlier diagnosis and treatment possible. On the other hand, in cases of atypical strokes retrospectively associated with HSV-2 vasculitis, there is a lack of consensus on the diagnostic approach for HSV-2 vasculitis. We demonstrated that HSV-2 vasculitis associated stroke can be diagnosed with non-invasive imaging and lumbar puncture. Having a baseline knowledge of HSV-2 vasculitis related complications and relevant diagnostic tools is critical in early diagnosis and treatment.

#### S114. Cardiac Troponin Patterns and Insula Involvement in Acute Ischemic Stroke

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**Background:** Elevated cardiac troponin (cTn), a biomarker of myocardial injury, is detected in 10-30% of acute ischemic stroke (AIS) patients and correlates with poor functional outcomes. Serial measurements of cTn differentiate a "dynamic" cTn pattern (rising/falling cTn>20%), specific for an acute evolving myocardial injury, from elevated but stable cTn levels (non-dynamic), typically secondary to chronic cardiac or non-cardiac conditions. We investigated the relationship between cTn patterns and early mortality and discharge disposition. We also assessed the relationship between AIS involving the insula, an integral area of the brain-heart autonomic axis, with cTn patterns and cardiac complications.

**Methods:** We retrospectively screened consecutive AIS patients admitted to 5 stroke centers to identify those with increased cTn at admission and at least one additional cTn measurement within 48 hours. Patients were excluded if they had in-hospital AIS, concomitant condition affecting cTn levels. Brain imaging (CT/MRI) were reviewed with specific interest to stroke side and insular involvement. Cardiac complications were: STEMI/NSTEMI, ECG changes, new-onset arrhythmia, Takotsubo syndrome, active coronary artery disease. Unadjusted and adjusted multivariable logistic regression analyses were performed to assess the association between rising cTn, insula involvement, and outcomes.

**Results:** Of 3,789 AIS patients screened, 300 with elevated troponin were included. Of these, cTn increased on subsequent measurement in 68, fell in 70, and was stable in 162. Groups differed in age ( $78 \pm 10$  rising vs  $70 \pm 14$  falling vs  $75 \pm 13$  non-dynamic;  $P < 0.01$ ), sex (female 63% vs 37% vs 52%;  $P = 0.02$ ), presence of coronary artery disease (31% vs 17% vs 35%;  $P < 0.01$ ). While groups did not differ in side of stroke, they did in right insula involvement (26% vs 16% vs 11%;  $P = 0.02$ ). In multivariate analysis, a rising cTn pattern was associated with higher risk of 7-day mortality (adjusted OR (aOR)=6.4 [95%CI:1.2-34.5] rising vs aOR=0.4 [95%CI:0.2-5.6] falling vs non-dynamic as reference OR=1) and a trend for unfavorable discharge disposition (aOR=2 [95%CI:0.9-4.1] vs aOR=0.5 [95%CI:0.2- 4.1] vs OR=1). Presence of right insula involvement correlated with a higher risk of rising cTn pattern (aOR=2.1 [CI:1.01- 4.3]) and any post-stroke cardiac complications (aOR=2.4 [CI:1.2- 4.6]). Left insula involvement was not associated with outcomes.

**Conclusions:** A rising cTn pattern was associated with an increased risk of 7-day mortality after stroke. AIS patients with injury in the right insula were more likely to develop a rising cTn pattern and post-stroke cardiac complications.

#### S115. Cerebral Blood Flow in Patients with Congestive Heart Failure

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**Introduction:** We have previously shown an association between a worse stage of heart failure and worse performance on some, but not all, measures of cognitive function. These changes may result from an abnormal cerebral blood flow velocity (CBFV) in congestive heart failure (CHF). However,



it is not well known if CBFV is associated with specific CHF characteristics. **Methods:** 230 CHF outpatients presenting for diuresis therapy at Johns Hopkins without dementia and with preceding transthoracic echocardiogram (TTE)  $\leq 1$  year were included. CHF characteristics considered were: New York Heart Association (NYHA) classification, CHF type (HFpEF/HFrEF), TTE left ventricular ejection fraction (LVEF; continuous (per 5%) or categorized ( $\leq 40\%$ , 40-55%,  $\geq 55\%$ )). 94 patients had Transcranial Doppler (TCD) sonography, which assessed the CBFV of proximal anterior cerebral arteries (ACA), proximal middle cerebral arteries (MCA), and internal carotid arteries (ICA) using standard techniques. T-test/ANOVA estimated differences in mean CBFV (average of right and left of each vessel) by CHF characteristic. Multivariable linear regression models (adjusted for age, sex, race, Charlson Comorbidity Index, and smoking) determined the association between CHF characteristics and CBFV measures, each in distinct models. **Results:** Patients were mean age  $67 \pm 13.6$  years, 34% Black, and 49% female. Mean ACA CBFV (54.5 cm/s,  $\Delta +4$ ), MCA (66.47 cm/s,  $\Delta +6.37$ ), and ICA (48.5 cm/s,  $\Delta +3.5$ ) were subjectively higher than standard average values. Mean MCA CBFV did not significantly differ between NYHA Class 1 and 2 (53.3 cm/s) and NYHA Class 3 and 4 (53.5 cm/s),  $p=0.97$ ; HFpEF (56.4 cm/s) and HFrEF (56.7 cm/s),  $p=0.96$ ; and LVEF  $\leq 40\%$  (base category, 56.0 cm/s), 40-55% (56.9 cm/s),  $\geq 55\%$  (56.7 cm/s),  $p=0.88$ . MCA CBFV had no association with NYHA Class 3 and 4 vs Class 1 and 2 ( $\beta$ : 4.78, 95%CI: -8.07,17.63); HFrEF vs HFpEF ( $\beta$ : -2.10; 95%CI: -14.15,9.96); continuous LVEF ( $\beta$ : -0.25; 95%CI: -1.96,1.46); LVEF  $\leq 40\%$  vs 40-55% ( $\beta$ : 0.36; 95%CI: -14.27,14.98); and LVEF  $\leq 40\%$  vs  $\geq 55\%$  ( $\beta$ : -2.10, 95%CI: -16.30,12.10), after adjusting for co-variables. All other CBFVs were not associated with any CHF characteristics nor did their means differ by CHF characteristic. **Conclusion:** Among CHF patients, all CBFVs measured were higher than those of reported norms. There was no difference in mean CBFV by CHF characteristic, nor were there statistically significant associations between CBFV in any vessel and CHF characteristics. Future studies with larger sample sizes are needed to determine the etiology of underlying elevated CBFV in CHF and whether this elevation contributes to the reported cognitive decline in CHF.

### S117. Characteristics and In-Hospital Outcomes of Adults with Acute Stroke Presenting with Seizures at the University Teaching Hospital in Lusaka, Zambia

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Hopkins University, Baltimore, MD, USA, <sup>4</sup>Brown University, Providence, RI, USA.

**Background and Aim:** The impact of seizures on the outcome of patients presenting with acute stroke in resource-limited settings, without dedicated stroke units, is unknown. We aimed to investigate risk factors for acute seizures and their association with in-hospital outcome among adults with acute stroke at the University Teaching Hospital (UTH) in Lusaka, Zambia. **Methods:** A prospective cohort study of adults ( $\geq 18$  years old) admitted to the neurology inpatient service at UTH with a suspected or confirmed diagnosis of stroke was conducted between November 2019 and August 2022. Participant demographics, stroke type and in-hospital outcomes were compared between those who developed seizures within 10 days of hospital admission and those without seizures using t-tests, chi-square analyses, and Wilcoxon rank-sum tests as appropriate. Multivariable logistic regression models were used to evaluate independent predictors of seizures and the impact of seizures on in-hospital outcomes. **Results:** Of 537 participants, 76 (14%) had acute seizures, with the majority (70%, 53/76) reporting seizures prior to hospital admission. Seizures were described by bystanders as generalized (70%), focal unaware (9%), focal aware (8%) and unspecified (13%). There was no difference in age, sex, traditional stroke risk factors or stroke type between participants with and without seizures. Patients with seizures were more likely to have a history of previous stroke (26% vs 13%,  $p=0.007$ ), a higher admission National Institutes of Health Stroke Scale (NIHSS) score [mean(SD) 18(9) vs 15(8),  $p=0.009$ ] and a higher admission modified Rankin score (mRS) [median(IQR) 5(4,5) vs 4(4,5),  $p=0.02$ ]. In multivariable modeling, admission NIHSS was the only predictor of seizures [aOR 1.05, 95% CI 1.01-1.08,  $p=0.005$ ]. There was no difference in discharge mRS. However, in-hospital mortality was higher in the seizure group (37% vs 23%,  $p=0.009$ ), although this did not maintain significance in the multivariable model of mortality (aOR 1.21, 95% CI 0.58-2.52,  $p=0.61$ ) after adjusting for age, stroke type and stroke severity. **Conclusion:** The incidence of acute seizures in our cohort of adults with stroke in Zambia was high and largely associated with more severe strokes (high NIHSS score). However, seizures were not associated with in-hospital mortality after controlling for age, stroke type, and stroke severity. Follow up of our cohort will inform whether acute seizures have an effect on long-term outcomes, particularly in those with recurrent strokes.

### S118. Characterization of Anxiety Disorders after Cerebrovascular Accident

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**Introduction:** Psychiatric disorders are common in a subset of individuals after stroke. Poststroke depression (PSD) occurred in approximately 31% of patients at the Houston

Methodist Neurological Institute, and individuals with a comorbid anxiety disorder were almost 6 times more likely to suffer from PSD. Research suggests history of anxiety is the strongest predictor of being diagnosed with depression within 1.5 years after stroke. Yet, as is common in extant literature, only screening tools estimated possible anxiety disorders. In this study, we used DSM criteria to identify specific anxiety disorder subtypes and evaluated what factors were associated with poststroke anxiety. **Methods:** The prospective IRB-approved database consisted of 325 stroke patients (44.9% left hemisphere stroke, 41.2% right, 13.8% bilateral). Stroke types included 65.1% ischemic and 31.9% hemorrhagic. Average evaluation occurred 8.1 months after stroke with the Mini International Neuropsychiatric Inventory to determine DSM-defined anxiety disorders and depression. A standard neuropsychological test battery was administered to all patients. Logistic regression analysis was computed to evaluate associations with poststroke anxiety. Variables included time from stroke, age, gender, stroke location and lateralization, stroke type (hemorrhagic/ischemic), sleep difficulties, fatigue, employment status, marital status, current depression, history of depressive disorder, history of anxiety disorder, memory difficulties, and executive function difficulties. **Results:** Most individuals did not experience poststroke anxiety (83.1% of sample). Fifty-five of the 325 patients (16.9%) were diagnosed with a DSM-IV or DSM-5 anxiety disorder. Of the 55 patients diagnosed with poststroke anxiety, 43.6% (N=24) were treated for an anxiety disorder prior to stroke. New onset poststroke anxiety occurred in 56.4% of poststroke anxiety patients (N=31). Types of anxiety disorders included panic attacks (N=20, 6.2%), generalized anxiety disorder (GAD, N=16, 4.9%), obsessive compulsive disorder (N=0, 0%), PTSD (N=2, 0.6%), social anxiety (N=5, 1.5%), anxiety NOS (N=2, 0.6%), panic attacks and GAD (N= 6, 1.8%), GAD and social anxiety (N=3, 0.9%), PTSD and social anxiety (N=1, 0.3%). Logistic regression indicated PSD (OR = 5.8,  $p < 0.001$ ), sleep difficulties (OR = 3.1,  $p = 0.003$ ), and female gender (OR = 2.8,  $p = 0.009$ ) were associated with poststroke anxiety. **Conclusions:** Patients with PSD were almost 6 times more likely to experience poststroke anxiety. This study extends the literature by identifying DSM-diagnosed panic attacks and GAD as the most common forms of DSM-defined anxiety disorders after stroke. Screening and treatment for both poststroke anxiety and depression may improve functional outcomes.

### S119. Defining the Age of Young Ischemic Stroke Using a Data Driven Approach

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**Introduction:** The cutoff we use to define the age of a “young” ischemic stroke (IS) is both clinically and epidemiologically important, however poorly defined in current literature. We utilized electronic health records (EHRs) and data science techniques to estimate an optimal aged cutoff to define a “young” IS. **Methods:** Data was extracted from the EHR of patients in 13 hospitals in rural Pennsylvania and was assessed in two parallel approaches. Approach 1: grouping patients based on their respective ICD9/10 code data and computing similarity scores between every patient pair. The optimal age of young IS was estimated by identifying the trend of patient similarity with respect to their clinical profile for different ages of index IS. Approach 2: case-control analysis using three sets of machine-learning models—generalized linear regression (GLM), random forest (RF), and XGBoost (XGB)—to classify patients for seventeen age groups. After extracting feature importance from the models, we determined the optimal age of young IS by analyzing the pattern of comorbidity with respect to the age of index IS. Both approaches were completed separately for male and female patients. **Results:** The stroke cohort contained 7555 IS patients, and the control group included 31,067 patients. In the first approach, the optimal age of young stroke was 53.7 and 51.0 years in female and male patients, respectively. In the second approach, we created 102 models, based on three algorithms, 17 age brackets, and two sexes. The optimal age was 53 (GLM), 52 (RF), and 54 (XGB) for female, and 52 (GLM and RF) and 53 (RF) for male patients. Different age and sex groups exhibited different comorbidity patterns. **Discussion:** Using a data-driven approach, we determined the age of young stroke to be 54 years for women and 52 years for men in our mainly rural population, in central Pennsylvania.

### S120. Determining the Impact of Occupation on the Association between Cardiac Structure and Mortality in Ischemic Stroke Patients

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**Background:** Abnormal left ventricular ejection fraction (LVEF) and left atrial diameter (LAD) are known risk factors for ischemic stroke (IS) and can also independently increase risk of mortality. However, if the association between LVEF or LAD and mortality among IS patients differs by occupation is not known. **Methods:** A prospective cohort of IS patients admitted to the Johns Hopkins Hospital (2017-2019) with transthoracic echocardiography and complete demographic data were included. The National Death Index and medical records were used to determine mortality. Occupation was classified according to International Standard Classification of Occupations and then grouped into blue-

collar (e.g., agricultural/trade workers, machine operators) or white-collar (e.g., managers, professionals, clerical workers). Multivariable logistic regression models were used to determine the association between mortality (dependent variable) and LVEF (per %, or <60% vs. ≥60%) or LAD (per 1mm, or <40mm vs. ≥40mm) with adjustment for sex, age, race, and current-smoking. **Results:** Participants (N=144) were mean age 61 years (SD=14), 58% male, and 60% black. Compared to white-collar workers (N=93), blue-collar workers (N=51) were male (75% vs. 48%,  $p=0.002$ ) and younger (57 years vs. 63 years,  $p=0.018$ ). Over an average of 4.4 years of follow-up, 25 participants (17.4%) died. There was a suggestion of higher odds of mortality (OR=1.09, 95%CI=1.01-1.18) per 1% increase in LVEF among white-collar workers but not among blue-collar workers (OR=1.001, 95%CI=0.90-1.11), however there was no difference in the association between LVEF and mortality by occupation ( $p$ -interaction=0.230). There was also no significant difference in the association between LAD and mortality by occupation ( $p$ -interaction=0.121) with a suggestion of a decrease in mortality per 1mm increase in LAD among white-collar workers (OR=0.89, 95%CI=0.81-0.98) but not among blue-collar workers (OR=0.94, 95%CI=0.78-1.14). Understanding limitations of small subgroups, we considered clinically meaningful cut-points in an exploratory analysis. There was no difference in the association between LVEF (<60 vs. ≥60) and mortality by occupation ( $p$ -interaction=0.224; white-collar: OR=3.25, 95%CI=0.82-13.00; blue-collar: OR=0.89, 95%CI=0.10-8.28). There was also no difference in the association between LAD (<40mm vs. ≥40mm) and mortality by occupation ( $p$ -interaction=0.511; white-collar: OR=0.52, 95%CI=0.13-2.02; blue-collar: OR=0.49, 95%CI=0.04-6.20). **Conclusion:** Among IS participants, we found no difference in the association between two markers of cardiac structure and mortality by occupational group, although our analysis was limited by small numbers. Future research that considers heart-brain outcomes should be informed by social factors, as occupation might influence vascular risk.

#### **S121. Developing STaR Medical Trainees: Knowledge Gains from Three Years of the Stroke, Thrombectomy, and Revascularization (STaR) Nexus Course**

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**Background/Objectives:** Despite the high prevalence and burden of stroke worldwide, exposure and education on stroke is limited and variable for medical trainees. We developed an online elective course, called Stroke, Thrombectomy, and Revascularization (STaR) to provide open-access education on the basics of stroke to anyone interested. The aim of this study was to evaluate the knowledge gains of participants across the first three years of the course. **Methods:** The STaR course consisted of weekly 90-minute Zoom sessions covering the fundamentals of stroke, from definition and classification

to presenting signs and syndromes, performance of the National Institutes of Health Stroke Scale, diagnosis, workup, and acute management. The course included eight sessions in the first year and was condensed to five sessions in the latter two years, with the core content remaining consistent. Participants completed identical 10-question pre- and post-tests at the beginning and end of each course, with questions reflecting course content and adapted from Continuum Cerebrovascular Disease. Each question was worth one point, and surveys were scored out of ten points. We analyzed the knowledge questionnaires for each year individually, as well as aggregated from March 2021 to February 2023. We assessed statistically significant knowledge gains using t-tests.

**Results:** From 2021-2023, a total of 54 and 22 learners of all different training levels (e.g., undergraduate to resident physician) filled out the pre- and post-test, respectively. Aggregated student knowledge scores significantly increased from pre-test 5.7 (n=54) to post-test 7.0 (n=22),  $p=0.00098$ . Each year student scores increased from pre-test to post-test; in 2021: 5.3 (n=19) to 7.3 (n=8),  $p=0.011$ ; 2022: 5.9 (n=11) to 6.8 (n=5),  $p=0.39$ ; 2023: 5.9 (n=24) to 7.0 (n=9),  $p=0.050$ , respectively. **Conclusions/Next Steps:** The STaR course is a novel, accessible, and effective platform for medical trainees to gain exposure to and learn the basics of stroke. Our data reveals that students increased their knowledge on high yield concepts related to cerebrovascular disease. In the future, we hope to increase enrollment worldwide to broaden exposure and education on stroke, with the ultimate goal of equipping those in healthcare to recognize signs of acute stroke and direct to appropriate treatment in their local setting.

#### **S122. Diagnosis in the Eye of the Beholder: Isolated Vein of Labbe Thrombosis, a Rare Disease with Textbook Presentation and Non-Contrast CT Scan Findings**

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**Background:** The Vein of Labbe (VOL), or inferior anastomotic vein, drains the temporal lobe and empties into the transverse sinus. Isolated vein of Labbe thrombosis (IVLT) is a rare condition that can result in temporal lobe hemorrhagic infarction. Common symptoms of IVLT include seizures and headaches, which can make diagnosis challenging due to the heterogeneity of presentation and rarity of the condition. In this report, we present a case of IVLT with two classical CT scan findings, the "Long Cord and Cashew Nut signs," that can aid in diagnosing IVLT. Early diagnosis of IVLT is crucial as treatment typically involves anticoagulation therapy which leads to a better prognosis. **Case Report:** A 48-year-old right-handed man presented with a sudden onset of left-sided headache, amnesia, and aphasia. The patient's vital signs were within normal limits except for an elevated blood pressure of 156/95mmHg. CT Head revealed a concave shaped intracerebral hemorrhage at juxtacortical region in the

left temporal lobe, as well as a linear hyperdensity at the temporal lobe's lateral boundary. It was discovered that the patient had recently begun a strenuous exercise program without adequate hydration, which was evidenced by polycythemia on initial labs. Further investigation did not find any evidence of infection, heart diseases, illicit drugs, sickle cell, hypercoagulable state, or malignancy. Digital Subtraction Angiography (DSA) confirmed left sided IVLT and MRI a day later showed left temporal lobe hemorrhagic venous infarct. The patient was started on a heparin drip and later switched to oral anticoagulation. He had significant improvement in his speech and his headache had resolved at the time of discharge. **Discussion:** Isolated vein of Labbe thrombosis (IVLT) is a rare clinical syndrome that can be caused by various thrombophilic states, including dehydration, which can be subclinical and easily overlooked. In our case, the long cord sign (a linear hyperdensity on the lateral margin of the temporal lobe) and Cashew Nut sign (juxtacortical hemorrhage) on the initial CT scan suggested IVLT. Intracranial bleeding in a young patient can have a broad differential, including vascular malformations such as arteriovenous malformation (AVM) and dural AV fistula. Anticoagulation in these cases is detrimental. Having a high index of suspicion for IVLT and characteristic CT scan signs can aid in early diagnosis and treatment with anticoagulation, which leads to better outcome.

### S123. Discontinuation and Non-Publication of Stroke Clinical Studies: A Cross-Sectional Analysis

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**Background:** Stroke is the second leading cause of both disability and death worldwide, with the highest burden of the disease shared by low- and middle-income countries. In 2022, there are over 101 million people currently living who have experienced stroke globally. Clinical studies in stroke are vulnerable to discontinuation and non-publication, representing significant sources of research waste in clinical medicine. This study aims to assess stroke clinical studies characteristics and summarize logistic, financial, and practical reasons behind early discontinuation and non-publications to prevent this in the future. **Methods:** ClinicalTrials.gov was searched for all studies registered between 1 January 2000 and 1 May 2022 and included patients with stroke. Publications from these studies were identified by extensive online

searching using the NCT identifier number and other related keywords. Multiple logistic regression analysis was performed to identify characteristics associated with trial discontinuation and non-publication. **Results:** A total of 3720 eligible registered studies were included; 2724 (73.3%) were clinical trials, and 994 (26.7%) were observational studies. Of these, 380 (10.2%) were discontinued. Of the completed studies, there were a total of 1786 (53.5%) non-published studies. The unadjusted logistic regression analysis revealed that the industrial (OR = 1.37, 95% CI [1.05-1.79]) and mixed funding (OR = 1.42, 95% CI [1.04-1.92]) were significant predictors of study discontinuation compared to non-industrial funding. Furthermore, the small sample size (less than 100) (OR = 2.79, 95% CI [2.13-3.66]) was also significant. Concerning the non-publication, a small sample size (less than 100) (OR = 1.68, 95% CI [1.46-1.93]) was also a significant predictor, while mixed funding (OR = 0.56, 95% CI [0.45-0.70]) compared to non-industrial funding has significantly decreased the likelihood of non-publication. Behavioral interventions were significantly less likely to be discontinued than drug interventions (OR = 0.40, 95% CI [0.27-0.60]). The Diagnostic interventions were significantly the most likely to be non-published compared to drug interventions (OR = 3.39, 95% CI [1.85-6.21]). **Conclusion:** There is evidence of non-dissemination bias in clinical studies of stroke. These biases distort the therapeutic information available to inform clinical practice and raise ethical concerns regarding exposing volunteering participants to potential risks without furthering practice.

### S124. Dynamic and Static Functional Network Connectivity Differentiates Cognitive Impairment in Individuals with CADASIL

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**Background:** Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a heritable cerebrovascular disease which affects arterial walls and can manifest in white matter lesions detectable with magnetic resonance imaging (MRI). Arterial deterioration in white matter tracts may inhibit communication between functional networks in the brain. In this work, we present a Functional Network Connectivity analysis of individuals with CADASIL and without, providing a first glimpse into arterial degradation inhibiting communication between networks. **Methods:** In this analysis, samples were

comprised of resting state functional MRI from 44 participants (20=male, 24=female) with modified Rankin Scale (mRS  $\leq 3$ ) at 8 data-collection sites. Individuals with Montreal Cognitive Assessment (MoCA) scores of 25 or lower were grouped into a Cognitively Impaired (CI) group, and the remainder were grouped into a normal cognition (NL) group. Resting fMRI “Eyes Open” data were gathered with a 3T Siemens Prisma Fit (Flip Angle = 50, TE = 0.032, TR = 0.607, Slice Thickness = 2.5mm, Multiband Acceleration Factor = 8) or a 3T Signa Premier (Flip Angle = 50, TE = 0.031, TR = 0.614, Slice Thickness = 2.5mm, Multiband Acceleration Factor = 8). Following preprocessing, Spatially Constrained Independent component analysis (Du et al, 2020) was run using the GIFT toolbox (Rachakonda et al. 2007). We then performed K-Means clustering to compute the dynamic functional network connectivity states (dFNC) computed with sliding-window pearson correlation, and then determined significant differences in connectivity between groups. **Results:** In both static and dynamic connectivity, we observe moderate to significant differences in connectivity between the CI and NL groups. We observe that static connectivity analysis shows moderate to significant differences (Wilcox effect size  $>0.7$ ) between 8 distinct intrinsic connectivity networks (ICNs) within 5 functional domains, with the Visual Domain most frequently represented. We observe that in dynamic states, 3/4 computed states show moderate to significant differences (Wilcox effect size  $>0.7$ ), with ICNs in the cognitive control domain most frequently differentiating the two groups. **Conclusion:** In this work, we demonstrated that dynamic and static functional network connectivity reveal differences between cognitively and non-cognitively impaired individuals with a *NOTCH3* gene mutation for CADASIL. Our analysis reveals static effects most frequently in the visual domain, and dynamic effects most frequently in the cognitive control domain. We also discover static and dynamic effects in other functional networks such as the default mode network. NIH Funding Acknowledgment: CADASIL Consortium (1RF1AG074608-01)

#### **S125. Greater Albumin Concentration in Serum May Be Protective against Stroke: The Northern Manhattan Study**

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**Introduction:** Higher albumin concentrations can be associated with lower risk of stroke. However, the role of diet in this association remains unclear. We investigated the association of serum albumin concentration with incident cerebrovascular and cardiovascular diseases considering dietary factors. **Methods:** Participants from the Northern Manhattan Study (NOMAS;  $n=2407$ ; mean age:  $68.65 \pm 10.21$  years) free of stroke and myocardial

infarction at baseline were followed for incident cerebrovascular and cardiovascular events for a median of 14.8 years (range from 0 to 28 years). Cox proportional hazard models were used to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of baseline serum albumin concentration for the risk of ischemic stroke, intracerebral hemorrhage, myocardial infarction and vascular death adjusting for traditional vascular risk factors, and diet, including daily calorie intake and gram intake of legumes, vegetables, fruits, cereals, fish, meat and dairy. **Results:** The mean baseline serum albumin concentration was  $4.22 \pm 0.32$  g/dL. There were 347 (14%) incident strokes, 738 (31%) vascular deaths and 999 (42%) cases of ischemic stroke, intracerebral hemorrhage, myocardial infarction or vascular death. Higher albumin concentration was associated with lower risk of stroke (HR = 0.59; 95%CI 0.41 - 0.85;  $p = 0.0046$ ), vascular death (HR = 0.62; 95% CI 0.48 - 0.81;  $p = 0.0004$ ) and ischemic stroke, intracerebral hemorrhage, myocardial infarction or vascular death (HR = 0.66; 95%CI 0.00- 0.82;  $p = 0.0002$ ) independent of traditional vascular risk factors and diet. **Conclusions:** Higher serum albumin concentration is protective from incident stroke, vascular death and composite outcome of stroke, ischemic stroke, intracerebral hemorrhage, myocardial infarction or vascular death.

#### **S126. Healthy Eating Index (HEI) and Mortality among Stroke Patients in the US: A Nationwide Study from the National Health and Nutrition Examination Survey (2003-2018)**

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Unhealthy eating habits is a leading cause of death in the US. Stroke is frequent and associated with a very high mortality. Yet there is a dearth of data on the association between unhealthy eating habits and mortality. We used the National Health and Nutrition Examination Survey (2003-2018) with mortality follow up until December 31, 2019 using national linkage records and death certificates. Our study population was adults (18+ years) with stroke, diagnosed by self-report. Healthy eating habits were evaluated using the Healthy eating index (HEI-2015). We stratified the HEI-scores into 3 categories ( $\geq 80$ : “good” diet; 51-79: “fair” diet;  $\leq 50$ : “poor” diet). Cardiovascular and stroke causes of mortality were identified using the International Classification of Diseases, 10th Revision codes. All estimates of means and proportions were adjusted for the survey weights. We performed a Cox proportional regression analysis to calculate the Hazard Ratios of all cause, cardiovascular, and stroke mortality adjusting for race/ethnicity, sex, socio-economic variables, and total energy intakes. We identified 1489 individuals with stroke. The mean age of individuals with a poor, fair, and good diet was 60 years, 68 years, and 74 years respectively. A total of 620 (41.0%) all-cause mortality were recorded, including 181 deaths (29.0% of total deaths) from

cardiovascular diseases, and 53 deaths (8.6% of total deaths) from stroke. Compared with those with a poor diet, individuals with stroke with a fair diet did not have statistically different mortality rates (all-cause mortality: HR, 95%CI 0.92, 0.73-1.17), cardiovascular mortality (0.94, 0.61-1.45), and stroke mortality (1.20, 0.61-2.39). Compared with those with a poor diet, those with a good diet did not have statistically significant differences in mortality rates [all-cause mortality (0.58, 0.270-1.24), cardiovascular mortality (0.56, 0.10-3.07), and stroke mortality (0.43, 0.04-4.30)]. In this US nationally representative sample of stroke participants, a good or fair health index was not associated with a lower all-cause, cardiovascular, or stroke mortality. However, our findings indicate possible effects of fair or good diets on mortality among individuals with stroke. Further investigation is warranted.

### S127. Improving Early Recanalization and Treatment Times with Transition to Tenecteplase at a Single Comprehensive Stroke Center

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**Background:** Numerous clinical trials have demonstrated efficacy and comparable safety outcomes with tenecteplase (TNK) rather than standard alteplase (ALT) intravenous thrombolytic therapy (IVT) for treatment of acute ischemic stroke (AIS). Improved large vessel occlusion (LVO) recanalization rate after IVT alone has also been reported. Here, we evaluate the initial patient outcomes after implementation of a tenecteplase-based thrombolytic protocol at a Comprehensive Stroke Center. **Methods:** This is a retrospective, interrupted time series cohort study of 130 consecutive patients receiving IVT for AIS over 15 months. At the midpoint, our thrombolytic protocol for patients presenting within 0-4.5 hours changed from IV-ALT to IV-TNK at 0.25 mg/kg. Patients receiving thrombolysis outside of standard criteria or with a final diagnosis of stroke mimic were excluded. Primary outcomes were recanalization rate of the subgroup presenting with LVO after IVT alone (prior to thrombectomy), treatment time (door-to-needle, DTN) and incidence of symptomatic intracranial hemorrhage (sICH) based on SITS-MOST criteria. Secondary outcomes were any neuroimaging ICH, all-cause mortality, and change in NIHSS and mRS at hospital discharge. Fisher Exact, Wilcoxon Rank Sum, and Student's T tests were used for statistical comparisons. **Results:** There were 65 patients in each treatment arm; 25 and 21 patients (38%/34%) in the TNK/ALT groups, respectively, presented with LVO ( $p=0.72$ ). Similarly, no significant differences were seen between treatment arms with respect to median initial NIHSS (8 TNK/7 ALT), baseline mRS (0/0), age (73/78), sex (49% female). LVO recanalization after IVT alone was

seen in 3 TNK/1 ALT treated patients ( $p=0.61$ ), with thrombectomy performed in all remaining patients. Mean DTN time was significantly lower in the TNK group than the ALT group (39.2 vs 46.8 minutes,  $p=0.039$ ). No significant differences were seen in the primary safety outcome of sICH (2 TNK vs. 3 ALT,  $p=0.65$ ), nor secondary outcomes of any neuroimaging ICH (18/17,  $p=0.84$ ), death/hospice-discharge (12/10,  $p=0.82$ ), change from baseline mRS (3/2,  $p=0.07$ ), or NIHSS (-2/-3,  $p=0.84$ ) at discharge. **Conclusions:** The transition to thrombolysis with tenecteplase for AIS at our site has improved time to treatment with similar initial safety and clinical outcomes when compared to alteplase. Although we observed more LVO recanalization with tenecteplase, it did not reach statistical significance due to our small sample size. Further study is required to establish longer term outcomes and elucidate potential benefits for specific stroke subtypes.

### S128. In-Stent Restenosis and Concomitant Infarction of Stented Area Following Carotid versus Vertebrobasilar Artery Stenting

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**Background:** Atherosclerotic narrowing of carotid and vertebral arteries is one of the major causes of ischemic stroke. The prognosis of an ischemic stroke depends upon the timely restoration of cerebral perfusion. Vertebrobasilar artery (VBA) stenosis is associated with a higher risk and mortality in acute ischemic stroke patients than carotid artery stenosis. This study evaluated the incidence and risk factors of restenosis and stented-area infarction after VBA stenting (VBS) and compared them with those of carotid artery stenting (CAS). **Methods:** 580 patients who underwent either VBS or CAS were enrolled in this study. Demographic and clinical factors were documented, along with procedure-related factors and complications. Patients were followed-up for two years to evaluate in-stent restenosis (reduction in the lumen diameter of > 50% compared to post-stenting diameter) and stented area infarction in both groups. We also compared the factors in both groups associated with in-stent restenosis and concomitant infarction. **Results:** Among 580 patients, 128 (22%) underwent VBS, and 452 (78%) underwent CAS. There was a statistically significant difference in in-stent stenosis between VBS and CAS (15.4% vs. 7%,  $p=0.0032$ ). Likewise, stented area infarction was also statistically significant in VBS compared to CAS (27.3% vs. 11.7%,  $p<0.001$ ). Poorly controlled diabetes, multiple stents, increased length

of stents, discontinuation of aspirin/clopidogrel in VBS and smoking, and young age in CAS increased the risk of in-stent restenosis. In VBS, higher HbA1c levels (5.42 [2.4-14.2]) and multiple stents (35.2 [5.61-291.3]) were associated with stented-area infarction. **Conclusions:** In-stent restenosis and stented-territory infarction occurred more frequently in VBS than in CAS. The periprocedural risk was similar; however, VBS patients showed a higher risk of stented area infarction at long-term follow-up. Proper monitoring and management of risk factors can minimize the morbidity and mortality associated with VBS.

### S129. Increased Interstitial Free Water and Disruption of the Blood-Brain Barrier are Independently Associated with Poor Cognitive Performance in Patients with Chronic Cerebrovascular Disease

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**Background:** Patients with chronic cerebrovascular disease are at risk of developing vascular cognitive impairment and dementia (VCID). While progression of white matter hyperintensities (WMH) is associated with VCID, increased interstitial free water (FW) and disruption of the blood-brain barrier (BBB) can be detected even in normal appearing white matter (NAWM) prior to WMH progression. We hypothesized that FW and BBB permeability in NAWM would be associated with cognitive performance. **Methods:** This cross-sectional analysis included a population of patients from an ongoing cohort study who have a history of stroke and evidence of WMH on prior imaging. Subjects underwent MRI scanning > 3 months after their clinical stroke event including diffusion tensor imaging (DTI), dynamic susceptibility contrast (DSC) imaging, FLAIR and T1. T1 and FLAIR were used to segment the white matter (WM) and WMH, DTI was used to calculate FW, and DSC was used to calculate BBB disruption. In aligned images, mean values were calculated in four regions: all WM, WMH, NAWM, and the region of NAWM adjacent to the WMH referred to as the WMH penumbra. Cognition was tested with the Montreal Cognitive Assessment (MoCA) at the time of the MRI. We tested univariate associations between MoCA score and each imaging marker in each region, followed by multiple linear regression. **Results:** For 58 included participants, mean age ( $\pm$ SD) was  $69 \pm 9$  years, 36% were female, median WMH volume ( $\pm$ IQR) was  $14 \pm 13$  mL, and mean MoCA score was  $26 \pm 3$ . In univariate analyses, elevated FW was associated with lower MoCA score when measured in all WM ( $R^2=0.18$ ), NAWM ( $R^2=0.16$ ), penumbra ( $R^2=0.12$ ) or WMH ( $R^2=0.10$ ). More severe BBB disruption was associated with lower MoCA score when measured in all WM ( $R^2=0.09$ ), NAWM ( $R^2=0.09$ ), and the penumbra ( $R^2=0.10$ ), but not in WMH ( $R^2=0.03$ ). The strongest association was in the penumbra, where penumbral FW (standardized beta -0.32 [-0.59 to 0.04]  $p=0.023$ ) and BBB (-0.29 [-0.57 to -0.014]  $p=0.040$ ) were each independently associated with MoCA score while covarying for age, sex, race, education and WMH volume

(model adjusted- $R^2$  0.23). **Conclusions:** In patients with chronic cerebrovascular disease and prior stroke, changes in interstitial free water and BBB permeability were independently associated with cognitive performance in this cross-sectional analysis. These biomarkers may help us to understand the pathogenesis and progression of VCID.

### S130. Inpatient Stroke Quality Improvement and Patient Safety Education: A Needs Assessment

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**Background:** Implementing quality improvement and patient safety (QIPS) education is challenging yet crucial to prepare graduate medical trainees for independence. While morbidity and mortality conferences (MMCs) investigate medical errors, their benefit for stroke care and education in the academic setting is unknown. We performed a needs assessment for a neurology resident and stroke/neuro-hospitalist fellow QIPS curriculum for inpatient stroke. **Methods:** We reviewed content of all patient cases presented at our stroke MMCs (7/2021-7/2022) and report the area of weakness regarding to patient care and patient safety. We also evaluate that how many of MM cases presented in multidisciplinary meeting of the root cause analysis (RCA) and or had variance reporting. We also distributed an anonymous survey to neurology residents, stroke/neuro-hospitalist fellows, neurology faculty, and partnering hospital QIPS leadership (HQL) to assess perspectives on QIPS education. **Results:** Of 44 cases presented at MMC, 33 involved near miss or adverse event, and 11 were presented purely for clinical educational purpose. Mean patient age was 66 (SD 15); 36% were female. Ischemic stroke comprised 77% of cases; hemorrhagic 22%. Among the 33 cases, 67% included communication error, 30% notification delay, 24% procedural complication, and 21% procedural delay. Eleven cases had associated variance reporting (VR), only once related to an MMC. No cases involved root cause analysis (RCA). Of 16 trainees (34% response rate), 75% were a little or not at all familiar with RCA and 75% had never performed RCA. Forty-two percent were moderately familiar with VR and 33% had utilized VR. A quarter had worked on a QIPS project. Of 13 faculty and HQL (13% response rate), 46% perceived trainees as a little or not at all familiar with RCA, and 23% perceived them as at least moderately familiar with VR. **Conclusion:** This study suggests that new method of MMC, further teaching on initiating and participating of RCA as well as reporting and following up on variances are needed. Residents, fellows, faculty, and HQL perceived trainees as unfamiliar with RCA and VR. QIPS education and hospital efforts were misaligned. Our findings guide a stroke QIPS curriculum integrating graduate medical education and hospital administration.

### S131. Iron Accumulates in Multiple Cell Types in the Brain Following Perinatal Hypoxic Ischemic Brain Injury

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**Background:** Intracellular iron accumulation can have toxic effects on cells by causing lipid peroxidation and ferroptosis. Iron deposition has previously been identified in areas of perinatal focal ischemic brain injury in pre-clinical models, but it is unclear which cell types are affected. We hypothesized that following perinatal ischemic brain injury, intracellular iron storage will be disrupted in neurons and glial cells, which could ultimately result in increased lipid peroxidation and ongoing oxidative stress that disrupts normal development of surviving cells. **Methods:** Postnatal day 9 pups underwent unilateral hypoxic-ischemic brain injury (HIBI) using modified Vannucci model with right common carotid ligation followed by 40 minutes of hypoxia in 8% oxygen (control animals underwent sham surgery and no hypoxia) and then euthanized 72 hours (72h) after hypoxia. Hippocampi were dissected out for total iron content measurement using a colorimetric iron assay kit. For cell specific analysis, two hippocampi were pooled (right and left hippocampi from sham animals, right hippocampus from two HIBI mice pooled) followed by magnetic or fluorescent cell sorting to isolate neurons (negative selection using magnetic sorting), microglia (CD11b+ FACS sorted cells) and oligodendrocytes (O4/PDGFRa+ FACS sorted cells). Iron status of unsorted and sorted cells was assessed by QPCR to evaluate expression of genes that regulate iron import (transferrin receptor), storage (L-ferritin) and export (Ferroportin). **Results:** Total iron content (ng iron per mg protein) in the hippocampus was not significantly different 72 hours post-HIBI (sham:  $0.066 \pm 0.015$ , HIBI:  $0.088 \pm 0.023$ ,  $p=0.47$ ). Immunofluorescent labeling for L-ferritin, a surrogate marker for intracellular iron content, showed elevated L-ferritin immunoreactivity in Iba1+ cells at 72 hours. Dissociated unsorted cells from hippocampi showed 2.5 fold increase in *FtL1* (L-Ferritin) gene expression ( $p=0.0093$ ), a 60% reduction in *Tfrc* (transferrin receptor) gene expression ( $p=0.0006$ ) and a 40% reduction in *Slc40a1* (Ferroportin) gene expression when assessed by QPCR. Cell fractions enriched for neurons, oligodendrocytes and microglia all showed similar changes. **Conclusions:** Following early postnatal hypoxic-ischemic injury, immunofluorescence showed upregulation of L-ferritin in Iba1+ microglia/macrophages, but gene expression data indicates that iron accumulation occurs in neurons and oligodendrocytes in addition to microglia/macrophages. These data suggest that this model could be useful in determining how iron accumulation causes lipid peroxidation and ferroptosis and which cell types are most vulnerable these pathologic processes in perinatal hypoxic ischemic brain injury.

### S132. Is Catheter Ablation Associated with Favorable Cognitive Function over Time? An Analysis from the SAGE-AF Observational Cohort Study

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**Objectives:** To examine associations between treatment with catheter ablation (CA) vs. medical management and cognitive impairment among older patients with atrial fibrillation (AF). **Methods:** Ambulatory patients who had AF, were  $\geq 65$ -years-old, and were eligible to receive oral anticoagulation could be enrolled into the SAGE (Systematic Assessment of Geriatric Elements)-AF study from internal medicine and cardiology clinics in Massachusetts and Georgia between 2016 and 2018. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA) tool at baseline, one-, and two years. Cognitive impairment was defined as a MoCA score  $\leq 23$ . Multivariate-adjusted logistic regression of longitudinal repeated measures was used to examine associations between treatment with CA vs. medical management and cognitive impairment among participants. **Results:** A prospective cohort of 887 participants were included in this analysis. On average, participants were  $75.2 \pm 6.7$  years old, 48.6% women and 87.4% white non-Hispanic. 193 (21.8%) participants who received a CA prior to enrollment, more frequently had an implantable cardiac device (ICD) ( $45.6\%$  vs  $27.5\%$ ,  $p < 0.001$ ) and persistent AF ( $31.1\%$  vs  $22.5\%$ ,  $p < 0.05$ ). Participants who had previously undergone CA were significantly less likely to be cognitively impaired during the two-year study period ( $aOR$  0.70, 95% CI 0.50-0.97) than those medically managed (i.e., rate and/or rhythm control), even after adjusting with propensity score for CA. We did not observe any significant difference in either the CA or the no CA groups between the use of warfarin vs other oral anticoagulants (OACs) on cognitive function. Both groups were treated at high rates, with the CA group receiving OAC at 89.6% throughout the study period and the no-CA group at 84.3% over the follow-up period. **Conclusions:** Patients with atrial fibrillation who underwent catheter ablation are less cognitively impaired than those medically treated over a two-year period. Cognitive function was similar at a two-year follow-up in those anticoagulated with warfarin compared to all other anticoagulants. Future research should include a direct comparison of varying CA procedures (e.g., radiofrequency, cryothermal) and objective measurements of cerebral hemodynamics (e.g. near-infrared spectroscopy, diffuse correlation spectroscopy, etc.) in those who undergo CA for AF compared to medical management alone.

### S133. IV Thrombolysis for Central Retinal Artery Occlusion - Experiences from a Comprehensive Stroke Center

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**Introduction:** Acute central retinal artery occlusion (CRAO) is a form of stroke that may be amenable to treatment with intravenous thrombolysis (IVT). We sought to study time to presentation, rates of eligibility and safety of IVT in patients with acute CRAO presenting to a comprehensive stroke



center (CSC). **Methods:** We performed an observational cohort study on consecutive patients with acute CRAO admitted to a CSC over 4 years, using data from an institutional, IRB-approved registry. Patients were offered IVT if they presented with acute vision loss with visual acuity of 20/200 or worse in the affected eye, had no other ophthalmologic or neurologic diagnosis better accounting for the vision loss (incorporating a dilated ophthalmologic exam), and met standardized institutional inclusion criteria akin to acute ischemic stroke. We collected socio-demographic data, time from onset to presentation, candidacy for iv thrombolysis and safety outcomes. **Results:** Of 36 patients with acute CRAO presenting within the study period, mean age was 70 (standard deviation (SD) 10.0) years, 52% (n=19) were female. Median time with interquartile range (IQR) to ED presentation was 10.9 (4 - 18.7) hours. 9 patients of those studied (25%) presented within the 4.5-hour time window. Of those eligible by treatment window and other inclusion criteria, 7 (77%) received IVT, 1 patient declined treatment and one patient was not offered IVT. There were no reported events of intracranial or extracranial hemorrhage. **Conclusion:** Our study confirmed that IVT for acute CRAO was safe. We found a high rate of treatment with IVT of those eligible. However, given that 75% of patients presented outside the treatment window, continued educational efforts are needed to improve rapid triage to emergency departments to expedite evaluation for possible treatment candidacy with IVT.

#### S134. Lemierre Syndrome Variant Following a Mild Head Injury and COVID-19 Infection

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Lemierre Syndrome classically refers to the concomitant findings of pharyngeal infection, internal jugular vein thrombosis and septic thromboemboli. It is most commonly preceded by oropharyngeal infections associated with *Fusobacterium necrophorum*, however variants with different sources and organisms have been described. We present a unique case of a Lemierre Syndrome variant consisting of septic cavernous sinus thrombosis, carotid artery occlusion, and clival osteomyelitis. A 15 year old patient presented with an isolated cranial nerve VI palsy and workup revealed the aforementioned. Treatment consisted of antibiotics, surgical sinus drainage, and anticoagulation with eventual deficit resolution. The identified source was a polymicrobial bacterial sphenoid sinusitis. Preceding events of unclear significance were a mild head injury and a COVID-19 infection. Although similar cases have been described in the literature, no documented cases of this specific constellation of findings have been reported to our knowledge. The classical features of Lemierre syndrome seen in our patient were septic thrombophlebitis involving *Fusobacterium necrophorum* following a head and neck infection. The additional unique and variant features were the paranasal sinus source, multiple organisms,

cavernous sinus involvement, carotid artery involvement, skull base osteomyelitis, preceding head trauma and antecedent Covid-19 infection. The cause of this unique constellation remains unclear; however, the preceding head trauma and Covid-19 infection appear to be plausible contributors. A theory of occult skull fractures and/or dural tears has been proposed. It is unclear if our patient's underlying sinusitis was the result of injury or the underlying pathology that predisposed to invasive disease. The Covid-19 infection could have resulted in secondary sinusitis and predisposed to migrating infection even in the absence of fracture or trauma. There is no doubt that the proximity of involved structures contributed to the ease of spreading infection in these areas. It is our hope that by sharing such a unique patient presentation, we may emphasize the importance of a thorough exam and understanding of head and neck anatomy which will aid in a timely diagnosis of this life threatening condition and its variants. A comprehensive workup is of the utmost importance, as it reveals the extent to which neighboring structures are affected and will serve to guide what treatments are indicated.

#### S135. MELAS Syndrome: Thrombolytics Treatment and Literature Review

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**Introduction:** Mitochondrial encephalomyopathy, lactic acidosis and stroke-like episodes (MELAS) is a maternally inherited disease caused by mutations in the mitochondrial DNA. The mutations resulting in MELAS cause defects in the respiratory chain enzymes. Adenine is substituted for guanine (A3243G) in 80% of the cases. This condition is relentlessly progressive resulting in seizures, cognitive impairment, weakness, hemianopia or cortical blindness. Treatment for MELAS have focused on reducing oxidative stress but limited resources were published on the treatment of stroke like symptoms in acute settings. **Case Presentation:** A 25-year-old male with a known diagnosis of MELAS was found down with right facial droop, and inability to speak. His exam demonstrated severe mixed aphasia, right facial paralysis, and right hemiparesis. Non-contrast CT head showed no acute intracranial abnormalities. CT Angiography with perfusion study showed partial occlusive thrombus in distal left middle cerebral artery (M2 segment) with large penumbra. The patient was treated with intravenous Tenecteplase, which resulted in complete resolution of his deficits. His brain MRI revealed bilateral, embolic-like, supra-tentorial infarcts while his echocardiogram revealed severe cardiomyopathy with a left ventricular thrombus. **Discussion:** MELAS is a disabling, progressive multisystem mitochondrial disease that frequently presents with non-ischemic stroke-like symptoms. However, an ischemic stroke should always be ruled out first. Also, cardiac dysfunction occurs in approximately a third of patients with MELAS syndrome predisposing them to have ventricular thrombus and subsequent strokes. Knowledge of this condition should lead to appropriate radiological and cardiac investigations in order to avoid missing ischemic strokes and

lifesaving acute treatment. **Conclusion:** MELAS associated acute neurological symptoms are frequently treated with conservative therapy including intravenous hydration and antioxidants supplements. Up to our knowledge, this is the first case to report the importance and safety of administering Tenecteplase in MELAS acute stroke-like deficits.

### S136. Multiple Sclerosis ‘Surge’ or a Variant of ‘Sturge’?: An Unusual Case of Sturge Weber Syndrome

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**Background:** White matter hyperintensities(WMHs ) are a hallmark feature of multiple sclerosis(MS), but the corollary does not always hold true. High rates of misdiagnosis of non-specific WMHs as MS has been reported. We discuss an interesting case of secondary white matter changes in an unusual case of Sturge Weber Syndrome (SWS) type III. **Case:** 66-year-old female with history of hypertension and hyperlipidemia, was initially diagnosed with MS at the age 44 years based on clinical presentation of acute right hemiparesis, and MRI findings of scattered T2 hyperintensities in bilateral subcortical white matter, left periventricular and left hemi-pons. No spinal cord lesions were noted. CSF was negative for Oligoclonal bands. No history of optic neuritis or bladder and bowel symptoms. She was treated with Copaxone for over 15 years. No history of relapses requiring IV steroid treatment and clinical course has been stable. Imaging also incidentally found asymmetrical left greater than right cerebral volume loss, extensive cortical and subcortical calcifications, and a stable large venous anomaly in the left cerebral hemisphere. CT angiogram showed no abnormalities. New diagnosis of intracranial variant of SWS type III was made based on imaging findings that better explains her clinical course. Copaxone was then discontinued and patient has remained stable for 8 months now. **Conclusions:** Adult diagnosis of Sturge Weber syndrome is rarely reported and often poses diagnostic challenges. SWS type III is an intracranial variant characterized by leptomeningeal enhancement only in the absence of port wine nevus and glaucoma. Amongst the intracranial imaging findings, a few cases have been reported without leptomeningeal enhancement. This can be explained secondary to chronic degeneration of vessels in the setting of widespread cortical atrophy and calcification. This case emphasizes the importance of identifying white matter changes that can occur secondary to other longstanding intracranial processes, often misdiagnosed as MS.

### S137. Neurovascular Imaging Markers of Cognitive Impairment in CADASIL

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**Background:** Vascular cognitive impairment and decline (VCID) is the second leading cause of dementia after Alzheimer’s and the most common contributing factor in mixed dementia. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is the most heritable form of vascular dementia and considered an excellent model for small vessel disease. Here we report imaging outcomes of a newly established CADASIL Consortium (1RF1AG074608-01). **Methods:** Forty-five ambulatory CADASIL participants (44% female; 87% white, modified Rankin Scale<sup>3</sup> ≤3) were grouped using the Montreal Cognitive Assessment (MoCA) total score (i.e., MoCA ≤25 cognitively impaired (CI) and >25 normal (NL). Participants were scanned at one of eight sites using a 3T Siemens Prisma Fit or a 3T GE Signa Premier Discovery MR750. Diffusion Weighted Imaging (DWI) and pseudo-continuous arterial spin labeling (PcASL) acquisition protocols based on Alzheimer’s disease neuroimaging initiative-3 (ADNI3) or Biomarkers for Vascular Contributions to Cognitive Impairment and Dementia (MarkVCID) were used. After correcting for distortion and motion artifacts, fractional anisotropy (FA) and mean diffusivity (MD) maps were produced using FSL. Peak width of skeletonized white matter mean diffusivity (PSMD) was estimated using the psmd-marker tool. PcASL data was analyzed using a FSL BASIL toolkit. A simple kinetic model applying spatial regularization, tissue type priors (from each patient’s T1w data) and voxelwise cerebral blood flow (CBF) calibration were used. Using SAS, exact Wilcoxon rank-sum procedures were used to compare PSMD and averaged CBF values between CI and NL participants using Rosenthal’s effect size *r*. **Results:** PSMD (n=16) and CBF (n= 11) measurements were available for a subset of participants. The distribution of PSMD was higher in the CI (n=6, *Mdn*=0.0003, IQR: 0.0002-0.0004) versus NL (n=10, *Mdn*=0.0003, IQR: 0.0002-0.0003) cohort (*r*=0.24, a small effect). Conversely, the distribution of CBF was lower in the CI (n=2, *Mdn*=0.70, IQR: 0.69-0.70) versus NL (n=9, *Mdn*=0.76, IQR: 0.73-0.78) cohort (*r*=0.46, a medium effect). **Conclusion:** Preliminary data suggests that CADASIL participants with cognitive impairment show higher PSMD and lower CBF compared to those who show intact cognition on the MoCA. Findings are consistent with small vessel disease findings showing that PSMD is a robust biomarker for VCID. The NIH-funded (1RF1AG074608-01) CADASIL Consortium will enroll 400 CADASIL *NOTCH3* carriers and 100 non-carriers allowing significant power to further explore the relationship of these and other imaging biomarkers in vascular dementia and small vessel diseases.

### S138. Overlap Syndrome of Sjogren's and Systemic Sclerosis with Moya Moya Morphology: A Rare Case

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**Introduction:** There are few case reports on Moya Moya syndrome in Sjogren syndrome or systemic sclerosis independently. Of those, most are reported in women. We describe a unique case of childhood onset Sjogren syndrome overlapping with systemic sclerosis in a young male adult presenting with an acute stroke due to Moya Moya vasculopathy. **Case:** A 30-year-old male with Sjogren syndrome diagnosed as a child and hypertension, presented with acute onset dysarthria, right facial droop, and dysphagia. He had history and physical findings compatible with Sjogren syndrome with systemic sclerosis, including Raynaud's phenomenon, telangiectasias, esophageal dysmotility, and multiple finger amputations from ischemia and infected ischemic digits. CT and MR imaging incidentally demonstrated sialadenitis and numerous small parotid gland cysts which are also compatible with Sjogren syndrome. CT head revealed a subacute left frontal transcortical infarction and chronic infarctions in the right caudate head and cerebellum. CTA showed marked narrowing of the left internal carotid artery to the cavernous/supraclinoid junction with occlusion of the supraclinoid segment and marked narrowing of the A1 segment of the left anterior cerebral artery with hypertrophy of the adjacent small skull base vessels and the lenticulostriate vessels with Moya Moya like morphology. Additionally, cerebral angiogram demonstrated collateralization via the left ophthalmic artery, external carotid artery branches and Circle of Willis. MRI showed evolving subacute infarcts in left frontal, parietal and occipital lobes with petechial hemorrhage and chronic infarcts in the right caudate head and right cerebellum. Labs significant for ANA positive, titer 1:640, speckled, Sjogren's antibody SSA 6.9, RNP antibody greater than 8. Initial diagnosis of CNS vasculitis in the setting of existing autoimmune condition and Moya Moya syndrome was made. He was started on a 5-day course of pulsed dose steroids followed by IV cyclophosphamide. **Conclusion:** Rare co-occurrence of Moya Moya syndrome in patients with overlap syndromes often lead to delayed diagnosis. It is crucial to track the evolution of immunological diseases and acquire early vascular imaging. Future research is needed to help prevent cerebrovascular complications and improve outcomes.

### S139. Oversweetened: Prolonged Treatment-Resistant Hemichorea-Hemiballismus Syndrome Due to Hyperglycemia

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**Background:** Hemichorea-Hemiballismus Syndrome (HCHB) is a self-descriptive continuous condition frequently caused by vascular insult to the contralateral basal ganglia usually characterized by T1 hyperintensity on MRI brain.

Previous cases of HCHB in patients with non-ketotic hyperglycemia describe rapid resolution of symptoms following normalization of blood glucose. Here, we discuss a patient with HCHB due to hyperglycemia without MRI findings with delayed symptom resolution persisting at 6 month follow up despite early and excellent control of blood glucose.

**Objective:** To describe a radiographically silent and treatment-refractory case of hyperglycemia-induced Hemichorea-Hemiballismus Syndrome (HCHB) despite return to euglycemic state. **Results:** 57-year-old man with severe uncontrolled diabetes mellitus (A1c >18%) complicated by retinopathy, nephropathy, and peripheral neuropathy presenting with 4 week history of worsening right-sided hemichorea and hemiballismus. He was admitted 3 weeks prior with non-ketotic hyperglycemia (blood glucose 757) resolving with initiation of insulin therapy and remained euglycemic through to time of presentation. Neurological exam showed right hemichorea and hemiballismus as well as stocking-and-glove neuropathy. MRI brain w/wo revealed no T1 hyper intensity, no diffusion restriction, no contrast enhancement and only mild microvascular changes on T2 FLAIR sparing the basal ganglia. Blood glucose ranged between 75 - 130. Serum nutritional, toxicological, and autoimmune workup was unremarkable. Unresponsive to haloperidol and risperidone, with subsequent modest improvement with tetrabenazine. At 2-month follow-up his blood glucose remained optimally controlled with mild interval improvement of hemichorea and hemiballismus on exam. At 6-month follow-up his A1C had improved to 5.7% with gradual resolution of hemiballismus and only mild residual hemichorea manifesting during sleep deprivation. **Conclusions:** HCHB is an important stroke mimic which must be considered due to its similar radiographic appearance but usually rapid and complete response to blood glucose control. Symptoms may persist beyond the acute period but resolve with treatment.

### S140. Perceptions of a Hybrid Telestroke Hub and Spoke Stroke Support Group

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**Introduction:** Nearly a quarter of strokes recur in stroke survivors. Education can empower stroke patients to seek timely treatment. Stroke support groups (SSGs) can help survivors engage in meaningful occupation, manage expectations, and navigate recovery positively. We assessed perceptions of a hybrid stroke support group formed in collaboration among a hub and a spoke site within a telestroke network. **Methods:** A spoke located 110 miles from our hub housed a monthly hybrid SSG (5/2022-3/2023). Stroke survivors and caregivers were invited from the city (population 65,000) that the spoke is located in, regardless of whether they had presented to the spoke prior for stroke. Sessions included discussion on stroke prevention topics and activities focusing on wellness and recovery. We administered an anonymous survey to assess

participant understanding of educational content and perceptions of the SSG. Our IRB deemed this project exempt, although required a letter of information for participants. **Results:** Overall, the SSG included 114 survivor/caregiver participation encounters and 70 from hub and spoke organizers/educators. Only one caregiver attended virtually. Hub participants attended virtual about half of the time (20/39 attendances). We collected the total of 90 surveys from participants excluding the core organizers (61% response rate). Of survey participants, 52% were stroke survivors, 34% caregivers, and 6% organizers/educators. A majority of respondents were comfortable participating (74%) and reported that SSG was supportive (78%). Less than half of respondents reported interacting a moderate amount (39%), 20% interacted a lot to a great deal, and 41% little to none. Ninety-two percent reported learning a moderate to great deal while 7% reported learning a little to not at all, and 77% would be extremely likely to recommend the SSG to others. Thirteen of 17 total questions were answered correctly by over 85% of respondents and 4 questions were answered correctly by about half of the participants (40% - 73%). Survivor/caregiver feedback guided topics for discussion each month: the most common themes suggested were nutrition, exercise, sleep, coping post-stroke, cardiac stroke etiology, medications, and vascular risk factors. **Conclusions:** Participants perceived the SSG as supportive and educational, and their survey responses directed content. Stroke survivors and caregivers retained educational content. Only one stroke survivor attended virtually. Hub staff attended both virtually and in-person: A virtual option mitigated clinical workload and adverse weather barriers. Further investigation is warranted on leveraging a hybrid environment to optimize spoke community education and support from a telestroke hub.

#### S142. Prognostication and Risk Stratification of Hemorrhagic Transformation in Patients with Acute Ischemic Stroke Based on Serum Homocysteine Levels

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**Background:** One of the severe complications of acute ischemic stroke (AIS) is hemorrhagic transformation (HT) which may lead to parenchymal hemorrhage (PH). This study sought to evaluate the association between serum homocysteine levels and HT/PH in all patients with AIS. **Methods:** AIS patients admitted and hospitalized within 24 hours of the stroke episode were enrolled in this study and subsequently divided into two groups based on homocysteine

levels at admission (Group A/Homocysteine levels  $\geq 15.5$   $\mu\text{mol/L}$ ; Group B/Homocysteine levels  $< 15.5$   $\mu\text{mol/L}$ ). After five days, HT was ascertained by follow-up imaging during hospitalization, while PH was diagnosed with hematoma in the infarcted parenchyma. Multivariate logistic regression analysis evaluated the association between serum homocysteine levels and HT and PH. **Results:** Three hundred eighty-five patients were included (mean age 64.17 years), out of which 49 (12.7%) developed HT and 25 (6.5%) developed PH. The association between serum homocysteine levels and HT (95%CI 1.001-1.064) and PH (95%CI 1.017-1.086) was statistically significant ( $p < 0.005$ ). The higher homocysteine group (Group A) was more likely to have HT (95% CI 1.041-4.646) and PH (95% CI 1.436-9.241) than the lower homocysteine group (Group B). **Conclusions:** Our study concludes that higher serum homocysteine levels are associated with an increased risk of HT and PH, thus increasing morbidity and mortality in patients with AIS. In addition, surveillance of serum homocysteine levels may prove helpful in triaging AIS patients with an increased risk of HT.

#### S143. Proteomic Profiling of Intracranial Atherosclerotic Plaque in the Human Brain

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**Background:** Intracranial atherosclerotic disease (ICAD) is a major cause of ischemic stroke and is associated with a high risk of stroke recurrence. However, there is no reliable and specific molecular biomarkers for ICAD. Human proteomic studies in atherosclerotic disease have primarily focused on peripheral blood and extracranial tissues obtained from endarterectomy or coronary bypass surgeries. Less is known about the proteome of ICAD. In this pilot study, we aimed to explore the feasibility of applying proteomics technology to profile intracranial atherosclerotic plaques extracted from postmortem human brains. **Methods:** 18 segments (5-10mm in length) of major intracranial arteries were collected from 10 postmortem brains at the Mount Sinai Neuropathology Brain Bank. Among these segments, 5 had no evidence of atherosclerotic disease, 3 had wall thickening without visible plaques, 3 had visible plaques with less than 20% stenosis, 3 had plaques with 20-50% stenosis, and 4 had plaques with over 50% stenosis. Proteins were extracted from the vessel segments, quantified, and digested into peptides. Subsequently, the peptides underwent TMT labeling, pooling, and analysis using two-dimensional liquid chromatography-tandem mass spectrometry (LC/LC-MS/MS). Protein identification and quantification were performed using the JUMP software. Differentially expressed proteins (DEPs) were defined as proteins with a false discovery rate (FDR) of less than 0.05. **Results:** A total of 7,492 unique proteins were detected and 6,726 proteins were quantified. Among these, 265 DEPs were found to be associated with intracranial atherosclerosis by comparing the arterial segments with

atherosclerotic changes to those without atherosclerotic disease. The top 5 most significant DEPs are RPS19, MRPL12, SNU13, LONP1 and AK3, all of which were elevated in arterial segments with atherosclerotic changes. Previously reported proteins associated with atherosclerosis, such as MMP12 and Cathepsin D, were also found to be more abundant in vessel segments with more severe stenosis and plaque burden. Gene set enrichment analysis revealed that pathways such as Nucleosome, Protein-DNA complex, DNA Packaging Complex, Lipoprotein metabolic Process, and Chromatin are most significantly upregulated in atherosclerosis. **Conclusion:** Direct proteomic profiling of postmortem fresh-frozen intracranial artery samples using MS-based proteomic technology is a feasible approach to identify proteins with differential abundance in arterial segments with atherosclerosis compared to those without. Further proteomics analysis of plaques with a larger sample size is warranted to uncover mechanistic insights into ICAD and discover novel biomarkers for early diagnosis, disease progression, and prognostication of ICAD.

#### **S144. Retrospective Study of Multi-Site CADASIL: Implications for Clinical and Research Practice**

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**Background:** Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is the most common monogenic cause of vascular cognitive impairment and dementia (VCID). Persons with NOTCH3 mutations causing CADASIL can be evaluated from presymptomatic to symptomatic phases of VCID. An NIH-funded (RF1AG074608) multi-site natural history study of CADASIL patients and non-carrier family members (www.cadasil-consortium.org) has begun to characterize cross-sectional and longitudinal VCID, detect the earliest changes in plasma, imaging and other biomarkers, and document the phenotype of CADASIL in North America. Here we present background data obtained from four US participating institutions. **Methods:** By requesting research collaboration via email from only a few scientific advisory board members of a CADASIL organization, more than 60 responses were received within two weeks. Following one in-person meeting at a national neurology meeting and >30 group teleconferences, a grant was developed and submitted for a multi-site CADASIL study in the US. In preparation

for the grant, several neurologists with active cohorts submitted clinical data obtained retrospectively from medical records. Phenotype data were harmonized and analyzed at UCSF; imaging data were harmonized and analyzed at GSU (not presented here). **Results:** 110 subjects with clinical data were identified at four US academic sites: UCSF (n=58), Loyola University Medical Center (n=32), Emory University (n=11) and Columbia University (n=9). Sample sizes for data points varied between sites. Median age of onset not including migraine was 47 years, but including migraine onset was 28. Anterior temporal pole white matter involvement on brain MRI was noted in 89%. 25% had microbleeds. 56% had migraine of any type with 49% having migraine with aura; nearly one-third had headache not otherwise specified. 24% had seizures noted in their records. 91% were considered symptomatic (other than migraine) based on their clinical history, neurological exam and/or cognitive performance. Half had MCI/mild cognitive dysfunction and 29% had dementia. Mean MMSE was  $27.0 \pm 4.5$  (range 8, 30) and mean MoCA was  $24.7 \pm 4.6$  (range 5, 30). **Conclusion:** Although most findings were consistent with reports from European and Asian cohorts, notable differences exist and will be presented. This retrospective data supported a recently NIH-funded multi-site CADASIL natural history study to follow 400 NOTCH3 carriers and 100 non-carrier family members undergoing systematic clinical, neuroimaging, genetic, and blood-based phenotyping.

#### **S145. Revolutionizing Stroke Diagnosis: The Role of Artificial Intelligence**

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**Introduction:** Stroke is one of the leading causes of death and disability worldwide. Stroke incidence has increased by 50% in the last two decades, which means 1 in 4 people will have a stroke in their lifetime. So early and accurate identification is critical for effective treatment and improved patient outcomes. Artificial intelligence (AI) plays an important role in this important aspect of stroke management. AI has emerged as a possible tool to assist physicians in stroke diagnosis. In this structured review, we look at the current research on using AI for stroke diagnosis, including the various AI techniques used, their effectiveness compared to traditional diagnostic methods, and their potential impact on stroke therapy. AI has shown promise in enhancing stroke diagnosis, but the extent of its efficacy is unknown. **Methods:** We thoroughly evaluated the database in Pubmed to assess the efficacy of AI in stroke detection. The search included articles published from January 2013 to March 2023 in the English language. All articles were included if they reported on using AI for stroke detection in human patients. **Results:** An initial Pubmed search yielded 195 papers, 15 included in the assessment after thorough analysis and screening. The study evaluated various types of imaging data, such as computed tomography (CT) and

magnetic resonance imaging (MRI), using different AI techniques, such as machine learning and deep learning. The experiments showed that AI could detect stroke accurately and rapidly, with high sensitivity and specificity rates. AI can also assist in detecting stroke subsets and forecasting patient outcomes. However, the studies also highlighted AI's flaws, such as the need for large amounts of data and the potential for overfitting. **Conclusion:** AI has the potential to revolutionize stroke identification by providing faster and more accurate diagnostics, identifying stroke subsets, and predicting outcomes. More research is needed, however, to confirm the effectiveness of AI in different patient groups and to address data access, communication, and medicinal utilization problems. **Keywords:** Artificial Intelligence in stroke, stroke management with Artificial intelligence, stroke diagnosis with AI.

#### **S147. Safety and Efficacy of Tenecteplase versus Alteplase for Thrombolysis in Acute Ischemic Stroke a Single Center Experience**

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**Background:** Thrombolytic therapy has been the gold standard for treatment of ischemic stroke since 1996. While alteplase (tPA) remains the only FDA-approved thrombolytic for acute ischemic stroke, recent studies suggest that tenecteplase (TNK) may be a preferable alternative because of its advantageous drug characteristics and ease of administration. **Methods:** The purpose of this study was to evaluate differences in clinical outcomes of patients treated before and after institutional transition from tPA to TNK as the thrombolytic agent of choice for acute ischemic stroke, which occurred in March 2022. The primary aim was to compare the effectiveness (i.e. improvement in functional status, defined as a Modified Rankin Scale (mRS) score of 0 or 1 at 90 days) and safety (i.e. side effects, incidence rate of spontaneous intracerebral hemorrhage (sICH) and mortality rate) of tPA versus TNK. Bivariate analysis was used to compare baseline characteristics across medication groups & for subgroup analysis of patients receiving mechanical thrombectomy. Multivariate tests were used for analysis of mRS scores. **Results:** A total of 148 consecutive acute ischemic stroke patients admitted to the Jamaica Hospital Medical Center were included. Seventy-five and 73 patients received tPA and TNK, respectively. At baseline, the tPA group had a significantly greater number of patients with mRS scores of 2+ compared to patients in the TNK group (34% vs. 18%, ( $\chi^2(1) = 3.9$ ,  $p = 0.05$ ). No other differences in clinical or demographic variables were observed between groups at baseline. No differences were observed when comparing mRS scores at discharge, 30 days, or 90 days. In addition, rates of intracranial hemorrhage (tPA=3%, TNK=7%), length of stay (median tPA=4, TNK=4) and the total hospitalization cost (median tPA=\$50,312, TNK=\$45,900) were comparable between both

groups. Although not significant, in-hospital mortality was higher among patients who received TNK versus tPA (12% and 9%, respectively). Among patients receiving mechanical thrombectomy, 10% of TNK had mRS <2 at discharge compared to 45% of tPA. However, this difference was not significant in bivariate analysis. **Conclusions:** TNK and tPA showed comparable effectiveness and safety profiles at our institution. Though in-hospital mortality was slightly higher in those receiving TNK, this was not significant. Although small, the results from this real-world setting support the use of TNK as a viable option for thrombolytic treatment.

#### **S148. Safety of Thrombolytics in Acute Stroke with History of Repaired Aortic Dissection: A Case Report**

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**Introduction:** Acute ischemic stroke with concurrent aortic dissection (AD) is a rare condition that poses a therapeutic challenge. According to AHA/ASA recommendations and clinical practice, administration of IV thrombolytics (IVT) in AD is not recommended due to the possibility of intracranial extension of dissection and increasing the risk of bleeding. We present a challenging case of a patient with AD who presented with acute stroke symptoms within window for thrombolytic therapy. **Case Report:** A 62-years-old aviation mechanic with hypertension, smoking, diabetes, coronary artery disease, right PCA stroke with mild residual partial hemianopia and type A (Stanford classification) aortic dissection 5 years prior s/p repair, was brought in with acute onset dysarthria and imbalance. The NIHSS score was 3 (Dysarthria- 1, Limb ataxia- 1, Partial Hemianopia 1). Symptoms were deemed disabling by patient as he cannot walk. Vitals were normal, CTH showed remote infarction with encephalomalacia in right occipital lobe and CTA demonstrated no large vessel occlusion but a repaired type-A AD, with left subclavian artery and left vertebral artery originating from the false lumen. The maximal diameter of the aortic arch remained steady at 4.8 cm, aortic root looked to have been largely repaired. He was within time window for thrombolytic therapy. Following a discussion about IV thrombolytics with the patient, emergency physician, cardio-thoracic surgeon IVT was administered at 3 hour of onset of symptoms. He had significant improvement in symptoms after IVT and discharged with no new residual deficits. Due to a non-compatible pacemaker, we were unable to obtain MRI for our patient. **Discussion:** While the AHA/ASA guidelines recommend against IVT in acute ischemic stroke with concurrent AD, it's important to note that the risk of bleeding and extension of dissection is significantly reduced in a repaired AD compared to an acute AD. Therefore, a multi-disciplinary discussion between the cardiovascular surgeon, patient, and family may be beneficial in determining appropriate course of treatment. It's crucial to weigh the potential benefits of IVT in treating acute ischemic stroke against the potential risks in patients with repaired AD. Withholding a lifesaving treatment from patients solely based on the history of AD may not be appropriate in all cases. Ultimately, decision to use IVT in patients with repaired AD should be made on a

case-by-case basis. **Reference:** 1. <https://www.ahajournals.org/doi/10.1161/str.0000000000000086> 2. IV tPA Administration in Chronic Aortic Dissection (P6.205), Sadeghikhah et al, *Neurology* Apr 2018, 90 (15 Supplement) P6.205;

#### **S149. Serum Neuregulin as a Predictive Biomarker of Severity and In-Patient Outcomes among Young Acute Intracerebral Hemorrhage Patients in Ghana**

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**Background:** Intracerebral hemorrhage (ICH) is the most lethal of the 3 stroke types. Even among survivors, only about 20% attain functional independence at 6 months. ICH victims in Sub-Saharan Africa are younger and have poorer outcomes. Proposed ICH research priorities include the identification and development of molecular targets with therapeutic relevance in the repair of injured brain tissue. Neuregulins (NRG) are growth factors that act as ligands for the ErbB family receptor tyrosine kinases. They play a key role in the complex processes that occur after brain injury and hence may be a potential candidate for specific ICH treatment. However, there are currently no studies evaluating the relationship between neuregulin and ICH outcomes.

**Aim:** This study seeks to determine the association between neuregulin levels in acute ICH patients and severity as well as in-patient outcomes. **Methods:** We conducted a pilot analytical cross-sectional study among 30 ICH cases who were aged 18 to 50 years, matched to stroke-free controls by age and sex at a ratio of 2:1, to compare circulating concentrations of serum neuregulin. Neuregulin concentration was measured using enzyme immunoassays in duplicates. ICH severity was assessed using the ICH score and in-patient outcomes were dichotomized as alive or dead. Correlative/associative analyses between neuregulin and these outcome measures were performed using Stata software version 17. **Results:** 80% of ICH cases were males with a mean age (in years) of  $44.07 \pm 6.27$ , which was similar to  $44.5 \pm 4.67$  in controls. The median neuregulin concentration for ICH cases was 67.46 pg/ml (IQR 45.77-109.73), which was significantly higher than 53.55 pg/ml (IQR 32.32-59.18) for controls (p-value 0.016). The correlation between neuregulin concentration among ICH cases and ICH score was not significant (spearman's  $r = -0.009$ ,  $p > 0.05$ ). The mortality rate among ICH cases was 26.7%. Univariate logistic regression showed no significant association between neuregulin concentration and in-patient mortality (OR=1.0, p-value  $> 0.05$ ). **Conclusion:** Further studies are underway to establish associations between neuregulin and pertinent outcomes of ICH in resource limited settings.

#### **S150. Sex Differences in Treatment Effect in Neuroprotectant Trials for Acute Ischemic Stroke**

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**Background:** Pre-clinical data suggest sex differences in mechanisms of cerebral ischemic injury, which could lead to differential outcomes of putative neuroprotectants by sex.

However, little clinical trial data is available to assess this. **Methods:** We performed a systematic review of indexed multicenter randomized controlled trials published until June 2022 that enrolled more than 100 subjects and tested novel neuroprotectants in acute ischemic stroke (AIS). For each trial, reported treatment effect by sex was extracted. For trials in which published results by sex were not available, we contacted clinical trial authors to attempt to retrieve these data.

**Results:** We identified 61 publications reporting 66 trials that met inclusion criteria. Of these, data on treatment effect by sex were available for 19/66 (29%) trials. After correspondence with investigators, unpublished data for an additional 4 trials was obtained. Two trials (one testing uric acid and one dexborneol) reported treatment benefit in women but not men. Pooled analysis of six trials of tirilazad reported worse treatment outcomes in women and no effect in men. No differences were apparent in primary outcome by sex for the other 11 trials. **Conclusions:** Most trials did not report treatment effect by sex. Of those that did, there was little evidence of systematic sex differences in treatment response. As newer neuroprotectants enter clinical trials, sex differences in treatment effect should be rigorously examined.

#### **S151. Susceptibility Vessel Sign as a Predictor of Intracranial Large Vessel Occlusion - A Retrospective, Single Centre Study**

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**Objective:** Vascular occlusion is known to alter susceptibility on imaging by reducing arterial flow and causing more deoxygenated blood to pool, which causes a higher level of deoxyhemoglobin. The susceptibility vessel sign (SVS), which can be seen on T2\*-weighted gradient echo (GRE) imaging, is typically described as a dark blooming artefact. The hypointense vessel's diameter is thus larger on imaging than the opposing vessel's diameter. While most existing studies have focussed on evaluating the role of SVS as a screening tool for specific large vessel occlusions, such as the MCA or PCA territory, very few have attempted to extrapolate the use of SVS as a screening tool for all acute intracranial occlusions. We thus conducted a study to investigate the sensitivity and specificity of this sign on susceptibility-weighted imaging (SWI) in the principal intracranial arteries in individuals with acute stroke and to further assess the 3-month outcome using the modified Rankin Scale. **Methods:** A single-centre retrospective observational study was conducted at Aster MIMS (Malabar institute of medical sciences) Calicut, Kerala. Data from 156 patients who presented to our centre with acute ischemic stroke was collected. **Results:** 106(63.5%) patients had a Large Vessel Occlusion(LVO) on MR Angiogram (88 with anterior circulation LVO and 18 with posterior circulation LVO), and 50 (36.5%) did not. Among the patients with LVO, a majority of 73 patients demonstrated a positive

SVS on MRI, while 33 patients did not. Among the patients without LVO, only 4 patients showed a false positive SVS, while 46 patients showed negative SVS. The sensitivity, specificity, positive predictive value and negative predictive value of SVS as a screening tool were 67.05 %, 90.7 %, 93.65 %, and 57.35 % in anterior circulation LVO, and 77.8%, 100%, 100% and 63.6% in posterior circulation LVO. The chi-Square test showed  $p < 0.05$ , demonstrating a significant association. In our study, though a statistical significance could not be established, 83.3% of SVS-positive patients had a successful recanalization, with mTICI scoring 2B or 3 and 64.4% of SVS-positive patients had an mRS score less than 3, showing SVS positivity could indicate good clinical improvement. **Interpretation:** Susceptibility vessel sign is a good screening tool for the presence of intracranial large vessel occlusion, with good sensitivity, high specificity and positive predictive value for LVO (posterior > anterior). SVS positivity could also be an indicator of good clinical outcomes, both with respect to successful recanalization and 90-day mRS outcome.

#### S152. Synergistic Contribution of Blood Pressure and Cerebral White Matter Hyperintensities to the Risk of Major Adverse Brain Events

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**Background:** Elevated systolic blood pressure (SBP) and cerebral small vessel disease (CSVD) each independently contribute to an increased risk of major adverse brain events (MABE) of incident stroke and dementia. We investigated whether the joint exposure of elevated SBP and CSVD on the risk of developing MABE is supra-additive. **Methods:** We analyzed the Atherosclerosis in Risk Communities cohort. Inclusion criteria were availability of a Visit 5 brain MRI, no stroke or dementia history, SBP data available at in-person Visits 1-5, and available demographic and outcomes data. SBP categories were defined by average SBP across Visits 1-5: 1) < 120, 2) 120-130, or 3) > 130 mm Hg. White matter hyperintensity (WMH) volume at Visit 5 was categorized into quintiles. The outcome of interest was adjudicated MABE occurring after Visit 5 through Visit 7. We built a Fine-Gray model to analyze the hazard of MABE as a function of SBP and WMH categories, accounting for the competing risk of death and adjusting for baseline demographic and clinical covariates. To determine whether the effects of SBP and WMH were supra-additive, we calculated the associated relative excess risk due to interaction (RERI) and attributable proportion (AP). **Results:** We included 1,435 ARIC participants [mean age 76; 59% female; mean SBP < 120 (48%), 120-130 (29%), > 130 (23%)]. There were 290 incident MABE (51 stroke, 239 dementia) and 115 deaths during a median follow-up of 6.3 years (SD 1.5 years). The variance inflation factor between the SBP and WMH categories was 1.44, indicating a degree of collinearity between the two exposures that was not problematic in regression modeling. In the adjusted Fine-Gray model

those with mean SBP > 130 versus < 120 (HR 1.8, 95% C.I. 1.3-2.4) and highest versus lowest WMH volume quintile (HR 2.9, 95% C.I. 1.9-4.7) were significantly more likely to develop MABE. When comparing the combination of mean SBP > 130 and highest WMH quintile to mean SBP < 120 and lowest WMH quintile, the HR for MABE was 8.67 (95% C.I. 3.9-19.5). RERI was 0.48 (95% C.I. 0.18-0.78,  $p=0.002$ ) and AP was 0.73 (95% C.I. 0.53-0.95,  $p<0.001$ ). **Conclusion:** The combined effect of SBP and CSVD on the risk of MABE is greater than the sum of their individual effects. Further studies are needed to elucidate the biological mechanism of this synergistic effect and its potential clinical and public health implications.

#### S153. Systematic Review and Meta-Analysis of Post-Stroke Upper Extremity Home Rehabilitation Clinical Trials

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**Purpose:** Activity based high dose arm rehabilitation improves motor function after strokes, however many patients do not have access to intensive outpatient therapy. Increasing number of clinical trials evaluate home-based rehabilitation techniques as an affordable and convenient alternative. Our objective was to evaluate the efficacy of treatment options and identify gaps of knowledge in home upper extremity rehabilitation trials. **Methods:** A systematic review of literature was conducted in 2 electronic databases and 4 clinical trial registries until Jan 2023 using the following keywords: stroke and telerehabilitation, stroke and home therapy, and community-based stroke rehabilitation. We excluded clinical trials that did not pertain to home rehabilitation for upper limb motor recovery of stroke patients and did not include published results. Studies were assessed for methodological quality and bias. Descriptive statistics was used for demographics. All meta-analyses were based on studies where both mean and SD were available to compare the effect of gamified therapy, robotic therapy, and teletherapy. One-way ANOVA for continuous variables and Fisher's exact test for categorical variables were used to compare the three therapies. **Results:** 48 clinical trials were included in the systematic review for analysis. We reviewed technologies related to telerehabilitation, VR, games, wearable sensors, robotics, and other techniques such as mirror therapy and CIMT. Most studies were small ( $N=24.68 \pm 20.27$  experimental;  $N=22.13 \pm 21.66$  control) and excluded patients with severe strokes, and patients with cognitive deficits. Mean age of patients in the experimental groups was  $59.74 \pm 5.26$  and control was  $62.47 \pm 4.72$ . Meta-analyses were based on 24 studies for gamified (8), robotic (4), and teletherapy (12). For the change from baseline to follow-up, the overall effect sizes (Hedges's  $g$ ) were 0.37, 0.40, and 0.43 for gamified therapy, robotic therapy, and teletherapy, respectively. There were no significant differences between the control and intervention groups. There was no significant difference among the three therapies ( $p=0.99$ ). There was heterogeneity in the meta-analysis data



( $p < 0.001$ ) however bias may not be a problem ( $p = 0.64$ ). **Conclusions:** Telerehabilitation, home gamified, and robotic therapy were comparable in efficacy to same intensity traditional treatment. There was no difference in therapeutic success between gamified, robotic, and teletherapy. Rehabilitation at home following mild-moderate stroke is feasible and has moderate effect size. Future studies should include larger patient groups including those with severe UE motor deficits, and cognitive impairments as these may require different methodology.

#### **S154. Takotsubo Cardiomyopathy in Patients with Acute Ischemic Stroke: A Case Series**

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**Background:** Takotsubo cardiomyopathy (TC) is a non-ischemic cardiac injury characterized by acute left ventricle dysfunction, often triggered by emotional stress. TC has also been reported after acute ischemic stroke (AIS). Injuries in key areas of the central autonomic network (CAN) including insular and cingulate cortex, amygdala, and hypothalamus, may be associated with post-stroke TC. Here, we report a case series of patients that developed TC in the setting of AIS to explore risk factors, characteristics, and outcomes. **Methods:** We included patients with AIS and TC from an institutional retrospective database of 300 AIS patients at five hospitals over two years with elevated cardiac troponin (cTn). TC was defined based on the International Takotsubo diagnostic criteria: presence of left ventricle apical hypo/akinesis with evidence of reversibility obtained when possible. **Results:** Six AIS patients were identified to have TC. Five were women; the mean age was  $77 \pm 12$ . Hypertension was seen in five, diabetes mellitus in three, hyperlipidemia in two, and tobacco use in two. All patients had a dynamic cTn pattern (rise/fall  $> 20\%$ ): rising in four and falling in two. Echocardiogram was obtained within three days after stroke onset: median ejection fraction was 35% (IQR=30-40), all patients had apical akinesis and/or ballooning, and none had a left ventricle thrombus. The median NIHSS was 12 (IQR=6-18). Stroke location included the left hemisphere in three, right hemisphere in one, and bilateral hemispheres in two. The insula and other CAN structures were involved in four patients. Two patients underwent coronary angiogram without obstructive coronary artery disease. Two patients died during the hospitalization (from heart failure and post-stroke cerebral edema, respectively); the other four had a mean length of stay of  $7 \pm 4$  days. The three patients with post-hospital follow-up had resolution of Takotsubo-related left ventricle changes; of the others, two died and one was lost to follow-up. **Conclusion:** In our case series, AIS patients with TC were mostly elderly women with a stroke affecting the structures of the CAN. However, a stroke in this region was not seen in all patients; thus, multiple mechanisms may produce TC. Echocardiography was not performed until after stroke onset, so it remains possible that TC was the cause rather than the effect of AIS in some patients. Pathophysiological studies are needed to clarify mechanisms underlying post-stroke Takotsubo, including the role of structural alterations of the CAN in triggering myocardial injury.

#### **S155. The Association between Hepatic Fibrosis Due to Non-Alcoholic Fatty Liver Disease and Post-Stroke Depression in Patients after Ischemic Stroke**

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**Introduction:** Depression is one of a stroke's most common and pressing neuropsychiatric complications, accounting for one-third of acute stroke survivors. Post-stroke depression (PSD) is related to an increased mortality risk and declining functional outcomes. Non-alcoholic fatty liver disease (NAFLD) leads to fibrosis and an increased risk of large and small vessel atherosclerosis. Our study sought to evaluate the association between the degree of hepatic fibrosis and PSD.

**Methods:** Patients with their first-ever ischemic stroke were prospectively enrolled from September 2020 to August 2022. The fibrosis-4 index (FIB-4) was used to calculate the degree of hepatic fibrosis and divided into two categories ( $< 2.67$  and  $\geq 2.67$ ). Hamilton depression scale was used to screen depression, and patients with a score  $> 7$  were further evaluated for diagnosis of PSD based on DSM-IV criteria at baseline and six months follow-up. **Results:** A total of 512 patients (mean age, 62.4 years) were enrolled in this study. Based on the FIB-4 score, 122 (24%) patients had advanced hepatic fibrosis. During the follow-up period, PSD was diagnosed in 159 (31%) patients (95% CI 28.2%-33.5%). The prevalence of advanced hepatic fibrosis was higher in patients with PSD than those without (46% vs. 28%,  $p = 0.001$ ). After adjusting for control variables in the multivariate logistic analysis, the association between advanced hepatic fibrosis and PSD was statistically significant (95% CI, 2.1-4.31;  $p < 0.005$ ). **Conclusions:** Our study concludes that advanced hepatic fibrosis is associated with an increased risk of six-month PSD. Therefore, the FIB-4 index may be a valuable parameter for screening depressive symptoms in patients with acute stroke.

#### **S156. Thrombolytic Therapy for Central Retinal Artery Occlusion: A Systematic Review and Individual Participant Level Meta-Analysis**

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**Background and Aims:** Thrombolytic therapy in acute non-arteritic central retinal artery occlusion (naCRAO, a neuro-ophthalmologic emergency with poor visual recovery) is a promising intervention, with various outcomes reported in previous studies. Herein, we aimed to evaluate the efficacy of intravenous (IV) or intraarterial (IA) thrombolytic therapy in

naCRAO, and other modulators of visual outcomes. **Methods:** We systematically searched six databases through February 2023 to record visual recovery rates in naCRAO patients presenting with visual acuity (VA) of 20/100 or worse, who received thrombolysis IV (within 4.5h) or IA (within 24h) with urokinase (UK) or tissue Plasminogen Activator (tPA). VA improvement  $\geq 0.3$  logarithm of the Minimum Angle of Resolution (logMAR), and VA improvement to  $\geq 20/100$  were considered as visual outcomes.

**Results:** Among 1153 identified studies, 72 reports in 9 languages were included in the systematic review (771 patients) and 63 articles (728 patients) in meta-analyses. Visual recovery for  $\geq 0.3$  logMAR was reported among 74.3% (CI: 60.9%-86.0%) of patients who received IV-tPA, 60.0% (CI: 49.1%-70.5%) after IA-tPA, and 46.8% (CI: 24.4%-69.8%) following IA-UK. VA of  $\geq 20/100$  was observed among 39.0% of patients after IV-tPA within 4.5h, 21.9% of those with IA-tPA within 24h, and 31.0% of patients with IA-UK. Results of 2 aggregated data meta-regression models and 12 individual patient level meta-analyses highlighted the association between improved visual outcomes and 1) shorter window to thrombolysis and 2) subsequent use of antiplatelet therapy. **Conclusions:** Thrombolytic therapy with tPA and addition of antiplatelet therapy after thrombolysis are associated with improved visual recovery. Prospective randomized studies should further refine the superiority of IV versus IA thrombolysis within early hours after visual loss in naCRAO.

#### **S157. To See or Not to See: Anton Babinski Syndrome Secondary to Posterior Reversible Encephalopathy Syndrome along with Alprazolam and Tramadol Withdrawal**

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**Objective:** To describe a rare case of Anton Babinski syndrome (ABS) secondary to Posterior Reversible Encephalopathy Syndrome (PRES) in the setting of benzodiazepine and Tramadol withdrawal. **Background:** Anton-Babinski syndrome is a rare neuropsychiatric syndrome that is characterized by cortical blindness, visual anosognosia (denial of loss of vision), and confabulation, but without cognitive impairment. Damage to the visual association cortex (Brodmann area 18 and 19) and the primary visual cortex (Brodmann area 17) can be responsible for this anosognosia and cortical blindness, respectively. **Design/Methods:** Case report and literature review. **Results:** 69-year-old man with a history of atrial fibrillation, hypertension, anxiety, chronic peptic ulcer disease, and chronic pain presented with sudden onset bilateral painless vision loss, headache, and delirium. Blood pressure was 170/70. Eye exam was unremarkable. Brain MRI showed PRES with extensive vasogenic edema in the bilateral occipital and parietal lobes, so he was started on IV Nicardipine. The next day, the patient developed visual anosognosia and confabulation with normal mentation. He reported that he ran out of his home medications 3-4 days prior to admission including Tramadol 50mg q6hr and Alprazolam 0.5mg q8hr. EEG

showed bilateral posterior quadrant epileptiform discharges without any seizures. Home Tramadol and Alprazolam were resumed and his symptoms resolved within a few hours. The patient was discharged home the next day in good condition with a normal neurologic exam. **Conclusions:** Anton Babinski syndrome, as a complication of PRES, is a very rare phenomenon. Though the anosognosia can be transitory, it is a cause of distress for the patient and family and can result in diagnostic and management challenges.

#### **S158. Transient Ischemic Event Secondary to Extrinsic Compression of the Cervical Internal Carotid Artery by the Lateral Process of C1 Vertebrae: A Case Report**

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**Objectives:** To report the first case to our knowledge of transient ischemic attack caused by extrinsic compression of the internal carotid artery (ICA) by the lateral process of the C1 vertebrae in a previously healthy young female. **Background:** Extrinsic ICA compression is very rare and can present as weakness, aphasia, visual loss, or syncope. Case reports described rare causes of extrinsic ICA compression, including adhesions of the atlas [1], hypoglossal-carotid entrapment [2], and compression by the digastric muscle [3]. Other causes include Eagle syndrome and traumatic ICA dissection. **Methods:** We report a 23-year-old previously healthy female presenting with a sudden onset of complete vision loss in her right eye while driving. The loss of vision lasted for 5-10 minutes, gradually regained her vision, starting from her peripheral field of vision, and regained full visual acutely after a short duration. There was no history of recent head or neck trauma, loss of consciousness, or other transient neurological deficits. Her symptoms were not reproduced by any head movements. Her neurological examination and initial CT brain were unremarkable. CT angiography with intravenous contrast showed right severe stenosis (more than 50% luminal narrowing) of the cervical ICA compressed by the lateral process of C1 with normal distal flow and no evidence of vascular occlusions, malformations or superimposed dissection. MRI brain and MRA were also done, confirming the previous findings. **Results:** Dual antiplatelet therapy was prescribed, and carotid artery stenting was planned by a neurosurgeon to relieve the compression, as the patient wanted to defer from any surgical procedures. The procedure was uneventful, and post-stenting follow-up showed no reemerging symptoms. **Conclusion:** Extrinsic ICA compression is caused mainly by anatomic variations and can lead to atypical presentations. Due to its rare occurrence, it can be easily missed. However, early diagnosis and management are key to preventing devastating complications.

#### **S159. Traveling Tumor: Papillary Fibroelastoma as an Unusual Etiology of Cardioembolic Stroke**

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**Introduction:** Primary cardiac tumors are uncommon with an approximate incidence of 0.02%. Although benign,

papillary fibroelastomas account for 75% of primary valvular tumors and can embolize. Two cases of fibroelastoma that caused cardioembolic stroke are described below. **Case 1:** A 66-year-old female with a history of hypertension, diabetes, and hyperlipidemia presented with 5 days of ataxia and vertigo. On exam, she was found to have vertical nystagmus and ataxic gait. Computed tomography (CT) scan of her brain showed bilateral cerebellar strokes and computed tomography angiogram (CTA) was absent for significant atherosclerosis. Transesophageal echocardiography (TEE) revealed a 0.7 cm x 0.7 cm mobile mass on the aortic valve that was concerning for a papillary fibroelastoma and was not visible on the initial transthoracic echocardiography (TTE). Aortic valve repair and mass resection were performed. Histologic examination of the resected mass confirmed fibroelastoma. **Case 2:** A 48-year-old male with history of hypertension, diabetes, and prior right middle cerebral artery ischemic stroke presented with aphasia and right hemi body weakness. Magnetic resonance imaging (MRI) of the brain showed a left middle cerebral artery ischemic stroke. No atherosclerosis of the large arteries was present on CTA. After clinical stabilization, TEE was done after a negative TTE, that demonstrated a 0.7 x 0.7 cm mass on the posterior leaflet of the mitral valve. While being evaluated for surgical candidacy, the patient suffered another ischemic stroke involving the right superior cerebellar artery with hemorrhagic transformation. **Conclusion:** Fibroelastomas are a rare cause of cardioembolic strokes. Our cases emphasize the importance of pursuing transesophageal echocardiogram despite a negative transthoracic echocardiogram, in presence of unclear stroke etiology.

#### **S160. Unraveling the Earliest Phases of Vascular Cognitive Impairment and Dementia Using CADASIL**

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**Goal:** To characterize the initial presentation and course of clinical, neuroimaging, and fluid markers of presymptomatic

and early to moderate symptomatic NOTCH3 carriers and compare them with non-carrier family member controls (NC) and to clarify genetic, health, and lifestyle factors which impact clinically meaningful outcomes in Cerebral Autosomal Dominant Arteriopathy Subcortical Infarcts and Leukoencephalopathy (CADASIL) using exome sequence data, genome-wide genotyping, medical history and lifestyle questionnaires. **Background:** CADASIL is the most common monogenic cause of vascular dementia. Persons with CADASIL have a very high risk of developing vascular cognitive impairment and dementia (VCID), which can be studied in presymptomatic and prodromal disease stages to detect the earliest changes in biological fluids, neuroimaging, and the emerging phenotype of symptomatic VCID. Unfortunately, there is little cross-sectional and particularly longitudinal data describing a large CADASIL cohort in the USA. Better understanding of the clinical progression and identification of potential biomarkers in CADASIL will be necessary for developing optimal future treatment trials. **Methods:** We are establishing an NIH/NIA-funded (RF1AG074608) longitudinal cohort of 400 NOTCH3 carriers and 100 non-carrier family members from 12 sites across the USA. Participants are undergoing systematic clinical, advanced neuroimaging, and blood-based phenotyping. Cognitive function being assessed with standard pen and paper testing will be compared to novel tablet-based measures from the NIH-EXAMINER (a battery emphasizing frontal-executive assessment, which is often impaired in vascular dementia). Diffusion tensor imaging (DTI) and several newer MRI techniques are being applied to our cohort to try to yield the lowest sample size estimates needed for clinical trials. Several scales and assessments including those for quality of life (QOLs) are being collected and will be compared to assess which track progression best. **Results:** Despite issues related to the Covid-19 pandemic, recruitment has begun at all 12 sites. Thus far, all subjects are functioning independently and the majority of subjects enrolled do not have cognitive impairment based on the Montreal Cognitive Assessment (MoCA). Initial imaging analyses have begun and are also being submitted for presentation. **Conclusion:** We hope to show that conducting such a large, multisite study in a rare disease is possible in the USA. Clinical outcome assessments in CADASIL should be developed from this study. The data generated from this study will be essential to design cost-effective, successful clinical trials in CADASIL and other vascular dementias.

#### **S161. Use of IV Thrombolytics to Treat Ischemic Stroke in a Patient with an Acute Myocardial Infarction and Intra-Aortic Balloon Pump**

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Intra-aortic balloon pumps (IABP) are used in peri-operative cardiac surgery patients with low cardiac output secondary to previous ischemic cardiomyopathy or low output cardiac syndrome. However, studies have shown complication rates up to 40-50% associated with IABPs. The 2019 updated guidelines for early management of acute ischemic stroke

recommends considering IV thrombolysis in patients with an acute myocardial infarction. However, to our knowledge this is the first reported case of IV thrombolytic use in a patient with an IABP. A 61-year-old male with a history of hypertension, hyperlipidemia, and type 2 diabetes mellitus presented to the emergency department with sudden onset substernal chest pain. The EKG showed T wave abnormalities concerning for anterior wall STEMI and troponin was elevated to 245,000 pg/mL. The patient underwent a cardiac catheterization which demonstrated a 80% stenosis of the left main coronary artery and 90% stenosis of the left anterior descending artery. The cardiology team proceeded to place an IABP to support cardiac function until patient could be taken for a coronary artery bypass graft (CABG) surgery. After the IABP placement, the patient was noted to have dysarthria, right sided facial droop, right arm weakness, right leg plegia along with right hemi-body sensory loss. His NIH stroke scale was 11 and the CT scan of the head did not show any hemorrhages. The patient was within the time window to consider IV thrombolytic therapy. The partial prothrombin time obtained was 34.9 seconds as the patient had recently received 1000 units of heparin during the cardiac catheterization. Following a risk versus benefit discussion with the patient, cardiology, and vascular neurology the patient received IV thrombolytic therapy. Several hours later the patient's symptoms improved. Repeat CT Head did not demonstrate a hemorrhagic conversion and the MRI brain showed an acute infarct involving the left basal ganglia. The patient was discharged to a rehab facility and six weeks later he underwent the CABG surgery without complications. Patient neurological deficits continued to improve and at the 3-month stroke clinic follow-up his Modified-Rankin score was 2. For providers presented with a rare case similar to this one, in which a patient with an acute MI and IABP placement suffered from an ischemic stroke, it is important to consider administration of IV thrombolytics. Elevated PTTs should be a point of caution as IABP patients are typically anticoagulated with heparin.

### S162. Validation of the Modified Rankin Scale for Stroke Clinical Research in Zambia

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**Introduction:** The modified Rankin Scale (mRS) is an important measure of disability after stroke and can be determined using in-person assessments or telephone-based surveys. However, the reliability of the in-person and telephone mRS have not been investigated in Zambia. **Methods:** In-person mRS scores were determined for all participants enrolled in a prospective stroke cohort study at the University Teaching Hospital in Lusaka, Zambia, by a neurologist or

neurology post-graduate trainee. For fifty consecutive participants, admission or discharge mRS was determined by two different clinicians who were blinded to the other clinician's assessment. In addition, the telephone mRS was translated and back translated into Nyanja and Bemba, the two most common local languages in Lusaka. A trained research coordinator called 124 participants less than 72 hours after discharge and administered the telephone mRS. This score was compared to the in-person discharge mRS. **Results:** Two in-person mRS scores were equivalent in 84% of cases with a correlation coefficient of 0.9451 ( $p < 0.001$ ) and a kappa coefficient of 0.7636 ( $p < 0.001$ ). Telephone mRS was equivalent to in-person mRS in only 40% ( $n = 50$ ) of 124 participants assessed and was 1-point higher than in-person mRS in 39% ( $n = 48$ ). Telephone mRS was 1-point lower than in-person mRS in 14% ( $n = 17$ ), and by 2 points in 3% ( $n = 4$ ). Correlation coefficient for telephone and in-person mRS was 0.7743 ( $p < 0.001$ ), but the kappa indicated fair agreement (0.225,  $p < 0.001$ ). While not significantly different, agreement was highest for telephone mRS interviews conducted in English (46% equal ratings, correlation coefficient 0.7816, kappa 0.2812) and lowest for interviews conducted in Nyanja (29% equal ratings, correlation coefficient 0.6328, kappa 0.0933). Agreement between dichotomized telephone and in-person mRS outcome (good: mRS 0-2; poor: mRS 3-6) was moderate (kappa 0.5472) with a correlation coefficient of 0.5557 ( $p < 0.001$ ). Of those with a good outcome on discharge exam, 10 (53%) had a good outcome on phone exam while 9 (47%) had a poor outcome on phone exam. Of those with a poor outcome on discharge exam, 101 (96%) had a poor outcome on phone exam while 4 (4%) had a good outcome on phone exam. **Conclusions:** In-person mRS had high inter-rater reliability amongst neurologists in Zambia, but the telephone mRS often resulted in higher ratings than in-person assessments, especially when conducted in Nyanja.

### S163. Work Smarter Not Harder- Improving Overall Efficiency on Stroke Service through Epic Handoff Tool

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**Background:** University of Kentucky transitioned to EPIC electronic health record system in June of 2021, which includes a real-time communication feature "Handoff Tool." Before this transition, an online word document was used for STITCH (Stroke team interdisciplinary care huddle) meetings, pre-rounding, rounding and Handoff at the end of the day. On an average day each neurology resident was spending up to an hour a day creating, updating, and maintaining these lists. There has been significant dissatisfaction among residents in using the manual word document due to the time investment and the amount of missing or erroneous information. The goal of this Quality Improvement project was to improve the efficiency of the stroke core team members in maintaining the list using Epic Hand off tool. **Design/Methods:** FOCUS-PDSA (Find a problem, Organize, Clarify, Understand, Select intervention; Plan-Do-Study-Act) methodology was used for this project. A

19-question survey was administered among both adult and child neurology residents, including first year neurology and off service residents, Stroke faculty, Stroke coordinators, Pharmacists, Physical, occupational, speech therapists, and Case managers who were all part of Stroke core team at the time of implementation of the tool. A neurology group specific unique ID for the list settings was created in Epic. Residents and stroke core team members were trained on the process of updating the lists through an hour long session of live interaction. The survey was administered after 3 months of implementation of the Handoff Tool. **Results:** A total of 56 responses were received, of which 75% (n=42) reported utilization of the Handoff Tool, 57.1% (n=32) agreed that Epic handoff is more streamlined process and prevented errors with demographics; 7.1% (n=4) responders were equivocal. Of the 42 responders who were utilizing the hand-off, 78.5 % (n=33) reported at least 10-25% improvement in overall efficiency on stroke service including time spent. Based on an estimate of the old process requiring approximately 1 hour per day, an estimated 15.2 days were spent updating the old list. With at least 25% improvement in efficiency, this equals 273.8 hours or 11.4 days, reflecting a time saving of 91.8 hours or 3.6 days per year of resident time. **Conclusions:** The Epic Handoff Tool has shown to improve overall efficiency and time needed for pre-rounding, rounding, checkout, and stroke core measure tracking by at least 25% among 78.5% of the stroke core team members, as opposed to the manually scripted version.

#### **K-S100. Arginase-1 Microglia and Efferocytosis after Murine Neonatal Brain Hypoxia-Ischemia**

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**Background:** Arginase-1 (ARG-1) is the key regulatory enzyme of inflammation and tissue repair. Recent studies in adult stroke show ARG-1 upregulation in microglia and macrophages during efferocytosis, a process of phagocytic clearance of apoptotic cells that prevents activation of inflammation. While increased ARG-1 levels are associated with better outcomes in various neuropathologies, little is known about ARG-1- expressing microglia and macrophages (ARG-1<sup>+</sup>Mi/Ma) after neonatal brain hypoxia-ischemia (HI). **Methods:** We exposed mice C57BL/6 (wild-type) to hypoxia-ischemia on postnatal day 9, as follows: permanent coagulation of left common carotid artery to induce ischemia, a 1-h recovery period and exposure to 10 % oxygen/balance nitrogen at 37°C for 50 min to induce hypoxia. Animals were perfused at 1h,4h,12h, day 1, 3, 5, 8, 14 and 50 with 4 % paraformaldehyde, brains were post-fixed, sectioned on a cryostat (12 um) and examined histologically with Cresyl-violet staining to assess the degree of damage and ARG-1<sup>+</sup>Mi/Ma spatiotemporal localization via immunohistochemistry (ARG-1<sup>+</sup>Mi/Ma = ARG-1<sup>+</sup>Iba-1<sup>+</sup> cells). **Results:** ARG-1<sup>+</sup>Mi/Ma localized to the ventral brain. The number of ARG-1<sup>+</sup>Mi/Ma was highest early in development (P9) and decreased with age (P14,P23) to undetectable in adult mice (P50). HI triggered change in ARG-1<sup>+</sup>Mi/Ma morphology

from resting to activated bushy and ameboid shape. These activated ARG-1<sup>+</sup>Mi/Ma then accumulated at the injury site as early as 4 h after injury, where they persisted also at 8 days after HI (at P17). HI also reactivated at least some expression of ARG-1 in adult mice as we have detected a few ARG-1<sup>+</sup>Mi/Ma at the injury site. While with the Cresyl-violet staining in our model we detect injury located predominantly in the cortex and hippocampus, the HI caused accumulation and persistence of ARG-1<sup>+</sup>Mi/Ma in the HI injured cortex and striatum. ARG-1<sup>+</sup>Mi at the injury site touched, enwrapped and engulfed dead neurons and expressed PPAR $\gamma$  suggesting the role of ARG-1<sup>+</sup>Mi/Ma in phagocytosis of dead/dying neurons. **Conclusion:** ARG-1<sup>+</sup>Mi/Ma formed a unique population located in specific anatomical areas of the neonatal brain. While the precise role of ARG-1<sup>+</sup>Mi/Ma remains unknown, ARG-1<sup>+</sup>Mi/Ma may play a role in regulation of efferocytosis specifically for the neonatal brain. Further studies are needed to elucidate the precise role of ARG-1<sup>+</sup>Mi/Ma in neurodevelopment and after brain HI.

#### **K-S101. Astrocyte TLR4 Signaling Mediates Astrogliosis Following Focal Cerebral Ischemia**

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**Background:** Astrogliosis is a key feature of central nervous system (CNS) injury that plays both a protective and detrimental role. The mechanisms responsible for determining its role in focal cerebral ischemia are unknown. Deletion of the TLR4 signaling pathway has been shown to be protective against focal cerebral ischemia in experimental ischemia models. In addition, most recently, therapies inhibiting TLR4 have shown protective effects following human stroke. Our previous published studies showed increased expression of toll-like receptor 4 (TLR4) in astrocytes following acute focal cerebral ischemia. Therefore, we hypothesized that astrocyte TLR4 signaling contributes to focal cerebral ischemia outcome by modulating astrogliosis. **Methods:** We used both in vitro and in vivo methods to determine the role of astrocyte TLR4-signaling in astrogliosis following ischemic injury. For our in vitro studies, we plated astrocytes isolated from wild-type (WT) and TLR4<sup>-/-</sup> Wistar rats on glass coverslips, which were subjected to oxygen-glucose deprivation (OGD) for 20h in a hypoxic incubator (5% CO<sub>2</sub>/95% N<sub>2</sub>/1% O<sub>2</sub>). Following OGD, we used immunohistochemistry to stain for GFAP as a measure of astrocyte reactivity. For the in vivo studies, we used mice with inducible, astrocyte-specific TLR4 deletion (*Aldh1l1*<sup>CreERT2/+</sup>; *TLR4*<sup>fl/fl</sup>) to determine the role astrocyte TLR4 signaling in astrogliosis following focal cerebral ischemia. Tamoxifen was used to induce TLR4 deletion, with corn oil-treated mice serving as controls. Mice were subjected to transient middle cerebral artery occlusion (MCAo), and brain sections obtained at 7 days of reperfusion. Using immunohistochemistry, brain sections were stained for GFAP, and the area covered by astrocytes and GFAP intensity were measured to evaluate astrogliosis.

**Results:** In the in vitro studies, astrocytes from TLR4-null animals expressed less GFAP compared to WT astrocytes. These findings were recapitulated vivo with astrocytes in brain sections from mice with inducible, astrocyte-specific deletion of TLR4 astrocytes covering significantly less area ( $4.2558 \pm 2.705$  mm compared to  $15.3976 \pm 14.3537$  mm,  $P=0.0499$ ;  $n=4$  per group) and had an average lower intensity compared to astrocytes from corn oil-treated mice following transient MCAo. **Conclusions:** Astrocyte TLR4 signaling modulates astrocytes reactivity and astrogliosis following focal cerebral ischemia. TLR4 contributes to the proinflammatory detrimental role of astrogliosis, and therapies inhibiting it may provide protection by inhibiting pro-inflammatory astrogliosis and promoting the anti-inflammatory reparative astrogliosis.

### K-S102. Targeting Microglial NF- $\kappa$ B to Improve Neurologic Outcomes after Aneurysmal Subarachnoid Hemorrhage

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**Background:** Delayed cerebral ischemia (DCI) is one of the significant contributors for poor outcomes after subarachnoid hemorrhage (SAH). NF- $\kappa$ B, a transcription factor and a key mediator of inflammation is upregulated after SAH and pharmacological inhibition of NF- $\kappa$ B is shown to attenuate vasospasm. NF- $\kappa$ B is also involved in critical physiological roles in brain and hence complete inhibition of NF- $\kappa$ B may lead to detrimental effects. So, identifying the specific cellular source of NF- $\kappa$ B contributing to its overproduction after SAH is critical. Interestingly, microglia are shown to activate after SAH and also associated with vasospasm. The aim of our current study is to investigate the role of microglial NF- $\kappa$ B in DCI and short and long-term neuro behavioral protection after SAH. **Methods:** Twelve-week-old male wild type mice (C57BL/6) were used for the experiments. Animals underwent either sham or SAH surgery via endovascular perforation model. Normothermia was maintained during the procedure. NF- $\kappa$ B, microglial activation and the cellular source of NF- $\kappa$ B were measured via Immunofluorescence staining on day 3 after SAH. Vasospasm measurement in the middle cerebral artery vessel and microvessel thrombosis by immunofluorescence staining was assessed after 72 hours of SAH. Neurological assessment was performed at baseline and for next three days after SAH. Appropriate statistical tests such as t test, one, two way, or grouped ANOVA followed by post hoc multiple comparison tests were applied using GraphPad Prism 9. Statistical significance was set at  $P < 0.05$ . **Results:** Our preliminary results show that NF- $\kappa$ B and microglia are activated after SAH and microglia mediates increased expression of NF- $\kappa$ B. We also show that pharmacological inhibition of NF- $\kappa$ B by Pyrrolidine dithiocarbamate (PDTC) provides robust protection against vasospasm, microvessel thrombosis and neurologic deficits. **Ongoing Experiments and Implications:** Current experiments are focused on generating microglial NF- $\kappa$ B null mice. We expect that microglial selective deletion of NF- $\kappa$ B would

attenuate vasospasm, microvessel thrombosis and improve short and long-term neurobehavioral outcomes after SAH.

### LB-S100. A Case of Reversible Cerebral Vasoconstriction Syndrome in a Young Female

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**Introduction:** Reversible cerebral vasoconstriction syndrome (RCVS) is a group of conditions that cause intermittent spasms of cerebral vasculature resulting in a wide range of effects from mild to severe. The condition usually presents as an intense headache that can reoccur over weeks. This intense headache is often the only symptom, but in some cases, it can progress to severe symptoms with neurological involvement such as ischemic stroke, intracerebral hemorrhage, and cerebral edema (Singhal, AB, Arch Neurol. 2011). We present a case of a 29-year-old female with a severe clinical presentation of RCVS. **Case Report:** A 29-year-old female with a past medical history of morbid obesity, migraines, vaping, depression, type 2 diabetes mellitus, and a levonorgestrel subdermal implant presented to the emergency department with a four-day history of intermittent headache. She was experiencing nausea, photophobia, and a throbbing headache. On day 12 of experiencing headaches, the patient revisited the emergency department with worsening left upper extremity weakness. Neurology was consulted for the management of presumptive stroke. The patient was initially treated with stroke protocol including being treated with aspirin, clopidogrel, and a high-intensity statin, and a hypercoagulable work-up was also started. Imaging modalities included CT head without contrast, CTA of head and neck, MRI, and angiogram. A four-vessel cerebral angiogram was performed and the pathological findings of moderate to severe vasospasms were found in the anterior and middle cerebral artery segments. Intra-arterial infusions of verapamil and milrinone were then administered, which resulted in significant angiographic improvement. As such, the stenoses were felt to be related to vasospasm, and the cerebral angiogram findings were felt to be most consistent with a diagnosis of reversible cerebral vasoconstriction syndrome. The patient was started on verapamil and advised against using offending agents, such as vaping, ergotamine, and triptan use. **Conclusion:** A major objective of this case presentation is to bring awareness to a differential diagnosis that should be considered in the evaluation of severe migraines, and even stroke. Although RCVS is predominately self-limiting, RCVS still has possible complications that result in permanent neurological deficits or death. Diagnosing this condition earlier can lead to improved outcomes and further education. Once diagnosed, offending agents can be stopped to cease the progression of symptoms.

### LB-S101. Cerebral Venous Thrombosis as Subarachnoid Hemorrhage, a Case Report

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**Background:** Cerebral venous thrombosis is a less frequent cause of stroke with a broad-spectrum presentation, attributed to local effect mechanisms with involvement of cerebral veins, and intracranial hypertension when present in major sinuses. Presentations relate to prominent mechanism at the time of diagnosis, including headaches - most frequent in young females; focal deficits, or encephalopathy - prominent in elderly. Prognosis varies with underlying risk factors with potentially fatal complication of herniation. **Case:** An elderly female, with history of breast cancer treated with mastectomy and chemoradiation, on hormonal therapy presented with acute change in mental status, transient unresponsiveness, right facial droop, and right arm weakness. Brain imaging demonstrated prominent left temporal lobe subarachnoid hemorrhage - concerning for ruptured aneurysm, extending to biparietal regions. Conventional angiogram showed no aneurysm which prompted venogram imaging study which revealed absent flow involving the superior sagittal, right transverse, and sigmoid sinuses. The convexity subarachnoid hemorrhage was then deemed secondary to the venous sinus thrombosis. **Discussion:** Uncommon manifestations of a known pathology often carry potential delays in diagnosis and possible fatal complications. This case highlights known features of variable presentations of cerebral venous thrombosis, how it mimics alternative pathologies with radically different management and treatment goals. Particularly to this patient, the pattern of bleed was suspicious for aneurysm and the history of neoplasia brought the differential of metastatic bleeding disease. All these factors account for the delay in venogram study leading to a late diagnosis and treatment that unexpectedly shifted from conservative subarachnoid hemorrhage management to full anticoagulation; eventually resulting in radical improvement. A thorough interrogation, proper physical exam along with exhaustive investigation of etiology remains key to prompt, successful treatment, and avoidance of fatal complications.

**LB-S129. A Structured-Textual Machine Learning Model to Classify Penumbra-Core Mismatch among Patients Presenting with Acute Ischemic Stroke from Large-Vessel Occlusion**

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**Background:** Endovascular thrombectomy is the standard of care for treating acute ischemic stroke (AIS) from large-vessel occlusion (LVO). Patient selection for thrombectomy in extended (6-24h after last known well) time window often relies on the ratio of penumbra-to-core (P:C) volumes determined by perfusion (CTP) imaging. However, CTP remains inaccessible to many hospital centers worldwide and often results in uninterpretable imaging findings, both of which may delay treatment decisions and result in patient harm. To circumvent these shortcomings, we sought to develop a machine learning (ML) algorithm to predict the P:C ratio in AIS using non-imaging data, including both structured and free-text elements, available at the time of hospital presentation. **Methods:** As part of a separate study evaluating the fusion of clinical and non-contrast CT imaging data to

predict CTP volumes, we retrospectively identified patients who were evaluated for AIS from LVO between 2019 and 2021 and had both a non-contrast head CT and CTP less than 30 minutes apart. After excluding 537 patients with uninterpretable CTP images, we recorded P:C ratios from each patient's CTP images, as well as patient demographics, medical comorbidities, and text from all clinical notes written in the 7 days preceding the patient's CTP timestamp. We used a combination of BioWordVec word embeddings and term frequency-inverse document frequency (TF-IDF) weightings to vectorize each patient's clinical notes, which were then combined with one-hot encoding of demographic data and Elixhauser scores derived from medical comorbidities. We used a 70%-30% cohort training-testing split and manually labeled CTP images as ground truth. We trained an extreme-gradient boosting (XGBoost) ML model to predict P:C ratio of 1.8 as a binary outcome and determined the area under receiver-operating curve (AUROC) on the test set to measure the model's discriminatory performance. **Results:** We identified 151 patients that met our inclusion criteria, 109 (72.2%) of whom had clinical notes in the prior week. Of those, 92 (84.4%) had a P:C ratio above 1.8. The median patient age was 69 years (IQR 59-79) and 51 (46.8%) were female. The AUROC of a combined structured-textual model was 0.75 (95%CI 0.41-0.96). At Youden's index, sensitivity was 0.89 (95%CI 0.75-1.00) and specificity was 0.80 (95%CI 0.40-1.00). **Conclusions:** We developed an ML model from non-imaging EHR data to classify key CTP findings with acceptable discriminatory performance. However, further studies in larger patient cohorts are needed to validate our findings.

**Epilepsy**

**M206. Activity-Dependent Ectopic Action Potentials in Regular Spiking Neurons of the Mouse Neocortex**

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**Objectives:** Action potentials typically originate at the axon initial segment, near the soma of a neuron, and propagate "forward" along its axon to terminals. It has been shown in various studies that neurons are also capable of firing action potentials that originate in terminals or the axon. These are often referred to as 'ectopic action potentials.' Ectopic action potentials have been previously documented in various cell types under pathological conditions, predominantly in seizure models. They have also been detected in cortical interneurons in non-pathological conditions. The purpose of this study is to determine whether RS neurons in the neocortex fire antidromic (ectopic) action potentials under non-pathological conditions, as well as to determine the most effective ways to evoke this type of firing. **Methods:** We recorded from RS cells in layers 2/3 of mouse orbitofrontal cortex, utilizing the whole-cell patch clamp technique in vitro. The protocols used to elicit ectopic firing were either 600 ms, incrementally increasing (by +5 pA), current steps presented every 2 seconds, or pulse trains at three

frequencies: 30, 60, and 100Hz. **Results:** Among 20 RS neurons, 10 (50%) fired ectopic action potentials in response to at least one stimulation protocol. The different frequencies of the current stimuli varied in effectiveness among different neurons, with the 30 Hz protocol eliciting ectopic firing in 30% of the neurons (6/20), the 60 Hz stimulation eliciting ectopics in 25% of neurons (5/20), the 100 Hz in 30% of neurons (6/20), and increasing current injections in 10% of neurons (2/20). No cells fired ectopic action potentials in all four conditions, four cells fired in three, three in only two conditions, and three in only one condition. **Conclusion:** Our experiments establish that approximately half of neocortical RS neurons in non-pathological mouse orbitofrontal cortex are capable of firing ectopic action potentials after sufficient excitation. Future work will focus on determining whether subtypes of RS cells are more or less likely to fire ectopic action potentials, including both short- and long-range projecting cells in multiple cortical areas, and what the mechanism underlying ectopic action potentials in RS cells is.

#### **M207. Alpha 3 Ganglionic Acetylcholine Receptor Antibody- Associated Seizure Disorder**

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**Objective:** To describe a rare case of Alpha 3 ganglionic acetylcholine receptor antibody-associated seizure disorder. **Background:** Autoimmune encephalitis with Alpha 3 ganglionic acetylcholine receptor autoantibody ( $\alpha 3$ -AChR Ab) usually present with symptoms of dysautonomia and peripheral neuropathies. Encephalitis and seizures are not typical presentations. **Design/Methods:** 53 years old male with a past medical history of seizure disorder and suspected Parkinson's disease presented with auditory hallucinations, impaired memory, and confusion. Patient was recently hospitalized for a similar complaint and EEG was concerning status epilepticus with seizures emanating from the right temporo-occipital lobe. The patient was discharged on levetiracetam and carbidopa-levodopa. **Results:** CT head and MRI of the brain were unremarkable. Extensive workup including serum ANCA, Anti-SSA antibodies, Anti-SSB antibodies, Anti-RNP antibodies, anti-double stranded DNA antibody, anti-SM antibodies, CRP, ANA, CSF meningitis encephalitis panel, and CJD testing was unremarkable. Repeat EEG did not show any epileptiform abnormalities. The patient was switched to sodium valproate from levetiracetam. Autoimmune encephalitis was suspected, and the patient was started on IV methylprednisolone with minimal improvement. Paraneoplastic testing was sent both from CSF and serum to the Mayo clinic (ENC2 panel). Although paraneoplastic panel in the CSF returned negative, eventually serum autoimmune panel returned positive for neuronal  $\alpha 3$ -AChR Ab at 0.11 nmol/L (normal <0.02 nmol/L). Patient received 5 days

of plasma exchange and IVIG with improvement. Patient was switched to Azathioprine at time of discharge. Extensive malignancy work was unremarkable. **Conclusions:** Patients with positive  $\alpha 3$ -AChR Ab usually present with neurological symptoms directly proportional to antibody titers. Medium antibody titers as in our case are usually associated with peripheral neuropathies and dysautonomia. Our patient presented with a seizure disorder, cognitive impairment, hallucinations, and encephalopathy. To our knowledge, epilepsy, and encephalitis associated with  $\alpha 3$ -AChR Ab LE has been very rarely reported. Clinicians should be vigilant of the diagnosis as these patients respond better to immunosuppressive therapy instead of tradition AEDs.

#### **M208. An Unusually Late Case of Myoclonic Epilepsy with Ragged-Red Fibers (MERRF) Syndrome**

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**Introduction:** Myoclonic epilepsy with ragged red fibers (MERRF) syndrome is a multisystem mitochondrial disorder and a type of progressive myoclonic epilepsy (PME). Significant phenotypic variability makes a timely diagnosis challenging if there is not a high degree of suspicion. While MERRF usually has an onset during childhood to adolescence, we present a case of late-onset MERRF diagnosis at the age of 42. **Clinical Case Summary:** A 42-year-old woman presented to the neurology clinic for evaluation of seizures and one year of cognitive decline. She was diagnosed with juvenile myoclonic epilepsy (JME) at age 31, which was supported by generalized convulsions, myoclonus and an EEG showing 5-6 Hz generalized spike-and-waves. Seizures had been controlled with levetiracetam until recently. The patient's worsening myoclonus, progressive cognitive decline, and increasing dependence in managing activities of daily living, were inconsistent with JME. The patient continued to deteriorate to the point that she was experiencing continuous myoclonus in her sleep. EEG now showed a slowed background and generalized spike-and-wave discharges at a slower frequency of 3-3.5 Hz. She underwent muscle biopsy, which was consistent with a mitochondrial myopathy. Genetic testing showed a mtDNA mutation 8344 A>G consistent with MERRF syndrome. The patient was started on high dose CoQ10 and levocarnitine. Levetiracetam was increased from 1500 to 2000 mg every 12 hours. She was sent for cardiology and ophthalmology evaluation to evaluate for co-morbid pathology in MERRF. **Discussion:** MERRF syndrome is characterized by myoclonus, often the first symptom, followed by generalized epilepsy, ataxia, myopathy, and dementia. Rarer features include cardiomyopathy, arrhythmias, lipomatosis, and retinal pigmentation. The diagnosis of MERRF includes a muscle biopsy showing ragged-red fibers and can be confirmed by molecular detection of a pathogenic variant associated with MERRF. An A-to-G transition (m.8344A>G) in the mitochondrial tRNA<sup>Lys</sup> gene has been reported to affect



80% of MERRF patients. Advances in molecular and histological techniques have made it easier to diagnose PME, but the treatment of PMEs remains primarily supportive. The antiepileptic medication of choice for myoclonus in PME is valproate but it is typically avoided in mitochondrial disorders as it can potentially precipitate liver failure. MERRF is an exception, as it does not affect the liver. **Conclusion:** Progressive myoclonic epilepsy should be considered in the differential diagnosis of juvenile myoclonic epilepsy when there are unusual features, such as intractable myoclonus, worsening of seizures and memory decline.

### M209. Association between Catamenial Epilepsy and Seizure Frequency during Pregnancy

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**Objective:** To compare seizure outcomes during pregnancy in females with epilepsy (FWE) by history of catamenial patterns. **Background:** Catamenial patterns are defined as increased seizure frequency during certain phases of the menstrual cycle (perimenstrual, peri-ovulatory, and/or luteal in anovulatory cycles). Animal studies suggest seizure improvement occurs with higher progesterone and allopregnanolone concentrations and lower estrogen concentrations. A prior study reported that FWE with catamenial patterns were more likely to have improved seizure frequency during pregnancy, presumably due to higher sensitivity to fluctuations in sex steroid hormones. **Design/Methods:** Females with epilepsy (FWE), ages 18-40yo, were enrolled in a longitudinal, prospective cohort study at time of attempting conception to compare fertility outcomes to healthy controls. We queried all FWE at enrollment if they had a history of **Perceived** catamenial patterns. Once enrolled, FWE used a daily diary customized app for menstrual and seizure tracking from preconception through delivery. For this secondary analysis, participants were excluded if they chose to discontinue the study, if they did not become pregnant, if their diary data was inadequate (defined as <80% of the days tracked), or if they had <1 month of seizure data tracked prior to conception. Prospective diary data was used to determine if participants met criteria for **Observed** catamenial patterns. Additional inclusion criteria for this subgroup included seizures in preconception phase. Seizure frequency during pregnancy was compared to preconception frequency for each participant. **Results:** Thirty-six of 89 enrolled FWE met inclusion criteria for the Perceived catamenial analysis; 25% reported catamenial patterns. Eleven FWE met inclusion criteria for the Observed catamenial analysis; three had Observed catamenial patterns. Seizure improvement or stability occurred in 44% in the Perceived, and in 33% in the Observed catamenial groups. However, in the non-catamenial groups, 96% and 75%, respectively, experienced seizure improvement/stability. The odds ratios for seizure improvement/stability with a Perceived catamenial pattern was 0.039 (CI 0.001-0.331,  $p=0.002$ ), and 0.209 (CI 0.005-3.84,  $p=0.303$ ) in the Observed group. Logistic regression on seizure improvement/

stability against presence of catamenial pattern gave coefficients as: -3.481 (CI -5.87 - -1.090,  $p<0.01$ ) for Perceived and -1.792 (CI -4.677-1.093,  $p>0.01$ ) for Observed groups. **Conclusions:** Statistical analysis indicates that the odds of observing seizure stability or improvement are better in women without catamenial patterns and contrary to prior reports. A more robust study with larger sample size is warranted to further validate results found in this study.

### M210. Association between Structural Brain MRI Abnormalities and Epilepsy in Older Adults

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**Objective:** To determine the association between structural brain MRI abnormalities and incident epilepsy in older adults. **Methods:** Men and women (ages 45-64 years,  $n = 15,792$ ) from the Atherosclerosis Risk in Communities (ARIC) cohort were followed up from 1987-1989 through 2018. We identified cases of late-onset epilepsy (LOE, starting at age 67 years or older) along with the date of first seizure from ARIC hospitalization records and Medicare claims data among 1,961 participants. Using 3T structural brain MRI scans (acquired in 2011-2013), we evaluated the relative pattern of grey matter abnormalities (i.e., cortical thinning and reduced subcortical volume) and white matter microstructural integrity among participants who developed LOE after MRI in comparison with participants without seizures. We examined the association between the number of abnormal brain regions and incident LOE using Cox proportional hazards regression. The number of abnormalities was dichotomized as either high or low based on median split. Models were adjusted for demographics, hypertension, diabetes, smoking, stroke, and dementia status. **Results:** Among 1,251 participants with non-missing brain MRI data, 27 (2.2%) developed LOE after MRI over a median of 6.4 years (25-75 percentile 5.8-6.9) of follow-up. Participants with incident LOE after MRI had considerably higher levels of cortical thinning and white matter microstructural abnormalities, present prior to seizure onset, when compared to those without seizures. In longitudinal analyses, a greater number of abnormalities was associated with incident LOE after controlling for demographic factors, risk factors for cardiovascular disease, stroke, and dementia (grey matter: hazard ratio [HR] 2.3, 95% confidence interval [CI] 1.0-5.0; white matter diffusivity: HR 3.2, 95% CI 1.3-7.7). **Conclusions:** This study demonstrates considerable grey and white matter pathology among individuals with LOE, which is present prior to the onset of seizures and provides

important insights into the role of neurodegeneration, both of grey and white matter, and the risk of LOE.

## M211. Disparities in Outcomes of 57310 People with Epilepsy Admitted for COVID-19 in the United States

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**Purpose:** The pathological burden of COVID-19 has significantly affected many neurological conditions, particularly epilepsy. Due to the paucity of nationwide data in the United States on people with epilepsy (PWE) who developed COVID-19, our study aims to uncover some common complications within this group compared to those without epilepsy. **Methods:** A group of COVID-19-positive patients, with and without a history of epilepsy, from the 2020 National Inpatient Sample between the months of April to December was surveyed. We compared the presence of potential complications during their hospitalization to patients without a diagnosis of epilepsy (control group) via multivariable regression analysis.

**Results:** A total of 57,310 patients with a diagnosis of epilepsy were admitted for COVID-19 treatment and management in the US between April and December 2020. This represented 3.5% of the total admission of all COVID-19 patients. The mean age of admissions was 62.18 years in 57,310 PWE (vs. 62.60 years in 1,570,800 controls/people without epilepsy,  $p < 0.001$ ). The mean length of stay was 9.32 days among PWE who developed COVID-19 when compared to those without a diagnosis of epilepsy (7.71 days,  $p < 0.001$ ). PWE were at increased risk of several in-hospital complications such as Aspiration Pneumonia (AP) (6.6% vs. 1.9%, aOR 2.794,  $p < 0.001$ ), Acute Ischemic Stroke (AIS) (2.2% vs. 1.4%, aOR 1.520,  $p < 0.001$ ), and Sepsis (29.8% vs. 23.9%, aOR 1.328,  $p < 0.001$ ). They appeared to report lower events of Acute Myocardial Infarction (AMI) (4.4% vs. 4.4%, aOR 0.954,  $p = 0.025$ ) and Pulmonary Embolism (PE) (2.3% vs. 2.8%, aOR 0.856,  $p < 0.001$ ). In addition, PWE were more likely to require mechanical ventilation (MV) (15.0% vs. 11.0%, aOR 1.570,  $p < 0.001$ ). No differences were seen for the use of non-invasive ventilation (6.0% vs. 6.4%, aOR 0.982,  $p = 0.321$ ). Furthermore, conditions such as Acute Kidney Injury (AKI) (29.1% vs. 27.9%, aOR 0.994,

$p = 0.578$ ) and Cardiogenic shock (0.6% vs. 0.6%, aOR 1.105,  $p = 0.066$ ) showed no difference. Unfortunately, more deaths (14.7% vs. 12.9%, aOR 1.083,  $p < 0.001$ ) were seen among PWE. **Conclusion:** PWE who were admitted for COVID-19 had reported more events of AP, AIS, and Sepsis. However, they were less likely to experience myocardial infarction and PE while hospitalized. The study revealed a higher use of MV in PWE but no differences were seen in the use of non-invasive ventilation. Though AKI and Cardiogenic shock did not show any statistical significance, death within PWE was significantly higher.

## M212. Effect of Vagus Nerve Stimulator (VNS) Signal Frequency on Vocal Cord Function: Case Report

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**Introduction:** The Vagal Nerve Stimulator (VNS) is an adjunctive treatment for drug resistant epilepsy (DRE) with minimal side effects<sup>1</sup>. Voice changes are a common side effect, occurring in about 62% of the cases and tending to improve with time or by decreasing frequency, pulse width and/or amplitude<sup>2</sup>. A small number of patients have serious complications, including vocal fold tension, supraglottic muscular hyperfunction, and reduced vocal fold mobility or paralysis<sup>3</sup>. Herein, we present a case that demonstrates a direct correlation of vocal cord side effects with various signal frequencies. **Case Description:** A 46-year-old male with DRE underwent VNS implantation. Patient tolerated the procedure well except for voice hoarseness. During the next 4 years, VNS was titrated to 1.75 mA output current, 20 Hz signal frequency and 250 usec pulse width at a 25% duty cycle with ongoing mild hoarseness. Further titration to an increase to 1.875 mA output current and a decrease to 10 Hz signal frequency along with a duty cycle increase to 29% resulted in significant worsening of voice side effects. At one week interval, the output current was reduced to 1.5mA and the pulse width to 130 usec, with reported ongoing voice tremor. At 6 months interval the frequency was further reduced to 5 Hz resulting in difficulties breathing and maintaining conversations which prompted further evaluation. A flexible laryngoscopy showed intermittent laryngeal spasm and tremor/myoclonus of epiglottis and larynx on the left that correlated with stimulation parameters of 5Hz and 25% duty cycle. Other parameters tested that resulted in vocal cord side effects were : at 20 Hz the vocal cord became tonic with improved breathing and voice and at 30Hz there was vocal cord spasm leading to discomfort. **Discussion:** This case demonstrates the relationship between vocal cord side effects and various signal frequencies. Signal frequency is a measure of total period cycles (the start of a pulse to the start of the next pulse) in a second. A commonly used signal frequency is 20 to 30Hz<sup>2</sup>. When there are associated vocal cord side effects, apart from the pulse width, most providers agree on decreasing frequency<sup>3</sup>. Our case report shows that lower frequencies may produce severe side effects when compared to

higher frequencies as confirmed directly on laryngoscopy. Larger studies are needed to study this relationship to determine an optimal range of frequencies.

### **M213. Exploring Interdisciplinary Cross-Talk and Gap of Knowledge for Catamenial Epilepsy in Puerto Rico**

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Catamenial Epilepsy (CE) is a type of epilepsy largely influenced by hormonal fluctuations during menstruation. In Puerto Rico, there is lack of data regarding prevalence and interdisciplinary treatment, especially concerning patients with female reproductive organs in reproductive age. Addressing the needs of women with epilepsy (WWE) is a reproductive rights concern, due to prevalent rates of infertility, congenital malformations, oral contraceptive anti-epileptic drug interaction, and sexual dysfunction in this population (Ahmed, et al, 2014). The management of CE commonly relies on neurology directed overview, however not much literature discusses neurological and gynecological crosstalk and how this may offer a well-rounded approach when treating patients. Throughout a series of surveys directed to the Neurology and Gynecology medical teams at University District Hospital in Puerto Rico we plan to assess the current status and interest in offering interdisciplinary care, as well as gaps in knowledge between both specialties. During the second phase of the study, we aim to gather patients' perspectives and interests in Neurology focused care vs interdisciplinary care for management of their condition. This data will offer insight into the needs of WWE and how an interdisciplinary approach may bring justice and equitable treatment to people with CE in Puerto Rico.

### **M214. Gelastic Seizures as a Presentation of NMDA Encephalitis**

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Gelastic seizures are seen in less than 1% of all epilepsies. Although gelastic seizures are usually described in children as a manifestation of hypothalamic hamartoma, other localizations, including frontal and temporal lobe foci, are more frequent among adult patients. 1N-methyl-D-aspartate (NMDA) receptor encephalitis was first recognized 15 years ago. It was initially described as a paraneoplastic disorder in young women with ovarian teratomas presenting with psychiatric or behavioral symptoms, making it difficult to differentiate it from a primary psychiatric disease.<sup>2</sup> We report a case of a 26-year female with no significant past medical history presented with a first-ever witnessed seizure. Her neurological assessment was concerning for unusual affect, with frequent laughter and inappropriate jocularity. Initial EEG was normal however later on long term monitoring the patient had behavior arrest, frequently with smiling or laughter.

Electrographically, each seizure arose as abrupt onset of sharply contoured theta activity, usually lasted less than one minute, with no post ictal attenuation. EEG also showed bimtemporal delta activity. MRI brain was negative and CSF routine studies showed normal cell count with no pleocytosis. CT scan of the chest/abdomen and pelvis was obtained which was negative however CSF was positive for anti-NMDA receptor antibodies and although the initial CT scan of the abdomen/pelvis did not reveal any abnormality, an MRI of the abdomen was obtained and revealed a left adnexal mass. Pathology confirmed the diagnosis of mature teratoma. During her hospitalization, she received plasmapheresis, steroid, and intravenous immunoglobulin, and finally two doses of Rituximab. The patient did not require admission to the intensive care unit and was discharged to inpatient rehabilitation with slow but remarkable improvement over few months. Seizures are a common presentation of anti-NMDAR encephalitis; approximately 70% of these patients develop seizures.<sup>3</sup> Generalized tonic-clonic seizures followed by focal seizures are the most common seizures seen in this condition. This case highlights the importance of clinical suspicion of seizures in adults with acute onset change in personality, especially when the initial EEG is normal. Although gelastic seizures are rare in adults, this case demonstrates that they do occur. Continuous EEG monitoring in such patients is crucial in clarifying the diagnosis.

### **M215. Health-Related Quality of Life in Transgender Individuals with Epilepsy**

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**Introduction:** Transgender individuals (TI) and people with epilepsy (PWE) face unique challenges that can impact their health and quality of life. Little is known about the intersection of these two populations, including the prevalence of epilepsy among TI, and their health-related quality of life (HRQoL). We sought to explore the relationship between transgender identity and HRQoL in PWE. **Methods:** We used data from the Behavioral Risk Factor Surveillance System (BRFSS), an annual population-based weighted survey conducted by the Centers for Disease Control (CDC), to identify factors affecting health outcomes. In 2017-2019, the BRFSS in Florida queried participants about sexual orientation, gender identity, HRQoL, and chronic conditions including epilepsy. HRQoL was measured using the Healthy Days Measure, which asked participants about number of recent days when physical and mental health was poor, and number of days with activity limitations due to poor health. We used negative binomial regression models to determine the association between demographics, epilepsy, and transgender identity on HRQoL indicators (physical health, mental health, limitations in usual activities). **Results:** 41,852 individuals were surveyed over the 3 years, representing

36 million people through weighted sampling. Of the weighted sample, 1.9% reported having epilepsy, and 0.6% identified as transgender. Among those with epilepsy, 1.8% identified as transgender ( $p=0.014$ ). Epilepsy was associated with poorer physical and mental health and limitations in usual activities, which remained significant after confounding adjustment. Transgender identity was associated with poorer mental health and limitations in usual activities in unadjusted analyses only. No significant interactions were found between epilepsy and transgender identity on indicators of HRQoL in unadjusted analyses. However, after adjusting for confounders, PWE who identified as transgender were more likely to report poorer physical and mental health and limitations in usual activities due to poor physical or mental health, compared to those who did not identify as transgender (Incidence rate ratio (95% CI): 2.69 (1.01, 7.11) for physical health). **Conclusions:** A notable proportion of PWE identify as transgender. Epilepsy is associated with poorer HRQoL, and TI with epilepsy experience greater impairments in physical and mental health and limitations in usual activities than do PWE who are not transgender. Increased attention and future research should be dedicated to this population to the potential social and medical challenges facing them.

#### **M216. How Well Can Machine Learning Predict Late Seizures after Intracerebral Hemorrhages? Evidence from Real-World Data**

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**Introduction:** One in 6 strokes are intracerebral hemorrhages, which carry a high risk of epilepsy or late seizures. Predicting epilepsy after intracerebral hemorrhage is central in planning treatments, allocating resources, and preparing post-stroke epilepsy clinical trials. Yet, existing risk models have limitations and have not taken advantage of readily available real-world data and artificial intelligence. This study aims to evaluate the performance of Machine-learning based models to predict post-stroke epilepsy in intracerebral hemorrhage survivors. **Design/Methods:** We identified patients with intracerebral hemorrhage (ICH) without a prior diagnosis of seizures from 2015 until inception (11/01/22) in the TriNetX Diamond Network, using the International Classification of Diseases, Tenth Revision (ICD-10) I61 (I61.0, I61.1, I61.2, I61.3, I61.4, I61.5, I61.6, I61.8, and I61.9). The outcome of interest was any ICD-10 diagnosis of seizures (G40/G41) at 1 year and 5 years following the index ischemic stroke event. We applied a conventional logistic regression and a Light Gradient Boosted Machine (LGBM) algorithm to predict the risk of seizures at 1 year and 5 years. The performance of the model was assessed using the area under the receiver operating characteristics (AUROC), the area under the precision-recall curve (AUPRC), the F1 statistic, model accuracy, balanced-accuracy, precision, and recall, with and without seizure medication use in the models. **Results:** A total of 210,771 patients with intracerebral

hemorrhage were identified, of whom 189,766 had no prior diagnosis of seizures, and 90,803 had no instance of ICD-9 codes in their EHR hence constituting our study cohort. Seizures were present in 4.57% and 6.27% of patients within 1 and 5 years after ICH, respectively. At 1-year, the AUROC, AUPRC, F1 statistic, accuracy, balanced-accuracy, precision, and recall were respectively 0.7051 (standard error: 0.0132), 0.1143 (0.0068), 0.1479 (0.0055), 0.6708 (0.0076), 0.6491 (0.0114), 0.0839 (0.0032), and 0.6253 (0.0216). Corresponding metrics at 5 years were 0.694 (0.009), 0.1431 (0.0039), 0.1859 (0.0064), 0.6603 (0.0059), 0.6408 (0.0119), 0.1094 (0.0037) and 0.6186 (0.0264). **Conclusion:** Machine learning-based models show moderate-to-good performance for predicting seizures after intracerebral hemorrhage. The model will need to be externally validated and updated by accounting for biomarkers of brain health.

#### **M217. Human Cerebral Organoids with PIDD1 Mutations Implicate AKT-mTOR Pathway Hypoactivity in Lissencephaly**

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**Background:** Lissencephaly is a congenital malformation of cortical development associated with epilepsy and intellectual disability. It is characterized by decreased neocortical folding, grey matter thickening, and abnormal cortical lamination, but the underlying molecular mechanism is unknown. Prior studies of lissencephaly have identified defective neuronal migration phenotypes without further molecular resolution. Mutations in *PIDD1* (*P53-Induced Death Domain Protein 1*) are associated with lissencephaly but its role in cortical development is unclear. **Objective:** We used human induced pluripotent stem cell (iPSC)-derived cerebral organoids, which are three-dimensional in vitro cultures of early cortical development, to investigate the cellular and molecular events underlying PIDD1-mediated pathogenesis of lissencephaly. **Methods:** We identified recessive *PIDD1* stop-gain mutations in families with lissencephaly using whole-exome sequencing and generated iPSCs from a single patient. To demonstrate genotype-phenotype causality, we used genome editing to correct both mutant alleles to wild-type, obtaining an isogenic patient-rescue line. We also introduced the mutation to control iPSCs to generate a homozygous knock-in line. We then differentiated iPSCs into cerebral organoids, which we characterized by immunostaining, single-cell RNA sequencing, and mass spectrometry. **Results:** At 70 days of differentiation, immunostaining revealed a ~16 and ~15% increase ( $p<0.0001$ ) in relative thickness of the cortical plate-like area, respectively in patient, knock-in versus control organoids. At 120 days, deep- and upper-layer neurons in the cortical plate were abnormally positioned in patient, knock-in versus control, patient-rescue organoids. Surprisingly, single-cell RNA sequencing and mass spectrometry analyses at 70 days revealed dysregulation of protein translation and metabolism, and downregulation of the AKT-mTOR

pathway in patient, knock-in versus control, patient-rescue organoids. AKT-mTOR pathway hypoactivity was validated by the ~63 ( $p < 0.001$ ) and ~60% ( $p < 0.01$ ) reduction in phosphorylated S6 immunoreactivity and decreased expression of several core pathway proteins in patient, knock-in versus control organoids. Underscoring translational significance, application of the mTORC1 activator NV-5138 (currently in clinical trials for treatment of depression) prevented cortical plate thickening in 70-day patient and knock-in organoids. **Conclusions:** This study in cerebral organoids demonstrates that 1) disruption of PIDD1 function recapitulates the thickened and abnormally laminated cortical plate phenotype seen in lissencephaly; 2) PIDD1 may play a role in AKT-mTOR-mediated protein homeostasis during cortical development; and 3) a mTORC1-activating drug compound could be considered for fetal therapy to prevent lissencephaly. Our study implicates AKT-mTOR hypoactivity as a novel molecular mechanism of lissencephaly, warranting further investigation in other genetic lissencephaly models.

#### **M218. Increased Degradation of FMRP Contributes to Neuronal Hyperexcitability in Tuberous Sclerosis Complex**

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Autism spectrum disorder (ASD) is a highly prevalent neurodevelopmental disorder but progress in the development of therapies has been impeded by a lack of understanding of the pathological mechanisms. Several highly penetrant, single gene disorders associated with ASD have provided important insights into key pathways underlying brain development and behavior. Tuberous sclerosis complex (TSC) and Fragile X Syndrome are two key examples that are associated with abnormalities in the function of the mechanistic target of rapamycin (mTOR) and Fragile X Messenger Ribonucleoprotein 1 (FMRP), respectively, both of which have been implicated in the development of ASD. Previously, we observed that transcripts associated with FMRP were down-regulated in TSC2-deficient neurons. In this study, we found that FMRP turnover was dysregulated in TSC2-deficient rodent primary neurons, and this was associated with increased ubiquitination and reduced phosphorylation of FMRP. Moreover, increased degradation of FMRP was dependent on the presence of a recognition motif in FMRP for the E3 ubiquitin ligase, the Anaphase Promoting Complex. We then used neurons derived from induced pluripotent stem cells (iPSCs) from patients with TSC, as well as isogenic corrected and second hit cell lines. We also observed increased FMRP degradation in human neurons, which was abrogated by mutation in the ubiquitination recognition site of FMRP. Finally, we used extracellular recordings of TSC2-deficient iPSC-derived neurons to show that over-expression of FMRP is sufficient to partially rescue hyperexcitability in these cells. Taken together, we have demonstrated how FMRP is dysregulated in TSC2-deficient neurons and that this represents an

important pathological mechanism in the development of abnormal neuronal activity in TSC. These data illustrate a molecular convergence between these two neurogenetic disorders and contribute to unraveling the pathogenesis of neurological symptoms in neurodevelopmental disorders.

#### **M219. Knowledge Translation of the Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) Study: A Survey of Healthcare Providers (HCPs) and Reproductive-Aged People with Epilepsy (RPWE)**

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**Objective:** To understand how HCPs and PWEGC perceive findings of the MONEAD study, and how they would like findings disseminated. **Methods:** A market research firm conducted surveys of: 1) HCPs serving people with epilepsy including primary care providers, obstetrician-gynecologists, and neurologists, and 2) RPWE ages 18-45 years old currently taking an antiseizure medication (ASM). Participants were recruited from nationally representative panels. Survey questions were informed by content experts and prior qualitative research with HCPs and RPWE. We summarized results using descriptive statistics. **Results:** 401 healthcare providers and 199 RPWE completed the survey. Sixty-six percent of HCP respondents ( $n = 265/401$ ) reported that findings from the MONEAD study were new to them, and sixty-five percent ( $n = 261/401$ ) reported that the findings seemed plausible. Findings most commonly selected as most important by HCPs included: 1) pre-pregnancy seizure frequency may be maintained during pregnancy (45%,  $n = 180/401$ ), 2) neurodevelopment at age 2-3 years old may be similar for children exposed and not exposed *in utero* to ASMs (35%,  $n = 143/401$ ), 3) safety of breastfeeding with some ASMs (34%,  $n = 138/401$ ). Forty-nine percent ( $n = 197/401$ ) reported that findings would definitely or probably change their management of pregnancy for RPWE. Preferred resources for sharing findings included online CME materials (54%,  $n = 216/401$ ), medical conferences (52%,  $n = 207/401$ ), and guidelines from professional societies (50%,  $n = 201$ ). Ninety-one percent of RPWE ( $n = 181/199$ ) reported that findings from the MONEAD study were new to them. Findings most commonly selected as important by RPWE included: 1) ability to maintain pre-pregnancy seizure frequency during pregnancy (27%,  $n = 54/199$ ), 2) ability to give birth to healthy babies (23%,  $n = 46/199$ ), and 3) safety of breastfeeding with some ASMs (23%,  $n = 46/199$ ). Sixty-four percent ( $n = 128/199$ ) of RPWE respondents reported that findings would influence their reproductive decision-making. RPWE reported that findings should be communicated to RPWE by neurologists (62%,  $n = 123/199$ ), obstetrician-gynecologists (58%,  $n = 115/199$ ), and primary

care physicians (41%, n=82/199). Preferred resources for sharing findings included general health websites (54%, n=107/199), epilepsy-specific websites (52%, n=104), and pamphlets (43%, n=85). **Conclusion:** Next steps for the MONEAD study include implementing and translating key study findings into clinical practice. Perspectives from HCPs and RPWE about study findings they consider most impactful and preferred means of dissemination will inform endeavors in patient education, professional training, and health systems interventions. **Funding:** One8 Foundation, NIH-NINDS U01-NS038455

### M221. Over the Counter (OTC) Supplements May Exacerbate Pre-Existing Neurological Abnormalities and Incite Neurological Episodes

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Though rarely reported, over the counter (OTC) supplements may potentially exacerbate underlying medical conditions without realization. One such supplement is silk protein hydrolysate, which has been shown to improve both short-term memory and executive function. Through reduction of pro-oxidant and pro-inflammatory mediators, it enhances acetylcholine levels in the brain, which is known to play a role in cognition. Here we report a case of recurrent aphasic seizures in a patient after OTC supplement containing silk protein hydrolysate. Currently there are no reported adverse effects of using this supplement and as such these seizures would likely be unrecognized in select groups. A 67 year-old female with a history of breast cancer, hypertension, and “neurological abnormalities” presented from home with aphasia. Approximately one year prior, the patient had a similar aphasic episode lasting for 30 minutes that was followed by a loss of consciousness. Prior to the first episode, the patient started taking an OTC supplement to improve memory function for three weeks. Subsequently, she developed aphasia and discontinued the supplement. She was treated with anti-seizure medication for six months and then tapered off due to an inconclusive neurological workup. However, she recently restarted the same supplement and developed the same symptoms. During the first admission, an Magnetic resonance imaging (MRI) brain showed an abnormality in the left hippocampus, suggestive of a possible low-grade glioma that was unchanged in repeat imaging one year after. Upon discharge during the second admission, the patient was instructed to discontinue the supplements due to unknown side effects or toxicity. This case suggests patients with preexisting neurological structural abnormalities may be at increased risk for developing neurological disorders when taking certain OTC supplements. Currently, the FDA does not require extensive clinical testing for natural vitamin supplements and has poor post-market surveillance for adverse events. With growing knowledge of silk protein hydrolysates health benefits, increased use without medical supervision may unmask underlying neurological abnormalities. Thus, we suggest caution in using such OTC supplements and recommend seeking medical attention if symptoms develop. Furthermore, physicians should be more aware of the need to

know whether their patients are taking OTC supplements. Just because the product is marketed as having “no known side effects” does not mean the potential for causing side effects is not there.

### M222. Peripheral T Cell Clonal Expansion as a Proxy for Intractable Epilepsy and Brain Atrophy

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**Introduction:** A degree of inflammatory reaction and adaptive immune response is identified in epileptic tissue specimen. However, it is not practical to assess the extent of adaptive immunity in patients with epilepsy through brain tissue. The T cell receptor (TCR) is located on the surface of T cells and recognize peptide antigens bound to major histocompatibility complex, responsible for adaptive immune response. Previous studies have demonstrated the changes in TCR repertoire in several autoimmune diseases including autoimmune neurologic disorders such as multiple sclerosis, Rasmussen encephalitis. We investigated whether TCR repertoire in circulating T cells reflect epilepsy associated inflammatory activity. **Methods:** Patients with intractable epilepsy, autoimmune encephalitis, and control are enrolled. T cell receptor (TCR) beta-chain repertoire were analyzed from peripheral blood mononuclear cells. Patients' demographic and clinical characteristics were collected, and volumetric analysis of magnetic resonance imaging was also performed. **Results:** A total of 36 subjects were enrolled in this study. Patients with intractable epilepsy (n=16) showed increased clonality compared to control population (n=7) and the degree was lesser than patient with autoimmune encephalitis (n=13) (Kruskal-Wallis p = 0.001). Seizure frequency in the patients significantly correlated with TCR repertoire clonality (R = 0.53, p=0.043). Normalized percentile of asymmetric index of temporal lobe showed higher correlation with TCR repertoire clonality (R = 0.68, p = 0.0081). **Discussion:** Clonally expanded T cells are more abundant in patients with intractable epilepsy than control population. Clonality also reflect seizure frequency and degree of brain atrophy which implicate that TCR repertoire can measure severity of epilepsy. Our study showed ongoing adaptive immune process in epilepsy and epileptic activity may be quantifiable using circulating TCR repertoire. There are many unanswered questions regarding TCR repertoire awaiting more in-depth studies and shortage of the studies in neurologic disorders necessitate future investigations.

### M223. Predicting Serum Concentration of Lacosamide: Effects of CYP2C19 Genetic Polymorphisms and Possible Correlation with Saliva Concentration

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**Background:** Lacosamide (LCM) is a third-generation anti-seizure medication and is one of the sodium channel blockers. Previous studies have confirmed that LCM has a dose-dependent serum concentration, and also demonstrated that it has serum concentration-dependent efficacy and toxicity. In this study, we will introduce the methodology for the study of predictive markers of LCM blood concentration and share some of the results to date. **Methods:** The study was divided into two parts. In part 1, the blood samples were obtained from 115 adult patients with epilepsy who was taking LCM for more than 1 month with unchanged doses. The obtained blood sample was used to analyze the serum LCM concentration, the concentration/dose (C/D) ratio and the single nucleotide polymorphisms (SNPs) of the cytochrome P450 (CYP) 2C9 and CYP2C19 genes. In part 2, we recruited additional patients and measured blood LCM concentrations and salivary LCM concentrations in a total of 128 LCM-treated epilepsy patients, and, as in part 1, we analyzed CYP2C19 polymorphisms to look for associations with blood drug concentrations. **Results:** In part 1 analysis, serum concentration of LCM was affected by genetic polymorphisms of CYP2C19 gene. In genetic analysis, 43 patients (38.7%) were extensive metabolizers (EMs), 51 (45.9%) were intermediate metabolizers (IMs), and 17 (15.3%) were poor metabolizers (PMs). The C/D ratios of IM (27.78 and PM (35.6) were 13% and 39% higher than those of EM (25.58), respectively. In the multivariate logistic regression analysis, serum concentration was a good predictive factor for both effective seizure outcome (odds ratio [OR] = 1.31,  $p = .013$ ) and adverse events (OR = 1.36,  $p < .001$ ), respectively. We are currently in the process of conducting Part 2 of the analysis, which involves the analysis of drug concentration in blood and saliva. So far, a total of 128 blood and saliva samples have been collected. We plan to analyze the concentration relationship between the two and further investigate the effects of CYP2C19 polymorphism to expand upon the findings from Part 1 of the study. **Conclusion:** We found a close relationship between the blood levels of LCM, the drug's anticonvulsant efficacy, and the occurrence of adverse events. Thus, maintaining stable blood levels is crucial for personalized treatment. The effect of CYP2C19 polymorphism on LCM concentration was confirmed in Part 1, and further analysis will be conducted to determine whether saliva samples can predict blood levels.

#### M224. Somatic Variants Activating Ras-MAPK Signaling Cause a Spectrum of Focal Lesions Associated with Mesial Temporal Lobe Epilepsy

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Mesial temporal lobe epilepsy (MTLE) is the most common focal epilepsy subtype and often refractory to anti-seizure medications. Although it has long been known that seizures in MTLE originate in the hippocampus, the cause of this unique predisposition is unknown. Recently, post-zygotic (i.e., somatic) variants, which are well-known causes of neoplasms, have emerged as a major cause of pediatric focal epilepsies associated with focal cortical dysplasia (FCD). Interestingly, mesial temporal sclerosis (MTS) which is the major histopathologic finding in MTLE may co-occur with FCD or low-grade epilepsy-associated tumors (LEATs), suggesting a possible causal role for somatic variants in MTLE. To test whether somatic variants in the hippocampus contribute to MTLE pathogenesis, we performed high-coverage whole-exome sequencing (WES, depth >500X) of hippocampus-derived DNA from 104 surgically-treated patients with MTLE and 30 neurotypical donors. We detected 9 pathogenic somatic variants activating Ras-MAPK signaling in patients with MTLE and none in the controls. All variant-positive patients were seizure-free >2 years after surgery with significantly increased likelihood of Engel class IA outcome. Given the limited sensitivity of WES, to determine the true burden of Ras-MAPK variants in the hippocampus in MTLE relative to the neurotypical donors, we designed a gene-panel and performed duplex sequencing (depth >1000X) on the same samples. We detected pathogenic somatic Ras-MAPK variants in 28.8% of MTLE hippocampi and none of the neurotypical controls ( $p < 0.001$ ). We also observed a correlation between variant allele frequency and the size and regional distribution of the lesion, such that low abundance variants were associated with MTS alone whereas high abundance variants also caused an FCD or a LEAT. Since *PTPN11* had the highest number of recurrent variants, we performed molecular assays to investigate the mechanisms of some of these variants. All the tested *PTPN11* variants increased Erk1/2 phosphorylation indicating increased Ras-MAPK signaling, but the *PTPN11* variants associated with LEATs demonstrated the

greatest degree of pathway overactivation. Additionally, Shp2 (protein encoded by *PTPN11*) variants overexpressed in HEK293T cells demonstrated increased liquid-liquid phase separation behavior, which provides a possible dominant gain-of-function mechanism through which these variants cause pathway overactivation. Overall, our findings strongly suggest that somatic Ras-MAPK variants give rise to a spectrum of temporal lobe lesions depending on the developmental time point at which they were acquired and their specific molecular mechanisms, but all are associated with drug-resistant MTLE.

### M225. Synaptic Changes in a Distinct Population of Hippocampal Neurons Activated by Early Life Seizures

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**Background:** Immature brains are more vulnerable to seizures and status epilepticus, leading to long-lasting cognitive deficits and intellectual disability. Seizures activate subpopulations of neurons but the characteristics of seizure-activated neurons are poorly understood. Identifying the synaptic reorganization and intrinsic properties of these neurons is essential for understanding the long-lasting abnormalities associated with early-life seizures (ELS). **Methods:** Using activity-dependent genetic labeling (TRAP, which relies upon the detection of Cre-induced permanent tdTomato (tdT) expression, driven by the immediate early gene *Fos*, a widely used marker of activated neurons), we identified and characterized a specific group of hippocampal CA1 neurons activated by ELS. **Results:** Tonic-clonic seizures were induced in Fos-TRAP mice by intraperitoneal injection of the chemoconvulsant kainate at postnatal day 10 (P10). At P14 and P30, a subset of CA1 pyramidal neurons were labelled as tdT+ and represented the previously ELS-activated neurons. Whole-cell patch clamp recording of these tdT+ neurons revealed persistently increased postsynaptic AMPAR-mediated excitatory inputs compared to surrounding non-TRAP'ed tdT- neurons. These neurons also had increased GluA2-lacking, calcium-permeable AMPARs (CP-AMPA) (rectification index, RI=3.58) compared to the surrounding tdT- neurons (RI=1.84) from the ELS mice, or compared to tdT- neurons from saline treated mice (RI=1.64,  $p < 0.05$ , one-way ANOVA). ELS-activated neurons showed premature diminishment of NMDAR-only silent synapses at P15 (tdT+ 25.5%, tdT- 63.8%, and saline 73.8%) but the percent with silent synapse was comparable among groups at P30. Furthermore, long-term potentiation (LTP) and long-term depression (LTD) were impaired specifically in tdT+ neurons at P30 (LTP: Kruskal-Willis ANOVA,  $p < 0.05$ ; LTD: one-way ANOVA,  $p < 0.001$ ). Given these ELS-induced changes at the AMPAR, we tested the efficacy of *in vivo* pharmacology with a selective CP-AMPA blocker administered for 48 hours after ELS, and this reversed the inward rectification in the tdT+ neurons (RI, IEM: 1.31 vs saline 2.34,  $p < 0.01$ , unpaired t-test). This treatment also resulted in a rescue of synaptic plasticity in tdT+

neurons, with restored LTP (one-way ANOVA,  $p < 0.01$ ) and LTD (one-way ANOVA,  $p < 0.01$ ) compared to tdT+ neurons from untreated ELS mice. **Conclusion:** Our findings suggest that seizure-induced alterations in AMPAR plasticity in specific neuronal populations contribute to later life seizure susceptibility and behavioral abnormalities, and that these changes can be prevented by early post-seizure treatment with antagonists of GluA2 lacking CP-AMPA.

### M226. The Effect of Anti-Seizure Medications on Lipid Values in Adults with Epilepsy

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**Rationale:** Some anti-seizure medications (ASMs) are known to induce liver enzymes and impact lipid values including total cholesterol (TC), low density lipoprotein cholesterol (LDL), high density lipoprotein cholesterol (HDL), and triglyceride (TG). Here, we explored the impact of enzyme inducing ASMs (EIASM) on lipid values in adults with epilepsy. **Methods:** A total of 228 adults with epilepsy were divided into four groups based on the ASMs they were taking: strong EIASMs, weak EIASMs, non EIASMs, and those on no ASMs. Demographic information (including gender, age, race, weight, physical activity level, history of smoking, hyperlipidemia, and diabetes mellitus), epilepsy-specific clinical history (including epilepsy type (generalized, focal or unknown) and number of ASMs (at presentation and previously tried), and lipid values (fasting serum levels of TC, LDL, HDL, and TG) were obtained through retrospective chart review. **Results:** There were no statistically significant differences in lipid values between each ASM group. However, there was a significant difference between ASM groups in the frequency of participants with dyslipidemia. There was a significant difference in the frequency of patients with high cholesterol level (TC > 200) among the four ASM groups ( $\chi^2(3) = 9.418$ ,  $p = 0.024$ ). Specifically, the frequency of study participants with elevated cholesterol was higher in the strong EIASM group compared to the non EIASM group (53.3% vs 28.1%,  $p < 0.05$ ). There was also a significant difference in the frequency of patients with high LDL level (LDL > 130) among the four ASM groups ( $\chi^2(3) = 14.980$ ,  $p = 0.002$ ). Specifically, the frequency of study participants with elevated LDL levels was higher in the strong EIASM group compared to the non EIASM group (46.7% vs 18%,  $p < 0.05$ ). Similarly, the frequency of study participants with elevated LDL levels was higher in the weak EIASM group compared to the non EIASM group (38% vs 18%,  $p < 0.05$ ). There were no other statistically significant differences in frequency of high TC, high LDL, high TG, or low HDL levels between ASM groups. **Conclusions:** Although we did not find statistically significant differences between ASM groups for absolute lipid values, we did find a difference in the proportion of participants with clinically defined abnormal lipid values between ASM groups. Thus, adults with epilepsy using strong and weak EIASMs should have careful monitoring of lipid values.



## M227. The Effect of Deep Brain Stimulation (DBS) on Cognitive, Psychiatric and Quality of Life Outcomes in Drug-Resistant Epilepsy

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**Objective:** The impact of deep brain stimulation (DBS) on neuropsychiatric and psychosocial outcomes has not been extensively evaluated outside of the original clinical trials and post-approval studies. The goal of this study was to ascertain potential real-world effects of DBS on cognitive, psychiatric, and quality of life (QOL) outcomes in relation to seizure outcomes by examining 44 patients undergoing DBS implantation for drug-resistant epilepsy (DRE). **Methods:** We performed a retrospective review of consecutive patients treated at our institution with DBS for DRE with at least 12 months of follow-up. In addition to baseline demographic and disease-related characteristics, we collected cognitive (Full-Scale Intelligence Quotient, Verbal Comprehension and Perceptual Reasoning Index), psychiatric (Beck Depression and Anxiety Inventory Scores), and QOL (QOLIE-31) outcomes at 6 and 12 months after DBS implantation and correlated them with seizure outcomes. **Results:** Forty-four patients (median age 36 years, 52% female) were implanted with bilateral thalamic DBS electrodes (82% including the anterior nucleus, 18% in the centromedian nucleus) for DRE in our institution from 2018 to 2022. From the 41 patients with available pre- and post-implantation seizure counts, the 6-month and one-year median seizure frequency reduction were 63% and 65% respectively, the response rate (50% or greater seizure frequency reduction) at one year was 70%, and 7% of patients were free of disabling seizures in this timeframe, irrespective of their thalamic target. From the 10 patients with complete pre- and post-implantation neuropsychological data and despite individual variability, there was no significant difference at a group level in any of the evaluated cognitive, psychiatric, and QOL outcomes at 12 months post-implantation compared to the pre-implantation baseline, irrespective of seizure outcomes and thalamic target. **Significance:** Within the confines of a small sample size, our single center study provides real world data that DBS is efficacious for seizure frequency reduction in DRE and it does not appear to have a statistically significant negative or positive impact on the neuropsychiatric and psychosocial outcomes. Given individual variability in clinical characteristics, careful patient selection and outcome monitoring is required.

## M228. The Ketogenic Diet in DEPDC5-Related Epilepsies: Clinical and Preclinical Observations

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**Introduction:** DEP domain-containing protein 5 (DEPDC5) pathogenic loss-of-function variants in humans are the most common genetic cause of familial focal epilepsy [1]. Many cases of DEPDC5-related epilepsy are medically refractory [2]. DEPDC5 is a negative regulator of nutrient signaling through mTOR [2]. Previous studies suggest caloric restriction reduces seizures through DEPDC5 signaling mechanisms [3]. *Depdc5*-knockout mouse models experience seizures and increased neuronal mTOR activity unresponsive to amino acid withdrawal [4-7]. The ketogenic diet (KD) is a common therapy for drug-resistant epilepsy [8]. KD has been shown to reduce mTOR and seizure activity across several rodent models [9-17]. It is unclear if KD would reduce seizures in patients with or preclinical models of DEPDC5-related epilepsy. **Methods:** A cohort of DEPDC5-related epilepsy patients were identified from the epilepsy genetics clinic. Clinical demographics and outcomes to medications, surgery, and dietary therapies for epilepsy were collected. To test the ketogenic diet in a preclinical model of DEPDC5-related epilepsy, we used mice with a functionally homozygous loss of *Depdc5* in the brain [7]. *Depdc5* knockout mice and littermate control mice were randomly assigned at wean (postnatal day 21) to start KD (90.5% kcal from fat; Envigo TD96355) or a control diet (5.1% kcal from fat; Envigo TD.00606). Diet tolerance was assessed by weekly weights and monthly blood ketones and glucose levels. **Results:** Eighteen DEPDC5-related epilepsy patients were identified of which 17% (n=3/18) tried the KD. KD was ineffective in all three cases, due to excessive acidosis at initiation (n=2/3) or no impact on seizures (n=1/3). KD *Depdc5* knockout mice (n=13) had greater ketone levels at 4 weeks than KD littermate controls (n=22) ( $p=0.008$ ). Interestingly, *Depdc5* knockout mice experienced unanticipated adverse side effects when on KD, either rapidly losing weight and dying within one week of diet assignment (n=5/26,  $\chi^2 = 8.966$ ;  $p=0.0297$ ) or experiencing severe dermatitis, requiring sacrifice (n=17/26). **Conclusions:** In our limited study of KD in a retrospective clinical and preclinical context of DEPDC5-related epilepsies, KD had little impact on seizures and unanticipated adverse effects. This finding warrants validation of these results in a larger patient sample size as well as identifying the cause of excessive ketosis in patients and preclinical models of DEPDC5-related epilepsy.

## M229. Therapeutic Range of Topiramate: A Lower Dose of Topiramate is Enough for an Anti-Seizure Effect

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Republic of, <sup>3</sup>Department of Genomic Medicine, Seoul National University Hospital, Seoul, Korea, Republic of.

**Introduction:** Topiramate is an anti-seizure medication (ASM) prescribed frequently in epilepsy. ILAE suggested a serum level of 5-20 mg/L and a prescription of 200-400 mg dose for topiramate, but previous research showed contradictory results on whether the serum level of topiramate is associated with anti-seizure efficacy. Also clinicians frequently encounter patients with low serum concentration showing perfect seizure control. We aimed to evaluate a therapeutic range of topiramate that fits better in the real world. **Method:** We reviewed data of the patients with epilepsy who visited outpatient clinic and had done topiramate therapeutic drug monitoring (TDM) between January 2017 to January 2022 at Seoul National University Hospital. Clinical data were collected including topiramate serum level, ASM regimens, seizure frequency and adverse events. ASM responses were categorized as follows : no change of seizure frequency as 'no-response', tolerable seizure frequency not requiring ASM regimen change as 'partial-response' and no seizure events in between two consecutive visits as 'good-response'. **Results:** Total 396 epilepsy patients with 565 TDM results were reviewed. The mean daily dose of topiramate was  $176.8 \pm 117.7$  mg/day, and the serum level  $3.9 \pm 2.8$  mg/L. 78 TDM tests were done using topiramate alone, while 487 tests were done under polypharmacy with  $2.9 \pm 1.1$  ASMs. The mean serum levels were  $3.3 \pm 2.5$  mg/L for the no-response group (n=33),  $4.2 \pm 2.8$  mg/L for the partial-response group (n=206), and  $3.7 \pm 2.8$  mg/L for the good-response group (n=326) showing no statistically significant difference. We analyzed the anti-seizure efficacy of topiramate as monotherapy with three response groups : no response (n=1), partial response (n=15) and good response (n=62). The good-response group had a significantly lower dose (148 vs 113 mg, p-value=0.02) and serum level (4.7 vs 3.3 mg/L, p-value=0.003) compared to the partial-response group. It was also noted that 6 out of 13 patients in the partial-response group became drug resistant while in the good-response group it was 2 out of 41. Topiramate serum levels of patients under polypharmacy also did not prove dose-dependent efficacy but showed a similar pattern having lower dose and serum levels in the good-response group compared to the partial-response group. Only one side effect, ataxia, showed dependency with serum level. Topiramate serum level of  $>10$  ug/ml showed a markedly increasing probability to have ataxia. **Conclusion:** For patients whose seizures are well controlled with topiramate monotherapy, serum level of 3.3 mg/L may suffice. Topiramate serum level above 10 mg/L increases risk of ataxia without incremental benefit of seizure control.

### M230. Vagal Nerve Stimulator Induced Artifact on Electroencephalogram

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**Introduction:** Electroencephalogram (EEG) artifacts are potentials that do not conform to an expected electrical field generated by the brain. Artifacts can be physiological, arising

from the eyes, heart and muscles. Extraphysiological artifacts can originate from EEG equipment and electrical devices both internal and external to the body, including neurostimulator devices used for epilepsy. The electrical signal generated by the devices' internal electronic circuitry is detected by the EEG electrodes that serve as antennas. In the published literature, it is described that Vagus Nerve Stimulators (VNS) generate either diffuse, high amplitude, sharply contoured waveforms that occur periodically lasting through the "on" phase of the VNS or "spiky" morphology with a distribution that is incompatible with a cerebral source. We describe a unique EEG artifact and to our knowledge, this is the first documented report of VNS causing a bitemporal rhythmic discharge corresponding to the "on" time of stimulation. **Methods:** We describe a single case report of scalp EEG artifact correlating to the "on-time" stimulation from VNS. **Results:** A 27-year-old female with cerebral palsy, cognitive impairment, and refractory focal epilepsy status post VNS placement is detected to have a prominent EEG abnormality in the bitemporal regions without apparent clinical change during continuous video EEG monitoring. The finding was noted to correspond to the VNS "on" time. The VNS (Aspire SR Model 106) settings were output current 2.50 mA, signal frequency 20 Hz, pulse width 250, signal on-time 60 seconds, signal off-time 1.8 minutes. Magnet current 3 mA, pulse width 250, signal on-time 60 sec. Auto-stimulation settings were output current 2.75 mA, pulse width 250, signal on-time 30 seconds. Tachycardia detection threshold was 20%. Scalp EEG revealed near continuous sharply contoured medium voltage rhythmic 17-18 Hz discharge in the bitemporal electrodes without evolution. This high frequency activity lasted 60 seconds corresponding to the "on" time of the VNS. The time between the artifact lasted 1 minute and 48 seconds corresponding to the "off" time. Knowledge of the parameter settings with correlation to the "on" time of the VNS led to the identification of the VNS as the source of the artifact, rather than abnormal cortical activity in this case. **Conclusion:** It is essential to recognize and differentiate non-cerebral waveforms to prevent misinterpretation of EEG. It is important for electroencephalographers to be aware of this artifact and future work aimed at validating our report is needed.

### K-M105. An Unsupervised Learning Approach for Discovering Pathological High-Frequency Oscillations

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**Rationale:** Interictal high-frequency oscillations (HFOs) are considered one of the promising neurophysiological biomarkers of the epileptogenic zone. However, distinguishing pathological HFOs from physiological ones presents a significant challenge, yet it's crucial for their clinical application. We hypothesize that the distinctive morphological features of

pathological HFOs can be discerned from physiological HFOs using an unsupervised learning approach, negating the need for pre-assigned training labels. **Methods:** We used chronic intracranial electroencephalogram (iEEG) data through subdural grids from 18 pediatric patients with medication-resistant neocortical epilepsy. After identifying 92,860 HFOs using an automated detector, each HFO event's EEG time-series data was transformed into time-frequency analysis imaging data. This data served as the input for the deep learning model, specifically a variational autoencoder (VAE). During training, the model was tasked with reconstructing the input time-frequency plot, ensuring the latent space followed a Gaussian distribution. This unsupervised approach didn't require labels indicating whether an event was pathological. Post-training, the HFO events' latent codes, stratified from all training patients, were clustered by the Gaussian Mixture Model (GMM) with  $K = 2$ . The cluster with a higher association with resection in post-surgical seizure-free patients was deemed pathological. The GMM model was then used to assign predictions, pathological or physiological, on all HFOs' latent codes from test set patients. **Results:** The effectiveness of our unsupervised method was gauged through a patient-wise 5-fold cross-validation. We projected randomly selected HFOs' latent codes into a two-dimensional (2D) space, comparing the pathological predictions from the VAE model with HFO-with-spike. Our analysis reveals that the pathological prediction from the VAE closely aligns with HFO-with-spike. Moreover, pathological HFOs, as predicted by our VAE model, established a pattern in the time-frequency plot. This pattern closely resembled the structure of an inverted T-shaped template, exhibiting characteristics akin to the ones we identified in our prior research. Using the resection ratio of pathological HFOs, as predicted by the VAE model, to forecast postoperative seizure outcomes resulted in an AUC of 0.91 ( $p < 0.001$ ), signifying an improvement compared to the AUC of 0.82 ( $p < 0.001$ ) obtained using the resection ratio of unclassified HFOs. Additionally, the VAE model outperformed the AUC of 0.89 ( $p < 0.001$ ) achieved using the resection ratio of HFOs with spikes. **Conclusions:** We have demonstrated the ability to classify pathological HFOs using unsupervised machine learning with VAE, eliminating the need for any labeling. This approach could significantly enhance the clinical utility of pathological HFOs, particularly in delineating the epileptogenic zone during epilepsy surgery.

**K-M106. Characterizing Sleep Architecture and Its Effects on Cognition in New-Onset Temporal Lobe Epilepsy**  
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Temporal Lobe Epilepsy (TLE) is characterized by disordered neural network activity and temporal lobe seizures. As many as 3 million individuals with TLE in the United States also experience cognitive and sleep problems, resulting in poor school performance in childhood, with high risk of underemployment in adulthood, and consequent lower socioeconomic status. Individuals with TLE frequently experience sleep

fragmentation, which disrupts memory consolidation and sustained attention, both of which are impaired in this disorder. While these comorbidities can be long-term consequences of repeated seizures and medications, it is now known that they also often present prior to the first recognized seizure and worsen over time even with successful seizure treatment. This suggests that an early neural network abnormality may underlie seizure development while simultaneously impairing sleep and cognitive development, even prior to the added effects of disorder chronicity. In spite of this, there has been limited research addressing mechanisms underlying these sleep and cognitive problems in TLE. This represents a critical unmet public health need and both the **National Academy of Medicine** and **NINDS** have identified this notable gap as a research priority. I will begin to address this gap with by investigating abnormal sleep architecture patterns in TLE that directly contribute to cognitive deficits using both an observational (Aim 1) and a mechanistic interventional (Aim 2) approach. In typical NREM sleep, electroencephalogram (EEG) slow wave oscillations are phase-locked and coupled with sleep spindle oscillations (SW-SSO), which facilitates memory consolidation and potentially improves attention. In TLE, disordered networks that result in interictal epileptic discharges and seizures may also contribute to altered SW-SSO coupling during sleep, resulting in memory and attention deficits. A single night of acoustic stimulation (AS) has been proven effective in enhancing SW-SSO coupling and improving cognitive performance in healthy older adults but has not been studied in TLE. My *central hypothesis* is that disordered networks in newly diagnosed TLE patients result in altered sleep architecture, which disrupt memory consolidation and attention capability. I will test this hypothesis by: (1) characterizing TLE sleep architecture using computational EEG - sleep spindle density, slow wave power, interictal epileptiform discharges, and SW-SSO coupling (Aim 1a), (2) linking these specific TLE-related sleep architecture patterns to cognitive processing (Aim 1b); (3) determining if AS enhances SW-SSO coupling in young adults with TLE (Aim 2a) and (4) determining if enhanced SW-SSO coupling improves memory and attention in TLE (Aim 2b).

**K-M107. Frequency-Responsive Ectopic Action Potentials in Neocortical Regular Spiking Neurons**

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In most mammalian neurons, strong synaptic inputs to the cell body and dendrites are transformed at the axon initial segment into action potentials that propagate orthodromically down the axon and backpropagate into the dendritic arbor. Action potentials can travel bidirectionally, and are also sometimes initiated in distal segments of axon, before backpropagating to the cell body and dendrites (Nat Neurosci. 14(2):200-209; Brain Res Rev. 21(1):42-92). We refer to these as Ectopic Action Potentials (EAPs). Hippocampal pyramidal cells sometimes fire EAPs during periods of increased excitation (Science. 336(6087):1458-61). We have

found that up to 71.4% of regular-spiking (RS) cells in the neocortex can fire EAPs in response to a prolonged sequence of somatic stimulations (Zhang, et al. *in prep*). Of the 37/67 cells that fired EAPs in our study, 15/37 (40.5%) fired EAPs in response to only a single stimulus protocol (30 Hz, 3 cells; 60 Hz, 6 cells; 100 Hz, 6 cells). Eleven cells (29.7%) fired EAPs in response to two protocols, and nine (24.3%) fired EAPs in response to any of the three frequencies. Two cells responded only to sequentially increasing current steps. These data suggest that some RS cells (those responding to all tested frequencies) generate EAPs, a non-canonical form of feedforward excitation, during various activated network states; other RS cells (those tuned to particular frequencies) generate feedforward excitation in response to a narrower range of states. This suggests that a subset of RS cells are ‘tuned’ to fire EAPs during specific—and variable, depending on the cell—activation states. This is a previously unknown property of neocortical pyramidal cells, with potential implications for both normal neural processing and disease states.

#### **K-M108. Homeostatic Sleep Need Increases Seizure Risk**

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A relationship between sleep loss and seizures has been appreciated since antiquity. Sleep deprived rodents are more likely to have seizures, and people with epilepsy also report a worsening of seizures after poor sleep. Despite this longstanding evidence, the mechanisms that tie sleep loss to increased seizure risk remain unclear. Here we leverage the fly model system and find that hyperactivation of circuits encoding sleep need is responsible for worsened seizures after sleep loss. Sleep loss induced with pharmacological or thermogenetic approaches leads to worsened seizures in 4 epilepsy models. Using a novel video-tracking platform with automated seizure detection, we find that spontaneous seizures after sleep loss are more frequent, severe, and lethal. To identify underlying mechanisms, we performed a Gal4 screen of known sleep- or wake-promoting neuronal populations and find that acute thermogenetic activation of structures known to encode sleep need, including the mushroom body and dorsal fan-shaped body, leads to more severe seizures. These brain regions also demonstrate increased activity after sleep restriction. Importantly, acute optogenetic inhibition of sleep-promoting structures with GtACR1 leads to inhibition of seizures. Transcriptomics of a sleep-promoting brain region implicates loss of serotonergic receptors as mediators of this increased seizure risk after sleep restriction. These findings demonstrate that hyperactivation of circuits that encode sleep need are responsible for the exacerbation of seizures after sleep loss. We find that manipulation of sleep circuits can be used to control seizure severity; this has translational implications for the management of epilepsy.

#### **K-M109. Predicting Post-Ischemic Stroke Epilepsy Using Quantitative Markers and Competing Risk Covariates**

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Post-Ischemic-Stroke Epilepsy (PISE) is a serious complication of ischemic stroke. The SELECT score is a model that was recently developed to predict patients at risk for developing PISE. However, many patients still fall into the intermediate risk category of PISE development. We wanted to determine whether quantitative variables could help augment the SELECT score performance and whether we could further understand how to differentiate patients who are more likely to die prior to developing PISE. We retrospectively reviewed patients  $\geq 18$  years old from 2014-2020 from Yale New Haven Hospital with acute ischemic stroke for the development of post-ischemic stroke epilepsy (seizures greater than 7 days) with EEG and CT/MRI within 7 days post-stroke. We conducted bivariate cox regressions to identify quantitative features of interest then built a random survival forest model using 231 patients for training (42 PISE) and 50 (10 PISE) unique patients for testing. We found in our cohort there is low specificity of the SELECT score when the select score is 4-5, which represents 58% of our cohort. However, within this group of patients, there were very different quantitative differences in 72-hour NIHSS (HR=1.20 [CI=1.01-1.33]), infarct volume (HR=1.05 [1.03-1.07]), peak 1-hr EA burden (HR=1.14[1.01-1.27]), total power asymmetry (HR=1.75[1.21-2.53]) and total rhythmicity asymmetry HR= (1.29[1.05-1.60]) between those who developed PISE and those who did not. Based on Shapley values for the test set, there is no single modality that exclusively explains the risk of PISE, suggesting a multimodal combination may be best. Competing risk analysis suggests that some covariates are PISE specific (e.g., MCA infarction, Peak EA burden, Power asymmetry) whereas others are more highly associated with death (e.g., older age, pre-stroke mRS, afib) and others are associated with both (e.g., high NIHSS). These data suggest that quantitative variables may augment prediction beyond the SELECT score in patients who are at moderate risk for PISE.

#### **K-M110. Repetitive Transcranial Magnetic Stimulation Modulates Brain Connectivity in Children with Self-Limited Epilepsy with Centrotemporal Spikes**

**Fiona M. Baumer, MD, MS, Xiwei She, PhD, Kerry Nix, BS, Kerry Nix, BS, Wendy Qi, BS. Stanford University School of Medicine, Palo Alto, CA, USA.**

**Rationale:** Self-Limited Epilepsy with Centrotemporal Spikes (SeLECTS), the most common focal childhood epilepsy syndrome, is associated with sleep-potentiated interictal spike waves emerging from the motor cortex that can occur in a unilateral or bilaterally-independent distribution. Electroencephalography (EEG) connectivity studies have shown that focal spikes are associated with large, diffuse increases in brain connectivity and furthermore, that connectivity is increased even during *spike-free* periods of sleep. Single pulses of transcranial magnetic stimulation (spTMS) paired with EEG can measure connectivity between the stimulated cortex and other brain regions. Repetitive TMS (rTMS) trains modulate excitability for extended periods. The purpose of this study was to investigate whether low-frequency rTMS reduces connectivity of the epileptogenic motor cortex in children with

SeLECTS. **Method:** Eight children (8-12 years old, 75% male, 62.5% on antiseizure medications) underwent a sham and a real rTMS session spaced a week apart. The rTMS intervention was applied to the hemisphere with the most spikes. Connectivity before and after rTMS was measured by administering 100 spTMS to the motor cortex and then calculating the weighted phase lag index (wPLI) of the beta frequency band in the second after each pulse. wPLI is a connectivity metric robust against volume conduction and can be measured in short time increments. We tested whether there was a change in connectivity between the stimulated motor region and 7 other regions of interest (contralateral motor; and ipsi- and contralateral frontal, temporal, and parieto-occipital regions) in either the real or sham condition using one sample t-test. **Result:** Following real rTMS, there were modest but significant decreases in connectivity between the stimulated motor region and all other brain regions (contraMotor: -0.06, CI -0.01 to -0.10,  $p=0.04$ ; ipsiFrontal: -0.05, CI -0.006 to -0.09,  $p=0.05$ ; contraFrontal -0.04, CI -0.01 to -0.07,  $p=0.03$ ; ipsiTemporal -0.06, CI -0.02 to -0.10,  $p=0.02$ ; contraTemporal -0.04, CI -0.01 to -0.07,  $p=0.03$ ; ipsiParietoOccipital -0.05, CI -0.008 to -0.10,  $p=0.05$ ; contraParietoOccipital -0.05, CI -0.006 to -0.09,  $p=0.05$ ). There were no significant connectivity differences after sham rTMS. **Conclusion:** Children with SeLECTS have global increases in brain connectivity both during spike waves and sleep. Real but not sham rTMS to the motor cortex leads to a transient global reduction in connectivity of this epileptogenic region. This mechanism could be explored to understand the pathophysiology and develop treatments for SeLECTS and potentially other pediatric epilepsy syndromes.

#### K-M111. Zebrafish Models of Genetic and Chemical Seizures: Opportunities and Challenges

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**Background/Methods:** Zebrafish is a model of genetic and chemical seizures. However, a recent study showed minimal phenotypes in ~32 of 40 epilepsy genes disrupted using CRISPR/Cas9, raising questions about the factors influencing phenotypic severity (**challenge #1**). *We hypothesize that lack of seizure phenotypes in stable mutant zebrafish may relate to genetic compensation, partial knock-out escape, or lack of X-chromosome inactivation.* We are evaluating models of an X-linked genetic epilepsy in zebrafish (*cdkl5*), including a nonsense variant (*cdkl5-sa21938*) and a novel knock-in variant, to test whether truncating variants are more robust than alleles invoking nonsense mediated decay. To test whether mosaicism influences hyperexcitability in zebrafish (which lack an X-chromosome), we generated a novel mosaic conditional by inversion (COIN) allele to recapitulate mosaic LOF. Zebrafish is ideal for higher-throughput reverse genetic screening, but this approach has not been applied to seizure

phenotypes (**challenge #2**). *We hypothesize that acute gene KO conferring proconvulsant resistance by loss-of-function may suggest candidates for new ASM development, while gene KO conferring seizures or enhanced susceptibility may suggest novel epilepsy genes.* We developed a method using machine learning to detect anti-seizure responses using calcium fluorescence with a minimum of biological replicates. To identify seizure-related genes, we propose a reverse genetic F0 screen of pre-synaptic targets using the MIC-Drop approach to deliver multiple sgRNA/Cas9 RNPs in oil droplets. **Results:** **Challenge #1.** The *cdkl5 sa21938* line shows no differences in spontaneous epileptiform abnormalities. For *cdkl5* mCOIN KI fish, we established one founder, and demonstrate *in vivo* evidence of deletion and inversion of the construct following heat-shock cre. The *cdkl5* KI line and additional characterizations using calcium fluorescence are still pending. **Challenge #2.** A logistic classifier detects seizure-like events in response to PTZ with high accuracy (AUC-ROC 0.98). Bootstrap simulation suggests anti-seizure responses can be detected with N=8 replicates based on robust strictly standardized mean difference (RSSMD) thresholds (RSSMD  $\leq -0.82$ , TPR 92.2%, FPR 5%). Injected F0 CRISPR knock-out fish (N=12 fish per gene; 4 sgRNA per gene; 310 genes) are assessed for seizure-like activity (before and after PTZ). DNA barcodes identify gene targets from positive fish. **Conclusions:** *Cdkl5 sa21938* fish lack prominent epileptiform abnormalities, but investigations in the *cdkl5* KI and mosaic COIN KI fish will address whether genetic compensation and mosaicism modulate seizure phenotypes in this genetic epilepsy. A logistic classifier based on calcium fluorescence in larval zebrafish is suitable to detect gene-specific changes in seizure-like activity. A MIC-Drop F0 screen may identify novel seizure genes and anti-seizure targets.

#### LB-M112. Cenobamate in the Treatment of Medically Refractory Seizures: A Single-Center Experience

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**Background:** Cenobamate (CNB) is a new anti-seizure medication (ASM) approved for the treatment of focal seizures in adults. Two phase 2 randomized, placebo-controlled clinical trials demonstrated its efficacy in reducing seizures in adults with medically refractory focal epilepsy, with 21-28% of patients becoming completely seizure free. We report a single center experience of CNB in a cohort of patients with medically refractory epilepsy. **Methods:** IRB-approved chart review was conducted through the outpatient electronic medical record at George Washington University using the medication name as a key. We extracted information, including patient characteristics, baseline seizure frequency, outcomes, duration of follow up, among others. **Results:** CNB was prescribed to 54 patients (32 men) between 2020 and 2023. Only 40 (27 men), who have follow-up exceeding 6 months, were included. 33 patients had intractable focal epilepsy and 2 had Lennox-Gastaut syndrome (LGS). The mean age at presentation was 37.4 ( $\pm 14.0$ ). The number of concomitant

medications at baseline was 2.1 ( $\pm 0.8$ ). Baseline seizure frequency per year was 45.2 ( $\pm 67.8$ ), and the longest seizure free period in the six months that preceded CNB initiation was 6.3 ( $\pm 8.0$ ) weeks. Duration of follow-up ranged between 6 and 37 months. The daily dose of CNB was 222.8 mg ( $\pm 104.5$ ). The mean percentage of seizure reduction in the whole group was 63.6% and the 50% responder rate was 74.2%. One of the individuals with LGS experienced 80% seizure reduction on 100 mg/d after 6 months, and the other individual didn't experience seizure reduction on 250 mg/d after 24 months. 12 (30%) became completely seizure free. The need for surgery was obviated in 12 patients, including 5 patients who had undergone intracranial EEG, in view of the response to CNB. Only 1 patient on CNB underwent temporal lobectomy. Improvement in quality of life occurred in 27 (77.2%) patients while 8 (22.8%) had no amelioration. Five subjects (12.5%) didn't tolerate CNB due to adverse events, including drowsiness, fatigue, and forgetfulness. **Conclusion:** Our results regarding the efficacy and tolerability of CNB mirror the outcomes of the pivotal trials with a substantial subset of patients achieving seizure freedom, and some avoiding epilepsy surgery. We suggest modifying the definition of intractable epilepsy to include CNB as one of two ASMs failing to achieve seizure control.

#### LB-M113. Inducible Genetically-Encoded Voltage Indicator for Non-Invasive Functional Analysis of Human Stem Cell-Derived Neurons

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Ascertaining an electrophysiological phenotype from human stem cell-derived neurons (iPSC) can be time-consuming and is subject to considerable variability due to the need to examine one cell at a time with the gold standard of patch clamp. This technique also requires disruption to the cell membrane which could result in the loss of critical unknown components, and does not easily scale for examination of neuronal population properties. Here we employ a well-characterized genetically-encoded voltage indicator called ASAP3Kv under a doxycycline-inducible promoter, which allows labeling of neurons with the rapid lentiviral-mediated NGN2 differentiation protocol widely used. Simultaneous patch clamp with high-speed fluorescent imaging demonstrates the fidelity of this reporter system with evoked action potentials in human neurons. Importantly, neurons in populations can be assessed for spontaneous and synchronized activity with single-neuron resolution. This platform further supports the perfusion of exogenous drugs; we were able to demonstrate the effect of glutamate and GABA on populations of neurons without relying on indirect measurements like local field potentials or multi-electrode arrays (MEAs). To demonstrate the impact of non-invasive population analysis using the inducible GEVI, a gain-of-function SCN2A variant patient iPSC line was compared to its isogenic control line, allowing for comparison of spontaneous firing properties. Future applications include the ability to analyze specific neuronal populations in co-culture

and investigation of novel therapeutics on spontaneous firing properties.

#### Global Neurology

#### M231. A Phase 3 Clinical Trial of Leriglitazone with Adaptive Placebo-Controlled Treatment Duration in Adults with Cerebral Adrenoleukodystrophy

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X-linked adrenoleukodystrophy (X-ALD) is a rare, inherited neurodegenerative disorder. Adult and pediatric patients with X-ALD develop cerebral lesions that can evolve to progressive cerebral ALD (cALD), a rapidly fatal form of the disease characterized by inflammatory brain demyelination. Autologous hematopoietic stem cell transplantation (HSCT) and ex vivo lentiviral gene therapy can arrest progressive cALD but carry risk, are associated with delays between cerebral lesion identification and treatment onset and have limited availability. There is an unmet need for treatments that can be administered immediately upon lesion identification to halt disease progression. Leriglitazone is a peroxisome proliferator-activated receptor  $\gamma$  agonist with potential for treatment of cALD. In a previous trial (ADVANCE; NCT03231878) in adult male patients with X-ALD and adrenomyeloneuropathy, 6 of 39 patients receiving placebo developed progressive cALD compared with 0 of 77 receiving leriglitazone. Here we present the methods for a multicenter, phase 3, placebo-controlled, randomized trial to investigate further the efficacy and safety of leriglitazone for treatment of adults with progressive cALD (NCT number pending). The study will have a double-blind period of up to 36 months followed by an open-label extension. Forty male adults with a confirmed genetic diagnosis of X-ALD and gadolinium-enhancing cerebral lesions and a Loes score (LS) of  $\geq 0.5$  to  $\leq 12$  will be enrolled. Patients must be classified as not recommended for HSCT by the investigator or be unwilling to undergo HSCT. Patients will be randomized 1:1 to receive once-daily oral leriglitazone (180 mg) or placebo; randomization will be stratified based on LS (low:  $\geq 0.5$  to  $< 6$ ; high:  $\geq 6$  to  $\leq 12$ ). The primary efficacy endpoint is time to death or the patient becoming bedridden with requirement for permanent ventilatory support, whichever occurs earlier. Secondary

endpoints include change in LS from baseline (key secondary), time to increase of  $\geq 1$  major functional disability in the Neurological Function Score, change from baseline in Activities of Daily Living and time to major neurocognitive impairment. Exploratory endpoints include assessment of biomarkers. Safety will be assessed by the number of adverse events and serious adverse events, recording of vital signs and clinical laboratory test results. Two interim analyses are planned to occur after all patients have been followed up for 18 and 27 months; if the primary endpoint is met at either, patients will transition to open-label leriglitazone. Recruitment begins in May 2023.

### M232. Acute Neurological Inflammatory Diseases in Colombia during the COVID-19 Pandemic: A Multi-Center Observational Study

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**Objective:** To evaluate clinical, laboratory, and epidemiological features of acute neuroinflammatory disorders (ANIDs) during the COVID-19 pandemic in Colombia. **Background:** The Neuroinfections Emerging in the Americas Study (NEAS) network, was established in 2016 as a multicenter-based observatory of ANIDs to investigate the role of emerging infections as etiological factors in neuroinflammatory disorders. The NEAS Network is based in 10 hospitals across 7 cities in Colombia. **Methods:** We conducted a combined retrospective and prospective, longitudinal, cohort study of newly diagnosed patients (<30 days of symptom onset) who fulfilled established criteria for Guillain-Barre Syndrome (GBS), encephalitis, myelitis, meningoencephalitis, or cranial nerve disorders, of unknown etiology, accrued between January 2020 and December 2022. **Results:** 439 patients with ANIDs were recruited during the study period. 54.0% of cases were male and had a median age of 39 (IQR 21-58) years. The most common preceding events during the 4 weeks prior to the onset of

neurological symptoms were upper respiratory tract infection (12.9%) and gastroenteritis (11.3%), although the majority of the population (70.3%) denied preceding events. The most frequent ANIDs were GBS (46.0%), facial nerve palsy (16.9%), and optic neuritis (10.5%). The diagnosis of encephalitis (7.6%), myelitis/encephalomyelitis (7.8%), and meningitis (3.4%) were less frequent. Patients with GBS were predominantly male (65.6%) and had a median age of 49 (IQR 25-63) years. **Conclusions:** ANIDs continued to present during the recent COVID-19 pandemic in Colombia. However, we did not observe a significant increase in the incidence of GBS or other ANIDs in our centers, as compared to the ZIKV epidemic (2015-2016) or endemic phase (2017-2019). SARS-CoV2 did not produce a significant impact in the incidence of ANIDs in Colombia.

### M233. Anatomically Interpretable Brain Age Prediction in Alzheimer's Disease Using Graph Neural Networks

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**Background:** Aging is a prominent risk factor for neurodegeneration and age-related pathologies can manifest as accelerated biological aging. Hence, the gap in biological estimates of age and actual chronological age (also referred to as brain age gap) may statistically capture accelerated aging. Graph neural networks (GNN) are widely popular deep learning models that are adept at leveraging spatial information inherent in the dataset for inference tasks. Here, we report a cortical thickness (CT) based brain age prediction framework using GNNs that provides a feasible mechanism to identify contributing regions leading to elevated brain age gap in Alzheimer's disease (AD). **Method:** We used CT from 3T MRI in 148 parcels (organized according to Destrieux's atlas) from OASIS-3 dataset consisting of 652 healthy controls (HC; age=67.76 $\pm$ 7.88y, 382 females) and 209 individuals with AD dementia diagnosis (AD; age=74.61 $\pm$ 7.13y, 102 females, CDR sum of boxes =3.38 $\pm$ 1.73). A GNN model that used the anatomical covariance matrix derived from the HC cohort was trained to predict chronological age from associated CT for HC cohort. The output of the GNN provided the chronological age estimate and was evaluated as an unweighted mean of entities associated with the brain regions in the final layer of the GNN model. Hence, we could quantify individual contributions to the GNN output by each brain region. Final brain age prediction was obtained after correcting the GNN outputs for age-bias using linear regression model. For all individuals, we evaluated residuals at regional level (regional age-gap) by comparing the contribution of each parcel with corresponding GNN output. The residuals between predicted brain age and chronological age (age-gap) were evaluated subsequently. **Result:** ANCOVA (with correction for age and gender) with post-hoc analyses revealed that regional age-gap was greater for AD relative to HC in bilateral temporal pole, medial temporal, entorhinal, parahippocampal, precuneus, and subcallosal regions (Bonferroni corrected p-value<0.05). Subsequently, age-gap

was significantly elevated in AD relative to HC (mean for AD=2.36y, mean for HC=0y, Cohen's  $d=0.797$ ). Also, age-gap in AD was correlated with CDR sum of boxes (Pearson's correlation = 0.375,  $p<10^{-6}$ ), reflecting a linear increase with dementia severity. **Conclusion:** Our proposed framework identified regional CT associations as contributors to age-gap in AD, suggesting that our GNN approach may be used to further our understanding between aging and neurodegeneration.

#### M234. Assessing the Effectiveness of Instagram in Teaching Functional Neuroanatomy to Medical Students

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**Background:** The COVID-19 pandemic greatly affected the delivery of medical education. Anatomy was one of the subjects that was more impacted as it heavily relied on cadaveric dissections and in-person teaching. These developments necessitated a shift towards online learning. The effectiveness of social media, and specifically Instagram, in teaching functional neuroanatomy (FNA) has not been widely assessed.

**Objective:** To determine if using educational content posted on Instagram will improve the performance and satisfaction of second year medical students in the FNA course.

**Methods:** Twenty-six students taking the FNA course enrolled as volunteers. Participants were granted access to an Instagram page, where educational content was posted after every teaching session. For 3 consecutive weeks, student participants completed a pre-content quiz after the teaching session and prior to the material being posted on Instagram, and a post-content quiz after having access to the material for 1 week. Pre- and post-content scores were compared. Students also completed a survey to assess their feedback on the use of Instagram and its effectiveness in teaching FNA.

**Results:** In 2 of the 3 sets of quizzes, students' performance improved by 2 and 2.4 points ( $p=0.0114$  and  $0.0142$ , respectively). Most students accessed Instagram >15 times/day (30.8). A small portion of the students (23.1%) interacted with the material using the comments section. Most students (73.1%) found the page helpful in their learning of FNA. **Conclusion:** Instagram can be an effective learning tool when utilized for teaching FNA to second-year medical students. It has the potential of becoming a valuable adjunct and resource in medical education.

#### M235. Current Practice for Continuous EEG Monitoring in the Critically Ill Patient: A Latin American Survey

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**Background and Purpose:** Seizures, clinical and electrographic, are common complications in critically ill patients and are associated with worse outcomes. Continuous electroencephalogram monitoring (cEEG) is the only non-invasive tool for continued brain monitoring. There has been an increased use of cEEG in high-income countries.

However, knowledge of the access and use of cEEG in Latin America is scarce. Hence, the objective of this study was to conduct a survey to evaluate practice patterns and access to cEEG monitoring in critically ill patients in Latin America.

**Methods:** We disseminated a web-based, anonymous survey to providers caring for critically ill patients through Latin American Brain Injury Consortium, a large established network of intensivists in LA. The survey consisted of 10 questions and was designed to describe the availability of EEG in LA. **Results:** Of 182 participants from 17 countries who completed the survey, the majority were intensivists (85.9%) working at public hospitals (61.2%), with 85.43% working in polyvalent critical care units. Of the participants, 71% had access to EEG, of whom 40.17% could perform long-term cEEG monitoring, and 59.82% could perform only routine EEG. EEG monitoring was available 24/7 in 43%, Monday-Friday from 7am to 5 pm in 26%, and only in the mornings in 21% of whom had access to EEG. Remote neurotelemetry was only available to 15.96% of all respondents. Of all respondents, neurophysiologists executed the EEG report in the majority (35.9%), followed by neurologist non-neurophysiologist (19.7%) and by intensivists (7.4%). In some cases, the EEG was read by neurosurgeons or interns (10.1%). **Conclusion:** Our survey demonstrated limited access to cEEG in LA and a significant variability in the delivery of cEEG care in critically ill patients. Future research should focus on assessing the primary limitations of access to cEEG, aiming to provide improved standard patient care.

#### M238. Metabolic Syndrome-Associated Microbiota Disrupts Fatty Acid Receptors Leading to Peripheral Neuropathy

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Metabolic alterations associated with diabetes, dyslipidemia, prediabetes, and metabolic syndrome lead to peripheral neuropathy (PN). Much effort has been undertaken to understand the pathophysiology of PN and the link between metabolic dysregulation and peripheral nerve injury. One potential mechanism involves the gut microbiota. Our aim is to understand how different diets shape the gut microbiota, and uncover the association between these microbiotas and PN. Work by our group and others using a high fat diet (HFD)-mouse model has shown that microbiota of the HFD-fed mice is significantly different than those of control littermates. Moreover, dietary reversal (DR) of the HFD to a standard diet (SD), or an oleate-rich monounsaturated fatty acid (MUFA) diet, rectifies the disruption in microbiota and reverses PN. We used C57BL/6J mice (5-week-old) that received an antibiotic cocktail (for 10 days) to deplete their microbiota, followed by fecal microbial transplant (FMT) from animals fed a variety of diets (HFD, SD, or MUFA). Mice were then phenotyped for any metabolic and PN abnormalities. After 10 weeks of FMT inoculation (16 weeks of age), feces collected from all mouse groups underwent 16S rRNA sequencing to analyze microbiota. Sciatic nerves, and colons were harvested to determine expression of signaling proteins



involved in fatty acid signaling (FXR and GPR43). Our results show successful colonization of different FMTs. FMT inoculation alone did not induce PN. HFD microbiota had differential abundance of bacterial species belonging to Lachnospiraceae and Lachnospiridae. This was coupled with changes in the protein expression of FXR and GPR43. However, these changes did not reach statistical significance. Collectively, our results show that gut microbiota is involved in fatty acid signaling in the colons and nerves. However, microbiota alone couldn't induce PN in HFD mouse models. Funding: Financial support for this work provided by the NIDDK Diabetic Complications Consortium (RRID:SCR\_001415, www.diacomp.org) and grants DK076169 and DK115255.

### **M239. Neural Wave: The Brain Dynamic Neural Equation, Patterns and Alert by Artificial Intelligence to Predict Seizures on Epileptic Patients**

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The evolution and understanding of brain activity is the greatest challenge of physiology and medicine, its importance and difficulty lies in the large number of cells involved. The present work shows a biophysical-mathematical brain model that allows understanding the brain dynamics of millions of interconnected neurons, explains the origin of brain waves, characterizes the neuronal state of a patient, quantifies microscopic parameters of neuronal internal functioning from measurable macroscopic parameters that can be applied in the study of various neurological diseases such as Alzheimer's, Parkinson's, Epilepsy, among others. The model is applied to understand the waves coming from the EEG and specifically in the interpretation of brain waves in epileptic patients, allowing clinicians to predict epileptic seizures before they occur and adjust treatment and medication accordingly, thus allows avoiding crises and side effects in the short and long term both in the pediatric and adult population with timely medical treatment. In the medical field, the model shows a new way of looking at the functioning of the brain, contributing to the pathophysiological understanding of the brain as a whole, making it possible to quantify the neural state of the patient in a quantitative way. The results of the model predict a neural footprint that uniquely characterizes the brain of each patient and through the application of technologies such as artificial intelligence, discharge constants of an epileptic seizure are shown, which makes it possible to detect epileptic seizures. Model validation was performed using an open database created by MIT (Massachusetts Institute of Technology) and BCH (Boston Children's Hospital) containing 43 Gb of information with 916 hours of continuous recording of encephalographic data with the detection of 173 epileptic seizures in 23 male and female patients in a wide range of ages. Data were analyzed in a multi-cluster linux system and code in python, MNE and MATLAB was developed to allow the successful construction of a probability function to predict future epileptic seizures, in addition to showing a practical and applicable methodology of this model to understand brain activity of patients. This model opens the door to new neurological studies and new medical tools

that can be used in the clinical diagnosis of various mental illnesses beyond epilepsy.

### **M240. Neurologic Sequelae Following Ebola Virus Disease in a Liberian Pediatric Population**

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**Objective:** To characterize the neurologic sequelae of Ebola Virus Disease (EVD) in children one year following infection. **Methods:** Under the Liberia-U.S. Partnership for Research on Vaccines and Infectious Diseases in Liberia (PREVAIL) III study, pediatric survivors of EVD as well as their close contacts without known EVD were enrolled in the neurology substudy of a larger natural history study of Ebola survivors. Participants between the ages of 3 and 17 were seen at John F. Kennedy Hospital in Monrovia, Liberia approximately one year after resolution of their acute EVD. A control group comprising family members of the Ebola survivors was also assessed. A total of 79 pediatric participants (34 survivors and 45 close contact controls) were evaluated. All were seen for a single neurology visit that included a full neurologic physical exam, neurologic history, and current symptoms assessment via a questionnaire. Survivors were compared to controls in terms of percentages, and tests for differences between the two groups for categorical variables were done using Fisher's exact test. **Results:** On a neurologic symptom questionnaire, 26.5% of survivors reported difficulty walking compared to 8.9% of controls ( $p=0.045$ ); 17.6% had fecal incontinence versus 0 controls ( $P=0.005$ ). There were no statistically significant differences on neurologic exam in the survivors when compared to the control group. In total, 8.8% of survivors met "slight disability" on the Modified Rankin Scale (MRS) versus none of the control group ( $p=0.0012$  across all observed categories of the MRS). Based on executive function questions and rater determined executive function scoring, 41.2% of survivors had a minor issue and 17.6% had a moderate issue with executive function versus 35.6% and 2.2%, respectively, in the control group ( $p=0.031$  across all observed categories of the rater determination). **Conclusions:** At one year following infection, pediatric survivors of EVD were found to have a higher prevalence of neurologic symptoms such as ambulation difficulties when compared to controls. On neurologic exam, no statistically significant difference was found in comparison with the control group. However, there was found to be higher MRS scores and more executive function concerns in survivors.

### **M241. Patient Knowledge of Epilepsy and Seizure Safety in Lusaka, Zambia**

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**Introduction:** Epilepsy affects more than 50 million people worldwide, with nearly 80% of people with epilepsy living in low- or middle-income countries [1]. Epilepsy is associated with increased morbidity from issues like burns, injuries, depression and anxiety and impacts quality of life due to social stigma [2]. Assessing a patient's understanding of epilepsy is critical in developing a therapeutic relationship and providing optimal care [3]. **Methods:** This study was performed at the University Teaching Hospital, a tertiary referral center with neurology care, in Lusaka Zambia. Participants were recruited from neurology clinic and completed a survey to assess patient knowledge about their diagnosis, treatment and experience living with epilepsy. **Results:** Fifty-six participants (55% male) completed the survey. Nearly half of all participants (48%) reported missing anti-seizure medications due to forgetting, expense, pharmacy stock out, or other issues. Over half of participants (55%) had discussed medication side effects with their physician. Fifty-five percent of participants reported injury from a seizure, ranging from tongue bites to burns; only 44% had discussed seizure safety precautions with their physician. While nearly all participants agreed that anti-seizure medications can prevent seizures, around 20% were not aware that missing a dose of medication could make seizures more likely. Around two thirds of participants knew that alcohol can lower seizure threshold, but less than half (48%) knew that sleep deprivation can be a trigger. Thirty-seven percent of participants believed placing something in a person's mouth during a seizure is safe. Around a third of participants knew women on anti-seizure medication should take folic acid (32%) and that anti-seizure medications may interact with certain birth control methods (30%), while only 23% knew that anti-seizure medications may cause increased risk of pregnancy complications. **Discussion:** This survey of patients living with epilepsy in Lusaka, Zambia, evaluated the baseline knowledge about epilepsy and seizure safety. There are a number of safety concerns with regards to epilepsy that up to 30-50% of patients were not aware of. This highlights the opportunity to target educational interventions in the clinic to improve patient safety. **References:** 1. World Health Organization. (2019). Epilepsy fact sheet. Retrieved from <https://www.who.int/news-room/fact-sheets/detail/epilepsy>. 2. De Boer, HM, Mula, M, Sander, JW. (2008). The global burden and stigma of epilepsy. *Epilepsy and Behavior*; 12: 540-546. 3. Birbeck, GL. (2010). Epilepsy care in developing countries: Part I of II. *Epilepsy Currents*; 10: 75-79.

#### M242. Prediabetes Disrupts Lactate Trafficking in Peripheral Nerves: A Novel Mechanistic Target?

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Prediabetes affects approximately 541 million individuals worldwide, of which 30% suffer from peripheral neuropathy (PN). Under normal conditions, Schwann cells (SCs) maintain peripheral nerve health by supplying axons with energy substrates, such as lactate through monocarboxylate transporters (MCTs). We propose that prediabetes compromises

MCT-dependent lactate shuttling, leading to energy failure and PN. Twelve-wk old male mice were fed standard diet (SD; 10% fat) or high fat diet (HFD; 60% fat) for 6 wks. At study termination, metabolic and neuropathy phenotyping as well as flux analysis were performed. Complimentary *in vitro* work in cultured rat primary SCs further characterized MCT-mediated lactate trafficking following palmitate treatment to mimic metabolic dysfunction. At study termination, we found that HFD mice were significantly heavier than their control littermates and had impaired glucose tolerance. They also developed PN with both nerve conduction velocity and intraepidermal nerve fiber density deficits. Flux analysis showed that these metabolic and neuropathic changes were associated with a significant reduction in lactate abundance in the sciatic nerves of HFD mice. *In vitro*, exposure of rat primary Schwann cells to increasing palmitate concentrations (31.25-250  $\mu$ M) resulted in an early *MCT1* upregulation coupled with increased lactate release. However, chronic palmitate exposure significantly reduced *MCT4* gene expression, concomitant with SC oxidative stress and injury. In summary, our results suggest that prediabetes impairs MCT-mediated lactate transport, which is likely to result in bioenergetics failure, peripheral nerve injury and PN.

#### M243. Relationships between Cortical Excitability, Segregation of Functional Networks, and Concentrations of Plasma pTau181 in Healthy Middle-Aged Individuals

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**Background:** Cortical hyperexcitability is a hallmark of Alzheimer's disease, possibly caused by the complex interaction of tau and amyloid  $\beta$  pathologies. High segregation of functional brain networks might be protective against tau pathology propagation and cognitive decline, and manipulating cortical excitability with non-invasive brain stimulation techniques could improve cognitive deficits. The relation of these measures to tau or amyloid biomarkers is uncertain. **Methods:** We examined the relation between plasma concentrations of phosphorylated Tau181 (pTau181), segregation of functional brain

networks, and cortical excitability in 530 participants, 40 to 65 years of age, from the Barcelona Brain Health Initiative cohort, who had resting-state functional magnetic resonance imaging (fMRI), electroencephalography (EEG), and pTau181 available. A subsample of 47 participants also underwent transcranial magnetic stimulation of the left prefrontal cortex (L-PFC), concurrently with EEG (TMS-EEG). Cortical excitability was estimated by the aperiodic component of the EEG spectrum (1/f-slope), and the area under the curve of the TMS evoked response (TEP) at the L-PFC, between 160-240ms after the TMS pulse. To quantify the extent of segregation between major functional networks we used the system segregation statistic. **Results:** A generalized linear model with a gamma distribution revealed that steeper 1/f-slopes are associated with higher pTau181 concentrations, particularly when either age increases, or system segregation decreases,  $R^2 = .07$ ,  $F(6, 524) = 3.35$ ,  $p = .005$ . A multiple linear regression within the TMS-EEG subsample revealed that the TEP response is also positively associated with pTau181 as age increases, and that this model, despite including a smaller sample size, better explains pTau181 concentrations,  $R^2 = .31$ ,  $F(6, 41) = 3.63$ ,  $p = .008$ . **Conclusion:** Our results reveal that cortical excitability is associated with pTau181, contingent upon age and system segregation. The TEP response is a more sensitive marker of the relationship between excitability and pTau181 concentration than metrics from the unperturbed EEG. Combining TMS with EEG may represent a scalable and inexpensive approach for an early identification and longitudinal tracking of middle-aged adults at risk for cognitive decline and dementia.

#### **M244. The Utility of the Anatomage Virtual Dissection Table and OsiriX in Creating Clinical Anatomy and Radiology Learning Modules on Brain Lesions**

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**Background:** In recent years with the advent of technology in medical education, teaching methodology has shifted towards heavy use of online-learning modalities. This has been especially the case for anatomy and radiology courses since they require students to visualize structures of the human body. Anatomage, a virtual dissection table, and OsiriX, a software that can process medical imaging, have both been shown to enhance students' learning experiences. Their utility in supplementing neuroanatomy learning has not been widely assessed. **Objective:** To determine if virtual modules created using Anatomage and OsiriX will improve the performances of medical students learning about different types of brain lesions. **Methods:** We enrolled 36 fourth-year medical students at Weill Cornell Medicine-Qatar who have completed a required course in neuroanatomy during their second year. Students were randomized to a control group and a study group. Students assigned to the study group completed two 20-minutes case-based modules (one on glioblastoma multiforme and the other on pituitary adenomas) created using Anatomage and OsiriX. All students completed a 10-questions quiz to assess their knowledge of anatomical concepts and relevant pathology. Students in the study group also completed a survey to assess their perception of the

quality and convenience of the modules. **Results:** For both quizzes, students who completed the online module performed better than those who did not (Quiz 1: mean = 6.56 vs 3.28,  $p < 0.01$ . Quiz 2: mean = 6.67 vs 3.06,  $p < 0.01$ ). The majority of the students who took the modules agreed (72%) that the modules were easy to navigate and reported that the modules helped them understand the concepts (78%). **Conclusion:** The Anatomage virtual dissection table and OsiriX can be effectively utilized in creating clinical anatomy and radiology learning modules on brain lesions. This new online-based learning medium can provide a more enriching and engaging learning experience for medical students.

#### **M245. Thoracic Disc Herniation and Syrinx Formation: The Anatomic Connection**

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**Background:** Intervertebral disc herniations, in which the nucleus pulposus pushes through the annulus fibrosus, is a common cause of back pain that can lead to nerve compression or myelopathy. Of these disc herniations, very few are found in the thoracic spine as compared to the lumbar or cervical spine and they are less often treated surgically. They are more likely to be calcified, increasing the risk of intradural extension. Interestingly, several cases in the literature have described incidental findings of syrinx formation at or near bulging or herniated thoracic discs. The most common causes of syrinx formation include Chiari malformations or post-traumatic syringomyelia formation. Less commonly, they are observed forming near arachnoid ossifications or disc herniations. The cases reported in the literature document resolution or near-resolution of these fluid expansions within the spinal cord after correction of a herniation via surgery. It is not clear why these syrinx form in the first place, particularly in patients who have disc bulges that do not compress the spinal cord, and why the thoracic spine may be more vulnerable to their formation. **Purpose:** This project seeks to compare case studies of patients that had thoracic disc bulges or herniations with associated syringomyelia and perform a literature review on the etiology of syrinx formation. The anatomy of the thoracic spine makes the spinal cord at this level particularly vulnerable, as the kyphotic curve in this area presses the dural sheath against the posterior disc, the posterior longitudinal ligament is weaker here, denticulate ligaments limit mobility, and there is an area of reduced medullary vascularization. These unique characteristics of the thoracic spine may explain cases in which incidental syrinx are observed near bulging or herniated thoracic discs. The Bernoulli theorem or Venturi effect, that states increased fluid velocity within a narrow area of flow paradoxically decreases pressure of the fluid, has been used to explain a suction effect in spaces filled with cerebrospinal fluid that in turn distends the spinal cord above and below an obstruction. The etiology of syrinx formation is still incompletely understood. This project seeks to better elucidate the formation of syrinx associated with thoracic disc herniations or bulges and the implications of their treatment for patient outcomes.

## M246. Two Case Reports of Movement Disorder in Adolescents from Ghana with Psychiatric Manifestation: Juvenile Huntington's (Westphal Variant) and Sydenham Chorea

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**Introduction:** Neurological disorders in low-resource economies are often late to diagnose or go undiagnosed as a result of few neurologists in the region. Particularly, the gradual onset of movement disorders is often overlooked until significant behavioral changes ensue, making children more liable to such neglect. We discuss two causes of chorea in two adolescents presenting with psychiatric manifestations at Korle-bu Teaching Hospital, Accra, Ghana. (Case 1: Juvenile huntington- Westphal variant and Case 2: Sydenham chorea). **Case Presentation:** Case 1 discusses a nineteen-year-old man, who presented to our clinic with a two-year history of difficulty walking and abnormal gait. Further questioning revealed involuntary movements, forgetfulness, and declining academic performance over the past two years, complicated by selective mutism, auditory hallucinations, and attempted suicide. Choreoathetoid movements were spontaneous and uncontrolled involving the extremities and face. Genetic testing revealed 63 CAG nucleotide repeats in one allele and 16 CAG nucleotide repeats in the other allele. Improvement in psychiatric and motor symptoms was evident a few days after the patient was started on medications with tetrabenazine, olanzapine, and clonazepam and on behavioral therapy. Case 2 discusses a previously healthy twelve years old man, who presented to our facility with a month-long history of abnormal bilateral arm movement. It initially involved the upper limbs but gradually progressed to the lower limbs and heads. It was then associated with worsening anxiety, depression, and psychomotor agitation. Antistreptolysin O titer was 669 IU/mL and Anti DNase B titer was 1600 IU/L helping to cling the diagnosis. Clinical improvement was apparent within a week after starting risperidone and tetrabenazine with regular psychiatry, neurology, and cardiology follow-up. **Conclusion:** These reports add to the body of evidence that childhood movement disorders are often late to diagnose or go undiagnosed. This increases the psychosocial and disease burden on children in low to middle-income countries. There is however a need to create awareness in these economies to enhance early diagnosis and treatment alleviating the psychosocial effects and disease burden.

## M247. Understanding the Spectrum of SCA1, SCA2, SCA3, and SCA6: Self-Reported Functional Status and Quality of Life

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**Background:** Spinocerebellar ataxias (SCAs) are ultra-rare, progressively debilitating, neurodegenerative disorders with no available treatments to slow or halt disease progression. Patient experiences with SCA offer essential insights regarding care and treatment. This study captures experiences of persons with SCA (PWSCA) to identify disease aspects that are paramount to them. **Methods:** This global, cross-sectional, mixed-methods study involving PWSCA (including SCA1, SCA2, SCA3, and SCA6) includes a quantitative, self-reported component for sharing demographic data, rating current functional status, and completing the SF-36<sup>®</sup> on a secured, HIPPA/GDPR-compliant, multilingual, online portal. The CoRDS Registry, National Ataxia Foundation, and Ataxia UK assisted with recruitment and participant engagement. **Results:** 183 PWSCA were provided the online assessment (**PWSCA1 = 25, PWSCA2 = 36, PWSCA3 = 60, PWSCA6 = 62**; 59.1% female, 40.9% male). Mean ages were 49.6, 47.7, 50.1 and 64.5 years for PWSCA1, PWSCA2, PWSCA3, and PWSCA6, respectively. Among all PWSCA, 6.5% reported no functional difficulties; 55.4% experienced difficulty walking but engaged in other activities independently (n = 103; PWSCA1 = 16, PWSCA2 = 21, PWSCA3 = 33, PWSCA6 = 33); 31.7% were unable to walk unaided (n = 59; PWSCA1 = 6, PWSCA2 = 11, PWSCA3 = 19, PWSCA6 = 23); and 5.4% could not walk at all (n = 10; PWSCA1 = 1, PWSCA3 = 7, PWSCA6 = 2). PWSCA1, PWSCA2, and PWSCA6 had mean SF-36 scores ≤50 on every scale (general health, physical functioning, physical and emotional role limitations, vitality, social functioning, and mental health) except bodily pain (54.8, 52.2, and 52.0, respectively). Mean physical functioning scores were highest in PWSCA1 (41.7) and lowest in PWSCA3 (35.8). Mean SF-36 scores in PWSCA3 were <50 across all scales, and highest in mental functioning (47.3); PWSCA3 consistently scored well below general population norms. PWSCA reported greatest morbidity on the physical functioning scale: mean scores of 41.7, 37.5, 35.8, and 37.0 among PWSCA1, PWSCA2, PWSCA3, and PWSCA6, respectively. Mean summary scores among PWSCA1, PWSCA2, PWSCA3, and PWSCA6, respectively, were 46.6, 42.0, 37.9, and 41.5 on physical components and 47.3, 49.8, 47.9, and 49.9 on mental components. **Conclusions:** This study demonstrates that among patients with the 4 most common SCA subtypes, most have difficulty walking and many experience significant morbidity associated with physical and mental health. PWSCA3 consistently scored well below population norms and had the lowest scores amongst PWSCA.

# K-M112. Distal Symmetric Polyneuropathy Prevalence and Predictors in Urban and Rural Zambia: A Population-Based, Cross-Sectional Household Survey

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**Introduction:** Studies in Zambia and Uganda have reported high (11-12%) prevalence of distal symmetric polyneuropathy (DSP) in HIV negative populations, but little is known about DSP outside of clinical settings. This study evaluates DSP prevalence and predictors in Zambian communities to guide future interventions. **Methods:** Two-stage cluster sampling using population proportional to size sampling was undertaken in two districts. Government health facility catchments were randomly selected in each district for a door-to-door survey. All adults ( $\geq 18$  years) in selected households were examined and interviewed about DSP, sociodemographic and medical characteristics, food security, and alcohol intake. DSP was defined as  $\geq 1$  bilateral symptom (pain, numbness, paresthesias) and  $\geq 1$  bilateral sign (diminished/absent distal pin, vibration, or reflexes) using the Brief Peripheral Neuropathy Scale and Utah Early Neuropathy Scale. HIV testing and counselling was offered to all participants. **Results:** Among 514 households, 1339 adults enrolled (73% participation rate). Median age was 35 (IQR 26) years and 62.7% were female. Diabetes ( $n=28$ ; 2.1%) or leprosy ( $n=2$ ; 0.2%) history was rare. HIV prevalence was 22% among 1080 (81%) participants tested. Urbanicity was associated with higher HIV prevalence (24% v 17%;  $p=0.007$ ) and more years of education (8.8 v. 6.8;  $p<0.00001$ ). DSP prevalence was 13.2% ( $n=177$ ; 95% CI 11.4-15.2%) and did not differ by urbanicity. DSP cases were more likely to be female (14.9 v. 10.4%;  $p<0.02$ ), were older (median age 56.5 versus 32 years;  $p<0.00001$ ), had less education (mean 6.2 versus 8.4 years;  $p<0.0001$ ), more likely to be food insecure (19.5% v. 11.5%;  $p=0.0001$ ) and have low dietary diversity (15.6 v. 10.1%;  $p=0.004$ ). DSP cases were more likely to have HIV, (21.5% v 11.0%;  $p<0.001$ ), report prior tuberculosis treatment (26.1 v. 12.3%;  $p=0.0001$ ), have diabetes (50 v. 12.4%;  $p<0.0001$ ), and prior history of syphilis (25.7 v. 12.1%;  $p=0.0001$ ). There was no association with alcohol intake ( $p=0.268$ ). Age (OR 1.04;  $p<0.0001$ ), food insecurity (OR 1.8;  $p=0.005$ ), HIV (OR 1.8;  $p=0.008$ ), diabetes (OR 5.1;  $p=0.001$ ), and history of syphilis (OR 2.3;  $p=0.005$ ) remained significant DSP predictors in a multiple logistic regression model ( $p<0.00001$ ). **Conclusions:** DSP prevalence is high in Zambian communities, mirroring data from prior clinic-based studies. Community health worker engagement to identify DSP cases and screen for HIV,

diabetes, and consider nutritional/dietary interventions may reduce DSP and lessen other associated noncommunicable diseases morbidity and mortality through early intervention.

# K-M113. Longitudinal Cognitive Outcomes in Children with HIV in Zambia

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**Objective:** To describe longitudinal outcomes and predictors of cognitive outcomes in children with HIV in Zambia.

**Background:** Multiple studies have shown that children with HIV are at risk for impaired cognition. However, there are limited data on longitudinal cognitive outcomes in children with HIV. **Methods:** We conducted a prospective cohort study of 208 perinatally-infected children with HIV ages 8-17, all treated with antiretroviral therapy, and 208 HIV-exposed uninfected (HEU) controls. Participants were followed for 2 years. Cognition was assessed with a custom NIH Toolbox cognition battery, and tests were combined to generate a Summary Cognition Score (SCS). The contribution of potential risk factors to outcomes was explored using regression models and group-based trajectory modeling.

**Results:** HIV was strongly associated with lower SCS at baseline ( $\beta=14$ , 95% CI -20, -7,  $p<0.001$ ). Change scores over time were similar between groups, but poorer average performance in children with HIV persisted at the two-year follow up visit (adjusted  $\beta = -11$ , 95% CI -22, -0.3,  $p=0.04$ ). Other than HIV, the strongest predictors of baseline SCS included Socioeconomic Status Index ( $\beta = 3$ , 95% CI 1, 5,  $p=0.004$ ) and history of growth stunting ( $\beta=-14$ , 95% CI -23, -6,  $p=0.001$ ), history of CD4 count below 200 ( $\beta = -19$ , 95% CI -35,-2,  $p=0.02$ ) and history of WHO Stage 4 disease ( $\beta = -10$ , 95% CI -19 ,-0.2,  $p=0.04$ ). In the group-based trajectory model, HIV+ status predicted membership in the lowest performing trajectory group (OR 2.5, 95% CI 1.2, 5.1,  $p=0.01$ ). **Conclusion:** Children with HIV are at risk of poor cognitive outcomes, despite chronic treatment with antiretroviral therapy.

# LB-M114. Association between Migraine Diagnosis and Low Psychological Resilience among Teenage Mothers in Peru: The Role of Adverse Childhood Experiences and Postpartum Mental Health

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**Background:** Teenage mothers face significant adversity, especially in low-middle-income countries like Peru. Psychological resilience (PR) is a vital resource to adapt to this new role. No previous study has assessed the role of prepartum migraine as a risk factor for low PR levels. This study aimed

to evaluate the association between migraine diagnosis and the levels of PR among adolescent mothers in Peru. Also, we want to test the role of adverse childhood experiences (ACEs) and postpartum mental health in this association. **Methods:** Our cross-sectional study included 788 teenage mothers (14-18 years old) in Peru. In-person interviews were conducted postpartum, in the hospital, within two days of delivery. The migraine diagnosis was confirmed using the ICHD-3. PR was measured with a validated scale and was categorized to define low and high PR levels. Multivariable logistic regression procedures were used to estimate odds ratios (ORs) and 95% confidence intervals (95% CI). Interaction tests were, and causal mediation analyses were performed. The number of ACEs types (abuse, neglect, and household dysfunction) was explored as an effect modifier. Maternal mental health and social support were evaluated as potential mediators. The models were adjusted by demographics, baseline mental health, ACEs, and obstetric data. **Results:** The prevalence of migraine in teenage mothers was 26.9%. We found that adolescent mothers with migraine have lower PR scores than those without ( $b = -1.1741$ ,  $p = 0.009$ ). From the adjusted model, migraine diagnosis was associated with 39% lower odds of having adequate levels of PR (aOR=0.61, 95% CI 0.38 - 0.95) compared to teenage mothers without migraine diagnosis. The number of ACEs was a significant effect modifier. The association between migraine and low PR levels was stronger in participants with a history of four or more ACEs (interaction aOR=0.36, 95% CI 0.14 - 0.88). Finally, our mediation analysis showed that postpartum depression and anxiety levels explained the association by 40% and 25%, respectively. Social support was not a mediator in the association. **Conclusion:** Exposure to migraine is prevalent in adolescent-aged mothers and is associated with reduced odds of adequate psychological resilience. Childhood traumatic events modified the association, and postpartum depression and anxiety are potential causal pathways. These findings suggest the opportunity of targeting migraine management to improve the PR levels of adolescents; and the need for providing culturally appropriate, trauma-informed headache care.

## Headache and Pain

### S164. A Rare Presentation of Migraine in an Adolescent Male

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**Case Diagnosis:** Migraine **Objective:** Migraines in adolescents typically present with bifrontal, bitemporal, or retro-orbital pain and may also present with photophobia, phonophobia, nausea, vomiting, and abdominal cramping. Complicated migraines may manifest with focal neurological deficits such as ataxia, hemiplegia, dysarthria, impaired hearing, and ophthalmoplegia. Diagnosis of migraines is clinical; however, with atypical presentations, it is important to rule out life threatening causes of any focal neurological deficits. **Case**

**Description:** 11-year-old male with a past medical history of migraines presented with new onset of blurry vision, dizziness, intermittent sharp "shock-like" pain in the right eye, and gait imbalance. The patient has no previous management for his migraine attacks. His mother noted that nine days prior, he was on a camping trip and slept in a tent outdoors. The patient denied any insect bites or exposure to possible environmental toxins. On physical exam, his vision was 20/200 bilaterally without pupillary changes and there was no evidence of papilledema. Extraocular movements were intact and no nystagmus was present. Muscle tone and bulk were normal with 5/5 strength throughout. MRI of the brain and orbit showed no acute abnormalities. Lumbar puncture and culture were normal with no evidence of encephalitis or meningitis. **Discussion:** Complicated migraines tend to manifest with focal neurological deficits such as ataxia, hemiplegia, dysarthria, impaired hearing, and ophthalmoplegia. Atypical presentations are uncommon and require additional testing to rule out life threatening causes of any focal neurological deficits such as neoplasm and infection. Treatment for acute migraine in adolescents includes oral medications such as acetaminophen, NSAIDs, and triptans. Furthermore, lifestyle modifications, behavioral approaches, and prophylactic medications are also indicated to prevent any exacerbation. **Conclusions:** The management of pediatric migraines requires an interdisciplinary approach to avoid diagnostic errors. It is imperative to document and assess the patterns and episodes of headaches over time to identify potential triggers and address red flags as they come up. Improvement in education on the various, rare and uncommon presentations of migraines is needed to prevent unnecessary diagnostic testing and expenses to the patient and their family and delay of their diagnosis and treatment.

### S166. Altered Functional Connectivity of the Thalamus and Salience Network in Patients with Cluster Headache

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**Background:** Previous studies have shown that the salience network (SN) and the thalamus are involved in the cluster headache (CH) attacks. However, very little is known regarding the altered thalamic-SN functional connectivity (FC) in CH. The aim of this study was to explore whether there existed the alterations of FC between the thalamus, both ipsilateral and contralateral to the headache side, and the SN in patients with CH in the headache attack remission state during in-bout periods and to further gain insight into the pain modulation pathway involved in the pathophysiology of CH. **Methods:** Resting-state fMRI (rs-fMRI) data of 21 patients with CH (1 women and 20 men, aged 18-50 years, 13 with right-sided headache and 8 with left-sided headache) and 21 age- and sex-matched normal controls (1 women and 20 men, aged 18-50 years) were obtained. All the participants were right-handed. The rs-fMRI data were analyzed by the independent component analysis (ICA) method using the FMRIB's Software Library (FSL) tools (<http://www.fmrib.ox.ac.uk/fsl/>) to identify the

group differences of the thalamic-SN FC between the patients with right-sided and left-sided CH and normal volunteers. **Results:** There was no significant difference in demographic characteristics between the CH patients of each group and the corresponding normal controls. No significant difference was found between the two CH groups in the clinical headache features. Decreased rs-FC was found between the thalamus, both ipsilateral and contralateral to the headache side, and the SN during the headache remission state in both right-sided and left-sided patients with CH, in comparison with healthy controls. **Conclusion:** The same results in both right- and left-sided headache patients suggest that the decreased rs-FC between the thalamus and SN might be one of the pathologies underpinning the CH. This helps us to understand better the nature of the brain dysfunction in CH and the basic pathologies of CH, which implies this deserves further investigation.

#### **S167. Central Sensitization is the Main Mechanism Underlying Chronic Pain in Patients with Persistent Post-Concussive Syndrome**

**Christopher File, BSA, Alejandro Villasante-Tezanos, Ph.D., Sean Pappolla, Assoc. Sci., Ahmed Harazeen, M.D., Remi Nader, M.D., Xiang Fang, M.D., Miguel Pappolla, M.D. Ph.D. University of Texas Medical Branch, Galveston, TX, USA.**

Several studies show that two-thirds of patients with mild traumatic brain injury (mTBI) will experience chronic pain. Chronic pain is often incapacitating and one of the main contributors to long-term disability in this population. There is a scarcity of studies describing the type of pain and mechanisms at play in mTBI. This critical gap in knowledge prevents the development of rational therapies. This study was undertaken to begin understanding the key features of chronic pain afflicting patients with mTBI. In addition to cerebral trauma, most patients with mTBI are simultaneously subject to multiple somatic (extracerebral) injuries also leading to chronic pain. In contrast to the inflammatory processes primarily involved in nociceptive pain, (i.e., orthopedic injuries), central sensitization (also called "pain centralization" or "brain pain" by some authors) is one of the main mechanisms involved in chronic neuropathic and chronic nociplastic pains. In this study, we used a diagnostic instrument for measuring the degree of central sensitization, designed primarily for clinical research, to evaluate a population of patients with mTBI and chronic pain. We found that patients with mTBI almost universally, exhibited high scores for central sensitization, suggesting that this mechanism is a major contributor to chronic pain in these patients. We also found, using bivariate analysis, a significant positive correlation between the extent of central sensitization and other symptomatology present in these patients as measured by a post-concussion instrument. Patients with a high degree of central sensitization frequently present with pain in one or more, dominant body parts (spine, joints, others), misleading the clinician toward treating the painful body site with anti-nociceptive therapies that are often ineffective. Recognition of central sensitization, which requires a different therapeutic approach is, therefore, a critical step for appropriate pain management in this population.

#### **S168. Developing and Delivering a Migraine Disparities and Diagnosis Undergraduate Medical Educational Program to Underrepresented in Medicine Medical Student Members of the Student National Medical Association**

**Larry Charleston, IV, MD, MSc, FAHS. Michigan State University College of Human Medicine, East Lansing, MI, USA.**

**Background:** Migraine is underdiagnosed. Medical students have ~3 hours of exposure to headache education throughout medical school training on average and some have racially-based biases in pain. There is a paucity of underrepresented in medicine (UIM) headache practitioners. UIM practitioners are more likely to practice in underserved communities and provider-patient ethnic concordance may help eliminate health care disparities. The Student National Medical Association (SNMA) is an organization committed to supporting current and future UIM medical students and addressing the needs of underserved communities. The goal of this project was to develop and deliver a brief Migraine Diagnosis and Disparities Undergraduate Medical Education Program "MD<sup>2</sup>UMEP" to increase awareness of migraine diagnosis and disparities in UIM medical students in the SNMA. (Project funded by the Disparities in Headache Advisory Council.) **Methods:** Connecting/Relationship Building with SNMA - The SNMA Region V website was reviewed. Calls were made to Wayne State University School of Medicine (WSUSOM) Office of Diversity, Equity, and Inclusion (ODEI) explaining the educational initiative with subsequent emails to the Director of WSUSOM's ODEI followed by a video-conference meeting (VCM). VCMs were conducted with two SNMA member leaders from WSUSOM. A local and regional presentation/delivery of the MD<sup>2</sup>UMEP was planned. Communication was maintained electronically. Development/Delivery of the MD<sup>2</sup>UMEP - Headache literature was reviewed for key concepts underpinning migraine diagnosis and migraine disparities with a focus on African Americans. Slides with talking points were developed with references. Pre and post test questions were drafted and made accessible via a QR code. The MD<sup>2</sup>UMEP was presented and students completed the questionnaires. **Results:** A professional relationship was established with SNMA leadership. A MD<sup>2</sup>UMEP was developed then administered in the 2022 SNMA Region V Medical Education Conference. Headache medicine was introduced to UIM SNMA medical students. Nine individuals responded to the MD<sup>2</sup>UMEP pretest questions. Eight individuals answered the posttest questions. UIM student performance improved on 9 of 10 test questions on migraine diagnosis and disparities and remained at 100% on 1 of 10 test questions, at the program's conclusion. **Conclusions:** There is great need for migraine diagnosis and disparities education among medical students. A new migraine diagnosis and disparities program was developed for medical students. SNMA members were receptive to the MD<sup>2</sup>UMEP and it strengthened their knowledge of migraine diagnosis and disparities. This program exposed UIM medical students to headache medicine.

### S169. Feasibility and Acceptability of Remote-Delivered Mindfulness-Based Cognitive Therapy (MBCT) for Patients with Migraine and Depressive Symptoms

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**Objective:** This study evaluated the feasibility, acceptability, and fidelity of remotely-delivered MBCT for patients with migraine and comorbid depressive symptoms. **Background:** Migraine and depressive symptoms are comorbid. Depressive symptoms are associated with higher levels of disability. MBCT is an evidence-based treatment that has demonstrated efficacy to reduce depressive symptoms and headache disability. This study evaluated the feasibility, acceptability, and fidelity of remotely-delivered MBCT for patients with migraine and comorbid depressive symptoms. We also evaluated preliminary clinical signals for headache disability and depressive symptoms. **Method:** In a single-arm, open label clinical trial, participants were recruited from NYU's electronic health record system. After an online prescreen and a phone screen, 16 eligible participants were assigned to receive either phone-delivered MBCT or video-delivered MBCT. The MBCT intervention was based on the standardized protocol and was abbreviated to 1hr/week (rather than 2.5 hrs/week) and was adapted for migraine. Primary outcomes were feasibility (session attendance), acceptability (Client Satisfaction Questionnaire (CSQ-8)), and fidelity (MBCT-T Adherence & Competence Scale). Homework adherence was also assessed. The treatment was considered feasible if average session attendance met or exceeded 75% (e.g., 6 of 8 sessions). The treatment was considered acceptable if the average CSQ-8 score met or exceeded 24. Optimal fidelity was considered a MBCT-T Adherence & Competence Scale score of greater than or equal to 2.5. Clinical outcomes were assessed pre- and post-intervention: headache disability (Headache Disability Inventory (HDI)) and depressive symptoms (Quick Inventory of Depressive Symptomatology - Self Report 16 (QIDS)). Related-Samples Wilcoxon Signed Rank Tests were used to evaluate changes in clinical outcomes from pre- to post-intervention. **Results:** Participants (n = 16) were all women with a mean age of 45 (SD = 13). The intervention met criteria for feasibility (M session attendance = 7.9/8, SD = 0.3), acceptability (M CSQ-8 = 28.8, SD = 3.3), and fidelity (MBCT-T Adherence & Competence Scale = 2.9). The average proportion of mindfulness homework activities completed was 0.65. When evaluating changes from pre- to post-intervention, we observed significant reductions in headache disability (HDI:  $p = .004$ ) and depressive symptoms (QIDS:  $p = .003$ ). **Conclusion:** The remotely-delivered MBCT for migraine and depressive symptoms intervention

was feasible and acceptable to all participants. The intervention also exceeded the threshold for fidelity. We observed reductions in headache disability and depressive symptoms.

### S170. Headache-Related Stigma in Adults Experiencing High-Frequency Headache/Migraine and High Acute Medication Use: Results of the Harris Poll Migraine Report Card Survey

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**Objective:** From the Harris Poll Migraine Report Card survey, stigma in US adults was evaluated by those currently or previously experiencing high-frequency headache/migraine with acute medication overuse (HFM+AMO), and further examined by race/ethnicity, gender, and employment status among those with current HFM+AMO. **Background:** Data on stigma relating to migraine are limited. **Methods:** US adults ( $\geq 18$ yr) with migraine completed an online survey and were classified into "current HFM+AMO" ( $\geq 8$  days/month with headache/migraine with  $\geq 10$  days/month of acute headache medication use) or "previous HFM+AMO" (previously experienced HFM+AMO, currently experiencing headache  $\leq 7$  days/month with  $\leq 9$  days/month of acute medication use). This subgroup analysis was limited to those with current HFM+AMO. The 8-item Stigma Scale for Chronic Illnesses (SSCI-8) assessed internal and external stigma; T-scores of  $\geq 60$  were considered clinically significant. Statistically significant differences were calculated by standard t-test at 90% and 95% confidence levels. **Results:** US adults (N=440) were classified as having current HFM+AMO (54% women, mean age 41.1yr, 57% White, 66% employed, 15.2 mean monthly headache days) or previous HFM+AMO (n=110, 49% women, mean age 47.2yr, 75% White, 54% employed, 4.2 mean monthly headache days). Among those with current HFM+AMO, a higher percentage of men had clinically significant SSCI-8 scores than women (52% vs 41%, respectively;  $P < 0.05$ ) and were more likely ( $P < 0.1$ ) to always/often feel embarrassed because of their illness (42% vs 27%), feel people avoided looking at them (29% vs 13%), and say people were unkind to them (25% vs 16%; individual SSCI-8 items). There were similar rates of clinically significant SSCI-8 T-scores across race/ethnicity subgroups (non-Hispanic Black, 51%; Hispanic, 48%; non-Hispanic White, 45%;  $P > 0.1$ ); however, non-Hispanic Black respondents were more likely ( $P < 0.1$ ) than White respondents to always/often feel embarrassed because of their physical limitations (51% vs 35%), feel embarrassed because of their illness (48% vs 32%), and feel that people were unkind to them (30% vs 17%). A higher percentage of employed



respondents had clinically significant SSCI-8 scores than non-employed respondents (53% vs 32%;  $P<0.05$ ) and were more likely ( $P<0.05$ ) to always/often experience 6 of the 8 SSCI-8 items. **Conclusions:** Among US adults with current HFM+AMO, men, Black respondents, and employed respondents reported higher stigma compared to their counterparts. Together, these data suggest that migraine management, particularly for people with HFM+AMO, requires significant attention to reduce associated stigma.

#### **S171. Health Concerns and Treatment Perspectives among US Adults with Current versus Previous High-Frequency Headache/Migraine and Acute Medication Overuse: The Harris Poll Migraine Report Card Survey**

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**Objective:** This US population-based survey compared the self-reported experiences of individuals with current versus previous high-frequency headache/migraine (HFM) with acute medication overuse (AMO) and characterized experiences with care in these groups. **Background:** Migraine is a disabling neurological disease that can negatively impact all aspects of life. **Methods:** Eligible respondents to this ~15-minute online survey were categorized into “current HFM,” having  $\geq 8$  headache/migraine days/month and  $\geq 10$  days/month of acute headache medication (AHM) use, or “previous HFM,” having  $\leq 7$  headache days/month with  $\leq 9$  days/month of AHM use. Survey questions pertained to diagnosis, living with migraine, healthcare provider (HCP) communication, and treatment. Raw data were weighted to the US adult population, allowing current and previous HFM groups to be representative of their respective overall populations. **Results:** US adults ( $N=550$ ) were categorized as having current ( $n=440$ ; mean age, 41.1yr; mean headache days/month, 15.2; mean acute headache medication days/month, 17.4) or previous ( $n=110$ ; 47.2yr; 4.2days; 4.1days) HFM+AMO. Racial demographics (White [current, 57%; previous, 75%], Hispanic [24%; 13%], Black [11%; 4%]) were similar to the US population. Despite most respondents with HFM+AMO describing their overall health as “good” or “excellent” (current, 64%; previous, 72%;  $P=ns$ ), 80% of current HFM+AMO versus 66% of previous HFM+AMO expressed concern with their health ( $P<0.05$ ). Of the current and previous HFM+AMO groups, 37% and 35%, respectively, wished their HCP better understood their mental/emotional health. Respondents wished HCPs discussed headache management goals with them (current, 66%; previous, 43%;  $P<0.05$ ) and roughly half of both groups worried about asking too many questions (current, 47%; previous, 54%;  $P=ns$ ). Respondents with previous HFM reported greater acute treatment optimization per the Migraine

Treatment Optimization Questionnaire, while those with current HFM had poor acute treatment optimization and wanted to change multiple aspects of their treatment. Current migraine preventive treatment use was low (15-16%), while acute medication (28-37%) and over-the-counter medication (57-59%) use was higher use was higher. Those with current HFM were more likely to currently or recently use non-pharmacological treatments than those with previous HFM (65% vs 45%,  $P<0.05$ ). **Conclusions:** This novel US survey of patient-reported experiences with HFM+AMO has revealed several areas in which HCPs can provide better care, including addressing mental health concerns and optimizing acute treatment, which may be a critical factor in improving migraine outcomes.

#### **S172. Inflammatory and Cell Adhesion Biomarkers are Associated with Distal sensory Polyneuropathy in People with HIV**

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**Background:** Neuropathy is a disabling, chronic condition in people with HIV (PWH), with a wide range of complications, such as reduced quality of life. Previous studies demonstrated that distal sensory polyneuropathy (DSP) is associated with neuro-inflammatory cytokines in PWH. Adhesion molecules are perturbed in other conditions linked to DSP, but no prior study has examined this in PWH. **Aim:** This study aimed to determine whether DSP signs and symptoms were associated with a panel of plasma biomarkers, including d-dimer, sTNFR1, ICAM-1, VCAM-1, uPAR, MCP-1, IL-6, IL-8, VEGF, IP-10, and sCD14, and whether they differed between PWH and people without HIV (PWoH). **Materials and Methods:** A cross-sectional study was conducted among 197 participants (81 PWH and 116 PWoH) at the UC San Diego HIV Neurobehavioral Research Program. We assessed DSP signs and symptoms for all participants. DSP signs were defined as the presence of  $\geq 2$  of the following DSP signs: reduced, bilateral, symmetric, distal vibration, sharp sensation, and ankle reflexes. Symptoms were neuropathic pain, paresthesias, and loss of sensation. Factor analyses were used to reduce the dimensionality of the biomarkers in PWH and PWoH separately. Logistic regression was used to assess the associations, controlling for age, sex, ethnicity, and diabetes. Statistical analyses were done using JMP Pro version 16.0.0 (SAS Institute, USA, 2021). **Results:** There were a total of 197 participants (mean age:  $43.2 \pm 14.5$ ), of whom 61 (31.1%) were women and 64 (33.0%) were Hispanics. Among PWH, the median nadir and current CD4+ T-cells were 350 (IQR 198, 606) and 689 (544, 890), respectively. Participants with DSP signs 2 were older and more non-Hispanic but had gender similarity, compared to those with signs  $<2$ . Using factor analysis, 11 inflammatory biomarkers in plasma were grouped into 4 factors in PWH and PWoH separately. The analyses showed that Factor 1 (sTNFR1, ICAM-1, and VCAM) was independently associated with DSP signs (OR [95% CI]: 2.83 [1.01-7.93]) and Factor 2 (d-dimer, IL-6, and uPAR) was independently associated

with the presence of any DSP symptoms (OR [95% CI]: 2.12 [1.03-4.38]) in PWH but not in PWOH. **Conclusion:** These findings suggest that inflammation and alterations in cell adhesion may contribute to the pathogenesis of DSP in PWH, possibly through endothelial dysfunction and demyelination.

### **S173. Migraine Abortive Therapy for Severe Hyperemesis Gravidarum, a Case Report**

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Morning sickness and migraine symptoms are both most prominent during the first few months of pregnancy, suggesting the possibility that morning sickness is a form of abdominal migraine. Heinrichs suggested that hyperemesis gravidarum and migraine headache share a common mechanism [Am J Obstet Gynecol. 2002;186(5 Suppl Understanding):S215-19]. Antiemetic agents and steroids are the most commonly used hyperemesis gravidarum treatments, often with limited efficacy. We report the case of a 19-year-old woman, G1P0, 24 weeks gestation, with a strong catamenial migraine history who presented with severe hyperemesis gravidarum throughout pregnancy with intractable nausea, vomiting, and anorexia and deficiencies of folate and vitamin B12 resulting in sensorimotor peripheral neuropathy manifested by 16 weeks of progressive bilateral leg weakness with areflexia and stocking-and-shield distribution sensory loss with numbness, paresthesias, allodynia, and hyperalgesia who had complete resolution of hyperemesis gravidarum (no nausea or vomiting and able to tolerate full, regular meals) after one day of intravenous therapy with magnesium sulfate 1 g, metoclopramide 10 mg, and diphenhydramine 25 mg every eight hours. Since menarche at age 11, she had had multiple migraine types, all triggered by menstruation, including migraine headaches without aura (top-of-the-head or bioccipital pounding pain with nausea, photophobia, and phonophobia), migraine headaches with visual aura (moving white stars), migraine headache with vertigo aura (world rocking like she's on a boat), upper abdominal migraine (nausea and vomiting), lower abdominal migraine (lower abdominal cramping pain and diarrhea), and precordial migraine (midsternal chest pain, often with headache). Complete and prompt resolution of severe hyperemesis gravidarum symptoms with intravenous migraine abortive therapy suggests that this condition is a form of abdominal migraine similar to cyclic vomiting syndrome. Antiemetic therapy alone is not likely to be as effective as migraine abortive therapy for hyperemesis gravidarum and one should avoid ondansetron in particular since it may trigger migraine attacks.

### **S174. Recurrent, Severe Coital Headaches Associated with Bilateral Carotid Artery Aneurysms**

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Coital headaches account for a small subset of clinical presentations in the outpatient neurology setting. Malignant coital

headaches can present as acute emergencies involving hemorrhagic or ischemic events, while others can present as insidious processes consisting of cerebral aneurysms, arteriovenous malformations, hydrocephalus, and reversible cerebral vasoconstriction. An estimated 4 to 14.5% of patients presenting with a subarachnoid hemorrhage had an aneurysmal rupture immediately following coital activity. There is only one reported case of recurrent coital headache related to an unruptured saccular aneurysm of the carotid artery. We present a 41-year-old female with a past medical history of migraines, blood loss anemia, and uterine leiomyoma status-post hysterectomy who presented to clinic for severe coital headaches and worsening migraines starting 8 months ago. Computer tomography angiogram (CTA) head and neck demonstrated bilateral paraophthalmic internal carotid artery (ICA) aneurysms (right, 7.5, left 6 mm). Diagnostic cerebral angiogram was subsequently done and confirmed the CTA findings. Patient underwent left and right flow diverting stent placement at 2 and 4 months later respectively. One week after the right ICA stent placement, her headaches had improved to 1-2 times per week. At 6 months after the stent placement, she resumed her normal sex life and her migraines returned to baseline. Timely diagnosis and intervention through endovascular flow diversion, stenting and coiling are very important in preventing intracranial hemorrhage, alleviating headaches and improving quality of life in this specific patient population. Reference: 1. Anish Bahra. Journal of Neurology. 2020 2. Doo-Sik Kong. Journal of Head and Face Pain 3. Juan M. Uterga. Headache. 2009. 4. Matthew R. Reynolds. Journal of Neurosurgery. 2010

### **S175. Targeting the Photoreceptor Basis of Light Aversive Behavior in Mice**

**Eric A. Kaiser, MD/PhD, Audrey Cavanah, BS, Geoffrey K. Aguirre, MD, PhD, Frances E. Jensen, MD.** University of Pennsylvania, Philadelphia, PA, USA.

**Background:** The characteristic photophobia of migraine may be mediated by intrinsically photosensitive retinal ganglion cells (ipRGCs), which transmit melanopsin and cone signals. Light sensitization after calcitonin gene-related peptide (CGRP) administration has been used as a rodent model of migraine, but the photoreceptor basis of this behavior has not been studied. Here we measured light avoidance in mice to varying levels of broadband illumination and to chromatic variation designed to target melanopsin or the cones. **Methods:** Light aversion was tested in a modified light-dark box. Both zones were illuminated by narrow-band LEDs that targeted three different photopic opsins: 365 nm (UV; S-cone), 460 nm (blue; melanopsin), and 630 nm (red; ML-cone). During 30 minutes of habituation, the two zones had equivalent illumination (Expt 1: dark; Expt 2: UV+red at 30% intensity; Expt 3: blue at 30% intensity). During the subsequent 30 minutes, the zones were set to have differing illuminance (Expt 1: off vs. all LEDs set to ~log spaced intensity between 5% and 100%; Expt 2: blue 10% vs. 50% intensity in addition to the habituation background; Expt 3: UV+red 10% vs. 50% intensity in addition to the habituation background). Animals were studied initially, and then

retested following peripheral CGRP or vehicle administration. Expt 4: c-Fos immunohistochemistry was measured in mice exposed to 100% intensity of all three LEDs following CGRP treatment. **Results:** Expt 1: wild-type C57BL/6J mice avoided the light zone, and the degree of aversion increased monotonically with increasing LED intensity following a sigmoidal functional form. Following either CGRP or vehicle treatment, there was increased light aversion at all light intensity levels. There was no overall difference in aversion between CGRP and vehicle treatments, although in post-hoc tests CGRP-treated animals showed greater light avoidance at the highest intensity levels. Expts 2 and 3: mice spent less time in the zone with the higher level of either blue or UV/red light. There were no reliable effects of treatment. Expt 4: Mice exposed to bright red/blue/UV light following peripheral CGRP administration demonstrated c-fos activation in lateral geniculate and visual cortex as well as the trigeminal nucleus caudalis and amygdala. **Conclusions:** We demonstrate that light avoidant behavior in the mouse can be measured as a psychometric function of light intensity. The aversive effect of both melanopsin and cone stimulation is consistent with the response properties of the ipRGCs and may provide a suitable model for evaluating mechanisms underlying migraine-associated photophobia.

#### S176. Weight Loss Medications in the Setting of Chronic Migraine

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**Background:** Weight loss has been studied extensively as a treatment for chronic migraine and may be associated with improved headache symptoms. Glucagon-like peptide (GLP-1) receptor agonists are now used widely to treat obesity and may have similar efficacy to bariatric surgery. We explored if patients with chronic migraine taking weight loss medications, including GLP-1 agonists, experienced changes in their headache. **Methods:** We conducted a retrospective chart review of all patients seen for treatment of chronic migraine as defined by the International Classification of Headache Disorders ICHD-3 between January 2022 and March 2023 at one academic center's headache clinic. We categorized participants based on if they were currently taking or had previously taken a medication for weight loss. We identified the change to their body mass index and if their headache improved while on these medications. This retrospective chart review study was approved by the institutional review board (IRB) at our institution. **Results:** Of the 211 patients seen for treatment of chronic migraine, 9.0% (n=19) were currently on or had previously taken a medication for weight loss. The medications used were phentermine (n=3), bupropion (n=1), naltrexone-bupropion (n=2), metformin (n=2), or GLP-1 agonists (n=14). Eighty-nine percent (n=17) of participants were female, 10.5% (n=2) were male, and mean body mass index after treatment was 31.7 (21.03-49.09).

Among the 14 patients on GLP-1 agonists, 64.3% (n=9) had subjective improvement in headache pain intensity and/or frequency, 28.6% (n=4) experienced worse headache, and 7.1% (n=1) had no change in headache symptoms. Interestingly, 64.2% (n=9) of patients on GLP-1 agonists experienced temporarily worse headache with increases in GLP-1 dose, with 66.7% (n=6) of these patients eventually having overall improved headache. Of the 8 participants who used weight loss medications other than GLP-1 agonists, only 37.5% (n=3) had improvement in their headache while 62.5% (n=5) worsened. **Conclusions:** Based on the results of this study, GLP-1 agonists may be preferred to other pharmacologic modalities for weight loss in patients with chronic migraine. More research, including a larger sample size and randomized controlled studies, would be helpful in further elucidating the relationship between body mass index (BMI), weight loss medications, and chronic migraine.

#### K-S103. Measuring Descending Pain Modulation with Offset Analgesia and Onset Hyperalgesia in Patients with Chronic Musculoskeletal Pain

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Chronic pain intensity varies considerably, even in a group of patients with peripheral pain generators of equivalent disease severity. Central mechanisms may contribute to this clinical heterogeneity, as evidenced by associations between clinical pain and quantitative sensory testing (QST) measures such as temporal summation or conditioned pain modulation. However, these measures are not strongly correlated with clinical pain. One potential reason for this is that key central mechanisms are incompletely measured with current techniques. Animal models have established that descending inhibitory and facilitatory pathways strongly modulate afferent nociceptive input. Offset analgesia and onset hyperalgesia are QST measures thought to reflect descending inhibition and facilitation, respectively. The current study tests the hypothesis that a pronociceptive descending modulatory balance (offset analgesia < onset hyperalgesia) is associated with greater clinical pain. We use knee osteoarthritis as a model, enrolling patients with equivalent knee joint degeneration but high or low knee pain in a case-control observational design. In our interim analysis from this ongoing study (ClinicalTrials.gov NCT05003323), we find evidence of robust offset analgesia and onset hyperalgesia, validating our measurement technique in this population. Across individuals, there is a large range in offset analgesia, onset hyperalgesia, and offset-onset balance. There is a trend towards a more antinociceptive descending modulatory balance (offset analgesia > onset hyperalgesia) in participants with low compared with high knee pain. This suggests that robust descending inhibition may protect against intense pain from a given peripheral pain generator in musculoskeletal pain. Data collection is ongoing and future analysis will examine the relationship between pain modulation phenotypes, clinical knee pain, and functional impairment over time.

#### K-S104. Time It Right! The Application of Circadian Medicine Interventions for the Management of Migraine

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**Background & Objective:** Migraine is linked to circadian rhythm dysregulation. The RLB (regular lifestyle behavior) protocol includes consistent sleep patterns, mealtimes, and exercise. We are piloting a clinical trial to test the feasibility and efficacy of the RLB intervention and examine its underlying mechanisms. **Methods:** The RLB clinical trial involves a 28-day baseline/observation period, followed by a 12-week study period where participants will receive weekly virtual training sessions, keep daily headache logs, maintain a lifestyle diary, and wear an actigraphy device. Monthly migraine frequency is the primary outcome. Secondary outcomes include RLB score, migraine severity, and headache self-efficacy. Exploratory outcomes involve measuring circadian rhythm, serum multi-omics, and MRI changes. The RLB framework uses the MOST (Multiphase Optimization Strategy) approach and includes a double-randomized preference trial (DRPT) extension to assess patient preference. **Results:** Out of 83 interested participants since July 2022 recruitment, 35 (42%) were available for phone screening of which 30 (85%) met inclusion criteria and were enrolled in the study's baseline/observation phase. Recruitment rate is 1-2 participants/week. Screening-to-enrollment takes about three days. So far, 15 completed their baseline phase and were randomly assigned to either the APC or RLB group for the 12-week study. Three participants withdrew from the study due to time constraints and interest in drug intervention. Participants found the weekly sessions time-consuming, but appreciated the convenience of the virtual platform. All weekly training sessions had 100% attendance. The questionnaires received an 80% response rate. Participants fully complied with the wearables. Questionnaires took an average of 5 minutes to complete. 5% of data was missing. Participants' feedback included: *"This program has been really helpful. I've had decreased migraine, taking medication much less often, increased strength & physical endurance, and became even more familiar with my body's sensitivities."* The retention rate is 27/30 (90%) so far. Four/six participants in RLB intervention group experienced reduced migraine frequency from 14 to 2 days from baseline to end-of-intervention. The APC arm (n=2) had more migraines during the same period, from 14 to 16 days. The intervention group's RLB score increased by 106% while the APC group had a 47% increase. DRPT extension, actigraphy/circadian, biofluid, and MRI analysis are in progress. **Conclusion:** Preliminary results show promise for circadian-based biobehavioral interventions in managing migraine. Changing weekly sessions to biweekly may improve intervention acceptability due to time constraints.

#### LB-S102. Alleviation of Burning Mouth Syndrome Pain through Retronasal Olfaction

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**Introduction:** The analgesic effect of enhancement of retronasal smell in Burning Mouth Syndrome (BMS) has not heretofore been described. **Methods:** This 64-year-old right-handed male underwent a dental procedure where his tongue was accidentally lacerated. This was followed, three days later, by a sensation of swelling and dryness of the tongue, which would transiently improve with food. Over the next month, this transformed into a metallic taste followed by a sour-bitter taste over the entire tongue, with tingling, like a battery being placed on the tongue, but only five to ten percent as strong. Over the next four months, this burning-like sensation spread to involve the entire tongue, upper and lower lips, upper and lower gums, throat, and palate. The burning was constant, day and night, 5/10 in severity. The pain was exacerbated by acidic foods, lemons, and oranges and improved with bland food, water, milkshakes and moving his tongue. It has been unresponsive to prednisone, amoxicillin/clavulanic acid, sertraline, duloxetine, and nystatin. **Results:** Abnormalities Motor Examination: Drift testing: left pronator drift with left abductor digiti minimi sign. Reflexes: 1+ both upper extremities and 0 both lower extremities. Chemosensory testing: Olfactory testing: Brief Smell Identification Test: 11 (normosmia). Retronasal Olfaction: Retronasal Smell Index: 9 (normal). Gustatory testing: Propylthiouracil Disk Taste Test: 2 (hypogeusia). MRI of the brain with and without infusion: scattered deep white matter chronic microvascular ischemic changes. Upon mandibulation of cappuccino flavored Jelly Belly jelly bean with retronasal olfaction occluded with nose clips: BMS pain 5/10. Upon introduction of retronasal smell with removal of nose clips: BMS pain 0/10 **Discussion:** Enhancement of retronasal smell as a method of analgesia for burning mouth syndrome can be undergroped within the construct of chemosensory dysfunction in BMS. Contrary to our findings of analgesic effect of retronasal olfaction, orthonasal stimulation through ambient aromas has been reported to exacerbate the pain in BMS (Hirsch, 2005). In BMS reduced orthonasal olfactory ability has been reported (Yakov, 2010; Siviero, 2011) and normosmia has also been described (Hirsch, 2017; Lopez-Jornet, 2021). Exacerbation of BMS attributed to taste has similarly been described (Hirsch, 2018). Such exacerbation may be due to taste stimulation itself, or due to retronasal smell, which is then due to physiologic synesthesia, perceived as taste (Gruss, 2023). In those with BMS, a trial of utilization of devices to enhance retronasal olfaction is worthy of investigation.

#### LB-S103. Chronic Neuropathic Pain: PTPRD Phosphatase Inhibitors Provide Novel Therapeutic Approaches

**George R. Uhl, MD PhD.** University of Maryland School of Medicine/VA Maryland Healthcare System, Baltimore, MD, USA.

PTPRD, the receptor type protein tyrosine phosphatase D, is one of the genes whose mRNA is most robustly upregulated in the spinal cord dorsal horn and dorsal root ganglion ipsilateral to chronic constriction injury (CCI) models of chronic neuropathic pain. The upregulation timecourse parallels the

development of allodynia following CCI. We have developed a lead compound PTPRD phosphatase inhibitor, 7-BIA, and a developmental candidate, pentilludin that displays a number of drug like features. 7-BIA treatment robustly reverses the allodynia that follows CCI. Neither 7-BIA nor pentilludin alter acute nociception in hotplate or tailflick assays. Pentilludin spares morphine analgesia in these hotplate and tailflick assays. Taken together, these data support use of pentilludin in trials for relieving allodynia characteristic of postherpetic and other chronic inflammatory pain states as we advance this compound to human use.

#### LB-S104. Psychological Resilience in People with Primary Headache Disorders: A Systematic Review and Meta-Analysis

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**Background:** Primary headache disorders (headaches) are frequent, start early in life, and produce episodic disability. Therefore, they could influence the levels of psychological resilience (PR) and indirectly affect the risk of other comorbidities. However, to the best of our knowledge, there is no previous evidence synthesis on the PR levels in patients with headaches. We aim to describe the characteristics of PR in people with headaches, the psychometric characteristics of the resilience scales, and explore the potential influencing factors. **Methods:** We searched in PubMed/MEDLINE and Embase (February 22, 2023), for observational studies, randomized control trials' baseline data, or qualitative studies including adults or children with a diagnosis of headaches according to the ICHD-3, including or not healthy control group, and reporting a measure of psychological resilience. We conducted a narrative synthesis summarizing the PR scales. Random-effects model meta-analyses of continuous outcomes were conducted, as effect sizes using standardized weighted mean differences (SMDs) with 95% confidence intervals (CIs). The I2 statistic was calculated for heterogeneity. We assessed the risk of bias in the individual studies and evaluated the certainty of the evidence. **Results:** We included five studies and a total sample of 635 participants (480 patients with headaches and 155 controls). Each study used a different resilience scale. The percentage of the PR score obtained by patients with headaches was 53.50% (95% CI 36.17 to 70.82, I2=96%). Second, the standardized mean differences (SMD) of the scores obtained by the patients with primary headache disorders were compared with those from the healthy controls. The pooled value of the SMD of the scores from the patients was -0.40 (95% CI -0.79 to -0.01, I2=0%). In headache patients, PR scores were negatively associated with psychological health (depression, anxiety, and stress), negative coping mechanisms, being

female and smoking; and positively associated with practicing mindfulness, and having higher levels of self-compassion, well-being, and positive coping mechanisms (self-confident, and seeking social support). The risk of bias was low to moderate, and the evidence certainty was low to moderate too.

**Conclusion:** Psychological resilience is reduced in people with primary headache disorders, within the patient population and compared with healthy subjects, influenced by protective and risk factors which were mostly modifiable, with the exception of being female (negative correlation). These results suggest a potential bidirectional influence of PR and the presence of primary headache disorders.

#### LB-S105. Randomized Controlled Trial of a Smartphone-Based Preventive Migraine Self-Management Program in the Emergency Department Setting: A Promising Teachable Moment

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**Background:** The emergency department (ED) is a critical point of contact with the health care system for many patients with migraine and an opportunity to initiate accessible non-pharmacologic migraine treatment. We examined whether a smartphone self-management progressive muscle relaxation (PMR) based therapy improved patient-centered outcomes for migraine compared to enhanced usual care (EUC). **Methods:** We conducted a randomized controlled trial of the smartphone application RELAXaHEAD with and without PMR in patients who visited the ED for headache and met migraine criteria. We collected follow-up data on our main outcomes (migraine related disability (MIDAS), migraine related quality of life (MSQv2), and monthly headache days (MHDs) to determine whether there were improvements up to 3-months post-study initiation and report quantitative analyses. **Results:** Of the 94 patients (Control (n=48); PMR (n=46)), 69/94 (73%) had baseline MIDAS and ≥1 follow-up MIDAS score. MIDAS mean change scores differed for the two groups (Control =6.86 and PMR -25.09, p=0.007. There was a statistically significant difference in the number of respondents improving by >5 MIDAS points for the PMR arm compared to the Control arm (PMR 28/34 (82.4%), Control 16/35 (45.7%), p=0.002) and in the number of respondents improving by ≥10 MIDAS points, with (PMR 21/34 (61.8%), Control 13/35 (37.1%), p=0.041). This effect persisted in Logistic Regression Models that included baseline MIDAS scores. For the MSQv2, Role function preventive and Emotional function change scores were higher among the PMR arm (n=34) compared to Control (n=35) with PMR 16.9 vs. Control 11.3 and PMR 26.5 vs. Control 19.8, respectively, while

Role function restrictive change scores were similar between groups (PMR 18.1 vs. Control 18.7) but independent sample t-tests found no statistically significant differences between PMR and Control groups for any MSQv2 subscale (RFR  $p=0.917$ , RFP  $p=0.357$ , EF  $p=0.409$ ). Of the 94 patients, 48 had three-month follow-up MHD data. PMR respondents ( $n=23$ ) had a  $-2.9\pm 8.0$  mean MHD change, and those in the control group ( $n=25$ ) had a mean MHD change of  $-1.6\pm 6.5$ ,  $p=0.533$ ). **Conclusion:** In one of the few studies assessing how to help patients with migraine post-discharge from the ED, we found that a PMR-based self-management program yielded clinically significant results in reducing migraine-related disability and a clinically significant decrease in MHDs. Future work should examine how to implement this treatment into the ED workflow and how to make this treatment more accessible to patients.

## Health Services and Health Equity Research

### S177. Barriers to Publishing Scholarship: A Cross-Sectional Study on Physician Residents and Fellows in Neurology

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**Background:** Peer-reviewed journals' opportunities for open access continue to grow, however substantial article processing fees to publish are reported as key barriers. Factors contextualizing the motivation and support for neurology trainees' scholarly activities, including opportunities for open access publishing are largely unknown. This project describes the factors that promote or limit U.S.-trained neurology residents and fellows from publishing scholarly activities, including in open access journals. **Design/Methods:** A prospective, cross-sectional survey that sampled physician residents and fellows training in US-accredited neurology residency and fellowship programs during the academic year of 2022-2023. The survey's construct on trainees' awareness and perceived barriers were designed from our preliminary work investigating the context of open access publishing in the neurology specialty. The web-based survey included 17 categorical and dichotomous items on trainee socio-demographics, experience with publishing, institutional support for publishing, and awareness of open access journals. Association of factors were determined by performing chi-squared ( $X^2$ ) and odds ratio (OR) statistical tests. **Results:** 70 neurology residents and fellow from all census regions (New England, Midwest, South, West), with the majority from academic health centers (75.7%) responded to the survey. The mean (SD) number of postgraduate training years to date was 3.5 (1.22), with 23.9% and 27.1% self-reported as underrepresented in medicine and an international medical graduate (IMG), respectively. 22.1% reported a history of socioeconomic and disadvantaged status during their career development. Trainees in academic health centers (OR 0.14 {0.02 - 0.61},  $p<0.01$ ) were more likely motivated to publish because of program requirements. IMG trainees were associated to

report publishing based on journal audience (OR 0.15 {0.03 - 0.65},  $p<0.01$ ). Most trainees were familiar with open access publishing (89.6%) and would submit to an open access journal (94.7%). 37.3% reported financial barriers to publishing. Trainees who published during their formal training were more likely to have heard of open access opportunities ( $X^2 = 5.3$ ,  $p<0.05$ ). Trainees successfully publishing during training reported prior research experience (OR = 4.1, {0.92 - 24.9},  $p<0.05$ ) and access to research mentors (OR = 6.2 {1.7 - 23.9},  $p<0.001$ ). **Conclusions:** More than one third of our survey respondents face financial barriers to open access publishing; those with prior research experience and access to mentors during formal training are more likely to publish successfully. This study supports the role of institutional support to assist neurology trainees in pursuing their scholarly work.

### S178. Community-Driven Brain Health Workshop Series in Historically Marginalized Communities: A Novel Approach to Brain Health Promotion and Education

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**Background:** Neurological disorders are the leading cause of disability worldwide—yet, many of these are preventable, including up to 80% of strokes and 40% of dementias. Brain health is an emerging concept that promotes the importance of protecting brain structural and functional integrity throughout the life span. Encouraging brain health and lifestyle modifications can decrease or delay the risk of developing neurologic disorders—including stroke, dementia, and, to a lesser extent, Parkinson's disease, bipolar disorders, depression, and obsessive-compulsive disorders. Many historically marginalized communities in the US lack access to the knowledge, tools, care, and environments to practice and maintain brain healthy behaviors, which contributes to disproportionate morbidity and mortality across a range of neurologic conditions within those communities. **Objective:** To pilot a novel community-driven brain health learning series to bolster neurologic health literacy and self-efficacy in a historically marginalized community. **Methods:** Results of a preliminary focus group indicated RFA community members found that lifestyle factors affect their quality of life and they were interested in brain health education and collaborative wellness initiatives. In 2022, we conducted a community-driven Brain Health Workshop Series that combined community brain health needs assessment, goal setting, education, and small group discussion to improve neurologic health literacy and self-efficacy among residents of the Rochester, NY Focus Area (RFA)—a region of eight inner city contiguous zip codes where health disparities are most evident. The pilot program was developed and implemented in direct partnership with Rochester community-based organizations Interdenominational Health Ministry Coalition (IHMC) and Foodlink. The five-session series took place between 08/20/2022 and 11/19/2022. **Results:** Participants

who attended at least one session included 22 adults residing in the RFA. With an approach of deep listening, bi-directional learning and empowerment of participants, the program utilized an iterative process, with discussion and provision of resources driven by the stated wishes and ideas of the participants, including a final Resource Book informed by participants. Program participants, facilitators, and community partners mutually benefited as we learned together about strengths and barriers to cognitive health within the RFA. Participants indicated a strong interest in future education programming around brain health topics such as stroke, sleep, suicide prevention, and depression. **Conclusion:** The robust engagement in this pilot program underscores the importance of bringing community-led education initiatives to historically marginalized communities around topics of brain health.

### S179. Comorbid Psychiatric Disorders are Associated with Lesser Use of Mechanical Thrombectomy in Patients with Ischemic Stroke

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**Background:** Mechanical thrombectomy is used for treating acute ischemic stroke due to large artery occlusion. Patients with psychiatric diagnoses tend to have more severe strokes and a higher prevalence of poor outcomes. The goal of our study was to identify if having comorbid psychiatric diseases in patients with ischemic stroke is associated with different chances of receiving a mechanical thrombectomy. **Methods:** Using The National Inpatient Sample, we retrospectively identified patients with ischemic stroke admitted between 2017 and 2019. We used Clinical Classification Software (CCS) diagnostic categories to divide patients with psychiatric comorbidities into five major diagnostic groups: anxiety and fear-related disorders, bipolar and related disorders, depressive disorders, schizophrenia spectrum and other psychotic disorders, and substance use disorders. We conducted separate multivariable logistic regression analyses to examine the relationship between mechanical thrombectomy and psychiatric diseases while considering individual and hospital-related factors as potential confounding variables. **Results:** In the primary cohort of 2,038,860 patients with ischemic stroke, we identified 706,040 with psychiatric diseases. Mechanical thrombectomy was used in 19,625 (31%) of those with and in 43,540 of those without psychiatric diseases (69%,  $p<0.001$ ). Patients with mental conditions had less chance of receiving a mechanical thrombectomy ( $aOR=0.79$ , 95%CI: 0.74-0.84,  $p<0.001$ ). Compared to patients who didn't have psychiatric comorbidities, having any number of them was associated with a lesser chance of getting mechanical thrombectomy: one psychiatric comorbidity ( $aOR=0.82$ , 95%CI: 0.77-0.88,  $p<0.001$ ), two psychiatric comorbidities ( $aOR=0.69$ , 95%CI: 0.61-0.79,  $p<0.001$ ), two plus comorbid mental disorders ( $aOR=0.77$ , 95%CI: 0.61-0.97,  $p=0.025$ ). Compared to patients without mental conditions, patients with depressive disorders ( $aOR=0.83$ , 95%CI: 0.78-0.89,  $p<0.001$ ), anxiety and fear-related disorders ( $aOR=0.77$ , 95%CI: 0.71-0.83,  $p<0.001$ ), bipolar and related disorders (0.72, 95%CI: 0.59-0.88,  $p=0.001$ ) had a lower chance of receiving

mechanical thrombectomy. There was no statistically significant difference in getting mechanical thrombectomy in patients with substance use disorder ( $aOR=1.01$ , 95%CI: 0.96-1.06,  $p=0.6$ ), and schizophrenia spectrum and other psychotic disorders ( $aOR=1.02$ , 95%CI: 0.84-1.23,  $p=0.9$ ). **Conclusions:** Psychiatric comorbidities, particularly depressive disorders, bipolar and related disorders, and anxiety and fear-related disorders, are associated with a decreased likelihood of receiving mechanical thrombectomy in patients with ischemic stroke. We did not find any significant difference in the likelihood of receiving mechanical thrombectomy among patients with substance use disorder, and schizophrenia spectrum and other psychotic disorders.

### S180. Development of a National, Clinically-Focused, Virtual Journal Club in Neurology

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**Background:** While journal clubs are a fundamental part of academia and training for physicians, once out in practice many neurologists do not have access to journal club discussions. theMednet is an online platform that allows for dissemination of expert knowledge in a searchable, private, and moderated question and answer format. We set out to design a national, high impact, clinically focused journal club hosted by theMednet to engage neurologists in all practice settings. **Methods:** A physician editorial team reviewed major neurology publications and identified journal articles with significant clinical impact. An academic partnership with the journals allowed for sharing of the article with theMednet community. The article was distributed to theMednet neurology community with a call for questions. Study authors and content experts were recruited to answer questions submitted by our neurology community. The Q&A was distributed over 3-4 weeks in our email newsletters. **Results:** theMednet neurology community includes 2398 practicing neurologists across the US. Two neurology journal clubs were run. The first article was the CHANCE-2 trial in stroke<sup>1</sup> and the second was the CENTAUR trial in ALS<sup>2</sup>. A total of 9 questions were included between the two programs resulting in 526 neurologists engaging with the programs and 1970 unique Q&A views. Each question received 3-4 different expert answers. There were 361 unique paper downloads between the two programs. One hundred thirty neurologists participated in the polls associated with these programs. Question themes included whether outcomes were clinically meaningful, how to apply study findings to patient care, and strategies for counseling patients on side effects. **Conclusion:** theMednet Journal Club feature is an engaging and effective way to connect academic and community neurologists to conduct journal clubs around high impact publications in the field of neurology. It allows physicians to share insights on clinical practice and to exchange viewpoints on translation of data into clinical practice. Future initiatives include expansion of the journal club to regularly feature articles published in Annals of Neurology.

**References:** 1. Yongjun Wang, M.D., et al. Ticagrelor versus Clopidogrel in CYP2C19 Loss-of-Function Carriers with Stroke or TIA. *N Engl J Med* 2021; 385:2520-2530. 2. Sabrina Paganoni, M.D., et al. Trial of Sodium Phenylbutyrate-Taurursodiol for Amyotrophic Lateral Sclerosis. *N Engl J Med* 2020; 383:919-930.

## **S182. Disparities in Access to and Experience with Technology and Teleconferencing in MCI Subjects**

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**Introduction:** Usage of teleconferencing technology in clinical and research settings has become more prevalent in the COVID-19 era with a corresponding increase in disparities in access to and confidence in using technology (Shahid et al. 2020). This abstract aims to identify disparities in digital literacy amongst older adult populations with aMCI. **Methods:** Data from a screening questionnaire as part of the NIH funded, multi-site Memories2 clinical research study was used for analysis. Amnesic mild cognitive impairment (MCI) status was determined with a neuropsychological battery using standard criteria. Subjects who passed the initial medical and MCI screening were given the questionnaire to gauge access to and comfortability with using teleconferencing. Subjects were given the opportunity to participate in a 15-minute troubleshooting session to increase comfortability with using teleconferencing technology. **Results:** Data from 399 participants from the University of Pennsylvania site were analyzed. The average age was 65.4 years (SD=7.0), 65% of subjects were female, and 44% of subjects were black. Black persons were significantly less likely to have access to a computer (77.4%) and a smartphone or tablet (75.1%) than Non-Black persons (90.5% and 88.3%, respectively) ( $p<0.001$ ). Black persons were significantly less likely to have used teleconferencing before (70.6%) compared to Non-Black persons (91.9%) ( $p<0.001$ ). A troubleshooting session to address challenges with digital literacy was offered to all subjects, and was completed by 204 participants. After the session, the average self-reported confidence in teleconferencing technology increased from 7.6/10 to 8.6/10 (10 = "Extremely Confident"; 1 = "Total lack of confidence"). Participants' access to technological devices was also associated with their comfort level using technology (Pearson  $r = 0.23$ ;  $p < 0.0001$ ). **Conclusion:** Overall, the majority of participants appeared to have access to technology and felt comfortable using it. Confidence in ability to use technology increased after a troubleshooting session, suggesting that comfort levels can be improved with even a brief, 15-minute

supervised support session. This is also an indication that the less access one has to technology, the less comfortable they are likely to be with using technology for health care/medical research. Future research should explore how variation in socioeconomic status affects digital technology accessibility and consequently, confidence in utilizing telehealth applications.

## **S183. Effectiveness of a Short Brochure-Based Educational Intervention on the Clinical Applications of Alzheimer's Disease Biomarkers in Cognitively Healthy Older Adults**

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**Background:** Advances in Alzheimer's disease (AD) biomarkers now allow researchers to characterize pre-clinical stages of cognitive impairment. However, the disclosure of AD biomarker results, particularly in research settings, may pose an ethical risk if patients lack an accurate understanding of their meaning across the AD continuum, and there is little known about the most effective educational program. **Methods:** We implemented a quasi-experimental design with Emory Healthy Brain Study (EHBS) participants. Our pre-test/post-test analysis was comprised of two study arms for the proposed interventions, a video or educational brochure, along with a pre-/post-intervention survey. The brochure consisted of clinical vignettes describing the utility of AD biomarkers in pre-clinical and prodromal stages, while the video provided similar information communicated by the EHBS Principal Investigator. 40 participants, matched for demographic features, were enrolled in each study arm. Participants were invited by email to participate and view materials electronically. The pre-/post-intervention survey consisted of 17 true-false questions concerning the implications of AD biomarker tests (APOE genotype, AD cerebrospinal fluid (CSF) biomarkers, and amyloid Positron Emission Tomography (PET) scans) in clinical scenarios spanning the AD continuum. Associations between the assigned educational material and post-intervention survey scores were estimated with multiple linear regression controlling for potential confounders (age, gender, race/ethnicity, years of education, and pre-intervention survey score). **Results:** There was an overall participation rate of 40%, with N=16 participants remaining in each arm. The brochure [ $\beta$ : 0.177; 95% confidence interval (CI): 0.060, 0.294] was significantly associated ( $p=0.007$ ) with an increase in post-intervention survey scores in comparison to the video. The median pre-/post-intervention survey score changes among the brochure and video arms were 0.36 and 0.30, respectively. **Interpretation:** Participants assigned to the brochure intervention scored on average 18% higher on the post-intervention survey than participants who were assigned to the video. Our results suggest that the brochure was superior



to the video in increasing the overall understanding of AD biomarkers, which may be explained by the interactive nature of the brochure versus passive video viewing.

#### **S184. Evaluating Current Perception, Cultural Beliefs, and Associated Social Stigma of Autism Spectrum Disorder in Uganda. Insights from an Educational Intervention Study**

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**Objectives:** Autism spectrum disorder (ASD) is a neurodevelopmental condition that affects communication, social interaction, and behavior. In Uganda, there is a widespread misconception and stigma associated with ASD. Autism is considered a shameful condition that leads to discrimination and ostracizing of affected individuals. This study aimed to address the perceptions and stigma associated with ASD in Uganda through an educational intervention program.

**Methods:** A mixed-methods approach employed both quantitative and qualitative data collection using pre- and post-intervention surveys and interviews with parents and teachers of children with ASD. The educational intervention program was delivered through a 2-day conference workshop targeting teachers, parents, and community leaders. The workshop covered topics related to the characteristics of ASD, its diagnosis, and management. The program also aimed to improve the participants' understanding of the needs and challenges faced by individuals with ASD. **Results:** N=94 participants attended the educational conference. N=28 participants completed both parts of the pre-and post-intervention survey. Results showed a significant improvement in the participants' knowledge and attitudes towards ASD after the intervention. The intervention significantly improved participants' knowledge and attitudes towards ASD. The study identified factors contributing to stigma, such as misconceptions, lack of awareness, and cultural beliefs. Parents reported that community members lacked an understanding of the nature of autism, and their children were publicly shunned. Community members and family often believed that children with autism were cursed or possessed by evil spirits, which led to isolation, denial of medical care, and even physical harm. Mothers were often blamed for their children's condition. In light of these findings, the post-intervention survey revealed a significant increase in knowledge about ASD, and participants felt empowered to become local community educators to decrease stigma on a rural community level. **Conclusion:** An educational intervention program can combat ASD stigma in Uganda and potentially other countries where there is a social stigma of ASD. This intervention enhances the knowledge and attitudes of educators, parents, and leaders. Education has been proven to directly combat stigmatization against people living with disabilities by disproving misconceptions associated with disabilities. We propose that education at the community level is similarly crucial to combat autism stigma in Uganda and other

developing countries. Learners can educate others, expanding the program's reach. Further research is needed to determine if stigma reduction improves health outcomes for those with autism and their families.

#### **S185. Evidence-Based Implementation of Free Phenytoin and Free Valproate Therapeutic Drug Monitoring to Reduce Costs and Improve Patient Care at the University of Texas Medical Branch**

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**Background:** Excessive laboratory testing is estimated to occur in 30%-50% of all hospitalized patients in the US. Phenytoin and valproate are commonly prescribed anti-convulsants and must be monitored to ensure adequate seizure control while avoiding toxicity. Total serum drug levels have been shown to vary in patients with differing comorbidities and are thus less reliable in clinical practice. Reducing the number of total levels ordered would significantly decrease healthcare costs while improving patient care. A quality improvement (QI) assessment performed by the UTMB Neurology department in 2019 revealed total levels made up the majority of tests ordered institutionally. Consequently, educational interventions were implemented throughout the Neurology department to promote testing of free levels only. This current QI project aimed to quantify the change in number of free vs. total levels ordered and assess for adverse outcomes post-intervention. **Methods:** Our data was collected retrospectively from patients with phenytoin or valproate laboratory tests (729 total) performed at UTMB who were at a UTMB hospital or UTMB clinic from 4/1/2022 to 10/30/2022. We analyzed frequencies of tested phenytoin total (PT), phenytoin free (PF), bundled PT+PF, valproate total (VT), valproate free (VF), bundled VT+VF to determine changes in tests ordered after educational intervention. We also assessed whether therapeutic indices aligned in cases where both total and free levels were ordered. **Results:** We found 84.6% of valproate and 77.7% of phenytoin labs ordered post-intervention were solo free levels compared to 11-12% of labs ordered pre-intervention. Therapeutic indices did not align in 34.0% of cases when total and free levels were ordered. Additionally, no negative impact was observed from ordering only free levels appreciated by the fact no follow-up orders of total levels were required to determine dosage adjustments. **Conclusions:** Previously, solo free level tests composed only 11-12% of all lab orders. After implementation of evidence-based phenytoin and valproate monitoring at UTMB facilities, percentages of solo free levels ordered significantly increased to 81.2% of labs ordered. Total serum labs and associated downstream costs have considerably decreased by more than 50% while quality of patient care improved by decreasing unnecessary workups. Additionally, the lack of equivalency in therapeutic indices between free and total levels emphasizes the inefficacy of ordering total levels. Future steps include implementation of similar educational interventions across UTMB and eventually the nation to alleviate excessive and gratuitous ancillary testing.

### **S187. Free Neurology Community Clinic: Characteristics, Trends, and Needs**

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**Background:** The number of uninsured and underinsured patients in the United States continues to grow, and their access to medical care is limited. A network of free clinics has developed over time to address insurance-based inequities, however only a small number incorporate specialty care. DAWN Health Clinic was established in 2013 to address the need for primary care services for uninsured patients in Aurora, Colorado in partnership with the University of Colorado - Anschutz Medical Campus. The DAWN Health - Neurology Clinic (DHNC) was incorporated in 2018 to supplement the need for outpatient neurologic care. **Objective:** Characterize the patient population evaluated and treated at a free neurology community health clinic in Aurora, Colorado, and identify limitations of neurologic care within this setting. **Design/Methods:** DHNC is scheduled one half-day a month, staffed by 1-3 neurology attendings and 1-3 neurology residents/fellows. Care coordinators, in-person interpreters, and nursing students provide additional services including food/housing resources, transportation, language services, and lab draws. Retrospective chart review of patients who attended DHNC between October 2019 and March 2023 was collected, with follow-up data as available. **Results:** 57 patients were included in the analysis, with a total of 149 new or return clinic appointments (91.9% show rate). 52.6% of patients were women and average age at first visit was 47. Most commonly spoken language was Spanish (67.2%) followed by English (22.4%). The most frequent reasons for referral were headaches (29.3%), seizures/spells (25.9%), stroke/vascular (20.7%), and neuromuscular disorders (12.1%). The most commonly prescribed class of medications were anti-seizure drugs, with topiramate being the most prescribed medication overall. 29.8% of patients were referred for neuroaxis imaging. Diagnostic studies unable to be obtained through the free clinic included EMG (2/57), EMU (1/57), sleep study/PAP (3/57), and Humphrey visual field testing (2/57). **Conclusion:** The DHNC has expanded substantially since its inception, initially run by a single attending and now regularly staffed by 2 attendings and 2-3 neurology residents. The majority of patients speak Spanish with slightly more than half identifying as women. There is a diverse representation of chronic neurologic diseases treated within the clinic, with less than 10 patients with diagnostic needs outside the capabilities of this clinical space. With a sustainable staffing model well-established, future studies should focus on the (1) educational value of this experience for resident and attending physician volunteers and (2) proportion of care successfully transitioned to outpatient setting after ED visit/hospitalization in uninsured or underinsured patients.

### **S188. From Resident to Chair: Gender Disparities in Child Neurology Pipeline**

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**Background:** Achieving gender equity is fundamental to creating a balanced healthcare workforce within each medical specialty. This study aims to analyze trends in the proportion of male-to-female residents in child neurology from 2011 to 2022 and compare this data to the gender diversity of the current pediatric neurology residency program director and department leadership. **Methods:** This is a retrospective analysis of data extracted from the Accreditation Council of Graduate Medical Education (ACGME) Data Resource Books between 2011 and 2022. The data collection and trend analysis were conducted on Microsoft Excel. Gender was categorized as male, female, and unreported. In the last two academic years, 2020-2021 and 2021-2022, non-binary was introduced as a gender category, with no reported data in child neurology. We also utilized the Child Neurology Society program guide to identify the chair/director of each pediatric neurology department/division and the training program director (PD). We utilized the pronouns used in their publicly available biographies to classify their gender. **Results:** The reported data indicates that from 2011 to 2022, female representation in Child Neurology residency increased from 60% to 69%. In the same period, male residents decreased from 38% to 31%. The representation of female residents is approximately 30% higher than male residents for each academic year in the period reported. Of the seventy-five pediatric neurology programs evaluated, 24% of chairs/department directors and 60% of program directors were female. This indicates that although the representation of female program directors correlates with the pipeline of child neurology trainees, there is still a significant underrepresentation of women in department/division leadership. **Conclusion:** More than two-thirds of pediatric neurology trainees are women; however, women make up less than 30% of department chairs/division leadership. While pediatric neurology has done an excellent job of recruiting women into the field, there is a discrepancy regarding the promotion of women to the high visibility leadership positions. It is important to ensure that female physicians within all specialties are represented in leadership positions in academic medicine and compensated equally and fairly to achieve gender equity. Women in these roles can serve as role models for future trainees and thus increase the likelihood of women pursuing medicine and academia. Medical practice should promote integrated patient care, diversity, and equitable career opportunities and progression regardless of gender identity.

### **S189. Implementation of an Interactive Neuroradiology Curriculum for Neurology Residents: Interim Results**

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**Objective:** To create a practical and educational neuroradiology curriculum for neurology residents. **Background:** Interpretation of neuroimaging is crucial in many time-sensitive clinical decision in neurology. Although two thirds of

neurology residency programs report having a neuroradiology educational component, many program directors believe neurology trainees have inadequate neuroimaging training. Anecdotal from our tertiary center residency, differences in image interpretation skills largely stem from unique case exposures, individual neuroimaging practice and patient-centered independent study. **Design/Methods:** We implemented an interactive neuroradiology curriculum focused on practical imaging interpretation through interactive patient cases. Nine 1-hour lectures were allocated, each dedicated to a disease category (Vascular, Trauma and Toxic, Neuroinfectious Disease, Auto-immune and Demyelinating Disease, Metabolic and Genetic, and Neoplasm). Each lecture was divided into didactics highlighting pathognomonic findings and interactive patient cases curated from our inpatient services. Junior residents practice interpreting case images. We invited subspecialty attendings to teach pertinent radiographic findings during interpretations. Neuroradiology questions from AAN RITE exams 2018-2021 guided key topics for each lecture. We created 6-question multiple-choice tests per lecture. Pre-tests completion was necessary prior to lecture attendance, while post-tests were distributed after lecture; post-test completion was voluntary. Pre-test completion rate was used as surrogate for attendance. Scores across residency classes were tabulated; paired t-test was performed to evaluate for difference in test scores from pre to post-test. **Results:** Seven of nine lectures and tests are complete. The PGY2 residents have the highest attendance (73.5%). Mean pre-test scores are lowest in PGY2 (55.8%) and highest in PGY4 class (83.6%). Post-test completion rate is 53.5%. 42 pre and post-test scores were paired and demonstrated statistically significant improvement in test scores (pre-test 75.2%, post-test 90.7%,  $p=0.000001$ ). **Conclusion:** Our interactive neuroradiology curriculum was well attended and educational, especially for junior neurology residents. Further data collection, comparative RITE scores, higher post-test adherence, and resident feedback will further improve the curriculum.

#### **S190. Improving Communication Barriers among Patients with Limited English Proficiency and Neurological Illness**

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**Introduction:** Patients who have limited language proficiency (LEP) are a growing population, increasing by 80% between 1990 and 2013 according to the U.S. census. Although federal civil rights protections necessitate the provision of language services to patients with LEP, this population still faces significant barriers to health care, including access to neurology specialty care and subpar quality of care. One national study found that only 30% of physicians regularly used an interpreter. Within the neurology context, patients with LEP face unique barriers as changes in cognition, speech, or ways to communicate compound existing language barriers. Yet the literature is sparse on these unique challenges. In this qualitative study, we explore

the perspectives of medical interpreters, clinicians, and patients/caregivers to understand the unique experiences of patients with both neurological illness and LEP status.

**Methods:** We conducted 20 interviews from April 2022 to February 2023 with interpreters (n=8), clinicians (n=6), and English and Spanish-speaking patients/caregivers (n=6), who were recruited from Massachusetts General Hospital (MGH) and MGH Chelsea HealthCare Center. We analyzed the data using a hybrid deductive-inductive thematic analytic approach.

**Results:** We identified themes at the 1) individual level, 2) relating to communication among patients, family, medical interpreters, and clinicians involved in an encounter, and 3) hospital system level. At the individual level, patients' culture, education, and socioeconomic status (SES) and factors related to their neurological illness (e.g., low-volume speech or memory loss) influenced how clinicians adjusted the neurological exam to meet patients' needs. Interpreters' prior experience working with patients with neurological illness and LEP status, and their sense of belonging in the healthcare team also influenced this experience. Communication-level themes included differences across telemedicine platform modality, with a preference for in-person visits across all participants, and verbal and non-verbal communication strategies used to mitigate challenges, including but not limited to pre- and post-encounter huddles with interpreters. Finally, hospital system-level themes included challenges with the time allotted for clinical encounters. **Discussion/Conclusion:** Our findings showcase a need for explicit discussion and training around how to best meet the needs of patients with neurological illness and LEP status, who may require changes to current interpreter and neurological practice. This could include targeted training for interpreters around the neurological exam or for clinicians on how to best use interpreters, alongside broader system-level changes. By triangulating the perspectives of interpreters, clinicians, and patients/caregivers, we can achieve more equitable care for this patient population.

#### **S191. Journey from Junior Resident to Senior Resident: Neurology Residents' Perspective of Meaningful Transformative Experiences**

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**Introduction:** Understanding the meaningful training experiences that promote professional and personal growth is key as it informs training programs. The purpose of this study is to qualitatively explore the key factors that facilitate professional growth and independence during the first two years of neurology residency at Penn State Health Medical Center (PSHMC). **Methods:** This was a single-center, qualitative study involving semi-structured interviewing of PGY-3 and PGY-4 residents and those who completed neurology residency at PSHMC between 2018 and 2021. Participants were contacted via recruitment email and provided a summary of explanation of research. Informed consent was given and a demographic survey was completed by the participant on REDCap. A scheduled 30-minute Zoom interview was

recorded, transcribed, and qualitatively encoded using MAXQDA software. A Cohen's kappa coefficient of at least 0.7 was reached and categories with themes were analyzed according to qualitative rigor guidelines. Responses to interview questions were confidential and de-identified from the neurology department. **Results:** Eighteen participants responded to the recruitment emails and completed the informed consent forms, demographic surveys, and interviews. The semi-structured Zoom interviews were on average 31.4 minutes long and incorporated open-ended questions covering elements such as mentorship, support network, teamwork environment, career planning, development of independence, a specific transformational event, situation, or social interaction, or elements that may have encouraged transformative growth and independence during neurology residency. **Discussion:** A few common themes amongst current residents and recent alumni include high-pressure environments and a heavy workload during PGY-1 leading to development in multitasking and triaging difficult situations, gaining independence as a PGY-2 with increased responsibility of neurology patients, and adapting to the variability of patient encounters as well as teaching styles of attendings, therefore accelerating personal development, decision-making, and confidence in one's capabilities. **Conclusion:** We anticipate that this study will inform faculty, future trainees, and program leadership in terms of mentorship and make the necessary changes to facilitate meaningful experiences to promote personal and professional development. Future work incorporating multiple residency programs will offer a more robust perspective on evaluating residents' transformative experiences.

#### **S192. Penn Multiple Sclerosis and Related Disorders Center's Approach towards Addressing Disparities in Care in Resident Clinic**

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In July 2020, the Penn Multiple Sclerosis (MS) and Related Disorders Center team members decided to focus our annual Neuroscience Service Line project on improving disparities in care for people living with MS and related disorders cared for in our resident clinic. Evaluation of care quality metrics included number of patients on high efficacy therapy and number of visits annually demonstrated that the most critical issue to address was annual number of visits per patient. Chart

review demonstrated that patients seen in resident clinic had overall fewer visits than patients seen in attending clinics. We found that often patients were seen only once annually in resident clinic, while in attending clinics they are seen every 3 to 6 months for re-evaluation and safety monitoring. One patient was "lost to follow-up" and went 18 months between visits while on infusion therapy. Limited visit access means that patients are not getting optimal safety monitoring on high efficacy therapies, including labs and imaging, and there is less time for overall symptomatic management and QOL improvement. We aimed to improve care by ensuring that patients were seen close to twice annually, on average. A major barrier to appointment access is that resident time is split between outpatient and inpatient responsibilities; while covering inpatient rotations such as the NICU, they do not have outpatient clinics scheduled which limits their availability for in-person appointments. We found that residents were trying to manage urgent care issues with My Chart messaging as they did not have adequate return slots in their clinic schedules. Resident turnover in July is another barrier to visit access and patients may get lost to follow-up during that period of transition. We aimed to increase the number of visits in year 1 to 1.8 visits annually and year 2 to 1.9 visits annually. Interventions included better harmonization of MS faculty staffing resident clinic when patients with MS and related disorders are scheduled, "freeze and thaw" appointment slots that were designated specifically for people living with MS and related disorders, educational initiatives including a "Neuroimmunology Bootcamp" lecture series and resource guide with MS treatment protocols. We also kept track of patients and provided more personal outreach to patients to schedule visits through our administrative team. We met the goal at 1.83 in year 1 and 1.9 in year 2.

#### **S193. Promoting Research in Graduate Medical Education: A Longitudinal Integrated Research Track Designed for Neurology Residents**

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**Introduction:** The ACGME milestones mandate that neurology residency programs include research in their educational programs. Conducting research in residency may be challenging given the inherent time constraints and varied prior research exposure by residents. An optional longitudinal resident research experience was developed to address research gaps in a neurology residency curriculum. **Methods:** A two-year integrated research curriculum was developed in which residents can conduct their own research during their neurology residency training. Residents are encouraged to apply during their PGY1-2 year. Requirements include a research proposal and minimum background in research. Applications are reviewed by the department of neurology leadership. Participants are paired with a clinical or basic science faculty mentor with research experience and aligned interests. Additional guidance is provided by multiple invested parties, including the residency program faculty, the Neurology Chair, Vice Chair for Research, and other research faculty. Residents receive additional instruction through a self-directed learning curriculum and/or Penn State's Physician

Scientist Training Program. The structure of the program is designed to mirror a "real life" clinician researcher experience. **Results:** Since its onset in 2020, seven residents have participated in the research track. Research productivity increased from prior years including more peer reviewed publications, one with associated "press release," and two residents obtained research grant awards. Residents comfort level towards research during residency was enhanced, as well as the program's "research culture." Recruitment of residents with strong research backgrounds has improved each year. **Conclusions:** This longitudinal integrated resident research track curriculum can be applied to any residency looking to enhance research comfort and research culture during the busy residency training. It allows trainees to participate in their own research early in their training under the guidance of dedicated and experienced research faculty mentors. This resource is a tool for trainees to approach research during residency, but is not intended to be a substitute for a comprehensive research curriculum.

#### **S194. Recruiting and Retaining a Diverse Child Neurology Workforce: Disparities in Child Neurology Residency Programs from 2011 to 2022**

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**Background:** The number of child neurologists in the US is 20% below the national necessity and this shortage is more pronounced in underserved communities. Black and Hispanic patients are 30% and 40%, respectively, less likely to receive continual outpatient neurological care than their White counterparts. Gregerson and colleagues highlighted disparities in epilepsy remission among children, emphasizing that Hispanic patients with epilepsy had a reduced likelihood of achieving seizure control. Physicians from demographics underrepresented in medicine (URiM) are more likely to work in underserved communities and contribute diverse perspectives to medical practice. In this study, we explore trends of racial and ethnic diversity among US child neurology residents and consider the consequences of these results on healthcare access, quality, and outcomes. **Methods:** This is a quantitative analysis of the Accreditation Council for Graduate Medical Education (ACGME) Data Resource Book from 2011 to 2022. Demographic data, including the race and ethnicity of child neurology residents, were extracted, and analyzed in Microsoft Excel. Chi-Square analysis was utilized, and expected values were calculated using the 2010 census data (2011 to 2019) and the 2020 US census data for 2020 onwards. The primary outcome was trend in URiM representation (as defined by Licensing Committee on Medical Education) in pediatric residency programs. The data was publicly available therefore IRB approval was not required. **Results:** There were 4035 child neurology residents between 2011-2022. Chi-square analysis demonstrated significant underrepresentation of Black, Hispanic, and Native Americans ( $p < .000001$ ) in US child neurology training programs.

There were 6.9% Hispanic (292/4035), 3.4% Black (136/4035), and 0.1% Native American ((4/4035) residents. There has been a gradual increase in percentage of Hispanic residents, however, there has been no significant change in Black and Native American residents. The data indicates that the percentage of URiM residents in child neurology programs is lagging compared to US demographic shifts. **Conclusion:** To help eradicate health inequities, the ACGME has prioritized the expansion and support of a diverse physician workforce, representative of the population it serves. The stagnant rates of URiM physicians in child neurology pipeline are alarming. Medical institutions should be intentional in cultivating diversity by recruiting and retaining URiM residents and creating a culturally informed and inclusive clinical environment. This improves healthcare accessibility in underserved populations by having more physicians available in those communities, encouraging patients' trust in the healthcare system and increasing rates of follow-up and therapeutic success.

#### **S195. Recruiting and Retaining a Diverse Neurology Workforce: The Pipeline from 2011 to 2022**

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**Background:** The 2006-2013 medical expenditure panel survey revealed that despite being disproportionately impacted by many neurological disorders, Black and Hispanic patients respectively were 30% and 40% less likely to see an outpatient neurologist when compared to White patients. Black and Hispanic individuals comprise 13.4% and 18.3% of the general population respectively, but only 8.7% and 11.3%, respectively, of US medical students. Physicians from demographics underrepresented in medicine (URiM) are more likely to work in underserved communities and contribute diverse perspectives from varied experiences to the medical community. In this study, we explore trends of racial and ethnic diversity among US Neurology residents, focusing on URiM as defined by the Licensing Committee on Medical Education (LCME). **Methods:** A quantitative analysis of Accreditation Council for Graduate Medical Education (ACGME) publicly available GME Data Resource Book from 2011 to 2022. Demographic data including race, ethnicity, and gender of US neurology residents were extracted. A Chi-Square test was utilized with the observed ACGME data and expected values were calculated using the 2010 census data for years 2011 to 2019 and the 2020 US census data for 2020 onward. Microsoft Excel was used for data collection and analysis. **Results:** The percentage of Hispanics, African-Americans, and Native Americans in US neurology residency programs were analyzed. A Chi-square analysis demonstrated significant underrepresentation of Black, Hispanic, and Native Americans ( $p < .000001$ ) in US neurology training programs. Furthermore, trend analysis demonstrated that although there has been an increased number of neurology residents nationwide, there has been no significant change in the percentage of URiM entering the field of neurology. Summary of all years analyzed demonstrated the demographics of adult neurology residents in training to be

6.04 % Hispanic (1754/29035), 3.55% Black (1031/29035) and 0.15% Native American (46/29035). **Conclusion:** Although there has been increased emphasis on diversifying the field of neurology and increasing access to care in underserved communities, the pipeline of neurology residents has not shown any significant increase in the percentage of URiM neurologists in training. The medical and neurology community must prioritize strategies for diversifying the pipeline of US Neurology residents to reflect the patient population of the US. Such steps include promoting the pipeline of URiM entering medical school, neurology residency and neurology fellowship programs. It is essential to ensure early and sustained exposure of URiM youth to the neurosciences via career awareness, mentorship and access to research and education opportunities.

#### **S196. Retrospective Assessment of Equitable Inclusion of Subjects in the National Institute of Neurological Disorders and Stroke Clinical Studies**

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**Background:** Equitable selection of study participants in clinical research is a requirement under 45CFR46 and addresses the fair distribution of risk and benefit on research subjects. Representative participation in clinical research is crucial to improve the validity and generalizability of study results and may address the lack of diversity in research. **Objective:** The purpose of this study was to investigate the racial and ethnic representativeness of study subjects within intramural National Institute of Neurological Disorders and Stroke (NINDS) protocols, with an initial focus on epilepsy studies, to assess the equitable selection of subjects. **Methods:** A retrospective assessment of all intramural NINDS clinical trials from January 2005 to December 2022, including four representative epilepsy protocols, was performed. Demographic data included race, ethnicity, zip code, and home state. Data was compared to the CDC, US Census Bureau, and published literature estimates. **Results:** 20797 participants across 331 NINDS protocols from 2005-2022 were analyzed, including 739 participants in four epilepsy protocols (2008-2022). Compared to the Census, overall NINDS protocols' white enrollment was lower (73.3% vs 77%) and black enrollment was only slightly lower (13.1% vs 13.26%). All other races were comparable to the Census. Total NINDS recruitment for Hispanic or Latino was lower (7.9%), compared to the Census (17.4%). Recruitment in the epilepsy protocols to 2013-2015 CDC epilepsy data demonstrated higher Black non-Hispanic enrollment at NINDS (29% vs 18%), and a lower rate of White non-Hispanic enrollment (56% vs 66%), with 14% of NINDS epilepsy enrollments being Hispanic/Latino. Regarding DC-specific enrollment for NINDS, epilepsy participants on average were more likely to be Black Non-Hispanic (47% vs 31%) and less likely to be White Non-Hispanic (42% vs 53%). Rates of Hispanic/Latino were similar (5% epilepsy vs 4% overall;  $p=0.02$  for overall proportions). Published estimates demonstrate significantly higher Black Non-Hispanic epilepsy prevalence in DC than is captured by the NINDS cohort (74%;  $p=0.001$ ).

**Conclusion:** NINDS demographic enrollment demonstrated lower white, higher Black, and comparable other racial groups when compared to US Census data. The largest disparity was a 9.5% difference in NINDS Hispanic/Latino subject enrollment, indicating a potential recruitment target. The epilepsy cohort revealed that while rates of Hispanic/Latino were comparable to the local DC population, there were significantly fewer local Black subjects enrolled than expected, even though the overall trend at NINDS was a higher Black subject enrollment.

#### **S197. Social and Health Characteristics, and Racial/Ethnic Disparities among Community-Dwelling Adults with Intellectual and Developmental Disabilities:**

**National Data from 2004-2018**

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**Background:** Adults with intellectual and developmental disabilities (IDD) constitute a marginalized population within neurology, experiencing significant health disparities and poverty as compared to those without disabilities. However, there has been only sparse data, largely limited by smaller samples, in characterizing marginalized racial and ethnic groups of adults with IDD. In addition, more adults with IDD now live in the community, therefore it is critical to better understand this population, while shedding light on racial and ethnic disparities. **Methods:** Using national data from 2004-2018 from National Health Interview Survey, I examine social and health characteristics of adults with IDD. Self-reported racial/ethnic data were categorized as follows: 55.9% Non-Hispanic White, 19.96% Non-Hispanic Black, 16.9% Hispanic, and 7.24% Non-Hispanic Non-White. I use multivariate logistic regression models (with appropriate survey weights), with Non-Hispanic White as the comparison group. Covariates included age, sex, insurance coverage, educational attainment and employment status. **Results:** Mean age of this adult IDD population ( $n=5,196$ ) was 38.9 years (SD 15.9), with 54.8% being female. Overall, 18% reported lived alone, 23.1% in two-person households, and the rest (58.9%) in three or more person households; with 77.7% reporting never being married. About 42% did not graduate high school, and only 25.1% were in the labor force, with Black (OR=0.7,  $p=0.001$ ) and Hispanic (OR=0.59,  $p<0.001$ ) individuals having lower odds of being in labor force. Among those reporting earnings, the median annual total earnings was between \$5000-\$9999. Black (OR=1.4,  $p=0.03$ ) and Hispanic (OR=2.06,  $p<0.001$ ) individuals were more likely to not have health insurance. Regarding health care access and preventive services, only 43.2% reported receiving a flu vaccine in the previous 12 months, with Black (OR=0.67,  $p=0.007$ ) have significantly lower odds even after controlling for covariates. About 25.9% reported problems paying or unable to pay medical bills, with lack of insurance coverage driving this (OR=3.4,  $p<0.001$ ). **Discussion:** Characterizing adults with IDD is challenging due to scarcity of data. Here, examining a large sample of community-dwelling adults with IDD, I show persisting gaps in integrating this population into the higher education

system and labor force. Adding to existing literature on poor health outcomes for IDD population in general, I also show significant racial/ethnic disparities in metrics for health care access. This descriptive data lays groundwork for future mechanistic work in understanding how education, employment integration and wages can affect health care access and outcomes in this population.

### **S198. Telemedicine Use before and during the COVID-19 Pandemic among People with Neurological Disorders: A Cross-Sectional Study Using US Commercial Claims Data**

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**Objective:** To evaluate telemedicine (TM) use during the COVID-19 pandemic among people with neurological disorders (pwND), including multiple sclerosis (MS), Alzheimer's disease (AD) and Parkinson's disease (PD). **Background:** Use of TM increased during the pandemic; however, it is unclear how its use and accessibility varies among pwND. **Design/Methods:** This cross-sectional study used US PharMetrics Plus commercial claims data from January 1, 2019–December 31, 2021. TM use, identified using  $\geq 1$  current procedural terminology codes, was assessed in each study year (2019, 2020, 2021) among people with  $\geq 1$  inpatient or  $\geq 2$  outpatient diagnosis codes  $\geq 30$  days apart for MS, AD or PD. Any TM use and ND-related visits (MS, AD, PD diagnosis code within TM claim) were summarized, and characteristics of TM users vs nonusers during the pandemic (2020 and 2021) were described. **Results:** Among pwND, 0.9% (933/101,598 pwND) used TM in 2019 compared with 58.0% (55,517/95,715 pwND) in 2020 and 42.5% (46,315/109,029 pwND) in 2021. Among TM users in 2020 and 2021, the majority had ND-related TM visits (73.2% and 64.6%, respectively); the mean (SD) number of claims was 2.9 (2.8) in 2020 and 2.7 (3.0) in 2021. During the pandemic, nearly 26% of total TM visits ( $n=296,434$ ) were provided by a neurologist. Mean (SD) age of TM users was similar to nonusers (60.5 [15.1] and 61.5 [15.3] years), but TM users were more likely to be female (62% vs 60%), enrolled in Medicare (33% vs 30%) and reside in western and eastern regions compared with nonusers. The proportion of pwND using TM was highest in Massachusetts (81.3%), Vermont (77.1%) and California (72.4%). **Conclusions:** About half of pwND in a commercially insured population used TM during the pandemic; its use varied most notably by region and state. Additional analyses will inform gaps in TM access and its long-term utility.

### **S199. The Current State of Feedback: A Mixed-Method Analysis of Medical Student Feedback in Neurology Clerkships**

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**Background:** Effective feedback is paramount to education. Despite this, it is often vague and non-constructive. Studies

suggest that specific feedback curated and directed by the student can improve performance. We sought to 1) assess the impact of a novel feedback form focused on medical student self-reflection to guide conversation 2) compare perceptions of faculty vs. resident feedback 3) understand barriers to effective feedback. **Methods:** We implemented a novel self-reflective feedback form to be completed by students and used to guide their mid-clerkship feedback session. Students were surveyed with identical questions about the quality and nature of mid-clerkship feedback in the 9 months before and 8 months after implementation. Surveys included quantitative and qualitative assessment of the feedback process. Results were compared pre- and post- implementation. **Results:** 29 students completed the survey pre-implementation and 17 post-implementation. Feedback was perceived similarly pre and post, described as “useful and actionable” (86% pre vs 71% post,  $p=0.5$ ) and an “active conversation” (86% vs 77%,  $p=0.5$ ). Students felt feedback gave an opportunity for self-assessment (72% vs 65%,  $p=0.3$ ), targeted areas for improvement (83% vs 53%,  $p=0.4$ ), and was constructive (97% vs 94%,  $p=0.6$ ) with both formats. Among all forty-six students, only 22% ( $n=14$ ) received feedback from an attending where 80% ( $n=37$ ) reported feedback from residents. 28 students received feedback only from residents, 8 only from attendings, and 6 from both. Students rated the quality of resident feedback higher than that from attendings (8.0 vs 6.1 out of 10,  $p=0.004$ ). Students also felt feedback from residents was more applicable to performance than that from attendings (7.6 vs 5.9 out of 10,  $p=0.02$ ). Qualitatively, comments were similar pre- and post- implementation. Students reported insufficient time allotted to feedback and that it was given in haste. Additionally, students felt feedback lacked specificity and was impersonal. While students “enjoyed the ability to self-reflect” with the new form, they felt it was “intimidating” to ask attendings for feedback “given their busy schedules.” Students also found “people uncomfortable giving [feedback]”. **Conclusions:** In this small pilot, a novel feedback form to promote self-reflection and student-driven conversation did not alter students’ perceptions of feedback. Students rated feedback highly overall. Surprisingly, attending feedback was perceived as lower quality and less applicable than resident feedback. Next steps should attempt to understand this dichotomy and to elucidate reported barriers of time and personal attitudes to giving and receiving quality feedback.

### **S200. The VA National TeleNeurology Program (NTNP): Targeting Rural Veterans to Provide Equitable Access to Specialty Care**

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**Objective:** To describe the NTNP clinical implementation and impact on access to outpatient neurology care. **Background:** Telehealth has become increasingly utilized in healthcare systems to improve access to specialty care and better allocate limited resources. The Veterans Health Administration (VHA), through the Office of Rural Health, has funded and developed the first national-scale tele-neurology program. The NTNP began seeing patients in October 2020 and is now serving 14 VA medical centers in 10 states, with additional sites planned. This hub/spoke program currently includes 20 active neurologists, 7 nurses, 4 telehealth technicians, program manager, medical director, and additional administrative and support staff. **Design/Methods:** The NTNP targets regions with insufficient neurology services both in VHA and the community. Neurology encounters are completed through video visits, either directly to the Veteran's home or to a VHA clinic. Documentation and all aspects of patient care are completed directly in the spoke-site medical record. An 8-week implementation process includes weekly telephone calls with facility outpatient and telehealth managers to facilitate administrative, documentation and scheduling practices. NTNP referrals completed during FY21 and FY22 were included. Demographics, diagnoses and rurality were examined. Comparisons between NTNP and community referrals were analyzed using Wilcoxon-Mann-Whitney tests. Likert scales were used to evaluate Veteran and provider satisfaction and experience (ranges were 1-7 for Veterans and 1-10 for providers). **Results:** There were 1306 total encounters (new plus follow-up visits) and 3730 total encounters in FY21 and FY22, respectively, with 58% living in rural areas. NTNP consults were scheduled more quickly with a median of 5.0 days compared to community referrals with a median of 14.0 days ( $p < .001$ ). The NTNP was also significantly faster to complete consults (median of 66 days vs. 91 for community referrals,  $p < .001$ ). The top three diagnosis categories for patients referred to the NTNP were headache (23.2%), movement disorder (17.7%) and other symptoms (14.9%). Veterans were overwhelmingly satisfied with their tele-neurology visit ( $6.7 \pm 1.2$  s.d.). Overall provider satisfaction with the NTNP was also high ( $8.9 \pm 1.7$  s.d.). More than 95% of Veterans reported that video visits enabled access to care that was otherwise unavailable. **Conclusions:** The NTNP has leveraged telehealth technologies to provide the first national-scale outpatient general teleneurology service, creating timely and equitable access to care, particularly for rural America. Future goals include incorporating virtual subspecialty consultations, patient education programs and case management initiatives.

#### **S201. Thymectomy in Myasthenia Gravis: Enhancement or Expense?**

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**Objective:** To evaluate the pros and cons of thymectomy in myasthenia gravis (MG) patients in Los Angeles County. **Background:** Myasthenia gravis, a disorder of the neuromuscular junction induced by the body's own immune system, has been associated with the production of autoantibodies in the thymus. The disorder causes muscle weakness that can manifest in different ways: double vision, drooping eyelids, limb weakness, and trouble speaking and swallowing. Current treatment options often include acetylcholinesterase inhibitors, immunomodulation, immunotherapy, and monoclonal antibodies. Considering the expensive nature of MG treatment, including but not limited to the cost of medications, IVIg infusions, plasmapheresis, and ICU visits, thymectomy is also suggested as a preventative treatment to increase the chances of clinical improvement. The financial impact of thymectomy on the disease may be an important factor to consider when deciding on treatment options. **Design/Methods:** In 2022 the study was conducted at Olive View-UCLA Medical Center in Los Angeles County analyzed the medical records of 9 patients diagnosed with seropositive MG. Out of these patients, four underwent thymectomy via CellCept intake while the other five were managed conservatively. The expenses associated with the following were calculated before and after surgery for the thymectomy group: outpatient medications, ICU admission, IVIg infusions, plasmapheresis, and thymectomy. **Results:** Patients who underwent thymectomy experienced a significant reduction in their yearly medical expenses, from \$665,723.61 to \$245,182.41 resulting in annual savings of \$420,541.20. Additionally, the number of ICU admission days decreased by 45 days annually post-surgery. Furthermore, the thymectomy group showed a higher rate of clinical improvement and enhanced long-term survival compared to the group managed conservatively. **Conclusions:** Thymectomy can induce clinical improvement and alleviate the economic burden specifically for non-thymomatous MG patients. Thymectomy can be performed with several surgical techniques including trans-sternal, transcervical, and combined transcervical transsternal. Recent developments have also explored minimally invasive approaches such as robotic thymectomy and video-assisted thoracoscopic thymectomy (VATS). This analysis supports the justification and recommendation of elective thymectomy as a treatment modality for non-thymomatous MG patients. The use of this interventional treatment will ultimately result in reduced expenses for both hospitals and patients, improved well-being of patients, and decreased hospitalization duration.

#### **S202. To Neuro or Not to Neuro; That is the Question: A Focus on Women Neurologists Leaving Our Work Force** **Aparna M. Prabhu, MD, MRCP.** *Einstein Medical Center, Philadelphia, PA, USA.*

**Objective:** 1. To study the contributors of burn out in Women Neurologists in the face of excessive administrative burden, resulting in women moving away from a career in clinical neurology. 2. To offer solutions to help prevent



moral injury in all neurologists - Based on our experience in an Academic Urban Medical Center **Background:** The term burnout implies that the neurologist is at fault. More recently, we have come to understand the term moral injury which puts the onus of the issue on the system rather than on the individual. When we find systemic problems, we can find strategies to manage them. This is the first step in coming up with effective solutions to help us sustain so that we prevent moral injury and attrition of neurologists in a world where there is already a predicted shortage of neurologists. **Design/Methods:** An online survey of a 100 Women neurologists who moved away from Neurology, revealed surprising results. The survey covered the key drivers that made women leave neurology, the phase in their career when the change was made, subspecialty, practice setting and eventually what turn their career took. **Results:** Career women in their early phase of career were moving away while they should have been looking at academic growth. Burnout/Moral Injury was a huge driver - administrative interference contributing largely to it. The COVID-pandemic didn't seem to be a key player. **Conclusions:** The survey revealed a lot of potential fixable issues which were brought together as a project for our department to work on. We came up with practical solutions at our academic center - addressing the challenges of administrative burden, introducing flexible schedules, providing physician autonomy, ensuring fair and transparent compensation for the women physicians, and trying to close the gender gap. We also realized that wellness activities were not a solution to the systemic issue - no amount of yoga, meditation, team building would mitigate the sense of dissatisfaction the neurologist faced from administrative burdens, in fact it was seen as an additional burden. In addition to everything else, a collegial work environment played a huge role in retaining the work force at our institution.

#### K-S105. Clinician and Patient Stakeholder Perspectives on Cognitive Rehabilitation Interventions for Asylum Seekers and Refugees

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**Background:** Traumatic brain injury (TBI) disproportionately affects asylum-seekers and refugees (ASR). They endure blows to the head due to exigent circumstances necessitating resettlement (e.g., torture, war, interpersonal violence) and during their dangerous journeys to refuge. Yet TBI remains underdiagnosed and undertreated in this marginalized population. Cognitive rehabilitation represents one evidence-based approach to managing cognitive impairment, a common sequela following brain injury that has clinical, legal, and social economic consequences. Involving stakeholders in co-design processes can facilitate an intervention's acceptability, satisfaction, and implementation. Our study interviewed clinicians and ASR to better understand potential adaptations to existing cognitive rehabilitation interventions for managing

cognitive impairment among ASR with TBI. **Methods:** We conducted six focus groups of 16 clinicians across two academic medical centers in Boston, Massachusetts, United States. We are actively recruiting and conducting focus groups and interviews with ASR patient participants. We have analyzed the clinician's qualitative data using the Framework method and will use the same analytic approach to examine the patient qualitative data. **Results:** Clinicians proposed sociocultural adaptations across seven categories: 1) Linguistic; 2) Cultural, including addressing deference to authority and traversing stigma around both brain injury and mental health; 3) Literacy level, including prior patient experience with educational frameworks and "homework" as part of skill acquisition; 4) Consideration of family role and involvement; 5) Incorporating the migratory context within a larger Trauma-Informed Care framework; 6) Strengths-based approach and individual empowerment, including focusing on individual's strengths and goals; and 7) Telehealth as a tool to address barriers like transportation. The ASR patient participant qualitative data has not yet been collected or analyzed. **Conclusion:** This study qualitatively explores clinician and ASR perspectives on adaptations to cognitive rehabilitation interventions among ASR with TBI. Integrating clinicians' and patients' perspectives in intervention adaptation allows us to meet their needs in TBI recovery best. The results inform the adaptation of a cognitive rehabilitation intervention to prepare for open pilot testing.

#### LB-S106. Case-Based Didactic Curriculum in Neurology Residency Continuity Clinic

**Jose Montes-Rivera, MD.** UConn Health, Farmington, CT, USA.

**Background:** The bulk of residency training is inpatient focused (Furr Stimming et al, 2023). However, many neurologists report mainly working in the outpatient setting (Naley et al, 2006). A large portion of outpatient neurology education in residency is through the continuity clinic. Limitations of the clinic include suboptimal case variety and time constraints. **Methods:** We designed a curriculum consisting of monthly case-based discussion sessions in a flipped classroom model. Residents and faculty preceptors receive an article on evidence-based guidelines, quality measures, or a review on outpatient neurology topics. Cases for discussion and a quiz were given before the session and a second quiz after the discussion. Once a month, the 30 minutes prior to each clinic session were reserved for this discussion. 28 residents (PGY1 - PGY4) participated in the UConn Health/HHC neurology residency program continuity clinic. Two faculty members supervise the clinic sessions and the case discussions. At the end of the academic year, residents and faculty were given a 12-item and 8-item evaluation survey, respectively. Questions were rated using a 5-point Likert scale. **Results:** 21 residents and 4 faculty completed the program evaluation survey. It was well-received with residents agreeing the program was useful for clinical practice (4.14), made them better prepared to manage outpatient neurological conditions (4.19), covered a diverse constellation of topics (4.3), improved teaching in continuity clinic (4.14), and apply what was learned to clinic encounters (4.05). Lower

scoring items included concerns about sufficient time to review articles beforehand (3.52/5), enough time allotted for discussion (3.95), appropriateness of selected papers (3.95), and ability to retain information that was learned (3.6). Faculty agreed the program improved their ability to be a general neurology clinic preceptor (4.75), had good variety of neurology fields (4.23), papers were appropriate (4.5), and had interest in the topics and articles (4.5). Faculty thought the program did not disrupt the clinic flow (1.75/5) whereas residents were neutral on this measure (3.1). Since implementation of the program, overall rating of the continuity clinic experience improved from 2.5 (2018) to 3.14 (2020) and 3.08 (2020). **Conclusion:** This is a new flipped classroom, case-based discussion didactic series which was well-received by neurology residents and faculty. It introduces residents to a broad array of topics starting in PGY1 and improved the teaching and overall experience in continuity clinic. Similar curricula can enhance the teaching and learning experience in the outpatient neurology clinic.

#### **LB-S107. Medical Student Interest in Neurology at a Historically Black College & University (HBCU)**

**Britney Pitter, BS Neuroscience, John Degraft Hanson, B.S. Biology, Minnie Mitchell, BS Biology, Erica Sutton, MD FACS, Uma Menon, MD, MBA (Healthcare), FACNS, FAES, FAAN, FANA. Morehouse School of Medicine, Atlanta, GA, USA.**

**Background:** According to the US Census Bureau, the United States has an aging population that is projected to outnumber children by 2034. As the population ages, the prevalence of neurological disorders will likely increase, and so will the demand for neurologists. According to the AAN (American Academy of Neurology), by 2025, the demand for Neurologists will be 21,440 and the estimated supply will be 18,060, leaving a shortfall of 19%.<sup>1</sup> Racial disparity in neurology residencies accompanies the overall neurologist shortage. According to AAMC (Association of American Medical Colleges), the 2021 neurology residency cohort comprised of 4.2% African Americans, 8% Hispanic, Latino or of Spanish origin, 20.8% Asians, and 40.2% Caucasians. **Methods:** According to a 2022 study conducted at Morehouse School of Medicine (HBCU), Atlanta, Georgia, only 7% of 163 medical students preferred Neurology as their specialty. Most participants who did not prefer neurology attributed their decision to a lack of knowledge about the field. Other reasons included limited exposure to clinical neurology and finding neurology to be a complex field of study. The small percentage of students who preferred Neurology as a specialty is echoed in the limited number of neurologists practicing in Georgia. **Discussion:** According to the Georgia Board of Healthcare Workforce, only 449 neurologists were practicing in 2020 compared to the 261 neurologists that were practicing twenty years earlier. The number of neurologists per 100,000 people in Georgia increased only minimally, from 3.1 (2000) to 4.2 (2020).<sup>2</sup> The consequences of the shortage disproportionately affect underserved areas where access to care is already limited. This exacerbates disparities in diagnosis and treatment. In 2022, the minimum wait time was 35 days for a neurology appointment<sup>3</sup> compared to the average wait of 20.6 days for family medicine and 16.9 days for

orthopedic surgery.<sup>4</sup> **Conclusion:** In addition to recognizing the magnitude of the impact of limited neurologists and an aging population, significant changes need to be made in undergraduate and graduate medical education to include and expand Neurology exposure. Investing in all students, especially minorities, and fostering their interest in neurology will not only bridge the supply-demand gap that plagues the aging US population but also provide culturally competent high-quality neurological care to all.

#### **LB-S108. National Epilepsy Learning Healthcare Registry Uncovers Disparities in Care and Outcomes for LGBTQ Community**

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**Background:** In the US, 14.8 million people identify as LGBTQ+. Despite this, there is little understanding of their health status and healthcare disparities. Gender-affirming hormone therapy (GAHT) can affect seizure control, and gender-queer individuals are at a heightened risk of depression and anxiety, overrepresented in epilepsy populations. No real-world data exists on seizure control in the LGBTQ+ community. **Objective:** Report early insights from a national registry identifying disparities in epilepsy care and outcomes by gender identity. **Methods:** We conducted a cross-sectional analysis to compare the proportion of individuals with seizure control between cis-gender men and women and other gender identities. The data was collected from three pediatric and four adult sites across the US, as part of a national quality improvement initiative, the Epilepsy Learning Healthcare Systems (ELHS), from 2019 to 2023. Standardized data elements, including demographics, social determinants of health, gender identity, seizure frequency and type, and seizure data using the ILAE classification, were collected. We grouped individuals who identified as gender queer, gender non-conforming, transgender, or other into a category called gender-queer, and those who identified as men or women into a category called cisgender. We described the proportion of individuals with seizure control (defined as the absence of a seizure for more than 12 months from the most recent visit) and the quality of data documentation within each group. **Results:** Our registry included 13,724 individuals and 24,000+ office visits, with 27% (N = 3,677) having gender identity reported and 41% having real-world follow-up data with standardized outcomes. Gender queer individuals

reported seizure frequency information more often when asked directly 38% (97/256) than through electronic health records 24% (61/256), indicating the value of patient-facing data collection. Disparities in provider data documentation quality were observed among gender queer individuals 24% (61/256) compared to those who identify as cisgender 44% (1,618/3,421). The proportion of individuals with seizure control was lower among gender queer individuals 28% (14/50) compared to cis-gender men and women 39% (587/1,522) (standardized difference = -0.25,  $\chi^2 = 10.13$ ,  $df=1$ ,  $p<0.01$ ). **Conclusion:** Our cross-sectional analysis revealed a difference in seizure control between gender queer and cis-gender individuals. Our registry offers a foundation for future research for LGBTQ+ individuals with epilepsy. Our finding highlights the need to investigate further healthcare disparities experienced by the growing LGBTQ+ population with epilepsy.

## Movement Disorders

### S203. A Genome-Wide CRISPR Interference Screen Reveals Genetic Modifiers of Lysosomal Glucocerebrosidase Activity

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Mutations in *GBA1* gene, leading to decreased activity of lysosomal glucocerebrosidase (GCase), represent a relatively common risk factor for development of Parkinson's disease (PD) and dementia with Lewy bodies (DLB)<sup>[1-3]</sup>. As the penetrance of pathogenic *GBA1* variants is incomplete, additional genetic factors could play a role in disease onset. Therefore, identifying genes and cellular pathways specifically modulating lysosomal GCase activity may provide novel insights into disease risk. In the present study, we performed an unbiased genome-wide pooled CRISPR interference (CRISPRi) screen to identify genetic modifiers of lysosomal GCase activity. Upon transduction with the sgRNA library hCRISPRi2<sup>[4]</sup>, lysosomal GCase activity was assessed by measuring single cell fluorescence intensity resulting from hydrolysis of the  $\beta$ -glucosidase substrate 5-(pentafluorobenzoylamino)fluorescein di- $\beta$ -D-glucopyranoside (PFB-FDGlu). Approximately 340 genes either reduced or increased GCase activity by a Z-score exceeding |3|, and were called as hits. Importantly, *GBA* and *SCARB2* were identified as hits associated with reduced lysosomal GCase activity, thus confirming internal validity of our approach. A subset of genes from the primary screen were selected for follow-up studies, based on previous genetic link to disease, implication in disease-relevant pathways, and expression in cell types of the central nervous system. Three complementary approaches were used: 1) individual gene knock down via siRNA, 2) pharmacological modulation of druggable targets in iPSC-derived neurons and microglia, 3) CRISPR/Cas9 knock out of selected top hit

genes in iPSCs-derived neurons and microglia. Mechanistic studies focusing on a subset of genes validated using this workflow are ongoing. Our unbiased screen and systematic validation of genetic modulators of GCase activity could provide novel insight into disease penetrance, with potential therapeutic implications for PD, DLB, and additional neurodegenerative diseases with underlying lysosomal dysfunction. References: 1. Chia, R., et al., *Nat Genet*, 2021; 2. Sidransky, E., et al., *N Engl J Med*, 2009; 3. Tsuang, D., et al., *Neurology*, 2012; 4. Horlbeck, M.A., et al., *eLife*, 2016.

### S204. A Minimal Clinically Important Difference for UHDRS® Total Maximal Chorea Score as a Measure of Chorea Severity in Huntington Disease

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**Objective:** To establish a minimal clinically important difference (MCID) for the Unified Huntington's Disease Rating Scale (UHDRS®) Total Maximal Chorea (TMC) score as a measure of chorea severity in Huntington disease (HD), using data from KINECT™-HD (NCT04102579), a 12-week, phase 3 trial of valbenazine in adults with HD-related chorea. **Background:** In KINECT-HD, the efficacy of valbenazine was demonstrated by the least squares mean (LSM) change from screening/baseline in TMC score, which was significantly better with valbenazine versus placebo at Week 10/12 (prespecified primary endpoint). Currently, no MCID has been established for the TMC score in individuals with HD-related chorea. **Methods:** Anchor-based analyses were performed to identify MCID thresholds for TMC score (range, 0 to 28). MCID was defined as the mean of within-subject TMC score change that corresponded to a 1-point improvement in the Clinical Global Impression of Severity (CGI-S: range, 1="normal, not at all ill" to 7="extremely ill") or Patient Global Impression of Severity (PGI-S: range, 1="none" to 5="very severe"). MCID analyses included all assessment data regardless of treatment. Results are presented for responders, defined as participants who had a CGI-S or PGI-S score change <0 at Wk12. **Results:** 46 participants (valbenazine=30, placebo=16) had a CGI-S score change <0 at Wk12 and were considered responders for analysis; 63 (valbenazine=26, placebo=37) were considered non-responders. Based on 34 responders who had a 1-point reduction on the CGI-S, the MCID for TMC was -4.0. 33 participants (valbenazine=22, placebo=11) had a PGI-S score change <0 at Wk12 and were considered responders; 76 (valbenazine=34, placebo=42) were non-responders. Based on 22 responders who had a 1-point reduction on the PGI-S, the MCID for TMC was -4.3. Per these anchor-based results, the LSM change of -4.6 found for valbenazine on the primary endpoint exceeded the MCID. In addition, 57% of participants in the valbenazine group had  $\geq 4$ -point reduction

in TMC compared to 20% in the placebo group. **Conclusions:** Data from KINECT-HD suggest that a change in UHDRS® TMC score of -4.0 (CGI-S anchor) or -4.3 (PGI-S anchor) corresponds to a minimal clinically meaningful TMC improvement in individuals with HD-related chorea. These MCID thresholds were exceeded by the LSM change of -4.6 for valbenazine in the primary endpoint, and substantially more valbenazine-treated participants had a  $\geq 4$ -point change in TMC (57% vs 20% for placebo).

### S205. Adolescent Onset Ataxia Neuropathy Spectrum Disorder with a G737R POLG Variant

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**Background:** Mitochondrial diseases with varying phenotypes and onsets have been linked to mutations in the gene encoding the mitochondrial DNA polymerase gamma 1 (POLG gene on chromosome 15). There are six major phenotypes associated with POLG mutations: i) Alpers-Huttenlocher syndrome; ii) Myocerebrohepatopathy spectrum; iii) Myoclonic epilepsy myopathy sensory ataxia; iv) Ataxia neuropathy spectrum (ANS); v) autosomal dominant progressive external ophthalmoplegia; and vi) autosomal recessive progressive external ophthalmoplegia. Most POLG-related disease patients, particularly those with adolescent or adult-onset disorders, do not exhibit a specific clinical syndrome, making diagnosis challenging. This report details the case of a man with POLG-ANS.

**Case Presentation:** Patient presented to our clinic at the age of 29 years with a history of hand tremors since age 14 years that had progressed to involve his head over five years. He also endorsed gait imbalance, difficulties with fine motor skills, and exercise-induced cramping since the age of 23 years. At around age 37, he began experiencing paresthesias in his feet as well. Examination demonstrated mild slurring of speech, NO-NO head tremor, cervical dystonia, postural hand tremor, upper extremity dysmetria, heel to shin ataxia on the left, wide based gait, and inability to stand without support. Diagnostic workup at age of 29 was unremarkable aside from a heterozygous mutation c.2209G>C (p.G737R) in the POLG-1 gene. Multiple therapeutic options were tried with limited benefit and worse side effects. He ambulates with a rolling walker and takes primidone, riluzole, BOTOX injections for symptomatic benefit. **Discussion:** ANS typically includes mitochondrial recessive ataxia syndrome and sensory ataxia neuropathy dysarthria and ophthalmoplegia, with POLG mutations accounting for about 10% of the ataxia cases. A Norwegian and Finnish population-based study suggested that POLG testing should be included as a primary diagnostic tool for ataxia syndromes due to the high incidence of POLG mutations. Neuropathy in ANS typically presents as an axonal or mixed neuropathy with a predominantly sensory component, although some may also have demyelination. Interestingly, over a third of Italian patients with POLG-related neuropathy reported neuropathic pain, which is an uncommon manifestation of mitochondrial neuropathy. Most POLG-related disorders have been associated with four common mutations: G848S, A467T, W748S, and the T251I-P587L allelic pair. **Conclusion:** POLG-related

disorders cause variable onset overlapping phenotypes, of which ANS presents as ataxia, neuropathy, dysarthria and ophthalmoplegia. Diagnosis is via genetic testing, and treatment is supportive.

### S206. An Atypical Presentation of Tardive Dyskinesia in an Adolescent Patient with Complex Neuropsychiatric History: A Case Report

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**Introduction:** Tardive Dyskinesia (TD) is a movement disorder associated with the use of dopamine antagonist medications, such as first and second-generation antipsychotics. We describe an unusual presentation of TD in the setting of underlying structural neurologic abnormalities and rhythmic movement disorders. **Case Description:** A 13-year-old male with past medical history of developmental delay, ADHD, bipolar disorder, autism spectrum disorder, and Tourette's syndrome presented to the emergency department after 3 weeks of progressively worsening dystonic movements. His symptoms began with a slight limp and developed into rhythmic movements of the extremities and severe opisthotonos. His gait was noticeably disturbed by these movements and had a unique "hopping" quality with fully plantar-flexed feet. He would writhe uncomfortably when seated and endorsed severe bilateral lower extremity pain. Creatine kinase was 5,800 U/L on admission. The patient had a 5-year history of aripiprazole use for bipolar disorder prior to symptom onset, and his daily dose was reduced from 15 mg to 7.5 mg 1 week prior to admission in an attempt to alleviate symptoms. Discontinuation of aripiprazole and inpatient tetrabenazine trial was ineffective. The patient's dystonic movements persisted for 4 years. In the interim since his initial admission, he underwent a comprehensive workup, including for infectious, metabolic, autoimmune, and genetic/mitochondrial disorders, none of which were diagnostic. Brain MRIs demonstrated an unchanging area of encephalomalacia and porencephaly involving the posterior right frontal lobe white matter, with enlargement of the right lateral ventricle, white matter volume loss in the posterior right frontal lobe and thinning of the corpus callosum in the posterior body and splenium. Treatment included trials of guanfacine, escitalopram, clonidine, propranolol, hydroxyzine, clonazepam, valproate, and carbidopa/levodopa, with little to no response. However, clonazepam showed the greatest improvement in restless movements and agitation. The patient also underwent chemodervation of multiple muscle groups without improvement. Treatment was complicated by adjunct antipsychotic medication usage throughout his admissions including risperidone and chlorpromazine. **Discussion:** This patient's complicated history included developmental, psychiatric, and neurological findings that overlap both in character and time. His frontal lobe imaging findings could be associated with his chronic behavioral concerns, mood dysregulation, and myoclonic jerks that preceded the onset of dystonic symptoms. However, extensive history of

antipsychotic use and timing of dystonic features suggest TD. This case exemplifies the nuance of movement disorders and the importance of comprehensive clinical and historical analysis to ensure appropriate diagnosis and treatment.

## S207. ATN<sub>PD</sub> Framework Using Biofluid Markers

### Predicts Cognitive Decline in Early Parkinson's Disease

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**Background:** In Parkinson's disease (PD), Alzheimer's disease (AD) co-pathology is common and clinically relevant. However, the longitudinal progression of AD cerebrospinal fluid (CSF) biomarkers -  $\beta$ -amyloid 1-42 ( $A\beta_{42}$ ), phosphorylated tau 181 (p-tau<sub>181</sub>) and total tau (t-tau) - in PD is poorly understood, and may be distinct from clinical AD. Moreover, it is unclear if CSF p-tau<sub>181</sub> and serum neurofilament light (NfL) have added prognostic utility in PD, when combined with CSF  $A\beta_{42}$ . **Objectives:** First, we describe longitudinal trajectories of biofluid markers in PD. Second, we modified the AD  $\beta$ -amyloid/tau/neurodegeneration (ATN) framework for application in PD (ATN<sub>PD</sub>) using CSF  $A\beta_{42}$  (A), p-tau<sub>181</sub> (T), and serum NfL (N), and tested ATN<sub>PD</sub> prediction of longitudinal cognitive decline in PD. **Methods:** Participants were 364 PD and 168 Controls selected from the Parkinson's Progression Markers Initiative (PPMI) cohort, clinically-diagnosed with sporadic PD or as normal Controls, and followed annually for 5 years. Linear mixed effects models (LMEM) tested the interaction of diagnosis with longitudinal trajectories of analytes (log-transformed, FDR-corrected). In PD, LMEMs tested how baseline ATN<sub>PD</sub> status (AD [A+T+N] *vs.* not) predicted clinical outcomes (rank-transformed, FDR-corrected), covarying for education and gender. Cognitive assessments included Montreal Cognitive Assessment (MoCA; global cognition), Symbol Digit Modalities Test (SDMT; processing speed), Semantic Fluency (semantic knowledge), and Movement Disorders Society modified

Unified Parkinson's disease rating scale (MDS-UPDRS) part I item 1.1 Cognitive Impairment (MDS-UPDRS I Cog).

**Results:** PD had overall lower CSF p-tau<sub>181</sub> ( $\beta$ =-0.16, 95% CI=-0.23 - -0.092,  $p$ =2.2e-05) and t-tau than Controls ( $\beta$ =-0.13, 95%CI=-0.19 - -0.065,  $p$ =4e-04), but not  $A\beta_{42}$  ( $p$ =0.061) or NfL ( $p$ =0.32). Over time, PD had greater increases in serum NfL than Controls ( $\beta$ =0.035, 95% CI=0.022 - 0.048,  $p$ =9.8e-07); PD slopes did not differ from controls for CSF  $A\beta_{42}$  ( $p$ =0.18), p-tau<sub>181</sub> ( $p$ =1) or t-tau ( $p$ =0.96). Using ATN<sub>PD</sub>, PD classified as A+T+N $\pm$  (n=32; 9%) had consistently worse cognitive decline than all other ATN<sub>PD</sub> statuses including A+ alone (A+T-N; n=75; 21%): MoCA ( $\beta$ =-73, 95%CI=-110 - -37,  $p$ =0.00077), SDMT ( $\beta$ =-60, 95%CI=-88 - -32,  $p$ =0.00044), Semantic Fluency ( $\beta$ =-73, 95%CI=-100 - -46,  $p$ =1.3e-06), and MDS-UPDRS I Cog ( $\beta$ =65, 95%CI=30 - 100,  $p$ =0.0036).

**Discussion:** In early PD, CSF p-tau<sub>181</sub> and t-tau were low compared to Controls and did not increase over 5 year follow-up. Even so, classification using modified ATN<sub>PD</sub> (incorporating CSF p-tau<sub>181</sub> with CSF  $A\beta_{42}$  and serum NfL) identified biological subgroups of PD to improve prediction of cognitive decline in early PD.

## S210. Cropland Density and Risk of Parkinson Disease in Medicare Beneficiaries

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**Background and Objectives:** Several studies suggest that agricultural pesticide exposure may play a role in Parkinson disease (PD) pathogenesis. In addition, PM<sub>2.5</sub> (particulate matter with a diameter  $\leq 2.5$  micrometers) is a byproduct of agricultural activity, and PM<sub>2.5</sub> has been recently implicated as a PD risk factor. Previous studies of agriculture-based variables and PD focused on relatively small areas, relied on a single exposure measure, and did not account for PM<sub>2.5</sub> exposure. To understand the role of agriculture-linked exposures on PD risk, we used a large, population-based, geographic approach to explore residential cropland density, county-level pesticide-use, and residential PM<sub>2.5</sub> exposure in Medicare administrative claims data. **Methods:** We conducted a population-based geographic study of 21,639,190 Medicare beneficiaries aged 66-90 and identified 89,390 with incident PD in 2009. Beneficiaries' residences were geocoded to counties and zip+4 in the contiguous U.S. We used the integrated nested Laplace approximation to compute spatially smoothed, county-level PD relative risk (RR), and we adjusted for age, sex, race, smoking, healthcare utilization, and PM<sub>2.5</sub> in all our models. The county-level RRs were used as input in Geographic Weighted Regression (GWR) to identify subregions of the U.S. to perform high-resolution analysis of case-control data. Our high-resolution logistic regression analysis used individual-level patient data, PM<sub>2.5</sub> from a 1 x 1 km grid, and cropland density within a 5-mile radius of residential zip+4. As a post hoc analysis, we also explored our low-resolution (pesticide-use) and compute-intensive (nationwide cropland) data as county-level variables in nationwide linear models. **Results:** We identified a 9-state subregion in the Rocky Mountain/Great Plains, which had

the highest GWR coefficients for the relationship between cropland density and PD risk. The strongest GWR coefficients centered around Williams County, North Dakota, and its surrounding counties, where the RR of PD increased by 6% (95% CI 5%, 7%) with each additional decile of cropland density (square kilometers). Our high-resolution analysis of case control data in the 9-state region revealed a robust association between individual-level cropland density and PD, where the odds ratio for PD was 1.17 (95% CI 1.04-1.31) when comparing the lowest to the highest quartile of cropland density. **Discussion:** Using state-of-the-art geographic techniques, we identified a region-specific association between cropland density and PD in the U.S. Great Plains Region. Further investigation into specific types of cropland and pesticides in this region may identify novel agricultural PD risk factors.

### S211. Differential Diagnoses for Patients Presenting to a Multi-Disciplinary Normal Pressure Hydrocephalus Clinic

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**Introduction:** Normal pressure hydrocephalus (NPH) is a neurological disorder characterized by the clinical triad of progressive gait disturbance, cognitive impairment, and urinary incontinence, in association with radiological evidence of enlarged cerebral ventricles and normal CSF pressure on lumbarpuncture (LP). The clinical presentation of NPH overlaps with many other neurodegenerative conditions. Therefore, establishing a clear diagnosis is vital for appropriate management. The objective of this study was to evaluate the final diagnoses of patients referred to our multi-disciplinary NPH clinic. **Methods:** We analyzed the records of the NPH clinic at Rhode Island Hospital (RIH) (from April 2022 to March 2023). Patients were assessed by a multidisciplinary team comprised of movement disorder specialists, neurosurgeons, neuropsychologists, and physical therapists. Demographic, clinical, and imaging data were examined. Based on the multidisciplinary team consensus, patients were classified as having: 1) probable idiopathic NPH (iNPH) (presence of >1 triad symptom + objective gait improvement post high-volume LP); 2) possible iNPH (>1 triad symptom + lack of atypical clinical features or secondary causes of ventricular dilatation); 3) secondary NPH; 4) unlikely NPH (due to presence of atypical clinical features). **Results:** A total of 89 patients (male/female: 54/35) were evaluated during the first year of the clinic. The mean age of patients was 72.5 years (range: 28-86 years). Based on

a comprehensive evaluation, the final diagnosis was probable iNPH in 33 (37.1%) patients, possible iNPH in 19 (21.3%) patients, secondary NPH in 4 (4.5%) patients, and unlikely NPH in 33 (37.1%) patients. Of the 33 cases with probable iNPH, 26 (78.8%) underwent ventriculoperitoneal (VP) shunt placement. The differential for non-NPH cases was broad and included vascular parkinsonism (n = 1, 1.1%), Parkinson's disease (n = 3, 3.3%), drug-induced parkinsonism (n = 3, 3.3%), Alzheimer's disease (n = 9, 10.1%), other dementia (n = 4, 4.5%), peripheral neuropathy (n = 3, 3.3%), myelopathy (n = 4, 4.5%), and other neurological diagnoses (n = 6, 6.7%; e.g., essential tremor, spinocerebellar ataxia, corticobasal syndrome). **Conclusions:** Our findings illustrate the wide spectrum of neurological conditions that can share similar presentation to iNPH and highlight the importance of a multidisciplinary evaluation to ensure proper diagnosis and management of patients with suspected NPH.

### S212. Disturbances of Basal Ganglia and Cerebellar Bioenergetics in Patients with X-linked Dystonia-Parkinsonism and Heterozygous TAF1 Insertion Carriers

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**Introduction:** X-linked dystonia-parkinsonism (XDP) is a rare movement disorder that affects individuals of Filipino descent caused by an X-linked inherited, intronic insertion of a SINE-VNTR-Alu (SVA)-type retrotransposon in the *TAF1* gene. The disorder is associated with profound neurodegeneration in the basal ganglia and structural changes in the cerebellum. Despite elucidating the underlying genetic cause, the molecular consequences remain widely elusive. Disturbances of cerebral bioenergetics, i.e., caused by mitochondrial dysfunction, are a unifying concept in the development and progression of neurodegenerative disorders. However, evidence for bioenergetic disturbances in patients with XDP (PwXDP) and heterozygous *TAF1*-mutation carriers (hetTAF1) is lacking. **Methods:** In this study, we enrolled five male PwXDP (age: 39.6 ± 4.9), six female hetTAF1 (age: 60.2 ± 6.5) without a diagnosis of XDP, and four non-*TAF1*-carrying, age-, and ethnicity-matched healthy controls (HCs, four female, age: 42.0 ± 7.7). All study participants underwent clinical assessments and multimodal neuroimaging, including <sup>31</sup>P-magnetic resonance spectroscopy imaging (<sup>31</sup>P-MRSI) of the basal ganglia and the cerebellum. Metabolite ratios of interest, (ATP+phosphocreatine)/inorganic phosphate (ATP+PCr/iP), ATP/iP, and PCr/iP were normalized to the respective <sup>31</sup>P-MRSI values of the HCs group. **Results:** In the basal ganglia, only PwXDP revealed a reduction of high-energy phosphorus-

containing metabolites (HEP): (ATP+PCr)/iP (-10.4%), ATP/iP (-11.6%), and PCr/iP (-9.3%). In the cerebellum, PwXP revealed an increase in HEPs of (ATP+PCr)/iP (+13.7%), ATP/iP (+7.8%), and PCr/iP (+17.5%). A similar increase in cerebellar bioenergetics of (ATP+PCr)/iP (+10.3%), ATP/iP (+17.6%), and PCr/iP (+5.7%) was identified in hetTAF1. **Discussion:** Despite the small sample size, we demonstrated alterations in HEP levels in PwXDP and hetTAF1. Reduced levels of HEP in PwXDP appeared to be a state marker indicating dysfunction of the mitochondrial machinery in the manifest disease phase. The increase of cerebellar HEP levels in hetTAF1 may point towards compensatory mechanisms counteracting the dysfunctional cortico-striato-pallido-thalamic loop in XDP.

### S213. Dopaminergic Neuronal Cell Therapy for Parkinson's Disease: Results from a Phase 1 Study of Bemdaneprocel

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**Objective:** This first-in-human Phase 1 study aims to assess the safety, tolerability, functional imaging measures, and exploratory clinical efficacy of bemdaneprocel in subjects with Parkinson's Disease (PD). **Background:** None of the available therapies for PD directly address the loss of dopaminergic neurons, one of the principal pathophysiologic processes underlying PD. Bemdaneprocel is an investigational cellular therapy product composed of midbrain dopaminergic neuronal cells derived from human embryonic stem cells that is under development for the treatment of PD. **Methods:** In this open-label, non-controlled study, 12 subjects have received 1 of 2 different doses of bemdaneprocel to the post-commissural putamen bilaterally, along with a 1-year immunosuppression regimen. Safety and tolerability have been assessed, along with assessments of engraftment and clinical impacts. **Results:** At screening, the average age was 66.4 yrs (57-77) and the mean time since diagnosis was 9.1 yrs (5-14). All subjects presented at screening with a Hoehn and Yahr stage of 2 in the on-medication state. The mean MDS-UPDRS part III score was 46.6 (15-73) when assessed in the off-medication state, and patients presented with 4.3 (1.4-6.2) average daily hours of OFF time as assessed by PD diaries. In both cohorts, the safety profile is favorable with the vast majority of reported treatment-emergent AEs being mild to moderate in nature. In the five subjects assigned to the low dose cohort who have completed 1 year of follow-up, 31 AEs were reported. All but 1 incident of a fall were mild to moderate in severity. 16/17 AEs deemed potentially

related to the intervention were attributed to the immunosuppression regimen. There were no AEs reported as possibly related to the cell therapy. Patients enrolled in both cohorts to date have demonstrated clinical improvement as measured by the MDS-UPDRS, PD diaries, PDQ-39, and others. F-DOPA PET imaging is also providing evidence of engraftment, survival and functionality of the cells at 1 year. **Conclusions:** Results from at least 1 year of follow-up on all patients included in a phase 1 study of bemdaneprocel will be presented. An acceptable safety profile, evidence of sustained engraftment, and positive exploratory clinical outcomes in this study will support further investigation of bemdaneprocel for the treatment of PD.

### S214. Early Changes in $\alpha$ -Synuclein Membrane-Binding in the Central and Enteric Nervous System in Parkinson's Disease

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The physiologic, synaptic functions of Synuclein ( $\alpha$ Syn) are mediated by its membrane-binding region, and loss of membrane-binding leads to  $\alpha$ Syn aggregation.  $\alpha$ Syn aggregates are the main components of Lewy bodies found in both the brain and in the enteric nervous system of Parkinson's disease (PD) patients. Pathological changes and accompanying neurodegeneration precede diagnosis by years, with changes in gastrointestinal motility among the earliest prodromal symptoms of PD, pointing to the gut as a potential starting point for pathology. We hypothesize that changes in  $\alpha$ Syn membrane-binding occur first in the gut and are a marker of early pathology. We measured  $\alpha$ Syn membrane-binding in the enteric and central nervous system using both a novel, humanized mouse model and PD human tissue. First, we characterized motor and gastrointestinal function in  $\alpha$ SynBAC mice, which express human  $\alpha$ Syn under all its regulatory elements, thus enabling human-like spatiotemporal expression of  $\alpha$ Syn.  $\alpha$ SynBAC mice demonstrate typical motor impairments, as well as impairments of gastrointestinal motility. We then examined expression of  $\alpha$ Syn in the brain and gut in these mice, as well as in post-mortem human brain, and colon tissue collected during routine screening colonoscopy in subjects with PD and healthy controls. We show reduced membrane-binding of  $\alpha$ Syn in brain and gut in our mouse model as well as in PD cortex. In preliminary results from human PD gut tissue, compared to healthy controls, we see a trend towards decreased membrane-binding of  $\alpha$ Syn in the colon as well as changes in post-translational modifications that are known to affect membrane-binding. Changes in  $\alpha$ Syn membrane-binding can be detected in a mouse model of PD and in tissue from humans with PD. This study represents the first biochemical assessment of  $\alpha$ Syn in the gut, and suggests that decreased  $\alpha$ Syn membrane-binding can serve as an early biomarker of disease.

### S215. Early Onset Parkinson's Disease Patients with Rem Behavioral Disorder and Constipation Show Poor Performance on the Mental Rotation Task

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Parkinson's Disease (PD) presents with unilateral onset of motor symptoms (stage I/hemi parkinsonism) and progresses to bilateral symptoms (stage II) over time. Evidence suggests that constipation and REM behavioral Disorder (RBD), can appear long before the onset of motor symptoms required for PD diagnosis, constituting a significant prodromal phase. Subtle cognitive deficits in attention, executive functioning, memory and visuospatial abilities have been reported in early stages of PD, in the absence of clinical criteria for mild cognitive impairment (MCI). Previous research indicates that PD patients have decreased performance in the mental rotation task (MRT) compared to age and sex matched healthy controls. Furthermore, MRT has also been proposed as a marker for MCI in Alzheimer's disease. We tested the hypothesis that stage I right-handed PD subjects with disease onset between 40-60 years (EOPD), without any known genetic forms of PD, and having comorbid constipation and RBD as non-motor symptoms will have a greater deficit in MRT scores compared to subjects that do not have constipation and/or RBD. A total of 45 EOPD and 14 non-PD healthy control subjects were enrolled in an IRB approved prospective observational study. Mean UPDRS part III score was  $11.1 \pm 5.4$ . Duration of illness  $3.9 \pm 2.6$  and mean age at testing was  $57.3 \pm 6.7$ . All subjects had MoCA score of  $>27$ , Edinburgh Handedness Inventory (EHI) scores that confirmed left hemispheric dominance and screened negative for depression with the Beck Depression Inventory (BDI). The mean MRT score was compared across 5 groups: patients with RBD only, constipation only, both RBD and constipation, neither RBD nor constipation, and healthy controls. We included patients scoring 5 or more in the RBD screening questionnaire (RBDSQ) and those who satisfied the Rome IV diagnostic criteria for constipation ( $<3$  complete spontaneous bowel movement/week) for the respective groups. T-test results indicate that mean MRT score of patients with both RBD and constipation is significantly lower than those who did not have either RBD or constipation ( $p=0.026$ ) as well as healthy controls ( $p=0.009$ ). Initial data from this ongoing longitudinal study suggests that EOPD subjects with constipation and RBD have visuospatial impairment as noted by lower MRT scores when compared to those without constipation and RBD. Thus, MRT may serve as a simple bedside tool along with RBDSQ and Rome IV criteria to assess EOPD subjects for early cognitive deficits prior to meeting the criteria for MCI in PD.

### S216. Elucidating the Retromer-Mediated Neuroprotective Mechanisms in Parkinson's Disease

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Reducing  $\alpha$ -synuclein ( $\alpha$ S) levels in dopaminergic neurons may have neuroprotective potential in Parkinson's disease (PD). Mutations in the VPS35 gene are a rare cause of familial PD. The most common VPS35 mutation, Asp620Asn, is associated with an increase in  $\alpha$ S aggregates and neuronal death in PD patients' brains. VPS35 is a component of the retromer, a heteropentameric complex involved in protein trafficking. VPS35 regulates the trafficking of proteins involved in three  $\alpha$ S degradation pathways: macroautophagy, chaperone-mediated autophagy (CMA), and the endosomal-lysosomal system (ELS). Our aim is to validate the role of VPS35 in increasing  $\alpha$ S clearance and to test a novel VPS35-targeting small molecule, aminoguanidine hydrazone (2a). 2a acts as a retromer stabilizer and has a neuroprotective effect *in vivo* in an ALS mouse model. Additionally, we investigated the 2a effect on the ubiquitin-proteasome system (UPS), a well-documented route for  $\alpha$ S degradation. We overexpressed exogenous mutant A53T  $\alpha$ S by transient transfection in SH-SY5Y cells, co-treated this group with 2a (or vehicle) at 20  $\mu$ M for 2, 3, or 5 days, and analyzed levels of  $\alpha$ S, VPS35, and  $\alpha$ S degradation pathway markers by western blot and ELISA. We also studied the effect of blocking macroautophagy for 1 day with bafilomycin A1 (BfA1) at 50 nM on the 2a-induced reduction of  $\alpha$ S levels. 2a increased VPS35 protein levels ( $\sim 75\%$ ). The retromer function was also increased based on higher levels of the retromer cargo proteins Sortilin and VMAT2. This correlates with a reduction of phospho-Ser129  $\alpha$ S (P129 $\alpha$ S,  $\sim 50\%$ ) and oligomeric  $\alpha$ S ( $\sim 50\%$ ) in the soluble fraction. 2a boosted the cytosolic  $\alpha$ S clearance pathway based on increasing a catalytic subunit of the proteasome (PSMB5), and the lysosomal  $\alpha$ S clearance pathways based on increasing the lysosomal activity (LAMP1), CMA markers (LAMP2a, Hsc70), and a macroautophagy marker (LC3b). In A53T  $\alpha$ S-transfected cells, treatment with 2a induced a reduction in P129 $\alpha$ S of  $\sim 80\%$  compared to a reduction of  $\sim 60\%$  in A53T  $\alpha$ S-transfected cells treated with both 2a plus BfA1, with a non-statistical difference between the two groups. Thus, 2a can decrease  $\alpha$ S levels even when macroautophagy is blocked by BfA1, a result that may be explained by continued clearance and possibly compensatory upregulation of CMA, ELS, and UPS to clear  $\alpha$ S. These findings highlight 2a as a regulator of multiple  $\alpha$ S degradation pathways and as a promising candidate for neuroprotection in PD.

### S217. Evaluation of $\alpha$ -Synuclein in Blood CNS-Originating Extracellular Vesicles for Parkinsonian Disorders: Systematic Review and Meta-Analysis

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Parkinsonian disorders, including Parkinson's disease (PD), multiple system atrophy (MSA), dementia with Lewy bodies (DLB), progressive supranuclear palsy (PSP), and corticobasal syndrome (CBS), present shared early motor symptoms but differing cellular and regional pathophysiology. Accurate



premortem diagnosis is challenging, highlighting the need for reliable biomarkers. Extracellular vesicles (EVs) contain cell-state-specific biomolecules and can cross the blood-brain barrier to the peripheral circulation, providing a unique central nervous system (CNS) insight. Measuring biomarkers in blood CNS-originating EVs have become a promising avenue for minimally invasive diagnostics. This study evaluated the potential of blood-isolated neuronal and oligodendroglial EVs (nEVs and oEVs)  $\alpha$ -synuclein ( $\alpha$ -syn) proteoforms as discriminatory biomarkers for Parkinsonian disorders. We conducted a comprehensive systematic review and meta-analysis following PRISMA 2020 guidelines. We searched PUBMED, EMBASE, google scholar, and literature reviews to include studies with mean  $\pm$  SD  $\alpha$ -syn in putative blood neuronal or oligodendroglial EVs (nEVs and oEVs) in patients with PD and at least one other Parkinsonian disorder or healthy controls (HCs). Thirteen studies were included in the meta-analysis. Demographic/clinical variables were further collected for meta-regressions. Standardized mean differences (SMD) based on Cohen's d were used to quantify the effect size using an inverse-variance random-effects model. QUADAS-2 was used to assess the risk of bias, Begg's, Egger's tests and Funnel plots were used to assess publication bias. The meta-analysis included 1,565 patients with PD, 206 with MSA, 21 with DLB, 172 with PSP, 152 with CBS and 867 HCs. Findings suggest that a combination nEVs and oEVs  $\alpha$ -syn is higher in PD vs HCs ( $k = 14$ , SMD = 0.21; 95% CI 0.01, 0.42;  $p = 0.021$ ), while nEVs  $\alpha$ -syn is lower in PSP and CBS vs. PD ( $k = 6$ , SMD = -1.04;  $p = 0.0017$ ) or HCs ( $k = 4$ , SMD = -0.41,  $p < 0.001$ ). Additionally,  $\alpha$ -syn levels in oEVs didn't effectively differ among PD, MSA, or HCs, contradicting the literature. Meta-regressions showed demographic/ clinical variables including age, gender, disease stage, motor and cognitive impairment severity were not significant predictors of nEVs or oEVs  $\alpha$ -syn concentrations. Heterogeneity was high in most analyses (>88.0%) but sensitivity analyses did not alter the results, suggesting robustness. Findings highlight the need for adopting more rigorous, standardized procedures and independent validations across all laboratories studying biomarkers in CNS-originating EVs. Additionally, there is a pressing need for improved biomarkers to distinguish among Parkinsonian disorders more effectively.

#### S218. Extensibility of Machine Learning Models for Remote Monitoring of Parkinson's Disease Motor Symptoms across Geography and Disease Severity

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**Background:** Wearable sensors enable remote, objective, and frequent monitoring of motor symptoms in people with Parkinson's disease (PD) via digital measures. Applying machine learning (ML) models trained on one population to a different population (e.g., different PD stage/geography)

requires caution as population characteristics may impact model performance. Recalibration of models can be a practical solution to mitigate this without having to re-develop distinct models for each study population. Our work is among the first applications of utilizing recalibration techniques on wearable sensor based models in PD populations. **Objective:** To describe a practical approach to apply wearable sensor-derived measures in PD across different disease severity and geography. **Method:** Smartwatch-based remote active motor assessments were used to collect sensor datasets in two groups of people with PD. The first was people with early-stage PD in the Netherlands (N=388). We tested the analytical validity of digital measures derived from sensor data via ML methods to measure motor symptom severity individually (bradykinesia, gait, and rest tremor) and in composite measures against consensus clinical scores (MDS-UPDRS; Burq et al., 2022). The second was people with more severe PD in Japan who performed the same smartwatch-based motor assessments during levodopa on and off states. The data was previously used to evaluate model performance for analytical and clinical validity as a pharmacodynamic biomarker for levodopa treatment after recalibration using a subset (N=10; Oyama et al., 2023). **Results:** In the first dataset, correlations (spearman  $r$ ) between clinician-rated consensus scores of MDS-UPDRS part III and the digital measures ranged from 0.46 to 0.70 across tremor, gait, and bradykinesia. In the second dataset, correlations between MDS-UPDRS part III and the digital measures ranged from 0.41 to 0.70 using recalibrated ML models. Levodopa effect size (Cohen's D) for composite measures on the motor symptoms ranged from 0.56-1.37. **Conclusion:** Applying ML models developed in one population to another with different disease severity and geographic location, after recalibration using a small data subset demonstrated: 1) similar analytical performance compared to the original dataset and 2) sufficient sensitivity to discriminate between levodopa medication states. This work provides a practical approach of applying ML models across different PD populations. **References:** Burq M et al. npj Digit Med. 2022; Oyama G et al. Sci Rep. 2023

#### S219. Feasibility of Neurofilament Light Chain as a Blood-Based Biomarker for Screening across Neurological Diseases

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**Objective:** To assess the utility of plasma neurofilament light chain (pNfL) as a biomarker of neurodegenerative diseases using a fixed threshold for screening in clinical practice. **Background:** Elevated pNfL is a marker of neuroaxonal injury in neurodegenerative diseases. However, no threshold has been established for clinically meaningful pNfL elevations for use as a routine screening tool in primary care settings. **Design/Methods:** For this post hoc analysis, baseline pNfL levels were analyzed from clinical studies of patients with Stage I or II Huntington's disease (HD; NCT03664804; n=89), prodromal to mild Alzheimer's disease (AD; NCT03114657; n=1124),

early Parkinson's disease (PD; NCT03100149; n=270) and a cohort of healthy controls (HC; n=690) using the Elecsys platform, and among patients with primary progressive multiple sclerosis (PPMS; NCT01194570; n=498) and an HC cohort (n=117) using the Quanterix pNfL Advantage kit. Median  $\pm$  IQR unadjusted pNfL levels were calculated, and differences from median HC levels were determined for disease cohorts.

**Results:** In patients with HD, pNfL levels were elevated 12.9-fold over the HC median level. pNfL levels were elevated to a lesser extent in patients with AD (1.5-fold) and were slightly lower than HCs among patients with early PD (0.9-fold). Among patients with PPMS, pNfL levels were elevated 1.8-fold over the HC median. For all disease cohorts except HD, pNfL IQRs overlapped with those of HCs. **Conclusions:** Elevated pNfL levels vs HCs were observed among HD, AD, and PPMS cohorts but not in early PD, consistent with previous reports. The large differences in NfL levels between patients with early HD and HCs are consistent with the extent of neuronal damage and axonal injury early in the course of HD. However, no clinically meaningful threshold using a fixed cutoff for pNfL elevation across neurodegenerative diseases could be established. The findings from this study, the first to evaluate pNfL levels from clinical trials across multiple neurological diseases, support further investigation of the clinical utility of pNfL as a neurological screen in primary care.

#### S221. Guanidine Hydrazone (2a): A Novel Disease-Modifying Treatment for Parkinson's Disease

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Compound 2a is a pharmacological stabilizer of the retromer complex that reduces the complex degradation, increasing retromer-subunit protein levels in the brain. Missense mutations of the VPS35 gene, which encodes for a subunit of the retromer complex, are a rare cause of familial Parkinson's disease (PD). Previous results have shown that the retromer complex may control the clearance of  $\alpha$ -synuclein ( $\alpha$ Syn) aggregates, whose accumulation represents a key pathogenetic event for the loss of dopaminergic (DA) neurons in the *substantia nigra* (SN) of PD patients. Our aim is to validate 2a efficacy in protecting against  $\alpha$ Syn pathology and dopaminergic neuronal degeneration in wild-type mice, unilaterally injected into the right SN with a viral vector expressing human  $\alpha$ Syn A53T (AAV1/2 A53T). 2a (or saline control) was administered by daily intraperitoneal (IP) injections and we confirmed that 2a significantly increased VPS35 protein levels ( $\approx$  2 fold) and retromer cargoes (Sortilin) in PD-related areas. We assessed motor function with the rotarod test and  $\alpha$ Syn-induced forelimb asymmetry with the cylinder test. The rotarod test showed a 0.5-fold decrease ( $p<0.002$ ) in the latency to fall for AAV-A53T- $\alpha$ Syn treated daily with 2a compared to saline control mice ( $p=0.0001$ ), indicating that 2a rescued the  $\alpha$ Syn-induced motor deficit. The cylinder test demonstrated that the asymmetrical defects in forelimb use in the AAV-A53T- $\alpha$ Syn injected mice were completely

rescued by 2a administration. The chronic administration of 2a in AAV-A53T- $\alpha$ Syn injected mice significantly protects DA neurons and striatal dopaminergic fibers and leads to the rescue in the accumulation of total and pathological phospho-Serine 129  $\alpha$ Syn. Lastly, we analyzed the molecular levels of dopamine and its metabolites on the ipsilateral striatal side of AAV-A53T- $\alpha$ Syn mice compared to the control AAV-empty vector mice treated with saline or 2a. Treatment with 2a protected against this  $\alpha$ Syn-induced loss of striatal dopamine ( $p<0.0068$ ) and prevented the decline of dopamine metabolites DOPAC ( $p=0.034$ ) and HVA ( $p=0.0147$ ). Daily IP administration of 2a led to protection against behavioral deficits, reduction in total and pathological  $\alpha$ Syn aggregates, rescue of the loss of striatal dopaminergic fibers and striatal monoamines, and protection against dopaminergic neuronal loss in the SN. Our results illustrate the neuroprotective effect that 2a has on dopaminergic neurons and identify 2a as a promising disease-modifying treatment for PD.

#### S222. Higher Plasma Concentrations of Peripheral Inflammatory Markers in Parkinson's Disease Linked to Cognitive Impairment and Worse Clinical Outcomes

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**Intro:** Parkinson's disease (PD) is defined clinically by progressive motor symptoms (e.g., rigidity, bradykinesia, tremor) but also involves many non-motor symptoms (e.g., cognitive decline, depression/anxiety) that further reduce quality of life (QoL). Neuroinflammation plays a key role in the disease process, but the impact of peripheral inflammation on motor and non-motor progression (particularly cognitive decline) remains poorly understood. **Methods:** We measured concentrations of 9 inflammatory markers in baseline plasma collected from 91 non-demented PD patients and 88 controls participating in a longitudinal, 36-month study as part of the Parkinson's Disease Biomarkers Program. Clinical data [Montreal Cognitive Assessment (MoCA), United Parkinson's Disease Rating Scale (MDS-UPDRS), Hoehn & Yahr (HY), Hamilton Anxiety Rating Scale (HARS), and Parkinson's Disease Questionnaire (PDQ)] were obtained at baseline and longitudinally. Of the 9 inflammatory markers, we identified 6 (IL-6, TNF- $\alpha$ , CRP, SAA, ICAM, VCAM) that were correlated negatively with MoCA scores at baseline

in PD but not controls. We then used K-means clustering to group PD patients by baseline plasma concentrations of these 6 markers, identifying 5 clusters [relatively high overall (n=8), high IL-6/CRP (n=16), high TNF- $\alpha$  (n=22), high ICAM/VCAM (n=17), and low overall (n=28)]. Using linear mixed effects models, we then investigated whether these inflammatory clusters were associated with MoCA, other clinical outcomes, and change in these metrics over time.

**Results:** Mean MoCA for the relatively high overall cluster was impaired at baseline (MoCA<26) and significantly lower ( $p<0.01$ ) than that of the relatively low overall cluster, which was within the normal range. This difference remained stable over 36 months. MDS-UPDRS-III motor scores and HY severity ratings did not differ at baseline but showed a cluster\*time interaction ( $p<0.05$ ,  $p<0.01$ , respectively) in which relatively high overall patients progressed faster over 36 months than relatively low overall patients, who remained stable. Several non-motor scores also were consistently higher, or worse, in the relatively high overall cluster than any other cluster over 36 months, including HARS ( $p<0.001$ ) and PDQ, a measure of QoL ( $p<0.001$ ). **Conclusions:** Within PD, patients with relatively high peripheral inflammation reflected by a combination of higher IL-6, TNF- $\alpha$ , CRP, SAA, ICAM, and VCAM concentrations showed poorer cognition, faster progression of motor symptoms and disease severity, higher anxiety, and poorer QoL compared to patients with lower concentrations of all of these markers. These findings suggest peripheral inflammation in PD is associated with cognitive impairment and worse clinical outcomes.

### S223. Human Astrocyte Lipid Trafficking Dysregulation in Parkinson's Disease

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**Objective:** Mutations in the GBA gene represent the highest risk factor for developing Parkinson's disease (PD) and Lewy Body Dementia. It encodes glucocerebrosidase (GCase), which is a lysosomal enzyme that catalyzes glycolipids. Recent studies have highlighted the important role of astrocytes in breaking down otherwise toxic fatty acids from active neurons. However, lipid trafficking and metabolism in the context of PD pathology remains obscure. **Methods:** We differentiated induced pluripotent stem cells from two PD patients and one healthy control into astrocytes with or without CRISPR-Cas9 complete knockout (KO). We analyzed the cell identity using astrocyte-restricted markers. We next examined PD hallmarks using a combination of immunohistochemistry, confocal imaging, RNA sequencing, and GCase activity assays. We then performed an unbiased lipid analysis using mass spectrometry. Finally, we investigated fatty acid trafficking between astrocytes and neurons in bioengineered neural organoid cultures within physiological and inflammatory conditions using fluorescent-labeled fatty acids. **Results:** We

successfully differentiated patient-derived astrocytes that express biomarkers GFAP, CD44, and S100B. We found that astrocytes that carry the GBA mutation had approximately one third of the wild-type GCase activity and KO had no activity. GBA KO astrocytes exhibited larger lysosomes and higher levels of sphingomyelins. Interestingly, they also had lower level of baseline triglycerides similar to inflammatory astrocytes. We optimized fatty acid uptake analysis in astrocytes and discovered lower fatty acid uptake in KO. Lastly, we will investigate how reduced uptake affects neuron-astrocyte intercellular communication within brain organoids. **Conclusions:** The findings suggest that fatty acid metabolism may play a crucial role in the pathology of PD and is expected to be an important target for the development of new therapeutic approaches focused on fatty acid metabolism in astrocytes.

### S224. Late-Onset Wilson's Disease in an Elderly Woman with Unusual Natural History: A Case Report

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**Objective:** To report a case of late-onset Wilson's disease (WD) with a prolonged asymptomatic phase. **Background:** WD is a rare autosomal recessive disease. Symptom onset typically occurs in childhood or young adulthood with elderly onset being rare. **Methods:** Case report. **Results:** A 72-year-old woman presented to the neurology clinic with a 3-year history of progressively slurred speech and unsteady gait. The neurologic exam revealed dysarthria, mild dysmetria, rigidity, and moderate bradykinesia in bilateral upper and lower extremities, and a wide-based gait with truncal ataxia. Past medical history was significant for asymptomatic WD diagnosed at age 20 by blood, urine tests, and liver biopsies. The tests were conducted as part of a family screening after the patient's brother was diagnosed with WD. She was treated with d-penicillamine for approximately 5 years but discontinued due to cost. She lived a normal life until about 3 years ago when she began having difficulty with balance and walking. Laboratory tests demonstrated low serum ceruloplasmin (11.2 mg/dl), low serum copper (63 mcg/dl), and elevated 24-hour urine copper (87 mcg / 24h). Liver function tests were grossly normal. Brain MR reported extensive T2/FLAIR hyperintensities involving the subcortical white matter, thalami, midbrain tegmentum, and pons. The abnormal MR signal in the midbrain was consistent with the "Giant Panda Sign", which was typical with WD. CT abdomen showed signal change consistent with chronic liver disease with fibrosis. The slit lamp exam performed by a neuro-ophthalmologist reported no evidence of Kayser-Fleischer (KF) rings. ATP7B genetic test reported a heterozygous pathogenic variant at c.2128 G>A (p. Gly 710 Ser) and a heterozygous variant of uncertain significance at c. 3473G>T (p. Gly1158Val). **Conclusions:** Our case highlights the heterogeneous clinical presentation of WD: 1) late symptom onset around age 70; 2) prolonged asymptomatic phase without treatment; 3)

predominately neurological symptoms without clinical hepatic manifestation nor KF rings although imaging demonstrated structure abnormalities involving both liver and brain.

### **S225. Limitations in Biomarker Discovery Efforts for Prodromal Huntington's Disease**

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**Background:** Biomarkers are critical to the rational development of medical therapeutics, but significant discrepancy persists regarding fundamental definitions, data collection, standardization and validation practices that impede advancements. Reducing the burden of central nervous system (CNS) disorders requires the identification and validation of biomarkers to predict, monitor and propel treatment development. Given the autosomal dominant nature of HD, efforts to develop biomarkers across the life course of HD could change the landscape for clinical care and preventive interventions. The objective of this research is to compare the effects sizes of biomarkers proposed for use in prodromal Huntington's disease (pHD). **Methods:** Review publications for biofluid markers in HD are available in 2016, 2018, 2021, and 2023. Reports from these reviews were considered for inclusion in this project. This research, however, is limited to studies that included healthy normal controls and participants considered in the prodrome (before diagnosed according to the standard motor exam). Data sources included PubMed, the reviews above, and references included in other papers of interest that included biofluid measures of pHD. Both measures for blood and cerebral spinal fluid were included. Study-specific sample sizes, means, and standard deviations were extracted from all identified publications and assessed via the standardized mean difference between pHD and healthy controls. Standardized mean differences were estimated by Hedges' g. **Results:** A majority of publications failed to report sufficient summary statistics to allow a comparison across studies be conducted. Findings from this review will be documented to encourage authors to report necessary values to facilitate comprehensive analyses of existing biofluid markers for prodromal HD. To date, only 11 publications were eligible (included relevant pHD and healthy control statistics). For 31 biomarkers, the standardized mean difference (SMD) between pHD and healthy controls was meaningful for 3 of them (NfL, YKL-40, and sCD27). Effect sizes for mHTT were not included, as it was consistently below the limit of detection (LOD) for healthy controls. **Conclusions:** The field of biomarker research lacks robust scientific methodology. The study design, reporting quality, and defining of participant cohorts and disease stages are inconsistent across studies. The ability to select clinically relevant biomarkers is dependent on the transparency and reproducibility of studies. Despite weaknesses, several

biomarkers (NfL, YKL-40, sCD27, and mHTT) show evidence of usefulness in monitoring HD progression.

### **S226. Lower Doses of Tofacitinib Extend Survival in ALS Mice**

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Amyotrophic lateral sclerosis (ALS) is a devastating neurodegenerative disease resulting from motor neuron loss, resulting in progressive loss of movement and eventually death 2-5 years from onset. Despite the aggressive and ultimately fatal nature of the disease there is no cure, and treatment options are severely limited. We and others have shown that the immune system contributes to the progression of amyotrophic lateral sclerosis (ALS), suggesting that immunomodulatory treatments may be viable therapeutic options. However, some immune mechanisms are protective while others accelerate disease, meaning that any immune-based treatment must highly specific. Natural killer (NK) cells are a particularly attractive target: these cells are responsible for dispatching damaged and dying cells, and during ALS they accumulate in the CNS, promote microglia activation, and increase the rate of neuronal cell death. Thus, targeting NK cells may slow disease progression via multiple mechanisms. We have previously shown that the drug tofacitinib, a JAK/STAT inhibitor, suppresses NK cell function *in vitro* and overall NK cell levels *in vivo*. We therefore hypothesize that the treatment of ALS with tofacitinib will slow disease progression via the suppression of NK cell function. To test this, SOD1<sup>G93A</sup> ALS mice were treated with low and high doses of tofacitinib either before or after disease onset. Survival was then assessed, and neuroinflammation was also assessed using flow cytometry. Physical phenotyping including grip strength, time on the rotarod, and weight were assessed as well. We found that tofacitinib suppressed neuroinflammation in ALS mice under all treatment regimens, but survival was increased only by lower doses of tofacitinib. Moreover, tofacitinib did not slow the loss of strength or agility in ALS mice, and it accelerated weight loss. Together, these data suggest that tofacitinib may be a viable therapeutic option in ALS, but efficacy may require dietary intervention to counteract weight loss, a known side effect of tofacitinib use. Perhaps more strikingly, the results suggest that immune-modifying treatments may require specific dosing to be effective in ALS and that previous immunomodulatory drugs should be revisited.

### **S227. Measurement of Systemic Phospho-Tau, Ab, NfL and GFAP in Patients with Essential Tremor and Parkinson's Disease after MR-Guided High Intensity Focused Ultrasounds**

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Patients with Essential Tremor and Parkinson's disease have a higher incidence of cognitive impairment and dementia compared to the general population. Postmortem

examination of brain tissue from patients with Essential Tremor and cognitive impairment has revealed the presence of tau aggregates in the brain of these patients. The use of MR-guided High Intensity Focused Ultrasounds (MRgHIFU) is approved for the treatment of both patients with Essential Tremor and tremor-predominant Parkinson's disease. The disruption of the blood brain barrier by MRgHIFU can potentially lead to the release of intraparenchymal proteins into the systemic circulation based on studies in mouse models. In a mouse model of tauopathy, sonobiopsy led to a significant increase in the levels of phosphorylated tau species and neurofilament light (NfL). In this study, we sought to explore the effect of MRgHIFU treatment on the systemic levels of phospho-Tau (pTau-181), amyloid beta 40 (Ab40) and 42 (Ab42), neurofilament light (NfL) and glial fibrillary acidic protein (GFAP) in serum samples from patients with Essential Tremor and Parkinson's disease. A stratified analysis was performed based on the presence or absence of cognitive impairment. The preliminary analysis of 17 treated subjects (13 ET patients, 4 PD patients) shows that the levels of pTau-181, Ab42 and NfL are elevated in those subjects with both Essential Tremor and Parkinson's disease with known cognitive impairment, when compared with those with normal cognition. However, no significant differences were observed in the levels of these proteins before and after treatment with MRgHIFU. In contrast, a significant increase in the levels of GFAP was observed after delivery of MRgHIFU when compared to prior to this therapy in all subjects. Our study is ongoing, and we expect it to be completed this year. This study has the potential to provide insights into the use of sonobiopsy for releasing neurodegenerative disease biomarkers into the systemic circulation, which could aid in predicting the risk of cognitive impairment progression or its presence in this patient population.

#### **S228. Movement Disorders in Adults with X-linked Adrenoleukodystrophy**

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X-linked adrenoleukodystrophy (ALD) is a progressive neurological disease due to mutations in the *ABCD1* gene, resulting in impaired degradation of very long chain fatty acids. The phenotypic spectrum in males ranges from rapidly progressive inflammatory cerebral demyelination in children and adults to a slowly progressive myelopathy in adulthood. Although females with ALD rarely develop the demyelinating phenotype seen in males, most females develop myelopathy in adulthood. While the common manifestations of ALD have been well-described, there are no systematic studies of movement disorders in this population. To investigate the prevalence and characteristics of movement disorders in this population, we performed a retrospective chart review of all adults with ALD who were seen in a single leukodystrophy clinic from 2015 through 2022. We noted neurological exam

findings suggestive of myelopathy or a movement disorder. We reviewed brain MRI data to identify patients with a history of inflammatory brain demyelination. We included 161 adults with ALD (82 female, 79 male) with a median age of 41.7 years. Seventy-five females and 70 males had signs or symptoms of myelopathy. At least one type of abnormal movement was present in 118 (73.3%) patients (59 females, 59 males). The most common type of abnormal movement among both males and females was ataxia, found in 105 (65.2%) patients. Other abnormal movements identified in our cohort were tremor (28.0%), dystonia (9.9%), hypokinetic movements (13.7%), speech abnormalities (13.7%), and hyperkinetic movements (4.3%). Females were more likely than males to present with cervical tremor ( $p=0.018$ ) and dystonia ( $p=0.042$ ). Forty (50.6%) male patients had evidence of cerebral demyelination on MRI and were more likely to present with a movement disorder than males with a normal brain MRI ( $p=0.005$ ). In this study, we observed a variety of abnormal movements in both males and females with ALD. Interestingly, while these movement disorders were associated with brain demyelination in males, they were also present in females despite normal brain MRIs. Females were also more likely than males to manifest with specific abnormal movements including cervical tremor and dystonia. Our results suggest a movement disorder phenotype in females with ALD that is distinct from the one seen in males.

#### **S229. Myelin Lipid Composition of Sciatic Nerves in a HNPP Mouse Model**

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**Introduction:** Myelin is formed by glia which wrap axons concentrically in consecutive segments. Lipids account for 70% of the dry weight of myelin membranes. Myelin is enriched with cholesterol and glycolipids relative to non-myelin producing glia. Damage to myelin can alter the surplus of depolarizing current at the node of Ranvier (safety factor). Myelin is often damaged in many neurological disorders such as demyelinating polyneuropathies and hereditary neuropathy with liability for pressure palsy (HNPP). HNPP is caused by a heterozygous deletion of PMP22 gene. However, investigations into lipid composition of myelin in HNPP is limited even though this information would be critical in understanding the pathogenesis of myelin abnormalities in the disease. **Methods:** Utilizing our murine models for HNPP, we processed sciatic nerves at three different age groups, 1-month, 3-month, and 6-month, for TLC. The protein concentration and cholesterol concentrations were measured using a BCA assay and cholesterol assay, respectively. TLC plates were processed in polar and nonpolar solvents to differentiate between various major lipid species present in the sciatic nerve. **Results:** Our results demonstrate the ratio of the glycosphingolipid galactosylceramide over cholesterol was significantly increased in the HNPP group at 3-months old. The lipid over cholesterol ratios of sphingomyelin, phosphatidylcholine, phosphatidylethanolamine, and cholesteryl ester were similar among groups and ages. **Conclusions:** This

study reveals a new mechanism that may alter myelin capacitance, leading to the impaired safety factor in HNPP. Ongoing efforts in our lab are evaluating other myelin lipid species that can be affecting myelin capacitance in the animal model. This work is supported by the National Institute of Neurological Disorders and Stroke (R01NS115748).

### **S230. Neuroanatomical Origin of Anxiety in Cervical Dystonia: Are the Basal Ganglia the Culprit?**

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**Objective:** To map brain regions associated with anxiety in cervical dystonia using voxel-based morphometry. **Background:** Cervical dystonia (CD) clinically is diagnosed as patterned, abnormal movements involving the head and neck. It is the most common form of focal dystonia seen in clinic affecting approximately 60,000 people in the US. Anxiety in dystonia is widely prevalent and often goes underappreciated adding to disease burden. It may not improve when motor aspects of dystonia are treated posing it as a distinct manifestation of dystonia. The basal ganglia are implicated as the source generator for motor manifestations of dystonia, with contributions from the cerebellum. The objective of this study was to assess whether there are similar neuroanatomic substrates underlying dystonia and anxiety. **Methods:** Participants with idiopathic CD were prospectively recruited from the Rush Movements disorders clinic. Assessment of dystonia (Toronto Western Spasmodic Torticollis Rating Scale 2 or TWSTRS-2 parts I-III) and anxiety (State-Trait Anxiety Inventory or STAI) were done. A cut-off of 37 on the STAI-Y2 was used for the determination of anxiety. Demographic and clinical data were also collected. All subjects underwent a 3D structural T1 MRI Brain without contrast. Optimized voxel-based morphometry (VBM) methods, in statistical parametric mapping (SPM) 12, were used to assess whole-brain differences in gray matter by an investigator blinded to group allocation (TS). Between group analyses were done using t-test and Chi squared test, as appropriate. *p* values less than 5% were considered significant. All statistical analyses were performed using SAS. **Results:** Data on a total of 26 patients were collected, 11 with and 15 without anxiety. The mean age of subjects was 58.4 years (SD 11.8) and 76.6% of the sample were female. The mean total TWSTRS-2 score was 30.8 (SD. 11.2). The mean duration of symptoms was 17 years (SD. 15.8). There was no significant difference between the two groups in terms of their age (*t* *p* = .19), symptom duration (*t* *p* = .14), sex (*X*<sup>2</sup> *p* = .39) or dystonia severity (*t* *p* = .22). Analysis of the MRI data showed a significant difference in gray matter in a 16-voxel area in the left lateral substantia nigra and subthalamic nucleus was appreciated in CD patients with anxiety compared to those without. (*p*=.00). **Conclusion:** These results suggest that anxiety associated with CD may arise from similar basal ganglia structures and may be intrinsic in CD.

### **S231. Nicotinamide Riboside Supplementation for Early Parkinson's Disease: Clinical Benefit Correlates with a Distinct Resting State Network**

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**Background:** In the recent NADPARK study (Brakedal et al. *Cell Metabolism*, 2022), a randomized, double-blinded phase I trial of nicotinamide riboside (NR) versus placebo in early PD, network analysis of FDG PET scans performed before and after treatment revealed a significant metabolic covariance pattern induced selectively by NR. While this pattern can potentially be used as a treatment marker in future NR trials, a non-invasive alternative to PET is desirable for broader applicability. **Objective:** To characterize a significant functional NR-related pattern (fNRRP), we used rs-fMRI scans acquired simultaneously with PET in the NADPARK participants. Changes in pattern expression with NR were correlated with motor ratings obtained concurrently under the blind. **Methods:** We analyzed rs-fMRI scans from drug-naïve PD subjects who received either NR (*n*=13) or placebo (*n*=14). Scans were obtained simultaneously with FDG PET at baseline and 30 days on the Siemens 3T Biograph mMR dual PET-MRI platform at Haukeland University Hospital (Bergen, Norway). To isolate a significant fNRRP network, we applied group independent component analysis (ICA) to identify independent components (ICs) corresponding to resting-state functional networks (Calhoun et al. *Human Brain Mapping*, 2001). Next, we computed expression scores for each IC in every subject (Vo et al. *Human Brain Mapping*, 2017), and selected those with the greatest expression changes with treatment over 30 days. IC values were averaged to obtain a composite fNRRP topography, which was considered significant for paired contrasts at *p*<0.05. **Results:** Analysis of rs-fMRI data from the NR group showed a significant fNRRP, which involved treatment-induced changes in 3 ICs. This network was represented by increases in activity with NR in the medial frontal and parietal regions, anterior cingulate cortex, thalamus, and caudate nuclei. Treatment-induced changes in network expression were significant in the NR group (*p*<0.005, permutation test), with consistent increases in 11/13 NR subjects. Analogous changes were not observed with placebo: increases were present in only 6/14 of these subjects (*p*=0.84). With NR, treatment-induced changes in expression levels correlated with motor outcomes under the blind (*r*=0.75, *p*<0.005). Clinical correlations with fNRRP changes were not significant in the placebo group. **Conclusion:** Using rs-fMRI and ICA, we identified a significant NR-induced network that was modulated by NR and not placebo, correlating with clinical outcome in the active group. fNRRP may be a useful non-invasive treatment biomarker in future randomized clinical trials.

### S232. Online Self Report of Problems and Functional Consequences in Huntington Disease: Feasibility and Informativeness

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**Objective:** Direct to patient online research tools may facilitate the conduct of clinical research by increasing patient access and engagement. We assessed the feasibility of collecting online verbatim patient reported outcomes from adults who self-identified as having been diagnosed with Huntington Disease (HD) using the myHDstory research platform developed by the Huntington Study Group <https://huntingtonstudygroup.org/myhdstory/>.

**Methods:** Data were collected online from consenting United States residents who self-identified as 1) having a HD diagnosis; 2) being able to ambulate independently; and 3) independently meeting most of their daily needs. Verbatim reports were collected by keyboard or voice entry of participants' most bothersome problems due to their HD using the Huntington Disease Patient Report of Problems (HD-PROP), a semi-automated natural language processing tool. Demographic data and, if known, CAG repeats were collected. **Results:** HD-PROP verbatim reports were obtained from 345 participants during the study period from March 1, 2022 through August 8, 2022. Reported residence included 37 states, with large representation in California and New York. Participants were 63% male, 34.5±9.9 (mean ± SD) years old, and 9.5 (±8.4) years since HD diagnosis. Racial self-identification was 46.4% White, 28.7% African American, 15.4% American Indian/Alaska Native, and 9.5% other/not reported. CAG repeat data was reported by 59.7%, and 30.4% had previously participated in a randomized HD clinical trial. All participants reported at least one verbatim HD-related problem; the average number reported was 1.4. Examples of verbatim reports of most bothersome HD problems and functional consequences included "impulsiveness and stress" resulting in "can't be as productive as I would wish," and "falling often" resulting in "not wanting to go outside." 69% of participants rated user satisfaction with myHDstory as "good" or "excellent." **Discussion:** Online research participation was feasible for adults who self-reported a HD diagnosis. Increased geographic and racial/ethnic diversity was found in online participants compared with distributions in HD clinical trial populations. This combined with the relatively low rate of prior clinical trial participation among online participants suggest that online research tools may improve access for patients in relatively underserved areas. Human-in-the-loop, semi-automated curation of HD-PROP verbatim reports will be presented to identify clinically meaningful outcomes for HD research and care.

### S233. Palingenetic Delusional Movement Disorder as Part of Kandinsky-Clerambault Syndrome

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**Introduction:** Kandinsky-Clerambault syndrome is the delusion of being possessed and has been noted to be associated with disorders of movement (Gedevani, *European Psychiatry*, 2022). Two different specific movement disorders, as in Parkinson's Disease or postural tremor, as a pathoplastic manifestation of delusional possession by different entities in Kandinsky-Clerambault syndrome, have not heretofore been described. **Methods/Case Report:** A 37-year-old right-handed female with Schizoaffective Disorder, Bipolar subtype with 4 past psychiatric admissions presented with presence hallucinations, the perception that others were near her, even though she could not see or hear them. She believed a spirit at times would touch her and felt an energy all over her face "like powder". This energy around her lips would force her lips closed. She was convinced that spirits were controlling her, these apparitions were at times of her sister and other times of her grandmother. Such fantasmic powers possessed her and controlled her movements. She described how the phantasms saw what she was seeing when inside her. When the animus of her grandmother possessed her, the patient would develop a pill-rolling tremor of the left hand, similar to the movements her grandmother with Parkinson's Disease had suffered from. Alternatively, when the numen of her sister would possess her, she would experience a postural tremor and horizontal titubation, similar to that what her sister displayed. She would not have these movements when she was not controlled by the phantasmagoria. **Results:** Abnormalities in Neurological Examination: Mental Status Examination: poor hygiene and poor eye contact. Hyperverbal, grandiose with expansive affect, poor insight and judgment. Cranial Nerve (CN) examination: CN I: Alcohol Sniff Test 8 (Hyposmia). Motor Examination: Mild left pronator drift. Cerebellar Examination: Finger-to-nose dysmetria bilaterally. Reflexes: Absent in both lower extremities. Bilateral positive Hoffman's reflexes. Other: Magnetic Resonance Imaging/ Resonance Angiography of Brain with Infusion: Normal. **Discussion:** She acquired characteristics of the specific movement disorder of the entity who possessed her, Parkinsonoid-like movements disorder or cerebellar dysmetria, respectively, assuming the specific abnormal movements of the specter possessors. Given that 46% of the normal population believe in the devil (Ferracuti, *Journal of Personality Assessment*, 1996) and 0.6% of Canadians report that they themselves have been subjected to demonic possessions (Ross, *Journal of Nervous and Mental Diseases*, 1992), assessment for the presence of delusional disorder in those with movement disorders may be worthwhile.

### S234. Pathophysiology and Radiological Features of Hemichorea Hemiballismus Syndrome: A Literature Review

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**Introduction:** Hemichorea Hemiballismus Syndrome (HHS) is a hyperkinetic movement disorder characterized by involuntary, irregular, continuous, unilateral body movements. The major causes of this disorder include ischemic stroke, hemorrhagic stroke, autoimmune conditions, and hyperglycemia. Hyperglycemia and uncontrolled diabetes have been reported with more frequency. The exact mechanism of striatal dysfunction related to hyperglycemia is mainly unknown, but numerous mechanisms have been proposed. This literature review article reviews the pathophysiology, mechanisms, and radiological features of this disease.

**Methods:** We used an advanced PubMed search with the following terms: ((hemichorea-hemiballismus [Title/Abstract]) OR (diabetic striatopathy[Title/Abstract])) OR (hyperglycemia Chorea[Title/Abstract])) OR (hyperglycemia hemiballismus[Title/Abstract]). We included only full-text papers written in the English Language in the last 20 years. We only used articles that explained the pathophysiology of HHS and detailed radiological findings of this disease.

**Results:** Increased levels of glucose cause hyperviscosity; these osmotic abnormalities impair the blood-brain barrier and increase cerebrovascular resistance resulting in ischemia of the vulnerable striatal neurons. This leads to inflammation which causes the accumulation of gemistocytes. The accumulation of gemistocytes causes neural dysfunction that may explain the striatum lesions evidenced on MRI in these patients, usually contralateral to the hemichorea-hemiballismus. The disease is more common in postmenopausal women because low levels of estrogen may cause hypersensitivity to dopamine in these patients which may explain the motor symptoms. Decreased levels of acetylcholine (ACh) and gamma-aminobutyric acid (GABA) in the striatum cause a disbalance in the direct and indirect pathways of the basal ganglia circuit. **Conclusions:** The main radiological findings in HHS are hyperintensities in the T1 sequence, which are contralateral of the side of the Chorea/Hemiballismus. Hypo intensity of SWI contralateral to the Chorea/Hemiballismus, the area of the hypo intensity of SWI is equivalent to smaller than the area of the hyperintensity on the T1 sequence. Patients with HHS showed decreased glucose uptake on PET sequence and decreased perfusion on SPECT. These findings are related to the hypermetabolism generated by hyperglycemia, causing a malfunction of the striatum neurons and thalamic disinhibition. Regarding the DAT scan, these patients have decreased dopamine transporter uptake, which increases clinical confusion. Hyperviscosity might cause decreased dopamine uptake, which could cause neuronal loss or internalization of dopamine re-uptake sites in the presynaptic dopamine terminals. MRS studies showed striatal ischemia with elevated lactic acid and depleted N-acetyl aspartate (NAA) in the affected basal ganglia, suggesting fewer functional neurons.

## S235. Quantifying the Value of Multimodal MRI in Outcomes Prediction for STN DBS in PD

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**Objective:** To compare the predictive value for motor outcomes of multimodal MRI to clinical predictors alone in STN DBS for PD. **Background:** STN DBS is an effective treatment for the motor symptoms of PD, yet outcomes remain highly variable. Currently, pre-surgical levodopa response provides the most established prediction of clinical outcome, although its predictive power varies greatly across studies. MRI-based methods including resting state functional connectivity (FC), subcortical and cortical volumetrics, and DTI-based structural connectivity (SC) independently predict DBS outcomes, while a comprehensive model integrating these methods has not yet been developed. **Methods:** We included 61 participants who had multimodal MRI prior to STN DBS for PD and who had adequate clinical data before and after DBS, as well as good quality volumetric, DTI, and rs-fcMRI data. We applied clinical and MRI-based predictors from published studies including thalamic and ventricular volumes, FC and SC connectivity between STN and GPI, VL thalamus, and motor cortex. Regularized linear regression using the least absolute shrinkage and selection operator (LASSO) and leave-one-out cross-validation was used for model construction and factor selection, optimized to RMSE to avoid overfitting with addition of more variables. The primary outcome was percent change in UPDRS-III from the initial preoperative OFF-medication examination to the average OFF-medication, ON-stimulation score over the first year after DBS. **Results:** The “traditional” model, constrained to only clinical predictors (including levodopa response, age, sex, handedness, LEDD, preoperative UPDRS-III) was modestly predictive of motor improvement ( $R^2 = 0.29$ , RMSE = 14.9). In comparison, the total model, which included FC, SC, volumetric, and clinical predictors more strongly predicted motor improvement ( $R^2 = 0.55$ , RMSE = 13.6). Factors included in the optimized model included STN-GPI FC, GPI-VL thalamus SC, VL thalamus-motor cortex SC, ventricular volume, age, preoperative UPDRS-III, and levodopa responsiveness. **Conclusions:** Multimodal MRI greatly outperforms levodopa responsiveness alone in prediction of motor outcomes for STN DBS in PD. Addition of cognitive and psychiatric features both as predictors and as outcomes may further enhance the predictive power and clinical utility of this approach.

## S236. Racial and Ethnic Differences in Suicidal Ideation in North American Patients with Huntington's Disease: Analysis Using the Enroll-HD Dataset

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**Objective:** To identify racial and ethnic differences in history of suicidal ideation among Huntington's Disease patients, using the ENROLL-HD, 2020 periodic dataset. **Background:** Suicidal ideation (SI) and suicidality are leading causes of



morbidity and mortality among Huntington's Disease (HD) patients. Although HD is frequently described in White Non-Hispanic communities, many HD centers in the US care for many racial and ethnic minoritized groups. **Methods:** In this cross-sectional study, we evaluated the odds of reporting a history of suicidal ideation (yes/no) across different racial and ethnic groups during baseline ENROLL-HD visit. We used multivariate logistic regression models adjusting for sex, age, total functional capacity score (TFC), history of cognitive impairment, employment status, educational attainment, and participant's residential location. **Results:** This analysis identified 4717 genetically confirmed HD participants (36+ CAG repeats) in North America. 56% of participants were female, and only 10% (n=494) of participants identified as a race or ethnicity other than White. 3.4% identified as Latino, 2.3% as Black, 1.1% as Native American, and 0.7% as Asian. Female participants had higher odds of reporting SI (OR 1.15, CI 1.00-1.30). There was a higher proportion of Native American participants who reported a history of SI (47.2%). Those who listed "Other" as their race/ethnicity were more likely to deny a history of SI (93.0%). Native American participants had higher odds of a history of SI (OR 2.36, CI 1.37-4.06). Similar differences were noted when adjusting for biological variables (AOR 2.27, CI 1.3- 3.96) and sociodemographic variables (AOR 2.17, CI 1.22-3.84). Factors associated with lower odds of a SI included race listed as "Other" (AOR 0.20, CI 0.06-0.66), being employed during baseline visit (AOR 0.75, CI 0.63-0.89), and completing higher education (AOR 0.86, CI 0.74-0.99). **Conclusions:** Our findings suggest Native American individuals with HD are more likely to experience SI than other racial groups. Qualitative studies with Native American patients with HD are needed to better understand specific risk factors of SI in this patient population and identify culturally appropriate interventions to manage psychiatric symptoms in this group.

### S237. Remote Monitoring of Physical Activity for Tracking Disease Progression in Friedreich Ataxia

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**Objective:** To investigate the association of sensor-based measures of physical activity with validated patient-reported outcomes (i.e., Friedreich Ataxia Rating Scale activities of daily living (FARS-ADL)) and clinical assessments (e.g., mFARS) in Friedreich's ataxia (FRDA). **Background:** FRDA is an autosomal recessive neurodegenerative disease and, over time, affects coordination, balance, and movement. The insensitivity of clinical outcome measures of the physical dysfunction in FRDA has been a significant challenge for clinical trials. The standard clinical outcome measure remains the mFARS exam, a quantified neurologic exam focused on FRDA disease symptoms. While sufficient in some situations, the mFARS have subjective components, ceiling effects, day-to-day variability, and a modest sensitivity to change. Thus, novel measures might prove more sensitive and relevant to daily activities. Wearable sensors allow continuous measurement of physical activity and mobility in

real-world environments and thus can provide relevant data from daily living. **Methods:** 19 participants (Age = 25.5 ± 1.3 years, BMI = 22.8 ± 0.9, 42% female) were recruited in the study. Subjects were given sensors during their annual Friedreich Ataxia Clinical Outcome Measures Study (FACOMS) visit with instructions for their use. The subjects wore a PAMSys pendant sensor (BioSensics LLC, Newton, MA) for one week and then returned the sensors by mail using a prepaid label. We then compared results from sensor-derived measures collected remotely during activities of daily living. **Results:** Multiple variables from the PAMSys pendant sensor correlated significantly ( $p < 0.05$ ,  $\rho = 0.46$  to 0.53) with FARS-ADL scores, even in this small sample. Additionally, there was a trend towards a significant correlation between sensor-derived measures and upright stability subscale (e.g., FARS Section E). Interestingly, sensor-based outcomes only modestly correlated with mFARS scores, perhaps reflecting the multidimensional aspects of the mFARS. Overall, correlations of sensor values with ADL were more significant than those with exam-based measures, showing their potential superiority in capturing dysfunction in daily living. **Discussion:** Wearable devices accurately measured physical activity and were suitable for long-term monitoring. Our results provide a background for the types of analysis needed to advance sensor measurement. In order to realize their potential, one must understand their features over larger cohorts, as well as the characteristics of outliers in the analysis. Overall, the present approach should provide novel sensor-based measures that can be used in clinical trials in FRDA with due speed.

### S238. Remote UHDRS Motor Exam Using Machine Learning

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**Background:** Objective ratings of movement in Huntington's disease (HD) are critical determinants of diagnosis and severity. Pandemic contact restrictions led to explorations of virtual motor ratings in research and care, during and after outbreak peaks. We used data from large databases (Enroll-HD<sup>1</sup> and Predict-HD<sup>2</sup>) to determine the agreement of the complete Unified Huntington's Disease Rating Scale (UHDRS)<sup>3</sup> Total Motor Score (TMS) and a truncated scale removing three items that cannot remotely be obtained. Hypotheses tested addressed whether remote exams are feasible for clinical care or research data completion. **Methods: Exam:** We conducted remote visits for 30 participants in the Prevent-HD study<sup>4</sup>. Visits were standardized. Participants were mailed an iPad, tripod, sealed envelopes, and tape measure. Visits were conducted over high-speed internet in a private, quiet location. The camera of a vertically-mounted tablet (Apple iPad<sup>5</sup>) faced the participant from 10 feet away. The virtual rater assessed UHDRS motor items. The visits were recorded to an MS

teams<sup>6</sup> video for review by the primary and additional raters. **Machine Learning (ML):** Ratings from certified (European HD Network) raters were used for training and testing. Eight predictive ML models were used to compare performance metrics to determine the best imputation approach for the three missing items (rigidity of both arms and retropulsion). **Results:** An XGBoost<sup>7</sup> prediction model used a 5517-observation training set and an 1839-observation testing set. Prediction accuracy was (9a=0.87, 9b=0.86, 15=0.74). The mean squared error was (9a=0.14, 9b=0.14, 15=0.31). **Conclusion:** We demonstrated a robust predictor for missing/skipped UHDRS motor values. External validation was performed on the larger, diverse ENROLL-HD, and the ongoing Predict-HD/Prevent-HD projects. Prediction results were accurate for the TMS. Future work will advance efforts for remote HD monitoring.

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#### **S240. Sex Differences for Clinical Correlates of Lewy Body Pathology, Alzheimer Disease Pathology and Substantia Nigra Neuron Loss in Lewy Body Dementia** **Ece Bayram, MD, PhD, Irene Litvan, MD. University of California San Diego, La Jolla, CA, USA.**

**Objective:** Lewy body (LB), Alzheimer's disease (AD) pathology and substantia nigra neuron loss are associated with clinical features in Lewy body dementia (LBD) (McKeith, *Neurology* 2017). Higher LB pathology staging and nigral neuron loss increases; higher AD pathology staging reduces the likelihood of a typical LBD phenotype. In those with pure LB pathology, limbic and neocortical LB pathology are associated with worse cognition than brainstem-predominant LB (Ryman, *J. Alzheimer's Dis.* 2021). However, both the prevalence and clinical correlates of pathologies differ based on sex. Neocortical LB is more common and co-pathologies are less common in men (Nelson, *J. Neurol.* 2010; Barnes, *Brain Res.* 2019). Women are less likely to have a typical LBD phenotype and dementia compared to men with limbic or neocortical LB pathology (Bayram, *J. Neurol. Neurosurg. Psychiatry* 2021; Bayram, *Mov Disord.* 2022). To complement our previous findings, we investigated sex differences across all LB pathology stages with different levels of AD pathology and nigral neuron loss.

**Methods:** Data was obtained from the National Alzheimer's Coordinating Center Uniform Data Set (UDS) and Neuropathology Data Set for UDS visits conducted between September 2005 and August 2019 (Besser, *Alzheimer Dis. Assoc. Disord.* 2018; Besser, *J. Neuropathol. Exp. Neurol.* 2018). Analysis included 267 women and 370 men from 31 AD Research Centers with LB pathology, available nigral neuron loss and AD pathology data, excluding other neuropathologic diagnoses. Sex-specific clinicopathological correlations were analyzed controlling for age. For significant associations, sex interaction was assessed controlling for age and other pathologies. **Results:** At first visit with dementia, women were older and had more severe dementia. At last visit before death, women were older, but had similar dementia severity. Women died older, had higher AD pathology staging and lower LB pathology staging. Women were less likely to have clinical LBD diagnosis. Higher AD pathology stage was associated with worse dementia, more so for women. Higher LB pathology stage and more nigral neuron loss were associated with higher likelihood for LBD phenotype, more so for men. **Interpretation:** Sex impacts the clinical correlates of LB pathology, AD pathology and nigral neuron loss in LBD. AD pathology may impact cognition more for women; LB pathology and nigral neuron loss may be associated with LBD phenotype more in men. These sex differences can affect the diagnostic accuracy and treatment efficacy.

#### **S241. Spastic Ataxia 4 Due to mtPAP Deficiency, Case Presentation and Literature Review**

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**Objective:** To report a rare case of Spastic Ataxia 4 with delayed presentation and literature review of the underlying disease process. **Background:** Spastic Ataxia 4 (SPAX4) is a rare congenital disorder (prevalence < 1/1,000,000) with autosomal recessive inheritance due to homozygous mutations of the mtPAP gene (10p11.22) that leads to a defect of mitochondrial mRNA maturation in which the poly(A) tails are severely truncated. The gene is highest expressed in the brain, heart, and skeletal muscles. Patients typically present within the first 3 decades of life with limb and truncal ataxia, spastic paraparesis (increased lower limb tone with brisk knee jerks and extensor plantar responses), cerebellar and spastic dysarthria, learning difficulties and emotional lability as prominent features. Older individuals have slow and spastic tongue movements with brisk jaw jerk, and increased tone in the upper limbs. Motor function progressively declines with increasing spasticity and gait ataxia. Some patients develop optic atrophy with horizontal and/or vertical nystagmus. There is no known treatment for the disease, but individualized education plans and physical rehabilitation services play an important role in improving quality of life. **Methods:** Case report and literature review. **Case:** 54-year-old man with hypertension, chronic gait instability requiring cane to ambulate since age 16 who was admitted to our hospital with acute worsening of gait instability with recurrent falls and

dysarthria. On exam, he was awake, alert, and fully oriented with scanning speech, naming and comprehension intact. He had left lower facial weakness with intact sensation, tongue fasciculations with right tongue atrophy. Strength and sensation intact in all extremities. He was diffusely hyperreflexic with bilateral Hoffman's sign. Coordination exam revealed severe ataxia on bilateral finger to nose, slight titubation, positive rebound and applause sign. MRI Brain revealed moderate diffuse cerebral atrophy with severe cerebellar atrophy. Preliminary serologic evaluation unremarkable for etiology of clinical presentation. Ataxia Comprehensive Genetic Panel via Athena revealed a heterozygous missense mutation of the mtPAP gene (c.1134C>A; p.Phe378Leu), which is a variant of unknown significance for SPAX4. **Conclusion:** Genetic ataxias account for a large portion of adult-onset ataxia. While individual syndromes may be rare, we can improve diagnostic accuracy, prognostication, genetic counseling, and quality of life for our patients by obtaining detailed history and physical, maintaining a broad differential, and utilizing genetic testing when appropriate.

#### S242. Statewide Burdens of Parkinson's Disease across the United States between 1990-2019: A Systematic and Comparative Benchmarking Study

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**Background:** Following Alzheimer's, Parkinson's disease (PD) comprises the second most common neurodegenerative disorder in the United States (U.S.), responsible for afflicting nearly one million people. The statewide divergence in PD rates within the U.S. is significant. Comparable and consistent state-level measures of national PD burden were not previously available. **Method:** The Global Burden of Disease (GBD) tool was used to compute PD prevalence, incidence, and nonfatal health outcomes, stratified by age group, sex, and year from 1990 to 2019 for all U.S. residents using standardized data processing approaches and statistical modeling. **Results:** Prevailing cases of complete PD doubled from 314,242 (95% uncertainty interval [UI]: 257,007 to 374,825) in 1990 to 618,189 (95% UI: 557,325 to 679,007) in 2019, and disability-adjusted life years (DALY) nearly doubled from 217,440 (95% UI: 199,906 to 234,518) in 1990, reaching 492,367 (95% UI: 452,936 to 521,652) in 2019. The overall age-standardized incidence rate (ASIR) was 11.32 per 100,000 in 2019, and it increased with an annual average estimated annual percentage change (EAPC) of 1.34% from 1990 to 2019 (95% CI: 0.97-1.70). The number of total prevalent cases was found to be higher in California (72,260; 95% UI: 64,669 to 79,618), followed by Florida (49,020; 95% UI: 43,722 to 54,290) and Texas (45,474; 95% UI: 40,867 to 50,390) in 2019. Compared to females, males had a higher significant incident number and a higher increasing trend in ASIR (EAPC = 1.96%, 95% CI: 1.48-2.47). Within the age groups, the highest incidence of

PD was observed in patients over 75, whereas the most substantial percentage increase occurred in the group above 80 (394 cases, 95% CI: 312-495 per 100,000 population).

**Conclusion:** The prevalence of PD is rising in every state, which signifies a growing concern in the U.S. Persistent disparities exist between U.S. states regarding the total burden that PD places upon them, but it is clear there is a pressing need for more efficient methods to reduce the prevalence of PD. Through the combination of early diagnosis and better access to high-quality care, it is necessary to raise public awareness of the importance of restorative lifestyles.

#### S243. T1 MRI Reveals Differential Hippocampal Atrophy in Lewy Body Disorders with and without Alzheimer's Copathology

**Jesse Cohen, MD**, Jeffrey Phillips, PhD, Sandhitsu Das, PhD, Emma Rhodes, PhD, Kathryn Cousins, PhD, Paul Yushkevich, PhD, David Wolk, MD, Daniel Weintraub, MD, David Irwin, MD, Corey McMillan, PhD. University of Pennsylvania, Philadelphia, PA, USA.

Lewy body disorders (LBD) include Parkinson disease (PD), Parkinson disease dementia (PDD), and dementia with Lewy bodies (DLB). Around half of LBD patients have coexisting AD pathology (LBD+AD), which correlates with shorter time to dementia and death. Verbal memory impairment correlates with worse hippocampal tau pathology at autopsy in LBD. It remains unknown whether hippocampal tau burden in LBD+AD causes neurodegeneration detectable by *in vivo* structural MRI, and whether hippocampal atrophy explains verbal memory impairment. We studied 125 patients with clinical diagnoses of LBD (PD, n = 68; PDD, n = 20; DLB, n = 37) with available T1 MRI and AD biomarkers or autopsy, and cognitively-normal controls (n = 170). AD copathology was defined hierarchically by: a) AD "intermediate" or "high" by ABC neuropathologic criteria (n = 40); 2) positive amyloid PET (n=2); and 3) CSF total tau:β-amyloid<sub>1-42</sub> ratio > 0.3 (autopsy-validated cutpoint) (n=83). The Automated Segmentation of Hippocampal Subfields pipeline was applied to subjects' T1 MRIs. Hippocampal volume (HV) was compared between controls, LBD-AD, and LBD+AD, and correlated with verbal memory scores. Linear regression was used to test the association of AD copathology and HV (dependent variable), covarying for age, sex, race, and education. Significant differences (ANOVA p=1.2e-6) in bilateral HV (expressed as percentage of intracranial volume) were seen between groups (mean 0.455±0.042 for controls, 0.440±0.048 for LBD-AD, and 0.405±0.064 for LBD+AD). Tukey's test showed significant differences between LBD+AD vs controls (p<0.001), LBD+AD vs. LBD-AD (p=0.001), and LBD-AD vs. controls (p=0.035). Using controls as the reference group, linear regression controlling for age, sex, race, and education showed a significant association of LBD+AD with HV (beta= -0.043, p=4.98e-6); LBD-AD association with HV did not meet statistical significance in the linear model (beta = -.011, p = 0.056). Among LBD patients, HV positively correlated with VM (immediate recall: r<sup>2</sup> = 0.17, p<0.001, delayed recall: r<sup>2</sup> = 0.15, p=0.002, recognition

discrimination  $r^2 = 0.13$ ,  $p = 0.004$ ). Thus, in patients with LBD, AD copathology associates with greater hippocampal atrophy on T1 MRI, which correlates with greater verbal memory deficits. This supports the hypothesis that AD copathology impairs cognition in LBD via hippocampal neurodegeneration.

#### **S244. Tandem Gait Step-Width Increases More Rapidly In More Severely Affected Patients With Parkinson's Disease**

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**Objective:** To determine if tandem gait progression is dependent on disease severity in Parkinson's disease. **Background:** Tandem gait performance is used clinically to assess for ataxia, has been reported to predict fall risk in idiopathic Parkinson's disease (PD), and helps distinguish PD from atypical parkinsonism. We previously showed in a cross-sectional cohort that tandem gait step-width widens with increasing Hoehn and Yahr (H&Y) disease severity. **Design/Methods:** Participants enrolled in a longitudinal monitoring study underwent an instrumented tandem gait measurement every 6 months. Participants who had completed at least 2 years of follow-up with at least 3 visits were included in the analysis. The mean and variability of 4 tandem gait parameters were calculated at each visit: step-width, step-length, step-time, and step-velocity. The annual percent change (delta) in each parameter for each participant over time was calculated. The delta in tandem gait parameters was correlated with initial disease features using Kendall's  $\tau_B$ . PD participants were also divided into 3 groups based on their initial H&Y disease stage and the mean delta was compared among these groups with Kruskal-Wallis test. **Results:** 66 participants met criteria (46 PD, 20 controls). Delta step-width was correlated with initial motor Unified Parkinson's Disease Rating Scale (UPDRS) scores (Kendall's  $\tau_B = 0.229$ ,  $p = 0.008$ ), total UPDRS scores (0.249, 0.003), H&Y scores (0.266, 0.005) and inversely correlated with Montreal Cognitive Assessment (MoCA) scores (-0.209, 0.019). Delta CV step-width was also inversely correlated with H&Y stage (-0.204, 0.031). On subgroup analysis, delta mean step-width also showed a significantly faster decline (increasing step-width) in an H&Y stage-dependent manner (Kruskal-Wallis test = 8.312,  $p = 0.040$ ). While none of the pairs showed significance after Bonferroni correction, uncorrected there was a difference between controls and H&Y stage 2 PD participants (-12.831,  $p = 0.021$ ). **Conclusion:** Tandem gait step-width widens over time in people with PD and more rapidly in more severely affected PD patients. These results suggest that tandem gait should be evaluated in PD patients in the clinic setting and should be taken into consideration when managing imbalance in PD. As growing evidence suggests that cerebellar pathways contribute to the pathology of PD, future correlation with imaging is indicated.

#### **S245. Tau Maturation in Clinicopathological Spectrum of Lewy Body and Alzheimer's Disease**

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In Alzheimer's disease neuropathologic change (ADNC), maturation of neurofibrillary tangles and tau pathology are characterized by posttranslational modifications of tau. ADNC and Lewy body disease (LBD) commonly co-exist in aging brains and there are overlapping clinical syndromes and heterogeneity in clinical features among cases with mixed ADNC and LBD pathology. Given this clinical and pathological overlap, we examined the postmortem expression of tau conformational epitopes that mark various stages of tangle maturation in the clinicopathologic spectrum of Alzheimer's disease (AD) and LBD. Autopsy-confirmed cases with diffuse neocortical LBD with/without ADNC ( $n = 59$ ) were selected. We used digital histology methods to measure the percent area occupied (%AO) with pathology in three regions (middle frontal, anterior cingulate, and superior temporal cortices) immunohistochemically stained with MJF-R13 (alpha-synuclein), NAB228 (beta-amyloid), and tau monoclonal antibodies marking phosphorylated (AT8), early conformational (MC1, preferentially reactive in pre-tangles), and C-terminally truncated tau epitope (TauC3, preferentially reactive in mature intracellular and ghost tangles). Linear mixed effect models tested the group comparisons and correlation between alpha-synuclein or beta-amyloid with the outcome of neocortical tau. In models, %AO were log-transformed, and age and sex were included as covariates. Our data suggested alpha-synuclein strongly correlated with early tau epitopes labelled with AT8 ( $\beta = 0.72$ ,  $p < 0.001$ ) and MC1 ( $\beta = 0.27$ ,  $p < 0.001$ ), but not with mature tau epitopes detected by TauC3 ( $p = 0.99$ ). There were significant positive correlations between all tau epitopes and beta-amyloid, including TauC3 immunoreactive tau ( $p < 0.007$ ). Among cases with ADNC, there was greater MC1 ( $\beta = 1.93$ ,  $p = 0.03$ ), AT8 ( $\beta = 2.24$ ,  $p = 0.007$ ), and TauC3 ( $\beta = 1.41$ ,  $p = 0.038$ ) pathology in patients with clinical AD compared to clinical LBD. In LBD, higher alpha-synuclein was associated with greater phosphorylated and early tau epitopes, but not later conformation of mature tau, which was selectively associated with amyloid-beta burden. Our findings suggest that tau pathology may predict the clinical expression of synucleinopathies, and C-terminal truncation of tau may be more closely related to AD pathophysiology than synucleinopathy.

#### **S246. The Adaptive Immune System is Not Necessary for $\alpha$ -Synuclein Pathology Formation or Dopaminergic Neuron Loss after $\alpha$ -Synuclein Pre-Formed Fibril Injection**

**Esteban Luna, MD/PHD.** University of Pennsylvania, Philadelphia, PA, USA.

Intracellular aggregates of the protein  $\alpha$ -synuclein (asyn) pathologically define Parkinson's Disease (PD), and

mutations and genetic polymorphisms of the SNCA gene that encodes asyn genetically link asyn to PD. Microglia, the chief immune cell of the CNS, change in morphology in the presence of PD pathology. How neuroinflammation mediated by microglia is involved in PD pathogenesis is a key knowledge gap. If understood, we could provide novel neuro-protective therapeutic strategies in PD. To understand the role of the adaptive immune (B & T cells) and innate immune systems (i.e. microglia) in PD, I utilized a PD model where I intracerebrally injected a misfolded form of recombinant asyn that can template native asyn *in vivo* replicating PD, termed pre-formed fibrils (PFFs). I injected mouse lines that exhibit dysfunctional immune activity or C57BL/6 mice, which have intact adaptive and innate immune function. Mice that lack B & T cells, Rag2;IL2Rγ double knockout (RDKO) mice, exhibited similar levels of asyn aggregates and neurodegeneration relative to C57BL/6 mice. Interestingly, I found that Non-obese Diabetic SCID Gamma (NSG) mice, a mouse line that contains innate immune dysregulation and are deficient in B & T cells, develop increased asyn protein inclusions by 3-fold and 2-fold worse neurodegeneration of the substantia nigra pars compacta and ventral tegmental areas by 6 months post injection indicating that innate immune dysregulation mediates the potentiated phenotype independent of the adaptive immune system. NSG mice injected with PFFs also developed weight loss and a worse motor phenotype measured by rotarod and grip strength. To determine what genes predispose NSG mice to form increased asyn inclusions after PFF exposure, I compared the intracerebral neuroinflammatory gene expression profiles between NSG mice and control strains using a Nanostring microarray panel. I found that the gene *MPEG1* is down-regulated 8-fold in NSG mice. *MPEG1* is a lysosomal protein found in the brain primarily in microglia and involved in cytokine secretion. These data illustrate that microglia may play a role in the spread of asyn pathology and neurodegeneration in PD and indicate that *MPEG1* may be a novel target to modulate PD pathogenesis. Future directions for this work include 1) determining the role *MPEG1* has in microglial cytokine secretion after PFF treatment and 2) determining if dysfunctional microglia correlate with neurodegeneration in post-mortem tissue examining microglial morphology and cytokine expression with RNA-scope/IHC dual staining.

#### S247. The Effect of Deep Brain Stimulation on the Sequence Effect in Speech in Parkinson's Disease

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**Objective:** To determine the effect of subthalamic nucleus deep brain stimulation on the sequence effect in speech in Parkinson's disease. **Background:** The sequence effect is known as progressive deterioration in speed or amplitude of

ongoing movements including speech, limb movements, and gait [1-3], which is unique to Parkinson's disease (PD) [4]. Up to 90 % of individuals with PD develop speech impairment classified as hypokinetic dysarthria, and the sequence effect in speech can further cause reduced intelligibility, articulatory imprecision, and altered speaking rates [5]. The progression of speech impairment can limit the ability to communicate and contribute to social isolation. So far, studies have shown that the sequence effect does not respond well to dopaminergic medications [6-8]. Here, we investigated whether subthalamic nucleus deep brain stimulation (STN DBS) improved the sequence effect in speech in people with PD. **Methods:** Nine individuals with PD who underwent bilateral STN DBS surgery participated in this study. The speech intelligibility test, sustained phonation test, and verbal diadochokinetic test were performed and compared OFF therapy, to ON open-loop STN DBS and to ON closed-loop STN DBS. **Results:** Overall, both open-loop and closed-loop DBS improved the sequence effect in speech compared to off therapy. Detailed quantitative analysis for verbal accuracy, speaking rate, and volume will be presented. **Conclusions:** This study demonstrated that open-loop and closed-loop DBS is beneficial for the sequence effect in speech in PD. Further studies assessing long term effects will be needed to address long term benefits of DBS on the sequence effect in speech in people with PD.

#### S248. Therapeutic Suppression of Tubulin alpha 4a Rescues HABC Leukodystrophy in Mice

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Hypomyelination and atrophy of basal ganglia and cerebellum (H-ABC) is a rare leukodystrophy associated with causal variants in tubulin alpha 4A (*TUBB4A*). The recurring variant p.Asp249Asn (D249N), which impacts the majority of affected individuals, presents in infancy with dystonia, speech deficits, progressive gait impairment and loss of ambulation during the first decade of life. We have generated and characterized a series of mouse models from our previously published CRISPR-Cas9 knock-in D249N mutant *Tubb4a* mouse and the asymptomatic *Tubb4a* Knockout model (*Tubb4a*<sup>KO/+</sup>): wild-type (WT), *Tubb4a*<sup>KO/KO</sup>, *Tubb4a*<sup>D249N/+</sup>, *Tubb4a*<sup>D249N/KO</sup> and *Tubb4a*<sup>D249N/D249N</sup> mice in order of increasing phenotypic severity. The *Tubb4a*<sup>D249N/D249N</sup> model shows an onset of tremors at ~postnatal day 9 (~P9) with progressive motor dysfunction, ataxia and decreased survival ~P35-P37. *Tubb4a*<sup>D249N/D249N</sup> mice demonstrate severe myelination deficits and neuronal atrophy in the striatum and cerebellum. The compound heterozygote *Tubb4a*<sup>D249N/KO</sup> mouse demonstrates an intermediate phenotype with tremors at ~P21-P30 (n=15-20, p<0.001 vs WT), gradual loss of motor function from ~P30-P90 (n=15-20, p<0.0001 vs WT), mean survival ~P108-P110 with hypomyelination (P21) and degeneration of cerebellar granule neurons close to end-stage (~P108-P110). Our previously

published data shows the *Tubb4a*<sup>D249N/+</sup> model displays the mildest phenotype with limited hypomyelination, no behavioral or neuronal deficits and a typical lifespan (Mean survival = P600-720). We confirmed that *Tubb4a*<sup>KO/KO</sup> mice exhibit no deficits in myelin, neuronal, and motor skills (n=20) with normal survival (Mean survival = P600-720). Overall, disease severity correlates with expression of mutant Tubb4a and relative preservation of wild type tubulin. Thus suppression of Tubb4a expression might provide a general therapeutic strategy for H-ABC. To evaluate the translational potential of this strategy, we generated and identified *Tubb4a*-targeted antisense oligonucleotides (ASO) that stably decrease Tubb4a mRNA and protein in cortex (n=5-6, 50-60% Tubb4a reduction, p=0.01) and striatum (n=5-6, 70-80% Tubb4a reduction, p=0.001) *in vivo* after a single intracerebroventricular bolus (i.c.v.). The selected ASO candidate showed no toxicity *in vivo* at 5, 15 and 20µg/g in WT mice. Single i.c.v. administration of *Tubb4a*-targeting ASO into postnatal *Tubb4a*<sup>D249N/KO</sup> mice significantly improved motor and behavioral deficits as assessed by rotarod, grip strength and tremor assay (n=12-15, p<0.001 vs. untreated *Tubb4a*<sup>D249N/KO</sup> mice). ASO treatment extended the lifespan of these mice more than 2-fold (Mean survival = P260-P280) (n=12-15, p<0.01 vs untreated *Tubb4a*<sup>D249N/KO</sup> mice). Collectively, this is a first preclinical proof-of-concept for Tubb4a suppression via ASO as a disease-modifying therapy for H-ABC.

#### S251. Understanding How GBA Mutations Influence Parkinson's Disease Progression

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We are investigating mechanisms underlying the clinical observation that GBA mutations are associated with increased risk of developing PD, along with faster progression of motor and cognitive symptoms. Mutations in the gene *glucosidase, beta acid 1* (*GBA*) are the strongest genetic risk factor for Parkinson's Disease (PD) and accelerate disease progression. Our prior work using a *Drosophila* *GBA* deficient model revealed altered exosomes may act as vehicles to accelerate protein aggregate spread. We are now further investigating how *GBA* affects neuronal endolysosomal trafficking and exosome biogenesis. To do so, we are using a *Drosophila* and human cell culture model. We have developed a *Drosophila* model of *GBA* deficiency (*GBA*<sup>del</sup>) by deleting the *Drosophila* homolog of the *GBA* gene. We have generated human induced pluripotent stem cells (iPSCs) from fibroblasts of an individual with PD carrying the IVS2+1G>A *GBA* mutation (*GBA*<sup>IVS</sup> PD). Dopaminergic neurons were differentiated from *GBA*<sup>IVS</sup> PD, isogenic *GBA*<sup>WT</sup> PD, and age- and sex-matched healthy control iPSCs using StemCell Technologies reagents and protocols. Confirmation for differentiation was performed by

IHC. We isolated neuronal EVs by size exclusion chromatography from conditioned media. Our *Drosophila* model has shown us that isolated exosomes from from *GBA*<sup>del</sup> mutant flies have altered protein cargo, including increased levels of exosome-intrinsic proteins Rab11 and Rab7, and increased oligomerized Ref(2)p, the *Drosophila* ortholog for p62. Expression of wildtype d*GBA1b* in flight muscle or glia of *GBA*<sup>del</sup> mutant flies rescued protein aggregation in the brain, and also rescued levels of exosomal Rab11, Rab 7 and Ref(2) p. Our *Drosophila* model supports the hypothesis that *GBA* deficiency alters exosomes, which may act as a vehicle to accelerate the spread of Lewy pathology. We are now extrapolating these results to our iPSC model, by examining how *GBA* alters endolysosomal trafficking leading to exosome biogenesis. We have performed IHC for essential markers of the endolysosomal trafficking pathway, to analyze differences in the amount and spread of these proteins in control vs. *GBA* mutant neurons. By understanding how altered exosomes can be a vehicle for Lewy pathology propagation could elucidate mechanisms to halt or slow down the spread of pathogenic protein aggregation in PD.

#### S254. Variability between Patient and Caregiver QUIP-RS Scores before and after Subthalamic Nucleus Deep Brain Stimulation in Parkinson's Disease

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**Introduction:** The Questionnaire for Impulsive-Compulsive Disorders in Parkinson's Disease-Rating Scale (QUIP-RS) assesses the severity of Impulse Control Disorders (ICDs) and related behaviors, including gambling, eating, sexual behavior, buying, punting, hobbyism, and dopamine dysregulation syndrome in Parkinson's disease (PD). Patients and their caregivers rate the questionnaire independently. Previous studies showed a moderate agreement between patient and informant reports (kappa=0.408); however, the effect of STN-DBS on this agreement has not yet been studied. **Methods:** Fifty-nine PD patients who underwent STN-DBS and their caregivers completed the QUIP-RS before (on-medication) and approximately 6 months after STN-DBS (on-medication/on-stimulation). A linear mixed model was applied to examine the effect of surgery on the discrepancy between patient and caregiver QUIP-RS scores. In the first model, all scores were included, and interaction term was applied between the two categorical variables-the rater (patient vs. caregiver) and the time (before vs. after the surgery). Then the stratified model was applied for pre- and postoperative scores. All models included a random intercept for each patient-caregiver pair, and a random intercept for every QUIP-RS question. **Results:** The average total patient-rated QUIP-RS score decreased after STN-DBS (baseline: 17.59 ± 14.57, follow-up: 14.57 ± 14.02) while the total caregiver-rated QUIP-RS score increased (baseline: 16.57 ± 13.65, follow-up: 20.25 ± 18.02). The full model showed statistically significant changes in discrepancy between patient and caregiver QUIP-RS scores before and after surgery (coeff=-1, 95% CI: -1.51, -0.48). Stratified

analysis showed that the discrepancy was only observed after surgery (coeff=−0.85, 95% CI: −1.19, −0.51), not at baseline (coeff=0.14, 95% CI: −0.20,0.49). In a post-hoc analysis, we compared the average Caregiver Burden Inventory (CBI) score before (17.35 ± 12.22) and after (21.05 ± 12.86) STN-DBS to see if this influenced the caregiver-rated QUIP-RS score. Average CBI significantly increased following STN-DBS (t-stat = −2.72,  $p=0.008$ ). After adding CBI in the full model as a controlling variable, the change in discrepancy was still significant (coeff=−0.95, 95% CI: −1.50, −0.49). **Conclusion:** There is a significant change in discrepancy in patient-rated vs. caregiver-rated QUIP-RS scores after STN-DBS surgery compared to baseline, and the effect was independent of increased caregiver burden as measured by CBI. More research is needed to explore the underlying cause behind this change.

## S256. White Matter Lesion Characteristics of Patients with Multiple Sclerosis and Parkinsonism

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**Objective:** To evaluate whether patients with multiple sclerosis who develop parkinsonism have significant differences in regional lesion burden compared to multiple sclerosis patients who do not develop parkinsonism. **Background:** While multiple sclerosis (MS) and Parkinsonism/Parkinson's disease (PoPD) represent independent disease processes, there have been multiple case reports of co-occurrence and nationwide cohort studies suggesting higher incidence rates and risk of PD in the MS population. There have been no studies beyond case reports comparing imaging characteristics of patients with and without this co-diagnosis to clarify the potential pathophysiologic basis of the increased risk of PD. **Methods:** We reviewed medical records from 2012-2022 within a single health care system for patients with multiple sclerosis and parkinsonism. An ICD code search resulted in 104 patients; on manual chart review 17 patients met final inclusion criteria. Ten patients had available MRI brain images for which lesion quantification was possible. Eight patients could be matched 1:3 to a control MS only cohort by sex, age at MS diagnosis, and MRI images near the age of PoPD diagnosis. T2 FLAIR lesions were identified and outlined with livewire mode segmentation to calculate volumes. Volume and location (basal ganglia, brainstem, cerebellum) were recorded for each lesion. **Results:** Among 17 cases, the age of onset of MS ranged from 24-67 with a mean of 49 and median of 52, which was an older cohort compared to the general MS population where the age of diagnosis typically ranges from 20-49. The age of PoPD diagnosis ranged from 41-74 (mean 59). For the eight cases in which MRI images and controls were available, Wilcoxon matched pairs signed rank test showed no statistically significant difference in lesion burden globally or in specific regions (basal ganglia, brainstem, cerebellum) between cases and controls. There was a potential trend of increased global lesion burden in the co-diagnosis group that did not reach statistical significance (mean lesion volume

$p=0.19$ , total lesion volume  $p=0.74$ ). **Conclusion:** Our preliminary data did not find a statistically significant difference in white matter lesion burden globally or regionally in the comparative MRI brain image analysis between eight patients with a dual diagnosis of MS and PoPD and a matched cohort of MS patients who did not develop PoPD.

## K-S106. In Humans, Striato-Pallido-Thalamic Projections are Largely Segregated by Their Origin in Either the Striosome or Matrix Compartments

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Cortico-striato-thalamo-cortical (CSTC) loops are fundamental organizing units in mammalian brains. CSTCs process limbic, associative, and sensorimotor information in largely separated but interacting networks. CSTC loops pass through paired striatal compartments, striosome (aka patch) and matrix, segregated pools of medium spiny projection neurons with distinct embryologic origins, cortical/subcortical structural connectivity, susceptibility to injury, and roles in behaviors and diseases. Similarly, striatal dopamine modulates activity in striosome and matrix in opposite directions. Routing CSTCs through one compartment may be an anatomical basis for regulating discrete functions. We used differential structural connectivity, identified through probabilistic diffusion tractography, to distinguish the striatal compartments (striosome-like and matrix-like voxels) in living humans. We then mapped compartment-specific projections and quantified structural connectivity between each striatal compartment, the globus pallidus interna (GPi), and twenty thalamic nuclei in 221 healthy adults. We found that striosome-originating and matrix-originating streamlines were segregated within the GPi: striosome-like connectivity was significantly more rostral, ventral, and medial. Striato-pallido-thalamic streamline bundles that were seeded from striosome-like and matrix-like voxels transited spatially distinct portions of the white matter. Matrix-like streamlines were 5.7-fold more likely to reach the GPi, replicating animal tract-tracing studies. Striosome-like connectivity dominated in six thalamic nuclei (anteroventral, central lateral, laterodorsal, lateral posterior, mediodorsal-medial, and medial geniculate). Matrix-like connectivity dominated in seven thalamic nuclei (centromedian, parafascicular, pulvinar-anterior, pulvinar-lateral, ventral lateral-anterior, ventral lateral-posterior, ventral posterolateral). Though we mapped all thalamic nuclei independently, functionally-related nuclei were matched for compartment-level bias. We validated these results with prior thalamostriate tract tracing studies in non-human primates and other species; where reliable data was available, all agreed with our measures of structural connectivity. Matrix-like connectivity was lateralized (left>right hemisphere) in eighteen thalamic nuclei, independent of handedness, diffusion protocol, sex, or whether the nucleus

was striosome-dominated or matrix-dominated. Compartment-specific biases in striato-pallido-thalamic structural connectivity suggest that routing CSTC loops through striosome-like or matrix-like voxels is a fundamental mechanism for organizing and regulating brain networks. Our MRI-based assessments of striato-thalamic connectivity in humans match and extend the results of prior tract tracing studies in animals. Compartment-level characterization may improve localization of human neuropathologies and improve neurosurgical targeting in the GPi and thalamus.

#### K-S107. Quantifying the Value of Multimodal MRI in Outcomes Prediction for STN DBS in PD

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**Objective:** To compare the predictive value for motor outcomes of multimodal MRI to clinical predictors alone in STN DBS for PD. **Background:** STN DBS is an effective treatment for the motor symptoms of PD, yet outcomes remain highly variable. Currently, pre-surgical levodopa response provides the most established prediction of clinical outcome, although its predictive power varies greatly across studies. MRI-based methods including resting state functional connectivity (FC), subcortical and cortical volumetrics, and DTI-based structural connectivity (SC) independently predict DBS outcomes, while a comprehensive model integrating these methods has not yet been developed. **Methods:** We included 61 participants who had multimodal MRI prior to STN DBS for PD and who had adequate clinical data before and after DBS, as well as good quality volumetric, DTI, and rs-fcMRI data. We applied clinical and MRI-based predictors from published studies including thalamic and ventricular volumes, FC and SC connectivity between STN and GPi, VL thalamus, and motor cortex. Regularized linear regression using the least absolute shrinkage and selection operator (LASSO) and leave-one-out cross-validation was used for model construction and factor selection, optimized to RMSE to avoid overfitting with addition of more variables. The primary outcome was percent change in UPDRS-III from the initial preoperative OFF-medication examination to the average OFF-medication, ON-stimulation score over the first year after DBS. **Results:** The “traditional” model, constrained to only clinical predictors (including levodopa response, age, sex, handedness, LEDD, preoperative UPDRS-III) was modestly predictive of motor improvement ( $R^2 = 0.29$ , RMSE = 14.9). In comparison, the total model, which included FC, SC, volumetric, and clinical predictors more strongly predicted motor improvement ( $R^2 = 0.55$ , RMSE = 13.6). Factors included in the optimized model included STN-GPi FC, GPi-VL thalamus SC, VL thalamus-motor cortex SC, ventricular volume, age, preoperative UPDRS-III, and levodopa responsiveness. **Conclusions:** Multimodal MRI greatly outperforms levodopa responsiveness alone in prediction of motor outcomes for STN DBS in PD. Addition of cognitive and psychiatric features both as predictors and as outcomes may further enhance the predictive power and clinical utility of this approach.

#### LB-S109. Genetic Factors and Clinical Heterogeneity of Parkinson's Disease: Genome-Wide Association Study on PD Subtypes

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**Background:** Parkinson's disease (PD) presents with a combination of motor and non-motor symptoms and substantial variability among individual patients, which led to the clustering of PD patients into distinct subtypes. The genetic underpinnings of the clinical heterogeneity in PD are not understood. Therefore, we performed a genomewide association study (GWAS) to investigate the genetic architecture of distinct PD subtypes. **Methods:** A total of 799 PD patients who reported to our clinic between 1998 and 2016 were included in the study. The patients were divided into four clinical PD subtypes: tremor-dominant (TD) (n=345), akinetic-rigid (AR) (n=227), gait-difficulty (GD) (n=82), and mixed (n=145). Array genotyping (Illumina NeuroChip) was performed, followed by genomewide imputation with TOPMed Imputation Server array and reference panel based in Minimac4. A total of 7,918,344 variants were studied for association with each PD subtype with logistic regression models adjusted for age, sex, and the top five principal components of GWAS data. **Results:** We found one genome-wide significant ( $p < 5 \times 10^{-8}$ ) association between the rs7504760 (MIR3976HG) variant and AR subtype (OR=6.12,  $p = 2.57 \times 10^{-8}$ ). Suggestive associations ( $p < 1 \times 10^{-6}$ ) were observed regarding TD subtype for rs7304254 (RP11-497G19.3/RP11-497G19.1) (OR=3.33,  $p = 3.89 \times 10^{-7}$ ), GD subtype for rs111473931 (HES2) ( $p = 6.85 \times 10^{-7}$ ), rs149082205 (RP11-400D2.3/CTD-2012I17.1) ( $p = 9.08 \times 10^{-7}$ ), and rs56161738 (RN7SL408P/SGK1) (OR=2.97,  $p = 6.19 \times 10^{-7}$ ), and mixed for rs112991171 (MMRN2) (OR=4.98,  $p = 1.02 \times 10^{-7}$ ). None of the 103 variants previously associated with PD or essential tremor (ET) were of genome-wide significance; however, 17 were nominally significant, including rs10221156 (CHD9) with mixed, rs7938782 (RNF141) with AR, and rs35749011 (KRTCAP2) with TD PD subtype. Additionally, we observed divergent effects in GD vs. AR/mixed/TD subtypes in 5, AR vs. GD/mixed/TD in 4, TD vs. AR/GD/mixed in 2, and mixed vs. AR/GD/TD in 1 variant. **Conclusion:** We identified the first genome-wide significant association between rs7504760 (MIR3976HG) variant and the AR subtype. We also noted several other suggestive associations. We did not replicate findings from the previous study, nor did we observe an overlap between essential tremor and TD subtype. We provide evidence that clinical heterogeneity in PD is impacted by genetic factors. However, further collaborative studies on larger groups of patients are needed to elucidate the genetic basis of PD subtypes. Genetic markers of PD subtypes would enable reliable and stable over time clustering of PD patients for clinical trials.



### LB-S110. Paired Deep Brain Stimuli Elicit Short-Term Facilitation in Globus Pallidus Interna and Subthalamic Nucleus

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**Background:** Deep brain stimulation (DBS) pulses elicit local event-related potentials (DLEPS) at or near the stimulation in patients with Parkinson disease and other movement disorders (Sinclair NC, et al., *Ann Neurol*. 2018; Sinclair NC, et al., *Neurobiol Dis*. 2019; Awad MZ, *Ann Clin Transl Neurol*. 2021). The earliest peaks occurring less than 0.5 ms after stimulus onset presumably represent direct depolarization of proximal neural elements by the stimulus pulse. Subsequent oscillations, termed evoked resonant neural activity (ERNA), occur at longer latencies (~4 ms) in the subthalamic nucleus (STN) and globus pallidus interna (GPi) but not Vim. Greater knowledge on the dynamics of these responses could both shed light on mechanism of action and disease pathophysiology and inform innovative approaches to neuromodulation therapies. **Objective:** To contrast features of ERNA in the STN versus the GPi, the canonical stereotactic functional targets for Parkinson's disease. We hypothesize peak amplitude, latency, frequency, and short-term plasticity differ in STN vs GPi. **Methods:** We delivered pairs of DBS pulses across a range of interstimulus intervals and amplitudes during surgery and recorded locally evoked responses from unused contacts on the implanted lead. Following stimulus artifact removal, we contrasted the magnitude and time dynamics of local evoked responses by interstimulus interval and brain target. **Results:** DBS-evoked resonant neural activity (ERNA) amplitude is larger in STN than in GPi. Regardless of brain target, ERNA displays similar onset latencies, peak-to-peak frequencies, and paired-pulse short-term facilitation. Furthermore, ERNA is markedly larger than the associated spontaneous field potentials (4-30 Hz band). **Conclusions:** Pairs of DBS pulses in STN elicit larger amplitude local evoked responses than in GPi, which might correspond with therapeutic differences observed between these targets. Otherwise, these dynamic oscillatory responses display similar timing and short-term plasticity. ERNA features and other local evoked responses might guide programming of open-loop DBS and serve as control signals for closed-loop DBS therapy.

### LB-S111. Plasma-Derived Alpha-Synuclein Strains Distinguish Parkinson's Disease from Dementia with Lewy Bodies

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There is significant phenotypic heterogeneity in neurodegenerative diseases associated with alpha-synuclein (aSyn) misfolding and aggregation, including Parkinson's disease (PD), dementia with Lewy bodies (DLB), and Multiple Systems Atrophy (MSA). Multiple, recent studies have demonstrated that disease-specific aSyn "strains", conformations with distinct biochemical properties, can be isolated from brain tissue. Strain-specific properties may influence clinical and pathologic trajectory in synucleinopathies. To determine whether antibodies recognizing two, distinct *in vitro*-generated aSyn strains have biological relevance, we evaluated their ability to distinguish aSyn strains *in vivo* using immunohistochemistry, immunoblotting, and ELISA. These strain-selective antibodies recognize different subsets of aSyn pathology in human brain tissue but do not readily detect aSyn in cerebrospinal fluid by ELISA. Remarkably, plasma levels of aSyn species recognized by strain-selective antibodies using ELISA reliably differentiated individuals with DLB from PD in two independent cohorts (AUC up to 0.83, n = 25-115 / group). Furthermore, elevated plasma levels of aSyn recognized by one of these antibodies predicted a slower rate of cognitive decline in individuals with PD. However, levels of plasma aSyn species did not reflect brain levels within two years of autopsy and the biochemical properties of plasma aSyn species isolated by immunoprecipitation differed from those in brain. Finally, aSyn species isolated by strain-selective antibodies from plasma but not brain were able to induce fibrillization of aSyn *in vitro*. In summary, this study has multiple important findings: 1) aSyn strains are enriched in plasma but not CSF suggesting an origin outside the central nervous system (CNS), 2) plasma aSyn strains could serve as novel biomarkers to differentiate PD and DLB for which no reliable biomarkers exist, and 3) plasma aSyn strains differ from brain counterparts in size and ability to induce aSyn fibrillization. As aSyn pathology is increasingly identified outside the CNS, understanding how and where these strains develop may inform PD and DLB pathogenesis. Determining whether plasma aSyn contributes to the spread of aSyn pathology within the CNS may also lead to novel targets for drug development.

### LB-S112. Prediction of Phenoconversion Time in REM Sleep Behavior Disorder (RBD) with Brain Metabolic Network and Dopaminergic Imaging: A Longitudinal Study

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**Objective:** The risk of phenoconversion in patients with idiopathic RBD (iRBD) to synucleinopathies remains unclear. We previously showed that higher expression of abnormal PD-related metabolic pattern, PDRP, in iRBD subjects is associated with a greater likelihood of phenoconversion to

Parkinson's disease (PD). [Holtbernd et al, Neurology, 2014] In this longitudinal study, we examined whether metabolic network and dopaminergic imaging can together provide a more accurate prediction of the phenoconversion time to PD in individual iRBD subjects over time. **Methods:** 13 iRBD subjects (age:  $63.5 \pm 8.4$  years) underwent dual-tracer imaging with [ $^{18}\text{F}$ ]-fluorodeoxyglucose (FDG) and [ $^{18}\text{F}$ ]-fluoropropyl  $\beta\text{CIT}$  (FPCIT) PET at baseline, 2 and 4 years. 13 age-matched healthy controls (HC; age:  $62.0 \pm 10.3$  years) were scanned at baseline. Expression values of PDRP and PD-related cognitive pattern (PDCP) were measured in FDG PET scans of individual subjects at each timepoint. Dopamine transporter (DAT) binding in caudate and putamen was also calculated in FPCIT PET scans for each subject. Individual growth model was used to analyze the rate of change for each network/dopaminergic marker in individual iRBD subjects across the three timepoints. **Results:** At baseline, expression values of PDRP, but not PDCP, was significantly higher in iRBD subjects than HC. Over time, both PDRP and PDCP expression in iRBD subjects increased significantly across the three timepoints at rates of 0.231/year ( $p < 0.001$ ) and 0.190/year ( $p < 0.007$ ), respectively. By contrast, DAT binding decreased significantly in caudate ( $-4.4\%/ \text{year}$ ;  $p < 0.001$ ) and putamen ( $-4.8\%/ \text{year}$ ;  $p < 0.002$ ) over time. Three of the 13 iRBD subjects, who had both higher PDRP expression ( $> 1.0$ ) and lower DAT binding in the posterior putamen ( $< 80\%$ ) at the last timepoint, phenocconverted to PD in the subsequent years. Based on the model of combined PDRP expression and posterior putamen DAT binding, two other iRBD subjects were estimated to have higher risk for phenoconversion and predicted to phenoconvert to PD 8.3 and 9.5 years after the last follow-up timepoint. **Conclusions:** The progression of iRBD is associated with significant increases in PDRP/PDCP network activities and decreases in caudate/putamen dopaminergic function over time. Our findings indicated that the combination of higher PDRP expression and lower posterior putamen DAT binding could be used to better estimate the risk of phenoconversion, as well as accurately predict the phenoconversion time of individual iRBD subjects to PD.

### LB-S113. Social Determinants of Health and Health-Related Quality of Life in Individuals with Isolated Dystonia

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**Introduction:** Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions, leading to abnormal, often repetitive movements or postures. Non-motor symptoms include anxiety, depression, sleep and cognitive dysfunction. Motor and non-motor manifestations of dystonia may impact Health Related Quality of Life (HRQoL), with lower HRQoL scores compared to the healthy population. Furthermore, patients with generalized dystonia report worse HRQoL scores than patients with focal distributions. Social determinants of health (SDOH) may play a role in HRQoL outcomes in dystonia, but scant data

exists. We aim to assess for differences in HRQoL scores in patients with focal vs. non-focal (e.g., segmental, multifocal, generalized) dystonia and the association of SDOH. **Methods:** 129 participants with a confirmed diagnosis of a primary dystonia were enrolled. Participants completed a survey of 75 questions on SDOH and HRQoL, including the Quality of Life in Neurological Disorders Version 2.0 Short Form (Neuro-QoL-SF) and the EuroGroup 5-level (EuroQoL). **Results:** 71.3 % of participants had focal dystonia and 28.7% had non-focal dystonia (i.e., segmental, multifocal, or generalized). Focal and non-focal dystonia participants were predominantly female (71.7% vs 73.0%), non-Hispanic white (84.8% vs 67.6%), and highly educated (80.4% vs 78.4%;  $\geq$  bachelor's degree). Compared to non-focal participants, focal participants were older at the time of assessment ( $63.7 \pm 10.5$  vs.  $57.14 \pm 18.0$ ;  $p = 0.01$ ), had a later age of symptom onset ( $44.3 \pm 14.2$  vs  $33.52 \pm 22.0$ ,  $p = 0.003$ ), and age at diagnosis ( $49.2 \pm 6.9$  vs  $8.1 \pm 11.4$ ). On the NeuroQoL, focal participants reported higher ability to participate in social activities ( $51.3 \pm 7.7$  vs  $47.2 \pm 6.0$ ,  $p = 0.003$ ), lower fatigue ( $44.7 \pm 8.4$  vs  $49.8 \pm 7.2$ ,  $p = 0.001$ ), lower sleep disturbance ( $48.0 \pm 8.2$  vs  $53.0 \pm 7.9$ ,  $p = 0.002$ ), and better overall health scores ( $80.36 \pm 13.93$  vs  $72.81$ ,  $\pm 13.52$ ,  $p = 0.005$ ), on the EuroQoL, than non-focal participants. Preliminary regression results indicate that the independent predictors of higher overall health ratings on the EuroQoL were focal distribution ( $b = 7.5$ ;  $p = 0.01$ ), and a higher level of education ( $b = 9.2$ ;  $p = 0.04$ ). A predictor for lower health ratings was having a mental health diagnosis ( $b = 7.5$ ;  $p = 0.01$ ). **Conclusions:** Individuals with focal dystonia were diagnosed later and had higher HRQoL measures compared to participants with non-focal dystonia. Predictors of better HRQoL were having focal dystonia and higher level of education, whereas the presence of a mental health diagnosis was associated with lower HRQoL scores. Additional research is needed to better understand these findings and the role of SDOH on HRQoL.

### Neurocritical Care and Traumatic Brain Injury

#### M249. A Novel Treatment to Reduce Secondary Damage in Traumatic Brain Injury

**Siyan C. Liu, MD, PhD, Ryan Bertossi, BS, Tammy McGuire, BS, Chian-Yu Peng, PhD, John A. Kessler, MD.** Northwestern University, Chicago, IL, USA.

Traumatic brain injury (TBI) is a leading cause of death and hospitalization among Americans. Its effects can be devastating and acute through intracranial hemorrhage, skull fracture, and diffuse axonal injury, or long-lasting with seizures, cognitive impairment, depression, and anxiety. The acute phase results from direct tissue damage and impaired cerebral autoregulation. The secondary phase reflects the effects of infiltrating immune cells, cytokine release, mitochondrial dysfunction, reactive oxygen species, excitotoxicity, and other mechanisms. Current therapies primarily treat the resulting symptoms of TBI and do not target the pathophysiologic mechanisms underlying the secondary damage. Previous work from our lab has that a novel treatment, highly negatively

charged Immuno-Modifying Nanoparticles (IMP) can reduce the immune-mediated secondary damage following TBI. IMP are engineered, biodegradable, FDA-approved biopolymers that upon intravenous injection, are taken up by hemogenous monocyte-derived macrophages. IMP administration leads to a decrease in the inflammatory response through a reduction both in immune cell infiltration and in cytokine and chemokine release. Our recent work has found that 200mg/kg is the minimum effective dosage in reducing secondary damage in a controlled-cortical impact TBI model. We also have found that IMP administration within 6 hours of injury leads to better functional outcomes as measured by ladder rung and rotarod testing as well as a smaller lesion volume as compared to animals injected at 12- or 24-hours post-injury. Using single-cell RNA sequencing, we have found that the gene expression of neurons, astrocytes, and microglia are significantly different in animals treated with IMP versus saline. We also have found that IMP administration reduces reactive astrogliosis, microgliosis, and cells undergoing apoptosis after 72 hours. Taken together, we have determined the optimal timing and dosage for IMP administration in a CCI model of TBI. We have also shown, in greater detail, the mechanisms of how IMP treatment reduces secondary inflammatory changes in the brain. Our work further signals that IMP delivery can be an effective clinical intervention in TBI patients.

#### **M250. A Rare Case Report of CHANTER Syndrome**

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**Introduction:** Cerebellar, hippocampal, and basal nuclei transient edema with restricted diffusion (CHANTER) syndrome is a rare syndrome in the setting of opioid intoxication and overdose. It is thought to represent a combination of opioid neurotoxicity and hypoxic ischemic effects, hence the overlapping anatomical distribution between areas of the brain with high opioid concentration and areas susceptible to hypoxic ischemic brain injury. Diagnosis is made with a combination of history, physical exam, and characteristic imaging findings. Oftentimes, large areas of symmetric restricted diffusion represent irreversible injury and poor prognosis. However, improved clinical and neurological outcomes have been reported in other cases with early aggressive intervention, making early identification and intervention crucial. **Case Presentation:** A 59-year-old male with a history of hypertension, polysubstance use disorder including a prior overdose was found unresponsive by EMS. He received naloxone with improvement of GCS from 8 to 11, although requiring intubation due to worsening somnolence and hypercapnia. He was afebrile, BP was 132/83 mmHg, HR 91 beats per minute; neurological exam was nonfocal without significant motor deficits. Urine drug screen was positive for cocaine and fentanyl. Initial CT head demonstrated bilateral cerebellar and left parieto-occipital lobe hypoattenuation and slightly decreased volume of the fourth ventricle. MRI brain demonstrated multiple areas of

restricted diffusion involving both cerebellar hemispheres, bilateral occipital lobes, posterior left temporal lobe, and bilateral hippocampi. MR angiography of the head and neck did not visualize significant stenosis or occlusions. Patient self-extubated the next day but remained agitated and hypertensive requiring sedation. Repeat CT head demonstrated partial effacement of the fourth ventricle and significant parenchymal edema throughout the cerebellum concerning for early developing obstructive hydrocephalus. Patient was initiated on hypertonic saline and neurosurgery was consulted. Interval CT head images were stable; no additional surgical interventions were required. Patient was subsequently discharged home on lisinopril 20 mg daily, thiamine 100 mg daily, and counselled on substance use disorder. Repeat MRI brain at five weeks demonstrated improved cerebral edema and decreased mass effect. At 3-months follow-up he continues to have difficulty with short-term memory and requires assistance with instrumental activities of daily living. **Conclusion:** CHANTER is a rare and under-recognized novel syndrome. Early diagnosis, aggressive medical management, and surgical interventions can lead to improved neurological outcomes. Hence, CHANTER should be considered on the differential in unresponsive patients following opioid use with the distinct neuroimaging pattern.

#### **M251. An Explanation of the Vascular and Functional Anatomy of Thoracic Spinal Cord Ischemia and Its Clinical Presentation in the Setting of Radicular Artery Occlusion**

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Spinal cord ischemia (SCI) is a rare but devastating disorder. A majority of infarctions occur in the anterior thoracic cord resulting in paraparesis below the level of ischemia. A significant majority of these events, either iatrogenic or spontaneous, are instigated by compromise of the critical radicular arteries. The dogmatic clinical picture is often presented as complete paraplegia, bilateral loss of pinprick sensation, areflexia, and hypotension. This pattern in the hyperacute setting is not universal; we feel that at least initially many patients first develop more significant unilateral weakness in proximal leg muscles. It is important that clinicians recognize this pattern early as interventions may be begun expeditiously and prevent progression to complete paraplegia. The following is a brief case to detail this phenomenon: The patient is a 72-year-old male with vascular risk factors including heart failure due to ischemic cardiomyopathy, peripheral arterial disease, and atrial flutter off of anticoagulation who presented in acute decompensated heart failure due to atrial flutter. After initiation of heparin infusion for a trans-esophageal echocardiogram with cardioversion, he developed a right abdominal wall hematoma secondary to an intercostal artery bleed. He underwent endovascular embolization of his right T10 intercostal artery, and post-operatively, developed right

proximal>distal lower extremity weakness. However, greater than 24 hours after the initial insult, this subsequently progressed to classic anterior cord syndrome with bilateral lower extremity paraplegia and hypotension. We feel the vascular anatomy of the thoracic spinal cord allows for watershed that most affects the unilateral anterior horn cells (AHC) ipsilateral to the compromised vessel. Anterior SCI impacts both corticospinal tracts (CST) and AHC, but the CST is supplemented by the posterior spinal arteries thus preferentially protecting CST innervation to the entire leg below the highest-risk AHC supplying the large proximal legs muscles. The Great Radicular Artery typically enters the spinal cord from the left leaving the left hemicord more susceptible to watershed ischemia, although in the presented case a right radicular artery was compromised leaving the large right AHC most susceptible. The authors acknowledge that the vascular anatomy of the thoracic spine can be variable, but we feel that given our prior clinical experience with this complication and the vascular anatomy, the presence of a proximal unilateral pattern of weakness may allow even earlier intervention strategies that have been very successful in the thoracic aneurysm repair literature.

## **M252. Associations of Head Injury with Risk of Injurious Falls: Results from the Atherosclerosis Risk in Communities (ARIC) Study**

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**Objective:** To examine the association between head injury and risk of falls requiring hospital care among community dwelling older adults. **Methods:** This analysis included 13,081 participants in the Atherosclerosis Risk in Communities (ARIC) Study enrolled in 1987-1989. The association of head injury (self-reported and/or ICD-9/10 code identified hospitalizations/emergency department encounters) with risk of falls requiring hospitalization or emergency department care (ICD-9/10 code defined) was modeled using Cox proportional hazards regression. Secondary analyses included Fine-Gray proportional hazards regression to account for competing risk of death, analyses of head injury frequency and severity, and formal testing for interaction by age, sex, and race. Models were adjusted for age, sex, race/center, education, military service, alcohol consumption, smoking, diabetes, hypertension, and psychotropic medication use. **Results:** Participants were a mean age of 54 years, 58% female, 28% were of Black race, and 12% had at least one head injury. Over a median of 23 years follow-up, 29% of participants had a fall requiring medical care. In adjusted

Cox proportional hazards models, individuals with a history of head injury had 2.01 (95% CI=1.85-2.18) times the risk of falls compared to individuals without a history of head injury. Accounting for the competing risk of mortality, individuals with a history of head injury had 1.69 (95% CI=1.58-1.82) times the risk of falls compared to individuals without a history of head injury. We observed evidence for stronger associations among men as compared to among women (men: HR=2.60, 95% CI=2.25-3.00; women: HR=1.80, 95%CI=1.63-1.99, p-interaction<0.001). We observed evidence of a dose-response association for head injury number and severity with fall risk (1 head injury: HR=1.68, 95% CI=1.53-1.84; 2+ head injuries: HR=2.37, 95% CI=1.92-2.94 and mild head injuries: HR=1.97, 95% CI=1.78-2.18; moderate/severe head injuries: HR=2.50, 95% CI=2.06-3.02). **Conclusions:** Among community-dwelling older adults followed from 1987 through 2019, head injury was associated with falls requiring medical care. We observed stronger associations among men and a dose-response with number and severity of head injury. Whether individuals with head injury might benefit from fall prevention measures should be a focus of subsequent research.

## **M253. Beyond the Injury: The Impact of Traumatic Brain Injury on Quality of Life and Life Satisfaction**

**Sara K. Heide, BS**, Rasheed Hosein-Woodley, BA, Jason A. Morency, BS, James Williams, BA, Mill Etienne, MD, MPH. New York Medical College, Valhalla, NY, USA.

**Objective:** Describe the impact of Traumatic Brain Injury (TBI) on patient quality of life (QoL) by illustrating the ways that TBI may affect patients' independence, relationships, activities, and vision of their future. **Background:** Each year, approximately 1.5 million Americans have a traumatic brain injury (TBI), resulting in a myriad of symptoms that impact patients' ability to work, socialize and partake in their hobbies. Therefore, it is important to elucidate which factors most significantly impact life quality after TBI. **Design/ Methods:** This was a descriptive cross-sectional mixed methods study with a questionnaire that consisted of questions graded on a 5-point Likert scale, two validated surveys, and open-ended questions that aimed to identify the impact of TBI on QoL. Every patient who received treatment for TBI by one neurologist in an outpatient practice from 01JAN2022 to 30JUN2022 was invited to participate. Patients received the survey via email. Qualtrics was used for data collection and SPSS was used for statistical analysis. Descriptive statistics were performed for demographics and survey questions. Chi-square and Mann-Whitney U analyses were used to determine relationships between questions and categorical variables. LISAT-11 and QOLIBRI questions were evaluated using logistic regression, controlling for categorical variables. This study was approved by the New York Medical College IRB. **Results:** 129 patients were invited to participate in the survey, from which we recruited 53 subjects who responded to the questionnaire. The most commonly reported primary concern was "the future," which was cited as a concern by 71.7% of participants. This included concern about reinjury, fear of new symptoms, and uncertainty about their disease course. We found 67.9% of

subjects reported that TBI negatively impacted their QoL. Patients' reported their TBI impacted their QoL by affecting their independence (60.4%), relationships (73.6%), hobbies (61.2%), and careers (54.7%). Those who lived alone and those who were single scored lower on some measures of life satisfaction compared to those who lived with others and those who were in relationships ( $p < 0.05$  for both). We also found that women reported a greater impact of their TBI on some activities, including driving ( $p = 0.009$ ) and exercising ( $p = 0.026$ ), than men. **Conclusions:** The majority of survivors of TBI reported a significant negative impact of their injury on their QoL. Predictors of lower quality of life after TBI included female gender, living alone and being single. This stresses the importance of understanding patients' social situation during recovery from neurologic illness, including TBI.

#### M256. Delayed Diagnosis of HIV and Cerebral Toxoplasmosis Resulting in Massive Cerebral Edema and Brain Death

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**Introduction:** Cerebral toxoplasmosis is a serious opportunistic infection (OI) associated with untreated human immunodeficiency virus (HIV). In the absence of appropriate prophylaxis, susceptible individuals may reactivate toxoplasmosis primarily involving the central nervous system (CNS). Overlapping clinical and imaging findings with other OIs make the diagnosis challenging. Delayed diagnosis and treatment often result in fatal consequences. **Case:** A 41-year-old woman who recently immigrated from Togo, West Africa presented to care with fever and headache with one episode of generalized tonic-clonic seizure. Imaging with MRI of the brain revealed a single 2.7 cm hyperintense left parietal lesion with surrounding edema. The initial suspicion was of neoplastic etiology. The patient was discharged with consideration for an intracranial biopsy in the ambulatory setting. Five days later, she experienced worsening headache with emesis that prompted her to return to care. Repeat imaging showed multiple new lesions of various sizes throughout the cerebrum and cerebellum. Due to acute worsening of mentation, patient was intubated and transferred to the neurocritical care unit. On detailed questioning, the husband revealed that the patient was tested for HIV months ago but did not take treatment. Repeat HIV 4<sup>th</sup> generation antigen/antibody assay was positive with a high viral load of 405,706 copies/mL and low CD4 count of 3 cells/mm<sup>3</sup>. A workup for OIs revealed positive toxoplasma serum IgG. Patient was started on anti-toxoplasma therapy with high dose trimethoprim/sulfamethoxazole and clindamycin. Despite treatment, patient worsened with loss of brainstem reflexes the next morning with 7 mm midline shift on imaging. She underwent decompressive craniotomy with drainage of 60 mL of pus from the lesion; a biopsy of the brain tissue was also

taken. Polymerase chain reaction (PCR) of the brain tissue was positive for toxoplasma. Additionally, EBV and CMV PCR were also positive, which is likely due to reactivation in the setting of severe illness. Despite all efforts, serial imaging showed diffuse severe cerebral edema with subfalcine herniation. Patient was eventually declared brain dead. **Discussion/Conclusion:** In patients presenting with focal intracranial lesions, one should suspect an underlying immunocompromised status, mainly HIV. A thorough workup for OI should be initiated due to the possibility of a broad range of differentials. Toxoplasmosis is a preventable OI that should be considered in the absence of prophylaxis and in the appropriate clinical scenario with low CD4 count and positive toxoplasma serology.

#### M257. Discontinuation and Non-Publication of Traumatic Brain Injuries Clinical Studies: A Cross-Sectional Analysis

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**Background:** Traumatic brain injuries (TBIs), which account for a sizeable amount of the world's injury burden, are mostly brought on by accidents on the road and in falls. According to the Global Burden of Disease Research, TBI caused 69 million disability-adjusted life years (DALYs) in 2016. There were roughly 223,135 hospitalizations for TBI in 2019 and 64,362 deaths from TBI in 2020. Clinical studies discontinuation and non-publication represent major sources of research waste in clinical medicine. This study aims to investigate the factors influencing the discontinuation and non-publication of clinical studies of TBIs. **Methods:** ClinicalTrials.gov was searched for all types of studies registered between 1 January 2000 and 1 May 2022 and included patients with spinal injuries. Publications from these studies were identified by extensive online searching using the NCT identifier number and other related keywords. Multiple logistic regression analysis was performed to identify characteristics associated with trial discontinuation and non-publication. **Results:** A total of 838 eligible registered studies were included; 565 (67.4%) were clinical trials, and 273 (32.6%) were observational studies. Of these, 662 (79%) were completed, and 176 (21%) were discontinued. A large sample size

(more than 100 patients) was less likely to be discontinued (OR= 0.266, 95% CI [0.1590, 0.446],  $P<0.001$ ). The drug interventions compared to other types of interventions (OR= 2.166, 95% CI [1.2538, 3.744],  $P=0.006$ ) was more likely to be discontinued. While the studies that used the behavioral interventions were less likely to be discontinued (OR= 0.216, 95% CI [0.089, 0.523],  $P<0.001$ ). Nearly half of the completed studies were published, 318 (48.2%), while 342 (51.8%) were not. Single-centered studies were the least published (OR = 1.546, 95% CI [1.0450, 2.29],  $P= 0.03$ ).

**Conclusion:** There is evidence of non-dissemination bias in clinical studies of traumatic brain injuries. These biases distort the therapeutic information available to inform clinical practice and raise ethical concerns regarding exposing volunteering participants to potential risks without furthering practice.

### M258. Eye-Tracking to Optimize a Digital Goals-of-Care Decision Aid for Patients with Severe Acute Brain Injury

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**Objective:** To optimize the usability of a digital goals-of-care shared decision-making tool (decision aid [DA]) for clinicians and families of patients with severe acute brain injury (SABI), including traumatic brain injury, hemorrhagic, and large ischemic stroke. **Background:** Shared decision-making may ameliorate breakdowns in clinician-surrogate prognostic and goals-of-care communication in neuroICUs. To increase portability, shareability, and ease-of-implementation, we have converted our validated paper-based DA for families of SABI patients to a digital web/mobile-based DA and communication tool (WebDA+C-tool). We employed principles of User Experience Design with eye tracking to optimize user engagement and usability as crucial measures of digital DAs. Eye tracking is an unobtrusive technology to detect user attention and focus on the screen. **Methods:** Between October-November 2022 we recruited clinicians and surrogates of SABI patients for WebDA+C-tool test-user sessions over 4 iterative cycles (two for general feedback; two with eye-tracking) with WebDA+C-tool reprogramming after each cycle. Eye-tracking was performed in surrogates viewing our WebDA+C-tool on a laptop with a Tobii-X-60 eye-tracker. Afterwards, we replayed their eye-tracking and collected feedback through a retrospective “think-aloud” protocol, conducted exit-interviews, and measured usability with the validated System Usability Scale (SUS). **Results:** Over 4 iterations, we recruited 14 surrogates and 8 clinicians

(neurocritical care, neurosurgery, palliative care). The initial two cycles (7 surrogates, 8 clinicians) provided insights about design and content changes. The next two cycles with eye-tracking (7 different surrogates) provided us user engagement metrics before and after programming adjustments. While initially showing search behaviors and user confusion, all metrics improved after targeted WebDA+C-tool re-programming: average-visit-duration 46,213ms -> 50,956ms; saccade-to-fixation-frequency 57% -> 48%; and fixation-to-visit-duration 64% -> 54%. Usability was excellent (mean SUS  $81\pm16$ , with values  $>68$  indicating good usability). **Conclusion:** We optimized the user experience design of our WebDA+C-tool using eye-tracking and achieved improved user engagement and excellent usability; it is now ready for real-world testing in surrogates of patients with SABI. Employing user experience design principles is an important step in the development of digital interventions.

### M259. Head Injury and Incident Ischemic Stroke in Community-Dwelling Adults

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**Objective:** To examine the association between prior head injury and incident ischemic stroke. **Background:** Traumatic brain injury (TBI) may increase stroke risk through direct mechanisms, such as microvascular injury or endothelial dysfunction, or through co-occurring arterial dissection. Evidence regarding stroke risk after TBI remains limited, particularly in community-dwelling populations. **Methods:** The Atherosclerosis Risk in Communities (ARIC) Study is an ongoing prospective cohort study comprised of 15,792 community-dwelling adults in the U.S. who were initially recruited in 1987-1989 with follow-up through 2019. Head injury was defined using self-report and hospital-based International Classification of Diseases diagnostic codes and was analyzed as a time-varying exposure. Incident ischemic stroke was identified through semi-annual telephone follow-up calls and community surveillance of hospitalizations with physician adjudication of all events. We used Cox proportional hazards models to estimate hazard ratios (HRs) for the association between head injury and incident ischemic stroke. Models were adjusted for sociodemographic and cardiovascular risk factors. In secondary analyses we used Fine-Gray proportional hazards models to account for competing risk of death, considered associations of the number and severity of head injuries with ischemic stroke, and conducted subgroup analysis by race, sex, and age. **Results:** Our analysis included 11,833 individuals with no history of head injury, stroke, or

cardiovascular disease at baseline. Median baseline age was 54 years (25<sup>th</sup>-75<sup>th</sup> percentile=49-59). More than half were female (59.6%) and 28.4% were Black. Head injuries occurred in 1,973 participants (16.7%) over study follow-up, most of which were classified as mild. In adjusted Cox models, head injury was associated with increased risk of subsequent ischemic stroke (HR=1.42, 95%CI=1.17-1.71). The association was slightly stronger, but consistent in Fine-Gray proportional hazards models accounting for competing risk of mortality (HR=1.88, 95%CI=1.56-2.26). In secondary analyses, we observed evidence of a dose-response association for the hazard of stroke associated with number of head injuries (one: HR=1.27, 95%CI=1.05-1.54; two or more: HR=2.04, 95%CI=1.43-2.92) but not for severity (mild: HR=1.50, 95%CI=1.19-1.89; moderate/severe/penetrating: HR=1.41, 95%CI=0.85-2.31) with no head injuries as the referent. There was no significant evidence for interaction by race, sex, or age (all  $p$ -interaction>0.05). **Conclusions:** In this community-based cohort, head injury was associated with increased risk of incident ischemic stroke, with evidence of dose-response association with the number of head injuries. These results suggest the importance of primary stroke prevention among individuals with prior TBI.

#### **M260. Loss of Sarm1 Attenuates Functional Deficit Severity and Pathological pTDP-43 and pTau Accumulation in a Murine Repetitive Traumatic Brain Injury Model**

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**Background:** Traumatic brain injury (TBI), particularly if moderate-to-severe, is a strong environmental risk factor for many neurodegenerative diseases that are characterized by the pathological accumulation of phosphorylated TDP-43 (pTDP-43) and phosphorylated tau (pTau). SARM1 (sterile alpha and TIR motif containing) enzyme is known for driving the cellular destruction pathway in several categories of neuronal injury including TBI. We and others previously demonstrated that blocking the SARM1 pathway suppresses neuronal injury after TBI. We aim to determine whether the loss of SARM1 *gene* could attenuate TBI-associated pTDP-43/pTau accumulation and improve functional outcomes in our moderate-to-severe mouse repetitive TBI (rTBI) model. **Methods:** *Sarm1*<sup>-/-</sup>, *Sarm1*<sup>+/-</sup>, and *Sarm1*<sup>+/+</sup> ( $n=37$  per group) male mice were subjected to rTBI using a previously established paradigm. We serially assessed the neurological severity score from baseline to 1 month after rTBI. In addition, we assessed the burden of impact seizures and 1-month survival. Histopathology ( $n=9$  per group; NeuN, MBP, GFAP, IBA-1, pTDP43, pTau) was assessed in non-overlapping cortical regions at 1 month after rTBI. Unless stated otherwise, between-group comparisons of continuous variables over repeated measurements were conducted using longitudinal mixed models. **Results:** Compared with *Sarm1*<sup>+/+</sup> mice, *Sarm1*<sup>-/-</sup> mice had less severe neurological deficits ( $P=0.009$ ), a lower burden of impact seizures ( $P<0.05$ , Chi-Square test), and improved survival (Log-rank

$P=0.004$ ). Moreover, they had a significantly attenuated neuronal loss ( $P=0.009$ ), axonal loss ( $P=0.018$ ), and microgliosis ( $P=0.034$ ), whereas there was no significant difference in the cortical GFAP signal between groups ( $P=0.26$ ). *Sarm1*<sup>-/-</sup> mice had significantly fewer pTDP-43 positive cells ( $P=0.0003$ ) and fewer pTau positive cells ( $P=0.012$ ) in the cerebral cortex as compared with *Sarm1*<sup>+/+</sup> mice. While the extent of the neuronal and axonal loss was not significantly reduced in *Sarm1*<sup>+/-</sup> mice ( $P>0.05$ , each), we found that *Sarm1* haploinsufficiency significantly attenuated the number of cortical cells containing pTDP-43 ( $P=0.0002$ ) and pTau ( $P=0.021$ ). **Conclusions:** Loss of *Sarm1* attenuated neurological deficit severity and neuropathology after moderate-to-severe rTBI. We show for the first time that *Sarm1*<sup>-/-</sup> may attenuate injury-associated seizures, and improve survival. Both *Sarm1*<sup>+/-</sup> and *Sarm1*<sup>-/-</sup> mice had suppressed pTDP-43 and pTau accumulation. Targeting SARM1 may be a promising strategy to improve outcomes after moderate-to-severe TBI. Further studies are needed to understand the role of SARM1 in TBI-associated neurodegenerative diseases that are characterized by TDP-43 and tau pathology.

#### **M262. Relation of Hypertension and Elevated Body Mass Index to Duration of Symptoms Following Concussion**

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**Objective:** Most people with a concussion experience symptom resolution within days to weeks after injury. However, approximately one-third of patients report symptoms lasting for months. Developing an understanding of risk factors for prolonged concussion-related symptoms is clinically important in order to identify at-risk patients and to develop new and targeted treatment modalities. The purpose of this study was to examine associations of concomitant hypertension and elevated BMI with persistence of concussion symptoms. **Methods:** This study included review of medical records for 422 patients who sought care at the NYU Langone Health Concussion Center from 2013-2022. Included were patients with no prior history of concussion who received care within one year of injury. Captured variables included blood pressure and body mass index (BMI) at initial visit, existing hypertension diagnosis, number of clinical visits, number of days between injury and final visit, and diagnosis of post-concussion syndrome (PCS). Hypertension was defined as systolic blood pressure >130 mmHg, diastolic blood pressure >80 mmHg, or hypertension diagnosis. A BMI value >25.0 was considered elevated. **Results:** Patient mean age was 41±17 years. The cohort was 65% female, 72% white, 92% Non-Hispanic/Latino and the most common mechanism of concussion was mechanical fall (31%). Patients with hypertension had a greater average number of days between injury and last appointment compared with non-hypertensive patients (465 vs. 237 days,  $p<0.0001$ , Wilcoxon rank-sum test). The same pattern was observed for patients with elevated BMI compared to those without (388 vs. 259,  $p<0.01$ ). Hypertension and elevated BMI were also

associated with greater total numbers of appointments at the concussion center (4.5 vs. 2.5 visits for patients with vs. without hypertension,  $p < 0.0001$ ; 3.8 vs. 2.7 visits for patients with vs. without elevated BMI,  $p < 0.01$ , Wilcoxon rank-sum test). The probability of PCS diagnosis was also increased for hypertensive patients (35% vs. 17%,  $p < 0.001$ , chi-square test) and patients with elevated BMI (29% vs. 19%,  $p = 0.02$ ). When accounting for mechanism of injury, race, ethnicity, age, and gender, all reported associations for hypertension, but not for BMI, remained statistically significant. **Discussion:** Hypertension may be a risk factor for greater symptom severity and increased duration of clinical care following concussion. Elevated BMI presented similar patterns of risk; however, these associations were less conclusive. Further investigations are needed to determine whether treatment of hypertension prior to or following injury could improve concussion-related symptom outcomes.

### **M263. The Recovery of Consciousness via Evidence-Based Medicine and Research (RECOVER) Program: An Innovative Paradigm for Advancing Neuroprognostication**

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**Objective:** Neuroprognostication, or the prediction of neurologic recovery in patients with disorders of consciousness (DoC) due to acute brain injury, is an impactful determination that often dictates whether life-sustaining treatments are continued or withdrawn. However, the conventional approach to neuroprognostication is fragmented across time, providers and disciplines, impeding clinical care as well as research and education. We sought to establish an innovative approach to neuroprognostication - the Recovery of Consciousness Via Evidence-Based Medicine and Research (RECOVER) program - that provides specialized, comprehensive, and longitudinal care. **Methods:** Inpatients requiring neuroprognostication are evaluated by a dedicated RECOVER consult service, which collects prognostic data per evidence-based guidelines, advises clinical teams, and counsels families. Patients are discussed systematically in a weekly interdisciplinary conference (with representation from neurology, psychiatry, neuroradiology, palliative care, social work, physical and occupational therapy, ethics, and others) to formulate holistic prognostic determinations and treatment plans. For patients who survive to hospital discharge, the RECOVER program provides continuity of care through partnered post-acute facilities and outpatient clinics. This clinical infrastructure is leveraged to build a registry of clinical data and outcomes. Trainees are incorporated into each phase of the program. **Results:** Between August 2022 and March 2023, the RECOVER program evaluated 66 patients (~9 per month, mean age 55y [SD = 16]), with brain injury etiologies including anoxia (69%), ischemic stroke (18%),

intracranial hemorrhage (8%), and others including traumatic brain injury (5%). Of those, 32 (48%) survived to hospital discharge without transition to hospice care. Of the 23 patients discharged for  $\geq 3$  months, five have returned to clinic (22%), either in person or virtually. Seven patients have undergone functional magnetic resonance imaging, interpreted during interdisciplinary conferences with the aid of neuroradiology and ethics. Preliminary survey data suggest high rates of satisfaction with the RECOVER program, across both primary clinical teams and patient families. **Interpretation:** The RECOVER program permits systematic, guideline-based and interdisciplinary care, provides continuity to patients and families, and facilitates clinical translation of research. Given a vulnerable patient population, due to their neurologic injury and demographic composition, the RECOVER program helps provide ongoing healthcare access, although clinic retention remains low. The RECOVER program also promotes trainee education and serves as an effective platform for data collection. If adopted broadly, the RECOVER program may advance DoC care and facilitate multi-center research.

### **M264. Thyrotoxic Periodic Paralysis Triggered by COVID-19 in Undiagnosed Graves Disease: A Case Report Highlighting Risks Associated with Potassium Overcorrection**

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Thyrotoxic periodic paralysis (TPP) is a complication of thyrotoxicosis, resulting in reversible episodic muscle weakness secondary to low serum potassium. Treatment includes supportive care while correcting hypokalemia; however there is increased risk for potassium overcorrection in TPP. We present the clinical course and management of a 21-year-old man without significant past medical history, who was transferred to our neurointensive care unit from an outside hospital after presenting with severe four-limb weakness from significant hypokalemia as a result of COVID-19 triggered thyrotoxicosis. Prior to his transfer he was found to have a potassium level of 2.0 mEq/L, and received a total of 60 milliequivalents of intravenous and 40 milliequivalents of potassium within a short time. He had worsening weakness to essentially quadriplegia, tachypnea and coughing difficulty, prompting intubation out of concern for airway protection. He was heli-transferred to our neurointensive care unit. Over the next 12 hours, potassium levels rose to 6.8 mEq/L. Prompt hyperkalemia treatment was initiated, including three insulin shifts in the first 8 hours of hyperkalemia with concurrent potassium wasting diuresis requiring vasopressor supplementation. Serology revealed evidence of hyperthyroidism, prompting the use of propylthiouracil, propranolol and hydrocortisone for thyroid blockade. He was later found to have autoimmune thyroiditis (Grave's disease). Fortunately the patient recovered and was discharged from the neurointensive care unit several days later. In acute episodes of TPP, potassium correction is needed to reverse paralysis; however, only a functional serum hypokalemic state



exists, with out any true whole body potassium depletion. This report highlights the important challenges of potassium repletion in TTP. During thyrotoxicosis, thyroid hormone excess results in intracellular potassium sequestration, which can rapidly resolve upon resolution of the triggering factor. This creates an increased risk for overcorrection in TPP, leading to dangerous hyperkalemia, as was seen in this case. A suggested correction protocol is 30mEq of oral potassium every two hours until symptoms improve, with no more than 90 mEq of potassium in 24 hours (Gutmann and Conwit, 2022). Especially when rebound hyperkalemia is of concern, some have suggested no more than 10 mEq per hour (Lu et al. 2004).

## **M265. Trends in Traumatic Brain Injury Mortality in the United States: 1999-2019**

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**Background:** Nationally representative trends in TBI-related mortality in the U.S are not well-characterized. We aimed to characterize trends in TBI-related mortality in the U.S. from 1999 through 2019. **Methods:** Data on TBI-related deaths were obtained from the National Vitals Statistics System multiple-cause-of-death files available via CDC WONDER for 1999-2019. In accordance with the CDC surveillance definition, TBI-related deaths were defined as an injury-related cause of death with a TBI-related ICD-9/10 code in the multiple-cause-of-death fields. We calculated age-standardized TBI mortality rates per 100,000 population for the entire study period and by seven-year epochs (1999-2005; 2006-2012; 2013-2019) overall, and stratified by age group, sex, and race. Rates were age-standardized to the 2000 Standard Population. We further investigated states and counties with the greatest increases and decreased in TBI-related mortality between 1999-2005 and 2013-2019. **Results:** The overall age-standardized TBI-related mortality rate was 17.71 per 100,000 population (95% CI=17.67-17.74) from 1999 through 2019. In general, the age-standardized TBI-related mortality rate decreased from 1999 to 2019 (1999-2005: 18.31 [95%CI=18.25-18.36], 2006-2012: 17.13 [95%CI=17.08-17.19], 2013-2019: 17.50 [95%CI: 17.45-17.56]). Age-standardized TBI-related mortality rate from 1999 to 2019 was higher among older individuals ( $\geq 75$  years: 69.25, 95%CI=68.99-69.50) compared to younger individuals ( $< 74$  years: 14.40, 95% CI=14.37-14.43), among American Indians/Alaskan Natives (18.74, 95%CI=18.41-19.07) compared to other races (Whites: 18.26 [95%CI=18.23-18.30]; Blacks/African Americans: 16.34 [95%CI=16.25-16.43]; Asians/Pacific Islanders: 8.84 [95%CI=8.73-8.95]), and among men (27.79, 95%CI=27.73-27.85) compared to women (8.69, 95%CI: 8.66-8.72). While TBI-related mortality rates decreased from 1999-2005 to 2013-2019 in all sex and race groups, mortality rates increased among individuals aged  $\geq 75$  years (1999-2005: 60.78 [95%CI=60.34-61.23]; 2013-2019: 76.97 [95%CI=76.53-77.42]). Between 1999-2005 and 2013-2019, Alaska had the greatest increase

in age-adjusted TBI-related mortality rate (1999-2005: 20.35 [95%CI=18.85-21.86]; 2013-2019: 33.94 [95% CI=32.27-35.61]), followed by Vermont and North Dakota. In contrast, Washington D.C. had the greatest decrease in age-adjusted TBI-related mortality rate (1999-2005: 23.58 [95%CI=22.11-25.06]; 2013-2019: 11.44 [95% CI=10.46-12.42]), followed by Mississippi and Delaware. On a county level, Monroe County, Arkansas had the greatest increase (1999-2005=28.82 [95%CI=17.60-44.51]; 2013-2019: 55.07 [95%CI=35.28-81.94]) and Boundary County, Idaho had the greatest decrease in in age-adjusted TBI-related rate (1999-2005: 72.70 [95%CI=53.42-96.67]; 2013-2019: 26.35 [95%CI: 15.86-41.15]). **Conclusions:** Although TBI-related mortality in the U.S. has decreased overall between 1999 and 2019, rates have notably increased among individuals aged 75+ years and in certain geographic regions. This work identifies high-risk populations which may benefit from targeted TBI prevention strategies.

## **K-M114. Association of Dexmedetomidine Utilization with Clinical Outcomes Following Moderate-Severe Traumatic Brain Injury**

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**Background:** Traumatic brain injury (TBI) is a major public health problem. Management of critically ill and mechanically-ventilated patients with moderate-severe TBI (msTBI) often includes sedation. Dexmedetomidine has emerged as a possible candidate for early sedation after TBI due to its potential modulation of autonomic dysfunction. We examined early sedation patterns, as well as the association of dexmedetomidine exposure with clinical and functional outcomes among mechanically ventilated patients with msTBI in the United States. **Methods:** We conducted a retrospective cohort study using data from the Premier Healthcare Database and identified a cohort of critically ill adult patients with msTBI who required mechanical ventilation (MV) from Jan 2016 to June 2020. msTBI was defined by head-neck abbreviated injury scale (AIS) values of 3 (serious), 4 (severe), and 5 (critical). We described early sedative utilization patterns. Next, using propensity-matched models, we examined the association of early dexmedetomidine exposure [within 2 days of intensive care unit (ICU) admission] with the primary outcome of hospital mortality and the following secondary outcomes: hospital length of stay (LOS), days on MV, vasopressor use after the first two days of admission, hemodialysis (HD) after the first two days of admission, hospital costs, and discharge disposition. **Results:** The study population included 19751 subjects who required MV within 2 days of ICU admission. The patients were majority male and white. The most utilized sedative was propofol (82.7%), followed by benzodiazepines (26.0%), dexmedetomidine (6.5%), and ketamine (0.9%). From 2016 to 2020, the annual percent utilization of dexmedetomidine increased from 4.05% to 8.60%. After propensity score matching, early dexmedetomidine exposure was associated

with reduced hospital mortality (OR 0.43; 95% CI 0.31-0.61), higher likelihood of discharge to home (OR 1.23; 95% CI 1.01-1.50), and reduced number of days on mechanical ventilation (HR 1.16; 95% CI 1.04-1.29). Exposure to early dexmedetomidine was not associated with hemodialysis utilization (OR 0.66; 95% CI 0.39-1.10), vaso-pressor utilization (OR 1.12; 95% CI 0.91-1.38), hospital length of stay (HR 1.04; 95% CI 0.95-1.14), or total hospital costs (OR 1.02; 95% CI 0.94-1.09). **Conclusion:** Dexmedetomidine is an increasingly popular sedative among mechanically ventilated patients with msTBI. Early dexmedetomidine exposure may lead to improved patient outcomes when used in this population. Prospective randomized-controlled trials are needed to confirm these findings.

#### K-M115. Biomarkers Associated with Progression of Intracranial Hemorrhage in the Prehospital TXA for TBI Trial

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**Background:** Progression of intracranial hemorrhage is a common, potentially devastating complication after moderate/severe traumatic brain injury (TBI). Patients that have progression of intracranial hemorrhage are more likely to require an intracranial pressure monitor and/or a craniotomy. Clinicians have few tools to predict which patients with traumatic intracranial on their initial head computed tomographic scan (hCT) scan will progress. In this study, we sought to identify clinical or imaging biomarkers which associate with intracranial progression. **Methods:** We analyzed a subset of subjects from the phase II double-blind, multicenter randomized "Prehospital Tranexamic Acid Use for TBI" trial. This subset was limited to subjects in the placebo arm of the parent trial with evidence of hemorrhage on initial hCT and a follow up hCT 6 hours after the initial hCT. Intracranial progression was defined as an increase in size by 30% or more or the development of new hemorrhage in the intra-axial and extra-axial intracranial vault between the admission/baseline and follow up hCT. Two independent radiologists evaluated each hCT, and conflicts were adjudicated by a third. Clinical and radiographic characteristics were collected, along with plasma protein biomarkers at admission (GFAP, UCH-L1, MAP, VCAM-1, ICAM-1, Ang-1, Ang-2, Thrombomodulin, Syndecan-1, Thrombospondin, IL-6, and TNF- $\alpha$ ). **Results:** In the subset (n=104), 46% (n=48) showed progression as defined above. Age, sex, GCS motor and total GCS scores were similar between progressors and non-progressors. Those with progression had higher Marshall (2 [2-6] v. 2 [2-2], P=0.007) and Rotterdam scores (2 [2-3] v. 2 [2-2], P=0.004), and larger initial hematoma sizes (2.2 [ $\pm$ 13.7] v. 0.6 [ $\pm$ 26.5] mL, P=0.005) than non-progressors. Of the plasma proteins, only elevated levels of GFAP (2350 [587-3730] v. 327 [158-1210]  $\mu$ g/dL, P=0.001) and MAP (131 [21-513] v. 37 [13-125]  $\mu$ g/dL, P=0.015) were

associated with progression. **Conclusions:** We identified radiographic and blood-based biomarkers associated with progression of intracranial hemorrhage. Next steps include creation of predictive models of progression including these features, and validation in separate datasets.

#### K-M116. Head Injury and Cognitive Change over 30 Years

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**Background:** Traumatic brain injury (TBI) is associated with short-term cognitive impairment and later-life dementia risk, but there is limited evidence regarding long-term cognitive change after head injury in community-dwelling populations.

**Objective:** To examine the association between head injury and cognitive change over 30 years. **Methods:** The Atherosclerosis Risk in Communities (ARIC) Study is an ongoing prospective cohort of 15,792 adults recruited from 4 U.S. communities in 1987-1989. Head injury was defined by self-report and hospital-based International Classification of Diseases diagnostic codes and was analyzed as a time-varying exposure over study follow-up. Cognitive testing was performed at 5 study visits (1990-1992, 1996-1998, 2011-2013, 2016-2017, and 2018-2019) and scores were combined into a previously validated global factor score. We used linear mixed effects models with random intercepts, random slopes for time from baseline (1990-1992; modeled with splines at 1996-1998 and 2011-2013), and an unstructured covariance matrix to estimate the association between head injury and the change per decade in cognition. Models were adjusted for sociodemographics, cardiovascular and APOE $\epsilon$ 4 genotype. Formal testing for interaction by age, sex, and race was performed. In secondary analyses, we considered the associations of number of prior head injuries and injury severity with cognitive factor scores. Multiple imputation by chained equations was employed to impute missing data.

**Results:** Our analysis included 11,677 individuals who attended the second ARIC study visit in 1990-1992 with no history of head injury. Participants were a mean age of 58 years, 58% were female, 26% were of self-reported Black race, and 18% experienced a head injury over study follow-up, the majority classified as mild. In adjusted models, the average decline in cognition per decade was -0.045 (95% CI=-0.082,-0.007) in individuals without head injury and -0.105 (95%CI=-0.163,-0.048) in individuals with head injury (difference=-0.061, 95%CI=-0.103,-0.019). This difference in cognitive decline is equivalent to individuals with head injury being 6 years older at baseline. In secondary analyses, there was evidence supporting a dose-dependent association for greater cognitive decline with higher number of head injuries (additional decline in head injury compared to no head injury group per decade: 1 injury=-0.047, 95% CI=-0.089,-0.004 and 2+ injuries=-0.071, 95%CI=-

0.167,0.024, which is equivalent to being 4.5 years and 6.9 years older at baseline for 1 and 2+ head injuries, respectively), but not with injury severity. There was no evidence for interaction by age, sex, or race (all  $p$ -interaction > 0.05). **Conclusions:** Head injury was associated with accelerated cognitive decline over 30 years. Future work investigating mechanisms underlying long-term cognitive decline observed among individuals with TBI is warranted.

#### K-M117. Symptomatic Baroreflex Abnormalities

##### Following Concussion

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**Background:** Post-traumatic onset headache, brain fog, and dizziness, are common following concussion. Clinically, these symptoms are often equated to altered autonomic function and resultant changes in cerebral blood flow. Baroreceptor function plays a key role in monitoring and maintaining blood flow to the brain. Thus, impairment to this reflex arc may be of particular interest in understanding symptoms resulting from head trauma. **Methods:** Participants with concussion and healthy controls, aged 15-60, were recruited through the University of Utah electronic medical record and word of mouth. Inclusion criteria: head injury within 14 days, ongoing symptoms. Age/sex matched healthy controls, without a history of concussion or recurrent headaches. Exclusion criteria: medications that alter autonomic function and could not be held for 5 half-lives; medical diagnoses known to alter autonomic function (e.g., diabetes, heart disease, neuropathy). This study received approval from our Institutional Review Board; all participants were consented. Study participants completed symptom assessment (Rivermead) and standardized autonomic testing, including heart rate (HR) variability to deep breathing (HRDB), Valsalva, and 10-minute head-up tilt testing (HUTT) using continuous beat-to-beat heart HR and blood pressure (BP) monitoring. Physiological measures were analyzed for cardiovagal and cardiovascular adrenergic reflex function via standard methods, and for sympathetic and parasympathetic contributions during supine and HUTT states, via continuous wavelet transform to identify very low (VLF), low (LF), and high frequency (HF) domains. **Results:** 36 concussed and 19 control subjects completed the study. LF during HUTT was significantly lower in concussed subjects, compared to controls. Heart rate variability (SD and CV) generally trended lower, while mean HR (supine and upright), mean BP, and VLF power trended higher in concussed participants. There were no significant differences in parasympathetic function (mean HR range, Valsalva Ratio, HF). For concussed subjects, using univariate correlation analysis, there were moderate positive correlations between symptom scores and resting mean HR, resting HR variability, upright BP variability, and upright VLF and LF power. **Conclusions:** These data support a blunted sympathetic response to HUTT in concussed participants, where a robust increase in sympathetic activity is expected. There were also more subtle features of increased sympathetic activation in the supine state,

relative to controls, though this pattern was not statistically robust. Finally, while subtle, the overall pattern suggests relative sympathetic hypofunction to upright challenge, with resting state sympathetic activation, which correlate with increased symptom burden. Subtle changes in baroreceptor function may explain clinically observed activity intolerance and related symptoms in concussed individuals.

#### K-M118. Systemic Metabolic Alterations after Aneurysmal Subarachnoid Hemorrhage

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**Background:** Aneurysmal rupture resulting in subarachnoid hemorrhage (aSAH) results in a robust systemic inflammatory response. We hypothesized that a shift in circulating metabolites with prominent changes in lipids would occur early after aSAH and predict outcomes. **Methods:** aSAH patients and controls were analyzed from two tertiary care centers (University of Texas Health Science Center and University of Maryland). Clinical data for all patients were abstracted including comorbidities as well as adjudicated outcomes such as occurrence of delayed cerebral ischemia (DCI) and modified Rankin Scale (mRS) score. Paired samples were collected within 24h and at 7d after aneurysm rupture. Mass spectrometry-based untargeted metabolomics was performed. A total of 1,370 metabolites were detected. Principal component analysis (PCA) was used to segregate controls from aSAH patients. Hierarchical clustering algorithms were developed to group sets of metabolites. Volcano plots were utilized to visualize fold changes for each metabolite relative to  $P$ -values comparing patients with or without DCI. Receiver operating curves (ROC) as well as multivariable logistic regression models were developed to assess utility of metabolites for predicting outcomes. **Results:** A total of 70 aSAH patients and 30 age matched controls were included. Metabolites readily distinguished control from aSAH patients in PCA analysis. Hierarchical clustering revealed significantly higher levels of free fatty acids in patients with aSAH but lower levels of acylcholines. Volcano plots demonstrated that in patients with DCI, sphingosine and sphinganine were significantly increased (fold change > 2, false discovery rate [FDR] corrected  $P$ -value < 0.1), while S-adenosylhomocysteine and two acylcarnitines were significantly decreased (fold change < -2, FDR corrected  $P$ -value < 0.1). Sphingosine had an AUC of 0.723 (95% CI 0.6001, 0.834) for predicting DCI. In multivariable regression models corrected for age, clinical severity, and sex, sphingosine [OR 10.2 (95%CI 2.46, 59.8)] and sphinganine [OR 4.52 (95%CI 1.57, 20.9)] were associated with DCI. Levels of sphingosine 1-phosphate were higher in women with DCI but not men. Levels of the enzyme autotaxin, which can produce sphingosine 1-phosphate, were significantly higher in women than men ( $P=0.0045$  among patients with DCI and  $P=0.0029$  among patients without DCI). **Conclusions:** Plasma metabolites readily distinguish

aSAH from controls. Increased circulating sphingosine and sphinganine were associated with DCI, while sphingosine 1-phosphate was increased in DCI only in women. Sex differences in enzymes involved in sphingolipid metabolism may contribute to risk of DCI after aSAH.

#### **LB-M115. Cocaine Intoxication Resulting in an Atypical Stroke**

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**Introduction:** Short term and long-term cocaine intoxication can have detrimental effects on the brain, specifically in the reward pathway in the nucleus accumbens, ventral tegmental area, and hippocampus. Vascular insults are typical due to the vasospastic effect of cocaine. However, bilateral atypical stroke with involvement of the basal ganglia and hippocampi has not been reported in cocaine use. **Case Description:** A 51-year-old man with a history of polysubstance was brought in by EMS after being found unresponsive. He was given naloxone in the field without improvement. He eventually returned to baseline awareness except for residual amnesia. On physical exam, vitals were normal, lungs were clear, and he had a slight tremor but no evident focal deficit. MRI brain revealed subacute infarct with bilateral symmetric basal ganglia diffusion restriction along with bilateral hippocampal diffusion restriction. Over the course of three days of hospitalization, the patient was persistently amnesic. A diagnosis of cocaine intoxication with possible neurological damage was established. He was discharged with outpatient neurology follow up and started on dual anti-platelet therapy for 21 days to eventually taper to aspirin only. **Discussion:** This case illustrates the potential for an alternative mechanism for stroke secondary to cocaine use, irreversible ischemic effects in bilateral basal ganglia and hippocampus. Potential detrimental effects of amphetamines on the basal ganglia have been reported in literature, particularly the caudate nucleus with increased vulnerability to oxygen and glucose deprivation. Since our patient did not have any evidence of hypoperfusion or vascular occlusion, the main potential explanation resides in either reversible vasoconstriction, not detectable on imaging, or neurotoxic effect of cocaine on particular areas of the brain with high metabolic demand. While cases of deep cerebral gray matter infarcts in the setting of cocaine intoxication have been reported, none described bilateral basal ganglia and hippocampus stroke out of the setting of clear hypoperfusion such as cardiac arrest. Our case is unique since our patient did not report any sign of hypoperfusion, yet a multi-territorial cerebral infarct was noted on imaging with resultant long-term consequences. Future studies are required to determine cocaine effect on neural vasculature. It is important that clinicians keep low threshold for atypical cerebral infarcts in patients with cocaine intoxication along with importance of early hydration to avoid detrimental consequences.

#### **LB-M116. Enhanced In Vivo Blood Brain Barrier Transcytosis of Macromolecular Cargo Using an Engineered pH-Sensitive Mouse Transferrin Receptor Binding Nanobody**

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**Background:** The blood brain barrier limits entry of macromolecular diagnostic and therapeutic cargos. Blood brain barrier transcytosis via receptor mediated transport systems, such as the transferrin receptor, can be used to carry macromolecular cargos with variable efficiency. Transcytosis involves trafficking through acidified intracellular vesicles, but it is not known whether pH-dependent unbinding of transport shuttles can be used to improve blood brain barrier transport efficiency. **Methods:** A mouse transferrin receptor binding nanobody, NIH-mTfR-M1, was engineered to confer greater unbinding at pH 5.5 vs 7.4 by introducing multiple histidine mutations. The histidine mutant nanobodies were coupled to neurotensin for *in vivo* functional blood brain barrier transcytosis testing via central neurotensin-mediated hypothermia in wild-type mice. Multi-nanobody constructs including the mutant M1<sub>R56H</sub>, P96H, Y102H and two copies of the P2X7 receptor-binding 13A7 nanobody were produced to test proof-of-concept macromolecular cargo transport *in vivo* using quantitatively verified capillary depleted brain lysates and *in situ* histology. **Results:** The most effective histidine mutant, M1<sub>R56H</sub>, P96H, Y102H -neurotensin, caused >8°C hypothermia after 25 nmol/kg intravenous injection. Levels of the heterotrimeric construct M1<sub>R56H</sub>, P96H, Y102H -13A7-13A7 in capillary depleted brain lysates peaked at 1 hour and were 60% retained at 8 hours. A control construct with no brain targets was only 15% retained at 8 hours. Addition of the albumin-binding Nb80 nanobody to make M1<sub>R56H</sub>, P96H, Y102H -13A7-13A7-Nb80 extended blood half-life from 21 minutes to 2.6 hours. At 30-60 minutes, biotinylated M1<sub>R56H</sub>, P96H, Y102H -13A7-13A7-Nb80 was visualized in capillaries using *in situ* histochemistry, whereas at 2-16 hours it was detected in diffuse hippocampal and cortical cellular structures. Levels of M1<sub>R56H</sub>, P96H, Y102H-13A7-13A7-Nb80 reached more than 3.5 percent injected dose/gram of brain tissue after 30 nmol/kg intravenous injection. However, higher injected concentrations did not result in higher brain levels, compatible with saturation and an apparent substrate inhibitory effect. Nanobody constructs have been labeled with the metal chelators NOTA and DOTA, plus the long half-life positron emitter [64] Copper in preparation for *in vivo* PET scan studies. **Conclusion:** The pH-sensitive mouse transferrin receptor binding nanobody M1<sub>R56H</sub>, P96H, Y102H may be a useful tool for rapid and efficient modular transport of diagnostic and therapeutic macromolecular cargos across the blood brain barrier in mouse models. Additional development will be required to determine whether this nanobody-based shuttle system will be useful for brain imaging and fast-acting therapeutic applications in TBI.

## S276. Age-Dependent Changes in Perineuronal Nets and Associated Parvalbumin Interneurons in the 5xFAD Amyloidosis Mouse Model

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Perineuronal nets (PNNs) are extracellular matrix structures that surround neurons and proximal dendrites and regulate synaptic transmission, plasticity, and several facets of memory. PNNs are commonly associated with parvalbumin-positive (PV+) fast-spiking interneurons which are hypothesized to play physiological roles in memory and cognition. Despite a growing literature related to PNNs and PV+ neurons' roles in synaptic maintenance and memory, much remains unknown regarding how these structures are affected in neurodegenerative diseases such as Alzheimer's Disease (AD). In this study, we used the 5xFAD amyloidosis mouse model to investigate how AD-like pathology affects PNNs and PV+ neurons. Using immunofluorescence microscopy of mouse brain, we stained 5xFAD and Wild Type (WT) mice at 1.8, 3, 6, and 10 months of age. We stained for PV+ neurons (using anti-PV antibody), PNNs (using a WFA antibody), and for Amyloid-Beta (A $\beta$ ) plaques (using a 4G8 antibody). Images were then processed using ImageJ to quantify the presence of PV+ neurons, PNNs, and the association between them in several regions of interest across genotypes and age groups. We found that PNNs, but not PV+ neurons, are significantly depleted in the anterior cortex, posterior cortex, and subiculum of the 5XFAD mice in early amyloidosis (3-6 month old 5XFAD mice). Furthermore, analyses investigating the co-localization of PNNs and PV+ neurons in these regions found that PNNs were depleted surrounding PV+ neurons in an age-dependent manner in the 5XFAD mice compared to WT. Specifically, in early amyloidosis (3-6 months) there was a general depletion of PNNs, but in later amyloidosis (6 -10 months) the depletion of PNNs was preferentially surrounding PV+ neurons. Finally, assessing the relationship between A $\beta$  plaque proximity and the co-localization between PNNs and PV+ neurons revealed that PNNs closer to A $\beta$  plaques were more likely to be associated with PV+ neurons. Collectively, these findings may indicate the time-dependent impact of A $\beta$  pathology on PNNs, both in general and specifically surrounding PV+ neurons. Our ongoing studies will further characterize PNN and PV changes across a wider age spectrum.

## S277. An Overview of Peripheral Nervous System Aging Findings in Human and Animal Studies

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**Background:** The natural aging process results in various changes to the functional systems within the body. The nervous system contains two main parts: the central nervous system (CNS) consisting of the brain and spinal cord, and the peripheral nervous system (PNS) consisting of the spinal nerves and cranial nerves that run throughout the body. Research on the aging of the PNS has long been overlooked. More focus has been on age-related changes in the CNS, especially on neurodegenerative changes and disorders. Even though the exact etiology of PNS aging is not well understood, it is thought to be multifactorial, including but not limited to oxidative stress, dietary and hormonal factors, changes within the mitochondria, and a decrease in gene expression (genetics). **Objective:** In this paper, we aim to review the current etiopathogenesis of PNS aging and available treatments that may suggest future strategies to enhance preventive measures and potential therapies. **Methods:** For the purpose of review, we evaluated various published papers from available resources such as UCLA libraries, VA libraries, USC libraries, and Pubmed. **Results:** We review the anatomical and physiological changes that occur within the peripheral nervous system due to aging, along with various etiopathogenesis of PNS aging and specific treatments that could help slow down changes that occur to the PNS. Studies have shown that aging can affect cells within functional systems in a multitude of different ways; aging has been shown to induce loss of nerve cell mass, decrease the excitability of axons, and cause a decline in the vasopressin response. Morphological and electrophysiological studies have also revealed that an increase in peripheral sensory loss in large fibers is positively correlated with increasing age. **Conclusion:** This article will shed some light on the age-related changes in the mammalian peripheral nervous system. Furthermore, there are various treatment modalities, which have been brought forward, but there has not been a definitive treatment approach established. Proposed treatments mainly focus on preventive measures such as dietary restriction and the use of antioxidants. Currently, some study strategies used are hormone replacement and gene therapy, which hopefully will play a significant role in the future. Additionally, future studies involving the manipulation of elements suspected in being involved in the aging process can potentially spearhead the creation of novel therapies that can work against the progression of aging within the PNS.

## S278. Brain Tau and $\alpha$ -Synuclein Seeding Activity Correlates with Pathological Disease Stage and Precedes Neurofibrillary Tangle and Lewy Body Formation

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$\alpha$ -synuclein ( $\alpha$ Syn) is the primary pathology in Lewy body diseases (LBD: Parkinson's disease and Dementia with Lewy bodies) and 3R/4R tau aggregates are a hallmark of Alzheimer's disease (AD) and are also found in moderate to severe degrees in at least 50% of LBD cases postmortem. Recently,  $\alpha$ Syn and 3R/4R tau isoform selective real time quaking-induced conversion (RT-QuIC) methods have been utilized to analyze seeding activity frozen brain tissue. We investigated 3R/4R tau seeding activity from frozen midfrontal lobe samples in a set of AD (n=47) and LBD (n=21) cases with a range of Braak tau stages (B0=3, B1=25, B2=24, B3=16) and used Spearman Karber analyses to calculate the seeding dose necessary to turn 50% of wells positive ( $SD_{50}$ ).  $\alpha$ Syn  $SD_{50}$  values from midfrontal lobe samples were available for a subset of cases (AD=22, LBD=21) who had a range of Lewy body stages (none=16, limbic=8, neocortical=15, amygdala-predominant=4). 3R/4R tau seeding increased across Braak tau stages ( $F=19.5$ ,  $p<0.001$ ) and  $\alpha$ Syn seeding increased across Lewy body stages ( $F=69.8$ ,  $p<0.001$ ) in frontal lobe samples. Significant tau seeding was noted Braak stages B0-2 as was  $\alpha$ Syn seeding at limbic and amygdala-predominant Lewy body stages which are stages where neurofibrillary tangle and Lewy bodies are not observed in frontal lobes. In the entire cohort, there was a trend towards AD cases having higher Braak tau stages than LBD cases ( $p=0.06$ ); however, when statistically controlling for Braak tau stage or performing a sub-analysis on matched B0-B2 cases, AD cases consistently had higher midfrontal tau seeding activity than LBD cases ( $p=0.03$ ,  $p=0.02$  respectively). Additionally, tau and  $\alpha$ Syn seeding correlated in LBD cases, even when controlling for Braak tau stage ( $R^2=0.72$ ,  $p<0.001$ ). These data show, that 3R/4R tau and  $\alpha$ Syn seeding activity from brain tissue samples is related to Braak tau stage and Lewy body stages respectively but that significant seeding occurs prior to the occurrence of immunohistochemically detectable deposits. Tau seeding activity appears to be greater in AD than LBD patients, even at pre-tangle levels, implying possible differences in tau seeding capacity. Lastly, there may be a relationship between tau and  $\alpha$ Syn seeding in LBD frontal cortex.

## S279. Developing a Scalable HiPSC-Based Model for Characterizing Genetic Modifiers of Synucleinopathies

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Studies have identified genetic risk factors associated with synucleinopathies, a group of neurodegenerative diseases (NDs) characterized by  $\alpha$ -synuclein ( $\alpha$ S) aggregation. Emerging evidence suggests shared risk profiles and pathways among synucleinopathies and with other NDs. However, no preventative or disease-modifying clinical interventions have been developed, in part due to the complexity of risk genes which may have variable and incomplete penetrance. We hypothesize that modulators of  $\alpha$ S are potential candidates that modify disease penetrance. To identify such genes, we propose to develop a scalable human iPSC-based functional genomics model system. Our model utilizes CRISPRi-i<sup>3</sup>N cells, an iPSC line knocked-in with inducible Ngn2 and

dCas9-KRAB, for expedited cortical neuron differentiation and flexible gene knock-down. CRISPRi-i<sup>3</sup>N-SNCA were first generated using lentivirus-mediated SNCA overexpression to mimic  $\alpha$ S toxicity and were compared to CRISPRi-i<sup>3</sup>N-control. Longitudinal imaging analysis demonstrated significantly higher neuronal death in CRISPRi-i<sup>3</sup>N-SNCA. To test gene knock-down efficiency, we targeted VPS35, a retromer gene previously linked to synucleinopathies, in both CRISPRi-i<sup>3</sup>N-SNCA and CRISPRi-i<sup>3</sup>N-control lines and achieved over 80% reduction. A further increase in neuronal death in CRISPRi-i<sup>3</sup>N-SNCA was observed, suggesting that VPS35 knock-down has a synergistic effect on  $\alpha$ S toxicity. A detailed mechanistic study is underway. Additionally, we have established a sgRNA library to examine 1771 candidate genes of  $\alpha$ S toxicity modification, which were determined from previous  $\alpha$ S genetic and physical interaction studies in diverse models of our lab. To efficiently construct 9864 sgRNA oligos targeting candidate genes and controls, we developed a quick and precise PCR-free system. Next-generation sequencing validated excellent quality of the sgRNA library with 99.88% presentation (1.86% underrepresentation; 0.02% overrepresentation). We plan to knock-down, in parallel, candidate genes with the sgRNA library in CRISPRi-i<sup>3</sup>N-SNCA and CRISPRi-i<sup>3</sup>N-control neurons and examine sgRNA dropouts to identify lethal and damaging genes that modify  $\alpha$ S toxicity. Positive hits will be followed by RNAseq, cellular assays and further validation in isogenic SNCA triplication hiPSC-derived neurons. Our system enables the validation of modifiers of  $\alpha$ S toxicity and will contribute to a mechanistic understanding of putative genetic modifiers of risk and penetrance. Ultimately, we aim to shed light on the elusive relationship between synucleinopathies and other proteinopathies. This platform allows for focused in-depth study of a single putative genetic modifier or high-throughput screening of thousands of candidates. The results will deepen our understanding of genetic interactions and could facilitate the development of novel strategies in precision medicine.

## S280. Development of a Rigorous Approach for Retrospective Natural History Studies in Rare Neurologic Diseases

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**Introduction:** Leukodystrophies are a group of rare genetic disorders affecting myelination. Emerging therapeutics primarily target the pre-symptomatic population, but this is challenging when diagnosis is delayed in part from under-recognition of early disease features. There is a gap in our understanding surrounding the impact of disease across the life span. To

address this, we propose to develop a standardized approach for retrospective natural history studies by leveraging existing medical records. **Methods:** As part of Global Leukodystrophy Initiative Clinical Trials Network (GLIA-CTN), we developed Standard Operating Procedures (SOPs) to map the impact of leukodystrophies across the life span. The SOP delineates study processes related to staff training, source documentation, and data sharing. Additionally, the SOP details the standardized approach to data extraction from the medical records including diagnosis, clinical presentation, and medical events, such as age at gastrostomy tube placement or loss of ambulation. The key variables for extraction were selected through a face validity process, and electronic case report forms (eCRF) were created to collect and manage analyzable natural history data. When appropriate common eCRFs are used across the leukodystrophies to allow for future comparisons and standardized analysis approaches. To enhance the depth of the data, clinical notes are extracted into “original” and “imputed” encounters, with imputed encounter referring to a historic event (e.g., loss of ambulation 3 months prior). Retrospective Functional Assessments are assigned by child neurologists, using a blinded dual-rater approach and any discrepancies are adjudicated by a third rater. Upon completion of extraction, the data is reviewed for accuracy and completeness. Finally, missingness is evaluated using statistics and efforts are made to retrieve additional data. **Results:** To date, the records from 875 subjects have undergone this process across the GLIA-CTN database and this includes 288 subjects with Metachromatic leukodystrophy, 212 with Aicardi Goutières Syndrome, 151 with Pelizaeus Merzbacher Disease, 15 with Multiple Sulfatase Deficiency, and 209 with Hypomyelination with Atrophy of Basal Ganglia and Cerebellum and other *TUBB4A*-related disorders. **Conclusion:** The proposed methodology will enable us to leverage existing medical records to accrue subjects and capture clinical information, specifically pre-symptomatic data, on a large cohort of subjects in a shorter duration. The robust data collection in the platform will enable (i) greater understanding of clinical course and diagnostics across leukodystrophies, and (ii) robust, regulatory-standard data that can be used as historic controls in clinical trials.

### S281. Diffusion Tensor Imaging of the Corpus Callosum as an Early Disease Marker in Adrenoleukodystrophy

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**Objective:** Cerebral adrenoleukodystrophy (ALD) is a severe demyelinating disorder that must be treated at a very early stage to prevent permanent brain injury and neurocognitive decline. Demyelination typically starts in the corpus callosum. Validation of disease markers including quantitative measures of white matter microstructure could enable earlier and more effective treatment with cell therapies. The purpose of this study was to compare longitudinal diffusion tensor imaging

(DTI) metrics over a 12-month interval in ALD patients with and without demyelinating lesions. **Methods:** Between May 2011 and November 2021, high-resolution anatomical MRI scans and DTI data for boys with cerebral ALD undergoing hematopoietic cell therapy (HCT) at our center (C-ALD group; N=34) were acquired at two time points: a baseline evaluation prior to HCT and 12-months post-HCT. Five patients in an ongoing, unpublished clinical trial were excluded. MRI severity (Loes) scores were obtained and regional neuroanatomical patterns determined. Longitudinal data from an age-matched comparison group of ALD patients without cerebral involvement undergoing routine MRI surveillance (N=15) were also acquired at baseline and 12-months later. Fractional anisotropy (FA) maps were generated from DTI data. Average FA was estimated within the corpus callosum and its sub-divisions, as defined by non-linearly co-registered white matter atlas. Between-group mean and slope differences in FA were compared according to disease status, Loes score and pattern of neuroanatomical involvement using Wilcoxon rank sum tests. **Results:** Patients without cerebral lesions showed stable or increasing FA values in splenium, genu and whole cerebral white matter during the 12-month study period, with positive slopes for all regions. These findings were robust on an individual patient level for 87% of cases. Boys with early stage (Loes<5) posterior C-ALD pattern showed lower FA in the splenium than the group without lesions (p<.001), as well as difference in slope direction in FA over the 12-month period (p<.001). Two patients with frontal white matter lesions showed lower FA in the genu relative to boys without lesions and those with disease restricted to posterior regions. **Conclusion:** DTI metrics in the corpus callosum may serve as biomarkers for cerebral ALD at early stages. These quantitative metrics were sensitive to disease severity, location, and progression. Future longitudinal research could examine the sensitivity and specificity of these methods to detect emergence of brain lesions and predict functional brain changes measured via neuropsychological testing.

### S282. Experimental Confirmation of PI3KR1 Gene Mutation as a Cause of ALS-Like Syndrome Associated with Primary Immunodeficiency

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Inborn Errors of Immunity typically present with recurrent infections and inflammatory diseases, but neurological complications are very common in these patients. How immune-related gene defects manifest in the nervous system is very unclear. A 42-year-old man with recurrent infections and hypogammaglobulinemia presenting in childhood was found to have a pathogenic heterozygous mutation (c.1710dup) in the *PIK3R1* gene. He developed spastic paraparesis at the age of 30, but an extensive neuroinfectious and neuro-inflammatory workup was unrevealing. Significant weakness in all limbs and bulbar symptoms progressed despite

treatment with IVIg, cyclophosphamide, and rituximab targeting of potential neuroinflammatory processes. Further neurological evaluation several years later showed both upper and lower motor neuron disease clinically consistent with the diagnosis of ALS. We used our newly developed pipeline to evaluate the potential contribution of mutated *PIK3R1* to his CNS disease. CSF cell immunophenotyping indicated active antigen presentation in myeloid cells and T cell activation in the CNS compartment, suggesting immune activation possibly due to neuronal destruction. To investigate the role of *PIK3R1* in neurons, we generated an iPSC line from patient CD34+ cells and repaired the mutation with CRISPR-Cas9 technology. We then differentiated patient-derived native and gene-edited cells into motor neurons (MNs), as well as iPSCs from a healthy donor. iPSCs from all three lines differentiated normally into neuroepithelial cells, motor neuron precursors, and terminally differentiated MNs. Electrophysiology showed significantly lower activity in patient-derived neurons compared to the healthy donor. NMDA treatment increased firing in motor neurons from the healthy but not the patient-derived cells. Finally, patient-derived neurons were more prone to apoptosis than control, as shown by higher expression of Caspase 3. The electrophysiology, NMDA activation and apoptosis abnormalities normalized in edited differentiated patient-derived neurons, indicating that this specific mutation in *PIK3R1* critically degraded neuronal function. These findings demonstrate a significant role for *PIK3R1* signaling in neuronal function and survival, identifying new and targetable pathways for neurodegeneration.

### **S283. Inhibition of Multifunctional MIF Protein Prevents Inflammatory- and Parthanatic- Mediated Neurodegeneration in the Context of Multiple Sclerosis**

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Nearly three million people worldwide are living with multiple sclerosis (MS), an autoimmune condition characterized by peripheral immune cell infiltration into the central nervous system (CNS) and reactive gliosis, demyelination, and neuroaxonal degeneration. Existing therapies target adaptive immune cells and treat relapsing MS, but are not effective in halting neurodegeneration in progressive MS. Numerous studies have identified prominent dysregulation of macrophage migration inhibitory factor (MIF), a multifunctional protein with cytokine and enzyme activity, in MS. MIF has two discrete enzymatic functions, as a tautomerase and a nuclease, that have not been well studied in MS. Our lab has shown that MIF nuclease acts as the final executioner of the caspase-independent cell death pathway, parthanatos, that is triggered upon DNA damage and contributes to neuronal loss in Parkinson's disease and stroke. Because neuroinflammation and parthanatos-inducing conditions, such as high ROS concentrations, are pathologically prevalent across many neurological diseases including MS, we hypothesized that MIF contributes to neurodegeneration in MS. Our lab

used a commercially available mouse line (P2G) with its MIF tautomerase activity selectively ablated and created a mouse line (E22Q) with its MIF nuclease activity selectively ablated. We have also synthesized a compound (PAANIB1) that specifically inhibits MIF nuclease. These tools were used to assess the therapeutic efficacy of blocking MIF activity in an experimental autoimmune encephalomyelitis (EAE) mouse model of MS. Our data showed that P2G-EAE and E22Q-EAE mice experienced a decreased clinical disease severity over time. P2G-EAE mice had less peripheral immune cell infiltration into the CNS, whereas E22Q-EAE mice did not undergo a change in gliosis or peripheral immune cell infiltration into the CNS. We further determined that E22Q-EAE mice, P2G-EAE mice, and PAANIB1-treated EAE mice were protected against retinal ganglion cell death. Lumbar spinal cord neuroprotection was also evident in E22Q-EAE mice and PAANIB-treated EAE mice. This suggests that MIF tautomerase activity contributes to inflammatory-mediated secondary neurodegeneration and MIF nuclease activity orchestrates an independent primary process of neurodegeneration in EAE. Both enzymatic activities of MIF act in concert, as MIF global knockout EAE mice experienced the most protection from clinical disease severity and neurodegeneration, while E22Q-EAE and P2G-EAE mice were partially protected. Altogether, if neurons degenerate by MIF-mediated activity in the context of MS as indicated by our data, this research could establish a pharmacological target to treat the ongoing loss of grey matter in patients with this disease.

### **S284. Investigating the Impact of $\gamma$ -Secretase Modulator BPN15606 on a Mouse Model of Down Syndrome**

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**Introduction:** Due to increased gene dose for the amyloid precursor protein (APP) elderly adults with Down syndrome (DS) are at markedly increased risk of Alzheimer's disease (AD), known as DS-AD. How increased APP dose acts and which APP products are responsible for DS-AD is not well understood, thus limiting strategies to target pathogenesis. A novel class of  $\gamma$ -secretase modulators (GSMs) that reduces longer A $\beta$ 42 and A $\beta$ 40 peptides by enhancing  $\gamma$ -site cleavages of the  $\gamma$ -secretase complex offers an opportunity to address relevant products and underlying mechanisms. **Methods:** In this study, we treated Ts65Dn mice, a model of DS, with 10 mg/kg/week-day BPN15606 (a potent novel pyridazine-containing GSM) via oral gavage, starting at age 3 months and continuing for 4 months. We examined the effects of the treatment on multiple AD-related neuropathologies. **Results:** BPN15606 treatment effectively reduced A $\beta$ 40 and A $\beta$ 42 levels without affecting full-length APP or its C-terminal



fragments in the cortex and hippocampus of Ts65Dn mice, demonstrating successful target engagement. Additionally, BPN15606 reduced hyperactivation of Rab5, a protein that regulates endosome function, and reversed neurotrophin signaling deficits. The treatment also preserved synaptic proteins and reversed tau hyperphosphorylation, reduced astrogliosis, and countered cognitive deficits. **Conclusions:** Our findings support a role for increased A $\beta$ 42 and A $\beta$ 40 in inducing molecular phenotypes linked to DS-AD, including hyperactivation of Rab5, neurotrophin signaling dysregulation, tau hyperphosphorylation, synapse protein loss, and astrogliosis. In so doing they speak to increased APP gene dose acting through increased levels of A $\beta$ 42 and/or A $\beta$ 40 to impact pathogenesis. These findings support the use of GSMs as a potential treatment and preventive strategy for AD in individuals with DS.

### **S285. Neuroprotective Impact of Ashwagandha (*Withania Somnifera*) on Titanium Dioxide Nanoparticle-Induced Neurotoxicity in the Frontal Cortex and Cerebellum in Male Rats: An Experimental Animal Study**

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**Background:** Titanium dioxide (TiO<sub>2</sub>) is often used in industry, primarily as a white pigment in paints, colorants, plastics, coatings, and cosmetics. TiO<sub>2</sub> can be exposed in three ways: orally, topically, and by inhalation. When TiO<sub>2</sub> NPs circulate through the body, they can reach all tissues, including the brain. Only a few studies have been conducted on the toxic effect of TiO<sub>2</sub> NPs on the brain. The current investigation sought to detect the neurotoxicity of TiO<sub>2</sub> on rats and evaluate the possible modulating effects of *Withania somnifera* as an antioxidant against neurotoxicity induced by titanium dioxide NP. **Methods:** Thirty mature male rats were assigned into three groups, each with ten rats. Group I is the control group, Group II is the group that received titanium dioxide (TiO<sub>2</sub>-NPs) treatment, and Group III is the protected group that received titanium dioxide along with *Withania somnifera* by orogastric feeding for a period of six weeks. **Result:** In vitro examination, several brain regions at the morphological and immunohistochemical levels revealed substantial changes in comparison to the control group. Group I was within normal limits; there were no significant histopathological changes. While Group II exhibits significant morphological changes in the form of decrease in the number of neuronal cells with signs of neuronal injury in the form of shrunken acidophilic cytoplasm, a pyknotic nucleus, and vacuolation of the neuropil. Moreover, the molecular layer was hypercellular due to an increased number of astrocyte processes with scattered Rosenthal fibers. Group III is the protective group revealed attenuation of the most damaging features illustrated in Group II. The mean time of immobility was much longer in group II compared to the protective group III, according to data from the forced swimming test ( $p < 0.001$ ). In comparison to group II, ashwagandha root

extract considerably decreased anxious index in group III ( $p < 0.001$ ). In comparison to group II, the density of GFAP positive in the *Withania somnifera* rats decreased significantly ( $28.63 \pm 0.931$  vs  $24.02 \pm 0.862$ ,  $P < 0.001$ ). **Conclusion:** TiO<sub>2</sub>-NPs administered orally to rats cause histological and immunohistochemical alterations, and the antioxidant *Withania somnifera* has been shown to mitigate the harm. It was determined that utilizing *Withania somnifera* could help prevent the harmful effects of TiO<sub>2</sub>-NPs neurotoxicity.

### **S288. Seizures Exacerbate Cognitive Deficits and Excitatory: Inhibitory Imbalance in Alzheimer's Disease**

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Seizures are prevalent in Alzheimer's disease (AD) with up to 64% of patients displaying epileptiform activity. Once largely considered a byproduct of beta-amyloid induced neuronal hyperexcitability, mounting evidence suggests that seizures can facilitate AD progression. There is increasing evidence of excitatory-inhibitory (E:I) imbalance in AD reminiscent of E:I imbalances involved in epileptogenesis. We hypothesized that seizures exacerbate cognitive deficits and E:I imbalance in AD. Thus, we compared clinical cognitive scores and temporal lobe cortices for markers of E:I balance from a well characterized cohort of control and AD patients with known seizure history. We found that AD patients with seizure history (AD+Sz) showed significant deficits in the Dementia Severity Rating Scale (DSRS) ( $p < 0.01$ ,  $n = 14-19$ ), global Clinical Dementia Rating (CDR) ( $p < 0.01$ ,  $n = 18-87$ ), and CDR-sum of boxes ( $p < 0.05$ ,  $n = 18-87$ ) compared to AD patients without seizure history (AD-Sz). From a subset of these patients and control tissue we performed western blots for the  $\gamma$ -Aminobutyric acid type A receptor (GABA<sub>A</sub>R) subunits  $\alpha 1$  and  $\alpha 3$ , Cl<sup>-</sup> transporters, K<sup>+</sup>-Cl<sup>-</sup> cotransporter 2 (KCC2) and Na<sup>+</sup>-K<sup>+</sup>-Cl<sup>-</sup> cotransporter 1 (NKCC1),  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) subunits, GluA2 and GluA1 and N-methyl D-aspartate receptor (NMDAR) subunits, GluN2A and GluN2B, given their roles in E:I balance. We found decreased GABA<sub>A</sub>R  $\alpha 1$ :  $\alpha 3$  ratios in AD patients ( $p < 0.05$ ,  $n = 11-19$ ), indicative of diminished GABA currents, and that seizures increased NKCC1:KCC2 ratios in AD patients ( $p < 0.05$ ,  $n = 11-19$ ), indicative of depolarizing GABA. Further, we found significant correlations between GluN2A and CDR-sum of boxes ( $p < 0.05$ ,  $r = -0.39$ ), and GABA<sub>A</sub>R  $\alpha 1$  and brain atrophy ( $r = 0.9$ ,  $p < 0.01$ ), further implicating E:I imbalance in AD progression. Overall, our results suggest that E:I imbalance may be a promising therapeutic target to slow AD progression and may be particularly relevant for AD patients with seizures.

### **S289. Transdifferentiation: A Novel Tool for Disease Modeling and Translational Applications in Alzheimer's Disease**

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**Background:** A majority of Alzheimer's disease (AD) cases are sporadic and manifest symptoms after age 65, suggesting that advanced age is the prominent risk factor. A tool for modeling aged human neurons, the cell type mostly impacted by AD, is still lacking, which hampers our understanding of disease mechanisms and therapeutic approaches. This study aims to develop a new cell model that overcomes cellular rejuvenation caused by stem cell reprogramming for aging and AD. As inspired by our preliminary proteomics data, we hypothesize that the trans-differentiated neurons (tNeurons) from human somatic cells retain aging signatures and are amenable to detailed biological characterization of mechanisms underlying proteostasis and endosome-lysosomal deficits in AD. **Methodology:** We leveraged a powerful direct reprogramming paradigm by combining proneural transcription factors and small molecules to transdifferentiate human adult fibroblasts into neurons. Human fibroblasts were derived from healthy controls differing in age and patients with genetic and sporadic forms of AD matched with gender and *APOE* genotypes. We used quantitative proteomics, high-throughput imaging and biochemical analysis of cell phenotypes, supported by histological validation in APP-transgenic mouse and patient brain tissue. We further integrated CRISPR genome engineering and drug discovery techniques to provide pharmacological strategies that protect against endosome-lysosomal defects, protein aggregation and neurodegeneration in AD. **Result:** Trans-differentiation approach yielded >85% of tNeurons as cortical glutamatergic neurons after 35-42 days in culture. We showed that tNeurons exhibit changes to DNA repair and histone modifications and the presence of amyloid- $\beta$  and hyper-phosphorylated tau deposits related to AD. Quantitative proteomics and trajectory analysis revealed neuronal proteome markers associated with AD risk from GWAS analysis and unexpectedly linked lysosomal quality control (LQC) pathway to AD. We molecularly defined LQC deficits and inflammatory responses in AD tNeurons and accumulations of LQC markers containing LAMP1/2-positive lysosomes, proteostasis factors and amyloid- $\beta$  inclusions in AD mouse and human brain tissue. The treatment of our newly discovered drug that specifically targets lysosomal v-ATPases successfully ameliorated these AD pathologies. **Conclusion:** This study generates and characterizes the next generation of neuronal models for late-onset AD. We demonstrate that tNeurons are a tractable system and predictive model for disease mechanism exploration and therapeutics development. The outcomes aligning with the pathophysiological features of AD provide novel insights into LQC deficits as the underlying mechanism of AD pathogenesis.

### K-S108. Amyloid Beta Fibrils Induce Microglial Biosynthesis of Heparan Sulfate Proteoglycans Leading to Increased Tau Phagocytosis and Seeding

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Emerging evidence now establishes a central role for microglia in Alzheimer's disease. The microglia cell-surface proteome, or *surfaceome*, is a critical hub that enables neuroprotective, neurotoxic, and neuroinflammatory signaling in the diseased brain. Targeting the microglia surfaceome with selective pharmacologic agents may allow for the manipulation of diverse microglia states and function and therefore holds tremendous experimental and therapeutic potential. Precise microglia targeting requires broad knowledge of how the surfaceome remodels in the disease environment and this biology has not been systematically explored. To elucidate how microglia remodel their surfaceome in the context of Alzheimer's disease pathology, I performed mass spectrometry-based surfaceome profiling of human iPSC microglia after exposure to A $\beta$  fibrils. My data reveals a robust upregulation of heparan sulfate proteoglycans (HSPGs) and proteins that promote phagocytosis. These A $\beta$ -primed microglia increase their capacity to bind and phagocytose tau aggregates via HSPGs. Specifically, I have identified the glypican family of HSPGs as the key core proteins responsible for this pro-phagocytic phenotype. Using immunohistochemistry, I have demonstrated that these glypicans are specifically enriched in AD-associated microglia and are not found in healthy aged-matched control human brain. Finally, I have developed a *Drosophila* model of amyloid-induced tau spread. Knockdown of microglial glypicans results in reduced tau spread as well as rescue of locomotion deficits and early lethality. Taken together, this data demonstrate that A $\beta$  alters the microglia surfaceome to promote tau uptake and spread through the brain and provides a mechanism to link A $\beta$  and tau pathology through microglia and HSPGs.

### K-S109. Diffusion Tensor Imaging of the Corpus Callosum as an Early Disease Marker in Adrenoleukodystrophy

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**Objective:** Cerebral adrenoleukodystrophy (ALD) is a severe demyelinating disorder that must be treated at a very early stage to prevent permanent brain injury and neurocognitive decline. Demyelination typically starts in the corpus callosum. Validation of disease markers including quantitative measures of white matter microstructure could enable earlier and more effective treatment with cell therapies. The purpose of this study was to compare longitudinal diffusion tensor imaging (DTI) metrics over a 12-month interval in ALD patients with and without demyelinating lesions. **Methods:**

Between May 2011 and November 2021, high-resolution anatomical MRI scans and DTI data for boys with cerebral ALD undergoing hematopoietic cell therapy (HCT) at our center (C-ALD group; N=34) were acquired at two time points: a baseline evaluation prior to HCT and 12-months post-HCT. Five patients in an ongoing, unpublished clinical trial were excluded. MRI severity (Loes) scores were obtained and regional neuroanatomical patterns determined. Longitudinal data from an age-matched comparison group of ALD patients without cerebral involvement undergoing routine MRI surveillance (N=15) were also acquired at baseline and 12-months later. Fractional anisotropy (FA) maps were generated from DTI data. Average FA was estimated within the corpus callosum and its sub-divisions, as defined by non-linearly co-registered white matter atlas. Between-group mean and slope differences in FA were compared according to disease status, Loes score and pattern of neuroanatomical involvement using Wilcoxon rank sum tests. **Results:** Patients without cerebral lesions showed stable or increasing FA values in splenium, genu and whole cerebral white matter during the 12-month study period, with positive slopes for all regions. These findings were robust on an individual patient level for 87% of cases. Boys with early stage (Loes<5) posterior C-ALD pattern showed lower FA in the splenium than the group without lesions ( $p<.001$ ), as well as difference in slope direction in FA over the 12-month period ( $p<.001$ ). Two patients with frontal white matter lesions showed lower FA in the genu relative to boys without lesions and those with disease restricted to posterior regions. **Conclusion:** DTI metrics in the corpus callosum may serve as biomarkers for cerebral ALD at early stages. These quantitative metrics were sensitive to disease severity, location, and progression. Future longitudinal research could examine the sensitivity and specificity of these methods to detect emergence of brain lesions and predict functional brain changes measured via neuropsychological testing.

#### **LB-S117. A CRISPR Library Approach to Identify Microglial Genes That Regulate Uptake and Endolysosomal Trafficking of Aggregated Alpha-Synuclein**

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Accumulation of misfolded alpha-synuclein (aSyn) protein is a hallmark of Parkinson (PD) disease and related illnesses termed “synucleinopathies” and likely contributes to their pathogenesis. aSyn is abundantly expressed in neurons and accumulates primarily in neurons in Parkinson disease and dementia with Lewy bodies. Misfolded forms of aSyn can induce aggregation of normal aSyn, and they can be released into the extracellular space where they can be taken up by neighboring neurons, a process that is thought to accelerate prion-like spreading of aSyn pathology across brain networks. In addition to neurons, other cell types including microglia are also known to take up aggregated aSyn from the extracellular space. As the resident macrophage-lineage immune cells

of the brain, microglia participate in phagocytosis and clearance of multiple pathogens and aggregated self-proteins, including aSyn. This process may serve a critical function in limiting the propagation of misfolded aSyn in neural networks. Because the molecular determinants of microglial clearance of aSyn aggregates are incompletely understood, we performed a CRISPR library screen in a BV2 microglial cell line to identify gene candidates that modulate uptake and endolysosomal trafficking of aSyn aggregates. We added aSyn fibrils incorporating the pH-sensitive dye pHrodo to the culture medium of BV2 cells transduced with mouse CRISPR Brie lentiviral libraries targeting approximately 20,000 genes. Following incubation, we harvested the cells and analyzed the pHrodo fluorescence by flow cytometry. By sorting the cells corresponding to the bottom 3% and the top 3% of pHrodo fluorescence intensity and sequencing the guide RNAs present in those pools, we identified candidate genes that either promote or inhibit uptake and endolysosomal accumulation of aSyn, respectively. Gene ontology analysis confirmed enrichment of multiple canonical endolysosomal genes in addition to several novel candidates. Pairing these results with human genetic data related to PD risk will inform an integrated approach to validation of potential disease-modifying targets for synucleinopathies.

#### **LB-S118. Exploring the Utility of ChatGPT in Enhancing Diagnostic Discussions in Neurodegenerative Disorders**

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ChatGPT, developed by OpenAI, represents a new generation of large language models that utilize artificial intelligence (AI) to generate contextually relevant text responses. As of May 11, 2023, a PubMed search for the term ‘ChatGPT’ yielded 402 manuscripts published in 2023 alone, reflecting the expanding influence and significance of AI-based models in scientific publications. Clinicopathological conferences (CPC) play a valuable role in medical education, fostering comprehensive discussions on complex disease processes and their related pathologies. These discussions are particularly valuable for neurodegenerative disorders, such as Alzheimer’s disease and Parkinson’s disease, given the complexity and diversity of clinical presentations. Our study aimed to investigate the potential use of ChatGPT in generating pathologic diagnoses from clinical summaries from CPC conferences of a range of neurodegenerative disorders. In this study, we selected 20 cases from CPC held at Mayo Clinic Florida from January to April 2023. The cases included a wide range of neurodegenerative disorders: five cases of Lewy body disease, three each of corticobasal degeneration, progressive supranuclear palsy, and pseudo-dementia, two each of multiple system atrophy and Alzheimer’s disease, and one case each of globular glial tauopathy and Creutzfeldt-Jakob disease. Clinical summaries of these cases were fed to both ChatGPT-3.5 and ChatGPT-4, which were tasked with proposing the most likely and other potential diagnoses. Our results showed that 30% of primary diagnoses made by ChatGPT-3.5 and 40% by ChatGPT-4 aligned with the neuropathological diagnoses. Correct diagnoses were listed in the differential diagnoses in 80% of cases for ChatGPT-3.5 and 70% for ChatGPT-4. Although the

prediction of primary diagnosis was not always accurate, the differential diagnosis suggested by AI tools often included the correct diagnosis. Notably, the models occasionally proposed diagnoses that were more clinical (e.g., primary progressive aphasia) than neuropathological (e.g., frontotemporal lobar degeneration), despite instructions to avoid clinical diagnoses. It also became clear that the accuracy of pathological diagnoses relied heavily on the quality and specificity of information in the clinical summaries. These findings suggest that AI models such as ChatGPT can generate an adequate range of differential diagnoses from clinical summaries of neurodegenerative disorders, thus facilitating discussions by novice participants in the CPC. The insights derived from this study contribute to the ongoing controversy on the role and effectiveness of AI models in medical education and clinical practice.

### LB-S119. Human iPSC-Derived Neurons Reveal Mechanisms of Selective Neuronal Vulnerability in TBCK Encephaloneuronopathy

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TBCK Encephaloneuronopathy is an autosomal recessive, pediatric-onset neurodegenerative disorder. We previously showed loss of function of TBCK protein leads to mitochondrial quality control defects and lysosomal dysfunction in patient-derived fibroblasts. We generated iPSC-derived neurons to further investigate the role of TBCK protein in human neurons. We found TBCK-deficient neurons are more susceptible to cell death relative to controls and have reduced neurite outgrowth. We then used healthy control neurons to determine the TBCK protein-protein interactome using unbiased mass spectrometry. Our data suggest a novel interaction with a lysosomal motor adapter protein. We further characterized lysosomal function in TBCK-deficient neurons and found significantly increased lysosomal pH, suggesting defects in acidification. We also found features reminiscent of lysosomal storage disorders, including aberrant size and distribution of lysosomes relative to control neurons. Using live confocal imaging in neurons cultured in microfluidic chambers, we tested if TBCK deficiency altered lysosomal motility in neuronal soma vs axonal compartments. Our data suggests TBCK deficiency may significantly impair axonal lysosomal trafficking. Furthermore, we found the protein-protein interactions mediating the lysosomal phenotype may be cell-type specific, as there were not evident fibroblasts, lymphoblasts or HEK293 cells. Our data provides novel insights into the mechanism underlying susceptible neuronal vulnerability in this rare pediatric neurodegenerative disorder.

### LB-S120. Poly-GA Pathology Affects Oxidative Stress Response Pathways in an AAV-Based Organotypic Brain Slice Model of C9-ALS/FTD

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The presence of expanded GGGGCC intronic hexanucleotide repeats in the C9orf72 gene is the most common inherited cause of amyotrophic lateral sclerosis (ALS) and frontotemporal dementia (FTD). This genetic defect results in the non-canonical translation of repeat RNA into five different dipeptide repeat proteins (DPRs), which form neuronal inclusions in affected patient brains. While several studies have used cell culture models to identify proteins associated with DPRs, the interactome in complex CNS tissues may differ considerably. Here, we establish a proximity proteomics approach in an AAV-based organotypic brain slice culture (BSC) to interrogate the formation and collective composition of DPR aggregates in the context of intact brain tissue. Proximity proteomics studies in organotypic brain slices demonstrate a novel poly-GA-associated interactome in the CNS that differs from those found in cellular models. Further investigations utilizing cellular models of poly-GA pathology uncover the sequestration of KEAP1 into dense cytoplasmic aggregates by poly-GA. This sequestration inhibits its function in regulating downstream Nrf2 pathway responding to oxidative stress. Additionally, pathological accumulation of poly-GA is observed to influence the solubility changes of specific proteins, including SQSTM1/p62, NBR1, and KEAP1. Confirmation of KEAP1 involvement in the poly-GA pathological processes is obtained through the examination of autopsy brain tissue, where colocalization between KEAP1 and poly-GA aggregates is observed in the frontal cortex, temporal cortex, and hippocampus of both c9FTLD and c9ALS cases. These findings provide valuable insights into the underlying pathological mechanisms governing DPR-induced neurodegeneration in C9orf72-related ALS/FTD. Moreover, our study highlights the organotypic brain slice model as a valuable tool for comprehending the formation and pathophysiological role of DPR aggregates in complex CNS tissues.

### LB-S121. Undercover COP (CO Poisoning) Carbon Monoxide Poisoning - Under-Diagnosed "Refractory Psychosis"

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**Introduction:** Carbon Monoxide Poisoning (COP) is a relatively rare diagnosis with approximately 50,000 people visiting the Emergency Department and at least 430 deaths annually in the U.S. (CDC, 2022). Presentation varies with nonspecific symptoms including headache, dizziness, fatigue and most relevant to this case is altered mental status and psychosis. Often, these patients are admitted to psychiatry and treated with antipsychotics to be diagnosed with "Refractory Psychosis." One case, in Hong Kong, describes a 65-year-old woman who attempted suicide with charcoal burning. When she began to have paranoid delusions and auditory hallucinations, she was given quetiapine with poor clinical response. She was switched to olanzapine augmented with amisulpride and valproate

sodium, and eventually switched to clozapine. As she remained psychotic, COP was the only explanation (Wong, East Asian Archives of Psychiatry, 2022). The diagnosis of COP is challenging due to the long-standing non-specific complications. Standard pulse oximetry cannot screen for COP because carboxyhemoglobin (COHb) is not differentiated from oxyhemoglobin. Moreover, COHb levels do not always correlate to the degree of poisoning, especially if time has passed since the exposure. Any abnormally elevated COHb level with major symptoms should be considered severe poisoning (Bozeman, Annals of Emergency Medicine, 1997). **Case Description:** We present a case of a 34-year-old male with disorganized behavior for one week. Upon initial evaluation he presented confused, disorganized, with poor eye-contact, increased speech latency, decreased volume and mumbling throughout the interview. He endorsed auditory hallucinations and denied illicit-drug use. He was disoriented to time and place. Physical exam revealed psychomotor retardation, poor arm swing, shuffling gait, unable to perform complex commands across midline, spelled “world” forward but not backward, and unable to perform simple calculations. He was started on risperidone 1 mg, up-titrated to 4 mg without significant improvement. He was found to have +RPR and started on penicillin G 2.4 MU. Lumbar puncture, blood cultures, and CT scan head thus far were inconclusive. MRI however, showed T2 hyperintense, heterogeneously enhancing lesions in the globus pallidus and cerebellum, bilaterally. The bilateral globus pallidus lesions are associated with subacute petechial hemorrhage suggesting a toxic/metabolic insult, particularly COP. **Discussion:** COP is often a missed diagnosis, but hopefully in the future a patient with vague clinical presentation and cognitive decline/psychosis will attain an MRI sooner. COP typically involves the globus pallidus due to its high vascular demand and lesions here should be considered diagnostic for COP.

## Neurodevelopment

### S291. Atypical Presentation of Vasovagal Episodes in Chiari Malformation Type 1

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**Introduction:** Chiari malformation is a congenital condition affecting the brain and spinal cord. Chiari malformation type I (CM-1), is the most common type. It is characterized by the displacement of the cerebellar tonsils below the foramen magnum, and may be associated with neural tube defects, syringomyelia, and hydrocephalus. Symptoms of CM-1 can include headache, dizziness, ataxia, and difficulty with speech or with swallowing. Surgery may be recommended for symptomatic patients, while all asymptomatic cases are typically monitored with a regular brain imaging. Some patients with CM-1 may also develop recurrent syncope, despite an unknown specific association or cause of this presentation. We present a patient who, among other symptoms, had intermittent neurally-mediated hypotension and bradycardia which we propose are associated with CM-1. **Case**

**Discussion:** A 52-year-old male presented with episodic headaches and dizziness associated with blurred vision and near-syncope. The patient repeatedly developed left eye abduction and disconjugate eye movements associated with subjective feeling of dizziness and near-syncope during eye movement and pupillary light response testing. A CT head scan resulted in diagnosis of CM-1, and the patient underwent a decompressive craniectomy with uneventful recovery and symptom resolution. Approximately nine months after decompression, episodic blurred vision and pre-syncope recurred. A brain imaging demonstrated good CSF passage through the foramen magnum. A tilt table test induced his typical symptoms, demonstrated hypotension without a cardio-excitatory response, and neurally-mediated hypotension and bradycardia were identified as the cause of these episodes. The patient was prescribed trials of several medications including fludrocortisone, gabapentin and levetiracetam without positive response. Patient's symptoms nearly completely resolved after being prescribed metoprolol tartrate. **Conclusion:** Authors propose that this case may represent a congenital abnormality in the brainstem's neural pathways connecting the brain centers for eye movements, pupillary accommodation, and autonomic centers. It is probable that this aberration is related to a broader congenital malformation associated with CM-1. Patients with CM-1 can have any type of syncope, and this does not mean that conditions are associated. In our patient, the episodes were induced by testing eye movements and pupillary light response, and transiently resolved after surgery. This points towards direct association of syncope and CM-1 in this case. With no gold standard of care, this case provides understanding, insight, considerations, and treatment in this rare presentation of CM-1 patient.

### S292. Blood-Brain Barrier Function Associates with Brain Iron Dynamics along Developmental Trajectory: A Combined Quantitative Magnetic Resonance Imaging Study during Childhood

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**Background and Purpose:** For many years, it was believed that iron entered the brain tissue intensively during early development because the blood-brain barrier (BBB) is “immature.” Meanwhile, there has been physiological evidence that iron transport across the BBB is functionally more active in the developing brain than in the adult, but these imaging profiles remain to be elucidated. The purpose of this study was to establish a relationship between brain iron dynamics and blood-brain barrier function during childhood by using a combined quantitative magnetic resonance

imaging (MRI) for both physiological systems. **Methods:** In this single-center prospective study, consecutive outpatients, 2-180 months of age, who underwent brain MRI between January 2020 and January 2021, were included. Children with histories of preterm birth or birth defects, abnormalities on MRI, and diagnoses that included neurological diseases during follow-up examinations through December 2022 were excluded. In addition to clinical MRI, quantitative susceptibility mapping (QSM; iron deposition measure) and diffusion-prepared pseudo-continuous arterial spin labeling (DP-pCASL; BBB function measure) were acquired. Atlas-based analyses for QSM and DP-pCASL were performed to investigate developmental trajectories of regional brain iron deposition and BBB function and their relationships. **Results:** A total of 78 children (mean age, 73.8 months  $\pm$  61.5 [SD]; 43 boys) were evaluated. Rapid magnetic susceptibility progression in the brain ( $\Delta$ susceptibility value) was observed during the first two years (globus pallidus,  $1.26 \pm 0.18 \times 10^{-3}$  ppm/month; substantia nigra,  $0.68 \pm 0.16$ ; thalamus,  $0.15 \pm 0.04$ ). The scattergram between the  $\Delta$ susceptibility value and the water exchange rate across the BBB was well fitted to the sigmoidal curve model, whose inflection point differed among each deep gray matter nucleus (globus pallidus, 2.96-3.03 [mL/100g] $^{-1}$ ; substantia nigra, 3.12-3.15; thalamus, 3.64-3.67) in accordance with the regional heterogeneity of brain iron accumulation. **Conclusion:** The combined quantitative MRI study of QSM and DP-pCASL for pediatric brains demonstrated the relationship between brain iron dynamics and BBB function during childhood, highlighting the feasibility and usefulness of these imaging techniques to assess both physiological systems along developmental trajectories.

### S293. Clinical Outcomes in Aicardi Goutières Syndrome: A Natural History Study

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Aicardi Goutières Syndrome (AGS) is a rare genetic leukodystrophy that results in profound psychomotor impairment. The increasing availability of genetic testing has led to an expanding phenotypic spectrum of AGS. In addition to the characteristic neurologic impairment, the autoinflammation associated with AGS results in poorly understood multi-systemic complications. In this project, we will report on the breadth and distribution of systemic sequelae. The study cohort was consented under a single IRB [Myelin Disorders Biorepository Project] as part of the Global Leukodystrophy

Initiative Clinical Trials Network (GLIA-CTN) research alliance. The GLIA-CTN Genomics core reviewed genotypes according to ACMG criteria. All available medical records were collected. Severity was assessed by application of the AGS Clinical Severity Scale. As defined by Standard Operating Procedures, key variables were extracted into electronic case report forms in REDCap. Information was collected on 9 organ systems for a total of 59 variables. Multi-systemic involvement was defined as >2 organ systems with AGS-related complications. The occurrence and age at key events were compared by severity and genotype. To date, 186 subjects have been enrolled, with a median age of last data collection of 6.38 years (Q1 3.35 years, Q3 10.6 years). Subjects came from a diverse genetic background. The most frequently represented genotypes are *RNASEH2B* and *ADAR1*. Systemic disease was noted to precede neurologic disease, and a majority of the cohort demonstrates multi-systemic involvement by age 2. The most frequent non-neurologic complications involve the gastrointestinal and genitourinary systems. By reviewing primary medical records from a diverse, global population, we can expand our understanding of the systemic impact of AGS and underscore the need for life-long monitoring of potential complications. Future analysis will include the role of genotype in systemic phenotype and will inform the creation of clinical guidelines.

### S294. Development of a Disease-Specific Scale for Multiple Sulfatase Deficiency

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Multiple sulfatase deficiency (MSD) is an ultra-rare, neurodegenerative pediatric disease. A major barrier to clinical trial readiness is the lack of validated outcome measures capable of capturing MSD severity and phenotypic heterogeneity. We anticipate that traditional outcome measures will not capture MSD functional phenotype. To address the need for a more sensitive outcome measure, we designed a disease-specific MSD Severity Scale (MSS) to measure neurologic severity and multi-systemic burden. The study cohort was consented under a single IRB (The Myelin Disorders Biorepository Project) as part of the Global Leukodystrophy Initiative Clinical Trials Network (GLIA-CTN). The GLIA-CTN Genomics Core reviewed diagnoses according to biochemical and genetic criteria. We included patients (n=15) meeting the criteria and collected medical records. Through expert consensus review, 11 motor and language milestones and 8 systemic items were chosen to comprise the Neuro and Systemic Subscores. The scale was applied to the most recent medical encounter with relevant information. The Vineland Adaptive Behavior Scale-3<sup>rd</sup> edition (VABS-3) explores caregiver-reported adaptive behavior abilities in four domains. The Communication, Daily Living Skills, and Socialization domains provide an Adaptive Behavior Composite score (ABC), while the Motor Skills domain captures gross and

fine motor function and does not contribute to the ABC score. The VABS-3 was administered non-concurrently from the MSS. Correlations between the MSS and VABS-3 were calculated by Spearman's rank correlation. Of the 41 MSD subjects, 15 participated in these assessments. The average age of participants is 8.43 years (SD=5.07, range=2.34-20.78). The average difference in age at MSS and VABS-3 administration is 1.88 years (SD=2.30, range=0.02-6.64 years). The VABS-3 and MSS composite scores had a significant correlation ( $r=0.7131$ ,  $p=0.0078$ ). The MSS Neuro Subscore had the highest significant correlations with the VABS-3 Communication ( $r=0.8398$ ,  $p=0.0008$ ) and Motor Skills ( $r=0.8672$ ,  $p=0.0053$ ) domains. This is the largest cohort of MSD patients reported to date. Despite the temporal difference in assessments, there was a strong correlation between the VABS-3 and MSS. The MSS Neuro Subscore's strong correlations with both the VABS-3 Motor and Communication domains suggest its validity in capturing motor and language milestones. Future projects will focus on cohort expansion and validation of MSS through prospective administration.

#### **S295. Early Disruption of Epigenetic and Transcriptomic Organization after Prenatal Hypoxia Predicts Persistent Functional Deficits in Glutamatergic Neurons**

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Prenatal hypoxic injury affects over a million births annually, leading to neurodevelopmental disability in one-third of those children. Yet, we lack targeted interventions for improving outcomes. A limitation toward developing therapeutics is that we lack understanding of the multifaceted, cell type-specific molecular consequences of this transient insult on the developing brain. To address this gap, we performed joint single nucleus RNA-sequencing and assay for transposase-accessible chromatin sequencing from the cortex of mice immediately after prenatal hypoxia exposure (8 hours, 5% inspired oxygen at embryonic day 17.5). This animal model phenocopies mild hypoxic injury seen in children. Over 140,000 nuclei were sequenced from 16 total samples evenly divided between normoxia and hypoxia and by sex. We identified clusters of known neuronal and glial cell populations. Prenatal hypoxia led to a slight increase in endothelial cells but no further changes in cell number for other cell types. We found several cell type-specific disruptions in gene expression and regions of chromatin organization after prenatal hypoxia. Many of the cell type-specific genes dysregulated by hypoxia were associated with pathogenic variants that cause neurodevelopmental disabilities or neurodegenerative disorders. Remarkably, we discovered that hypoxic glutamatergic neurons had a selective disassociation between global chromatin organization and gene expression. Glutamatergic neurons, which develop synapses postnatally, also demonstrated dysregulation of genes associated with neuron structure and synapse function after prenatal hypoxia. To test

whether these changes in the fetal brain suggested which cells and pathways may be disrupted by transient hypoxia in mature neurons, we used Golgi staining and whole-cell patch-clamp electrophysiology in juvenile mice to examine glutamatergic neuron structure and function. We found that these neurons had decreased dendritic spine density and prolonged action potential hyperpolarization one month after the insult. Notably, many of the potassium channels associated with hyperpolarization were not expressed in fetal glutamatergic neurons at baseline, but about 80% of these genes had abnormalities in nearby chromatin accessibility after prenatal hypoxia. Together, these findings suggest that prenatal hypoxia disrupts the organization of chromatin and the transcriptome in glutamatergic neurons, leading to persistent disruption of neuronal maturation and structure that may contribute to lasting behavioral deficits. Ongoing analyses will test (1) whether the shifts in the chromatin organization after prenatal hypoxia are persistent in juvenile mice and (2) which motifs are present at sites of differential accessibility that may suggest pathways that are amenable for intervention to improve outcomes.

#### **S296. Gross Motor Function in Pediatric Onset TUBB4A-Related Leukodystrophy: GMFM-88 Performance and Validation of GMFC-MLD Use**

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**Objective:** *TUBB4A* pathogenic variants are associated with a spectrum of neurologic conditions, including movement disorders and leukodystrophy. With the development of

targeted therapies in preclinical models, there is an urgent unmet need for validated tools to measure mobility limitations in children with this disease. The objective is to explore gross motor function in a pediatric-onset *TUBB4A*-related leukodystrophy cohort with existing outcome tools. **Methods:** The Gross Motor Function Measure-88 (GMFM-88), Gross Motor Function Classification System (GMFCS), and Gross Motor Function Classification-Metachromatic Leukodystrophy (GMFC-MLD) were selected for use by a panel of experts through face validity. The GMFM-88 is comprised of five dimensions (A-E) measuring increasingly complex motor function. Subjects with a confirmed molecular and clinical diagnosis of *TUBB4A*-related leukodystrophy were enrolled. Participants' sex, age, genotype, and age at disease onset were collected, together with GMFM-88 and concurrent GMFCS and GMFC-MLD scores. Performances on each measure were compared. A GMFM-88 floor effect was defined as a total score below 20%. Correlative statistics included the Spearman's Rank Correlation Coefficient and the Pearson's Rank Correlation Coefficient. **Results:** A total of 35 subjects participated in motor outcome assessments. At the time of the GMFM-88 testing and classification system scoring, the mean chronological age of patients was 8.36 years [median: 7.56; standard deviation: 5.17; interquartile range (IQR): 8.73]. The median performance on the GMFM-88 was 16.24% [range: 0-97.31%; IQR: 47.02], and 42.9% (n=15) of individuals performed above the floor effect threshold. In Dimension A, which evaluates lying and rolling, 82.9% (n=29/35) of participants performed above the floor threshold. In all other GMFM-88 dimensions, >50% of the population scored below the floor threshold. All levels of the Classification Scales were represented, except for the GMFC-MLD level '0.' Evaluation by GMFM-88 was strongly correlated with the Classification Scales [Spearman Correlations: GMFCS:GMFM-88  $r=0.90$ ,  $p<0.0001$ ; GMFC-MLD:GMFM-88  $r=0.88$ ,  $p<0.0001$ ; GMFCS:GMFC-MLD:  $r=0.92$ ,  $p<0.0001$ ]. **Conclusions:** Despite overall observation of a floor effect, the GMFM-88 accurately captures performance of individuals with attenuated phenotypes. GMFM-88 Dimension A shows no floor effect. The GMFC-MLD shows a strong correlation with the GMFCS and GMFM-88, supporting its use as an age-independent functional classification in *TUBB4A*-related leukodystrophy.

### S297. In Vitro Modeling of Human Neuron Development for Studying Prenatal Hypoxia Effects on Brain Development and Function

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Prenatal hypoxic injury disrupts brain development and causes long-term morbidity, with symptoms ranging from mild disability to severe impairment. *In vivo* models of prenatal hypoxia have been vital tools for understanding the effects of hypoxia on brain development and function. However, these models are expensive to develop and maintain and are cumbersome for high throughput screening of factors that may

modify injury. *In vitro* models offer researchers to simulate early brain development, cell type-specific research, and changes that occur after prenatal brain injury. The objective of this research aims to understand the dynamics of *in vitro* neuronal differentiation of immortalized neural stem cell line for studying the effects of hypoxia on brain development. First, to develop a robust *in vitro* model of human neurogenesis amenable to high throughput studies, we morphologically characterized the human ReNcell VM cell line after D0, D2, D7, D14, D21, D28 and D35 days of differentiation to a mature neuron-like and glial-like phenotype characterized by neuronal markers at different plating concentrations. After days of differentiation of low, medium, and high plating densities, these cells were evaluated for mature morphological characteristics such as soma area, neurite length, number of neurite branches, and synaptic markers. Our findings suggest that medium-density plated cells closely resemble mature neuron morphology and represent representative soma size, neurite length, and neurite branches with the presence of synaptic markers. Next, these differentiated ReN cells were exposed to 0.3% hypoxia for 0h, 8h, 24h, and 48h time points to better understand the cellular consequences of hypoxia. In medium-density differentiated cells, hypoxia exposure resulted in dysregulated gene expression of hypoxia-inducible factor 1 alpha (HIF1 $\alpha$ ) target genes. qPCR analysis revealed that VEGF, SLC1A1, and LDHA genes had time-dependent differential expression patterns. Overall, the study provides a framework for the differentiation process of human ReNcell VM cell line at different densities throughout the different days of differentiation. These observations suggest that *in vitro* differentiated ReN cells are able to respond to hypoxia signals via modulating HIF1 $\alpha$  target genes. Taken together ReN cells can be used as tools to study how prenatal hypoxia impacts brain development. Further studies will be performed to determine the effects of hypoxia on neuron structure and function to develop a high throughput method for screening modifiers on the effects of hypoxic injury.

### S298. Mapping Function Prior to Diagnosis is Essential in Metachromatic Leukodystrophy

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Metachromatic leukodystrophy (MLD) is characterized by rapid loss of motor skills in early childhood. There is a critical delay between symptom onset and age at diagnosis. We hypothesize that neurologic function can be captured even prior to diagnosis by using existing medical documentation. This study developed a standardized approach to the retrospective assessment of neurologic function in MLD. Neurologic function as documented from medical encounters from 41 children with MLD enrolled in the Global Leukodystrophy Initiative Clinical Trial Network Natural History Study. The Gross Motor Function Classification-MLD



(GMFC-MLD) is a categorical tool ranging from normal ambulation (M0) to loss of head control (M6). Because the documentation surrounding the quality of movement may be limited, we created additional categories to represent ambulation with unknown quality (M0b) and loss of mobility with unknown head control (M5b). Each medical encounter was provided to two independent neurologists, who applied the GMFC-MLD. A third rater confirmed scores and adjudicated disagreements. Weighted Cohen's Kappa was computed to assess the inter-rater reliability (IRR) of scores between M0-M6 (standard categories). Unweighted Cohen's test was used to assess IRR with new levels— M0-M1-M0b (high function range) and M5-M6-M5b (low function). The median age at symptom onset and diagnosis was 1.17 years (inter-quartile 25th-75th percentile: 1.00-1.50) and 2.53 years (2.18-2.69), respectively, with an average gap of 1.28 years (0.86-1.73). Of the 266 encounters, 122 encounters occurred post-presentation, but before diagnosis. Most individuals were noted to have ambulatory function (M0/M1/M2) prior to diagnosis (n=28/31 subjects), while only 12/28 subjects were noted to be ambulatory post-diagnosis. Across all available encounters, the weighted kappa coefficient for standard M0-M6 was 0.897 ( $p < 0.0001$ ). For the added categories (M0b, M5b), encounters within the high function range (n=57) demonstrated an unweighted kappa of 0.814 with disagreement of 3.5%, while encounters with low function (n=90) showed IRR of 0.297 with a 17.7% disagreement rate. This study highlighted the impact of delayed diagnosis in time and function in the MLD population. The majority of individuals lost ambulation prior to diagnosis. The high inter-rater reliability of the retrospectively applied GMFC-MLD suggests its potential to track gross motor dysfunction in MLD across the life span. The new categories allowed for the capture of 13 additional encounters. Further refinement of the definitions may further improve reliability and support the use of this expanded GMFC-MLD scale in retrospective analyses.

## S299. Measurement of Gross Motor Function in Pelizaeus-Merzbacher Disease (PMD)

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**Background:** Pelizaeus-Merzbacher Disease (PMD) is a rare X-linked hypomyelinating leukodystrophy characterized by motor and cognitive disabilities. PMD can be caused by a point mutation, deletion, or duplication/triplication of the gene encoding Proteolipid Protein 1 (PLP1) and features a wide phenotypic spectrum. It is unclear how variables such as genotype or age influence clinical presentation. As clinical trials emerge, it is critical to better understand the natural progression of the disease. This work aims to characterize functional motor abilities in PMD affected individuals. **Methods:** 83 subjects with molecularly confirmed PMD were enrolled in IRB approved natural history studies at participating international centers. Demographic information (age, sex, and race) and diagnostic information (genotype and age of onset) were collected. The Gross Motor Function Classification in Metachromatic Leukodystrophy (GMFC-MLD, range 0-6) and Gross Motor Function Classification System (GMFCS, range 1-5, age-dependent) were scored by a trained child neurologist based on available medical records. **Results:** The GMFC-MLD and GMFCS were applied to 301 encounters across 83 male subjects with varying ages [mean: 7.11 years, range: 0.01-26.8 years]. The mean (SD, range) GMFC-MLD and GMFCS score for the entire cohort was 4.31 (1.58, 0-6) and 4.17 (1.06, 1-5), respectively. Using Spearman's rank correlation coefficient, the GMFC-MLD correlated with the GMFCS on all encounters where both assessments were applied (n=81,  $r=0.806$ ,  $p < 0.0001$ ). We calculated the change in GMFC-MLD (median: 0, IQR: 1, range: -4-3) and GMFCS (median: 0, IQR: 0, range: -3-2) from the earliest and latest encounter for each subject to track progression longitudinally. The first and last encounter have a median (IQR) age difference of 5.25 (7.025) years. **Conclusion:** Our results suggest that PMD affected individuals experience severe motor limitations longitudinally, with slowly progressive motor disability. This work is limited by an ascertainment bias towards severely affected individuals because a) milder cases may be unrecognized or misdiagnosed, and b) our cohort included several older subjects. In the future, we aim to expand this work across various age and ability levels. We also show that the GMFC-MLD may be a useful tool in clinical trials to characterize functional motor abilities in PMD, especially in the early stages of life to discriminate between ability levels. Because the GMFC-MLD has 7 (whereas the GMFCS has 5) levels to characterize motor function, validation of this measure in PMD is especially promising.

### S301. Severe Congenital Brain Malformations in a Patient with Preserved Neurologic Function

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**Introduction:** Dandy-Walker malformation (DWM) is a sporadic developmental abnormality involving the rhombencephalon's roof. It is characterized by agenesis or hypoplasia of the vermis and cystic enlargement of the fourth ventricle, causing a high position of the tentorium and torcula. This malformation is usually diagnosed in pediatric patients, and it frequently presents with hydrocephalus, intellectual disability, and gait instability. Typically, isolated cases of Dandy-Walker have the best functional outcomes and long-term survival. We present the case of an adult, fully independent, and functional housewife despite a history of Dandy-Walker syndrome in association with several other posterior fossa malformations. **Case Presentation:** A 52-year-old female with diabetes, seizures, and remote history of stroke presented to the emergency room with acute onset dizziness, dysarthria, dysphagia, headache, gait instability, and right-sided numbness of the face, arm, and leg. Her neurological exam revealed decreased peripheral vision in her right eye, decreased sensation over the right side of the face, mild sensory hearing loss in the right ear, decreased tongue protrusion and lateral movements, and decreased proprioception in the lower extremities bilaterally. In addition, motor strength was mildly decreased in both upper and lower extremities with normal reflexes. Magnetic resonance imaging (MRI) of the brain revealed various cerebral malformations, including bifrontal encephalomalacia and atrophy, open lip schizencephaly, and Dandy-Walker malformation, which were first identified on a separate scan in 2014. Moreover, no acute intracranial hemorrhage or brain herniation was detected. **Conclusion:** Dandy-Walker Syndrome is a congenital neurological malformation with considerable mortality, characterized by hypoplasia of the cerebellum and defects in the formation of the vermis, dilation of the fourth ventricle, and cystic formation in the posterior fossa. Additionally, Dandy-Walker can be associated with other central nervous system defects such as schizencephaly (abnormal slits, or clefts, in the cerebral hemispheres of the brain). Although there is a highly variable prognosis depending on the severity of this condition, long-term survivors who carry additional posterior fossa malformations have marked disabilities. This case is unusual as this is a fully functional, bilingual middle-aged woman with a severe form of Dandy-Walker syndrome. Her acute presentation symptoms were determined to be related to recrudescence of stroke, seizures, or uncontrolled diabetes in the setting of multiple brain malformations. While the patient exhibited significant imaging findings that could imply the presence of marked neurological symptoms and dysfunction, her exam was relatively normal except for some sensory deficits on the right side of the body.

### K-S112. The Role of FOS and the BAF Complex in Neuronal Activity-Dependent Chromatin Remodeling and Gene Expression

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Pediatric neurodevelopmental disorders (NDD), including pediatric epilepsy, autism spectrum disorder, and intellectual disability, represent a major source of morbidity, yet our therapeutic options remain limited. Development of novel therapies for NDD will require a deeper mechanistic understanding of normal and abnormal brain development. Genetic programs that are activated in response to neuronal activity are fundamental to normal neurodevelopment and thus might play an important role in NDD pathogenesis. FOS is a major activity-dependent transcription factor that binds to distal enhancer elements and regulates downstream activity-dependent genetic programs in a cell-type-specific manner to promote key processes, such as synaptic pruning. Previously, FOS was shown to physically interact with the BAF chromatin remodeling complex and co-regulate stimulus-dependent chromatin accessibility and gene expression in non-neuronal cells. As pathogenic variants in many of the BAF complex subunits are a common genetic cause of NDD, the interaction between FOS and the BAF complex in non-neuronal cells suggests that mis-regulation of neuronal activity-dependent programs contributes to the pathogenesis of BAF complex-related NDD. However, the interaction between FOS and the BAF complex and the genetic networks that they regulate in neurons was previously unexplored. Using human neurons differentiated from human pluripotent stem cells (hPSCs), we identified activity-dependent FOS binding sites, some of which are near (and might help regulate) known NDD-related genes. We further demonstrate that neuronal activity leads to BAF complex binding and increased chromatin accessibility at FOS binding sites and that the activity-dependent increase in chromatin accessibility is diminished in *FOS* knock-out neurons. This work demonstrates that FOS and the BAF complex co-regulate neuronal activity-dependent transcription and provides putative downstream gene targets. To understand how human genetic variation in the FOS binding sites might alter activity-dependent gene regulation, we next used the SFARI SPARK database to find rare *de novo* variants within the FOS binding sites. We specifically focused on those variants that fell within the FOS binding motif (TGASTCA), as these would most likely disrupt FOS binding, thereby preventing BAF complex recruitment, activity-dependent chromatin remodeling, and subsequent downstream gene transcription. In preliminary data, we found that one of the rare *de novo* variants found in a patient with autism spectrum disorder does disrupt enhancer function in a reporter assay. In ongoing work, we will try to understand whether the identified rare *de novo* variants in the FOS binding sites disrupt

neuronal activity-dependent gene transcription and how this might contribute to NDD pathogenesis.

#### **LB-S122. Effects of Microglia Depletion on Brain Lesion Size and Developmental Milestones after Hypoxia-Ischemia in Male and Female C57Bl/6J Mice**

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Perinatal hypoxic ischemic encephalopathy (HIE) is a leading cause of mortality in neonates, and of disability among survivors. HIE can result in cognitive and motor impairments with outcomes often more severe in males than females. This sex difference has been observed in rodent models, where males have larger brain lesions than females after the same injury. Microglia, the resident immune cells of the brain that have distinct developmental trajectories and gene expression patterns by sex, likely play a different role in males and females following HI. However, there is conflicting literature on whether microglia worsen or improve HI lesions, and whether this differs by sex. In addition, no study has examined their role in cognition after HI. We tested the effect of microglia depletion on lesion size and developmental milestones using CSF1R inhibitor PLX3397 to pharmacologically deplete microglia. C57Bl/6J pups received daily intraperitoneal injections from postnatal day 7 (P7) to P12 of either 25mg/kg PLX3397 or vehicle (Veh). At P10, pups either underwent ligation of the right carotid artery followed by hypoxia at 8% FiO<sub>2</sub> for 45 min or a Sham surgery where the carotid artery was isolated followed by 45 min of normoxia (21% FiO<sub>2</sub>). This resulted in four groups tested (Veh/Sham, Veh/HI, PLX/Sham, PLX/HI); all groups included both male and female mice. Behavioral testing was performed both pre-HI (forelimb grasping [P8, P9]) and post-HI (open field traversal, ultrasonic vocalizations (USVs) [P12], gross behavior and appearance in homecage and new environment [P13]). Brains were fixed, sectioned, and immunolabeled for Cresyl Violet and Fluoro-Jade C to assess lesion. There were no differences among groups in forelimb grasp, open field traversal times, or weight gain. After HI, there was a higher proportion of mice who made few USVs; this normalized in PLX-treated HI mice. In preliminary analysis of lesion size and injury scores, Veh-males and PLX-females had higher injury scores than PLX-males and Veh-females. These results suggest microglial depletion may have opposite effects in male and female mice: worsening injury in females while ameliorating in males. Future studies will measure the effect of microglia depletion before HI on hippocampal function in an olfactory spatial learning paradigm.

#### **Neurogenetics and Gene Therapy**

#### **S302. Cross-Sectional and Longitudinal Functional Abilities of Individuals with Beta-Propeller Protein-Associated Neurodegeneration (BPAN)**

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Beta-propeller protein-associated neurodegeneration (BPAN) is a rare subtype of neurodegeneration with brain iron accumulation (NBIA) characterized by early developmental delay followed by parkinsonism in early adulthood. BPAN is associated with mutations in the X-linked dominant gene, *WDR45*. Individuals present with global psychomotor delay and seizures while the later stages are characterized by dementia and movement disorders. Because of the unique biphasic phenotype, it is important to carefully select and validate outcome measures in this condition in consideration of potential future clinical trials. In this study, we aim to explore cross-sectional and longitudinal functional abilities of pediatric subjects with BPAN through the administration of adaptive behavior and cognitive assessments. A total of 39 individuals with a clinical and molecular diagnosis of BPAN were enrolled in our IRB-approved natural history study, the Myelin Disorders Biorepository Project (MDBP). The Vineland Adaptive Behavior Scale-3<sup>rd</sup> edition (VABS-3) and Leiter International Scale 3<sup>rd</sup> edition (Leiter-3) were administered by a trained provider to evaluate Adaptive Behavior and Non-Verbal Cognitive abilities, respectively. Statistical analysis was performed using paired t-test and Ordinary one-way Anova. A cohort of 30 individuals underwent the administration of the VABS-3 (average age at administration 9.74 years, SD 7.11). Communication abilities (Expressive Language > Receptive Language) appeared more impacted by the disease when compared to Socialization abilities (Ordinary one-way Anova,  $p=0.002$ ). A subgroup underwent longitudinal assessments ( $n=14$ ). Communication, Daily Living Skills, and Adaptive Behavior Composite Standard Scores showed a decrease over time (paired t-test,  $p<0.05$ ), while raw scores comparison was non-significant. A group of 21 individuals underwent administration of the Leiter-3 (average age at administration 9.33 years, SD 5.94). Average non-verbal IQ was 47.52 (SD 18.32, range 30-100). Administration of outcome assessments in the BPAN population demonstrated significant impairment in adaptive behavior and cognitive abilities, although a subset presented with an attenuated phenotype. Preliminary data available for repeated assessments show that a decline of standard scores at the VABS-3 does not correlate directly with a loss of skills, but a stability of skills without age-expected improvements. This highlights the need for consideration of raw scores as a true indicator of adaptive behavior abilities when compared to normative data. Overall, non-verbal cognitive assessments appear to be more appropriate in this population due to the severe expressive language impairment.

#### **S304. Genetic Testing Trends in Adult Neurology: Increasing Access and Evolving Yield**

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Genetic testing has become a critical step in the diagnostic process in adult neurology. Long-term data on rates of testing and diagnostic yield is limited, though our team at the University of Pennsylvania has previously published temporal trends and a 30.7% diagnostic yield (Guo et al, AJMG, 2021). The clinical team collectively sees patients with a personal and/or family history of various neurologic indications including dementias, epilepsy, neuromuscular disorders, movement disorders, and white matter disorders. In the current study, we analyze genetic testing uptake and yield in our adult neurogenetics clinic between March 2020 and March 2023 to assess temporal trends. In our cohort of symptomatic patients seen in this timeframe, 79% (n=1019/1290) elected to complete genetic testing. Causal variants were identified in 16.4% of patients who underwent testing. We suspect several factors have contributed to this reduced yield. Our clinic has expanded from one certified genetic counselor to five, which has improved access to genetic counseling and testing. The average number of new monthly patients is higher now (42) than in the past cohort (24). Testing strategy has also evolved such that testing is offered to all symptomatic individuals regardless of the presence of suggestive family history for some indications, such as amyotrophic lateral sclerosis (ALS). Tests with overall lower yield, such as exome and genome sequencing, are ordered more often each month now (11) than previously (8), with more total genetic tests ordered per patient now (3.5) than previously (2). Additional research is needed to clarify ideal testing strategies and improve access to genetic counseling and testing.

### S305. Genotype-Phenotype Discordance in Siblings with Aicardi Goutières Syndrome

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Aicardi Goutières Syndrome (AGS) is a genetic interferonopathy leading to a multisystemic heterogeneous disease and neurologic dysfunction. The diversity of neurologic impairment in AGS can be pronounced. To better characterize the role of genetics, we characterized the genotype-phenotype association between siblings with AGS. Among thirteen families, twenty-six siblings with a diagnosis of AGS were identified from the Myelin Disorders and Biorepository Project (MDBP). Data were collected on the age of onset, genotype, neurologic impairment, and systemic complications. Neurologic impairment was assessed on a disease-specific scale (AGS Severity Scale) at the last available clinical encounter. Sibling pairs were categorized as discordant or concordant based on the difference in AGS Scale (discordant > 3 units difference). Five genotypes were represented: *TREX1* (n=4 pairs; 15.38%), *RNASEH2B* (8; 30.77%),

*SAMHD1* (6; 23.08%), *ADAR1* (6; 23.08%), and *IFIH1* (2; 7.69%). The older sibling was diagnosed at a mean age of 10.09 years versus 4.91 years old for the younger affected sibling. The median AGS score at the last encounter for the cohort was 8, while subjects presenting with symptoms before 1 year had a median AGS score of 5. The AGS scores were discordant for 5 of 13 sibling pairs. Common presenting symptoms were gross motor dysfunction (9/26) and tone abnormalities (8/26). Common early systemic complications included dysphagia and chilblains. Microcephaly and feeding tube placement were associated with lower AGS scores (Wilcoxon,  $p=0.00014$  and  $p=0.00001$  respectively). Even between siblings, there is a broad clinical spectrum associated with AGS, which genotype alone cannot explain. Prior to the implementation of early screening approaches, there is an unmet need to characterize prognostic factors associated with divergent clinical trajectories. Understanding the key variables associated with disease onset and severity can guide future therapeutic interventions and clinical monitoring.

### S306. Identification of Dysregulated Genes in SCA7 Mouse Model through Transcriptome Analysis

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**Introduction:** Spinocerebellar ataxia (SCA), one of the main causes of hereditary cerebellar degeneration, is clinically characterized as a progressive disorder with no cure. There are over 40 subtypes of SCA, some of which have CAG trinucleotide repeats encoding polyglutamine. Although previous studies have revealed that these CAG trinucleotide repeats are associated with oxidative stress, glutamate toxicity, and cell death, very limited information has been reported on the transcriptome level in relation to the pathophysiology. **Methods:** We purchased B6.129S7-Atxn7tm1Hzo/J hemizygous SCA7 mice from Jackson lab and in-vitro fertilized and raised them until they were 11 weeks old. SCA7 mice and wild type littermate C57BL/6 mice were tested by gait analysis and rotarod test on a weekly basis from 7 weeks old for 4 weeks. Then, the whole cerebrum and cerebellum of 11-week-old SCA7 and control mice were sacrificed to perform mRNA sequencing and whole-genome bisulfite sequencing. **Results:** At 11 weeks of age, SCA7 mice showed a shorter stride length compared to control mice (53.5mm vs. 60.8mm for week 7, 52.2mm vs. 69.8mm for week 9, 42.4mm vs. 54.5mm for week 11). In the rotarod test performed between week 10 and week 11, SCA7 mice recorded a mean time of 170 seconds, which was shorter than the 250 seconds recorded by control mice. Analysis of DNA methylation and mRNA expression in 11-week-old SCA7 mice revealed 62 genes that showed DNA hypermethylation and decreased mRNA expression, while 58 genes showed DNA hypomethylation and increased mRNA expression.

Genes with hypomethylation and upregulated mRNA were associated with inflammation, cell death factors, potassium channels, neuronal plasticity, and small molecule transporters. In contrast, genes with hypermethylation and downregulated mRNA were associated with cell survival factors, myelination, neuronal plasticity, and serotonin and dopamine release. **Conclusion:** Based on the SCA7 mouse model transcriptome analysis, promising drug targets for therapeutic intervention were identified.

### S307. Identification of Unique Peripheral Monocyte Phenotypes in CSF1R-Related Leukoencephalopathies

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**Background:** Pathogenic variants in *CSF1R* cause two ultra-rare, devastating neurological disorders. Autosomal dominant *CSF1R* variants cause ALSP (adult-onset leukoencephalopathy with axonal spheroids and pigmented glia) and autosomal recessive *CSF1R* variants cause BANDDOS (brain abnormalities, neurodegeneration, and dysosteosclerosis). *CSF1R* encodes colony-stimulating factor 1 receptor, which is primarily expressed by myeloid cells, including microglia. The underlying pathogenesis of these disorders is poorly understood, and there is a particular need for biomarkers to diagnose and measure response to emerging treatments. We report a BANDDOS case with novel compound heterozygote *CSF1R* variants and a newly developed peripheral blood mononuclear cells (PBMC) assay to provide key insights into monocyte dysfunction due to *CSF1R*-related disease. **Methods:** In parallel to clinical evaluation, we collected venous blood on three different occasions from a BANDDOS patient, her carrier parents, and age- and sex-matched controls. We performed deep phenotypic and functional immunophenotyping on whole blood and freshly isolated PBMC to characterize monocyte, T and B cell populations. **Results:** An 18-year-old female presented with right leg weakness, spasticity, hyperreflexia, and gait impairment. A brain MRI revealed patchy bilateral white matter lesions, with corresponding regions of diffusion restriction. Biallelic compound heterozygous *CSF1R* variants were identified on exome sequencing and inherited from her asymptomatic parents. Analysis of whole blood and PBMC from the patient revealed reduced CD115 (*CSF1R*) expression on monocytes, and graded expression in one of the carrier parents. There was also reduced CCL2 expression in the patient's monocytes following M-CSF or IL-34 stimulation, compared to controls. The frequency of non-classical (CD14<sup>lo</sup>CD16<sup>+</sup>) monocytes was diminished in the BANDDOS patient's blood, but no other myeloid cell populations were affected. Compared with controls, we found enhanced IL-10 expression by the patient's monocytes following LPS stimulation, while pro-inflammatory cytokine expression (IL-6, TNF, CCL2 and CCL3) was similar. **Conclusion:** Our data reveal reduced expression of CD115 (*CSF1R*) on monocytes and their diminished ability to respond to M-CSF and IL-34 stimulation, as

well as a selective reduction in the frequency of non-classical (CD14<sup>lo</sup>CD16<sup>+</sup>) monocytes, in a patient carrying compound heterozygous variants in *CSF1R*. Additional cellular functional outputs will be evaluated on frozen PBMC from the patient, her parents, and matched controls to fully investigate the impact of impaired *CSF1R* expression and/or signaling on monocyte function. Further study will determine whether this platform may be useful for disambiguation of variants of uncertain significance as well as the effect of *CSF1R* variants in ALSP patients.

### S308. Improved Survival, Strength, Weight, and Neuroinflammation in a Mouse Model of Sporadic ALS after Novel AAV-Mediated Delivery of RNAi Targeting Atxn2

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Amyotrophic lateral sclerosis (ALS) is a fatal disease characterized by death of motor neurons, which at autopsy show cytoplasmic aggregates of Tar-DNA binding protein of 43kDa (TDP-43). TDP-43 associates with cytoplasmic stress granules (SGs) and leads to toxicity through both cytoplasmic gain- and nuclear loss-of-function. In 2017, a seminal study showed that inhibiting SG formation through down-regulation of the SG-associated protein Ataxin-2 (*Atxn2*) using antisense oligonucleotides (ASOs) prolongs survival by 35% in a mouse model of sporadic ALS (Becker et al., Nature 2017), a strategy that is now in human clinical trials. However, frequent CNS administrations are required for sustained knockdown, and the intrathecal approach may have limited efficacy in reaching the brain, limiting safety and efficacy. Our group therefore developed an approach using AAV-mediated RNAi delivery to achieve lasting and targeted knockdown, a strategy that could be used to treat sporadic ALS. We designed and tested miRNAs targeting *Atxn2* in cultured cells, packaging the top candidate into a novel AAV9 variant, AAV1999, that we engineered for superior CNS targeting in mice and nonhuman primates. Mouse dosing studies demonstrated 55% *Atxn2* knockdown in frontal cortex and 25% knockdown throughout brainstem and cervical and lumbar spinal cord after intracerebroventricular injection. We then conducted an efficacy study in the same ALS mouse model used in the ASO study, in which wildtype human TDP-43 is overexpressed in neurons and mice exhibit a rapid decline in strength and survival. After treatment, mean and median survival were increased by 54% and 45% respectively ( $p < 0.002$ ). Mice showed a 47% recovery of weight and marked improvement across strength-related measures, including rotarod (2.6X duration,  $p < 0.001$ ); composite gait (40% improvement,  $p < 0.00005$ ); clasping (24% improvement,  $p < 0.05$ ); kyphosis (75% improvement,  $p < 0.00001$ ); tremor (39% improvement,  $p < 0.001$ ); foot angling (57% improvement,  $p < 0.005$ ); and limping (29%

improvement,  $p < 0.05$ ). Interestingly, treated mice showed an increase in vertical activity above that seen in wildtypes, perhaps suggesting an unmasking of an FTD phenotype with improved strength. Histologically, there was an increase in lumbar motor neurons, and a marked reduction in inflammatory markers in the brain and to a lesser degree, the spinal cord. Spinal cord transcriptomics revealed markedly dysregulated transcriptomes in mutant mice that were partly alleviated by treatment. AAV-mediated RNAi against *Atn2* is therefore a promising treatment strategy for the 97% of ALS characterized by TDP-43 pathology.

### S309. N-of-1 Use of Moberg CNS Monitor in an Inborn Error of Metabolism

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**Background:** Hyperammonemic (HA) episodes in urea cycle disorders (UCD) are medical emergencies. Prompt interventions and neuromonitoring are crucial to prevent mortality and morbidity. Our previous work has demonstrated the ability of cEEG to detect specific background changes that correlate with ammonia levels, allowing timely intervention. The Moberg CNS Monitor is a state-of-the-art device that time-synchronizes EEG data with over 30 physiological parameters, which allows us to further advance our understanding of the biophysiological time series during different states of acute decompensation. This monitor has been used in adult ICUs for traumatic brain injury, stroke, and other pathologies to provide precision care. **Methods:** In this pilot study, we investigated the utility of CNS Monitor in a patient with N-acetylglutamate synthetase (NAGS) deficiency presenting with neonatal HA. Continuous measurements of heart rate (HR), perfusion (Perf), respiratory rate (RR), oxygen saturation (SpO<sub>2</sub>), arterial blood pressure (ABP), and EEG were collected from the CNS monitor over a course of 24 hours and analyzed in MATLAB R2019b to correlate the electrographic, biochemical and hemodynamic changes. **Results:** A pairwise correlation was run across all signals. Positive correlation was found between HR-RR, and between SpO<sub>2</sub>-ABP. Negative correlation was seen between HR-ABP, and between RR-SpO<sub>2</sub>. During the HA episode, there was a significant increase of HR and RR compared with baseline. Continuous EEG revealed multiple electrographic seizures arising from occipital lobe as well as an increase in inter-burst interval that correlated with the high ammonia level. **Conclusion:** We demonstrate the role of advanced neuromonitoring devices during acute neurometabolic decompensation in HA episodes. Unsurprisingly, EEG demonstrated an encephalopathic pattern correlated with HA episodes. Time-synchronized data demonstrating changes in vitals, blood metabolites, and EEG can facilitate our understanding of real-time biomarkers in UCD which can be used for treatment and outcome measurement.

### S310. Patient-Reported Outcome Measures Describe Impact of Disease in TUBB4A-Related Leukodystrophy

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**Objective:** *TUBB4A*-related Leukodystrophy (*TUBB4A*-LD) is a rare, progressive genetic disorder of myelin caused by gain of function mutations in *TUBB4A*. *TUBB4A*-LD is associated with severe neurologic disability across cognitive and functional dimensions, but individual phenotypes are heterogenous. Validated tools are needed to characterize motor function, daily living skills, and communication abilities across the population. To support future clinical trials, the objective is to assess caregiver and patient-reported outcomes (PROs) that accurately capture *TUBB4A*-LD phenotypic spectrum, clinical diversity, and impact of disease. **Methods:** Caregivers of children with molecularly-confirmed *TUBB4A*-LD completed a semi-structured interview, the Vineland Adaptive Behavior Scales (VABS-3,  $n = 56$  participants), and qualitative questionnaires: (i) the Caregiver Priorities and Child Health Index of Life with Disabilities (CPCHILD,  $n = 56$ ), (ii) the Quality of Life in Neurological Disorders (Neuro-QOL,  $n = 57$ ), (iii) the Pediatric Quality of Life Inventory<sup>TM</sup> (PedsQL,  $n = 50$ ), and (iv) the PedsQL<sup>TM</sup> Family Impact Module (PedsQL-FI,  $n = 46$ ). All measures underwent face validity. Analysis of Variance (ANOVA) tests compared quality of life (QoL) domains within each measure. Demographic and diagnostic information were collected from medical records. **Results:** Median chronologic age at first VABS-3 assessment was 10.8 years [standard deviation (SD): 9.83; range: 0.9-31.4 years]. Median length of disease since onset was 10.3 years [SD: 8.43; range: 0.9-27.1 years]. The median time from first VABS-3 assessment to questionnaire administration was 0.29 years [range: -0.092-2.380 years]. VABS-3 demonstrated relatively preserved non-verbal communication but severe motor impairment (gross>fine). Motor performance showed a floor effect in the PedsQL, but not in the CPOCHILD. The CPOCHILD Modified Conjoint Analysis

showed that the cohort prioritized their children's comfort, overall health, and communication abilities, but this effect was somewhat biased by age and length of disease. The PedsQL-FI and Neuro-QOL showed very similar performance. Families were less likely to complete the Neuro-QOL (4/57, 7.0%) compared to the other questionnaires (with universal completion). **Conclusions:** Our data suggest that VABS-3 is an appropriate tool to capture functional abilities in a cohort of individuals with *TUBB4A*-LD. The absence of floor and ceiling effects supports the CPCHILD as the best PRO assessment to capture phenotypic variability in motor ability and communication in children affected by *TUBB4A*-LD. The Neuro-QOL and PedsQL-FI showed similar QoL impact, but the PedsQL-FI was shorter and improved compliance. This work emphasizes the importance of patient-centric outcome measures in future clinical trials.

### S311. Potential Treatment for CMT2S Caused by IGHMBP2 Cryptic Splice Variant, with ASO Based Therapeutic

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**Background:** Charcot-Marie-Tooth disease Type 2S (CMT2S; OMIM 616155) is a rare autosomal recessive Charcot-Marie-Tooth disease (CMT) subtype. Rare variants in *IGHMBP2* have been shown to cause CMT Type 2. Specifically, they have been shown to result in abnormal RNA processing leading to alpha-motor neuron degeneration. CMT2S is primarily characterized by distal muscle atrophy, weakness with areflexia, and relatively minor sensory involvement. A patient was reported with consequential variants within *IGHMBP2*. Whole genome sequencing (WGS) revealed a paternally inherited cryptic splice site variant (non-coding variant (c.1235+894 C>A) deep in intron 8). The resulting transcript undergoes nonsense-mediated decay (NMD), resulting in haploinsufficiency. Our objective was to target this cryptic splice site, rescuing *IGHMBP2* protein levels with a novel antisense oligonucleotide (ASO).

**Methods:** We obtained the patient's fibroblast cell line and confirmed the variant with WGS and the existence of NMD induced by cryptic splicing. We designed a 19mer ASO targeting deep in intron 8 (c.1235+894 C>A), around sequence CACTTCCAC(A)GGGGGAAGA. Several ASOs were designed with a phosphorothioate methoxyethyl (MOE) backbone and prioritized based on *in silico* binding affinity. Fibroblast cells underwent ASO treatment (1μM) and 48-hour incubation. Flow cytometry and fluorescein labelled ASO (GFP+99.8%) confirmed cellular entry. For additional exploratory analyses on the patient's phenotype, electrophysiology studies on iPSC cells and motor neurons derived from the patient's fibroblast cells were completed. **Results:** Upon treatment with ASO, we observed a significant *IGHMBP2* protein level increase (~30%) in oligo-treated samples compared to control (untreated) samples (WB antibody Sigma SAB2106426). qPCR results confirmed increased ratio of

restored wild-type transcript to cryptic exon-containing transcript (~1.3-fold). This ASO showed limited off-target effects *in silico*. Preclinical data supports this ASO as potential treatment restoring *IGHMBP2* protein levels. Electrophysiology studies revealed hyperexcitability and spontaneous firing of motor neurons, resembling an amyotrophic lateral sclerosis (ALS) phenotype. **Conclusions:** An increased number of cases of autosomal recessive CMT2S caused by *IGHMBP2* consequential variants are being reported. The N-of-1 precision medicine approach may prove instrumental to the design of treatments for this highly diverse genetic disorder. Patient-specific phenotypic analysis of motor neurons further confirms the genetic heterogeneity of this disorder, revealing a phenotypic resemblance to ALS. This case exemplifies the shifting boundary between rapid WGS based clinical diagnoses and research capabilities allowing for the design of personalized ASO based treatments.

### S312. The Natural History of Variable Subtypes in Pediatric-Onset TUBB4A-Related Disorders

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**Objective:** The objective of this project is to establish the natural history study of individuals affected by pediatric-onset *TUBB4A*-related disorders and characterize subcohorts to improve clinical trial readiness. **Methods:** An international cohort of 203 individuals with *TUBB4A*-related disease were



consented to IRB approved protocols at participating sites. Diagnosis was confirmed by review of sequencing reports. Data was extracted from medical records to determine age at onset, clinical signs at presentation, developmental milestones, genotype, and time to event measures. Correlation between presenting clinical features and genotype was sought. Disease progression was assessed by application of the Gross Motor Function Classification scale - Metachromatic Leukodystrophy (GMFC-MLD). Survival analysis was used to distinguish differences among longitudinal functional scores and to determine time to event. A decision tree was created to predict independent ambulation from early motor milestones.

**Results:** The most common genotypes were p.Asp249Asn (46/203, 22.7%), p.Val255Ile (15/203, 7.4%), p.Arg262His (14/203, 6.9%), and p.Glu410Lys (10/203, 4.9%). The mean age at disease onset was 1.1 years (SD 1.42, range 0-12), while the mean length of follow-up was 7.36 years (SD 7.02, range 0-35.7). The most common features at disease onset included the delayed acquisition of motor (126/193, 65.3%) and cognitive (43/183, 23.5%) milestones, muscle tone abnormalities (80/184, 43.5%), nystagmus (55/191, 28.8%), and feeding concerns (22/186, 11.8%). The most common medical complications during follow-up included later global developmental delay (60/64, 93.7%), loss of acquired motor skills such as independent ambulation (48/96, 50%), seizures (52/165, 31.5%), scoliosis (53/144, 36.8%), and feeding tube placement (64/164, 39%). The ability to sit at 9 months was strongly predictive of the ability to walk independently at 36 months. Subjects with p.Asp249Asn had a higher likelihood of gaining independent ambulation, but also of subsequently experiencing loss of ambulation with disease progression. **Conclusions:** *TUBB4A*-related disease can present in the early-infantile period (<9 months), the late-infantile period or in later childhood. Earlier disease onset appears associated with more severe phenotypes, with affected individuals being less likely to acquire complex motor milestones and with earlier time to event milestones (e.g. gastrostomy). The p.Asp249Asn was associated the late-infantile presentation, and though a milder phenotype was present at disease onset, there was subsequent more rapid disease progression. Study of less frequent genotype-phenotype correlations were limited by sample size. These findings support the existence of variable subtypes in pediatric-onset *TUBB4A*-related disorder, with differences in motor and health outcomes.

### S313. Time-to-Event Measures by Electronic Medical Record Extraction in a Multisite Leukodystrophy Population

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**Background:** Leukodystrophies are heritable disorders of myelin. Leukodystrophies profoundly impact motor function, leading to significant morbidity. Individuals may lose ambulation and oral feeding and have increased risk of urinary tract infections or respiratory failure. Data on frequency of key health outcomes are scarce. Extraction of data from the electronic health record (EHR) provides access to large, multi-site data sets within this rare disease population. **Methods:** Individuals with leukodystrophy are enrolled in the Children's Hospital of Philadelphia (CHOP) IRB approved biorepository and an exempt protocol permitting review of the EPIC EHR. Data capture includes CHOP, Children's Healthcare of Atlanta, Kennedy Krieger Institute, Massachusetts General Hospital, and Stanford University. Sites manually extracted time-to-event measures according to an established methodology for leukodystrophy-related health events using all available records from the EHR chart dating back to birth: orthopedic complications including scoliosis and hip dislocation, loss of ambulation, artificial ventilation, feeding by gastrostomy tube, and urinary tract infection. Results were recorded in REDCap. **Results:** Individuals affected by leukodystrophy (age range = 0.00 - 61.67 years) experience significant morbidity: loss of independent ambulation (median (IQR) = 7.09 (8.77) years); placement of gastrostomy (median (IQR) = 2.88 (6.57) years); hip dislocation (median (IQR) = 7.11 (6.33) years) and hip surgery (median (IQR) = 7.84 (5.80) years); scoliosis (median (IQR) = 8.86 (8.46) years); respiratory failure (median (IQR) = 6.05 (10.64) years) and urinary tract infections (median (IQR) = 6.30 (12.33) years). Multi-site frequency of events was similar (Chi-squared p=0.5073) but variable between disorders (e.g. earlier gastrostomy in MLD [median (IQR) = 6.61 (6.03) years] v.s. ALD [median (IQR) = 9.7 (3.34) years]), reflecting both identification of subjects through newborn screening and variable disease severity. Events were collected as EHRs became available at different sites and were fewer before 2010 (16.69%) than 2010 or later (83.31%). In a subset of the cohort (n=25) interrater reliability was assessed (mean Cohen's kappa=0.83). **Conclusion:** Detailed manual EHR extraction can reliably ascertain events across institutions in a comparable form, elucidating the variability of key events and how they influence care approaches. Future analysis will need to address selection biases related to timing of data capture and the increased presence of newborn screening in a subset of disorders. These results confirm that patients affected by leukodystrophy experience severe medical complications with a variable rate depending on leukodystrophy subtype.

### K-S113. Differential Post-Translational Sulfatase Activation Correlates with Disease Severity in Multiple Sulfatase Deficiency

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Sulfatases catalyze essential cellular reactions, including the degradation of the glycosaminoglycans (GAGs) including heparan sulfate (HS), chondroitin sulfate (CS), and dermatan sulfate (DS). All sulfatases undergo post-translational activation through the conversion of an active site cysteine into a formylglycine residue. This conversion is mediated by the formylglycine generative enzyme (FGE), which is deficient in Multiple Sulfatase Deficiency (MSD), an ultra-rare neurodegenerative lysosomal storage disease. Historically, MSD patients were presumed to be deficient of all sulfatase activity, however, a more nuanced relationship is emerging. Each individual sulfatase may differ in their degree of post-translational modification by FGE, and this may influence the phenotypic spectrum. Here, we evaluate if patterns of residual sulfatase activities and accumulating GAG nonreducing end (GAG-NRE) species distinguish cases from controls and stratify clinical severity groups in MSD. Using tandem mass spectrometry, we quantify sulfatase activities and GAG subspecies accumulation using three complimentary methods in samples from 13 subjects (9 severe, 4 attenuated). Sulfatases differed greatly in their tolerance of reduction in FGE activity. Enzymes mediating HS degradation demonstrated lower residual activities than those that act on CS and DS. Similarly, HS-derived urinary GAG-NRE species preferentially accumulated, distinguished MSD cases from controls and correlated with disease severity. Accumulation patterns of specific sulfatase substrates in MSD could both provide fundamental insights into sulfatase regulation and serve as much-needed diagnostic and severity biomarkers in MSD. This work highlights that biomarker investigation of an ultra-rare diseases can simultaneously inform our understanding of fundamental biology and advance clinical trial readiness. Ultimately, validation of urinary GAG profiles as MSD biomarkers will allow for the stratification of trial subjects and establish inclusion / exclusion criteria for upcoming clinical trials.

#### **K-S114 . Improved Survival, Strength, And Neuroinflammation In A Mouse Model Of Sporadic ALS After Novel AAV-mediated Delivery Of RNAi Targeting Atxn2**

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Amyotrophic lateral sclerosis (ALS) is a fatal disease characterized by death of motor neurons, which at autopsy show cytoplasmic aggregates of TDP-43 binding protein of 43kDa (TDP-43). TDP-43 associates with cytoplasmic stress granules (SGs) and leads to toxicity through both cytoplasmic gain- and nuclear loss-of-function. In 2017, a seminal study showed that inhibiting SG formation through down-regulation of the SG-associated protein Ataxin-2 (Atxn2) using antisense oligonucleotides (ASOs) prolongs survival by 35% in a mouse model of sporadic ALS (Becker et al., Nature 2017), a strategy that is now in human clinical trials. However, frequent CNS administrations are required for sustained knockdown, and the intrathecal approach may have limited efficacy in reaching the brain, limiting safety and efficacy. Our group therefore developed an approach using AAV-mediated RNAi delivery to achieve lasting and targeted knockdown, a strategy that could be used to treat sporadic ALS. We designed and tested miRNAs targeting Atxn2 in cultured cells, packaging the top candidate into a novel AAV9 variant, AAV1999, that we engineered for superior CNS targeting in mice and nonhuman primates. Mouse dosing studies demonstrated 55% Atxn2 knockdown in frontal cortex and 25% knockdown throughout brainstem and cervical and lumbar spinal cord after intracerebroventricular injection. We then conducted an efficacy study in the same ALS mouse model used in the ASO study, in which wildtype human TDP-43 is overexpressed in neurons and mice exhibit a rapid decline in strength and survival. After treatment, mean and median survival were increased by 54% and 45% respectively (p<0.0003). Mice showed marked improvement across strength-related measures, including rotarod (2.6X duration, p<0.005); composite gait (40% improvement, p<0.0001); claspings (24% improvement, p<0.05); kyphosis (75% improvement, p<0.0001); tremor (39% improvement, p<0.0001); foot angling (57% improvement, p<0.0001); and limping (29% improvement, p=0.005). Interestingly, treated mice showed a marked increase in vertical activity above that seen in wildtypes, perhaps suggesting an unmasking of an FTD phenotype with improved strength. Histologically, there was an increase in motor neurons, and a significant reduction in CNS inflammatory markers. Spinal cord transcriptomics revealed markedly dysregulated transcriptomes in mutant mice, several of which were corrected by treatment and have been described in the ALS literature. AAV-mediated RNAi against *Atxn2* is therefore a promising treatment strategy for the 97% of ALS characterized by TDP-43 pathology.

#### **K-S115. Increased Degradation of FMRP Contributes to Neuronal Hyperexcitability in Tuberous Sclerosis Complex**

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Autism spectrum disorder (ASD) is a highly prevalent neurodevelopmental disorder but progress in the development of therapies has been impeded by a lack of understanding of the pathological mechanisms. Several highly penetrant, single

gene disorders associated with ASD have provided important insights into key pathways underlying brain development and behavior. Tuberous sclerosis complex (TSC) and Fragile X Syndrome are two key examples that are associated with abnormalities in the function of the mechanistic target of rapamycin (mTOR) and Fragile X Messenger Ribonucleoprotein 1 (FMRP), respectively, both of which have been implicated in the development of ASD. Previously, we observed that transcripts associated with FMRP were down-regulated in TSC2-deficient neurons. In this study, we found that FMRP turnover was dysregulated in TSC2-deficient rodent primary neurons, and this was associated with increased ubiquitination and reduced phosphorylation of FMRP. Moreover, increased degradation of FMRP was dependent on the presence of a recognition motif in FMRP for the E3 ubiquitin ligase, the Anaphase Promoting Complex. We then used neurons derived from induced pluripotent stem cells (iPSCs) from patients with TSC, as well as isogenic corrected and second hit cell lines. We also observed increased FMRP degradation in human neurons, which was abrogated by mutation in the ubiquitination recognition site of FMRP. Finally, we used extracellular recordings of TSC2-deficient iPSC-derived neurons to show that over-expression of FMRP is sufficient to partially rescue hyperexcitability in these cells. Taken together, we have demonstrated how FMRP is dysregulated in TSC2-deficient neurons and that this represents an important pathological mechanism in the development of abnormal neuronal activity in TSC. These data illustrate a molecular convergence between these two neurogenetic disorders and contribute to unraveling the pathogenesis of neurological symptoms in neurodevelopmental disorders.

#### **K-S116. Loss of O-glycosylation via Neuronal Galnt2 Knock-Out in Mice Recapitulates GALNT2-CDG Patient Seizure Phenotype**

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Congenital disorders of glycosylation (CDG) are a group of neurogenetic disorders that disrupt cellular glycosylation machinery and exhibit multi-system dysfunction, including severe neurological deficits. These disorders emphasize that glycosylation is an essential posttranslational modification, yet the pathophysiology of neurological dysfunction in CDG remains unclear. Most CDG disrupt N-glycosylation, however, eight patients from five families with biallelic loss-of-function mutations in GALNT2, which encodes a Golgi-localized glycosyltransferase that initiates mucin-type O-glycosylation, confirms O-glycosylation is also critical to neurologic function. GALNT2-CDG patients exhibit global developmental delay, epilepsy, autistic features, and white matter changes on brain MRI. A mouse model of the neurological aspects of this neurogenetic disorder, GALNT2-CDG, using a floxed *Galnt2* allele and cell-type

specific Cre drivers, exhibits spontaneous seizures and deficits across numerous behavioral and learning domains. Time-locked video EEG recordings exhibit frequent abnormal electrographic spikes and identify seizures in the majority of neuronal KO mice, which increase in prevalence as the mice age. Power analysis of background EEG frequency composition demonstrates abnormalities across the major EEG frequency bands with increased power in the slow activity delta frequency band and decreased power in the fast activity frequency bands. Glycoproteomic analysis of synaptosomes isolated from brain identify candidate glycoproteins and disrupted O-glycosites that likely underly these abnormalities. Genetic dissection of the circuit suggests that molecular events in both excitatory and inhibitory neurons contribute to development of spontaneous seizures. These findings demonstrate the key role of O-glycosylation in neurons and implicate a role of O-glycosylation in diverse neurological processes, including learning, memory, and neurotransmission.

#### **K-S117. Reversal of C9orf72 Mutation-Induced Transcriptional Dysregulation and Pathology in Cultured Human Neurons by Allele-Specific Excision**

**Aradhana Sachdev, BA<sup>1</sup>, Kamaljit Gill, BA<sup>2</sup>, Maria Scaff, BS<sup>2</sup>, Alisha Birk, BS<sup>2</sup>, Olubankole Aladesuyi Arongundade, PhD<sup>2</sup>, Kathleen Keough, PhD<sup>1</sup>, Bruce Conklin, MD<sup>1</sup>, Claire Clelland, PhD, MD, MPhil<sup>2</sup>.**  
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Efforts to genetically reverse C9orf72 pathology have been hampered by our incomplete understanding of the regulation of this complex locus. We generated five different genomic excisions at the C9orf72 locus in a patient-derived iPSC line and a WT line (11 total isogenic lines), and examined gene expression and pathological hallmarks of C9 FTD/ALS in neurons differentiated from these lines. Comparing the excisions in these isogenic series removed the confounding effects of different genomic backgrounds and allowed us to probe the effects of specific genomic changes. A coding SNP in the patient cell line allowed us to distinguish transcripts from the normal vs. mutant allele. Using ddPCR, we determined that transcription from the mutant allele is upregulated at least tenfold, and that sense transcription is independently regulated from each allele whereas antisense transcription is regulated by the opposite allele. Surprisingly, excision of the WT allele increased pathologic dipeptide repeat expression from the mutant allele. Importantly, a single allele was sufficient to supply a normal amount of protein, suggesting that the C9orf72 gene is haplo-sufficient in cells. Excision of the mutant repeat expansion reverted all pathology (RNA abnormalities, dipeptide repeat production and TDP-43 pathology) and improved electrophysiological function, whereas silencing sense expression did not eliminate all DPRs, presumably because of the antisense expression. These data increase our understanding of C9orf72 gene regulation and inform gene therapy approaches, including ASOs and CRISPR gene editing.

### LB-S123. Reversal of C9orf72 Mutation-Induced Transcriptional Dysregulation and Pathology in Cultured Human Neurons by Allele-Specific Excision

Aradhana Sachdev, BA<sup>1</sup>, Kamaljit Gill, BA<sup>2</sup>, Maria Scaff, BS<sup>2</sup>, Alisha M. Birk, BS<sup>1</sup>, Olubankole Aladesuyi Arongundade, PhD<sup>2</sup>, Kathleen Keough, PhD<sup>1</sup>, Bruce R. Conklin, MD<sup>1</sup>, **Claire Clelland, PhD, MD, MPhil<sup>2</sup>**. <sup>1</sup>Gladstone Institutes, San Francisco, CA, USA, <sup>2</sup>UCSF Weill Institute for Neurosciences, San Francisco, CA, USA.

Efforts to genetically reverse C9orf72 pathology have been hampered by our incomplete understanding of the regulation of this complex locus. We generated five different genomic excisions at the C9orf72 locus in a patient-derived iPSC line and a WT line (11 total isogenic lines), and examined gene expression and pathological hallmarks of C9 FTD/ALS in neurons differentiated from these lines. Comparing the excisions in these isogenic series removed the confounding effects of different genomic backgrounds and allowed us to probe the effects of specific genomic changes. A coding SNP in the patient cell line allowed us to distinguish transcripts from the normal vs. mutant allele. Using ddPCR, we determined that transcription from the mutant allele is upregulated at least ten-fold, and that sense transcription is independently regulated from each allele whereas antisense transcription is regulated by the opposite allele. Surprisingly, excision of the WT allele increased pathologic dipeptide repeat expression from the mutant allele. Importantly, a single allele was sufficient to supply a normal amount of protein, suggesting that the C9orf72 gene is haplo-sufficient in cells. Excision of the mutant repeat expansion reverted all pathology (RNA abnormalities, dipeptide repeat production and TDP-43 pathology) and improved electrophysiological function, whereas silencing sense expression did not eliminate all DPRs, presumably because of the antisense expression. These data increase our understanding of C9orf72 gene regulation and inform gene therapy approaches, including ASOs and CRISPR gene editing.

### Neuroinflammation and Neuroinfection

#### S314. A Patient with CLIPPERS Initially Diagnosed as Parkinson's Disease and Responding Well to Cyclophosphamide

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**Background:** Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS), mostly involves infratentorial regions and can have a myriad of presentations. Here we describe a patient with CLIPPERS presenting with cognitive dysfunction and Parkinsonism. **Case Report:** A woman in her early 60s presented to an outside facility with 1-year history of progressive worsening of cognition, gait instability, and tremors. The patient was diagnosed with Parkinson's disease, however, dopaminergic agonists did not help. She had frequent falls and difficulty with ADLs. She developed bladder incontinence and dysphagia. On presentation to our institution, she

had an exam suggestive of Parkinsonism besides some atypical features of postural tremor and wide-based gait. MRI brain showed mild enhancing areas in the brainstem and nodular and punctate enhancement bilaterally within the basal ganglia and central pons. CSF studies were unremarkable except for mildly elevated protein and albumin. Extensive work-up including autoimmune and paraneoplastic panels in serum and CSF, and other tests for the systemic inflammatory process were unremarkable. MRI of the spinal cord and whole body PET scan was unremarkable as well. The patient had significant improvement with intravenous steroids. Later, the patient was placed on rituximab infusion but discontinued due to poor tolerance and lack of any significant improvement in symptoms. She responded well to induction with cyclophosphamide infusion and was started on methotrexate for maintenance. She has been stable for the last 3 years without any clinical or imaging relapses. **Conclusion:** This report highlights the importance of considering imaging to evaluate for the possibility of an autoimmune process in relatively rapidly progressive patients with the diagnosis of Parkinson's disease who may require aggressive treatment including Cyclophosphamide if patients are refractory to immunosuppressive agents including rituximab.

#### S315. A Progressive Multifocal Leukoencephalopathy (PML) Risk Genetic Test to Identify At-Risk Patients on PML-Linked Disease-Modifying Therapies (DMTs)

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**Objective:** To identify genetic risk variants in PML patient genomes for use in a PML risk test. **Background:** PML is a debilitating and potentially fatal neurological disorder. Immunosuppressed patients who are positive for JC virus (JCV) are at risk but typically do not develop PML. A growing number of drug-induced PML cases have been reported in the literature and/or to the FDA for patients on immunosuppressant therapies. Over 30 drugs list warnings for PML in their prescribing information, 8 of which have PML in a Boxed Warning. The highest drug-induced PML incidence rate is in multiple sclerosis (MS) patients on natalizumab, but cases have also been reported for other drugs (e.g., dimethyl fumarate, fingolimod, and the anti-CD20 DMTs ocrelizumab, ofatumumab, and rituximab). With limited treatment options, prevention of PML is paramount. We hypothesized that some patients have a genetic predisposition for developing PML. **Methods:** Genetic analysis of candidate PML risk variants in a cohort of 336 PML cases, 94 of which had MS and were exposed to PML-linked drugs before developing PML. Analysis focused on immune-modulating genes. Both population (gnomAD) and matched controls (JCV-positive MS patients on a PML-linked drug  $\geq 2$  years) were used for

the association and pharmacogenetic analyses. **Results:** We validated 4 candidate PML risk genetic variants in the largest genetic study to date of PML (Hatchwell E. et al. *Frontiers in Neurology*, 2022), which were associated with PML using both population and matched controls. In drug-exposed PML cases, there is ~9-fold increased risk of PML in carriers of at least 1 variant. All 4 risk variants are predicted to be deleterious and are found in two immune pathways involved in viral defense: complement system (*C8B*, in the terminal pathway, causes C8 deficiency; *FCN2* is part of the lectin pathway) and genes causing/linked to hemophagocytic lymphohistiocytosis (HLH) disorders (*STXBP2* causes FHL5; *LY9*, a *SLAMF* gene, interacts with *SH2D1A*, a cause of X-linked lymphoproliferative syndrome). Intriguingly, two case reports have been reported by others of patients with HLH who developed PML, underscoring the link between HLH genes and PML risk. **Conclusions:** A simple, low-cost genetic test for PML risk is now available to help prevent future cases of PML in patients on or considering treatment with PML-linked drugs. For the first time, PML risk can be assessed before patients start treatment.

### S316. A Rare Case of Wernicke's Encephalopathy Presenting as Idiopathic Intracranial Hypertension

**Jason Gandhi, MD, Hassan Abdullah Shakeel, MD. Allegheny Health Network, Pittsburgh, PA, USA.**

**Introduction:** Wernicke encephalopathy (WE) is a known neurological complication of thiamine deficiency. We present a diagnostically challenging rare case of severe WE manifesting as stupor, elevated intracranial pressure, and atypical MRI findings, while highlighting the importance of prompt diagnosis and treatment. **Case Presentation:** A 39-year-old woman presented with a 5-month history of episodic vertigo, transient blurred vision, and ambulatory dysfunction. Her symptoms eventually became disabling, leading to recurrent falls, inability to work, and difficulty with activities of daily life. Before the presentation, she had developed bilateral tinnitus, episodic vomiting, decreased oral intake, and 30-pound unintentional weight loss. She presented to the ED after being found unresponsive. In the ED, she was disoriented with a restricted gaze, and leftward-beating non-fatigable horizontal nystagmus with a per-torsional component, dysarthria, and bilateral upper extremity dystaxia on a finger-to-nose test. She was found to have a B1 level of 23.2 and started on thiamine IV administration. During her hospitalization, her mental status continued to wax and wane despite nutritional supplementation, thus an EEG was performed showing a generalized encephalopathic process without epileptiform discharges. An MRI brain with and without contrast was expedited revealing a mild motion degraded study with symmetrical T2 subtle diffusion restriction with questionable ADC correlate in the bilateral thalami and mild local mass effect. A CT Venogram was performed showing mild narrowing of the superior sagittal sinus and a left hypoplastic transverse sinus and therefore idiopathic intracranial hypertension evaluation was pursued. As she became stuporous, she was given pulse dose steroids and a lumbar tap to rule out autoimmune encephalitis. Her opening pressure was

54 mm Hg, but otherwise benign CSF studies. A lumbar drain was placed and was started on acetazolamide. After four days, her ICP began normalizing, becoming more awake and alert, and oriented. **Discussion:** Four potential pathways for thiamine are suggested: (a) by reducing intracranial hypertension and/or ventral brainstem compression; (b) by increasing blood flow to the brain; (c) by facilitating aerobic cellular respiration and lactate clearance through the Bohr effect; or (d) by dampening the pro-inflammatory Th-17 pathway. In vitro studies suggest thiamine functions as a carbonic anhydrase inhibitor like acetazolamide which is used in the treatment of elevated intracranial pressure. **Conclusion:** Elevated ICP is an underreported complication of thiamine deficiency that merits acknowledgment given its repercussions if neglected.

### S317. Autoimmune Glial Fibrillary Acidic Protein (GFAP) Astrocytopathy Causing an Eosinophilic Meningoencephalomyelitis

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**Objective:** To report a case of autoimmune GFAP meningoencephalomyelitis with persistent presence of eosinophils in the cerebrospinal fluid (CSF). **Introduction:** Autoimmune GFAP astrocytopathy is an inflammatory autoimmune disorder first described in patients with corticosteroid-responsive meningoencephalitis with or without myelitis. Here, we describe a case of what was initially suspected to be fungal meningoencephalomyelitis but was later confirmed to have autoimmune GFAP astrocytopathy. **Case Presentation:** A 44-year-old man without significant past medical history presented with acute onset of headache, nausea, vomiting, and fevers up to 104 °F for one week. Initial CSF studies were notable for a lymphocytic pleocytosis with eosinophils (69 white blood cells, 90% lymphocytes, 3% eosinophils), elevated protein (113 mg/dL) and normal glucose (53 mg/dL). Initial brain magnetic resonance imaging (MRI) with gadolinium was unremarkable. He was empirically treated with intravenous ceftriaxone, vancomycin, and acyclovir for meningitis. After a CSF fungal culture returned positive for *cryptococcus neoformans*, he was treated for cryptococcal meningitis with amphotericin and 5-fluorocytosine without clinical improvement. It was later determined that the fungal culture was contaminated given multiple negative cryptococcal antigen tests and identified possible contamination source in the lab. Serial CSF studies over the course of three weeks all demonstrated elevated protein and lymphocytosis with eosinophils up to 11 cells/mm<sup>3</sup>. Additional CSF studies included unique oligoclonal bands (6), elevated IgG index (1.03), and cytology/flow negative for malignancy but notable presence of eosinophils. Follow up brain and spinal cord MRIs, approximately one month following symptom onset, revealed diffuse leptomeningeal enhancement with perivascular involvement of the basal ganglia and multifocal ill-defined enhancing cervical and thoracic cord lesions. Five weeks following his initial presentation, GFAP antibody returned positive in CSF with a titer

of 1:1024 (Mayo Clinic Laboratories). Serum and CSF aquaporin-4 antibodies were negative. **Discussion:** Autoimmune GFAP astrocytopathy is often initially misdiagnosed as a central nervous system infection due to the presence of fever, headache, and CSF pleocytosis. The presence of eosinophils has been noted on cytology in CSF in a few reported cases of GFAP astrocytopathy, but the frequency of associated CSF eosinophilia is unclear. The presence of eosinophils in the CSF suggests a distinct set of etiologies, namely helminthic, neoplastic, fungal, or neuromyelitis optica spectrum disorder. This case demonstrates that autoimmune GFAP astrocytopathy should be in the differential for cases of eosinophilic meningoencephalomyelitis.

### S318. Central Nervous System Chagas Disease in an AIDS Patient: Differential Diagnosis of a Space-Occupying Lesion

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**Background:** Chagas disease is a parasitic infection caused by the protozoan *Trypanosoma cruzi*, which is transmitted through Triatomine bugs, blood transfusions, organ transplantation, and during pregnancy or childbirth. Although endemic in Latin America, migration and travel have made it a global health issue. Due to lack of screening in non-endemic areas, cases may go undetected. **Case Summary:** We present a 59-year-old Chilean man, recently diagnosed with Burkitt's lymphoma and human immunodeficiency virus (HIV). He was started on chemotherapy and antiretroviral therapy. After months of remarkable improvement, he experienced involuntary left-hand movements and progressive left leg weakness. Following an episode of altered mental status, he was hospitalized, and imaging studies revealed right hemisphere lesions with ring enhancement. Despite initial empirical therapy for toxoplasma, his condition continued to worsen. A biopsy was subsequently performed, which showed amastigotes, confirming the diagnosis of central nervous system (CNS) Chagas disease. Nifurtimox was initiated, resulting in a favorable therapeutic response. **Discussion:** Chagas disease often goes unnoticed; however, severe symptoms may develop. The acute phase tends to be asymptomatic, and the chronic phase may develop after several decades. Chronic Chagas disease is characterized by heart and gastrointestinal visceromegaly. CNS involvement is a rare but potentially fatal complication, especially in immunocompromised patients. In these patients, latent infection can reactivate, leading to pseudotumoral encephalitis, with space-occupying lesions that can mimic more prevalent infectious or neoplastic etiologies. **Conclusions:** Clinicians should be aware of the neurological manifestations of Chagas disease, particularly in individuals with a history of exposure and those living in endemic areas, even if it was decades ago. CNS Chagas disease should be included in the differential diagnosis of CNS tumors in immunocompromised patients, especially those with HIV. Early recognition and prompt treatment can improve outcomes and prevent morbidity and mortality. **References:** [1] Carod-Artal FJ. American

trypanosomiasis. In: *Handbook of Clinical Neurology: Neuroparasitology and Tropical Neurology*. Vol 114 (3<sup>rd</sup> series) 2013. [2] DiazGranados CA, et al. Chagasic encephalitis in HIV patients: common presentation of an evolving epidemiological and clinical association. *Lancet Infect Dis*. 2009;9(5):324-330. [3] Pitella JEH. Central nervous system involvement in Chagas disease: a hundred-year-old history. *Trans R Soc Trop Med Hyg*. 2009;103(10):973-978.

### S319. Cortical Microglia Heterogeneity in Remyelination and Aging

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We previously showed that regeneration of cortical oligodendrocytes following demyelination declines with cortical depth (Orthmann-Murphy et al eLife 2020). The mechanisms contributing to this depth-dependent effect remain unknown. Microglia, the innate immune cells of the brain, are a good candidate to mediate these differences in remyelination, as they play an important role in clearing myelin debris during demyelination. In the aging brain, microglia may contribute differently to remyelination, as they are less effective at clearing myelin debris. The goal of this study is to determine a) whether microglia adopt depth-dependent reactive states after demyelination that may contribute to impaired remyelination in deep cortex and b) whether these reactive states are altered in the aged brain. We administered cuprizone to young adult mice to induce oligodendrocyte death, followed by 2- and 5-weeks of recovery. Subsequently, cortical sections were stained with microglia-specific and reactive-state markers. We found that deep - but not superficial - cortical microglia upregulate activation marker CD68 and downregulate homeostatic marker P2RY12 in response to cuprizone treatment, indicating that deep cortical microglia lose homeostatic signatures and adopt an activated phenotype that persists through the early recovery period. Contrary to young adult mice, the timing of oligodendrocyte loss after cuprizone treatment was delayed in aged mice. In addition, aged microglia upregulated CD68 prior to treatment with cuprizone, suggesting aging itself may prime cortical microglia to adopt reactive phenotypes. To determine the role of deep cortical 'activated' microglia, young adult mice were treated with a CSF1R antagonist to deplete microglia during the post-cuprizone recovery period. We found that more oligodendrocytes are present in deep cortical regions when microglia are depleted compared to untreated young adult mice. This effect occurred during the early (2 weeks), but not late (5 weeks), post-cuprizone recovery period, and suggests an important role for microglia in early recovery. Together, our data indicate that in the young adult brain cortical microglia adopt spatially restricted responses to demyelination, and directly contribute to oligodendrocyte population density dynamics during the early recovery period. These dynamics are disrupted in the aging brain. Future studies will test how microglia alter oligodendrocyte population density in the early recovery period, as well as investigate how aging alters microglial function, leading to the delay in oligodendrocyte loss.

### S320. COVID-19 Induced Chemosensory Deficits Concurrent with Peripheral Neuropathy

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**Introduction:** COVID-19 infection has been found to be associated with myriad diverse neurologic symptoms. The prevalence of olfactory dysfunction in patients with COVID-19 ranges from 42% to 68% (Cardoso, JAMA, 2022). While descriptions of its impact on smell and taste are common, reports of involvement of the peripheral nervous system are more limited. Moreover, polyneuropathy and proximal radiculopathy affecting the lower extremities due to the demyelination of Schwann cells manifests as Guillain-Barré syndrome, a sequelae of COVID-19 (Kanou, BMJ Case Rep, 2022; Finsterer, Bosn J Basic Med Sci, 2022). However, the concurrence of distal polyneuropathy and olfactory dysfunction after COVID-19 infection has not heretofore been described. Seven such cases are presented. **Method:** This retrospective analysis included seven patients with confirmed COVID-19 infection, with no known prior neurological diseases. Each participant had been evaluated for taste and smell function and peripheral neuropathy functions by the same neurologist (ARH). **Results:** All 7 cases demonstrated chemosensory dysfunction and reduced Achilles reflexes, irregardless of smell and taste complaints or symptoms of polyneuropathy. **Discussion:** While COVID-19-induced polyneuropathy has been described (Odriozola, Diabetes Res Clin Pract, 2021), those reported cases also suffered from diabetes mellitus or other confounding factors which often cause polyneuropathy. However, in our current cases, there was an absence of preexisting diabetes mellitus. The pathological mechanisms of olfactory loss and peripheral neuropathy might be due to nerve inflammation, axon injuries and microvasculopathy in olfactory tissue, death of sustentacular cells and Bowman gland cells, which are supporting cells of olfactory receptor neurons (Ho, JAMA Neurol, 2022; Butowt, Trends Neurosci, 2023). The supporting cells of peripheral nerves and Schwann cells may be the primary target of COVID-19 virus. Alternatively, the mechanism may be through a neuroimmune response, with T lymphocytes infiltration induced by the direct invasion of coronavirus (Matschke, Lancet Neurol, 2020; Spudich, Science, 2022). Given the presence of distal lower extremity areflexia and hyporeflexia in individuals with olfactory loss after COVID-19 infection, investigations are needed to include all COVID comorbidities, as well as existence of other pathogenic agents involved in polyneuropathy and chemosensory loss, including B12 deficiency, thiamine deficiency, amyloidosis, and diabetes (Wahlstrom, Nutrition and Sensation, 2015). Further investigations are warranted for presence of polyneuropathy in those with COVID-19 induced chemosensory impairment.

### S323. Epidemiological Analysis of Lyme Meningitis among Adults within the United States

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**Purpose:** Lyme meningitis is a rare form of meningitis that arises as a complication of Lyme disease, a multisystem vector-borne disease. Our study sought to characterize the hospitalizations of Lyme meningitis. **Method:** A retrospective analysis was conducted using hospital records from the 2016 to 2020 National Inpatient Sample. Adults (ages  $\geq 18$  years) with a diagnosis of Meningitis due to Lyme disease were included. We further investigated differences in patient characteristics and outcomes of patients from our cohort. **Results:** A total of 1,375 cases of Lyme disease had meningitis between 2016 to 2020 in the United States, with 580 Males (42.2%) and 795 Females (57.8%). The cases rose between 2016 to 2018 from 295 in 2016, 315 in 2017, and 325 in 2018, but dropped between 2018 to 2020 as 240 cases were seen in 2019 and only 200 were recorded in 2020. The peak admission during all five years was in July (27.1% of patients in 2016, 27.9% of cases in 2017, 32.3% of cases in 2018, 39.6% of cases in 2019, and 30.8% of cases in 2020). Furthermore, 92.2% of all patients were Whites. In addition, 66.5% of cases were hospitalized in the Northeast region of the United States, and 70.9% involved Urban-teaching centers. The mean age of the patients was 49.75 years, and they had a mean length of stay of 5.46 days, with a mean hospital charge estimated at \$47,096. Several complications were also noted among these patients as 3.3% (45 cases) necessitated mechanical ventilation (MV), 8.0% (110 cases) developed septicemia, and 10.2% (140 cases) had acute kidney injury (AKI). We also found that 15 (1.1%) patients (all males) did not survive their hospitalization, and they were older than those who survived (mean age of 75.67 vs. 49.47 years,  $p < 0.01$ ). They also had a longer hospitalization (mean of 12.00 vs. 5.39 days), which was more expensive (mean hospital charge of \$231,955.78 vs. \$45,057.57). **Conclusion:** A higher proportion of Lyme meningitis patients were females. The number of reported cases rose from 2016 to 2018 and declined from 2018 to 2020. Most cases were recorded in July. Furthermore, Whites comprised the biggest portion of admissions. The distribution revealed more hospitalized patients in the Northeast region and urban teaching centers. Conditions such as sepsis, AKI, and MV use were seen in some cases. Interestingly, only males died during hospitalization with significantly older average age than the mean age.

### S324. Horner's Syndrome: A Rare Clinical Presentation of Giant Cell Arteritis

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**Background:** Giant cell arteritis (GCA) is a large artery inflammatory vasculitis involving large and medium-sized arteries that can result in various complications including

arterial dissection, blindness, and stroke. Rarely, GCA patients present with Horner's syndrome due to involvement of sympathetic neurons from intra or extracranial arterial inflammation. **Case Report:** An 82-year-old female with a history of hypertension, atrial fibrillation, and arthritis presented with a 24-hour history of right eye ptosis. She reported a constant drooping eyelid with blurred vision, dizziness, and aching eye pain. Further she endorsed a mild headache with tenderness over the right temporomandibular joint but no temporal artery tenderness. Her exam demonstrated right eye ptosis and miosis suggestive of Horner's Syndrome with no other focal neurological deficits. Labs were notable for elevated ESR of 68 mm/hr and CRP of 16 mg/L. MRI brain with contrast demonstrated mild to moderate stenosis and enhancement over bilateral MCA's and basilar artery suggestive of an inflammatory process. No acute ischemic stroke or hemorrhage was observed. Given the concern for GCA, the patient was initiated on prednisone 40 mg daily. The temporal artery biopsy demonstrated focal disruptions of the internal elastic lamina, multinucleated giant cells within the media, lymphocytic inflammatory infiltrates in perivascular soft tissue and focal medial calcifications, confirming the diagnosis of GCA. Her prednisone was increased to 60 mg/day and initiated on tocilizumab. At the 1-month follow up visit her Horner's Syndrome had resolved. **Conclusion:** This case illustrates the importance of considering GCA in patients presenting with Horner's syndrome, as prompt diagnosis and initiation of corticosteroids can prevent long term complications including vision loss and ischemic stroke.

### S325. Identification of *Mycoplasma Hominis* Infection in Neurosurgical Wound by 16S Ribosomal RNA Nanopore Metagenomic Sequencing Study

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**Introduction:** *Mycoplasma hominis*, a common genitourinary colonizer, rarely presents its deadly nature in immunocompromised or neonatal patients. Its cellular characteristics however hinder identification using Gram stain or culture. For this reason, extra-genitourinary *M. hominis* infection of healthy individuals can easily go misdiagnosed or undiagnosed. However, early identification of *M. hominis* is crucial for targeted antibiotic therapy. We present a case of post-neurosurgery wound infection diagnosed with 16S rRNA sequencing. **Case:** A 52-year-old male with primary hypertension incidentally found two unruptured intracranial aneurysms at the left middle cerebral artery (MCA). The neurological intervention was decided upon the aneurysms due to their size (7 and 9mm) and growing nature. During the superficial temporal artery (STA)-MCA double-barrel bypass surgery at middle and inferior MCA divisions, he experienced one intra-op seizure. After the seizure, a swollen brain was

noticed and the operation site was left open without replacing the bone flap. Starting from Post Op Day (POD) 1, the patient had a fever up to 38.3°C. The wound was clear with only a scanty amount of discharge not enough for culture. He did not show any symptoms of genitourinary or other systemic infection and cultures were negative in sputum and urine. Cerebrospinal fluid (CSF) was analyzed, which showed 4500/mm<sup>3</sup> of RBC, 94/mm<sup>3</sup> of WBC, 66 mg/dl of protein, and 56 mg/dl of glucose having borderline glucose ratio (0.52). However, the CSF culture and 16S rRNA PCR results were negative. Although empirical piperacillin/tazobactam had been administered, the patient continued to have fever over 38°C and elevated C-reactive protein levels (22mg/dL). Wound revision was done on POD 10. A moderate amount of purulent fluid collection was observed in the epidural space and subcutaneous layer. Pus was collected for investigation followed by massive irrigation. The Gram staining, AFB tests and culture showed negative results. However, the 16S rDNA PCR of the pus revealed a strong band and the sequencing identified *M. hominis* on POD 11. The antibiotics were changed to levofloxacin on POD 13 and continued for two weeks. The patient became afebrile after the surgery and was discharged without neurological complications. **Conclusion:** We report a rare case of neurosurgical wound infection by *Mycoplasma hominis* in an immunocompetent individual. 16S rRNA metagenomic sequencing helps establish early diagnosis, allowing prompt administration of targeted antibiotic therapy. Large-scale studies are needed to determine the prevalence of *M. hominis* infection in culture-negative cases after neurosurgery.

### S326. Long Term High-Fat Feeding: Connecting Metabolism, Cognitive Impairment, and Altered Microglial Morphology

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Obesity and metabolic dysfunction (Metabolic Syndrome, prediabetes, and diabetes) increase the risk of later life cognitive impairment, including dementias such as Alzheimer's Disease. One common etiology that might underly this increased risk is immune system dysregulation and inflammation. Specifically, microglial dependent mechanisms are thought to play an important role in pathology. However, the precise immune and inflammatory mechanisms promoting cognitive decline secondary to obesity and metabolic dysfunction are unclear. Therefore, we fed male BL6 mice either 60% HFD (high fat diet) or 10% SD (standard diet) for 1 year. Body weight, glucose tolerance, and cognition were assessed over time. Cognition was evaluated using Morris water maze, social recognition, and puzzle box. After 1 year of feeding, mice were given either an intraperitoneal injection

of lipopolysaccharide as an immune challenge or saline as a control. Activation of hippocampal microglia was assessed via immunohistochemistry (IHC) and analysis of microglial morphology. Correlation analyses were performed to understand associations between metabolic, cognitive, and microglial morphology parameters. HFD feeding caused early increases in weight and glucose intolerance, which persisted throughout the study. Cognitive deficits were also observed in HFD fed animals and were similarly persistent. In response to immune challenge, hippocampal microglia in SD mice had a normal morphological response indicative of activation. However, microglia of HFD mice had no change in their morphology in response to lipopolysaccharide injection. In terms of our correlation analysis, body weight in particular was predictive of cognitive changes, especially for later time points. Additionally, changes in morphology were significantly correlated with cognitive outcomes and indicate that a higher degree of microglial activation is associated with worse cognitive outcomes. Overall, we concluded that HFD feeding causes early and persistent cognitive impairment, which is associated with obesity. Our data also confirm a role for microglia in HFD-induced cognitive impairment. Indeed, microglial data strongly indicate a role for inflammation and inflammatory pathways in HFD-induced cognitive impairment.

### **S327. Neurosarcoidosis Presenting with Recurrent Strokes Due to Large Artery Vasculitis**

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**Introduction:** Neurosarcoidosis is a rare manifestation of sarcoidosis affecting approximately 5% of patients with sarcoidosis. It is hallmarked by the accumulation of granulomas in the CNS. The presentation of neurosarcoidosis can vary depending on its distribution, which includes the meninges, nerves, hypothalamus, pituitary gland, parenchyma, or blood vessel involvement. Therefore the manifestation varies and include meningitis, neuropathies, myelopathies, vasculitis or venulitis, dementia, or other neuropsychiatric components. The diagnosis is grouped into three categories: possible, probably, and definitive highlighted by proved biopsy, CSF, and MRI findings or neurosarcoid, which is seen in approximately 10% of sarcoidosis patients. **Case Presentation:** A 48-year-old female with a past medical history of hypertension, type 2 diabetes mellitus, former tobacco use, migraines, and sarcoidosis presented with left hemi-body weakness and numbness. She was hypertensive on arrival to 172/71 mmHg. Her LDL was elevated to 126 and HbA1c was 10.6%. Her CTA demonstrated intracranial stenosis involving the basilar artery, right ACA and PCA. MRI brain showed a pontine infarction. Eight years prior to this presentation, she had a lymph node biopsy demonstrating non-caseating granulomas. Her sarcoidosis was considered to be inactive without systemic manifestations. The patient declined a DSA and given her poorly controlled stroke risk factors, the stroke etiology was thought to be secondary to intracranial atherosclerosis. The patient was discharged on

aspirin, clopidogrel, and high-dose statin. The patient then had a seizure and 2 recurrent strokes in the right subcortex and the right MCA/ACA watershed territory with an interval development of right MCA high grade stenosis. No abnormal contrast enhancement was seen on MRI brain. Her LDL was 45 and HbA1c was 8%. The DSA was concerning for a vasculitis process. There was no CSF pleocytosis or oligoclonal bands, although protein was mildly elevated at 58. CSF cytology, ACE, and infectious workup including mycobacterium tuberculosis complex was negative. The patient was initiated on steroids and transitioned to Infliximab infusion for sarcoidosis with CNS involvement. During the 18 month follow up on immunosuppressive therapy, her neurological exam remained stable without symptomatic strokes on surveillance MRI brain images. **Conclusion:** Large vessel vasculitis is a rare complication of sarcoidosis. Clinical awareness of neurosarcoidosis is essential when considering stroke etiology for secondary stroke prevention. Neurosarcoidosis can be a challenging diagnosis as the initial clinical picture often has a broad differential diagnosis including primary CNS vasculitis, CNS lymphoma, and infection.

### **S328. Neurosyphilis: A Great Mimicker**

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**Introduction:** Neurosyphilis is a rare disease that until the 2000s was almost eradicated due to population awareness of HIV and efficient treatment. Since then, the prevalence of the entity is rising due to risk-associated behavior such as unprotected intercourse. The prevalence of neurosyphilis was nearly twofold higher in men and in people with human immunodeficiency virus. It is of great importance that clinicians realize that syphilis has had a strong reappearance during recent years. Especially among homosexual males the incidence has exploded. Patients with symptomatic early neurosyphilis typically present with meningitis or cranial neuropathies, most frequently involving cranial nerves II, VII, or VIII. **Case Presentation:** A 43-year-old, non-obese man presented with a 3 week history of visual disturbances described as radioactive sign spinning associated with progressive vision loss in both eyes left greater than the right. It was associated with morning headaches and left sided ear fullness. No nuchal rigidity, fever, night sweats, skin rashes, or arthralgia were reported. He had originally presented to ophthalmology and found to have bilateral papilledema with reduced visual acuity without relative afferent pupillary defect reflex. The rest of the cranial nerve and neurological exam was normal. The patient was admitted for intracranial hypertension and venous sinus thrombosis evaluation. MRI of the brain showed abnormal linear areas of enhancement within the internal auditory canals bilaterally left more than right along the intracanalicular segment of facial nerves with corresponding FLAIR hyperintense signal. MRA and MRV were unremarkable. A lumbar puncture revealed an opening pressure of 10 cm H<sub>2</sub>O which did not confirm intracranial hypertension. LP analysis revealed white cell count of 47/ul (mainly lymphocytes), and protein of 52 mg/dL. The atypical phenotype led to obtaining a more detailed history



revealing homosexuality. Further serum work up discovered positive treponemal antibody screen and treponema pallidum antibody particle agglutination. CSF VDRL and serum antibody HIV testing were negative. Early neuro-syphilis was the most likely diagnosis and was treated with 2 weeks of IV penicillin with improvement of his symptoms after 4 weeks. **Conclusion:** Neurosyphilis is rare but diagnosis is challenging as a great mimicker. Obtaining a thorough history of risk associated behavior will help to tailor the investigation. Physicians should have a high index of suspicion and low threshold for testing of neurosyphilis in the appropriate context to avoid missing the diagnosis and treatment of this treatable condition to prevent further complication of late neurosyphilis.

### S329. Not All Lower Back Pain is Sciatica, a Case of Meningitis Secondary to Septic Emboli from Infective Endocarditis

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**Background:** Lower back pain is caused by serious etiologies in <1% of instances. Cerebral septic emboli stemming from infective endocarditis (IE) carry a significant risk of stroke and neurologic complications, and a poor prognosis. The incidence of cerebral septic emboli detected by MRI remains markedly higher than those detected by clinical exam. **Case Presentation:** A 54-year-old female with a history of end-stage renal disease (ESRD) on hemodialysis (HD) and hypertension, presented to the ED with acute right-sided lower back pain while shopping. She had recently been seen for headache, but discharged with a normal CT head and labs, and resolution of symptoms. She provided her own history and denied radiation of pain or neurological deficits. She was afebrile, and exam was notable for a faint systolic murmur, positive straight leg raise test, and no focal neurologic deficits. She was admitted for monitoring given a mild leukocytosis of 12.3 (4.0-11.0 K/mm<sup>3</sup>) and blood cultures were drawn. **Clinical Decision-Making:** She was treated for sciatica with a reactive leukocytosis and given opiates for pain. She developed a fever (101.1° F) and was started on Vancomycin for a gram-positive cocci bacteremia. She became lethargic with constricted pupils, asterixis, but preserved motor function on exam. Labs were notable for an increased BUN of 119 from 85 mg/dL and increased leukocytosis of 19.1 K/mm<sup>3</sup>, and a STAT CT head and lumbar spine MRI revealed no acute pathology. Despite Naloxone for presumed opiate toxicity, her mental status continued to decline. Upon upgrade to the ICU, she was noted to have erythema overlying a thrombosed dialysis graft, and nuchal rigidity during placement of a temporary HD catheter. Despite HD for uremic encephalopathy, she continued to worsen and a STAT brain MRI showed multiple acute embolic infarcts. Lumbar puncture had 335 WBC, protein 79 mg/dL, glucose 46 mg/dL, and no organisms on gram stain. A transthoracic echocardiogram revealed a 0.9 x 1.1 cm vegetation on the posterior mitral leaflet, solidifying the diagnosis of IE. Blood cultures revealed methicillin-sensitive *Staphylococcus aureus*. **Conclusion:** We present an atypical case of mitral IE, presenting as acute lower back pain with developing secondary meningitis from either cerebral septic emboli or

bacteremia, in the setting of an infected dialysis graft. This case highlights the importance of maintaining a broad differential for worsening encephalopathy, especially in a patient with non-specific symptoms, high-risk comorbidities, and clinical worsening despite interventions.

### S330. Smell Recovery in Post-Acute Sequelae of COVID (PASC) - Drug Repurposing of Baricitinib

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**Background:** Covid-19 is a global pandemic that has infected about 660 million people worldwide with lacking information about its long term impact. Up to 70% of patients suffer from consequences after recovery including fatigue, myocarditis, neurological symptoms, persistent loss of taste and/or smell etc. termed as PASC. Covid-19 infects sustentacular cells in the olfactory epithelium which activate an antiviral response in olfactory sensory neurons through cytokines like interferon. Genomically encoded cytoplasmic double stranded RNA (dsRNA) leads to anti-viral type I interferon signaling in the olfactory epithelium of our Nd1 mouse model. This leads to a decrease in odorant receptor expression, reduced odor-evoked field potentials and diminished odor discrimination and replicates the immune response after Covid-19 infection. Baricitinib is a FDA-approved anti-inflammatory drug for rheumatoid arthritis, alopecia areata and for emergency use for Covid-19. This orally administered drug counteracts type I interferon signaling, including in human neurons. **Objective:** Data collection from in-vivo studies in mice and computer-based analysis of electronic health records evaluating the safety and efficacy of Baricitinib for smell recovery after Covid-19 infection. Together these results may support conducting a randomized placebo-controlled, double-blinded clinical trial using Baricitinib as a potential therapeutic drug to accelerate smell recovery in patients with COVID-19 induced anosmia and parosmia. **Methods:** 1. We will quantify the expression of odorant receptors using RT-PCR and immunohistochemistry and assess olfactory behaviour in Nd1 mice treated with Baricitinib. 2. In electronic health records we will deploy causal inference methods to determine whether hospitalized Covid-19 patients that received Baricitinib had reduced longitudinal incidence of anosmia and parosmia relative to hospitalized Covid-19 patients that did not receive Baricitinib. **Results:** We hypothesize an increased expression of odorant receptors and improved olfactory behaviour in Nd1 mice that are treated with Baricitinib. Additionally, we postulate that patients exposed to Baricitinib during the acute phase of their Covid-19 infection will have a reduced incidence of anosmia and parosmia relative to matched patients that were not treated with Baricitinib. Preliminary results from in-vivo studies in mice and analysis of electronic health records of patients will be presented. **Conclusion:** The results of our studies form a precedent to launch a clinical trial testing Baricitinib as a potent agent to alleviate anosmia and parosmia in PASC patients with an additional focus on biomarker discovery. This could be an important step in reducing global burden of PASC.

### S332. The Racial and Ethnic Disparities in Clinical Outcomes in Patients with Encephalitis

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**Introduction:** Encephalitis is estimated to occur in around 5-10 per 100,000 U.S. persons each year [1] with a mortality rate of 5.6% [2,3]. Encephalitis can generally be classified into infectious or autoimmune etiology. The influence of racial disparities on clinical outcomes has been studied in some autoimmune diseases, such as multiple sclerosis[4-6] but there is no literature on encephalitis including autoimmune encephalitis. **Objective:** The aim was to determine if there are significant differences in clinical outcomes among encephalitis patients of different racial backgrounds. **Method:** We conducted an IRB-approved, retrospective chart review of patients between 2005 and 2022, diagnosed with encephalitis at a large tertiary care academic center in Houston. We included 336 patients with an identified race and dichotomized race into Non-Hispanic Whites and ethnic minorities (African American, Hispanic, and Asian). Descriptive statistics were used to analyze the data being investigated, including mean with standard deviation and range for continuous variables, and proportions or percentages for categorical variables. Pearson correlation was used to estimate the correlation between continuous variables. **Result:** As expected, 63% of our patients were of an ethnic minority ( $n=213$ ) while 37% were Non-Hispanic White ( $n=123$ ) given the racial makeup of Houston. The Non-Hispanic White population had significantly more patients over the age of 60 ( $p = .013$ , 38%,  $n=47$ ) compared to our ethnic minority patient population (25%,  $n=54$ ). Significant findings include the data regarding encephalitis etiology and seizure incidence. 80% of patients with a definite autoimmune etiology were of an ethnic minority ( $p = .012$ ,  $n=28$ ). Ethnic minority patients also had a higher incidence of seizures ( $p = .046$ , 37%,  $n=78$ ) than Non-Hispanic White patients (26%,  $n=32$ ). Meanwhile, Non-Hispanic White patients had a significantly greater number of encephalitis cases due to viral causes ( $p = .028$ , 43%,  $n=53$ ), and HSV/VZV encephalitis was twice as common in these patients than in patients of an ethnic minority ( $p = .005$ , 26% vs 13%). **Discussion:** Our analysis demonstrates that race and ethnicity may play a role in the etiology and clinical outcome of encephalitis and highlights that racial disparities may factor specifically into autoimmune etiology and the incidence of seizures in our cohort of encephalitis patients. **References:** 1. Graus, Francesc. The Lancet. Neurology. 2016. 2. George, Benjamin P. PloS one. 2014. 3. Vora, Neil M. Neurology. 2014. 4. Amezcu, Liliana. Multiple sclerosis (Houndmills, Basingstoke, England). 2020. 5. Dobson, Ruth. Nature Reviews Neurology. 2022. 6. Onuorah, Helen-Margaret. Neurology. 2022.

### S333. Unilateral High Sciatic Neuropathy Associated with Severe COVID-19

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**Background:** Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) causes COVID-19 and has been associated with peripheral nerve injury as a result of an inflammatory neuropathy, positioning-related peripheral nerve or brachial plexus injury, nerve entrapment, and distal symmetric polyneuropathy. We care for a patient with severe COVID-19 with a left sciatic neuropathy associated with a chronic occlusion of the left tibial artery. **Case Summary:** A 56-year-old man with severe COVID-19 required endotracheal intubation and mechanical ventilation. Hospital course was complicated by septic shock and acute kidney failure. Upon extubation three weeks later, he had severe weakness of his left lower extremity. Neurological examination following hospital discharge demonstrated a left flail foot, absent left ankle reflex, and impaired sensation on the outer aspect of the left leg and the dorsum, sole, and inner aspect of the left foot. Electromyography showed prominent spontaneous activity of the left tibialis anterior, peroneus longus, medial gastrocnemius and left biceps femoris muscles. Nerve conduction studies showed absent sensory and motor responses on the left peroneal and tibial nerves. MRI of the pelvis demonstrated fatty atrophy and muscular edema of the left thigh. Arterial Doppler ultrasound showed a chronic left anterior tibial artery occlusion. The patient was diagnosed with a high left sciatic neuropathy. **Discussion:** Peripheral nervous system involvement in COVID-19 may result from dysregulation of the immune system or microthrombotic-induced nerve ischemia. The sciatic nerve is frequently damaged in the sacral plexus, the pelvis, the gluteal region, or at the sciatic notch. Based on the association of a left sciatic neuropathy with a chronic occlusion of the left anterior tibial artery, we suspect our patient had ischemia of the left sciatic vasa nervorum as the most plausible etiology. Further research is needed to unravel the best management of ischemic neuropathies associated with COVID-19. **Conclusions:** Clinicians should be aware of the various peripheral neurological manifestations of COVID-19. Ischemia of proximal nerve vasa nervorum is a plausible etiology of sciatic mononeuropathies. **References:** [1] Andalib et al. 2021. PMID: 33586020. [2] Acharya et al. 2021. PMID: 34306871. [3] Dietmann et al. 2022. PMID: 36333659. [4] Fernandez et al. 2021. PMID: 33258748. [5] Michaelson et al. 2022. PMID: 34971857.

### K-S118. Brain Capillary Obstruction by Leukocytes is Ameliorated by Integrin Blockade in an Immunocompetent Mouse Model of CAR T Cell Neurotoxicity

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**Background:** Neurotoxicity, also known as ICANS (Immune Effector Cell associated Neurotoxicity Syndrome) affects 30-50% of patients treated with CAR T cells for hematologic malignancies. Signs and symptoms include confusion, language disturbance, and in severe cases seizures,

coma, and death from fulminant cerebral edema. Systemic cytokine release syndrome (CRS) occurs as CAR T cells rapidly proliferate *in vivo*, and is a key risk factor for ICANS. Despite some evidence that ICANS is a disorder of the blood-brain-barrier, we still do not understand how cytokines and immune cells interact with the neurovascular unit to cause brain dysfunction. We have developed an immuno-competent syngeneic mouse model of CD19-CAR T treatment induced neurotoxicity that shows similar kinetics to patients, with peak neurotoxicity around day 6-7 after CAR T cell infusion. *In vivo* two-photon brain imaging of the microvasculature revealed obstructed blood flow in 11.9% of cortical capillaries during neurotoxicity, compared to 1.1% in controls treated with mock transduced CAR T cells. These obstructions were almost exclusively due to CD45+ leukocytes, 30% of which were CAR T cells. **Research Question:** Can we ameliorate neurotoxicity by reversing capillary leukocyte plugging via disruption of leukocyte-endothelial adhesion? For this study, we focused on the key T cell - endothelial interactions of LFA1/ICAM-1 and VLA4/VCAM-1. **Methods:** Wild type BALB/c mice treated with 10 million murine CD19-CAR T cells or mock transduced T cells received antibodies directed against integrin alpha 4, integrin alpha<sub>L</sub>, or ICAM-1 on days 1,3 and 5 after CAR T cell injection. We performed daily neurologic exams and open field testing on day 5. Brain capillary plugging was assessed *in vivo* via two-photon microscopy of the brain microvasculature through a cranial window, and histologically by quantifying the number of 2-micron fluorescent microspheres that became trapped intravascularly. **Results:** Soluble ICAM-1 and VCAM-1 were increased in blood after CAR T cell treatment, but only ICAM-1 protein was upregulated in brain capillaries. Blockade of integrin alpha 4 resulted in improved spontaneous locomotion on day 5 after CAR T cells (162% of isotype treated controls,  $P=0.0147$ ) and decreased capillary plugging on day 6 (49.7% of isotype controls,  $P=0.0179$ ). **Interpretation:** Our data show that CAR T cell treatment increases leukocyte-endothelial interactions, likely by upregulation of adhesion molecules which may be induced by systemic cytokine release. Blockade of the VLA4/VCAM-1 interaction resulted in improved locomotion and decreased brain capillary plugging, supporting a causative role for leukocyte plugging in the pathogenesis of ICANS.

#### K-S119. Satellite Microglia Have a Role in Regulation of Neuronal Excitability and Change in Response to Injury

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Microglia, the primary mediators of innate immune activation in the brain, are increasingly recognized as key modulators of neuronal activity and excitability. There is growing evidence in many neurological diseases, including traumatic brain injury (TBI), that prolonged activation of the innate immune system can impede repair and promote disease, and it is not understood if or how microglia's impact on neuronal activity might contribute. One interesting microglial subtype that may be critical in the monitoring and feedback of

neuronal excitability is the perineuronal satellite microglia. These microglia are juxtaposed adjacent to neurons with their soma and processes entwined around the neuronal cell body. To understand how these microglia modify neuronal excitability and change their interactions with neurons after injury, we utilized patch clamp recordings, immunohistochemistry, light microscopy and confocal imaging. We found an increase in the numbers of satellite microglia in the orbitofrontal cortex in both a murine model of TBI that is associated with network hyperexcitability and behavioral dysfunction with deficits in reversal learning several months after TBI, as well as human tissues from donors with a history of chronic TBI compared to sham and controls, respectively. Whole cell recordings in adult transgenic mice with GFP-labeled microglia (Tmem119-EGFP), utilized to record activity in neurons adjacent to and away from satellite microglia, also indicate that satellite microglia suppress neuronal excitability as measured by the action potential and firing frequency response to a series of depolarizing current steps. However, this effect is lost at chronic time points after TBI. These findings support continued investigation of satellite microglial response and neuronal interaction after chronic injury.

#### LB-S125. High Dimensional Analysis on Mechanism of Action of Siponimod

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Siponimod, a sphingosine 1-phosphate receptor (S1PR) modulator, was utilized to treat Experimental Autoimmune Encephalomyelitis (EAE). Spleens, draining lymph nodes, blood, and the brains and spinal cords (CNS) were surveyed at baseline (naïve), week 1, week 2 and week 4 of the EAE disease course. We performed high-dimensional analysis of cell surface markers and cytokines at the single-cell level using cytometry by time-of-flight mass spectrometry (CyTOF). A 33-marker CyTOF panel with 2 DNA markers, 1 live/dead marker, 22 cell surface markers and 8 cytokines was used to distinguish and profile T cells, B cells, monocytes, macrophages, granulocytes, NK cells, and CNS residential myeloid cells. Here we confirmed that Siponimod-treated mice were indeed lymphopenic by CyTOF profiling of the PBMCs. Both the CD4+ T and CD8+ T cell population frequencies were not noticeably accumulating within the spleens or lymph nodes during any of the weekly time points. Moreover, most of the T cell populations appeared to be notably absent in the spleens and lymph nodes by week 4, compared to both EAE Vehicle treated mice and healthy mice. These data indicate that Siponimod is capable of inducing lymphocyte apoptosis within the secondary lymphoid organs, similarly to what has been reported with FTY720 (Fingolimod) (Immunology 89:518; J. Immunology 160:5037.) In the CNS we observed an increase in residential myeloid cell frequencies in the residential myeloid cell populations in week 1 of both treatment groups. These residential myeloid cells produce either TNF alone or IFN $\gamma$  alone. A small number of infiltrating monocytes, that are not secreting any detectable cytokines from our panel, do begin to appear in the CNS of

the vehicle treated group by week 1. By week 2, the CNS of both treatment groups show an increase of infiltrating TNF-secreting monocytes, and smaller frequencies of infiltrating CD4+ T cells and CD8+ T cells that both secrete only TNF, and TNF secreting B cells. Leukocyte infiltration into the CNS is typically expected at around this week 2 time point when EAE disease is at its peak, although it was surprising to see leukocyte infiltration in the Siponimod treated group, given that the mice appeared clinically unaffected. The residential myeloid cells appear to still be active 4 weeks after EAE immunization. High dimensional single cell analysis provides an indepth profiling of the activity of Siponimod both outside the central nervous system and within, during a quintessential model of neuroinflammation.

#### **LB-S126. Pregnancy Outcomes among Multiple Sclerosis Patients on Disease Modifying Drugs: A Systematic Review and Meta-Analysis**

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**Objectives:** To report pregnancy outcomes among patients being treated for MS with disease modifying drugs (DMTs). Outcomes of interest include prevalence of birth defects, types of prenatal and natal complications, incidence of MS relapses, and requirement of steroids **Methods:** A retrospective chart review of PubMed, Google scholar, EMBASE, and Scopus, was conducted by two independent researchers for articles from June 1996 to January 2023. MS disease outcomes throughout pregnancy like number of relapses, DMTs used, steroid requirements were considered. Adverse outcomes included were premature delivery, stillbirth, ectopic pregnancy, spontaneous abortion, and live birth with defect. A meta analysis was done for individual DMTs including Interferon, Natalizumab, Glatiramer Acetate (GA), Fingolimod, Dimethyl fumarate (DF), Teflunamide, and Ocrelizumab. We performed summary data analysis and random effects model to estimate the overall prevalence of outcomes. **Result:** We conducted the meta-analysis of 44 studies-13 of interferon, 10 of natalizumab, 6 of GA, 7 of fingolimod, 4 of DF, 2 of cladribine and teflunamide each. The prevalence of premature birth was highest with DF (0.6667%, SD: 0.5236-0.7845), that of death was highest with interferon (0.009%, SD:0.005-0.0015), that of ectopic pregnancy was highest with cladribine (0.0234%, SD:0.0041-1217), that of spontaneous abortion was highest with Natalizumab (0.1177%, SD:0.0931-0.1477), that of still birth was highest with interferon (0.004%, SD:0.001-0.010), and that of live birth defects was highest with natalizumab (0.0755%, SD:0.0643-0.0943). We found that none of the outcomes were significantly different from outcomes of general population ( $p>0.05$ ), except ectopic pregnancy and spontaneous abortion ( $p<0.001$ ). The odds of these outcomes when compared to general population were 0.665 (0.061-0.886) for ectopic pregnancy and 0.537 (0.003-0.786) for spontaneous abortion. The pooled cohorts prevalence of having only one episode of MS relapse was 0.221% (SD 0.001-0.714), that of having more than one episode of MS relapse was 0.075% (SD 0.006- 0.167), and that

of having at least one episode requiring steroids was 0.141% (SD 0.073-0.206). None of which was significantly different from that of general population. **Conclusion:** We conclude that outcomes of pregnancy among patients being treated with DMTs for MS are suggestive of their safety in use throughout pregnancy. Based on this, we recommend that the use of MS DMTs according to the older recommendations of pregnancy drug categories should be reconsidered. We support the use of drugs depending on case-by-case basis. Further primary research on this topic with clinical trials is warranted.

#### **LB-S128. Neurosyphilis Presenting with Abducens Nerve Palsy**

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Syphilis is a sexually transmitted infection caused by the bacterium *Treponema pallidum* that has been on the rise. In 2021, there were a total of 176,713 reported cases of syphilis in the United States.<sup>1</sup> From 2020-2021, the rate of reported syphilis increased by 31.7% (from 40.4 to 53.2 per 100,000).<sup>2</sup> Neurosyphilis is an infection of the central nervous system with *Treponema pallidum* that may be a consequence of untreated syphilis. Presentation of syphilis and neurosyphilis is often non-specific and can make for a difficult diagnosis. Neurosyphilis infection with cranial nerve 6 palsy presentation is reported in only a few cases. We present the case of a 22-year-old male with no significant past medical history who presented to the emergency department with a chief-complaint of worsening diplopia and persistent left eye esotropia with no history of recent trauma. Apart from endorsing diplopia, the patient had no other neurologic complaints. The patient was hemodynamically stable and did not endorse systemic symptoms. Neurological examination with intact mental status exam revealed diplopia on primary lateral gaze, left eye esotropia with left CN 6 palsy and right eye INO. Otherwise, cranial nerve exam was unremarkable along with motor, sensory, and reflex examination. MRI w/wo contrast revealed abnormal enhancement in the distal cisternal segment of bilateral abducens nerves, distal intracanalicular segment of bilateral facial nerves and distal cisternal segment of right trigeminal nerve. The patient was started on a course of high-dose steroids due to concerns of inflammatory process with no improvement in symptoms. Lumbar puncture with CSF analysis revealed clear and colorless appearance, glucose 57 mg/dL, protein 63 mg/dL, RBC 3 / mm<sup>3</sup>, nucleated cell count of 7 / mm<sup>3</sup>, neutrophil count elevated at 11%, lymphocyte 80%, and monocyte count of 9%. RPR was reactive with titers at 1:32. Follow-up with FTAB test was positive indicating active syphilis infection. Treatment with penicillin G 4 million units Q4H for 14 days was initiated. One day after treatment, the patient endorsed significant improvement of diplopia with primary lateral gaze. This was supported by findings of improved left eye esotropia, and right eye INO with enhanced ability to adduct the right eye past midline. This case illustrates the non-specific and unusual presentation of neurosyphilis. With the recent increase in reported cases of syphilis, it is imperative

that clinicians maintain a high index of suspicion for neurosyphilis infection in patients presenting with neurological symptoms.

## Neuromuscular Disease

### M267. A Brief Report on Juvenile ALS in the National ALS Registry: 2010 - 2018

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**Background:** Amyotrophic lateral sclerosis (ALS) is a progressive, fatal disease with a prevalence of approximately 9.9 per 100,000 persons. Published reports suggest 5-10% of ALS cases are classifiable as juvenile ALS (jALS), defined as developing symptom onset before age 25. **Objective:** To describe the demographic characteristics of confirmed and likely jALS cases in a large cohort of ALS patients ascertained in the National ALS Registry (Registry). **Methods:** Established in 2010, the Registry collects and examines data on ALS patients in the US to better describe the epidemiology of ALS. The Registry compiles data from national administrative databases (from the Centers for Medicare and Medicaid Services, the Veterans Health Administration, and the Veterans Benefits Administration) and voluntary enrollment data through a web portal. Patients in the Registry must be at least 18 years of age. We examined Registry data from 2010-2020. **Results:** The Registry identified 45 patients, aged 18-24, who met the Registry definition of confirmed ALS (31 cases) or likely ALS (14 cases). Of those, 17 (37.8%) were diagnosed by age 24. jALS cases were more likely to be non-White (55.6%), male (77.8%), and live in the Midwest or Northeast regions (63.6%) of the US. Some 68.9% of the juvenile ALS cases were received from CMS, VHA, or VBA, and 17.8% came from the web portal only. **Conclusions:** Demographic characteristics for jALS cases in the Registry differed from previous publications examining ALS cases for all adults. More research is needed to understand jALS, which could lead to earlier diagnosis and therapeutic interventions.

### M268. A Case of Anti-Neurofascin Autoantibody Positive Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) Concurrent with Angioimmunoblastic T-cell Lymphoma

*Brandon Wei, MD, Bing Liao, MD. Houston Methodist Hospital, Houston, TX, USA.*

**Background:** CIDP is a clinically and pathologically heterogeneous autoimmune disorder of the peripheral nervous system. Autoantibodies against the node and paranode of Ranvier (i.e., anti-neurofascin autoantibodies) have been discovered in a subset of CIDP patients with distinct clinical features and treatment responses. Angioimmunoblastic T-cell lymphoma (AITL) is a rare, often aggressive form of peripheral T-cell lymphoma. Though many hematological disorders could be associated or mimic CIDP, AITL presenting as CIDP is uncommon. Cases of concurrent anti-neurofascin antibody

positive CIDP and AITL have not been reported. **Case:** A 63-year-old man with a remote history of treated prostate cancer presented with 7-month of progressive lower extremity weakness, sensory deficits resulting in loss of independent ambulation. Electromyography and nerve conduction study (EMG/NCS) showed findings suggestive of an active, severe, demyelinating sensorimotor polyradiculoneuropathy with secondary axonal loss. Cerebrospinal fluid (CSF) analysis was significant for albuminocytologic disassociation. Patient was diagnosed with CIDP and treated with therapeutic plasma exchange (TPE) with improvement of lower extremity strength. In the next two months, despite continued TPE, the patient declined in terms of muscle strength, sensory loss, along with new onset dry cough. He was readmitted to hospital, where diagnostic workup revealed lymphopenia and elevated serum kappa-lambda light chain ratio. CT thorax showed bilateral hilar and axillary lymphadenopathy with bilateral pleural effusions. Further workup including thoracentesis with flow cytometry, axillary lymph node biopsy and bone marrow biopsy confirmed diagnosis of CD30+ nodal T follicular helper cell lymphoma, angioimmunoblastic type. PET scan captured numerous hypermetabolic lymph nodes in the neck, chest, abdomen, and pelvis, as well as diffusely increased splenic uptake. Serum autoantibody test revealed presence of IgG anti-NF140, IgG anti-NF155, IgG4 anti-NF155 antibodies. Combination chemotherapy was initiated along with TPE, resulting in significant improvement of his motor and sensory function. **Discussion:** AITL is a rare peripheral T-cell lymphoma that is not commonly associated with CIDP. Anti-neurofascin autoantibody CIDP demonstrates distinct features compared to antibody negative CIDP, including poor responses to conventional immunotherapies. In this rare case with concurrent anti-neurofascin autoantibody CIDP and AITL, the pathophysiology and association between these two entities are unclear. It is reasonable to postulate that abnormal T cell function in AITL resulted in breakdown of self-tolerance and generation of autoimmunity.

### M269. A Case of Anti-NXP2 Dermatomyositis without Histopathological Evidence of Myopathy

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We report on the case of a previously healthy 18-year-old female patient diagnosed with Anti-NXP2 Dermatomyositis (DM). She initially presented to our outpatient neurology clinic for evaluation of painful, progressive, symmetric, proximal muscle weakness that had begun in her thighs and then progressed over course of months to her shoulders and arms. Symptoms were associated with violaceous/erythematous rashes along scalp, bilateral upper eyelids (heliotrope rash), upper chest (V-sign), bilateral knuckles (Gottron papules) and fingertips (periungual erythema). Prior to symptom onset, she was involved in high-performance athletics, participating in advanced gymnastics and cheerleading without issues. But by time of evaluation in clinic, her weakness had progressed such that she could not wash her hair or climb the stairs without difficulty. Her most recent symptoms included

progressive dyspnea (“unable to walk between classrooms without feeling “winded”) and dysphagia for solids. Due to the advanced nature of her condition, she was sent from clinic directly to the hospital to be admitted for more urgent work up. At that time, her General Physical exam was notable for the dermatological findings described above, as well as for a mild atrophy of proximal bilateral upper and lower extremities (BUE/BLE). Neurological exam was notable for bilateral weakness in her hip flexors (3-/5) and deltoids (4/5), along with a more diffuse muscle ache and pain in BUE/BLE. Respiratory testing was notable for Negative Inspiratory Force: -30 cmH<sub>2</sub>O and Vital Capacity 1.7 L. Laboratory studies were notable for CK:1189 (ref:26 - 192 U/L), ANA:1:320 (speckle), Aldolase: 11.6 (ref:1.2-7.6 U/L), Troponin:118 (ref:0-19 ng/L), and UA with blood but no RBCs (e.g. myoglobinuria). MRI bilateral thighs were obtained, revealing extensive muscle edema, worse in right, with small amounts of perifascial fluid. These imaging findings were deemed to be consistent with inflammatory myositis and used to guide a right quadricep skeletal muscle biopsy. Surprisingly, the initial histopathological analyses was normal. However, her extended ARUP Myositis panel did return “high-positive” for NXP2, confirming her diagnosis (and this was later supported by electron microscopy analysis that revealed endothelial tubuloreticular inclusions). Other negative workup of note included CT Chest/Abdomen/Pelvis with contrast, high-resolution CT Chest, transthoracic-echo and cardiac-MRI, paraneoplastic panels, autoimmune studies, thyroid, metabolic panels, and her dysphagia workup. She was started on IV Solumedrol x 5d with rapid improvement in symptoms, and subsequently discharged on hospital day 6 with methotrexate and slow prednisone therapy in stable condition.

#### **M270. A Case of Thrombocytopenic COVID-19 and Miller Fisher Syndrome on a Concurrent Chronic Immune Neuropathy**

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**Introduction:** Guillain-Barre Syndrome (GBS) classically has features of progressive symmetric muscle weakness with areflexia caused by preceding infections including COVID-19, while Miller Fisher syndrome (MFS), a rare GBS subtype, has classic features of ataxia, areflexia, and ophthalmoplegia. Various antibodies have been associated with both MFS and GBS. The mainstay of treatment for both is either IVIg or plasma exchange. While rare to find a multitude of demyelinating polyneuropathies and polyradiculopathies in various stages, it presents as an additional challenge for the diagnosis and treatment of the patient. **Case:** 60-year-old male presenting with acute symptoms of MFS including ataxia, areflexia, and ophthalmoplegia on a chronic immune neuropathy for at least 1 year. Patient also had concurrent asymptomatic COVID-19 positive infection with associated thrombocytopenia with elevated ganglioside panel antibodies. Physical exam noted to have muscle weakness with no sensory changes throughout including bilateral medial rectus

weakness causing ophthalmoplegia. Extreme ataxia was seen with finger-to-nose and heel-to-shin, and patient had truncal ataxia. Patient was areflexic in all reflexes except the bilateral brachioradialis. There also was atrophy in the bilateral hypothenar eminence, thenar eminence, interossei, and quadriceps with fasciculations seen in the quadriceps. Treatment was inpatient IVIg with monthly IVIg as an outpatient. Follow up in the long term was done in a neuromuscular clinic where an EMG was performed. **Discussion:** Typical clinical features of MFS were seen with improvement with treatment. The concurrent asymptomatic infection of COVID-19 is unique among cases of MFS. Thrombocytopenia has been shown in meta-analyses to be associated with more severe COVID-19 infections and high mortality among those patients. Continued monthly treatment was chosen given the clinical examination findings of an underlying neuropathy. **Conclusion:** Prompt recognition and treatment of GBS and its subtypes like MFS is essential. The full effect on COVID-19 on the various GBS subtypes is currently unknown, although it clearly can be a cause and precipitating infection. Follow up in patients is important to help reduce any post-complications or residual effects in such syndromes.

#### **M271. A Case Report of Systemic Lupus Erythematosus Presenting as Isolated Mononeuritis Multiplex**

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Mononeuritis multiplex is a pattern of progressive sensory and motor deficits in the distribution of two or more peripheral nerves. The differential for mononeuritis multiplex is broad and includes vasculitis, autoimmune disorders, infectious diseases, sarcoidosis, amyloidosis, cryoglobulinemia, and paraneoplastic disease. Here, we present a rare case of a 42-year-old woman with a past medical history of hypothyroidism who presented with one week of ascending numbness and weakness, persistent fevers, and three months of constant burning pain in both feet. Her neurologic exam was notable for diminished strength, sensation, and reflexes of her lower extremities bilaterally. Other than mild fever and tachycardia, there were no other systemic exam findings. Her laboratory workup was significant for elevated inflammatory markers, positive ANA, anti-RNP, smooth muscle antibody, and lupus anticoagulant, high anti-dsDNA titers, and low complement levels. An MRI of her lumbar spine was negative for spinal cord pathology. Cerebrospinal fluid studies demonstrated normal cell counts, glucose, and protein and no evidence of infection. An electromyography (EMG) demonstrated acute motor axonal neuropathy. Given the patient's symptoms, physical exam, laboratory results, and EMG findings, she was diagnosed with mononeuritis multiplex secondary to systemic lupus erythematosus (SLE) and was started on steroid and immunosuppressant therapy with symptomatic improvement. Overall, this case illustrates an unusual presentation of mononeuritis multiplex as the sole manifestation of SLE. Mononeuritis multiplex may lead to significant disability and poor quality of life. Thus, prompt

recognition of SLE as the etiology of mononeuritis multiplex is essential for timely initiation of treatment.

### **M272. Acute Motor Sensory Axonal Neuropathy with IgM Antibodies Against NS6S**

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**Objective:** We describe a rare case of acute motor sensory axonal neuropathy (AMAN) associated with NS6S antibodies and near complete resolution of symptoms with no immunotherapy. **Results:** A 42-year-old man presented with an acute asymmetric bilateral distal motor weakness and no sensory involvement. Neurological exam showed bilateral hand and feet weakness, diminished patellar and ankle reflexes and normal sensory exam. An extensive serum and CSF work up was significant for CPK of 706. Electro-diagnostic studies on day 10 of symptoms showed evidence of pure motor axonal neuropathy consistent with AMAN, his neuromuscular antibody panel was positive for IgM antibodies against disulphated heparin disaccharide (NS6S) with a titer of 29,000. His symptoms peaked at 10 days, and he had complete resolution of his symptoms after 4 weeks of onset. **Discussion:** IgM antibodies against NS6S are frequent in chronic acquired motor neuropathies and multifocal motor neuropathy, but less frequent in cases of Amyotrophic Lateral Sclerosis (ALS) and Chronic Inflammatory Demyelinating Polyneuropathy (CIDP) (1). IgG antibodies against GM1 & GM1b gangliosides as well as IgM antibodies against GM1 are associated with AMAN (2,3). This is the first reported case of an acute form of motor neuropathy or more specifically AMAN associated with IgM antibodies against NS6S. In this case, the patient had an earlier peak of symptoms and near complete resolution with no immunotherapy with normal CSF analysis which suggest a milder monophasic form of AMAN associated with antibodies against NS6S. References: 1. Pestronk, A., Chuquilin, M., & Choksi, R. (2010). Motor neuropathies and serum IgM binding to NS6S heparin disaccharide or GM1 ganglioside. *J Neurol Neurosurg Psychiatry*, 81(7), 726-730. <https://doi.org/10.1136/jnnp.2009.2027962>. Ogawara, K., Kuwabara, S., Koga, M., Mori, M., Yuki, N., & Hattori, T. (2003). Anti-GM1b IgG antibody is associated with acute motor axonal neuropathy and Campylobacter jejuni infection. *J Neurol Sci*, 210(1-2), 41-45. [https://doi.org/10.1016/s0022-510x\(03\)00013-33](https://doi.org/10.1016/s0022-510x(03)00013-33). Rees, J. H., Gregson, N. A., & Hughes, R. A. (1995). Anti-ganglioside GM1 antibodies in Guillain-Barre syndrome and their relationship to Campylobacter jejuni infection. *Ann Neurol*, 38(5), 809-816. <https://doi.org/10.1002/ana.410380516>

### **M273. AL Amyloid Neuropathy Clinical and Electrophysiological Characteristics**

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**Objective:** Immunoglobulin light chain (AL) amyloidosis is the most common form of neuromuscular amyloidosis. AL amyloid neuropathy is a rapidly progressive condition that can lead to severe disability in patients due to deposition of

monoclonal light chain. The objective of this study is to report clinical and electrophysiological characteristics in a cohort of patients with AL amyloid neuropathy. **Methods:** Retrospective chart review of patients with AL amyloid neuropathy at Houston Methodist Hospital. **Results:** In our cohort of nine patients, the majority (67%) were female. Age at evaluation by a neurologist ranged from 50-72 years. The chief complaint in the majority of these patients (66%) was sensory symptoms, followed by neuropathic pain (44%), weakness (22%) and dysautonomia (22%). One patient (11%) had no neurological manifestation. MRC sum score ranged from 48-60. Seven patients (78%) had cardiac involvement, five (56%) had liver, two (22%) had kidney involvement, and multi-organ involvement in six patients (67%). Seven patients (78%) had sensorimotor polyaxonopathy, one (11%) had bilateral peroneal/fibular neuropathy, and one (11%) patient had small fiber neuropathy. Four patients (44%) had unilateral median neuropathy. Diagnosis was made via kidney biopsy (33%), followed by liver and endomyocardial biopsy (22%). One patient (11%) had a lung biopsy. All the patients displayed the lambda subtype, with three (33%) found to have IgA and two (22%) with IgG monoclonal gammopathy. Patients were treated with various regimens. Two (22%) patients were on Cyclophosphamide, Bortezomib and Dexamethasone regimen, two (22%) were on Melphalan, two (22%) were on Lenalidomide and one (11%) was on Daratumumab. Three patients (33%) were deceased, one (11%) from cardiac arrest and two (22%) were transitioned to hospice. Five patients (56%) underwent solid organ transplants, with three (33%) undergoing concurrent stem cell transplantation. **Conclusion:** Most of the patients in this cohort were female and had sensory symptoms as their primary complaint. Many of the patients showed mild muscle weakness on MRC sum score grading. Majority of the patients had sensorimotor polyaxonopathy on electrodiagnostic study. All the patients were of the lambda subtype and the majority had cardiac and/or multi-organ involvement. Over half of the patients underwent solid organ transplantation and were on various chemotherapies.

### **M274. Algal Blooms and Amyotrophic Lateral Sclerosis: A Systematic Review**

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Smoking, herbicides, pesticides, heavy metals, silica, and numerous other environmental factors are thought to raise the risk of developing Amyotrophic Lateral Sclerosis (ALS). Researchers believe that blue-green algae or cyanobacterial blooms may be a contributing factor as they uncover clues that appear to link a few ALS cases to people's proximity to coastal areas and lakes. We intend to summarize the updated information on the controversial relationship between cyanotoxins and ALS in the context of ongoing algal blooms caused by climate change. This systematic review was conducted by following the Meta-Analysis of Observational

Studies in Epidemiology (MOOSE) and PRISMA protocol reporting guidelines. We include only studies written in the English language during the last 20 years. We excluded systematic reviews, meta-analysis, and case reports. In the 1950s, a high incidence of Amyotrophic Lateral Sclerosis /Parkinsonism Dementia Complex was noticed among the indigenous Chamorro people on the island of Guam. This was attributed to their diet being contaminated with the cyanobacteria-derived neurotoxin, beta-N-methylamino-L-alanine (BMAA). The growing scientific literature has established the fact that transfer RNA (tRNA) synthetases can aminoacylate amino acid analogs to their cognate counterparts. BMAA is incorporated at phenylalanine, proline, alanine, and glutamate sites during protein synthesis, thereby amplifying their potential for neurotoxicity. This misincorporation is one mechanism that may contribute to the onset of sporadic neurodegenerative diseases. Ingestion of contaminated food or water, as well as inhalation of aerosolized cyanotoxins, are the most likely routes by which the ubiquitous environmental bacteria can transmit BMAA to humans. The National Center for Environmental Health of the Centers for Disease Control and Prevention is currently conducting a study in Florida called the Cyanotoxins in Air Study to examine the health effects of exposure to cyanotoxins in the air. We emphasize the need for epidemiological studies using a variety of scales of analysis, including satellite remote sensing of cyanobacterial algal blooms, to establish the link between ALS and algal blooms.

#### **M275. Anti-RGMA Antibody Restores the Neuronal Actin Barrier against Disease-Implicated Protein and Prevents Neurodegeneration in an Animal Model of ALS**

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Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease characterized by protein aggregation in motor neurons. Studies of familial ALS have shown that disruption of the actin dynamics could be attributed to ALS. Repulsive guidance molecule A (RGMA) was originally identified as a neuronal growth cone-collapsing factor. Previous reports have demonstrated the multifunctional roles of RGMA mediated by neogenin1 (NEO1) in various neurological diseases such as spinal cord injury, multiple sclerosis, and Parkinson disease. However, the pathogenic involvement of RGMA in ALS remains unclear. Here, we demonstrated the RGMA concentration to be elevated in the cerebrospinal fluid (CSF) of both the patients with ALS and transgenic mice overexpressing the

mutant human SOD1 gene (mSOD1 mice). Elevation of RGMA in CSF was a specific phenomenon observed only in ALS patients, and it was correlated with the respiratory function of ALS patients. Therapeutic intervention with humanised anti-RGMA monoclonal antibody ameliorated motor function and body weight loss in the mSOD1 mice, leading to the prolonged survival. Histochemical analysis revealed that the anti-RGMA antibody significantly decreased the accumulation of mutant SOD1 protein in the motor neurons of mSOD1 mice via inhibition of actin depolymerisation. The *in vitro* analysis revealed that the anti-RGMA antibody inhibited the cellular uptake of the mutant SOD1 protein, presumably by reinforcing the neuronal actin barrier. Collectively, these data suggest that RGMA collapses the neural actin barrier and promotes aberrant protein deposition, resulting in the exacerbation of the ALS pathology.

#### **M276. Association between Urinary Metals and Amyotrophic Lateral Sclerosis (ALS) Survival**

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**Objective:** This study aimed to investigate the potential association between urinary metal levels and survival in patients with amyotrophic lateral sclerosis (ALS). **Methods:** A survival analysis was conducted using a Cox proportional hazards regression model with 136 ALS cases. Urinary metals including copper, nickel, tin, and zinc were measured in the study participants. **Results:** Our survival analysis demonstrated that increased levels of urinary copper (HR=1.34, 95% CI: 1.13-1.59, adjusted P=0.007), nickel (HR=1.27, 95% CI: 1.10-1.47, adjusted P=0.007), tin (HR=1.24, 95% CI: 1.06-1.44, adjusted P=0.030), and zinc (HR=1.53, 95% CI: 1.26-1.86, adjusted P<0.001) were significantly associated with a higher hazard of mortality in patients with ALS. Notably, these hazard ratios correspond to one standard deviation increase in log-transformed metal levels. **Conclusion:** Our findings suggest that increased levels of urinary copper, nickel, tin, and zinc may be associated with decreased survival rates in patients with ALS. Further investigation is needed to better understand the underlying mechanism of these associations.

#### **M277. Atypical Guillain-Barre Syndrome (GBS) Preceding High-Grade Burkitt Lymphoma with Central Nervous System (CNS) Involvement: A Case Report**

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**Introduction:** Guillain-Barre syndrome (GBS) presenting as an initial manifestation of Non-Hodgkin Lymphoma is a rarity. Here in, we report a case of a male patient who developed atypical GBS, and further diagnostic evaluation revealed high-grade Burkitt Lymphoma with CNS involvement. To the author's knowledge, this is one of the few cases of Non-Hodgkin lymphoma preceded by GBS, and probably the



first case in which GBS heralded the diagnosis of a high-grade Burkitt Lymphoma with CNS involvement. **Case presentation:** A 54-year-old male initially presented to the emergency department with concerns of sudden onset bilateral lower extremity numbness for two weeks and weakness for one week. His extremity weakness was more pronounced on the right side. His symptoms progressively worsened, including numbness in his genital region, urinary urgency without bowel or bladder incontinence, and gait ataxia. He denied having any recent respiratory, genitourinary, or gastrointestinal infections. MRI of the neural axis showed possible syrinx C7 through T12. The patient was guided to follow up with a neurosurgery clinic outpatient. On his follow-up visit, neurosurgery had a suspicion of demyelinating disorder and advised him to go to the ER again for further evaluation. This time, neurology service was consulted. Extensive imaging and broad infectious and neoplastic workup were done. Per neurology evaluation, the patient's acute onset asymmetric lower extremity weakness, numbness distal to the knee joint, lack of distal positional sense, ataxia, and areflexia were clinically consistent with GBS, however, his CSF pleocytosis was unusual for GBS. More importantly, cauda equina involvement with extensive enhancement on imaging, a band of intermittent pain in the right T8 dermatome, and the finding of a lytic bone lesion on the right iliac bone raise concern for an infectious vs neoplastic process giving rise to a polyradiculitis. Furthermore, CSF flow cytometry indicated large B-cell lymphoma vs follicular lymphoma. Right axillary lymph node excisional biopsy confirmed high-grade Burkitt's lymphoma. He was responsive to IVIG x5 and lower extremity weakness and numbness significantly improved. He was subsequently transferred to the comprehensive cancer center for further care. **Discussion and conclusion:** In conclusion, it is very rare for lymphoma to cause GBS, especially non-Hodgkin's lymphoma. Our case is peculiar, as GBS preceded the diagnosis of Burkitt lymphoma. Therefore, besides drug toxicity and nervous system infiltration, GBS should be considered a significant differential diagnosis of neurological manifestations preceding or following Non-Hodgkin's lymphoma.

#### **M278. Atypical Presentation of Chronic Inflammatory Demyelinating Polyneuropathy**

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**Introduction:** Chronic inflammatory demyelinating polyneuropathy (CIDP) is an acquired, immune-mediated neuropathy affecting peripheral nerves and nerve roots, typically characterized by a relapsing-remitting or progressive course of symmetric weakness of proximal and distal muscles. We present a unique acute onset CIDP with multiple cranial nerves involvement. **Case Presentation:** 28-year-old woman presented to our hospital with 14-day history of numbness and tingling, impaired coordination, hoarseness and areflexia. The patient reports viral infection 3 weeks prior to the symptom onset. MRI lumbar with contrast revealed thickening and enhancement of nerve roots and lumbar puncture

(LP) showed evidence of albuminocytologic dissociation. Gangliosides, autoimmune and HIV antibodies were negative. She was diagnosed with acute inflammatory demyelinating polyneuropathy (AIDP) and treated with intravenous immune globulin (IVIG) 2g/kg over 3 days with moderate improvement in her symptoms. The patient was discharged home, however, returned to the hospital 2 weeks after with worsening of neck weakness, proximal arm and leg muscle weakness, bilateral lower motor neuron type facial nerve palsy, and bilateral vocal cord paralysis. The patient received five sessions of plasma exchange (PLEX) with possible diagnosis of recurrent AIDP. She was discharged home with significant improvement of her symptoms. She returned to the hospital after a week with mild to moderate dysarthria, mild anisocoria, reduced sensation to pinprick in the right V3 distribution and tongue weakness in addition to worsening of prior symptoms. The patient admitted with CIDP diagnosis and received PLEX. Repeat LP revealed nucleated cell 4/uL and protein 257 mg/dL with negative cytology, flow cytometry, ACE, and Lyme. Electrodiagnostic study of one arm and leg revealed absent median and ulnar sensory responses, however, radial, sural and superficial peroneal sensory responses were normal. Median motor study revealed conduction block, temporal dispersion and slowed velocity. No response was recorded from the ulnar nerve. Needle examination was normal except chronic neurogenic changes in the distal leg muscles without ongoing denervation. The patient was discharged to rehab on weekly PLEX, prednisone 30 mg, and mycophenolate mofetil 1000 mg daily with significant improvement of her symptoms. **Conclusion:** CIDP typically does not present acute onset and multiple cranial nerves involvement. The most common affected cranial nerve is facial nerve and bulbar symptoms are very rare. The findings in this case report may prompt further understanding of clinical and imaging characteristics associated with acute onset CIDP and care measures that could help identifying patients at risk of severe course of the disease.

#### **M279. Baseline Data from a Phase 2 Clinical Trial of Repeated Intrathecal Autologous Adipose-Derived MSCs in ALS**

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**Background:** Mesenchymal stromal cells (MSCs) are being developed as a treatment for amyotrophic lateral sclerosis (ALS) and are hypothesized to exert their effects via growth factor secretion and immunomodulation. Following completion of a Phase 1 dose-escalation safety study, we initiated a multi-site Phase 2 clinical trial across Mayo Clinic to study the safety and efficacy of repeated intrathecal treatment with autologous adipose-derived MSCs in people living with ALS.

**Methods:** During a 3-month lead-in period subjects undergo a fat biopsy for isolation and expansion of MSCs. In this open-label design, subjects receive up to 4 injections (10-100 x 10<sup>6</sup> MSCs), spaced 3 months apart. The primary statistical analyses for efficacy endpoints will be: 1) average slope of ALSFRS-R progression in the study group will be compared with a cohort of subjects from the PRO-ACT ALS clinical trial database that will be matched for age, gender, and riluzole use (5 PRO-ACT subjects for every study subject), 2) average slope of ALSFRS-R progression in the 3 month lead-in period will be compared to the average slope of ALSFRS-R progression in the 12 month treatment period for study subjects. A Responder Analysis will be employed. Serial blood, cerebrospinal fluid, MRI spine imaging, and clinical phenotyping are collected for each enrolled subject. **Results:** As of March 2023, enrollment is complete with 75 subjects enrolled (Minnesota: 50, Florida: 19, Arizona: 6). 58 people with ALS have received at least one treatment, and 11 subjects are still receiving treatments. Mean age of subjects is 56.3 with a male predominance. 19% have familial ALS and the mean (range) ALSFRS-R at baseline is 37 (19-47). Mean (range) baseline plasma neurofilament light chain level is 83.7 pg/mL (16.3-373.8), which correlates with ALSFRS-R slope during the lead-in period. Intrathecal MSC therapy is generally well-tolerated with the most common adverse event being temporary back and leg pain. **Conclusions:** Our multi-site Phase 2 clinical trial of MSC therapy in ALS has completed enrollment, with anticipated reporting of top-line results in early 2024. The clinical trial endpoint data and biomarker analyses will help inform future studies of MSCs in ALS.

#### **M280. Cardiolipin Nanoparticles as Therapeutic Molecules for Providing Neuroprotection by Improving Mitochondrial Function in FTD/ALS**

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Several genes, such as *TADBP-43*, *SOD1*, *FUS*, *CHCHD10*, *VAPB*, *VCP*, and *OPTN* are mutated in FTD/ALS (frontotemporal dementia/amyotrophic lateral sclerosis) patient, and the protein products of these genes are related to mitochondrial health and function. Mitochondrial dysfunction is one of the common pathologies in neurodegenerative diseases. Especially the inner mitochondrial membrane (IMM) is damaged and disintegrated. Cardiolipin is an essential component of IMM and it is reduced in FTD/ALS. Due to its unique four fatty acid chains, it provides structural stability to IMM, which is critical for mitochondrial function. The long fatty acid chains of cardiolipin are susceptible to oxidation by free radicals, resulting in the disintegration of IMM. Therefore, we hypothesized that increasing cardiolipin levels could improve mitochondria function and neuronal health, and further investigated whether increased levels of cardiolipin via nanoparticle treatment had an impact on improving the stability of IMM and whether that would lead to improved health of diseased neurons in ALS/FTLD. High density lipoprotein (HDL) nanoparticles are a novel class of nanoparticles that can effectively deliver molecules to the

target cells and tissues. These nanoparticles are specifically designed to bind cells that express Scavenger receptor B1 (SR-B1) and deliver the molecular cargo to the recipient cells. The upper motor neurons (UMNs) that degenerate in ALS/FTLD patients express SRB-1. Therefore, we utilized nanoparticles to deliver cardiolipin to these diseased neurons both *in vitro* and *in vivo*. The prpTDP-43<sup>A315T</sup>-UeGFP mouse, is a well-characterized mouse models of ALS/FTD, and their fluorescently-labeled UMNs display mitochondrial dysfunction with IMM disintegration. We treated UMNs of prpTDP-43<sup>A315T</sup>-UeGFP mice with 5nM cardiolipin nanoparticles for 72 hrs, *in vitro*, using UeGFP mouse UMNs as healthy control. Likewise, we treated prpTDP-43<sup>A315T</sup>-UeGFP mice with 500nM cardiolipin nanoparticles by IP injections daily, from P60 to P120. Our ongoing studies suggest that cardiolipin treatment protects diseased UMNs both *in vitro* and *in vivo*. In addition, improving mitochondrial health leads to reduced astrogliosis and microgliosis in the motor cortex. In summary, our investigation lays the foundation for the assessment of cardiolipin-mediated therapy for improving mitochondrial stability, health, and function within the context of ALS/FTLD.

#### **M281. Case of Guillain-Barré Syndrome in Patient Receiving Checkpoint Inhibitor Therapy**

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**Introduction:** Immune checkpoint inhibitor (ICI) drugs are increasingly being used to treat advanced malignancies. However, immune mediated adverse effects have been commonly associated with their use. They typically involve GI, hepatic and endocrine systems, though on occasions neurological adverse events have been reported. We report a case of GBS that occurred while patient was on ICI therapy and evaluate current management strategy. **Case Summary:** A 69-year-old male with history of metastatic melanoma had developed Bell's palsy presumed to be secondary to Lyme disease and was treated with 3-week course of doxycycline. He had been on ipilimumab and nivolumab dual therapy, and this was reduced to nivolumab monotherapy one month prior to his presentation. He presented to Neurology with head drop, bilateral hand grasp weakness, difficulty sitting from a lying position, and dyspnea with mild exertion. Examination revealed right facial droop, quadriparesis with strength of 3/5, and areflexia. MRI brain, and spine showed multiple metastatic lesions. Nerve conduction studies were consistent with diffuse demyelinating motor sensory polyneuropathy. Albuminocytologic dissociation was noted on CSF analysis. Lyme IgG and IgM were positive. Pertinent negative labs included SSA, SSB, ANA, ANCA, B12, folate, TSH, and T4, which were all within normal limits. The patient was treated with 5 courses of plasma exchange for presumed diagnosis of GBS. Oncology started patient on steroids for potential neurotoxicity from checkpoint inhibitor treatment. Blood pressure and heart rate fluctuated significantly throughout his admission, consistent with dysautonomia. His negative inspiratory forces and forced

vital capacities remained stable, not requiring ventilator support. He stabilized with treatment and was eventually discharged to rehabilitation. **Discussion:** The pathophysiology of GBS secondary to ICI is thought to stem from overactivation of T-cells leading to autoimmune demyelination of peripheral nerves. The key difference in treatment of ICI induced versus classic GBS is that glucocorticoid treatment has been reported to have benefit in the ICI group when combined with traditional first line therapy of IVIG or plasma exchange as highlighted by our case report. On review of literature, GBS secondary to ICI has occurred anywhere from days to months following ICI therapy. It is therefore important to consider medication induced GBS in any patient on ICI therapy that develops acute onset of weakness and paresthesia associated with areflexia. Further studies are warranted to ascertain the role of corticosteroids in treating immune mediated neuromuscular complications of ICI.

**M282. Case Study: Botulism in Short Gut Syndrome**  
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**Introduction/Background:** Botulism toxicity from adult intestinal colonization is a rare condition but can be life threatening. Predisposing factors include previous bowel or gastric surgery, anatomical bowel abnormalities, or IBD. Botulism presents with cranial nerve palsies, ptosis, diplopia, fixed or dilated pupils, dysphonia, and dysphagia followed by descending symmetrical flaccid paralysis. We are reporting of case of a patient who developed botulism in the setting of short gut syndrome on TPN. **Case Report:** A 36 yo female with short gut syndrome on TPN presented to the hospital for dysarthria, ptosis, and dizziness. Patient initially had a stroke workup which was negative. Overtime, patient's dysarthria worsened with loss of gag reflex requiring patient to be intubated due to diaphragm weakness. There was concern for neuromuscular process and patient was transferred. Soon after, patient developed dilated pupils, loss of oculocephalic and corneal reflexes, neck flexion weakness and descending symmetrical weakness with loss of reflexes. Patient received 5 days of IVIG and methylprednisolone with no improvement. EMG/NC study was completed that showed deficit in the neuromuscular junction. Electrodiagnostic testing revealed reduced amplitudes in all motor nerves tested with relatively preserved sensory responses. Three Hz repetitive stimulation was performed but did not reveal any significant decrement. The patient was able to communicate and perform maximal exercise on the abductor pollicis brevis muscle, abductor digiti minimi, and tibialis anterior and rechecked motor amplitudes. There was a 40% increase in the tibialis anterior response but minimal change in the other motor amplitudes. We did not perform thirty Hz repetitive stimulation due to patient tolerance and pain. LP was done with normal protein and cell count. Infectious workup including VDRL, HSV, AFB/Fungal, and cultures were negative. Repeat LP was unchanged. Antibodies for Myasthenia Gravis, Lambert Eaton, ADAM, and Miller Fischer were negative. Specific antibodies were checked were the following: ACHR-

binding, ACHR-blocking, ACHR-modulating, Anti-MuSK, IgGM1, GQ1B. Botulism toxin was sent coming back positive. **Summary/Conclusion:** Botulism colonization in adult intestines is very rare, but we have shown a patient with an anatomic variant such as short gut syndrome on TPN can develop botulism toxicity.

**M283. Clingen's Neurological Disorders Clinical Domain Working Group: Advancing Gene-Disease Relationships through a Rigorous Validation Process**

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The Neurological Disorders Clinical Domain Working Group (Neurological Disorders CDWG), was established in 2023 as part of the larger Clinical Genome Resource (ClinGen). The Neurological Disorders CDWG is an international collaborative effort. The overarching goal is to validate gene-disease relationships and variant pathogenicity using established guidelines formulated by ClinGen. The Neurological Disorders CDWG currently encompasses neuromuscular, cognitive, and movement disorders, with active expansion into other areas e.g. cerebrovascular. There are a total of 8 active gene curation expert panels (GCEP) and variant curation expert panels (VCEP), focused on amyotrophic lateral sclerosis, congenital myopathies, Parkinson's disease, Charcot-Marie Tooth (CMT) and hereditary neuropathies and limb-girdle muscular dystrophies (LGMD), with panels focused on inherited prion disorders and CADASIL in active development. There is a critical need to determine the clinical validity of gene-disease relationships and variant pathogenicity of genes targeted for upcoming treatment strategies, especially genetic therapies, and to advance the practice of precision medicine. The Food and Drug Administration recognizes the variant interpretation process established by ClinGen, which is highly indicative of the rigor and transparency with which ClinGen expert panels are held for variant adjudication. Thus far, 50 genes were curated from the CMT GCEP, 45 genes by the congenital myopathies GCEP, 30 genes by the ALS GCEP, 24 genes from the LGMD GCEP and 7 genes by the Parkinson's disease GCEP. We will present a brief summary of the current efforts of these expert panels, as well as the CDWG's vision of areas of importance to target for future expert panel development. The main mission of the Neurological Disorder CDWG is to validate gene-disease relationships and variant pathogenicity to better inform clinical testing, reporting, and ultimately patient care. Participating clinicians, researchers, and biocurators directly contribute to this mission, including lasting impacts on shared understanding, data, knowledge and time to accelerate precision medicine in neurological disorders.

## M284. Clinical Implications of Specific Autoantibodies in Chronic Inflammatory Neuropathies

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**Background:** Chronic inflammatory neuropathies (CINs) can have varied clinical presentations and can be associated with several autoantibodies. The present literature suggests possible specific clinical phenotypes with some of these autoantibodies; however, the majority of these studies are based on small patient samples. A large-scale, in-depth analysis of the clinical, electrophysiological characteristics of CIN and treatment response is warranted to better understand the full ranges of the clinical spectrum of CIN associated with various autoantibodies. **Design/Methods:** We examined the electronic medical records of adult patients undergoing evaluation for possible immune-mediated neuropathies between 01/01/2012 and 04/01/2022 at our institution who were assessed for autoantibodies. Records with positive antibodies were reviewed for clinical presentations, laboratory work-up, electrodiagnostic studies, and treatment responses. They were grouped into categories of 1. Possible inflammatory neuropathy, 2. Probable inflammatory neuropathy, and 3. presentations incongruent with neuropathy. **Results:** A total of 1168 patients were evaluated for CIN-associated autoantibodies. Anti-trisulfated-heparin-disaccharide (TS-HDS) autoantibodies were present in 264 (22.6%) patients, anti-fibroblast-growth-factor-receptor-3 (FGFR3) autoantibodies were present in 198 (16.9%) patients, and anti-neurofascin (NF)-140/155 autoantibodies were present in 33 (2.8%) patients. Other autoantibodies were rare (<1%), and some patients had multiple autoantibodies. A few patients with anti-NF presented with focal sensorimotor dysfunction prior to subsequent bilateral involvement. Greater than 60% of patients with anti-NF autoantibodies had demyelinating features in electrodiagnostic studies. Anti-FGFR3 autoantibodies were associated with sensory involvement in >90% of cases, but motor dysfunction was also present in approximately 50%. Anti-TS-HDS-associated CIN had a more varied clinical presentation. There were differences in therapeutic response based on the associated autoantibodies as assessed by pre- and post-INCAT scoring; however, this was a retrospective study and the therapeutic decision was provider-specific. A direct, comparison to understand the impact of an intervention was not feasible. **Conclusions:** CIN associated with autoantibodies can have a variety of clinical phenotypes, and often present with overlapping motor and sensory presentations. While the pathogenicity of some of these autoantibodies is not well established, in a subset of patients, these autoantibodies can be helpful to assess clinical presentation, and therapeutic responsiveness.

## M285. Comparison of Diagnostic Efficacy of Electrophysiology and Magnetic Resonance Neurography in Patients with Nontraumatic Ulnar Mononeuropathy

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**Introduction:** The Ulnar nerve is the second most common nerve involved in mononeuropathies of the upper extremity. After clinical examination, neurologists opt for electrodiagnostic studies (EDSs) to determine the more precise nature of the lesion. Our study aimed to evaluate the diagnostic efficacy of magnetic resonance neurography (MRN) in cases with indeterminable EDS and its role in early diagnosis and management of ulnar mononeuropathies (UMNs). **Methods:** This prospective study enrolled consecutive patients with symptoms of non-traumatic UMN. A clinical exam followed by electrodiagnostic tests was performed in all patients. Patients with a localized ulnar nerve lesion on EDS underwent MRN. **Results:** Out of 83 symptomatic patients who underwent EDS, 70 (84%) were confirmed as cases of ulnar mononeuropathy. Based on EDS, 48 (68.5%) lesions were localized at the elbow, while 22 (31.5%) were localized at the wrist. Fifty patients underwent MRN, and a lesion was identified in 47 (94%). Mean ulnar nerve size and signal hyperintensity was recorded and compared with a standard control group. The mean ulnar nerve size was 0.31cm compared to the control group, which had a mean size of 0.08cm ( $p < 0.001$ ). Similarly, the mean signal hyperintensity in cases and controls was 3.4 and 1.1 ( $p < 0.01$ ). MRN had a sensitivity of 96% and a specificity of 85%. **Conclusion:** Our study concludes that the size and intensity signal was more significant in patients with UMN. Therefore, MRN can act as a surrogate tool to evaluate UMN of non-traumatic origin with ambiguous EDS results and better localization of lesions, thus aiding in targeted management.

## M286. Congenital Myasthenic Syndrome with Dual Loss-of-Function Variants in the $\alpha$ Subunit of Acetylcholine Receptor

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**Background:** The loss-of-function (LOF) variants in AChR subunits cause congenital myasthenic syndrome (CMS) by low expression of receptor, fast-channel kinetics, or both. The treatment options for LOF-CMS include an AChE inhibitor with or without 3,4-DAP and/or albuterol. Although the linker between transmembrane domains (M) 1 and 2 of AChR is known to determine desensitization, our previous study of a CMS mutation revealed that the M1-M2 linker in the  $\beta$  subunit also contributes to channel gating. Whether the M1-M2 linkers in the non- $\beta$  subunits play the same role is unknown, and no other CMS-causing mutation in this domain had been reported. **Methods:** Whole exome and Sanger sequencing, AChR expression in HEK cells,  $\alpha$ -bungarotoxin binding assay, single channel patch-clamp

recordings, and endplate potential (EPP) simulation. **Results:** A 3-year-old girl with severe CMS symptoms carries compound heterozygous variants of the AChR  $\alpha$  subunit: R313W in the M3-M4 linker, and G240W in the M1-M2 linker. The R313W and G240W mutants respectively reduced surface expression to 24% and 10% of wild type AChR and shortened the channel opening burst duration to 70% and 30% of the wild type. Simulation of EPP indicates that its amplitudes with mutant receptors are subthreshold for the muscle action potential. Combined treatment with 3,4-DAP, an AChE inhibitor, and albuterol markedly improved the patient's symptoms. Mutants at position 240 with substitution by residues with increased side-chain volume (G240A, G240P) or negatively charged (G240E, G240D) reduce the surface expression of the receptors to 31% to 44% of wild-type receptors, while positively charged mutants (G240R, G240K) do not alter the surface receptor expression. **Conclusions:** The patient's phenotype is due to two LOF mutations that both reduce surface AChR expression and shorten the length of channel opening bursts. Combined treatment with 3,4-DAP, an AChE inhibitor, and albuterol improved the patient's symptoms by respectively increasing ACh release, activating more AChRs, and likely stabilizing the post-synaptic region. Like the M1-M2 linker in the  $\beta$  subunit, the domain in the  $\alpha$  subunit also contributes to AChR activation. Increasing the side-chain volume and introducing negative charge in the M1-M2 linker hinders surface expression of the receptor, but the replacement by positively charged residues maintain the expression, indicating the residue size and polarity in the M1-M2 linker play a role in AChR expression.

#### **M287. Early B Cell Tolerance Defects in Anti-Neurofascin-155-Mediated Autoimmune Nodopathy**

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**Background:** In the majority of patients with chronic inflammatory demyelinating polyneuropathy (CIDP), no identifiable autoantibodies are present. However, autoantibodies against paranodal protein neurofascin 155 (NF-155) were recently identified in approximately 5% of patients fulfilling CIDP diagnostic criteria. Patients with anti-NF-155-mediated autoimmune nodopathy (AiN) present with a distinct clinical phenotype with predominantly distal involvement of weakness, sensory ataxia, and tremor, and they tend to respond better to B cell depletion therapy. NF-155 autoantibodies are predominantly of immunoglobulin G subclass 4 (IgG4). Our previous work in myasthenia gravis (MG) patients with muscle-specific tyrosine kinase (MuSK) autoantibody, another IgG4-mediated disease, showed that monoclonal antibodies (mAbs) bound to MuSK even when

they were reverted to their unmutated common ancestors, suggesting a breach in early B cell tolerance and self-reactive autoantibody production. Impaired fidelity of B cell tolerance checkpoints has been implicated in the pathogenesis of other autoimmune neurological diseases but remains unexplored in anti-NF-155-mediated AiN. **Methods:** Recombinant MABs from single B cells from the new emigrant (NE) and mature naïve (MN) compartments from patients with NF-155-mediated AiN were generated using a well-established protocol. The frequency of polyreactive clones in the NE compartment was measured by ELISA against dsDNA, insulin, and lipopolysaccharide, to assess the fidelity of the central B cell tolerance checkpoint. Furthermore, we performed gene expression profiling paired with full-length B cell receptor repertoire analysis at the single cell level from these early B cell populations between patients with NF-155-mediated AiN and healthy control. **Results:** 3 patients with NF-155-mediated AiN (age range 43-61 year) and one healthy young control were included in this study. A total of 60 and 58 unique clones of monoclonal antibodies were generated from the NE and MN B cells, respectively. Thirty-seven percent ( $\pm 11.5\%$ ) of clones from the NE B cells and 31.5% ( $\pm 2.5\%$ ) of clones from the MN B cells were polyreactive, compared to expected 5-11% polyreactivity from healthy controls (p-value 0.02 and 0.025 respectively). Phenotyping of the NE and MN B cells at the single-cell level by simultaneously profiling gene expression and full-length paired B-cell receptors from one healthy control and one patient with NF-155-mediated AiN patient showed aberrant expression of inflammatory markers including PI3K/Akt pathway, TXNDC5, MZB1. **Conclusion:** Our findings suggest that NF-155-mediated AiN is associated with early checkpoint tolerance defects. Further studies are warranted to understand the underlying pathomechanism driving such dysfunction.

#### **M288. Evaluation of Length of In Hospital Stay and Treatment Based Complications in Patients Hospitalized Due to Exacerbation of Myasthenia Gravis**

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**Background:** Myasthenia Gravis (MG) is a complex autoimmune neuromuscular disorder that affects skeletal muscles. 10-20% of MG patients suffer from a severe disease and recurrent exacerbations leading to hospitalization. This study aimed to determine the pre-treatment and treatment measures during the exacerbation of MG and their effect on subsequent disease prognosis and length of hospital stay (LOS). **Methods:** In this retrospective study, we analyzed the

documents of patients admitted with MG exacerbation in five tertiary care hospitals in Pakistan. The following variables were documented for disease prognosis and their effect on LOS: age, sex, BMI, comorbidities, Myasthenia Gravis Foundation of America (MGFA) class at the time of diagnosis of MG, and during admission due to exacerbation, treatment history, cause of exacerbation, thymoma/thymectomy, management after hospital admission including drugs, plasmapheresis and intubation, LOS, and any complication arising due to inpatient management. **Results:** One hundred and seventy-eight admissions were identified due to MG exacerbation. Plasmapheresis, steroid pulses, and intubation correlated positively with LOS ( $p < 0.005$ ) during crisis management. Medication compliance, thymectomy, and lower MGFA class at exacerbation correlated negatively ( $p < 0.001$ ) with LOS. Male sex, older age, and comorbid conditions resulted in a more extended hospital stay ( $p < 0.005$ ). Six hospitalizations resulted in death. **Conclusions:** Our study identified the factors that may increase mortality in MG exacerbation. It may help clinicians and scholars look for treatment gaps and pave pathways for developing novel targeted therapies.

#### M291. Higher Glycemic Index Diet is Associated with Slower Disease Progression in Amyotrophic Lateral Sclerosis

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**Objective:** Prior studies suggest that high caloric diet may be beneficial in attenuating advancement of amyotrophic lateral sclerosis (ALS), however, key macronutrients have not been identified. We examined whether dietary macronutrient (carbohydrate, protein, and fat) content and glycemic load and index are associated with the rate of progression and length of survival among the ALS Multicenter Cohort Study of Oxidative Stress (COSMOS) study participants. **Methods:** All 358 participants [60% male, mean (SD) age 60 (10) years] with a confirmed diagnosis of sporadic ALS enrolled in COSMOS were included in the current study. We evaluated baseline macronutrient intake in relation to change in total revised ALS functional rating scale (ALSFRS-r), and tracheostomy-free survival using linear regression and Cox proportional hazard models. Baseline age, sex, disease duration, diagnostic certainty, body mass index (BMI), ALSFRS-r, ALSFRS-r bulbar sub-score and forced vital capacity (FVC) were included as covariates. **Results:** In univariable linear regression, total calories, carbohydrate, protein, or fat intake were not significantly associated with ALSFRS-r change at 3-months. However, baseline higher glycemic index (GI) was associated with slower progression of

ALSFRS-r at 3-month follow up such that one unit of GI increase was associated with 0.19 less decline of ALSFRS-r at 3-month follow up ( $\beta = -0.19$ , 95% Confidence Interval (CI) [-0.30, -0.07],  $p = 0.0015$ ). Baseline ALSFRS-r bulbar sub-score was associated with GI and after adjusting for this, GI was still associated independently with 3-month decline of ALSFRS-r. Higher baseline glycemic load was also associated with slower progression of ALSFRS-r at 3-month follow up although the association was weaker than GI and not statistically significant ( $\beta = -0.012$ , 95% Confidence Interval (CI) [-0.02, 0.0002],  $p = 0.05$ ). In a multivariable Cox proportional hazard model, higher GI was associated with longer tracheostomy-free survival (Hazard Ratio 0.96, 95% CI [0.93, 0.99]  $p = 0.03$ ) after adjusting for age, sex, diagnostic certainty, disease duration, bulbar onset, baseline ALSFRS-r total score and FVC. **Conclusion:** Higher dietary GI is associated with slower functional decline and longer survival in patients with ALS.

#### M292. Lifesaving Treatments for Spinal Muscular Atrophy: Global Access and Availability

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**Background:** Spinal muscular atrophy (SMA) is a neurodegenerative disorder manifesting with progressive muscle weakness and atrophy. SMA type 1, historically fatal within the first two years of life, is now treatable with therapies targeting splicing modification and gene replacement. Nusinersen, risdiplam, and onasemnogene abeparvovec-xioi are proven to improve survival, motor strength, endurance, and ability to thrive, and have all been recently approved by major regulatory agencies. While these therapies have revolutionized the world of SMA, they are associated with a high economic burden, and access to these therapies is limited in some countries. The primary objective of this study was to compare the availability and implementation of treatment for SMA from different regions of the world. **Methods:** In this study, we surveyed healthcare providers from around the world regarding their experiences caring for patients with SMA. The primary outcomes were providers' survey responses on newborn screening, drug availability/access, barriers to treatment, and related questions. **Results:** Twenty-four providers from 21 countries with an average of 26 years of experience in treating patients with SMA responded to the survey. Nusinersen was available in 19 of the 21 countries, while risdiplam and onasemnogene abeparvovec-xioi were available in 15 of these countries. Our survey showed that while genetic testing is usually available, newborn screening was only available in 8 of the surveyed countries, with access limited by region in 5 countries (Australia, Brazil, Canada, Japan, and United States). The provider-reported treatment cost also varied widely between nations, even among countries within the Eurozone. Identified barriers to treatment included cost of medications and diagnostic testing (58% of respondents), difficulties in obtaining insurance authorization/reimbursement (33%), timely diagnosis (21%), lack of medication coverage by insurance (17%), lack of multidisciplinary teams (13%), limited infusion sites, and lack of follow-up care. **Conclusions:** This study highlights the global inequality in managing patients with SMA. The spread of newborn screening is an essential first step in improving access to lifesaving treatment modalities. With the advancement of neurotherapeutics, an increasing number of rare genetic diseases will soon be treatable, and novel approaches will be needed to address the global inequality in access to care.

### M293. Long-Term Outcomes of Offspring of Mothers with Fetal Acetylcholine Receptor Antibodies

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Rare cases of arthrogryposis multiplex congenita (AMC) can be strongly associated with maternal antibodies targeting the fetal acetylcholine receptor (AChR); these antibodies paralyse the baby *in utero* which leads to fixed joints and other defects. More recently children with milder myopathic presentations, termed fetal AChR inactivation syndrome (FARIS), have been identified in rare families. This study brought together clinical and antibody data on 29 novel families from a multi-national cohort (n=46 cases; 24 centres; 12 countries). All mothers (n=30) had AChR antibodies (by definition), and most of the maternal sera bound more strongly to the fetal AChR than to the adult AChR and, remarkably, 50% of the mothers had no diagnosis of MG. *In utero*, 15.2% had severe AMC and the pregnancies were terminated. Less severe were antenatal contractures (26.1%), polyhydramnios (51.1%), reduced fetal movements (26.2%), or intrauterine growth retardation (17.9%). Postnatally, four (8.7%) died during early life usually from respiratory failure. Thereafter, weakness, contractures, bulbar and respiratory involvement were prominent but improved gradually over time. Striking longer-term features in survivors were facial (73.5%), velopharyngeal insufficiency (75%), feeding difficulties (44.4%) and peripheral weakness (43.8%). In addition, there were unexpected features particularly hearing loss (37.5%), diaphragmatic paresis (14.3%), pyloric stenosis (8.1%) and CNS involvement (17.5%). Better outcomes, including fewer offspring deaths, were achieved for offspring of the 15 mothers who were treated with combined immunotherapies during pregnancies and oral salbutamol, used empirically in 16/37 (43.2%) offspring, resulted in symptom improvement in 81.3%. Maternal AChR antibody-associated disorders are not necessarily fatal, mimic other neuromuscular disorders, and are probably more common than previously recognised. Maternal AChR antibody testing is widely available and could easily be undertaken in any mothers whose babies show evidence of unexplained fetal growth retardation, fixed joints or polyhydramnios, with the possibility of further investigation.

#### M294. Long-Term Safety, Tolerability, and Efficacy of Subcutaneous Efgartigimod PH20 in Patients with Generalized Myasthenia Gravis: Interim Results of the ADAPT-SC+ Study

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**Objective:** Evaluate long-term safety, tolerability, and efficacy of subcutaneous (SC) efgartigimod PH20 (coformulated with recombinant human hyaluronidase PH20) in patients with generalized myasthenia gravis (gMG) enrolled in the ADAPT-SC+ open-label extension study. **Background:** In ADAPT-SC, efgartigimod PH20 SC was shown to have non-inferior total IgG reduction to efgartigimod IV (approved in US, Japan, and EU) resulting in similar clinical improvement in patients with gMG. Patients completing ADAPT-SC, or enrolled in ADAPT+, were eligible to participate in the ongoing open-label extension, ADAPT-SC+. **Design/Methods:** Efgartigimod PH20 SC 1000 mg was administered in cycles of 4 weekly injections. Subsequent cycles were initiated at least 28 days from the last dose based on clinical evaluation. Clinical efficacy was assessed utilizing the Myasthenia Gravis Activities of Daily Living (MG-ADL) scale. **Results:** As of March 2022, 164 participants received ≥1 dose of efgartigimod PH20 SC. Patients received ~3 cycles over a mean (SD) study duration of 170 (59) days, resulting in 72 patient-years of observation. Adverse events (AEs) were predominantly mild to moderate. The most frequent AEs were injection site erythema (25.6%), headache (15.2%), and COVID-19 (11.6%). All injection site reactions (ISRs) were mild/moderate and did not lead to treatment discontinuation. ISRs typically occurred within 24 hours of administration, resolved spontaneously, and incidence decreased with subsequent cycles. Two deaths were reported (metastatic renal cancer and COVID-19); neither were deemed efgartigimod-related per investigator. Improvement from cycle baseline in MG-ADL total score (mean [SE] improvement at week 4: -4.0 [0.25]) was observed in cycle 1, with consistent and repeatable improvements seen in subsequent cycles. Speed of onset, durability, and repeatability of improvements in MG-ADL were similar to those with efgartigimod IV during ADAPT/ADAPT+. Participants also



demonstrated improved quality of life, as determined by improvements in MG-QOL15r and EQ-5D-5L VAS scores, during each treatment cycle. **Conclusions:** Results suggest that treatment with multiple cycles of efgartigimod PH20 SC was well tolerated, with no new safety signals identified. Observed safety and efficacy profile was consistent with ADAPT/ADAPT+.

#### **M296. Monitoring and Prognostication of Dysferlinopathy Based on Novel Biomarkers: Myostatin and Follistatin**

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**Background:** Dysferlinopathy includes a spectrum of autosomal recessive muscle dystrophy characterized by gradual muscle weakness and atrophy. Myostatin is a skeletal muscle protein involved in growth regeneration inhibition. Follistatin is another endogenous protein that opposes the action of myostatin. This study sought to evaluate the predictive value of myostatin and follistatin as novel biomarkers for monitoring and prognosis of dysferlinopathy. **Methods:** This prospective study enrolled consecutive patients and controls for a follow-up period of two years. A clinical exam, routine laboratory investigations, and a baseline MRI was done. Blood samples were drawn to quantify myostatin with ELISA in 68 patients of dysferlinopathy and 34 controls. Follistatin was quantified in 60 patients and 29 controls. Subsequently, these biomarkers were correlated with the contractile muscle's cross-sectional area, muscle fat, and motor functions. Multi-variate logistic regression analysis evaluated the association of confounding variables. **Results:** Myostatin levels were significantly raised in all patients with dysferlinopathy compared to the controls ( $p < 0.05$ ). However, myostatin correlated negatively with motor function or follow-up MRI changes. Serum creatine kinase, C-reactive protein, and male sex were independent factors related to raised myostatin concentration. After endogenous antagonism by follistatin was considered, myostatin predicted ambulatory status at baseline and during a two-year follow-up period ( $p < 0.001$ ). **Conclusions:** Our study concluded that these proteins are potential muscular dystrophy biomarkers in monitoring and prognosis of dysferlinopathy and can be the target of novel therapies in the future.

#### **M297. National Trends in the Utilization of Thymectomy for Myasthenia Gravis**

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**Background:** Thymectomy is a well-established treatment for non-thymomatous myasthenia gravis, however, it was not

until a randomized control trial in 2016 that the transsternal approach was found to improve patient outcomes. Currently, minimally invasive transthoracic approaches are also being utilized. Therefore, our study aimed to investigate whether the number and types of thymectomy for non-thymomatous myasthenia have changed over time. **Methods:** To investigate whether there has been any change in the number and types of thymectomy for non-thymomatous myasthenia, we utilized the National Inpatient Sample (NIS) database from 2012-2019. Our study included patients aged 18 years and above, who had a diagnosis of myasthenia, and excluded those with a thymoma diagnosis. Our primary objective was to evaluate the number of thymectomies performed over time, including both transsternal and transcervical approaches. Additionally, we examined several predictive factors that may have influenced whether thymectomy was performed, such as age, gender, race, insurance payor, hospital size and teaching location, and elixhauser comorbidity index. **Results:** The total utilization of thymectomy for myasthenia gravis increased over time, by 8.43% per year from 2014-2019 ( $p < 0.002$ ). The transsternal approach increased by 6.88% per year ( $p < 0.001$ ) from 2012-2019 and transcervical approach increased by 5.58% per year ( $p < 0.043$ ) from 2012-2019. In a multi-variate regression, several factors increased the odds of a having a thymectomy for patients with myasthenia gravis: private insurance (OR 2.28, 95% CI 2.09 to 2.48), 76<sup>th</sup>-100<sup>th</sup> income zip code (OR 1.15, 95% CI 1.04 to 1.28), medium (OR 1.57, 95% CI 1.35 to 1.83) and large bed size (OR 2.34, 95% CI 2.04 to 2.69), urban (OR 2.31, 95% CI 1.71 to 3.12) and urban teaching hospitals (OR 3.76, 95% CI 2.85 to 4.95). Other factors decreased the odd of having a thymectomy: age (OR 0.98, 95% CI 0.97 to 0.98), female (OR 0.77, 95% CI 0.72 to 0.83), southern region (OR 0.88, 95% CI 0.79 to 0.98), and elixhauser comorbidity index (OR 0.83, 95% CI 0.81 to 0.84). **Discussion/Conclusions:** Thymectomy is being performed more frequently for non-thymomatous myasthenia gravis. There are several disparities in thymectomy utilization that warrant further investigation.

#### **M299. NMD670, a Novel First-in-Class Skeletal Muscle CIC-1 Inhibitor, Improves Symptoms of Myasthenia Gravis: A Randomized, Single-Dose, Double-Blind, Placebo-Controlled, Study**

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NMD670 is a novel first-in-class neuromuscular transmission enhancer working through selective inhibition of the skeletal muscle CIC-1 chloride ion channel, which is being developed

for the treatment of patients with myasthenia gravis (MG) and other neuromuscular disorders. The objective of the study was to investigate safety and tolerability, pharmacokinetics, and pharmacodynamics of single oral doses of NMD670 in patients with MG. This was a randomized, double-blind, placebo-controlled, three-way crossover study of two dose levels of NMD670 (400mg and 1200mg) and placebo. Pharmacodynamic outcomes were assessed pre- and post-dose (3-5h) on each of the three treatment days and included Quantitative Myasthenia Gravis (QMG) score and electrophysiological assessments. A total of 12 patients were enrolled and completed the study; mean age of 58yr (range: 36-78), 7 female patients, and a mean baseline QMG score of 9 points (SD: 3.6). NMD670 was safe and well tolerated. No serious or severe TEAEs were reported and the incidence of TEAEs was similar across treatment arms. Plasma concentrations increased with increasing dose. Time to maximal concentration was ~2h and terminal half-life was ~5h for both doses. Improvements in QMG total score and individual items were observed with NMD670 vs. placebo. The change from baseline vs. placebo for QMG total score [95% CI] was -1.5 points [-2.8;-0.1],  $p=0.03$ , for the overall NMD670 400mg treatment arm and -1.0 point [-2.3;0.3],  $p=0.14$ , for the overall NMD670 1200mg treatment arm. The largest treatment effect observed 5h post-dose was of -1.7 points [-3.3;-0.2],  $p=0.02$  for NMD670 400mg vs. placebo. Importantly, clinically relevant improvements on QMG of 2 points or more vs. placebo was achieved for 42-50% of patients dependent on dose level and timepoint. The QMG item of right-hand grip strength was improved overall by 1.4kg [-0.8;3.6],  $p=0.19$ , for NMD670 400mg and 2.8kg [0.7;5.0],  $p=0.01$ , for NMD670 1200mg vs. placebo. Similar directional changes were observed in left hand grip strength, ability to keep leg outstretched, ptosis, double vision, and dysarthria. Changes in electrophysiological parameters further confirmed pharmacological target engagement. In conclusion, NMD670 was safe and well tolerated and showed statistically significant and clinically relevant improvements in QMG in patients with MG, despite mild baseline severity. These results represent the first proof-of-mechanism for CIC-1 inhibition in MG which warrants further investigation of NMD670 in MG patients with increased severity and in other neuromuscular diseases.

### M300. PET Imaging of Neuroinflammation in ALS

#### Patients Using $^{18}\text{F}$ -OP-801, a Novel Nanoimaging Agent

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Inflammation plays a central role in the pathogenesis of many neurological diseases. Real-time mapping of

neuroinflammation in the CNS would aid diagnosis, monitoring of disease progression and response to therapies. Positron emission tomography (PET)/magnetic resonance imaging is ideally suited to this purpose because of its ability to superimpose signal onto spatial coordinates in the CNS. PET imaging that targets immune cell markers such as TSPO has demonstrated potential across a wide range of neurological disorders. Unfortunately, current PET imaging compounds suffer from low signal-to-noise ratio secondary to lack of specificity for inflammatory cells in regions of active disease pathology. We are developing  $^{18}\text{F}$ -OP-801, a novel hydroxyl dendrimer PET nanoimaging agent that readily traverses selective biological barriers in regions of inflammation. Studies in animal models of neuroinflammation show that  $^{18}\text{F}$ -OP-801 and other hydroxyl dendrimer-based precision nanomolecules are selectively taken up by activated microglia and macrophages in the CNS, leading to improved signal-to-noise ratio compared to current PET imaging agents. Here, we present data from an ongoing Phase 1/2 study evaluating the safety, tolerability and biodistribution of  $^{18}\text{F}$ -OP-801 in healthy volunteers and ALS patients (NCT05395624). The first stage of the trial studied whole body biodistribution, biodosimetry and clearance of single IV doses of  $^{18}\text{F}$ -OP-801 in healthy volunteers (N=5). The second Phase focuses on brain and cervical spinal cord uptake of  $^{18}\text{F}$ -OP-801 in ALS patients (N=10) and age-matched healthy volunteers (N=10). Subjects in this stage receive either 1 IV dose or 2 IV doses of  $^{18}\text{F}$ -OP-801 separated by several days. Semi-quantitative standardized uptake value (SUV) analysis of attenuation-corrected PET/MR brain images is conducted by placing regions of interest (ROIs) *a priori* in target brain regions associated with ALS pathology vs. background regions. ROIs from disease regions in ALS patients are compared to normal brain regions in the same patients and to corresponding brain regions in healthy, age-matched controls. Test/retest repeatability and correlations between  $^{18}\text{F}$ -OP-801 signal distribution/intensity and serum NfL, ALSFRS-R and PUMNS at Baseline will also be studied. IV administration of  $^{18}\text{F}$ -OP-801 to healthy volunteers was safe and well-tolerated. Clearance was predominantly renal, with little uptake in other organs including the brain. Imaging and correlation data from ALS patients vs. healthy, age-matched controls will also be presented. These results will provide proof of concept for use of  $^{18}\text{F}$ -OP-801 as a PET imaging agent to detect regions of neuroinflammation.

### M301. Phase 3b Extension Study to Evaluate the Efficacy and Safety of 2 Dosing Regimens of Oral Edaravone in Patients with Amyotrophic Lateral Sclerosis

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**Introduction:** Intravenous edaravone (Radicava®/Radicut) was shown to slow the rate of physical functional decline in amyotrophic lateral sclerosis (ALS). This ongoing, multicenter, phase 3b, double-blind, parallel group, randomized extension study is evaluating 2 dosing regimens of Radicava ORS® (edaravone) oral suspension. Oral edaravone was approved by the United States Food and Drug Administration for use in patients with ALS in May 2022 and gained approval in late 2022 in Canada and Japan. **Objectives:** Study MT-1186-A04 (NCT05151471) is evaluating and comparing the long-term safety, efficacy, and tolerability of 2 oral edaravone dosing regimens for up to an additional 48 weeks following the end of Study MT-1186-A02 in patients with ALS, comprising a total duration of up to 96 weeks. **Methods:** Study MT-1186-A04 will evaluate 2 dosing regimens of oral edaravone (105-mg dose): group 1 will have oral edaravone administered once daily for each 28-day cycle; group 2 will have oral edaravone administered for 10 days followed by placebo for 18 days in each 28-day cycle. Dosing in both groups will continue up to 48 weeks. Study MT-1186-A04 is anticipated to include approximately 300 adult patients who have completed Study MT-1186-A02. The primary objective is to evaluate the efficacy of each dosing regimen based on the date of randomization in Study MT-1186-A02 to at least a 12-point Revised ALS Functional Rating Score decrease or death, whichever happens first, over the course of the study. **Results:** Ongoing. **Summary/Conclusion:** This extension study will provide important information on the safety, efficacy, and tolerability of 2 oral edaravone dosing regimens in patients with ALS. **Sponsorship:** Mitsubishi Tanabe Pharma America, Inc. **Acknowledgments:** p-value communications provided editorial support.

### M302. Predictors of Longer Mechanical Ventilator Use among Amyotrophic Lateral Sclerosis Patients

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**Purpose:** Respiratory failure is one of the leading causes of death among Amyotrophic Lateral Sclerosis (ALS) patients. The timely use and length of mechanical ventilation (MV) use can impact survival. We aim at identifying key factors influencing the need for longer mechanical ventilation among hospitalized ALS cases. **Methods:** A retrospective study was conducted via the 2016 to 2020 National Inpatient Sample (NIS). Long-term ventilator usage among ALS patients was identified as MV usage >96 hours. Logistic models were applied to find factors influencing MV duration. **Results:** Around 61,600 cases of ALS needed hospitalization in the US between 2016 to 2020, with 16,250 (26.4%) requiring MV. Of all cases of MV, 61.3% (9,965 patients) used it for >96 hours (long-term) and were younger (61.38 vs. 62.01 years) compared to short-term (≤ 96 hours) users. Sepsis (aOR 2.085, p<0.01), Acute Kidney Injury (AKI) (aOR 1.317, p<0.01), and anemia (aOR 1.781, p<0.001) increased the length of MV use. However, smoking (aOR 0.814, p<0.001), history of stroke (aOR 0.818, p = 0.027), Chronic Kidney Disease (CKD) (aOR 0.824, p=0.033), and alcohol abuse (aOR 0.525, p<0.001) were associated with a shorter use. Weekend admissions (aOR 0.968, p=0.398 vs weekday admissions), Females (aOR 1.031, p=0.393), history of heart failure (aOR 1.100, p=0.068), cirrhosis (aOR 1.484, p=0.105), hypertension (aOR 0.932, p=0.054), and diabetes (aOR 1.073, p=0.081) showed no statistical difference. Most ALS patients requiring MV use were between ages 45-65, (47.9%, 7,790 cases out of 16,263 but analysis between all age groups showed no statistically significant difference. Compared to Medicare beneficiaries, privately insured patients (aOR 1.144, p=0.005) showed an increased need for long-term MV. However, no relationship existed between Medicaid users (aOR 1.103, p=0.104) and Medicare beneficiaries. Some racial differences existed, with higher odds among Blacks (aOR 1.166, p=0.001 vs Whites) and Hispanics (aOR 1.232, p<0.001 vs Whites). Finally, 27.1% of all cases with short-term MV use died during hospitalization, while 12.6% of patients with long-term use died (p<0.01). Among the non-survivors, the patients with shorter MV use were also older (65.38 years vs. 64.17 years, p<0.01). **Conclusion:** Sepsis, AKI, and anemia increased the length of time of mechanical ventilation usage while patients with a history of stroke, smokers, alcoholics, and CKD revealed a shorter length of time. Also, diabetes, hypertension, and cirrhosis showed no difference. Blacks and Hispanics also

had higher odds of requiring MV long-term. Long-term MV use recorded a lower mortality rate.

### **M303. Prognostication of Disease Severity and Mortality in Patients with Amyotrophic Lateral Sclerosis Based on Peak Expiratory Flow Measurements by Household Peak Flow Meter**

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**Introduction:** Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease, with most patients dying three to five years after diagnosis. The most common cause of fatality is respiratory failure. This study sought to screen the prognosis-related pulmonary function indices and investigate the predictive value of peak expiratory flow (PEF) in the prognostication of severity and mortality of patients with ALS. **Methods:** Two hundred patients were enrolled in the discovery cohort, and their demographic and clinical parameters were documented. Baseline spirometry was done using a master screen pulmonary function test (MS-PFT). Eighty-four newly diagnosed ALS patients were enrolled in the validation cohort, and PFTs were performed concomitantly using MS-PFT and a household peak flow meter. **Results:** We studied eleven pulmonary function indices, among which FVC, PEF, FEV1, MVV, and MEF75% were found to be independent predictors of mortality in ALS with respiratory complications. The values of PEF were positively associated with the severity of the disease (ALSFRS-R score,  $r_s = 0.731$ ,  $p < 0.005$ ) and negatively related to the rate of the disease progression ( $\Delta$ ALSFRS-R,  $r_s = -0.442$ ,  $p < 0.005$ ). We also found that the values obtained by the household peak flow meter were highly correlated with the MS-PFT spirometer ( $p < 0.001$ ). **Conclusion:** Our study concludes that PFTs are crucial in predicting the prognosis of ALS patients. A household peak flow meter, which measures PEF accurately, can be used to monitor for any respiratory compromise in these patients.

### **M304. RAD23 Enhances the Degradation of Proteins That Cause Familial Amyotrophic Lateral Sclerosis (ALS)** **Anahid Hamidianjabromi, M.D., Casey Dalton, B.S., Robert Gordon Kalb, M.D.** Department of Neurology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA.

Accumulation of aggregated disease-proteins in neurons is a cardinal feature of neurodegenerative diseases such as ALS and is direct evidence for abnormal protein homeostasis. Enhanced degradation of disease proteins is a promising strategy for re-establishment of proteostasis and neuronal health.

RAD23 was originally identified in a screen for proteins in yeast required for resistance to the toxicity of ultraviolet radiation and subsequently discovered to be a shuttle factor that presents ubiquitinated clients to the proteasome for degradation. Mammals have two orthologs of RAD23, rad23a and rad23b, that have similar overall structure. They have both redundant as well as unique cell biological activities. To determine if either protein influences a familial ALS causing protein, we expressed G85R superoxide dismutase (SOD) in primary rat cortical neuron cultures (lacking astrocytes) with or without RAD23A. We find that the overall abundance of mutant SOD (mSOD) is significantly reduced by co-expression of RAD23A. We hypothesized that RAD23A reduces the abundance of mSOD by accelerating its degradation. To test this idea, we co-incubated mSOD + RAD23A with the proteasome inhibitor MG132 or the autophagy inhibitor bafilomycin A1. Each inhibitor partially reverses the effect of RAD23A on mSOD abundance. These results suggest that RAD23A promotes degradation of mSOD by both the proteasome and autophagy. Going forward we will determine whether RAD23B has a similar effect on mSOD abundance and whether the effects of RAD23 are also seen with another familial ALS causing protein, TDP43. The identification of factors that reduce the abundance of toxic proteins in ALS may have therapeutic implications.

### **M305. Ravulizumab-Responsive Seronegative Myasthenia Gravis**

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Myasthenia gravis (MG) is a neuromuscular disorder characterized by impaired cholinergic transmission at the neuromuscular junction, resulting in fluctuating muscle weakness. More than 80% of the patients test positive for acetylcholine receptor (AChR) binding/blocking/modulating or Muscle-specific kinase (MuSK) autoantibodies. Those testing negative for both are called seronegative or 'double' seronegative cases. Ocular symptoms are observed to be more prevalent in this group and clinical courses are similar to AChR positive cases. In seronegative MG patients, electrodiagnostic studies remain the mainstay of diagnosis. Treatment options include pyridostigmine, corticosteroids, thymectomy, azathioprine, mycophenolic acid, cyclosporine, tacrolimus among others. Recently, several new treatments have demonstrated benefit in patients with generalized myasthenia gravis. These include eculizumab and ravulizumab, both C5 complement inhibitors and efgartimod, an Fc receptor inhibitor. Because the clinical trials leading to FDA approval included only AChR antibody positive patients, the FDA approval of treatment is limited to AChR positive patients. Their benefit in seronegative patients is unknown. Here we present a young woman who developed diplopia with ptosis at the age of 17 years. She repeatedly tested negative for AChR as well as for MuSK antibodies, and striated muscle antibodies. She was eventually diagnosed with seronegative generalized myasthenia gravis. Genetic testing for congenital MG was negative as

well. Since onset she has had baseline vertical and horizontal diplopia, ptosis and bifacial weakness with more recent development of dysarthria, dysphagia and extremity weakness. She remained symptomatic despite thymectomy at the age of 20 years and trials of azathioprine, mycophenolic acid, and cyclosporine. IVIG infusions offered only moderate benefit. She stayed in relative remission with prednisone and rituximab until 2019 (MG composite scores ranging from 8 to 15) but then required multiple hospitalizations for exacerbations with predominant bulbar symptoms. Eculizumab was started in June 2021 with negligible improvements in MG composite scores and modest improvements in MQ-QOL15r. Due to the inconvenient dosing regimen and lack of clear benefit, she was transitioned to Ravulizumab in December 2022. Following 3 infusions over 3 months, she sustained an improvement in MG-QOL15r (29 → 0) as well as MG composite scale (8 → 0). At her latest clinic visit, she was symptom-free for the first time in 40 years. While the follow-up period so far has been brief, this case indicates that Ravulizumab may be useful for treatment-refractory seronegative MG patients.

#### **M306. Results from First-in-Human Study of VRG50635, a PIKfyve Inhibitor for Treatment of ALS, in Healthy Adult Volunteers**

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Amyotrophic lateral sclerosis (ALS) is a disabling and fatal disorder characterized by progressive paralysis of voluntary muscles due to loss of motor neurons in the brain and spinal cord. Verge has identified a pathological deficiency in pathways from patients with sporadic and familial ALS. Within dysregulated pathways, the CONVERGE AI/machine learning platform identified PIKfyve/FIG4 as the top corrective drug target candidate. PIKfyve, a phosphoinositide kinase, has been implicated in regulating endolysosomal trafficking, exocytosis, and autophagy. Inhibiting PIKfyve improves motor neuron health and survival in preclinical ALS models (Y Shi Nature Medicine 2018; ST Hung Cell 2023). VRG50635 is a brain penetrant, orally administered small-molecule PIKfyve inhibitor under investigation for treating all forms of ALS. The Phase 1 study of VRG50635 (EudraCT: 2022-002747-22) is a first-in-human, placebo-controlled study in healthy adults investigating the safety, tolerability, pharmacokinetics (PK), and pharmacodynamics of VRG50635 in single (SAD) and multiple (MAD) ascending dose cohorts. Here we present preliminary blinded safety and PK data. 46 healthy subjects, randomized into five SAD cohorts, received VRG50635 at 60, 180, 540, and 1000 mg or placebo. A pilot food effect investigating the PK of VRG50635 (prodrug) and its active metabolite, VRG50468,

was completed in fasting (SAD cohorts 1, 2, and 3), high-fat meal (SAD cohort 3 crossover), or regular meal (SAD cohorts 4 and 5; MAD cohort 1) cohorts. Preliminary blinded safety and tolerability data indicate that VRG50635 has been well tolerated. No SAEs or significant AEs have been reported. All AEs were low grade (97% G1), with treatment-emergent AEs observed in 39% of subjects. There have been no study withdrawals or discontinuations. No dose related or clinically significant trends have been observed in vital signs, ECGs, physical examinations, or laboratory parameters. Following administration of VRG50635, the prodrug concentrations were generally below the limit of quantification (1 ng/mL). PK of VRG50468 showed dose-proportional increases in C<sub>max</sub> and AUC. A positive food effect was observed with both high-fat and regular meals. A terminal half-life of approximately 37 hours supports once/day dosing and is consistent with increasing C<sub>max</sub> and AUC observed in repeated daily dosing in the MAD1 cohort. These data support the continued development of VRG50635 as a potential treatment for all forms of ALS via PIKfyve inhibition.

#### **M307. SARM 1 Deficiency Attenuates Peripheral Neuropathy in Diabetic Mice**

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**Objective:** To determine if SARM 1 genetic deletion attenuates neurodegeneration caused by metabolic syndrome. **Introduction:** SARM 1 (Sterile alpha and TIR motif-containing protein 1) functions as an inducible pro-neurodegenerative nicotinamide adenine dinucleotide (NAD<sup>+</sup>)-cleaving enzyme. Under normal physiological conditions, SARM 1 is inactive though activation/overactivation of the SARM1 pathway causes axon degeneration. We assessed the role of SARM1 deficiency in an animal model of Type II diabetes (T2DM). **Design/Methods:** We investigated the neuroprotective role of SARM 1 deficiency in preventing damage to sensory and autonomic nerve fiber structure and function in the *db/db* T2DM mouse model. Groups (5-8 mice) included *db/db*, *db/+*, *db/db/SARM1*, *db/db/het* and *db+/SARM1*. Assessments included hind paw thermal latency, sweat production at 6 weeks and 24 weeks of age. **Results:** SARM1 deficiency did not affect blood glucose levels or weight of aging diabetic mice. *db/db/SARM1* mice exhibited marked preservation of autonomic sweat function via 37.5% more sweat spots after heat exposure compared to *db/db* mice (*p*<0.001). Additionally, SARM1 deficiency improved thermal latency by 52.9% reducing the withdrawal time of diabetic mice hind paws from heated surface (*p*<0.001). 24-week old *db/db* mice appeared to have more severe sweat gland dysfunction and thermal latency when compared to 6-week old *db/db* mice, visually. There was no significant difference between male and female sweat function or thermal latency. **Conclusions:** These results suggest that SARM1 inhibition has potential to attenuate peripheral neuropathy in type II DM.

### M308. Schmidt-Lanterman Incisure and Adherens Junction Defects in CMT1A and HNPP Myelin

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Increased and decreased dosage of the *Peripheral Myelin Protein 22 (PMP22)* gene cause dysmyelinating peripheral neuropathy, indicating that precise PMP22 expression is required for normal myelination. PMP22 duplication causes Charcot-Marie-Tooth Disease Type 1A (CMT1A) and PMP22 deletion causes Hereditary Neuropathy with Liability to Pressure Palsies (HNPP). CMT1A and HNPP are the most common inherited peripheral neuropathies, so it is remarkable how little we know about the physiological function of PMP22 and how underexpression and overexpression of this gene disrupts myelin integrity. To address these gaps, we are using CMT1A and HNPP mouse models. Our previous results suggest that primary myelin dysfunction as opposed to secondary axon degeneration drives pathogenesis in CMT1A model mice. Therefore, we focused on identifying mechanisms of myelin dysfunction in CMT1A. PMP22 is a member of the Claudin superfamily of proteins and current evidence suggests that PMP22 plays an undefined role in cell adhesion. Therefore, we characterized adhesion junction defects by performing confocal immunofluorescence imaging of teased tibial nerve fibers from these mice. Results reveal normal tight junctions but dramatically altered adherens junctions (AJs) in CMT1A myelin as compared to wildtype. AJs are prominently localized to Schmidt-Lanterman incisures (SLIs), the cytoplasmic channels running through the layers of compact myelin. E-Cadherin signal in CMT1A myelin is more punctate and the funnel shape distribution at SLIs is often disrupted. These defects correlate with changes in the AJ components  $\beta$ -Catenin and p120-Catenin. Additional SLI components, including the gap junction protein Cx29, also exhibit altered expression and disorganized patterning at SLIs suggesting that the barrier defining the SLI compartment is compromised. SLI density is also increased in CMT1A myelin as demonstrated by a reduced distance between SLIs in CMT1A nerve fibers as compared to wildtype. Our findings suggest that correct PMP22 stoichiometry in myelin is required to define the SLI compartment and organize SLI components including AJs, gap junctions and others. Proper AJ organization also likely reinforces the SLI architecture since this junction is known to provide structural support. The SLI defects in CMT1A myelin likely result in abnormal axo-glial communication and the increased SLI density likely reflects a higher metabolic need for these axons. Studies connecting the SLI density and organization defects to peripheral nerve dysfunction and with HNPP myelin are ongoing.

### M311. The Importance of Offering Exome or Genome Sequencing in Adult Neuromuscular Clinics

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Genetic testing is a critical component of care in adult neurology. The potential benefits of a genetic diagnosis extend beyond targeted treatment and include access to clinical trials; an end to the diagnostic odyssey with prevention of unnecessary, costly, or invasive evaluations; prognostic information and anticipation of medical needs; reproductive implications; and provision of risk information to family members. Historically, genetic testing was ordered in a targeted, sequential manner due to high costs; we have entered an era of falling genetic testing costs and increasing availability of broad testing. In our neurogenetics practice, for most indications we begin testing with a focused gene panel. However, we feel it is essential to offer exome sequencing (ES) or genome sequencing (GS) to those with nondiagnostic testing. In our practice, broad testing has resulted in genetic diagnosis in a significant number of patients whose cases we will present, including in the following categories: A) Variants in genes not well covered by next generation sequencing (NGS) panels, such as those with pseudogenes (e.g. *SORD* neuropathy); B) Repeat expansion disorders not detectable by NGS (e.g., *ATXN2* intermediate expansion in person with amyotrophic lateral sclerosis), including intronic expansions only detectable by GS; C) Multiple pathogenic variants in the same individual, including actionable secondary findings (e.g., *DNMT1* and *TTN* in person with neuropathy); D) Conditions for which a treatment is available (e.g., *SORD* neuropathy; *HADHB* neuropathy and myopathy; *TTPA*-associated vitamin E deficiency causing neuropathy). Furthermore, broad testing has expanded the phenotype for genes not included on condition-specific panels (e.g., *MECP2* variant identified in patient with suspected primary lateral sclerosis; myopathy in patient with *RAG2* variants (Henrickson, *J Clin Immunol*, 2018)). In addition to expanding the phenotypes of well-characterized genes, ES or GS can identify novel candidate genes not previously associated with a given phenotype (e.g., *PPP1R12B* as potential cause of myopathy). Besides the immediate yield of ES or GS following condition-focused testing (13% in Haskell, *Neurol Genet*, 2018 and 20% in our cohort), the sequencing data remains available for future reanalysis. This can lead to a within-lifetime or postmortem diagnosis as the field advances. The importance of integrating genetic counseling and testing into adult neuromuscular care cannot be overstated. With rapid advances in gene-targeted therapies, gene identification, and reproductive technologies, broad testing must be offered to create an informed, empowered, and trial-ready population.

### M312. The Notorious Drg: A Delayed Diagnosis of Dorsal Root Ganglionopathy

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**Objective:** N/A **Background:** Pure sensory ganglionopathies are often idiopathic, paraneoplastic, or inflammatory. They may present asymmetrically and lack motor involvement, differentiating them from length-dependent neuropathies. They also tend to be more disabling, with most patients requiring mobility aids during their clinical course. **Design/Methods:** N/A **Results:** A 50-year-old female presented to the hospital with one year of progressive generalized weakness and numbness, a recent loss of ambulation, and a mechanical fall. The patient was originally discharged to rehabilitation for ambulatory dysfunction following a mechanical fall. Past medical history includes remote alcohol abuse, peripheral neuropathy, coronary artery disease, deep vein thrombosis, and obesity. Examination initially revealed clumsiness with finger-to-nose testing that improved with conversational gesturing and inconsistencies raising suspicion for a functional component. Nerve conduction studies showed absent sensory responses in the arm and leg with preserved motor responses and normal electromyography. Repeat examination revealed sensory loss to all modalities in the legs, reduced sensation in the arm and face, and areflexia suggestive of a pure sensory ganglionopathy. Further history revealed that her symptoms were historically attributed to her alcohol consumption, despite significant progression during her four-year sobriety with normal TSH, B12, and folate levels suggesting no nutritional component. Due to progression, immune and paraneoplastic processes were pursued, but investigations were inconclusive, and the patient was empirically started on a monthly course of IVIG. After four months of treatment, the patient regained her ability to walk with a cane. **Conclusions:** Patients with subacute gait dysfunction and sensory loss should be thoroughly evaluated to differentiate the degree of motor and sensory deficits, often with the help of qualitative measures such as nerve conduction studies and electromyography. Thorough histories are important to delineate the timeline of their functional decline, as they can provide a clue to the etiology. In this patient's case, the subacute decline in the absence of known neurotoxic insult with absent sensory nerve conduction studies but preserved motor response suggested a rare sensory ganglionopathy diagnosis. These conditions often have an autoimmune etiology, requiring thorough investigation and examination. However, it is important to consider the clinical course and the patient's recent rapid functional decline prompted treatment.

### M313. The OMA1-DELE1 Mitochondrial Integrated Stress Response is Activated by Diverse Mitochondrial Stressors to Promote Growth and Survival in Mitochondrial Myopathy

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Mitochondrial dysfunction triggers a strong mitochondrial integrated stress response (mt-ISR), which correlates with survival in early-onset forms of mitochondrial myopathy (MM). Recently, it was shown that the mt-ISR can be activated through an OMA1-DELE1 signaling pathway, but whether

and when the mt-ISR is protective in MM remains unclear. Here, we compare four transgenic mouse models of mitochondrial stress, including models of early (CHCHD10<sup>G58R</sup>) and late (CHCHD10<sup>S59L</sup>) onset MM and mild (CHCHD2/10 double knockout (KO)) and severe (TFAM muscle KO) oxidative phosphorylation (OXPHOS) deficiency, to define the mt-ISR *in vivo*. Strikingly, DELE1 activated the mt-ISR in all models but had the most remarkable effects on growth and survival in the two models with early mitochondrial stress. Notably, the mt-ISR did not directly improve the underlying OXPHOS impairment or the associated reductive stress in these models but metabolically buffered the tissue by increasing tissue amino acids, nucleotides, and glycolysis intermediates. Thus, the mt-ISR may maintain growth despite mitochondrial dysfunction by rewiring the metabolome to bypass the OXPHOS deficiency. The mt-ISR was additionally responsible for the upregulation of mitochondrial protease LONP1 and accounted for most of the transcriptionally driven remodeling of the mitochondrial proteome. This resolves that in mammalian striated muscle, the mitochondrial unfolded protein response is a component of the DELE1 mt-ISR. Finally, we discovered that OMA1 and DELE1 have overlapping but separable effects on the mt-ISR and survival in MM. Indeed, neonatal survival in MM mice without OMA1 was associated with activation of an OMA1-independent mt-ISR. In summary, using four diverse mouse models of mitochondrial stress, we define the mt-ISR in striated muscle and identify a critical role for the mt-ISR in maintaining growth and survival in early-onset MM.

### M314. Treatment of Canomad with Rituximab: A Systematic Review

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**Background:** CANOMAD encompasses a clinical, radiological, and laboratory diagnosis characterized by chronic ataxic neuropathy, ophthalmoplegia, immunoglobulin M [IgM] paraprotein, cold agglutinins, and disialosyl antibodies. CANOMAD is a rare condition, with less than 100 cases reported in the literature. The treatment of CANOMAD is mainly unknown. For this systematic review, we aim to investigate the treatment of CANOMAD with rituximab and the clinical and biological response of the treatment. **Methods:** We used the PRISMA and MOOSE reporting guidelines for this systematic review. To analyze the bias of the study, we used the Ottawa Newcastle scale tool and the Robins Risk of bias. We only included case reports, case series, and observational studies written in English with patients formally diagnosed

with CANOMAD and treated with Rituximab. We excluded systematic reviews, literature reviews, and meta-analyses. **Results:** We gathered 34 patients. The literature uses a modified Rankin score to define a complete improvement (CR), partial response (PR), stable disease (SD), and progression. Clinically there were 3 patients with CR, 5 with PR, 15 with SD, and 11 with progression. The biological response was assessed by measuring the decrease in antibody titers in 27 patients. Among those, 6 patients had CR, 12 had PR, 8 had SD, and 1 had progression. Among 15 patients with neurological evaluation, 10 had ocular symptoms, and 2 presented with bulbar symptoms. Seven of the ten patients with ocular symptoms had SD, two with PR, and one with progression. Only 14 patients had a report of demyelinating features. 3 had an axonal pattern, 6 had a demyelinating pattern, and 5 had a mixed pattern. Among patients with an axonal pattern, the 3 had an SD. Among patients with a demyelinating pattern, 3 had a PR, 2 had an SD, and 1 had progression. Among patients with a mixed pattern, 4 had SD, and 1 had progression. **Conclusions:** Patients with CR have shorter disease duration than patients with PR, SD, and Progression. In addition, patients with CR had longer follow up than the other groups suggesting that being treated early with Rituximab improves the clinical outcome and has a sustained effect. There were no differences in the frequency of ocular and bulbar symptoms among patients with CANOMAD. The axonal pattern is more common in patients with SD, suggesting that axonal and mixed patterns could be a marker of a bad prognosis

### M315. Two Cases of Monomelic Amyotrophy (Hirayama Disease) in Young Caucasian Males

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**Introduction:** Monomelic amyotrophy (MMA) or Hirayama disease is a rare cervical myelopathy that typically affects males of Asian descent in the second to third decade of life. We present two cases of MMA in 18 and 20-year-old Caucasian males. **Case 1:** A 20-year-old Caucasian male with no significant past medical history presented with difficulty in adduction of the 4th and 5th digits of his right hand and progressive inability to straighten his wrists and lift objects with his arms. He also developed tremor like movements, contractures, fasciculations, and muscular atrophy in the right hand, forearm, and triceps. He had sensory changes including a reduction in temperature sensation and numbness in the 4th and 5th digits of the right hand. He also complained of mild neck pain with flexion. Physical exam showed atrophy of the right triceps, forearm, hypothenar eminence, and intrinsic hand muscles. Weakness was present in the right upper extremity. Sensory deficits were also present in a length-dependent manner with specific loss in the ulnar distribution of the right hand. There were no abnormalities in the lower extremities. **Case 2:** An 18-year-old Caucasian male with no significant past medical history presented with right upper extremity weakness, contractures, cramping, and muscular atrophy. He experienced a right-handed

tremor when exposed to cold temperatures. He also complained of back pain and neck pain with flexion. Physical exam showed atrophy of the right thenar eminence and weakness in the right upper extremity and neck flexors. There were no sensory deficits present on exam. There were no abnormalities in the lower extremities. **Discussion:** MMA involves the anterior horn cells and usually affects the C7 to T1 spinal nerves and their myotomes, resulting in self-limited asymmetrical lower motor weakness of hands and forearms. The cause is hypothesized as asymmetric growth of the vertebral column and spinal canal contents which leads to a displacement of the posterior dural sac anteriorly on neck flexion resulting in compression. Atrophy plateaus over the course of several years and stabilizes. Sensory and autonomic involvement are not usually seen in MMA but were significant in Case 1. MMA is typically prevalent in those of Asian descent. **Conclusion:** Our cases present MMA with two unique aspects of sensory involvement and rare racial categorization which present an opportunity to aid diagnosis in future patients with similar presentations.

### M316. Unilateral Abdominal Wall Hernia Secondary to Thoracic Disc Herniation: A Case Report

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**Objective:** To present a case of unilateral abdominal wall hernia secondary to thoracic disc herniation at the T11-T12 level.

**Introduction:** Thoracic disc herniation (TDH) only accounts for 0.24-0.75% of all spinal disc prolapses. Compared to protrusions at the cervical and lumbar level, TDH rarely induces motor symptoms. The literature review showed only five case reports regarding abdominal wall hernia due to THD. Our case contributes to the understanding and clinical awareness of this entity. **Case Presentation:** We report a 75-year-old right-handed man presented with right lower quadrant (RLQ) abdominal discomfort and bulging of the abdominal wall for three months. About a month before the symptoms occurred, he experienced sharp, non-radiating, and 10/10 pain in the right low back and lower thoracic regions after heavy physical work. Since then, he gradually developed discomfort and a bulging out of the abdominal wall in the same area. The exam revealed the abdominal reflexes were absent in the RLQ (videos provided) and a lateral bulging of the RLQ abdominal muscles with decreased tone. This bulge enlarged with increased abdominal pressure. MRI of the thoracic spine without contrast revealed right lateral disc extrusion at the T11-T12 level with severe right foraminal narrowing. We diagnosed him with abdominal muscle hernia due to right thoracic radiculopathy at the T11-T12 level. He underwent surgery to decompress the T11 nerve root. On clinical follow-up five months after surgery, his condition was unchanged; we reassured him that the strength might take over a year to recover. **Conclusion:** Abdominal wall hernia is an unusual clinical presentation of TDH. Surgery should be considered as soon as possible to minimize permanent damage. The abdominal muscle strength may take years to return to normal.



### M317. Using Unsupervised Machine Learning to Identify Phenotypic Clusters of Small Fiber Neuropathy

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**Introduction:** Small fiber neuropathy (SFN) is a debilitating, neurodegenerative disease characterized by loss of peripheral small myelinated and unmyelinated axons. Patients with SFN suffer from various combinations of positive and negative symptoms, including burning pain, paresthesias, numbness, muscle cramps, autonomic dysfunction and fatigue. Although strength remains preserved throughout the course of the disease, the pain, paresthesias, and fatigue are frequently profoundly disabling. Frustratingly, no treatments are available to stop or reverse progression of SFN and while the few neuropathic pain medications may be helpful for some patients, they lack efficacy in others. A major impediment for developing effective SFN therapies is the significant between-patient heterogeneity of the disease. Here, we used unsupervised machine learning partitioning on a large cohort of well-characterized SFN patients to identify SFN subgroups. **Methods:** Demographic and detailed clinical information was collected from 94 patients with symptoms of SFN who had received skin biopsies at the ankle and thigh. Using pandas, data consisting of eight SFN symptoms graded by the patients from 0 (absent) to 10 (highest intensity) were imported and framed in the Anaconda platform. Using scikitlearn, matlab, and scikitlearn.cluster.extra, the silhouette method was used to determine the ideal number of clusters. Subsequently, K Mediods analysis was run, and an ANOVA performed to compare variance. A heat map was constructed based on cluster membership and symptom severity. **Results:** Three clusters were identified that were statistically significant different in all eight symptoms. Patients in cluster 1 (n=24) had many symptoms of high intensity ("severe") whereas patients in cluster 2 (n=21) exhibited few symptoms, which were of low intensity ("mild"). Cluster 3 (n=49) was characterized by one or two intense symptoms plus a few symptoms at lower intensity ("intermediate"). Analyzing cluster 3 further revealed patients with severe muscle symptoms and numbness ("muscle group"), patients with moderate symptoms and severe pain and fatigue ("pain and fatigue") and patients who had several symptoms at a moderate level of intensity. The age distribution of patients in the clusters was similar, but size and pattern of intra-epidermal nerve fiber loss and co-morbidities differed between the clusters. **Conclusion:** Using unsupervised machine learning, we identified three distinct clusters of SFN patients based on SFN symptom co-occurrence and intensity. The identification of SFN subtypes may lead to a deeper understanding of pathobiological mechanisms, improve clinical trial design, and advance the development of targeted, personalized treatments.

### K-M119. Higher Glycemic Index Diet is Associated with Slower Disease Progression in Amyotrophic Lateral Sclerosis

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**Objective:** Prior studies suggest that high caloric diet may be beneficial in attenuating advancement of amyotrophic lateral sclerosis (ALS), however, key macronutrients have not been identified. We examined whether dietary macronutrient (carbohydrate, protein, and fat) content and glycemic load and index are associated with the rate of progression and length of survival among the ALS Multicenter Cohort Study of Oxidative Stress (COSMOS) study participants. **Methods:** All 358 participants [60% male, mean (SD) age 60 (10) years] with a confirmed diagnosis of sporadic ALS enrolled in COSMOS were included in the current study. We evaluated baseline macronutrient intake in relation to change in total revised ALS functional rating scale (ALSFERS-r), and tracheostomy-free survival using linear regression and Cox proportional hazard models. Baseline age, sex, disease duration, diagnostic certainty, body mass index (BMI), ALSFRS-r, ALSFRS-r bulbar sub-score and forced vital capacity (FVC) were included as covariates. **Results:** In univariable linear regression, total calories, carbohydrate, protein, or fat intake were not significantly associated with ALSFRS-r change at 3-months. However, baseline higher glycemic index (GI) was associated with slower progression of ALSFRS-r at 3-month follow up such that one unit of GI increase was associated with 0.19 less decline of ALSFRS-r at 3-month follow up ( $\beta = -0.19$ , 95% Confidence Interval (CI) [-0.30, -0.07],  $p = 0.0015$ ). Baseline ALSFRS-r bulbar sub-score was associated with GI and after adjusting for this, GI was still associated independently with 3-month decline of ALSFRS-r. Higher baseline glycemic load was also associated with slower progression of ALSFRS-r at 3-month follow up although the association was weaker than GI and not statistically significant ( $\beta = -0.012$ , 95% Confidence Interval (CI) [-0.02, 0.0002],  $p = 0.05$ ). In a multivariable Cox proportional hazard model, higher GI was associated with longer tracheostomy-free survival (Hazard Ratio 0.96, 95% CI [0.93, 0.99]  $p = 0.03$ ) after adjusting for age, sex, diagnostic certainty, disease duration, bulbar onset, baseline ALSFRS-r total score and FVC. **Conclusion:** Higher dietary GI is associated with slower functional decline and longer survival in patients with ALS.

### K-M120. Pathogenicity of Novel KIF5A Disease Causative Variants

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KIF5A is a neuronal specific subunit of the motor protein, Kinesin-1, which plays key roles in axonal transport and cytoskeletal dynamics. The central question of this project is how mutations in distinct regions of KIF5A lead to divergent clinical phenotypes such as Neonatal Intractable Myoclonus (NEIMY), a severe neonatal myoclonic epilepsy, and Amyotrophic Lateral Sclerosis (ALS), a motor neuron disease. Surprisingly, we found that very similar truncating mutations within the C-terminal domain of KIF5A cause both diseases. We developed *in vitro*

models of KIF5A ALS and NEIMY and used these to understand the consequences on cargo transport and the cytoskeletal structure. We found that while both ALS and NEIMY causative mutations disrupt autoregulation of the protein leading to its sequestration in the distal axon, NEIMY mutations led to more severe accumulation and aggregation. We show that gain of function is the predominant mechanism for both diseases. However, NEIMY aggregates cause cytoskeletal defects and create a physical obstruction to transport in the distal axon near the growth cone. These findings advance our understanding of the mechanistic basis underlying the clinical heterogeneity caused by mutations in KIF5A.

#### **K-M121. Predictors of Undiagnosed Peripheral Neuropathy in a Predominantly Low-Income, Black U.S. Primary Care Population**

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**Introduction:** Peripheral neuropathy is a disabling, often painful condition associated with falls and increased risk of nontraumatic amputation. There are limited data regarding the prevalence and burden of neuropathy among minoritized U.S. populations where risk factors, namely diabetes, are most common. The Flint Neuropathy Study is an ongoing study assessing gaps in neuropathy diagnosis and risk factor management in a predominantly Black, low-income population. **Methods:** We performed a cross-sectional study of patients  $\geq 40$  years of age presenting to an outpatient internal medicine clinic in Flint, Michigan. Demographics, clinical characteristics including access to healthcare, medication use, anthropomorphic measurements, fasting lipids, and Hemoglobin A<sub>1C</sub> were collected. Glucose intolerance was defined using the 2021 ADA diagnosis and classification of diabetes mellitus criteria, whereas metabolic syndrome was defined using the harmonized criteria. Neuropathy was defined using the modified Toronto Clinical Neuropathy Score (mTCNS, cutoff  $\geq 3$ ). Patients with undiagnosed neuropathy were those who met mTCNS criteria but did not have a prior neuropathy diagnosis either by chart review or patient self-report. We examined the association between undiagnosed neuropathy and potential risk factors, including age, race/ethnicity, health insurance status, frequency of healthcare access, metabolic syndrome, undiagnosed glucose intolerance, and presence of neuropathic pain through logistic regression. **Results:** We enrolled 200 participants and 169 (85%) completed all data collection. Ninety-three (55%) were female, mean age (SD) was 58.2 years (10.4), 105 (62%) Medicaid, and 116 (69%) non-Hispanic Black race/ethnicity. 135/169

(80%) saw their primary care doctor at least every 4 months. Eight-four (50%) had a history of diabetes. During the study, 3 participants were diagnosed with diabetes and 37 with prediabetes. 114/169 (67%) met criteria for metabolic syndrome. 123/169 (73%) met mTCNS criteria for neuropathy. Of those with neuropathy, 75% were previously undiagnosed and 40% endorsed neuropathic pain. Participants with undiagnosed neuropathy were more likely to be older (mean 61 years vs 55 years, (OR 1.1 [95% CI 1.01-1.1]) than those with diagnosed neuropathy. There were no other significant predictors of undiagnosed neuropathy, including frequency of healthcare access or undiagnosed glucose intolerance. **Conclusions:** Despite regular access to primary care, peripheral neuropathy is substantially underdiagnosed in this predominantly Black, low-income population. Age is the only significant predictor of undiagnosed neuropathy; therefore, interventions to reduce the neuropathy diagnostic gap should target the whole population and should not be limited to those with known neuropathy risk factors.

#### **LB-M118. Alternative Polyadenylation in the Pathogenesis of Amyotrophic Lateral Sclerosis**

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Amyotrophic Lateral Sclerosis (ALS) is a devastating neurodegenerative disorder characterized by progressive loss of upper and lower motor neurons. Dysregulation of RNA metabolism has emerged as a key driver of the underlying pathology of ALS. Indeed, almost all (>97%) ALS patients display proteinaceous cytoplasmic TDP-43 inclusions, which leads to widespread changes in post-transcriptional processing of various RNA species. Identifying key transcripts altered due to loss of nuclear TDP-43 could yield broadly applicable diagnostic and therapeutic targets for ALS. Recently, characterization of alternative splicing upon TDP-43 loss-of-function led to the development of a promising therapy approach by modulating the neuronal growth factor stathmin-2. However, other aspects of RNA metabolism regulated by TDP-43 remain unexplored. Thus, here we investigate changes in alternative polyadenylation (APA) upon TDP-43 mutation or depletion. APA is an RNA-processing mechanism that generates distinct 3' termini on mRNA transcripts. TDP-43 is known to regulate APA by binding target pre-mRNAs near a polyadenylation signal (PAS), thus creating mRNA isoforms with longer or shorter 3' untranslated regions (3'UTR) harboring regulatory elements, such as binding sites for microRNAs and RNA-binding proteins. This can affect RNA stability, protein translation, and subcellular localization of a given transcript without altering steady-state transcript levels. APA events occurring in TDP-43 proteinopathy remain understudied, since conventional RNA-sequencing analysis do not fully capture APA changes. To address this gap, we recently applied the dynamic analysis of APA from RNA-seq (DaPars) tool to published RNA-seq datasets, finding

previously unknown APA events that function in pathways implicated in ALS pathogenesis, (i.e. nucleocytoplasmic transport, oxidative stress response, and chromatin accessibility). Notably, in neuronal nuclei from the neocortex of postmortem ALS/FTD patients depleted of nuclear TDP-43, the most significant APA event occurred in MARK3 resulting in a longer 3'UTR upon depletion of TDP-43. We further confirmed that TDP-43 directly binds to the MARK3 transcript in the 3'UTR using eCLIP data generated by the ENCODE project. MARK3 is a tau kinase implicated in Alzheimer's disease, reflecting a potentially novel mechanistic link between TDP-43 and tau pathology. Interestingly, shRNA-mediated knockdown of MARK3 in HEK293T cells leads to a substantial increase in the accumulation of the TDP-43 C-terminal fragment, while overexpression of MARK3 markedly reduced TDP-43 burden. Importantly, APA can be directly modulated by antisense oligonucleotides (ASOs); thus, newly identified APA genes may be candidates for rapid therapy development in ALS.

#### **LB-M119. Descriptive Analysis of 12 Patients with Anti-Plexin-D1 Seropositive Small Fiber Neuropathy**

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**Introduction:** Small fiber neuropathy (SFN) is a painful sensory neuropathy defined by damage to small C and A-delta fibers. While it is associated with numerous disease processes, more than 50% of patients receive a diagnosis of "idiopathic" SFN. Moreover, as SFN affects both sensory and autonomic nerves, there is significant variability in clinical presentation. To solve the diagnostic and therapeutic challenges posed by SFN, researchers have sought to identify subgroups of patients using novel autoantibodies, amongst other methods. While significant research has been done studying trisulfated heparin disaccharide (TS-HDS) and fibroblast growth factor receptor 3 (FGFR-3), anti-plexin-D1 is less well understood. In this study, we seek to evaluate the demographics, symptomatology, comorbidities, therapeutics, and skin biopsy findings of anti-plexin D1 SFN to better define presentation and management of this subgroup. **Methods:** Demographic and detailed clinical information was collected from 204 adult patients at Saint Louis University Hospital with a clinical diagnosis of SFN. From this group, 12 patients were identified with confirmed anti-plexin D1 seropositivity by sensory neuropathy panel. Using Prism 9, data was collected, compiled, and analyzed. Average age at diagnosis and frequencies of other variables were reported. **Results:** Anti-plexin D1 patients were an average age of 41.1 years at diagnosis and the majority were female (91.7%). Commonly reported symptoms were numbness (75.0%) and tingling (50.0%) with fewer patients reporting burning (33.3%) and pins/needles (41.7%). The most strongly associated comorbidity was chronic pain in 75.0% of patients. Other neurologic, immunologic, metabolic, and psychiatric comorbidities occurred in 8.3%-41.7% of patients. The most common intervention was neuropathic pain medications (75.0%),

followed by interventional pain procedures (41.7%); less than 50% of patients used anti-spasmodics, NSAIDs, or opioid medications. While 58.3% of seropositive patients underwent skin biopsy, only 14% of this group demonstrated a length-dependent pattern. **Conclusions:** Anti-plexin D1 SFN appears to be associated with increased frequency of numbness, comorbid chronic pain, and female sex. Compared to SFN patients as a group, they were less likely to report burning pain or pins/needles. Similar to studies with TS-HDS and FGFR-3, most anti-plexin D1 patients did not show a length-dependent pattern. This is consistent with previous research demonstrating anti-plexin D1 IgG binding against DRG neurons and spinal posterior horns. This suggests a shared pathophysiological mechanism within seropositive SFN. Overall, our findings suggest that anti-plexin D1 patients have unique demographics, clinical phenotype, and pathophysiologic mechanism.

#### **LB-M120. Inclusion Body Myositis is a TDP-43 Proteinopathy with Nuclear Pore Disruption**

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Sporadic Inclusion Body Myositis (IBM) is a degenerative muscle disease affecting adults over the age of 50 with unknown cause and no effective treatment. Despite the intense endomysial infiltrate of T cells surrounding and invading myofibers, immunosuppressive therapies fail to slow progression of disease. Using a xenograft model of IBM, we have shown that T cell depletion has no effect on formation of rimmed vacuoles, p62-positive protein aggregates, or TDP-43 dysfunction (Britson et al, Sci Transl Med, 2022). Here, we demonstrate that myoblasts derived from IBM patient muscle biopsies display nuclear pore abnormalities leading to loss of nuclear TDP-43, even when cultured without inflammatory cells. We have developed a biomarker assay for detecting TDP-43 dysfunction by detecting cryptic exons which is 82% sensitive and 99% specific for diagnosing IBM (n=119 patients). Multiple nucleoporin proteins become mislocalized to the sarcoplasm, suggesting that nuclear pore dysfunction may underlie cytoplasmic TDP-43 mislocalization. Ongoing ATAC-seq and RNA-seq analyses from myoblasts and single nuclei derived from frozen muscle biopsies demonstrate critical pathways that underlie myofiber degeneration in IBM. Our studies demonstrate that IBM is a TDP-43 proteinopathy with pathophysiologic overlap with ALS and FTD.

#### **Neuro-oncology**

##### **S257. A Case of Diffuse Large B Cell Lymphoma Presenting with Neurolymphomatosis and Leptomeningeal Disease**

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Diffuse large B cell lymphoma can rarely spread to the leptomeninges, brain parenchyma, spinal cord, or peripheral

nerves. Patients with this pattern of metastatic disease typically have a worse prognosis and may exhibit characteristic neurological manifestations depending on the area of the nervous system involved. We describe a patient who presented with pain and numbness in the lower extremities, memory problems, and bowel and bladder retention. Her symptoms progressed over the course of two years and extensive neurophysiological workup was unrevealing. She was diagnosed with possible chronic inflammatory bilateral lumbar polyradiculopathy of L5-S1 and received plasmapheresis without improvement in symptoms. When she presented to the emergency room, she reported worsening sensory symptoms and memory changes over the month prior. Pertinent examination findings at this time included diffuse hyper-reflexia with crossed adductors at the patellars, impaired proprioception at the toes, positive Romberg, and decreased sensation on the lateral lower extremities. Labs were pertinent for elevated lactate dehydrogenase at 329. MRI brain showed multifocal gyriform T1 hyperintensities in the parietal and occipital cortices bilaterally with associated edema, leptomeningeal enhancement, and diffusion restriction. CT chest abdomen pelvis showed left pectoral lymphadenopathy, lobulated mass in the left adrenal gland measuring 5.4x2.7 cm, and left para-aortic lymphadenopathy. Lumbar punctures demonstrated elevated protein with negative flow cytometry. Biopsy of a para-aortic lymph node and brain showed diffuse large B cell lymphoma. Our patient, received intrathecal methotrexate and R-CHOP therapy which was switched to intrathecal Rituximab following radiographic response and had improvement in her neurological symptoms following treatment. Few cases are published in the literature of diffuse large B cell lymphoma, presenting with various lower extremity symptoms due to involvement of the peripheral nerves or nerve roots, termed neurolymphomatosis. This is thought to be due to endoneurial spread of tumor cells. MRI and LP results in these cases may vary, therefore, it is commonly misdiagnosed. Though our team did not have confirmatory imaging findings in the lumbosacral spine, it is felt this was the most likely diagnosis based on patient symptoms and prior unrevealing workup. Our patient is unique in that she had neurolymphomatosis and leptomeningeal disease at initial diagnosis of diffuse large B cell lymphoma. It is important to be aware of the neurological manifestations of lymphomas as prompt diagnosis can improve patient outcomes and potential irreversible neurological manifestations.

## S260. An Incidental Finding of a Dysembryoplastic Neuroepithelial Tumor

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**Introduction:** Dysembryoplastic neuroepithelial tumor (DNET) is a mixed glioneuronal, low-grade, and slow-growing tumor that is most commonly seen in the temporal lobe of children and young adults. Incidence among neuroepithelial

tumors is 1.2% in younger patients under 20 years and 0.2% over 20 years. We present the case of a 34-year-old man without symptoms beyond a cutaneous rash and an incidental finding on neuroimaging with a large T1 hypointense lesion in the left temporal cortex without contrast enhancement, edema, or mass effect. **Case Presentation:** A 34-year-old healthy man presented with a left facial rash for a few days without systemic or neurological symptoms. To rule out cellulitis, a head CT was done and revealed left parietal hypodensity concerning for a stroke. A brain MRI with and without contrast confirmed the presence of a large T1 hypointense lesion in the left temporal cortex without contrast enhancement, edema, or mass effect. The mass was removed at the patient's preference despite the reassuring imaging findings. Pathology reported the mass as a dysembryoplastic neuroepithelial tumor (DNET) positive for a fibroblast growth factor receptor (FGFR) mutation. **Discussion:** Although asymptomatic brain tumors are rare in the general healthy population, their incidence rate can range from 0.3 to 1.6%. The frequency of incidental DNETs found in adults is currently unknown. Only two cases of DNETs in healthy children under 12 have been reported, of which only one was confirmed by histopathology, and neither developed seizures during a ten-year follow-up. In this context, our patient represents the first incidentally discovered case of DNET in an adult without a history of epilepsy. DNETs are typically suspected in young patients with drug-resistant partial seizures. Although the age at seizure onset can vary widely, 90% of cases are diagnosed before age 20 (6). A temporal location is the most common (80%). However, an extra-temporal site is more prevalent in patients with childhood epilepsy. In addition, a pediatric-predominant study found that cortical dysplasia, an epileptogenic lesion, was highly prevalent in 86% of cases. In contrast, an adult-predominant study found no evidence of cortical dysplasia and suggested that this might explain the older onset of seizure presentation in adults.

## S261. Baroreflex Dysfunction after Neck Irradiation and Chemotherapy for Tonsillar Cancer

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**Background:** Afferent baroreflex dysfunction is an under-recognized yet clinically important potential late-sequela of neck irradiation and/or chemotherapy in the treatment of head and neck cancers. The main clinical features include hypertensive crisis, hypotensive episodes, and orthostatic hypotension. **Case Report (Video, 3 minutes 27 seconds):** We evaluated a 66-year-old man who had extensive neck irradiation and chemotherapy from right tonsillar squamous cell carcinoma. Six years later, after a neck massage during physical therapy, he developed episodes of right-sided neck and jaw pain, extreme blood pressure variability, asympathotonic orthostatic hypotension, and orthostatic intolerance with one episode of syncope. He would easily fatigue on minor exertion and could no longer keep up with his previous activity level. Orthostatic measurements on examination were BP: 166/104 mmHg, pulse: 98 bpm, supine; 146/92 mmHg,

99 bpm, sitting; and 95/38 mmHg, 109 bpm standing. Afferent baroreflex dysfunction was diagnosed and management focused on non-pharmacological interventions in addition to clonidine, preferring the use of longer-acting antihypertensive drugs over shorter-acting with the intent of not seeking to normalize blood pressure. **Discussion:** Patients with baroreflex dysfunction present a significant management challenge due to the exaggerated blood pressure responses to pressor or depressor stimuli, whether mechanical or pharmacological. They can have unpredictable clinical triggers for hypertensive or hypotensive events including extreme psychological stress or even ordinary degrees of physical exertion. Treatment of symptomatic patients should target improvement in symptoms rather than objective measures such as blood pressure alone, as the latter often proves difficult to reliably achieve. Use of long-acting central sympatholytic agents, with cautious dose titration, can be useful for dynamic hypertension. Use of nonpharmacologic methods such as abdominal binder, thigh-high compression stockings, isometric exercises, and maintenance of adequate hydration should be first-line for symptomatic orthostatic hypotension. Additionally, sleeping in a supine reverse-Trendelenburg position can reduce the risk of supine hypertension and its associated adverse effects, particularly in patients that require an oral vasopressor. Fallback to pharmacological therapy should only be in cases of conservative treatment failure. **Conclusion:** Awareness of baroreflex dysfunction as a late-sequel of neck irradiation or chemotherapy is critical in the management of patients with head and neck cancers. **References:** [1] Benarroch. 2008. The arterial baroreflex: functional organization and involvement in neurologic disease. *Neurology*, 71(21), 1733-1738. [2] Biaggioni et al. 2019. Blood Pressure Management in Afferent Baroreflex Failure. *JACC*, 74(23), 2939-2947. [3] Lamotte et al. 2021. Natural History of Afferent Baroreflex Failure in Adults. *Neurology*, 97(2), e136-e144.

## S262. Disparities among Astrocytoma Clinical Trials between 1996 - 2022

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**Background:** While there are no biological determinants of race, differences in disease course and response to treatment highlight the importance of racial information. Disadvantaged groups diagnosed with brain tumors experience higher morbidity and mortality, yet their inclusion in clinical trials remains limited. This is concerning given there are reports of differing efficacy across minority groups. Lack of racial reporting contributes to gaps in medical knowledge that further disproportionately affect minoritized groups. In this study, we perform a meta-analysis of astrocytoma clinical trials, with the primary objective of assessing the inclusion of race data in clinical trials. **Methods:** This meta-analysis consisted of publicly available astrocytoma clinical trials of

pharmacologic agents using ClinicalTrials.gov and included demographic data on race and sex categories. Two independent reviewers extracted study level data for a random effects analysis. Microsoft Excel was used for data collection and analysis. The primary outcome is the prevalence of studies that did not incorporate race/ethnicity data. The secondary outcomes are the prevalence of each demographic subgroup (White, Black, Combined Other) among all oncology clinical trials that reported this demographic information. **Results:** A total of 1857 studies were identified through a search of randomized clinical trials using ClinicalTrials.gov with search term *Astrocytoma* including years 1996 to 2022. After including only completed interventional studies with results, 219 total trials were analyzed. Out of 219 studies, 131 (59.82%) did not report race. The remaining 88 clinical trials that reported demographic data were analyzed. 40.32% of trial participants were female and 59.35% were male. 81.8% of trial participants were white, 4.98% were black, 3.71% were Asian, and 9.51% were "combined" category (Not reported, Unknown, Other, American Indian, Native Hawaiian, multiple races). **Conclusions:** Despite the importance of reporting demographic data, more than half of astrocytoma clinical trials did not report racial data. In addition, of those trials that did report race data, we found that White participants were disproportionately represented (81.8%) while Asians, Black, American Indian, Native Hawaiian and others were underrepresented in the clinical trials. These results highlight disparities in clinical trial participation, and questions how applicable targeted therapies might be if they are not used on diverse populations.

## S263. Integration of Neuroimaging, Patient-Reported Outcomes, and Genetics in IDH-Mutant Gliomas

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**Introduction:** Isocitrate dehydrogenase mutant lower-grade gliomas (IDH-mt gliomas) are incurable primary brain tumors with relatively long survival periods spanning decades. Developing novel surrogate endpoints of disease progression requires a deeper understanding of the relationship between tumor growth on neuroimaging with patient function and quality of life. We hypothesized that impairments in quality of life were associated with neuroimaging features obtained as standard of care. **Methods:** Patients with IDH-mt gliomas were enrolled in a prospective study that captured clinical, radiological, and molecular factors. Quality of life was assessed using standardized *t*-scores ( $\mu = 50$ ,  $\sigma = 10$ ) from the Patient-Reported Outcomes Measurement Information System (PROMIS), including its global score and NeuroQoL sub-score measures. **Results:** The study analyzed 15 patients including 8 (53.3%) males and 7 (46.7%) females. The

average age was 42.6 (SD = 12.0) years. The average PROMIS score for patients with a frontal location ( $M = 58.07$ ,  $SD = 6.41$ ) was higher (better) than those without a frontal location ( $M = 47.61$ ,  $SD = 8.72$ ;  $p = .02$ ). Additionally, patients with a parietal location had a significantly higher well-being score ( $M = 61.63$ ,  $SD = 4.48$ ) than those without a parietal location ( $M = 52.35$ ,  $SD = 6.58$ ;  $p = .04$ ). College graduates had a higher well-being score ( $M = 57.29$ ,  $SD = 4.79$ ) when compared to those with less than 16 years of education ( $M = 48.04$ ,  $SD = 7.60$ ;  $p = .01$ ). Regarding the stigma sub-score, there was a negative association between patients' pre-operative T2/FLAIR volume and their stigma response. That is, a one standard deviation increase in the pre-operative T2/FLAIR volume was associated with a  $-4.74$  (95% CI:  $-9.39$  to  $-0.09$ ) point decline (improvement) in the stigma score ( $p = .046$ ). Similarly, patients who were employed had a lower (better) stigma score ( $M = 49.09$ ,  $SD = 8.13$ ) when compared to those who were not employed ( $M = 63.42$ ,  $SD = 8.85$ ;  $p = .01$ ). Finally, every month increase from the date of diagnosis increased (worsened) the fatigue sub-score by  $0.17$  (95% CI:  $0.02$  to  $0.33$ ) points ( $p = .03$ ). **Conclusions:** Specific neuroimaging features correlate with impairments in quality of life in IDH-mt glioma. Integration of neuroimaging with patient function will be critical to provide targeted support and novel interventions in patients living with IDH-mt gliomas.

#### **S264. Large Frontal Meningioma Presenting with 10 Months of Major Depressive Disorder, Headache, and Catatonic Symptoms**

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**Background:** Psychiatric disorders underlying catatonia include psychotic disorders, bipolar disorder, unipolar major depression, and more. Other etiologies include autoimmune diseases like Lupus, and developmental disabilities like Autism. We present a case of Major Depressive Disorder with catatonic features occurring in a patient with a large frontal meningioma- the removal of which resulted in resolution of both catatonic and mood symptoms. This case depicts an uncommon presentation of meningioma, a relatively common tumor. **Case Presentation:** The patient is a 44-year-old female with a 10-month history of Major Depressive Disorder and fatigue associated with intermittent occipital headaches. Patient had been taking sertraline 50mg daily for 1.5 weeks at the time she presented to the emergency department with new onset catatonic features noted during a psychiatry telehealth visit. Catatonic features included flat affect, delayed response time, and psychomotor retardation. The patient was sent for hospital evaluation. Benzodiazepine challenge was negative. CT found a soft tissue mass of  $4.9 \times 5.6 \times 4.0$  cm in the posterior supraorbital frontal lobe region with edema and mass effect. Midbrain compression was also noted. The growth was later confirmed to be a meningioma via

histology. The patient underwent a craniotomy during which the base of the tumor was separated from the anterior fossa using a cautery. It was then debulked and removed piecemeal.

**Conclusions:** 4 days post-Op the patient reported stable non-depressed mood. Patient ambulated well and demonstrated no symptoms of catatonia. 1 month after initial presentation the patient continued to deny low mood, reported no longer wanting to take Sertraline and requested to be tapered off the medication. The patient also declined to schedule a follow up appointment with psychiatry. 6 months post op the patient continued to deny neurological or mood symptoms and her husband reports that she is, "back to her old self!" This case describes catatonia and depression which occurred concurrently with a large frontal lobe meningioma. Removal of said meningioma resulted in remission of both the patient's catatonic and depressive mood symptoms. The unprecedented etiology and resolution of this patient's catatonia present a unique addition to its differential diagnosis. Early diagnosis of inordinate underlying processes in psychiatric patients can prevent morbidity and mortality and represent the importance of widened differentials.

#### **S265. Receipt of Guideline Concordant-Care for Neurofibromatosis 1 (NF1) in the United States: A National Survey of NF1 Patients and Caregivers**

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**Background:** Recent clinical care guidelines from the AAP and ACMG recommend specific health screenings and education for children and adults with NF1, a rare neurogenetic disorder. We assessed the extent to which these guidelines have been implemented in the U.S. and socio-demographic predictors of receiving guideline-concordant care. **Methods:** An electronic survey was sent to U.S.-based NF1 patients and parents/caregivers enrolled in the Children's Tumor Foundation Neurofibromatosis Registry in May 2021. Survey topics included demographics, location and specialty of NF care providers, and self-reported receipt of guideline-concordant clinical care (including blood pressure measurement, skin exam, and scoliosis screening in children and adults; tracking of pubertal development and developmental milestone/school progress in children; and education about family planning and warning signs/symptoms of cancer for adults). We used inverse propensity score reweighting of survey responses to estimate receipt of guideline-concordant care among the entire NF1 registry population and used robust linear regression to look for potential socio-demographic disparities in the total number of age-appropriate recommended health services individuals received. **Results:** 322 individuals with NF1 responded (4.6% response rate, 160 adults and 162 parent/caregivers, 58% female, 78% white). 53.6% of children and 25.2% of adults received at least 4 out of the

5 recommended health services for their age group. Individuals who visited a specialized NF1 clinic within the past three years ( $\beta=0.86$ ,  $p<0.001$  for children;  $\beta=0.76$ ,  $p=0.002$  for adults) or who had an appointment with their NF1 care provider in the past year ( $\beta=1.62$ ,  $p<0.001$  for children;  $\beta=1.23$ ,  $p<0.001$  for adults) received more guideline-concordant evaluations. Among adults, White patients were more likely than Black patients ( $\beta=0.95$ ,  $p=0.027$ ) and patients of other races ( $\beta=0.70$ ,  $p=0.043$ ) to receive guideline-concordant care, as were adults with commercial insurance compared to Medicaid ( $\beta=1.096$ ,  $p=0.011$ ) and adults who saw a neurologist for their NF1 care ( $\beta=0.48$ ,  $p=0.038$ ). Family income, education, urbanicity/rurality, and seeing a geneticist for NF1 care were not significantly related to receipt of guideline-recommended care in children or adults. **Conclusions:** Specialized NF1 clinics and neurologists were more likely to provide patient-reported, guideline-concordant NF1 care than other providers, but some racial and economic disparities in quality of care persist. A recently funded online intervention to disseminate personalized, evidence-based care recommendations to patients and their local care teams could improve the quality of NF1 care in the U.S.

#### **S266. Risk of Intraparenchymal Metastasis from Castration-Resistant Prostate Carcinoma via Hematogenous Spread: A Rare Case Presentation**

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Central Nervous System (CNS) metastasis is an uncommon sequela of prostate cancer. Although known to frequently metastasize to the bone, lymph nodes, and lungs, the incidence of brain metastases from prostate cancer is  $<2\%$ .<sup>1,2</sup> Direct invasion of the brain via adjacent skeletal or dural metastases occurring more often than via hematogenous routes.<sup>1,2</sup> Nevertheless, risk of brain metastasis increases over time following the initial diagnosis and particularly so in stage IV or metastatic disease. The cellular mechanisms which potentiate CNS hematogenous spread among some patients and not others are poorly understood. We present an unusual case of hematogenous intraparenchymal metastasis from prostate cancer status post prostatectomy, adjuvant radiation, chemotherapy, and hormone suppression in a 64-year-old male 16 years after initial cancer diagnosis. We further investigate the risk factors associated with hematogenous brain metastasis from prostate cancer. The patient initially presented with worsening encephalopathy over the previous months. PET/CTs obtained showed the progression of known disease and diffuse skeletal metastases. MRI showed three metastases in the left lateral occipitotemporal gyrus, right inferior parietal lobule, and left cerebellar hemisphere. EEG suggested discharges on the ictal/interictal continuum without frank seizure. Left temporal craniotomy and resection were performed. The patient's behavior improved moderately with seizure medication and anti-psychotics; however, the patient and family ultimately elected for Hospice due to challenges with pain, residual psychosis, and

refractory seizures. This case is a rare example of hematogenous spread of prostate cancer to the brain without concurrent dural or skeletal involvement. Literature suggests the risk of hematogenous metastasis to the brain from prostate carcinoma is  $\sim 0.47\%$ .<sup>3,4</sup> Various risk factors increase the risk of hematogenous spread including higher grades of initial cancer, atypical histological subtypes, specific treatment history, increased time from diagnosis to detection of metastasis, and coinciding systemic metastases' locations.<sup>3,4</sup> This case demonstrated high-grade neoplasia on initial diagnosis and increased length of time from diagnosis to detection of brain metastasis. The exact cellular and microenvironmental factors potentiating hematogenous brain invasion remain poorly understood, restricting current therapies for this patient population. Existing literature is limited by the significant heterogeneity across study designs, data collection, and patient population. Further research is needed to elucidate these mechanisms and optimize treatment. **References:** 1. Tremont-Lukats, Ivo. Cancer. (2003). 2. Hatzoglou, Vaios. Journal of Neuroimaging. (2014). 3. Cagney, Daniel. Neuro-oncology. (2017). 4. Rajeswaran, Kobisha. Journal of Clinical Medicine. (2022).

#### **S267. Soft Tissue Metastasis in a Patient with Glioblastoma**

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**Introduction:** Glioblastoma multiforme is the most common malignant brain tumor in the adult population. With a median overall survival between 12-18 months, these tumors rarely spread outside the intracranial compartment. Extra-cranial metastasis occurs more frequently in the spine, vertebral bodies, pleura, and lymph nodes. Skin metastasis is very rare, with only a couple dozen cases reported in the literature. We present the case of a patient who was found to have metastasis to his scalp a few months after the resection of a left frontal glioblastoma. **Case Presentation:** A 67-year-old man with a history of left frontal glioblastoma reported a growing mass on his scalp for three weeks. Eight months prior, he underwent gross total resection of the glioma and completed treatment with radiation and chemotherapy with temozolomide. He was recovering well after treatment and his surveillance scans did not show evidence of recurrent disease. He denied any trauma or dermatologic history of similar issues. On examination, a 2 cm nodular lesion was found near the incision scar of his craniotomy. The mass did not have any discharge or bleeding, and it was painless and firm to the touch. The rest of his dermatologic and neurologic exam was unremarkable. A brain MRI confirmed the presence of a left frontal soft tissue subgaleal lesion and a biopsy of it was consistent with metastatic glioblastoma. Pre-operative MRI for resection of this mass 2 weeks later demonstrated an additional 1 cm contrast-enhancing lesion in the left temporalis muscle, which was concerning for another focus of metastasis. He underwent resection of the scalp lesion, which was complicated by a peri-procedural stroke with residual aphasia and right-sided weakness. He declined further treatment after that.

**Discussion:** Soft tissue metastasis from glioblastoma is a rare finding. Specific risk factors have not been established, but the fact that this nodule was near the craniotomy scar, makes post-surgical seeding of the subgaleal space the most likely mechanism of soft tissue invasion. Only a few days later, an additional focus suspicious of metastasis was found in the ipsilateral temporalis muscle, which would demonstrate the aggressive nature of this tumor even outside of the central nervous system.

## S268. The Natural History of Neurolymphomatosis

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**Purpose:** Neurolymphomatosis is a rare lymphoid malignancy of the peripheral nervous system. Patients suffer from debilitating neurological deficits due to lymphoma invasion into one or more peripheral nerves and the natural history of this disease is still poorly understood. **Methods:** We performed a PubMed search and extracted data on (i) year of publication, (ii) age, (iii) gender (iv), type of lymphoma, (v) nerves involved, (vi) imaging modalities, (vii) treatment received, and (viii) survival times. Kaplan-Meier statistics were used to determine outcome parameters over time and compare prognostic factors. Multiple comparisons were done to determine differences among groups. **Results:** Our search identified 559 patient cases from 286 published articles. Median age was 61 years (range 2- 92 years) from 326 males, 222 females, and 11 with unspecified gender. Median overall survival (OS) was 12.0 months (range 10.0-15.0) for the entire cohort. Most frequent histologies were (i) diffuse large B-cell lymphoma, (ii) unspecified T-cell lymphoma, and (iii) unspecified B-cell lymphoma, involving the (a) brachial plexus, (b) cranial nerves, and (c) sciatic nerve. None had molecular profiling. There was a progressive lengthening of OS in successive decades, from 0.5 (95%CI 0.0-0.8) to 26.4 (95%CI 18.0- 34.8) months between 1951 and 2022 ( $r^2=0.9432$ ,  $p<0.001$ ). Time from first treatment to progression also increased from 2.0 (95%CI N/A) to 28.3 (95%CI 23.1-33.5) months ( $r^2=0.6923$ ,  $p<0.001$ ). However, time from symptom onset to diagnosis remained unchanged during this period ( $r^2=0.6206$ ,  $p=0.277$ ). Patients were most frequently treated with (i) methotrexate or methotrexate-based combination chemotherapies ( $n=81$ ), (ii) rituximab alone or with other chemotherapies ( $n=176$ ), and/or (iii) radiation ( $n=79$ ). Only 12 received 3 or more regimens. Primary neurolymphomatosis had a better prognosis than secondary neurolymphomatosis, median OS 15.0 (95%CI 11.0-33.0) vs. 10.0 (95%CI 10.0-10.0) months ( $p=0.016$ ). No OS difference was noted between B- and T-cell disease ( $p=0.4393$ ), while patients with low-grade B-cell neurolymphomatosis did better than those with Burkitt's lymphoma ( $p<0.001$ ). **Conclusions:** Outcome for patients with neurolymphomatosis has improved over time from advances

in drug treatment. But timely diagnosis remains a major problem that needs improvement.

## Neuro-ophthalmology and Neurovestibular Disease

### S269. A Case of Opsoclonus Secondary to Increased Intracranial Pressure

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**Introduction:** Opsoclonus is a form of saccadic intrusions characterized by rapid, repetitive conjugate eye movement that are involuntary, arrhythmic, chaotic and multidirectional. Opsoclonus is usually associated with paraneoplastic syndromes, systemic infections, toxins, and metabolic abnormalities in adults. However, opsoclonus can also be idiopathic in many cases. Here we present a case of opsoclonus as a manifestation of increased intracranial pressure, which, to our knowledge, has not been reported in the past literature. **Case Description:** The patient is a 57-year-old woman with past medical history of hypertension came to the hospital with thunderclap headache. Her neurological exam was normal on arrival. Her blood pressure was 189/78. Head CT revealed diffuse cisternal subarachnoid hemorrhage, and CT angiogram showing a right sided anterior communicating artery aneurysm. She underwent diagnostic angiography followed by aneurysm coiling. Six days later, angiogram demonstrated vasospasm. Fourteen days after admission, the patient became tachycardiac, hypertensive and tachypneic with significant increased intracranial pressure (ICP) of 40s. Bedside neurological exam was performed. She was comatose. Her pupils were reactive and she had opsoclonus. She did not have motor response to pain at that moment. EEG revealed severe diffuse encephalopathy. MRI of the brain showed a left temporal infarction that had been previously identified and had not changed. Patient was kept on external ventricular drain with 5cm H<sub>2</sub>O, with hourly neurological and ICP checks. She was managed with sedation while continuing nimodipine and sustaining cerebral perfusion pressures. Over the next few hours her ICP normalized. The opsoclonus subsequently disappeared within an hour after ICP decreased. **Conclusion:** Our case demonstrated an association between opsoclonus with increased ICP in the setting of vasospasm. The presentation of opsoclonus is usually multidirectional, compared to restricted horizontal movement in ocular flutter. Opsoclonus is also different from nystagmus where there is saccade when the eye is moving away from the target. Interestingly, idiopathic opsoclonus has a better prognosis compared to the ones with paraneoplastic syndrome. The exact pathophysiology of opsoclonus is unclear, although there are several hypotheses including damage to omnipause neurons, synaptic membrane changes of burst cells, as well as dysfunctional cerebellar Purkinje cells. In our case, it is possible that increased ICP has damaged omnipause neurons or Purkinje cells, which resulted parallel opsoclonus. While opsoclonus has never been reported in association with increased ICP in the setting of vasospasm, this case suggested that opsoclonus can occur due



to concurrent neuronal lesions, and such mechanism warrants further investigation.

### **S270. A Patient with Takayasu Arteritis Developing Multiorgan Failure Including Multiple Strokes and Bilateral Optic Neuropathy**

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**Introduction:** Takayasu arteritis is a well-known large vessel vasculitis that can rarely involve the eyes. **Objective:** To report a woman with Takayasu arteritis developing recurrent strokes and bilateral optic neuropathy. **Case Report:** An Asian woman in her 30s developed uncontrolled hypertension and acute renal failure during her pregnancy. This led to a miscarriage and within a few weeks, she suffered a stroke secondary to carotid occlusion. The patient was readmitted for recurrent ischemic stroke and irregularity of the subclavian artery was seen that was suspicious of large vessel vasculitis. A conventional angiogram showed involvement of left ICA, subclavian artery, abdominal aorta, and renal arteries, eventually diagnosing Takayasu arteritis. During treatment with immunosuppressive agents, she developed right eye vision loss and MR imaging showed bilateral optic perineuritis. Orbital biopsy was unrevealing. Diagnostic work-up was unremarkable including testing for IgG4 subclasses, MPO, PR-3, AQP4 antibody, and MOG antibody. The patient was started on tocilizumab and oral prednisone and has been stable for two years. **Conclusion:** This case highlights the importance of early diagnosis and treatment of Takayasu arteritis and its atypical presentation of bilateral periopic neuritis.

### **S271. Diagnostic Challenge: A Case of Leptomeningeal Carcinomatosis Causing Severe Optic Neuropathy**

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A 70-year old male with notable past medical history of locally-invasive bladder cancer (s/p chemoradiation one year prior, now in remission) presented with 6-8 weeks of rapid-onset, progressive, painless, vision loss that occurred sequentially (initially left eye followed by right). Funduscopic exam noted optic disc edema. His MRI orbits revealed bilateral optic nerve diffusion restriction and enhancement, as well as T2 FLAIR changes extending into the optic chiasm concerning for an inflammatory versus ischemic optic neuropathy. He underwent bilateral temporal artery biopsy, which was unrevealing, but was empirically treated with high-dose intravenous methylprednisolone for five days without any improvement in vision. On the last day of steroids, MRI neuro-axis revealed numerous additional abnormalities including enhancement of bilateral posterior semicircular canals, leptomeningeal enhancement along the cerebellum and upper cervical cord, patchy/irregular T2 hyperintensities in his C/T spine, enhancement of cauda equina nerve roots and developing hydrocephalus. Serologic evaluation for inflammatory etiologies was unrevealing. Lumbar puncture was notable for elevated opening pressure, markedly elevated CSF protein and ultimately, CSF cytopathology revealed adenocarcinoma. PET imaging

revealed increased uptake in the upper gastric region, which was biopsied once with no malignant cells found. Ultimately, the patient and family elected to transition to hospice prior to identification of a primary malignancy. The leading hypotheses for the primary site were either bladder or gastric adenocarcinoma. It is uncommon to develop only leptomeningeal metastasis without clear lymph node involvement in both of these malignancies and there is no prior reported literature of a severe, ischemic-inflammatory optic neuropathy developing as a result of bladder or gastric adenocarcinoma. This case demonstrates the challenge in diagnosing leptomeningeal carcinomatosis after a clinical presentation of progressive optic neuropathy, however, the presence of initial MRI signal changes extending into the optic chiasm may support the need to consider neuroaxis imaging and lumbar puncture earlier in the clinical course to avoid misdiagnosis or unnecessary empiric treatment.

### **S272. Feasibility and Usability of a Smartphone Eye-Tracking Application (“EyePhone”) for Self-Recording of Eye Movements in ALS Patients**

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**Introduction:** Quantitative video-oculography (VOG) has previously demonstrated eye movement abnormalities in patients with amyotrophic lateral sclerosis (ALS). Saccadic pursuit abnormalities, decreased saccade velocity, and saccadic intrusions have been identified as potential biomarkers of ALS progression. Thus, in order to efficiently and repeatedly track eye movements abnormalities patients with ALS, we evaluated the feasibility of our smartphone application named “EyePhone” as a self-recording tool to objectively quantify eye movements in patients with ALS. **Methods:** We prospectively enrolled patients with ALS at the Johns Hopkins Outpatient ALS Center between June 2022 and January 2023. Participants were asked to utilize the “EyePhone” and perform the tests independently and/or with help from their caregivers but without any help from the study team. Participants watched a tutorial video describing use of the EyePhone application. Participants then engaged in vertical and horizontal saccades (20-degree amplitude), horizontal and vertical smooth pursuit (10 degrees/s), and passive head impulse tests. To evaluate the quality and accuracy of recorded eye movements, a trained study team member repeated the same tests using VOG goggles. Participants then completed a questionnaire regarding their experience with the EyePhone. **Results:** We enrolled 10 ALS participants, 70% female, with an average age of 56.5

$\pm 12.2$  years. The average ALS functional rating score (ALSFERS) was  $26.77 \pm 6.33$  out of 48. All participants were able to complete the eye movement recording process with EyePhone app without any help from study members. All participants agreed (40% strongly agreed) that recording their eye movements with EyePhone was comfortable. Similarly, all either agreed ( $n=5$ ) or strongly agreed ( $n=5$ ) that it was easy to perform the tests without help from the study team. Moreover, none of the participants found it difficult to follow the instructions. When asked to choose between EyePhone or VOG goggles, 70% stated that if they were to take the eye-movements tests again, they would go with EyePhone. Finally, all patients agreed (60% strongly agreed) that if they were provided the instructions, they would be able to record their eye movements using EyePhone at home. **Conclusion:** We demonstrated that regardless of the motor disabilities, patients with ALS were able to record their eye movements either by themselves or with help from their caregivers using the EyePhone application.

#### S274. Neuroadaptability to Multifocal Intraocular Lens after Cataract Extraction: Pilot Evidence of an Association with Cognition

**Victoria S. Pelak, MD, Michael Taravella, MD, Jennifer Patnaik, PhD, Nathan Grove, PhD Pending, University of Colorado School of Medicine, Aurora, CO, USA.**

**Purpose:** Implantation of multifocal intraocular lens (MFIOL) after cataract extraction presents an entirely novel visual image to the cortex: *a partially focused and partially defocused image from one eye only*, with the goal to achieve visual focus at multiple distances with one lens. Visual neuroadaptation is necessary to accommodate this non-physiologic sensory input, and failure to adapt leads to negative satisfaction and lens removal in some patients. This pilot study aims to investigate relationships between MFIOL postoperative satisfaction and cognitive functions that could expose neuroadaptation failure. **Methods:** We recruited patients who underwent cataract surgery with a MFIOL implant and assessed satisfaction with visual outcomes on a 1-10 scale (10 = most satisfied). A subset of participants, matched on satisfaction, underwent cognitive assessment, including Logical Memory 2 (LM2), Digit Span, Block Design, Symbol Digit, Stroop Test (ST), Optic Flow Threshold, and Rotating Object Recognition, as well as Eysenck Personality Test. Ordinal logistic regression (OLR) models were fit for gender, age at surgery, age at evaluation, education, and cognitive profiles except for ST, for which a linear model was fit due to OLR non-convergence. Satisfaction was the outcome variable for all models. 95% confidence intervals (CI) for odds ratios (OR) or linear regression coefficient ( $\beta$ ) not containing the value 1 (or 0 for  $\beta$ ) were considered statistically significant. **Results:** 84 participants who underwent cataract surgery completed a survey and were on average 118 weeks post-surgery (SD = 61 weeks) at recruitment. Mean satisfaction was 7.3 (SD = 2.6). OLR analysis showed no significant association between satisfaction and time since surgery, or demographic, refractive, and lens model characteristics. 10 subjects underwent cognitive testing with mean satisfaction of 6.6 (SD = 3.2). OLR revealed that education

(OR 2.03 (95%CI 1.14-4.44)), LM2 (OR 1.49 (95%CI 1.01-2.58)), and rotating object recognition (OR 0.02 (95%CI <0.01-0.30)) were significantly associated with satisfaction on the ordinal scale. The linear model for the Stroop test showed a significant association between score and satisfaction ( $\beta=1.0$  (95%CI >0.99-<1.01)). **Conclusions:** Results suggest that lower satisfaction (or neuroadaptive failure) with MFIOL is associated with worse memory, visuospatial function, attention, and processing speed. Findings support prior fMRI data suggesting that frontoparietal circuits play a role in neuroadaptation after MFIOL. The effect sizes observed in this study will be useful for sample size calculations in future, prospective research on whether pre-surgical cognitive functions can predict failure of neuroadaptation to MFIOL.

#### S275. When Clinical Symptoms Don't Match Imaging: A Case Report of WEBINO Syndrome

**Ramit Singla, MD, Mohammad Alzayadneh, MD, Ra'ed Alkhaddash, MD, Balaji Krishnaiah, MD, Cheran Elangovan, MD. University of Tennessee Health Science Center, Memphis, TN, USA.**

**Introduction:** Wall-eyed bilateral internuclear ophthalmoplegia (WEBINO) is a rare ocular motility disorder characterized by primary gaze exotropia, bilateral adduction dysfunction, and abducting eye nystagmus. While most published cases and literature reviews attribute WEBINO syndrome to two common causes, namely ischemic stroke and demyelination, there are instances where a patient presents with clinical WEBINO syndrome but has a negative initial MRI. This sheds light on the fact that a posterior circulation stroke can be negative on initial MRI but exhibit changes on repeat imaging. **Case Report:** A 58-year-old man with hypertension, diabetes, syncope, and symptomatic bradycardia was brought to our ED as a stroke code due to dizziness, double vision, and 'crossed eyes.' His blood pressure was 192/81mmHg, and his heart rate was 47/min. His ocular exam revealed bilateral horizontal eye adduction deficits and primary gaze exotropia otherwise normal. Initial MRI brain showed no lesions correlating to his clinical exam findings. Repeat thin cuts MRI brain with contrast was obtained two days later, showing bilateral pontine base and tegmentum infarction without any abnormal enhancement. His workup, including vessel imaging and ECHO, was unremarkable. A small vessel etiology was suspected, and the patient was started on antiplatelets with risk factor management for secondary stroke prevention. Ophthalmology began conservative diplopia therapy before his discharge. **Discussion and Conclusion:** WEBINO syndrome is a rare clinical condition characterized by highly distinctive ocular manifestations resulting from lesions involving bilateral medial longitudinal fasciculi commonly caused by stroke and demyelination. While emphasizing the rarity of WEBINO syndrome, our case highlights the importance of clinical localization and the limitations of MRI in diagnosing ischemic stroke. Neurologists should be cautious when ruling out a diagnosis of ischemic stroke based solely on MRI findings. A study conducted by Pektezel et al. found that 31% of brainstem strokes were not detected on the initial MRI. Consequently, physicians

should be aware of this limitation of early MRI, particularly in cases of posterior circulation stroke. **Reference:** Pektezel et al, Diffusion-Weighted-Imaging Negative Stroke Syndromes; Turk J Neurol 2021;27:151-157

#### **LB-S116. Estrogen-Induced IL-1 $\beta$ Mediates Retinal Ganglion Cell Loss in Murine Optic Glioma**

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**Introduction:** Optic pathway glioma (OPG) is a low-grade glioma found in 15-20% of children with the neurofibromatosis type 1 (NF1) cancer predisposition syndrome. Some children with NF1-OPG experience vision loss due to retinal ganglion cell (RGC) death, which occurs three times more often in girls than boys. Using a murine *Nf1*-OPG model, we previously demonstrated that estrogen is necessary for RGC death. Herein, we present evidence that estrogen mediates RGC death by inducing glial production of IL-1 $\beta$ .

**Methods:** Immunohistochemistry using IL-1 $\beta$ , S100 $\beta$  (glial cells), Sox9 (astrocytes), and CC1 (oligodendrocytes) antibodies was performed on paraffin-embedded optic nerve sections. Primary RGCs were isolated from *Nf1*-mutant pups and treated with 1  $\mu$ g/ml of IL-1 $\alpha$ , IL-1 $\beta$ , or vehicle (PBS). RGC death was assessed using a lactate dehydrogenase release assay and activated caspase-3 immunocytochemistry. To assess *IL-1 $\beta$*  expression, RNA was extracted from optic nerves of wild type, *Nf1*-mutant, and *Nf1*-OPG mice at 3 months of age and analyzed by qRT-PCR. To inhibit estrogen signaling, female *Nf1*-OPG mice were treated with 15 mg/kg/day of leuprolide or vehicle (saline) via intraperitoneal injection from 6 weeks to 14 weeks of age. IL-1 $\beta$  was neutralized in female *Nf1*-OPG mice with 50  $\mu$ g/day of IL-1 $\beta$  antibodies via intraperitoneal injection from 6 weeks to 14 weeks of age. At the end of the treatment, mice were harvested for immunohistochemical analysis of RGCs (Rbpm), retinal nerve fiber layer thickness (Smi32), and IL-1 $\beta$  expression. **Results:** The majority of IL-1 $\beta$ -expressing cells are glia, and female *Nf1*-OPG mice have increased IL-1 $\beta$  expression in their optic nerves compared to their male and non-tumor-bearing counterparts. IL-1 $\beta$ , but not IL-1 $\alpha$ , is neurotoxic to *Nf1*-mutant RGCs *in vitro*. Inhibition of estrogen production reduces IL-1 $\beta$  expression in the optic nerve and protects RGCs from death, while IL-1 $\beta$  neutralization prevents RGC death without affecting its expression *in vivo*. **Conclusion:** We demonstrate that IL-1 $\beta$  expression in *Nf1*-OPG is sexually dimorphic. IL-1 $\beta$  alone is sufficient to induce *Nf1*-mutant RGC death *in vitro*, and reduction of estrogen-mediated IL-1 $\beta$  production or direct inhibition of IL-1 $\beta$  signaling are neuroprotective *in vivo*. These results suggest that IL-1 $\beta$  may be the neurotoxic effector through which estrogen induces RGC death in the setting of *Nf1*-OPG. **Significance:** This study is the first to identify a tumor-associated molecule with a sexually dimorphic expression and direct neurotoxic effect in a murine model *Nf1*-OPG.

#### **Neurorecovery and Neuroplasticity**

##### **S334. Atypical Frey's Syndrome: A Case Report**

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**Background:** Frey's syndrome (FS) is an autonomic disorder characterized by sweating and hyperemia at the distribution of the auriculotemporal nerve subsequent to gustatory stimuli. Additional features include facial swelling, parasthesia, and itchiness. Auriculotemporal syndrome was first coined by neurologist Lucy Frey, describing a man with profuse gustatory sweating after suffering a bullet wound to the parotid gland<sup>1</sup>. FS is a frequent complication of parotid surgery, with an incidence as high as 23.5%<sup>2</sup>. Gustatory sweating is the hallmark feature; however, multiple atypical cases of FS without hyperhidrosis were recorded in children after perinatal trauma by forceps-assisted delivery<sup>3</sup>. We document the first case in our knowledge of FS without hyperhidrosis in adults. **Case**

**Report:** We report a 78-year-old lady that was referred to our clinic for a second trial of Botox<sup>®</sup> injection. In 1993, our patient underwent a right partial-parotidectomy for a pleomorphic adenoma. One-year post-surgery, she developed intense itching on the right side of her face at the angle of the mandible, swelling, and redness that lasted for 10-20 minutes post-food ingestion that was not associated with gustatory sweating. After establishing a diagnosis, 14 units of Botox<sup>®</sup> were injected into the affected area without symptomatic relief. The patient had no history of diabetes, atopy, facial weakness, paresthesia, tinnitus, visual disturbance, or trauma. A surgical scar was visible behind the angle of the mandible, and skin excoriations were apparent. The patient was instructed to eat a snack, after which she developed itchiness that progressed to redness and swelling, and a minor starch-iodine test did not reveal any associated hyperhidrosis. A second session of Botox<sup>®</sup> was differed as there was no gustatory hyperhidrosis. **Discussion:** The most accepted hypothesis is aberrant reinnervation of parasympathetic fibers of the auriculotemporal nerve to the surrounding denervated sweat glands and cutaneous blood vessels. Consequently, mastication will send nerve impulses to the sweat glands and subcutaneous vessels instead of the salivary gland<sup>4</sup>. Whereas, in our case, we theorize that there is no efferent aberrant reinnervation of the sweat glands. An observational study on 18 patients by Marchese et al, developed a sweating-flushing-itch-paresthesia-pain (SFIPP) Frey scale to assess symptom severity before therapy. They documented a 100% prevalence of gustatory sweating in their patients<sup>5</sup>, thus highlighting the atypical presentation of our case. **Conclusion:** Atypical FS is characterized by the absence of gustatory sweating. As a result, usual treatments that target hyperhidrosis, including topical anticholinergics, antiperspirants, and intradermal injection of botulinum toxin, are not effective.

### S335. Potential Effects of Untreated Moderate-to-Severe Sleep-Related Breathing Disorders on the Number of Silent Episodes of Autonomic Dysreflexia during Sleep in People with Spinal Cord Injury

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**Background:** Sleep-related breathing disorders (SRBDs) are common but under-recognized medical conditions among individuals with spinal cord injury (SCI). However, the effect of SRBDs on cardiovascular function in individuals with SCI is still unclear. Individuals with SCI commonly experience cardiovascular dysfunction, including low baseline blood pressure (BP), orthostatic hypotension and episodes of autonomic dysreflexia (AD) and, hence, any impact of SRBDs on cardiovascular function after SCI is important to characterize. This ongoing cross-sectional study examined on the potential association between moderate-to-severe SRBDs and more severe cardiovascular dysfunction post-SCI. **Methods:** This cross-sectional study included adults with subacute or chronic ( $\geq 1$  month after SCI onset), cervical or high-thoracic (T6 or above) SCI, who reported clinical symptoms and/or signs suggestive of SRBD. The diagnosis of SRBD was established using a home-based/hospital unattended sleep screening test that quantifies the apnea-hypopnea index (AHI). Moderate-to-severe SRBD was defined as an AHI  $\geq 15$  events/hour. Episodes of AD were defined as a sudden increase in systolic BP of at least 20 mmHg. For the purpose of this study, we did not count episodes of AD during sleep that were caused by triggers other than hypopnea or apnea. **Results:** This study included 45 individuals (14 females, 31 males; mean age: 57.0 years; age range: 20-84 years) with motor complete (n=22) or incomplete SCI at cervical (n=38), or high thoracic levels, who reported symptoms and signs suggestive of SRBDs. Time from SCI onset varied from 1.5 months to 52 years (mean time: 49.4 months). Their mean apnea-hypopnea index (AHI) was 16.0 events/ hour (AHI range: 0.8 to 51.7 events/hour). The AHI was not associated with systolic BP (mean  $\pm$  SEM: 122.0 $\pm$ 2.2 mmHg;  $p=0.903$ ), diastolic BP (72.6 $\pm$ 3.0 mmHg;  $p=0.639$ ), mean arterial pressure (90.1 $\pm$ 2.4 mmHg;  $p=0.714$ ), and heart rate (70.6 $\pm$ 1.4 bpm;  $p=0.669$ ) during sleep. However, the AHI was significantly and positively correlated with the number of silent episodes of AD (mean  $\pm$  SEM: 3.6 $\pm$ 0.4;  $R_{sq}=0.220$ ,  $p=0.001$ ) during sleep. **Conclusions:** The results of this cross-sectional study suggest, for the first time, that more severe SRBD is associated with frequent silent episodes of AD during sleep among individuals living with a cervical or high-thoracic SCI. Future research is needed to assess the effects of continuous positive airway pressure (CPAP) therapy on cardiovascular dysfunction following SCI. **Funding:** 2018-RHI-SLEEP-1056, Ministry of Health Grant #719.

### S336. The Effects of Race/Ethnicity on Epidemiology, Survival and Neurological Outcomes Following Acute Traumatic Spinal Cord Injury

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**Background:** Little is known about the impact of race/ethnicity on the epidemiology and outcomes after acute traumatic spinal cord injury (tSCI). This study was undertaken to evaluate the influence of race/ethnicity on the epidemiology, survival and neurological recovery within the first year after tSCI. **Methods:** This retrospective cohort study included all 306 cases enrolled in the First National Acute Spinal Cord Injury Study (NASCIS-1), who were grouped into: (a) African Americans (n=84), (b) non-Hispanic whites (n=159), and (c) other races/ethnicities that included Hispanics (n=60) and Asians (n=3). Outcome measures included survival and neurological recovery (as assessed using the NASCIS motor, and pinprick and light-touch sensory scores) within the first year after tSCI. Data analyses of neurological recovery were adjusted for major potential confounders. **Results:** The study included 39 females and 267 males with overall mean age of 31 years who mostly sustained cervical severe tSCI after motor vehicle accidents or falls. Overall, the three groups were statistically comparable regarding sex distribution, level and severity of tSCI, individuals' level of consciousness at admission, and total received dose of MPSS in the acute stage after tSCI. However, African Americans were significantly older than non-Hispanic white individuals with tSCI ( $p=0.0238$ ). Also, African Americans and individuals of other races/ethnicities more often had a tSCI caused by missile and water-related accidents that more frequently resulted in open wounds than non-Hispanic white individuals, who had a greater proportion of tSCI caused by motor vehicle accidents and fall-related accidents ( $p<0.0001$ ). However, survival rates within the first year following tSCI were statistically comparable among the three race/ethnicity groups ( $p=0.3191$ ). Among who survived the first year of tSCI, there were no statistically significant difference between older survivors and younger survivors regarding motor, and pinprick and light-touch sensory recovery in the multiple regression analyses adjusted for major potential confounders ( $p>0.05$ ). **Conclusions:** The results of this retrospective study suggest that demographics and epidemiology of tSCI might vary depending upon the individual's race/ethnicity. Nevertheless, race/ethnicity did not influence survival rate or neurological recovery within the first year following tSCI.

### LB-S127. Neural Correlates of Phantom Motor Execution: A Systematic Review and Functional Neuroimaging Meta-Analysis

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**Background:** The current understanding of the neural correlates of phantom motor execution (PME) and their ability to reduce post-amputation pain is limited and will therefore be further investigated in this multimodal neuroimaging meta-analysis. **Methods:** We systematically searched PubMed and Embase until February 28, 2023. We included studies that used multimodal neuroimaging techniques (fMRI, PET, and EEG). We performed a coordinate-based meta-analysis testing two contrasts: a) PME versus rest (within group comparison), and b) PME versus motor execution (ME) in healthy controls (between group comparison). We generated voxel-wise (random effects) activation effect size maps using seed-based d-mapping (SDM) software. we utilized the I-squared index to assess the between-study heterogeneity. Statistical significance was evaluated using a randomization test and SDM default thresholds (voxel-level  $P < 0.005$  uncorrected). Finally, we assessed the risk of bias and evidence certainty by applying the GRADE approach. **Results:** We included 17 studies ( $n=327$ , 181 amputees, and 146 controls). The average age ranged from 36 to 50 years old, and most of the participants were males. Fifteen studies targeted upper limb amputees, and only two studies lower limb amputees. Most studies were fMRI paradigms (12/17), two used PET, and three used EEG. Due to heterogeneity, only seven studies were included in the meta-analyses. We found that during PME, there is a differential activation of the supplementary motor area BA6 (SDM- $Z=2.692$ ,  $p<0.0001$ ), post-central gyrus (SDM- $Z=1.876$ ,  $p<0.0001$ ), and dorso-lateral superior frontal gyrus (SDM- $Z=1.943$ ,  $p<0.0001$ ) compared to resting state (5 studies). Interestingly, when comparing PME and ME (two studies), the right insula anterior cingulate (SDM- $Z=6.433$ ,  $p<0.0001$ ), left insula amygdala (SDM- $Z=2.388$ ,  $p<0.0001$ ), and right striatum (SDM- $Z=1.960$ ,  $p<0.0001$ ) were activated differentially. The I-squared index ranged from 10 to 25%. From the integrative synthesis, we found that the degree of BOLD signal of the PME-related areas correlated positively with the intensity of PLP ( $r=0.60$ ,  $p=0.017$ ). However, the risk of bias and the certainty level was graded as moderate. **Conclusions:** Our results suggest that the PME neural correlates represent a distinct type of motor network activation with partial overlap with ME and motor imagery activations (sensorimotor and premotor cortices) but with a differential engagement of the insular cortex, suggesting a maladaptive activation due to disrupted body awareness and motor control. The association of PME with PLP intensity requires further causal exploration and opens the possibility of modulatory PME interventions to revert PLP.

## Sleep Disorders and Circadian Rhythms

### S337. Actigraphy-Determined Physical Activity in Older Adults with MCI and Sleep Apnea: Correlation with Self-Reported Sleepiness

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**Introduction:** Daytime sleepiness in older adults with mild cognitive impairment (MCI) negatively impacts their quality of life and may result in car accidents and serious injury (Eckstrom et al., 2020). Vigorous physical activity (PA) may reduce daytime sleepiness in older adults, perhaps by improving their nighttime sleep or reducing apnea during sleep (Liu et al., 2022). The objective of this secondary data analysis from the Memories 2 study was to better understand the association between PA measured with wrist actigraphy and subjective sleepiness measured by the Observation and interview-based Diurnal Sleepiness Inventory (ODSI) and Epworth Sleepiness Scale (ESS) (Peter-Derex et al., 2020). **Methods:** Older adults with amnesic mild cognitive impairment (MCI) and moderate to severe OSA [apnea-hypopnea index (AHI)  $\geq 15$ ] or no OSA (AHI  $\leq 5$ ) that were part of the multi-site Memories 2 study were included. Participants wore Actigraph GT9X watches on their non-dominant wrists to measure PA for 14 days. Cutoff values of sedentary, moderate, and vigorous PA were determined based on criteria from the ENRICA-2 study (Cabanas-Sánchez et al., 2021). The relationship between PA levels and subjective daytime sleepiness, controlling for age, was determined using a Spearman correlation (non-parametric distribution noted). **Results:** The sample ( $n = 133$ ) was 50.4% male, 64.7% Caucasian, with an average age of  $66.8 \pm 7.4$  years. 57.9% had OSA and 42.1% did not. The times spent in light, moderate, and vigorous activity were (mean (min-max)): 163.7 (15-440), 32.1 (0-178), 0.35 (0-13) minutes, respectively. The mean ODSI was 6.2 (sd = 5.8, range 0-20), and 41% of subjects had excessive daytime sleepiness based on a standard cut-point of 6. When controlling for age, minutes in vigorous PA and ODSI scores were significantly correlated ( $r = -0.24$ ,  $p = 0.006$ ), indicating that in older adults with MCI, less time spent in vigorous PA was associated with greater daytime sleepiness. Furthermore, relationships between subjective daytime sleepiness and vigorous PA were significant in the no OSA group ( $r = -0.39$ ,  $p = 0.004$ ), but not in the OSA group ( $r = -0.13$ ,  $p = 0.26$ ). There were no significant relationships with ESS scores and PA. **Conclusion:** Approximately 40% of older adults with MCI complained of

excessive daytime sleepiness and lower daytime sleepiness was associated with vigorous PA. Future studies might further examine relationships between PA, daytime sleepiness, nighttime sleep quality, and cognition in older adults with MCI.

### **S338. COVID-19 Disrupts Sleep Architecture by Reducing N3 Stage Sleep**

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Coronavirus disease 2019 (COVID-19) is an infection caused by Severe Acute Respiratory Syndrome - Coronavirus 2 (SARS-CoV2) that has led to the most devastating global pandemic in recent history, causing more than 6 million deaths globally. Despite its primary association with respiratory symptoms, nervous system involvement of COVID-19 was recognized early on. Neurologic complications during acute SARS-CoV2 infection were associated with a higher risk for persistent morbidity and mortality. There is interest in understanding the long-term neurologic consequences of COVID-19, as more patients report chronic sequelae of COVID-19 (termed Post-Acute Sequelae of COVID-19 [PASC]). Among the neurologic symptoms of PASC, sleep disturbance has been consistently endorsed in clinical settings and cohort studies, but these symptoms are largely based on subjective reports. How COVID-19 impacts sleep architecture has not been examined in a quantitative manner. To address this, we performed a retrospective study of available polysomnography (PSG) data from adult patients within the University of Washington Medicine who had at least 2 sets of PSG studies done. COVID-19 participants ( $n = 9$ ) had one PSG study at least 1 month after COVID-19 (verified with positive SARS-CoV2 PCR) and another PSG study at least 1 month prior to COVID-19. For controls ( $n = 24$ ; matched to COVID-19 participants for age, gender, body mass index, comorbidities and duration between studies), PSG data were taken from studies performed before January 2020, in order to eliminate any possibility of prior SARS-CoV2 infection. All PSG tests in this study were obtained for the purposes of monitoring responses to sleep apnea treatment. We found that COVID-19 patients developed a significant decrease in percentage of N3 stage sleep in their post-COVID-19 study compared to their pre-COVID-19 study ( $p = 0.001$ ) despite similar total sleep duration and latency. To assess if these changes were truly due to SARS-CoV2 infection, our COVID-19 PSG data were compared to pre-pandemic matched control data. This demonstrated that over a similar time period, the percentage of N3 stage sleep significantly decreased in COVID-19 patients ( $-80.6 \pm 8.4\%$ ) in contrast to the controls who showed an increase ( $+62.9 \pm 23.6\%$ ;  $p = 0.0009$ ). This is one of the first study to demonstrate how COVID-19 impacts sleep architecture using PSG data. Given that reduced N3 stage sleep can contribute to the development of chronic fatigue syndrome and neurodegenerative diseases, these changes may have important implications for explaining the mechanisms underlying the neurologic symptoms of PASC.

### **S339. Differential Cortical Network Engagement during States of Un / Consciousness in Humans**

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What happens in the human brain when we are unconscious? Despite substantial work, we are still unsure which brain regions are involved and how they are impacted when consciousness is disrupted. A robust approach for understanding brain networks and their sensitivity to state is to examine responses to perturbations. Using intracranial recordings and direct electrical stimulation in  $N=20$  patients (115 stimulation sites, +1000 recording channels) with depth electrodes implanted to determine the origin of their epileptic seizures, we mapped global, network, and intrinsic neural correlates of un/consciousness. We compared wake vs. arousable unconsciousness (sleep;  $N=13$ ) vs. non-arousable unconsciousness (propofol-induced general anesthesia;  $N=14$ ). Perturbational complexity, stimulation connectivity, and the response's amplitude were reduced, while inter-stimulation trial variability increased during both unconscious states, compared to wake. These changes were more pronounced during anesthesia than sleep. They also involved different cortical engagement. During sleep, changes were mostly uniformly distributed across the brain while during anesthesia the prefrontal cortex was the most disrupted. These suggest that the lack of arousability during anesthesia results not from just altered overall physiology but from a disconnection between prefrontal and other brain areas. These findings provide direct evidence of the different neural signatures in humans for loss of consciousness and for loss of arousability.

### **S340. Dose Titration and Tolerability of Once-Nightly Sodium Oxybate: Interim Data from RESTORE**

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**Objective:** To assess dose titration and tolerability of once-nightly sodium oxybate (ON-SXB; FT218) and study continuation in people with narcolepsy in the ongoing open-label extension/switch study RESTORE (NCT04451668). **Background:** ON-SXB, an investigational, extended-release treatment for adults with narcolepsy, is administered once at bedtime. Long-term safety and tolerability of ON-SXB are being evaluated in RESTORE; safety and patient preference data are presented separately. **Design/Methods:** Individuals aged  $\geq 16$  years with a confirmed diagnosis of narcolepsy type 1 or 2 were enrolled.

Group A: prior participation in the phase 3 REST-ON clinical trial (NCT02720744); no current oxybate usage. Group B: switch from stable immediate-release (IR) oxybate. Group C: oxybate-naïve. Initial ON-SXB dose: 4.5 g/night (Groups A/C); dose equivalent/closest to the previous total nightly IR oxybate dose (Group B). ON-SXB dose can be adjusted in 1.5-g/night weekly increments at investigators' discretion. Data were analyzed descriptively. **Results:** As of July 1, 2022, 185 participants were enrolled and 180 received  $\geq 1$  ON-SXB dose (Groups A/C,  $n=50$ ; Group B,  $n=130$ ). Of Group A/C participants, 7 (14.0%) continued the 4.5-g dose, 14 (28.0%) increased to 6 g, 21 (42.0%) to 7.5 g, and 8 (16.0%) to 9 g; 36/50 reached stable dose (72.0%; median time to stable dose, 4 weeks). Most in Group B received initial ON-SXB doses of 7.5 g (50/130 [38.5%]) and 9 g (47/130 [36.2%]). Group B participants who attained stable doses ( $n=118$ ) maintained ( $n=70$ ; 61.6%), increased ( $n=43$ ; 38.4%), or decreased ( $n=5$ ; 4.3%) their initial dose. The majority (83.0%) of Group B participants receiving initial 9-g doses maintained this dose. Fifty-one participants (27.6%) discontinued from the study (withdrew consent,  $n=25$  [13.5%]; adverse events,  $n=9$  [4.9%]). **Conclusions:** Most RESTORE participants have successfully had their ON-SXB dose titrated to a tolerable therapeutic dose regardless of previous oxybate usage. If FDA approved, ON-SXB will offer a once-at-bedtime treatment option for adults with narcolepsy.

### S341. Effect of Continuous Positive Airway Pressure (CPAP) Treatment on Hippocampal Volume in Patients with Obstructive Sleep Apnea (OSA)

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**Introduction:** OSA is a sleep-disordered breathing condition caused by upper airway collapse, leading to hypoxia and long-term neurocognitive consequences (Abbasi et al., 2021). The effects of CPAP—the standard therapy for OSA—on mitigating these neurological outcomes is unknown (Rosenzweig et al., 2013). Studying potential neuroprotective effects of CPAP in an older population with OSA and objective cognitive decline involving memory, termed amnesic mild cognitive impairment (aMCI), is pivotal for advancing dementia prevention research. We hypothesized that CPAP adherence in OSA participants would protect against atrophy of the hippocampus, a structure linked to memory. **Methods:** The Memories2 study is a quasi-experimental clinical research trial. Participants aged 55–85 were assigned to the apnea (apnea-hypopnea index (AHI)  $\geq 15$  events/hour) or control ( $\leq 5$

events/hour) groups by polysomnography. Those with an AHI between 5 and 15 were excluded. Those in the apnea group were classified as CPAP-adherent ( $\geq 4$  hours/night) or CPAP-nonadherent ( $< 4$  hours/night) based on their adherence to the treatment. All participants underwent MRI with volumetric T1-weighted structural imaging at baseline and approximately 1–1.5 years later (variability due to COVID-19 restrictions) from which hippocampal volumetry was measured; 77 participants underwent both scans. Self-normalized percent change values for right and left hippocampal volumes were calculated using the following equation:  $[(\text{baseline volume} - \text{follow-up volume})/\text{baseline volume}] * 100$ . Due to non-normal data distributions, Kruskal-Wallis tests were utilized to analyze group differences in hippocampal volume percent change. **Results:** The control ( $n=38$ ), CPAP-nonadherent ( $n=8$ ), and CPAP-adherent ( $n=31$ ) groups, respectively, had median percent decreases for right hippocampal volume of 0.96%, 0.92%, and 0.84% and for left hippocampal volume of 0.75%, 0.18%, and 0.39%. The percent changes in right ( $p=0.92$ ) and left ( $p=0.43$ ) hippocampal volumes were not significantly different between the three groups, with small effect sizes of 0.02 and  $<0.01$ , respectively. **Conclusions:** Initial univariate analysis shows no statistically significant differences and small effect sizes in hippocampal atrophy over one-year follow-up in the control, CPAP-nonadherent, and CPAP-adherent groups, suggesting CPAP-adherent apnea patients do not show greater atrophy compared to controls. Limitations include small sample size for MRI imaging, partly due to COVID-19 restrictions, and a short follow-up period. Future analyses of the Memories2 study will involve analyzing the complete MRI dataset, accounting for covariates, such as age and amyloid status, as well as utilizing deformation-based morphometry measures.

### S342. Light Exposure before Bedtime in Pregnancy is Associated with a Higher Risk of Gestational Diabetes

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**Introduction:** Evidence suggests a link between mistimed light exposure and impaired glucose regulation among nonpregnant adults. However, little is known about the effect of evening light exposure during pregnancy on the risk of gestational diabetes mellitus (GDM), a common pregnancy complication with significant health implications for both mother and offspring. Our objective was to investigate the association between evening light exposure before sleep during pregnancy and the risk of GDM. **Methods:** In this prospective cohort study conducted at 8 clinical U.S. sites, nulliparous women wore a wrist actigraphy monitor and completed a daily sleep diary for seven days between 16<sup>0</sup>–21<sup>6</sup> weeks of gestation. Based on recent recommendations on the maximum evening light exposure, we defined the primary exposure variable as the minutes of light exposure  $\geq 10$ -lux (dim light) during the three hours preceding sleep onset (“Pre-sleep light”), averaged across

all valid days of recording and categorized to tercile groups (“Dim,” “Moderate,” and “Bright”). The primary outcome was the incidence of GDM. Associations of pre-sleep light with baseline characteristics and actigraphy-derived sleep variables were examined using Chi-square, Fisher’s exact, and Kruskal-Wallis rank-sum tests. Univariate and multiple logistic regression models were used to characterize the relationship between pre-sleep light exposure and GDM. **Results:** Our analysis included 741 women (ages 18–43; 63% White; 22% BMI  $\geq 30$ ). GDM occurred in 31 (4.2%) participants. Greater pre-sleep light exposure was associated with an increased risk of GDM (odds ratio [95% confidence interval]: Bright 5.49 [1.8–23.84]; Moderate 4.05 [1.27–17.94], vs. Dim group). After adjusting separately for age, BMI, race/ethnicity, education, insurance, employment schedule, season, sleep duration, sleep midpoint, sleep regularity index, and daytime light exposure, pre-sleep light exposure remained significantly associated with GDM. Women who developed GDM had greater light exposure in the three hours before sleep onset yet did not differ in their light exposure during daytime or sleep or in their activity levels compared to those who did not develop GDM. **Conclusion:** Our study suggests that greater light exposure before sleep during the second trimester is associated with an increased risk of GDM. This association was not explained by the timing or duration of sleep. Pre-sleep light exposure may affect glucose metabolism through sympathetic overactivity, altered circadian gene expression, or melatonin suppression. Reducing evening light exposure, such as limiting light-emitting devices, is a modifiable behavior. Future work will examine whether reducing light before sleep improves maternal and offspring health outcomes.

### S343. Long-Term Safety of Once-Nightly Sodium Oxybate for Narcolepsy: RESTORE Study Interim Analysis of Data

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**Introduction:** The pivotal phase 3 REST-ON trial (NCT02720744) evaluated the efficacy and safety of once-nightly sodium oxybate (ON-SXB; FT218), an investigational extended-release formulation for treatment of adults with narcolepsy. In REST-ON, ON-SXB met its 3 coprimary endpoints: improvement in mean sleep latency on the Maintenance of Wakefulness test, Clinical Global Impression-Improvement rating (% much/very much improved), and number of weekly cataplexy attacks at all doses tested ( $P < 0.001$  vs placebo). The safety profile of ON-SXB was consistent with that of immediate-release (IR) SXB. The ongoing RESTORE trial (NCT04451668) is an open-label/

switch study evaluating the safety and tolerability of ON-SXB. **Methods:** Participants aged  $\geq 16$  years with narcolepsy type 1 or 2 who completed the REST-ON trial, were on stable-dose ( $\geq 1$  month) IR oxybate, or were oxybate-naïve are eligible for RESTORE. Initial doses were 4.5 g/night or equivalent/closest to the previous total IR oxybate dose/night for those switching; incremental adjustments (1.5 g/week; maximum dose, 9 g/night) were allowed. Safety data for participants receiving  $\geq 1$  dose of ON-SXB as of 01 July 2022 are reported here. **Results:** This analysis includes interim data from 180 participants (REST-ON participants,  $n=15$  [8.3%]; oxybate-naïve,  $n=35$  [19.4%]; switch,  $n=130$  [72.2%]). Most participants are white ( $n=150$  [83.3%]) and female ( $n=122$  [67.8%]); mean age is 35 years [range, 16–84]. Most participants who reported an adverse event (AE;  $n=105$  [58.3%]) had AEs that were mild (61.9%) or moderate (32.3%) in severity. Three participants had serious AEs (abscess, deep vein thrombosis, rib fracture and pneumothorax); all were deemed unrelated to ON-SXB and all 3 participants continued in the study. Adverse drug reactions (ADRs; ie, AEs related/possibly related to study drug) were reported by 76 (42.2%) participants with 6 (3.3%) participants discontinuing ON-SXB owing to ADRs. ADRs occurring in  $\geq 3\%$  of participants were nausea (11.7%), somnolence (6.7%), headache (5%), enuresis (5%), somnambulism (3.9%), dizziness (3.9%), tremor (3.9%), and vomiting (3.3%). **Conclusions:** Interim data from the RESTORE study indicate that ON-SXB is generally well tolerated with a low rate of discontinuation owing to ADRs. If granted final FDA approval, ON-SXB will offer adults with narcolepsy a once-at-bedtime oxybate treatment option.

### S345. Patient Preference and Nocturnal Experience with Oxybate Treatment for Narcolepsy: Interim Analysis of Data from RESTORE

**Asim Roy, MD<sup>1</sup>, John Harsh, PhD<sup>2</sup>, Akinyemi O. Ajayi, MD<sup>3</sup>, Thomas Stern, MD<sup>4</sup>, Jordan Dubow, MD<sup>5</sup>, Jennifer Gudeman, PharmD<sup>5</sup>.** <sup>1</sup>Ohio Sleep Medicine and Neuroscience Institute, Dublin, OH, USA, <sup>2</sup>Colorado Sleep Institute, Boulder, CO, USA, <sup>3</sup>Florida Pediatric Research Institute, Winter Park, FL, USA, <sup>4</sup>Advanced Respiratory and Sleep Medicine, PLLC, Huntersville, NC, USA, <sup>5</sup>Avadel Pharmaceuticals, Chesterfield, MO, USA.

**Introduction:** Sodium oxybate (SXB) is a standard-of-care treatment for adults with narcolepsy. Existing oxybate formulations are immediate release (IR), requiring patients to awaken for a second dose 2.5–4 hours after the first bedtime dose. Once-nightly SXB (ON-SXB; FT218), an investigational extended-release formulation, replaces this middle-of-the-night dosing with a once-at-bedtime regimen. RESTORE (NCT04451668) is an open-label/switch study evaluating the safety/tolerability of ON-SXB and patient preferences for ON-SXB or IR oxybate. **Methods:** RESTORE includes participants aged  $\geq 16$  years with narcolepsy type 1 or 2 who completed the phase 3 REST-ON trial, were on stable-dose ( $\geq 1$  month) IR oxybate, or were oxybate-naïve. Initial doses for participants switching from IR oxybate are equivalent/closest to the previous total dose/night; incremental



adjustments (1.5 g/week; maximum, 9 g/night) are allowed. A nocturnal adverse event (AE) questionnaire about switch participants' IR oxybate experience in the previous 3 months was completed at baseline. Switch participants completed the preference questionnaire after 3 months of ON-SXB treatment. **Results:** Data available from preference questionnaires (n=78) and nocturnal AE questionnaires (n=130) were analyzed at the interim data cutoff (01 July 2022). Most common AEs thus far were nausea, headache, and somnolence. The once-nightly dosing regimen was preferred by 93.6% (73/78) of participants. The second nightly IR oxybate dose was unintentionally missed in the previous 3 months by 65.4% (85/130) of switch participants; 80.2% (73/91) who intentionally and/or unintentionally missed the second dose felt worse the next day. Participants who took their second nightly IR oxybate dose >4 h after the first dose (51/130 [39.2%]) reported being somewhat, quite a bit, or extremely groggy/unsteady the next morning (26/51 [51.0%]). Inconvenience of the second dose was reported by 70.8%. Other issues related to the second dose were anxiety (29.2%) and the need to be woken by someone else (23.1%). In the past 3 months, 118 participants (90.8%) arose from bed after waking to take the second dose; 9 of these participants reported having fallen, with 5 reporting injuries. **Conclusions:** These interim RESTORE data demonstrate patient preference for once-at-bedtime dosing of ON-SXB and indicate treatment burden associated with twice-nightly IR oxybate.

### S346. Sleep Insufficiency, Circadian Rhythms, and Metabolomics: The Connection to Metabolic Sleep Disorders

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**Purpose:** The majority of US adults who report experiencing insufficient sleep are more likely to suffer from metabolic disorders such as hyperlipidemia, diabetes, and obesity than those with sufficient sleep. Less is understood about the underlying molecular mechanisms connecting these phenomena. A systematic, qualitative review of metabolomics studies exploring metabolic changes in response to sleep insufficiency, sleep deprivation, or circadian disruption was conducted in accordance with PRISMA guidelines. **Methods:** An electronic literature review in the PubMed database was performed considering publications through May 2021 and screening and eligibility criteria were applied to articles retrieved. The following keywords were used: "metabolomics" and "sleep disorders" or "sleep deprivation" or "sleep disturbance" or "circadian rhythm." After screening and addition of studies included from reference lists of retrieved studies, 16 records were identified for review. **Results:** Consistent changes in metabolites were observed across studies between individuals experiencing sleep deprivation as compared to non-sleep deprivation controls. Significant increases in phosphatidylcholines, acylcarnitines, sphingolipids, and other lipids are consistent across studies. Increased levels of amino acids such as tryptophan and phenylalanine are also noted. However, studies are limited to small samples of young, healthy, mostly male participants conducted

in short inpatient sessions, limiting generalizability. **Conclusion:** Changes in lipid and amino acid metabolites accompanying sleep deprivation and/or circadian rhythms may indicate cellular membrane and protein breakdown underlying the connection between sleep disturbance, hyperlipidemia, and other metabolic disorders. Larger epidemiological studies examining changes in the human metabolome in response to chronic insufficient sleep would help elucidate this relationship.

### S347. The Dual Orexin Receptor Antagonist Lemborexant Induces Microglial Phagocytosis and Reduces Amyloid Plaque Deposition in APP/PS1 Mice

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**Background:** Disrupted sleep is implicated in the pathogenesis of Alzheimer's disease (AD). Not only is sleep-wake fragmentation prominent in early to advanced AD, sleep restriction has been shown to aggravate AD pathology in mice. Lemborexant (LEM), a dual orexin receptor antagonist, was approved by the FDA in 2019 for the treatment of insomnia in adults. We investigated whether chronic inhibition of the orexin signaling pathway via administration of LEM impacts amyloid plaque deposition in APP<sup>swe</sup>/PSEN1<sup>ΔE9</sup> (APP/PS1) mice. **Methods:** APP/PS1 mice were orally administered LEM for 6 weeks at ZT0 (lights on) starting just prior to the age of amyloid plaque onset. To gauge whether this effect was sleep-driven or sleep-independent, a comparator drug doxepin (DOX) was used. **Results:** We found that both DOX and LEM significantly increased total sleep, whereas, only LEM prevented the deposition of fibrillar plaques significantly in comparison to vehicle-treated or DOX-treated mice. We also observed more phagocytic CD68-expressing peri-plaque microglia in LEM-treated mice suggesting specific effects on microglial functions. Accordingly, gene expression suggested alteration in interferon beta1 expression in LEM-treated APP/PS1 mice. Ongoing studies are evaluating the effect of LEM on microglial plaque phagocytosis. **Conclusion:** Our results show that chronic orexin antagonism with LEM can prevent amyloid plaque deposition more effectively than another sleep agent (DOX), potentially via sleep-independent effects on microglia activation. Identification of the pathways involved in the clearance of plaque deposition by orexin antagonism creates new therapeutic opportunities for AD prevention.

### S348. The Impact of CPAP Therapy for 4 Months for Management of SRBDs on Psychosocial Outcomes in Individuals with Chronic Spinal Cord Injury: A Mixed-Methods Study

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Research Institute, Toronto, ON, Canada, <sup>3</sup>Sunnybrook Health Sciences Centre; University of Toronto, Toronto, ON, Canada.

**Background:** Sleep-related breathing disorders (SRBDs) are common but under-recognized after spinal cord injury (SCI). We report preliminary data from an ongoing study examining the potential psychosocial benefits of continuous positive airway pressure (CPAP) therapy in people with SCI and moderate-to-severe SRBDs. **Methods:** This single-arm clinical trial (NCT04007380) aims to evaluate the impact of 4 months of CPAP therapy among adults with chronic SCI who were newly diagnosed with moderate-to-severe SRBDs. Outcome measures included Epworth Sleepiness Scale (ESS), Medical Outcomes Study Sleep Scale (MOS-SS), Fatigue Severity Scale (FSS), Depression, Anxiety & Stress Scale-21 (DASS-21), Montreal Cognitive Assessment (MoCA), SF-36, and Craig Handicap Assessment & Reporting Technique (CHART). All participants were invited for a semi-structured interview to share their experience after the trial (qualitative analysis). Adherence was defined as the use of CPAP for  $\geq 4$  hours/night on  $\geq 5$  nights of the week. **Results:** By February/2023, we screened 33 individuals (10 females, 23 males; ages range: 37-79 years; mean age: 58.3 years) with complete ( $n=15$ ) or incomplete SCI at the cervical ( $n=22$ ) or thoracic level. Mean time from SCI onset was 180.3 months (range: 4-793 months). Of the 33 screened participants, the apnea-hypopnea index (AHI) varied from 2.6 to 83.7 events/hour (mean AHI: 24.6), and 25 individuals with moderate-to-severe SRBDs initiated CPAP therapy. Overall, 19 individuals have completed the trial, whereas 8 individuals withdrew from the study. The overall mean adherence rate to CPAP was 42.1% among those who completed the trial. Daytime sleepiness and sleep quality significantly improved with CPAP therapy (pre-ESS=9.4, post-ESS=4.9,  $p=0.0002$ ; pre-MOS-SS=27.9, post-MOS-SS=57.9,  $p<0.0001$ ). The FSS also significantly decreased with CPAP therapy (pre-FSS=44.0, post-FSS=34.9,  $p=0.0194$ ). Health-related quality of life also significantly improved after CPAP therapy (SF-36 physical component summary:  $p=0.0104$ ; SF-36 mental component summary:  $p=0.00561$ ). There was a numeric increase in MoCA, DASS-21 and CHART scores, but they did not yet reach significance (MoCA:  $p=0.079$ ; DASS-21:  $p=0.207$ ; CHART:  $p=0.221$ ). Notably, the DASS-21 anxiety subscore significantly reduced with CPAP therapy ( $p=0.043$ ). All 19 participants confirmed that CPAP therapy had a major beneficial impact on psychosocial outcomes in the qualitative study. **Conclusions:** Our preliminary results suggest that 4-month CPAP therapy significantly improves sleep quality, and quality of life, and mitigates daytime sleepiness, fatigue, and anxiety in people with chronic SCI. These findings were corroborated by the results of the qualitative analysis.

### S349. Understanding Narcolepsy Treatments from the Patient's Perspective: A Survey of People Living with Narcolepsy

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**Introduction:** Individuals with narcolepsy were surveyed to better understand desired treatment outcomes and how those outcomes map to commonly experienced symptoms, treatment awareness, and medication usage. **Methods:** In February 2022, an email invitation to a 27-question online survey was sent to US members of MyNarcolepsyTeam, a social network of >9,800 members. **Results:** In total, 110 members completed the survey. The most frequently mentioned desired treatment goals aligned with the most commonly reported symptoms: being able to stop sleeping during the day (77%); increased energy (62%); improved memory (36%); improved productivity (29%); improved sleep continuity (22%); and for patients with narcolepsy type 1, reducing cataplexy (28%). A common theme was desire for a medication that would treat the underlying cause and not just improve specific symptoms. In one patient's own words: "I want to see treatments that target the root problem of poor nighttime sleep rather than just being a band-aid for [excessive daytime sleepiness] EDS, like stimulants are." Only a small percentage of respondents (13%) were not currently taking any type of medication to address narcolepsy symptoms. 64% were currently taking  $\geq 2$  medications to address both the daytime and nighttime symptoms. Most commonly mentioned current treatments were dextroamphetamine-amphetamine (30%), modafinil (22%), melatonin (16%), armodafinil (15%), venlafaxine (14%), and oxybate (14%). Notably, 33% of patients taking sodium oxybate chose sleeping through the night as a desired outcome. Most common sources for learning about treatments were narcolepsy-specific websites (53%), MyNarcolepsyTeam specifically (45%), the patient's doctor (42%), scientific articles (42%), and advocacy groups (37%). **Conclusions:** Patients experience a wide range of both daytime and nighttime symptoms and seek relief from both sets of symptoms including EDS (93%), fatigue (79%), cognitive challenges (74%), as well as sleep disruptions (63%). As a result, the majority need multiple medications. Understanding the experiences and needs of people with narcolepsy provides significant opportunities for clinicians to support, educate, and treat their patients holistically. Additionally, content readily available on the internet, whether it is narcolepsy-specific content or social networks, helps patients proactively discuss options with their clinician.

### K-S120. Local Changes in Sleep Oscillations after Stroke

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Ischemic stroke disrupts neuronal activity, but the effect of stroke on sleep oscillations and their change over the course of recovery is unclear. To study changes in sleep oscillations, we used wide-field optical fluorescence imaging in mice expressing the genetically encoded calcium indicator GCaMP6 in excitatory cortical neurons fitted with plexiglass whole-cortex cranial windows. Sleep was recorded in the head-fixed position before and 24 hours, 1 week, and 4 weeks after photothrombotic stroke over the left somatosensory (forepaw) cortex. Acutely (24 hours) following stroke, mice exhibited a loss of broadband neuronal

activity over and around the region of ischemia in NREM and REM sleep that was not present to the same degree as wakefulness. In the subacute period following a stroke, we observed a sleep-independent emergence of a new, local slow oscillation (S.O.) at 1 week that renormalized over time. These local, time-dependent changes in neuronal activity and oscillations were predictive of residual stroke size in the chronic (8 weeks) period. Manipulating sleep neuronal activity or oscillations in a local- and time-specific manner may have clinical utility by altering the course of stroke recovery.

## PLENARY ABSTRACTS

All abstract information listed below has been provided to the ANA by plenary session speakers.

### Saturday, September 9, 2023: Opening Symposium: Gene Therapy in Rare Neurological Diseases

#### Vector-Based Gene Therapies – Advances in Capsids

*Beverly L. Davidson, PhD*

*The Children's Hospital of Philadelphia*

Diseases of the brain are as complex and varied as the many cell types, subcellular types, sub-structures, and complicated connectivity within. As such, it is unlikely that one platform or vector delivery approach can be broadly applied to safely and efficiently treat or attenuate inherited disorders that impact CNS function. We present a disease-centric approach wherein the most optimal route of delivery for the disease indication is used to identify the most efficient vectors for potential one and done and therapies. Efforts are made to use routes of delivery that minimize off-target effects, maximize transduction of the target brain regions and target cells within, and retain the ability to transduce similar cell types and regions in cell and rodent models of disease. Our methods are translatable to a range of CNS indications and aim to improve next generation gene therapies for greater impact to patients.

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#### Optimizing Outcomes in Neurometabolic Disorders with Gene Therapy

*Rebecca Ahrens-Nicklas, MD, PhD*

*The Children's Hospital of Philadelphia*

While individually rare, inborn errors of metabolism (IEMs) affect approximately 1:1,000 individuals. More than two-thirds of IEMs are characterized by significant neurologic dysfunction, a major source of morbidity and mortality in patients. Definitive molecular therapies including gene replacement and gene editing strategies are in preclinical and clinical development for several neurometabolic disorders. IEMs are attractive drug development targets as the molecular defect is known and most disorders have clinically relevant biomarkers. While some CNS gene therapy programs for IEMs have yielded promising results, many have failed to meet trial endpoints. Challenges have included achieving adequate distribution in key brain regions, designing safe and well-tolerated vectors, optimizing timing of drug delivery, and selecting meaningful clinical trial endpoints. Novel strategies to overcome each of these obstacles are needed to maximize the benefit of these potentially transformative therapies.

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#### Antisense Based Therapy for Rare Neurological Diseases

*C. Frank Bennett, PhD*

*Ionis Pharmaceuticals, Inc.*

Currently, there are multiple genetic-based medicines being pursued for rare neurological diseases including antisense technology, gene therapy, and gene editing technologies. Antisense oligonucleotides (ASOs) are one of the more advanced technologies. ASOs are synthetic, chemical-modified nucleic acid analogs designed to bind to RNA by Watson-Crick base pairing. Upon binding to the RNA, ASOs modulate the function of the targeted RNA through a variety of mechanisms. Both protein-coding, as well as non-coding RNAs, can be targets of ASO-based drugs, significantly broadening therapeutic targets for drug discovery compared to small molecules and protein-based therapeutics. The approval of nusinersen (Spinraza™) as a treatment for spinal muscular atrophy (SMA) validates the utility of antisense drugs for the treatment of motor neuron diseases. The application of antisense technology as a potential therapy for other rare neurodegenerative diseases and neurodevelopmental disorders will be discussed.

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## Gene Therapy as a Platform: From Giant Axonal Neuropathy to the PaveGT Program

Carsten G. Bönnemann, MD, Habil, FANA

National Institute of Neurological Disorders and Stroke

AAV mediated gene replacement therapy carries great promise for rare and ultra rare disease in which the mechanism is loss of function and the cDNA is small enough to fit the packaging capacity of AAV. However, the development of a new AAV gene therapy for every single such rare indication currently is difficult and often prohibitively expensive. At the same time, a predefined vector and expression cassette, administered by the same route, but used with exchangeable transgenes could be used to address biologically and clinically related but genetically distinct disorders - simplifying and shortening the pathway to clinical development by making use of various inherent platforms in such an approach. To illustrate this concept I will discuss the intrathecal gene therapy approach to the childhood neurodegenerative disease Giant Axonal Neuropathy and the Platform Vector Gene Therapy Project of NCATS, NINDS and NHGRI.

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# Sunday, September 10, 2023: The Role of RNA-Binding Proteins and RNA Metabolism in Neurological Development and Disease

## Same Gene, Different Variants, Different Phenotypes: The Puzzling Case of the RNA-binding Protein Pumilio1 (SCA47)

Vincenzo A. Gennarino, PhD

Columbia University Irving Medical Center

Recent work in our lab understanding the interactions of RNA-binding proteins and the functions of alternative polyadenylation (APA) has led to the identification of new neurological diseases involving the mutations in Pumilio1 (SCA47) [1] and the APA factor CPSF6 [2]. In this talk I will describe how questions in basic science led us to important clinical discoveries, while the clinical discoveries in turn led to new and fundamental questions—and answers—at the level of RNA neurobiology.

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## Disruption of RNA Metabolism in Neurodegeneration and Emerging Therapeutic Strategies

Clotilde Lagier-Tourenne, MD, PhD, FANA

Massachusetts General Hospital and Harvard Medical School

Alteration of RNA metabolism has emerged as a central theme in neurodegenerative diseases with mutations and/or mislocalization of RNA binding proteins, including TDP-43 and FUS, in amyotrophic lateral sclerosis (ALS), frontotemporal dementia (FTD) and Alzheimer's disease. Following the recognition of their crucial role in neurodegeneration, we have used genome-wide approaches to define their role in regulating the expression and splicing of their RNA targets. We recently demonstrated that the human RNA most affected by the loss of nuclear TDP-43 is encoding the neuronal growth-associated factor called stathmin-2. Reduced levels of stathmin-2 is a hallmark in sporadic and familial ALS/FTD, and restoration of stathmin-2 expression emerges as an attractive therapeutic strategy in TDP-43 proteinopathies. Using newly generated cellular and animal models, we have determined stathmin-2's essential role in neuronal regeneration and axonal maintenance and have established antisense oligonucleotides (ASOs) as a therapeutically viable approach to rescue stathmin-2 in TDP-43 proteinopathies. Other potential therapeutic approaches aim at directly targeting the cellular

mislocalization and abnormal phase transition of TDP-43 and FUS. We use small molecules and genetic screens, including high-content optical screens, to identify modifiers of disease-associated phenotypes that represent new therapeutic targets.

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## Repeating Themes in Human Neurologic Disease

Peter Todd, MD, PhD, FANA

University of Michigan

Over the past 30 years, nucleotide repeat expansions have emerged as common causes of many neurologic conditions, including ALS, FTD, Ataxia and Autism. Repeats create dynamic elements as DNA, RNA and translated proteins to drive disease pathogenesis. In this lecture I will describe how the structures of repetitive RNA elements directly influence their metabolism, binding partners, localization, translation, and degradation. I will then discuss how these same properties of repeats create unique molecular targets for modular therapeutic development through use of emerging technologies.

## References:

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## From Vesicle Trafficking to mRNA Metabolism: A Double-Life for the Parkinson's Protein Alpha-Synuclein

Vikram Khurana, MD, PhD

Harvard Medical School / Brigham and Women's Hospital

Alpha-synuclein ( $\alpha$ Syn) is a conformationally plastic protein that reversibly binds to cellular membranes. It aggregates and is genetically linked to Parkinson's disease (PD). Our laboratory has identified molecular perturbations at the proteome-scale that result from misfolding and mistrafficking of  $\alpha$ Syn. These investigations have strongly suggested that the resultant toxicity is closely related to its native function and molecular interactions. While  $\alpha$ Syn has been closely tied to vesicle trafficking at the presynaptic terminal, we have surprisingly found that  $\alpha$ Syn to be in close proximity to numerous RNA-binding proteins (RBPs). Moreover,  $\alpha$ Syn toxicity was both impacted by the genetic modulation of RBPs and associated with striking alterations of the RBP proteome. Recently, we showed that  $\alpha$ Syn is directly involved in gene regulation through RBP interactions and that this is likely important in PD. More specifically,  $\alpha$ Syn directly modulates Processing-bodies (P-bodies), membrane-less organelles that function in mRNA turnover and storage. The N-terminus of  $\alpha$ Syn, but not other synucleins, dictates mutually exclusive binding either to cellular membranes or to P-bodies in the cytosol.  $\alpha$ Syn associates with multiple decapping proteins in close proximity on the Edc4 scaffold. As  $\alpha$ Syn pathologically accumulates, aberrant interaction with Edc4 occurs at the expense of physiologic decapping-module interactions. mRNA-decay kinetics within PD-relevant pathways are correspondingly disrupted in PD patient neurons and the brain. Genetic



modulation of P-body components alters  $\alpha$ Syn toxicity, and human genetic analysis lends support to the disease-relevance of these interactions. Beyond revealing an unexpected aspect of  $\alpha$ Syn function and pathology, our data highlight the versatility of conformationally plastic proteins with high intrinsic disorder and their role in intracellular signaling.

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## Sunday, September 10, 2023: Presidential Symposium - Exploring Sleep Disturbance in CNS Disorders

### Sleep and Neurodevelopmental Conditions

Beth Malow, MD, MS, FANA

Vanderbilt University Medical Center

Sleep problems are common in conditions of neurodevelopment. In this presentation, the causes and contributors to sleep disturbances across the lifespan in autism and other conditions will be highlighted. These include attention to medical co-occurring conditions, sleep habits, and arousal dysregulation, melatonin processing, and genetic contributors. Approaches to treatment, including novel ways to disseminate findings into practice, and the use of practice pathways will be discussed. Medication options will be presented in the context of best practices.

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1. [A Practice Pathway for the Treatment of Night Wakings in Children with Autism Spectrum Disorder](#). Galion AW, Farmer JG, Connolly HV, Allhusen VD, Bennett A, Coury DL, Lam J, Neumeyer AM, Sohl K, Witmans M, Malow BA; Autism Treatment Network/Autism Intervention Research Network on Physical Health (ATN/AIR-P) Sleep Committee. *J Autism Dev Disord*. 2023 Jun 26. doi: 10.1007/s10803-023-06026-2. Online ahead of print. PMID: 37358787.
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### Bidirectional Relationship Between Sleep and Alzheimer Disease - Related Pathology

David Holtzman, MD, FANA

Washington University in St. Louis

Disrupted sleep has been found to both acutely increase soluble forms of proteins critical to Alzheimer's disease pathogenesis including amyloid-beta and tau in both mouse models and humans. Chronic sleep disruption increases aggregated forms of both amyloid-beta and tau and associated neurodegeneration. Evidence suggests that acute changes in these proteins are due to both altered release and clearance. New evidence suggests that microglia play a key role in both the chronic buildup of amyloid-beta and tau. Increasing sleep has also been shown to decrease both amyloid-beta and tau pathologies. Once amyloid-beta and tau accumulate, there is evidence that these changes disrupt sleep. These findings suggest that sleep may be a novel target to influence the pathogenesis of Alzheimer's disease.

#### References:

1. [APOE- \$\epsilon\$ 4 synergizes with sleep disruption to accelerate A \$\beta\$  deposition and A \$\beta\$ -associated tau seeding and spreading](#). Wang C, Nambiar A, Strickland MR, Lee C, Parhizkar S, Moore AC, Musiek ES, Ulrich JD, Holtzman DM. *J Clin Invest*. 2023 Jun 6:e169131. doi: 10.1172/JCI169131. Online ahead of print. PMID: 37279069
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### Glymphatic System – and Relationship to Disorder

Maiken Nedergaard, MD, DMSc

University of Rochester Medical Center / University of Copenhagen

The glymphatic system - A unidirectional fluid transport pathway that facilitates the clearance of waste products from

neuronal metabolism has recently been described (Iliff, Wang et al. 2012). Glymphatic clearance of macromolecules is driven by cerebrospinal fluid (CSF) that flows in along paravascular spaces and through the brain parenchyma via support from astroglial aquaporin-4 water channels. The glymphatic circulation constitutes a complete anatomical pathway; paravascular CSF exchanges with the interstitial fluid, solutes collect along para-venous spaces, then drain into the vessels of the lymphatic system for ultimate excretion from the kidney or degradation in the liver (Rasmussen, Mestre et al. 2022). The glymphatic system is mostly active during sleep and suppressed during wakefulness (Xie, Kang et al. 2013). Cardiovascular, neurological and several inflammatory diseases and aging have all been shown to inhibit glymphatic function and predispose to development of neurodegenerative diseases (Nedergaard and Goldman 2020). Chronic neuropathic and chronic stress are also negatively affecting glymphatic flow (Rasmussen, Mestre et al. 2018). These findings have led to the idea that glymphatic fluid transport acts as an integrator of general well-being and that common approaches that are known to reduce stress and improve sleep and life quality all act by improve glymphatic flow and restoring brain homeostasis.

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#### Genetic Sleep Variants Protect Against Alzheimer-Like Diseases

Ying-Hui Fu, PhD

University of California, San Francisco

Sleep occupies a significant portion of our daily lives, yet our understanding of sleep, in general, is minimal. Sleep of sufficient duration, continuity, and intensity is necessary to promote high levels of cognitive performance during the wake period and prevent physiological changes that may predispose individuals to many adverse health outcomes. Sleep insufficiency is prevalent in our society due to the high demand for work, school, and many environmental factors, thus significantly contributing to many health conditions we face. Interestingly, the biological need for sleep varies dramatically among humans. We

have identified a group of humans with unusual sleep behaviors and have used the human genetics approach to identify many genes/mutations that give them unusual sleep behaviors. Mouse models recapitulate the human condition, and in vitro, molecular and neurocircuitry studies offer insight into the underlying mechanisms. Because of sleep's fundamental role in our health, the pathways regulating sleep are intertwined with those regulating other functions. Thus, our method also offers opportunities to investigate how sleep can impact other conditions, including the pathology of various brain diseases.

#### References:

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## Monday, September 11, 2023: Prodromal Neurologic Disease: Early Markers and Earlier Opportunities for Treatment

#### Preclinical Alzheimer Disease

Marilyn S. Albert, PhD, FANA

Johns Hopkins School of Medicine

The hallmarks of Alzheimer's disease (AD) pathology, amyloid plaques, and tau tangles, begin to accumulate in the brain as early as middle age, when individuals are cognitively normal. Recent studies of cognitively unimpaired individuals who have been followed longitudinally over time indicate that AD biomarkers of these pathological features have accelerated rates of change prior to the onset of clinical symptoms of mild cognitive impairment (MCI), and are associated with time to onset of MCI. These, and related findings, suggest that this preclinical phase of AD offers a window of opportunity for early intervention. Additional research is needed to identify novel biomarkers that may improve prediction and reveal new treatment targets. It is also important to quantify the additional pathologies that are commonly seen in older individuals with cognitive impairment (e.g., vascular disease, TDP-43) in order to develop optimal treatment strategies.

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### Prodromal Parkinson Disease

Ronald Postuma, MD, MSc

Montreal Neurological Institute, McGill University

The presentation will outline the major features of the early stages of PD, discussing predictive power, specificity and lead time. The potential for prodromal PD as a means to test neuroprotective therapy will be outlined.

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### From Gene Mutation to Disease Prevention: Progress and Challenges in the Huntington Disease Continuum

Jane S. Paulsen, PhD, FANA

University of Wisconsin - Madison

As an autosomal dominant disorder, HD natural history studies have followed gene mutation carriers throughout the HD continuum. As early as 2001, large-scale multi-national prodromal HD research showed abnormalities decades before clinical expression. While over twenty years of research have now reported extensive biofluid, brain imaging and clinical outcome measures showing very early differences from healthy controls, no qualified biomarkers exist. Despite limitations, endeavors to prevent onset or delay progression of HD continue to propagate. Efforts to identify gaps in our knowledge base to better identify and intervene upon HD in its prodromal state are exigent. Two clear priorities for the HD field are to answer the questions, "when can treatments begin?" and "how can we determine whether a treatment is working?". Though applications have been limited, numerous strong susceptibility/risk and prognostic HD biomarkers have been identified. Assertions to address the first question have been offered though reproducibility is lacking. Monitoring biomarkers to date are largely restricted to smaller epochs of the HD continuum and most candidates are lacking sufficient longitudinal data. Diagnostic biomarkers to identify individuals with a subtype have been used in a few clinical trials. Efforts to map the current research landscape suggest that some elements essential to fill knowledge gaps and advance progress in prodromal HD are missing. Questions remain about how the scientific community might draw attention to the research, clinical, policy, and ethical considerations impacting prodromal HD intervention. Given rapid advances in technology impacting genetics, wearables, brain imaging and emerging multimodal biomarkers, the opportunities are vast for HD as well as other autosomal dominant neurodegenerative disorders. Progress shared across distinct genetic neurodegenerative diseases has often been synergistic for scientific advancements in the greater translational neuroscientific research fields. More recent ventures to build collaborative research partnerships using autosomal dominant diseases can be expected to further capitalize and expand our shared purpose to facilitate earlier opportunities for identification and intervention.

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## What are the Broader Implications of Diagnosing Preclinical Disease?

Emily Largent, JD, PhD, RN

University of Pennsylvania

"Preclinical" Alzheimer's disease (AD) presently remains a research construct. Yet, US Food and Drug Administration approval of disease-modifying therapies for symptomatic individuals and advancement toward more accessible AD biomarker testing suggest preclinical diagnoses may be introduced into clinical care sooner rather than later. This will change the lived experience of AD for millions of patients and their families, as well as surface ethical, legal, and policy challenges for society. The presentation will address individual and broader implications.

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## Monday, September 11, 2023: Derek Denny-Brown Young Neurological Scholar Symposium

### Inter-Organelle Contact Site Misregulation in Neurodegenerative Diseases

Yvette Wong, PhD

Northwestern University Feinberg School of Medicine

Inter-organelle contact sites represent key pathways for different organelles to interact with one another, and allow for the bidirectional regulation of organelle function and dynamics. These include contacts that have been shown to dynamically form between mitochondria and lysosomes, which result in the direct modulation of both mitochondrial network dynamics and lysosomal network dynamics by one another. Mitochondria-lysosome contact sites are further misregulated at different steps in various diseases including Parkinson's disease and Charcot-Marie-Tooth disease. Moreover, misregulation of additional inter-organelle contact site dynamics may be critical drivers of the pathogenesis underlying multiple other neurodegenerative diseases, such as Alzheimer's disease and Amyotrophic Lateral Sclerosis (ALS). Thus, further insights into organelle contact site dynamics and regulation using live super-resolution microscopy approaches will shed important light on the etiology mediating neurodegeneration.

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# From Agnosia to Action: Moving Toward Diversity, Inclusion, and Equity in Neurology

Roy Hamilton, MD, MS, FANA

University of Pennsylvania

Although the most common, serious neurologic disorders disproportionately affect marginalized and minoritized populations, the field of neurology has historically rarely been portrayed as having a special obligation to engage with persons from underserved and disadvantaged communities. One cause and consequence of this inattention to health equity may be the relative paucity of persons who hail from minoritized racial and ethnic groups who are drawn to careers in neurology. As patient populations in the US and elsewhere continue to become more heterogeneous, diversity in the neurology workforce is increasingly essential to the delivery of culturally competent care and the ability to conduct inclusive, generalizable clinical research. Unfortunately, there are formidable challenges to achieving diversity in the neurology workforce, including an inadequate pipeline of trainees entering the field, explicit and implicit biases experienced by minoritized trainees and faculty, and “diversity tax,” the disproportionate burden of service work placed on minoritized persons in many professions. In this session, Dr. Hamilton—Professor and Vice Chair for Inclusion and Diversity in the Department of Neurology at the University of Pennsylvania, former Assistant Dean of Cultural Affairs and Diversity for the Perelman School of Medicine, and inaugural Associate Editor for Equity, Diversity and Inclusion for the journal *Neurology* and its associated journals—will discuss ways in which diversity enhances the clinical, educational, and scientific missions of neurology. He will characterize the barriers that impede the advancement of diversity, equity, and inclusion within the field of neurology. Lastly, based on lessons learned in the course of developing the Diversity, Inclusion, Anti-Racism, and Equity (IDARE) program in the Department of Neurology at the University of Pennsylvania, Dr. Hamilton will identify practical steps that can be taken by academic neurology departments and the field of neurology more broadly to reduce these barriers, in order to create a more diverse, inclusive, and equitable field.

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## The Systems Cell Biology of Neurodegeneration: Proteins to Stem Cells to Patients.

Vikram Khurana, MD, PhD

Brigham & Women's Hospital

Our lab has generated and explored “proteinopathy maps.” These are integrative networks that depict changes in the cellular proteome as aggregation-prone proteins misfold. To generate these maps, genetic modifiers of proteotoxicities are integrated with protein-protein interaction data and local protein phase-transitions. Our first maps focused on the protein alpha-synuclein ( $\alpha$ Syn), a protein that aggregates in synucleinopathies including Parkinson's disease (PD). These maps tied  $\alpha$ Syn through defined molecular interactions to numerous other PD genes and directly connected it to perturbed vesicle trafficking and mRNA metabolism. Our follow-up studies have demonstrated the utility of such maps in understanding disease pathogenesis and motivating therapeutics. First, we have discovered new functions for aggregation-prone proteins of relevance to disease. For example, we recently showed that the N-terminus of  $\alpha$ Syn dichotomously interacts with membranes and P-bodies, membraneless organelles involved in mRNA stability and gene regulation. Second, by integrating our maps with phenotypic screens of small-molecule probes, we have identified druggable targets, including a novel lipid metabolism target for Parkinson's disease, stearyl-coA desaturase. Third, our proteinopathy maps have shed light on the genetic architecture of synucleinopathies and factors that underlie the heterogeneity of disease risk and progression. Technical innovation in statistical genetics, AI and population-scale stem-cell modeling enable patient stratification and validation of molecular subtypes “in the dish.” The integration of proteinopathy mapping with deep phenotyping, genome-sequencing and stem-cell modeling thus offers a viable path toward targeted therapeutics for heterogeneous neurodegenerative diseases. To this end, our center is establishing a clinical-trials unit in which iPSC models of deeply genotyped and phenotyped patients will be utilized to match patients to appropriate therapies, and to test those therapies in longitudinal observational/interventional trials.

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## Associations of Traumatic Brain Injury with Long-Term Outcomes: Insights from Epidemiologic Studies

Andrea Schneider, MD, PhD

University of Pennsylvania

Traumatic brain injury (TBI) is common and is associated with significant morbidity and mortality, especially among older individuals. Approximately 15.7% of U.S. adults aged

40 years or older have experienced a head injury with loss of consciousness, which amounts to approximately 23 million affected individuals. The current epidemiology of traumatic brain injury will be presented in this presentation. In addition, efforts focused on improving the characterization of the lifetime history of TBI in ongoing prospective cohort studies in diverse populations will be presented. Leveraging data with over 25 years of follow-up, studies presented herein will quantify the population-level burden of TBI and the dose-dependent long-term consequences of TBI (including data on cognitive decline, dementia risk, and mortality, among other outcomes) in a comprehensive manner. Data will also be presented showing how epidemiological study design and biostatistical methods can provide insights into mechanisms underlying observed associations. The robust and dose-dependent associations of TBI with adverse outcomes underscore the importance of public health measures aimed at preventing head injuries and targeted clinical interventions to reduce morbidity and mortality after head injury.

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## Genomic Approaches to Study Alzheimer's Disease Immunity

David Gate, PhD

Northwestern University

This presentation will cover recent findings from the Gate lab which identified a novel adaptive immune phenotype in Alzheimer's disease. The presentation will discuss Dr. Gate's use of novel genomic approaches to uncover mechanisms of T cell brain entry. Dr. Gate will also discuss the application of spatial transcriptomics to interpret mechanisms of amyloid clearance in post-mortem tissues from clinical trials for Alzheimer's disease.

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## Tuesday, September 12, 2023: The Evolving Role of Anti-Amyloid Therapies for Alzheimer's Disease

### Anti-Amyloid Monoclonal Antibodies: Mechanisms of Action and Clinical Trials

Michael Rafii, MD, PhD

Keck School of Medicine, University of Southern California

Alzheimer's disease (AD) is the leading cause of dementia worldwide and follows a pathological cascade involving amyloid plaques, neurofibrillary tangles and neurodegeneration. The FDA has granted accelerated approval for aducanumab and traditional approval for lecanemab, both amyloid-directed monoclonal antibodies and members of a new class of disease-modifying treatments for Early AD. Another amyloid-lowering monoclonal antibody, donanemab, is expected to receive approval later this year. Gantenerumab and Solanezumab are anti-amyloid monoclonal antibodies that did not significantly lower brain amyloid levels and both of these drugs failed to demonstrate clinical efficacy. I will discuss these treatments and the studies supporting their clinical use.

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### Pros of Anti-Amyloid Monoclonal Antibodies

Gil Rabinovici, MD, FAAN, FANA

University of California, San Francisco

This presentation will summarize results from recent clinical trials of anti-amyloid monoclonal antibodies in early stage Alzheimer's disease, including data from the EMERGE/ENGAGE (aducanumab), CLARITY-AD (lecanemab), TRAILBLAZER I-II (donanemab) and GRADUATE I-II (gantenerumab) trials. We will focus on clinical and safety outcomes and also explore biomarker effects, as well as the evidence for disease modification. The overall evidence will demonstrate that potent antibodies that effectively clear amyloid plaques from the brain significantly slow clinical decline, providing a modest but clinically meaningful benefit.

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### Cons of Anti-Amyloid Monoclonal Antibodies

*Madhav Thambisetty, MD, PhD, FANA*

*National Institute on Aging*

The clinical benefit associated with anti-amyloid immunotherapies, a new class of drugs for the treatment of Alzheimer's disease, is predicated on their ability to modify disease course by lowering brain amyloid levels. Two amyloid-lowering antibodies, aducanumab and lecanemab, have obtained United States Food and Drug Administration accelerated and full approval respectively. Further agents of this class are in the Alzheimer's disease treatment pipeline. Based on limited published clinical trial data to date, regulators, payors and physicians will need to assess their efficacy, clinical effectiveness and safety, as well as cost and accessibility. Attention to three important questions related to treatment efficacy, clinical effectiveness and safety should guide evidence-based consideration of this important class of drugs. These are: (1) Were trial statistical analyses appropriate and did they convincingly support claims of efficacy? (2) Do reported treatment effects outweigh safety concerns and are they generalizable to a representative clinical population of people with Alzheimer's disease? and (3) Do the data convincingly demonstrate disease course modification, suggesting that increasing clinical benefits beyond the duration of the trials are likely? I will propose specific approaches to interpreting trial results for these drugs and highlight important areas of uncertainty where additional data and a cautious interpretation of existing results is warranted. Safe, effective and accessible treatments for Alzheimer's disease are eagerly awaited by millions of patients and their caregivers worldwide. While amyloid-targeting immunotherapies may be promising disease-modifying Alzheimer's disease treatments, rigorous and unbiased assessment of clinical trial data is critical to regulatory decision-making and subsequently determining their provision and utility in routine clinical practice.

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### Challenges of Implementing Anti-Amyloid Therapies in the Clinic

*Liana G. Apostolova, MD*

*Indiana University*

The recent FDA and CMS approval of anti-amyloid therapies places our healthcare system under unprecedented demands. There will be an urgent need to establish a carefully thought-out workflow for the evaluation of patient eligibility and for the safe and efficient administration of MAB infusions. This necessitates an unprecedented coordination of care between neurologists, radiologists, emergency room and intensive care unit physicians with the necessary training and skills to address potential treatment side effects. In addition, the modest number of racial and ethnic minority individuals included in MAB trials to date has led to a limited insight into potential ethnic/racial differences in efficacy and risk/benefit ratio.

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### Improving Inclusiveness in Research and Clinical Settings

*Monica Parker, MD*

*Goizueta Alzheimer's Disease Research Center- Emory University*

AA are disproportionately affected by Alzheimer's disease, consistently underserved by social and health care systems, and greatly underrepresented in Alzheimer's research. To better engage the Metropolitan Atlanta population of African Americans, the Goizueta Alzheimer's Disease Research Center (GADRC), has established a 10-year dedicated focus on the recruitment and retention of African American (AA) individuals into ADRC research and brain donation programs. We have increased the percentage of active AA clinical research participants, URM investigators, and investigations focused on ethnic differences in Alzheimer's and Related Dementias. Equity in research participation has been improved by creating an educational outreach whereby the population of older adults, regardless of color, are similar in age, educational attainment, and overall health status. African American and European Americans, who committed to research enrollment in Emory's NACC- UDS longitudinal study



2015-2020, demonstrate different behaviors in response to educational outreach programming.

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# ANA 2023 Author Index

Aamodt, Whitley	S255	Alaimo, Darrick	M316	Antaki, Fadi	M164
Abaluck, Brian	S340	Alapatt, Paul J.	S151	Apple, Stephen	M301
Abbate, Zachary	S262	Al Awwad, Ahmad	M160	Arar, Amina	S123
Abdalla, Yomna	S123	Al-Awwad, Ahmad	M106, S157	Aravamuthan, Bhooma	S107
Abdelall, Nasser	S158	Albakri, Khaled	M257	Arbatti, Lakshmi	S232
Abdelall, Nasser A.	S334	Albay, Ricardo	S284	Arezoumandan, Sanaz	LB-S111, M191, S245
Abdelazim, Marwa	S123, M257	Albers, Mark	S330	Armengol, Victor D.	M292
Abdelfattah, Nourhan	LB-S114, LB-S115	Aldridge, Georgina M.	M165	Arnold, Frederick J.	LB-M118
Abdelhady, Mariam	S123	Alegria, Margarita	K-S105	Arnold, Jennifer	M102
Abdelhak, Tamer	S134	Alexandrescu, Sanda	M224	Arnold, Steven E.	M159
Abedi, Vida	S119	Aleyadeh, Rozaleen	S132	Arvanitakis, Zoe	M159
Abe-Hatano, Chihiro	S299	Algeciras-Schimmich, Alicia	M279	Asad, Syed Daniyal	S101
Abella, Benjamin S.	M263	Alhusaini, Saud	S211	Asare-Bediako, Serwaa	S149
Abellana-Pérez, Kilian	M243	Ali, Rubiya	S128, S142, M288	Asghar, Ayesha	M221
Abend, Nick	LB-S108	Alicea-Delgado, Miosotis	LB-S119	Askari, Asra	S254
Abolfazli, Amin	S145	Aljabali, Ahmed	S123, M257, S285	Aspromonte, Christopher	M312
Abulaban, Ahmad A.	M292	Al-Janabi, Omar M.	S107	Assad, Elena	K-S112
Acero-Garces, David O.	M232	Alkhaddash, Ra'ed	S275	Astudillo, Olga M.	S234, M314
Adams, William	S263	Al-Khalidi, Hussein	M192	Asukile, Melody	K-M112, S162, M241
Adams, William H.	S124, S137, S225, S238	Alkhawaldeh, Ibraheem	S285	Asukile, Melody T.	S117
Adang, Laura	K-S113, S280, S293, S294, S296, S298, S299, S302, S305, S310, S312	Alkhawaldeh, Ibraheem M.	S123, M257	Asuncion, Ria	M102
Adelsberg, Adam	M118	Allam, Ahmed	S123, M257	Athiraman, Umeshkumar	K-S102
Adikari, Thiuni N.	M224	Allen, Nicholas M.	M293	Ati, Shomik	S217
Adjei, Patrick	M246	Allman, John	M181	August, Pauline	S108
Adney, Scott K.	LB-M113	Almeida, Leonardo	S255	Aung, Thandar	M212
Agbinko-Djobalar, Babbel	M211, M246, S323	Al-Mukhaini, Suad	M171	Aurangzeb, Madiha	S147
Aghlara-Fotovat, Samira	S223	Al Qahtani, Xena	S228	Auriemma, Catherine L.	M172
Aguirre, Alex S.	S234, S260, M314	Al-Rasadi, Khalid	M171	Autry, Cristy	S140
Aguirre, Geoffrey K.	S175	Alrefae, Doaa	M258	Avalos, Gloria	M293
Agyman Badu, Nana Boakye	M246	Al-Saady, Murtadha L.	S299	Avula, Venkatesh	S119
Ahima, Rexford S.	M159	Al Shamli, Siham	M171	Awad, Mohammad	LB-S110
Ahlem, Clarence	M183	Al Shaiqi, Ola	M160	Ayirebi-Acquah, Ewuradjoa	M211, M302, S323
Ahmadi, Gelareh	M100	Alshehri, Ali	M292	Azage, Meron	S304, M311
Ahmed, Aftab	S128, S142, S155, M285, M288, M296, M303	Alter, Benedict	K-S103	Ba, Djibril	S126
Ahmed, Hamza	S157	Alvarez, Enrique	M134	Babaian, Nareen	S304, M311
Ahn, Seon-Jae	M110, M222, M223, M229, S306, S325	Alvarez-Velasco, Rodrigo	M293	Baban, Babak	M180
Ahrens, Angela M.	M280	Al-Waili, Khalid	M171	Bacharach, Rae	S193
Ahrens-Nicklas, Rebecca	S294	Alwaki, Abdulrahman	M227	Bachuwa, Ghassan I.	K-M121
Ahrens-Nicklas, Rebecca C.	K-S113	Alzayadneh, Mohammad	S275	Badihian, Shervin	S272
Aikins, Minas	S149	Alzyoud, Lamees	M272	Badjatia, Neeraj	K-M118
Ajayi, Akinyemi O.	S343, S345	Amado, Defne	S304	Badran, Aya M.	S264
Akbar, Umer	S211	Amado, Defne A.	K-S114, S308, M311	Baehring, Joachim	S267
Akhtar, Rizwan S.	LB-S111	Amartino, Hernan	M231	Back, Jonggyu	K-M102
Akpalu, Albert	M246	Amin, Vishrant	S242	Baggi, Fulvio	M135
Aktas, Selma	M293	Amos, Dandre	S313	Bahena, Alejandra	M191
Alaboudi, Malak	M148	An, Hongyu	K-M100	Bahouth, Mona	S117, S162
Al-Adawi, Samir	M171	Anadani, Nidhiben	M193	Bahti, Melanie	M172
Aladesuyi	Arongundade,	Anandram, Sanjay	M138, M207	Bai, Qing	S287
Olubankole	K-S117, LB-S123	Anderson, Karen E.	S232	Baird, Alyssa J.	M174
		Andreoli, Mia	M271	Baker, Bradley T.	S124
		Andres Florez Realpe, Julio	M239	Baker, Cristina	K-M111
		Ankrah, Prince T.	M246	Balabhadra, Anvesh	S101, S111, S112
		Annis, Christine	S178	Balanza Villegas, Gustavo A.	S339
		Ansari, Muhammad	M132		



Balcer, Laura	M262	Bennett, Jeffery	M124	Bonato, Alberto	M176
Baldwin, Aaron	S304, M311	Bennett, Jeffrey L.	M112	Bondy, Monica	K-S109
Ballance, Elizabeth	S296	Ben-Omran, Tawfeg	M292	Bondy, Monica T.	S281
Banerjee, Dhruva	M175	Bentley, Brenna	K-S113	Bonilha, Leonardo	M227
Banerjee, Mousumi	K-M121	Bentley, Nicole	LB-S110	Bonomi, Samuele	M168, M176
Banks, Russel	M202	Benzinger, Tammie	K-M100, S341	Borch, Lauren	M293
Banks, Russell	M179	Benzinger, Tammie L.	M168	Bordelon, Yvette	S236
Banwell, Brenda	M124	Berger, Joseph	S192	Borden, Neil	S109
Bao, Fen	M141	Berkovic, Sam	M224	Borko, Tyler L.	M112, M134
Barbero, János	S231	Bernard, Genevieve	S296, S310, S312	Borland, Hannah	LB-S115
Barbieri, Elena	M153	Bernard, Geneviève	S299	Bosco, Daryl A.	M260
Barbosa, Daniel	S255	Bernert, Günther	M292	Bostic, Ryan	LB-S105
Barbour, Aaron	M197, M225, S288	Bernitsas, Evanthia	M141	Boucher, Leanne	M195
Barcelos, Isabella	S280, S293	Berry, Jasmine	M267	Boudreau, Denise M.	S198
Barcelos, Isabella P.	S305	Bertini, Enrico	S299	Bouley, James	M260
Bardakjian, Tanya	S304	Bertossi, Ryan	M249	Boulos, Mark I.	S335, S348
Bardakjian, Tanya M.	M311	Betances, Gabriela	M213	Boyer, Angelique	S262
Barišić, Nina	M292	Betner, Abigail	S140	Boyle, Bridget R.	S106
Bar-Or, Amit	S192, S307	Bhamidipati, Abhinav	S182, S341	Bozorgui, Shima	S140
Barr, Emily	S324	Bhandari, Bidhan	M180	Bracamontes, Maria	S147
Barreau, Ariana	M208	Bharil, Sarika R.	S190	Bradshaw, Deborah	M305
Barreras, Paula	M100	Bhatia, Ankush	S263	Brahmaroutu, Ankita	S114
Bartrés-Faz, David	M243	Bhatti, Karandeep S.	M133	Brakedal, Brage	S231
Basheer, Noufal	S151	Bhatti, Muhammad	M150	Brandstadter, Rachel	S192
Bass, Geoffrey D.	M263	Bhojwani, Manish M.	M105	Braun, Rosemary I.	S342
Bastani, Pouya B.	S272	Bhutta, Ramsha	S241	Braun, Sarah	S117, S162
Bastin, Grace	S200	Bilguvar, Kaya	M217	Breen, Elizabeth	S211
Bateman, Randall J.	M200	Biller, Jose	S144, S160, S261, S333	Breining, Bonnie	S104
Batra, Vivek	S122	Billieux, B. Jeanne	M240	Breiter, Hans C.	K-S106
Bauer, Adam Q.	K-S120	Birbeck, Gretchen	K-M112, K-M113	Brennan, Cameron	S213
Baumer, Fiona M.	K-M110	Birk, Alisha	K-S117	Brennan, KC	K-M117
Bausano, Sarah	M112, M134	Birk, Alisha M.	LB-S123	Brent, Jonathan R.	K-M120
Bavarsad Shahripour, Reza	S156	Birznicks, Gunther	S311	Breville, Gautier	S307
Bayram, Ece	S240	Bitu, Manuel	S126	Briano, Juan	S214
Bean, Karen	M144	Bizzotto, Sara	M224	Brier, Matthew R.	K-M100, M170, M178
Bearden, David	K-M113, M240	Blackbourn, Lisle	M270	Brilot, Fabienne	M124
Beasley, Alexandra	LB-S109	Blackwood, Spencer	K-S120	Brinkerhoff, Sarah	LB-S110
Beck, Christopher	S232	Blaha, Michael	S120	Briones, Melissa R.	S180
Beck, Goichi	M275	Blair, Tiffany	M135	Brodie-Mends, David	M246
Becker, Ann	S284	Blanchfield, Lori	M135	Brody, David L.	LB-M116
Becker, Catherine	S228	Blanco-Suarez, Elena	S106	Bronkowski, Joshua	S312
Becker, Paloma	S318	Blewusi, George S.	M211	Bronte-Stewart, Helen M.	S247
Beckman, Andrew	S329	Block, Cady	M227	Brooks, Julianne	LB-S108
Behn, Jordan	M153	Blood, Anne J.	K-S106	Brown, Alexandra	K-M121
Beiner, Melissa W.	M247	Bloom, Emma	S262	Brown, Christopher	S110
Beke, Matthew	S255	Blümcke, Ingmar	M224	Brown, Robert H.	K-M102
Belakhlef, Sami	S266	Blume, Gregory	M270	Brown, Spencer	LB-M115, LB-S121
Bellinski, Irena	M219	Boateng, Richard	S149	Browne, Danielle F.	S278
Benard, Shawna W.	LB-S108, LB-S108	Bockholt, H. J.	S144, S160	Brüggemann, Norbert	K-S106, S212
Benavides, David R.	K-M101, M126	Bockholt, H. Jeremy	S124, S137, S225, S238	Brumm, Michael C.	S207
Benavides-Melo, Julie	M232	Boes, Michael	S269	Brundin, Lena	S222
Benisano, Kendra	M174	Boeve, Bradley	M185	Brundin, Patrik	S222
Benisaro, Kendra	M203	Bold, Jane	M299	Bruno, Askiel	M180
Benitez, Bruno A.	LB-S117	Boldig, Catherine	S257	Bruno, Christopher D.	S315
Benitez, Sara	M273	Boldig, Kimberly	S105	Bryan, Robert N.	S341
Benitez, Sara E.	LB-M100	Bonakdarpour, Borna	M153	Bu, Guojun	M170
Bennett, David A.	M185			Buchhalter, Jeffrey	LB-S108

Bui, Esther	M215	Chahine, Yasmine	M224	Choudhari, Jinal	S145
Bui, Quoc	M168	Chakravartty, Akash	S161	Chow, Christina R.	S315
Bunevicius, Adomas	S125	Chalia, Papul	S135, M164, M278, S328	Chu, Kon	M110, M222, M223, M229, S306, S325
Burns, Jennie	S244	Chan, Moon F.	M171	Chukwunke, Florence	S127
Burq, Maximilien	S218	Chan, Wing-Ki	M293	Chum, Marvin	M301
Burré, Jacqueline	S214	Chandaka, Asha	S182	Chung, Alexander	S330
Burton, Edward A.	S287	Charles, Jeremy	M263	Chung, Hyunglok	LB-S124
Burton, Tina	S133	Charleston, Larry	S168	Chunyk, Allison	M135
Buse, Dawn C.	S170, S171	Charsar, Brittany	S296, S310, S312	Ciesla, Marissa	M179, M202
Bushlyar, Victor	M284	Chatterjee, Jit	LB-S116	Claassen, Daniel O.	S204
Bushnell, Cheryl	S327	Chaudhary, Durgesh	S119	Claeys, Kristl	M293
Butt, Faiza	S241	Chaudhry, Hassan	S242	Clanton, Austin	S241
Butt, Maayra I.	M172	Chaudhry, Huriyyah	S215	Clark, Heather M.	M205
Buttar, Rupinder S.	M138, M207	Chauhan, Preeti S.	S295, S297	Claros-Ortiz, Katherine V.	M232
Buzby, Meghan	S170, S171	Chen, Chen	S218	Clawson, Lora L.	S272
Byun, Shin Yun	M293	Chen, Cidi	K-S115, M218	Clegg, Nancy J.	S312
Cabello-Toscano, María	M243	Chen, Hua	K-M118	Cleland, Jeffrey L.	M300
Cabot, Jackson	M122	Chen, KerCheng	S337	Clelland, Claire	K-S117, LB-S123
Cadavid, Diego	M306	Chen, Kevin S.	M177	Clemons, Kristen	S263
Cady, Roger	S170, S171	Chen, Ryan	K-S115, M218	Clemons, Jordan	S137
Cagle, Jackson	S255	Chen, Shu-hsia	LB-S115	Coban, Hamza	M104
Cahn, Elliot	LB-S109	Chen, Wei	K-S120	Cobb, Bryan R.	S198, S219
Cai, Long	M181	Chen, Wei-Liang	S309	Coffey, Christopher S.	S207
Calabresi, Peter	M142	Chen, Xu-Qiao	S284	Cohen, Jesse	S243
Calabresi, Peter A.	S283	Chen, Yilun	K-M109	Collins, Bailey	M167, M204
Calco, Brice	S282	Chen, Yun	LB-S117	Collyer, Eileen	S106
Calderson, Kary	S177	Cheng, Cindy	S182	Colwin, Michael R.	LB-M118
Calhoun, Vince D.	S124, S137, S238	Cheng, Cynthia	S337, S341	Comella, Cynthia	S230
Callaghan, Brian C.	K-M121	Cheng, Jocelyn	S347	Coni, Jani	S337
Calmet, Michelle	M278, S328	Cheng, Man-Hin	M293	Conklin, Bruce	K-S117
Camargo, Fernando	LB-S115	Cheng, Roger	S127	Conklin, Bruce R.	LB-S123
Cameron, Briana	S219	Chen-Plotkin, Alice	LB-S111, S245	Connor, James R.	S222
Camryn, Lane	S192	Chen-Plotkin, Alice S.	S207	Connors, Barry	K-M107
Capan, Colt D.	S222	Chhouk, Brian H.	M224	Connors, Barry W.	M206
Capp, Noah	M191	Chi, Luqi	S182, S337, S341	Consonni, Alessandra	M135
Caprihan, Arvind	S124, S137	Chiappe, Milena	S318	Cook, Philip	S132
Capuano, Ana W.	M159	Chibnik, Lori	S265	Coppola, Carmina	M287
Cardenas Castillo, Ylec Mariana	M284	Chien, Yin-Hsiu	M292	Corboy, John R.	M134
Carlos, Arenn F.	LB-M103, M205	Chilando, Mulenga	S117, S162	Coresh, Josef	K-M116, M259
Carmolingo, Angelica	S192	Chillon Bosch, Guillem	K-S114, S308	Cornwell, Benjamin	S109
Carrizosa, Jorge	M235	Chin, Eva	M299	Cortez, Melissa	K-M117
Carter, Andrew	M238, M242	Chio, Adriano	M301	Cosgrove, G. Rees	S339
Carter, Ava	K-S112	Chiong, Winston	LB-M109	Costin, Carrie	K-S113
Case, Jordan	M198	Chishimba, Lorraine	K-M112, S117, S162	Couch, Ronan	K-S101
Casey, Emma	S183	Chitnis, Tanuja	M124	Coughlin, David G.	S278
Casey, Megan	M174	Cho, Kolette	M174, M203	Cousins, Katheryn	S243
Cash, Sydney S.	S339	Choi, GiHun	K-S112	Cousins, Katheryn A.	M191, S207, S245
Cassarly, Christy	S104	Choi, Huimahn A.	K-M118	Coutinho-Budd, Jaeda	K-S108
Castiglioni, Claudia	M292	Choi, Irene	M306	Cowan, Robert P.	K-S104
Cattaneo, Gabriele	M243	Chomba, Mashina	K-M112, S117, S162	Crary, John F.	S143
Cavanah, Audrey	S175	Chorzepa, Aldona	S147	Craver, Emily C.	M166
Cavanaugh, Gesulla	M195	Chou, Ching-Chieh	S289	Crawford, Carl	S214
Cavendish, John	S191	Chou, Kelvin	S254	Cristancho, Ana G.	S295, S297
Cella, Rachael	S101	Chouchane, Mondher	M293	Criswell, Amber	S118
Cernera, Stephanie	S255			Cronin, Dianna	S349
Cervellione, Kelly	S147			Crokin, Patrick J.	S262
Cervenka, Mackenzie C.	M226				

Cross, Anne	K-M100	DeKeyser, Jean-Marc L.	LB-M113	Dominguez-Penuela,	
Crossland, Daven	S144	DeLanerolle, Nihal	M224	Susana C.	M232
Cruchaga, Carlos	M185	De la Rosa, Lizbeth	S228	Donahue, Maria A.	LB-S108
Cruz-Flores, Salvador	S269	Delcourt, Nicole	M122	Dong, Zhao	S165
Cucchiara, Brett L.	S114, S150, S154	Delgado-Gallen, Selma	M243	Dono, Antonio	S263
Cuddapah, Vishnu A.	K-M108	Della Marina, Adela	M293	Dorfman, Katherine	LB-S111
Cueva, Wilson	S145	Delpirou Nouh, Claire	M160, M193	Dougherty, Chase	S215
Cui, Ya	LB-M118	Delpirou-Nouh, Claire	S139	Dougherty, Darin D.	S339
Culver, Joe	K-S120	Demian, Ereny	M164	Doyu, Manabu	M301
Czeisler, Barry	M189	Deng, Han-Xiang	K-M120	Drane, Daniel L.	M227
Dacquel, Maxwell V.	M170	Deniz, Kaancan	M162, M165	Dratch, Laynie	M194, M199, S304, M311
Daggy, Joanne	S200	DePietro, Daniel	M251	Driscoll, Theresa	S144, M174, M203
Daghighi, Parnaz	S206	DeRavin, Suk See	S282	Du, Austin	S176
Dai, Wei	S165	Desai, Hardik Dineshbhai	S242	Du, Guangwei	S222
Daida, Atsuro	K-M105	Desai, Kunal	M284	Dubbs, Holly	S302
D'Aiello, Russel	S280, S299	Desai, Troy	M129	Dubey, Divyanshu	M131, M147
D'Aiello, Russell	S293, S298	Deshpande, Mugdha	K-M102	Dubow, Jordan	S340, S343, S345
D'Aiello III, Russell	S310, S313	De Silva, Shari	M301	Duffy, Joseph R.	M205
Dalakas, Marinos C.	M139	de Souza, Daniel N.	M262	Dulay, Mario F.	S118
Dalton, Casey	M304	Dessain, Scott K.	K-M101, M126	Dulski, Jaroslaw	LB-S109
Damisah, Eiyemisi C.	M224	Detre, John	S110	Dumitrascu, Oana	S156
Dangayach, Neha	M107	Detre, John A.	M186, M201, S341	Dunaief, Joshua L.	S131
Dar, Kamil	LB-S121	Devenney, Brooke	S136	Dundamadappa, Sathish K.	K-M102
Darkwah, Kwaku A.	M302	Devenyi, Ryan	S209	Dunham, S. Richard	M170, M178
Darras, Basil T.	M292	De Vivo, Darryl	M293	Dunston, Randy	S324
Darrell, Megan	S188, S194	Dey, Mahua	S263	Duodu, Fiifi	M211, M246, M302, S323
Das, Sameeran	M287	Dezha Peralta, Jaquelin	S339	Dy-Hollins, Marisela	LB-S113
Das, Sandhitsu	S243, S341	Dhawan, Vijay	LB-S112	Ecker, Sarah	M189
Das, Sandhitsu R.	M201	Dhillon, Balkiranjit K.	M211, S323	Edmondson, Andrew C.	K-S116
Dasgupta, Savanna	S103, M282	Dhyani, Ruchi	M212	Egle, Marco	M155, M156
Davidson, Beverly L.	K-S114, S308	Diab, Rehab	S123, M257	Eichler, Florian	S228, M231, S293, S313
Davies, Rupert	M135	Diamond, Marc	S227	Eichler, Florian S.	M152, M184
Davila-Rivera, Roseanne	LB-S111	Diaz-Arias, Luisa A.	M226	Eid, Stephanie	M242
Davis, Albert A.	LB-S117	Diaz-Arrastia, Ramon	K-M116, M210, M259	Eidelberg, David	LB-S112, S231
Davis, Christopher	K-S112			Eis, Peggy S.	S315
Davis, Eric	S337, S341	Diaz Rojas, Maria	M214	Eisch, Amelia J.	LB-S122
Davis, Eric M.	S182	Dibble, Lee	K-M117	Eisenmenger, Laura B.	S124, S137
Davis, Jennifer	S211	DiCapua, Daniel	M284	Eisinger, Robert S.	S255
Davis, Marie	S251	Dichter, Abigail I.	K-S114	Elafros, Melissa A.	K-M121
Dawood, Thair	K-M121	Dickson, Dennis W.	LB-M103, LB-S118, LB-S120	Elahi, Fanny	S143
Dawson, Ted M.	S283			Elahi, Fanny M.	S108, S144, S160
Dawson, Valina L.	S283	Diehl, Daniel	M281	Elangovan, Cheran	S122, S148, S275
Day, Gregory S.	M166, M170, M178	Diesta, Cid C.	S212	ElBaz, Zainab	S123
Daya, Annika	S191	Dietz, Allan	M279	Eleuteri, Simona C.	S216, S221
Deal, Ieshia	S140	Dillon, Stacey R.	M135	ElHassan, Aya	LB-S108
Deal, Jennifer A.	M155	Diokpa, Chijindu	S314	Elkind, Mitchel S.	S125
Dean, Rebecca	M144	Dixit, Karan	S189, M271	Elliot, Jamie L.	S160
De Bleecker, Jan L.	M294	Djakovic, Mirjana	S144	Ellis, Colin	S304
De Castro, Mauricio	K-S113	Djamasbi, Soussan	M258	Ellis, Ronald J.	S172
de Cuba, Kaye	M299	Dobrowolska Zakaria, Justyna A.	M200	Elm, Jordan	S104
Deeds, Michael	M279			Elman, Lauren	S304, M311
Deerlin, Viviana M.	M199	Dobyns, William	K-S109	Elnagheeb, Marwa	M283
de Goede, Annika A.	M299	Dobyns, William B.	S281	Elsayed, Maged	M257
Degraft Hanson, John	LB-S107	Doelfel, Savannah R.	M206	Elsder, Holly	M252
de Havenon, Adam	S152	Dogan, Elif O.	M260		
Deik, Andres	S245	Dolan, Rachel	S109		
de Kam, Marieke L.	M299	Dölle, Christian	S231		
		Dolui, Sudipto	S110		

El Seblani, Nader	S135	Ferman, Tanis J.	M166	Gadani, Sachin	S256, S283
Elser, Holly	M259, M265	Fernandez-Garcia, Miguel	M293	Gadra, Elyse	S295
Elser, Holly C.	K-M116	Fernandez, Raquel	M283	Gadra, Ethan	S295, S297
Elzinga, Sarah	M169, S326	Ferriero, Donna	K-S100	Galasko, Douglas	S278
Emanuel, Olivia M.	M156	Feuerhake, Walter	S318	Galasko, Douglas R.	S207
Emmerson, Danison	S112	Fiallos, John	S234, M314	Galemmo, Robert	M306
Emrick, Lisa	S293	Ficker, David	LB-S108	Gallagher, Michael	M282
Enayetallah, Ahmed	S213	Fields, Christopher	M144	Gallegos, Joseph	S319
Enciso, Jose M.	M232	Figdore, Daniel	M279	Gallegos, Joseph T.	M119
Engebretson, Eric	M134	File, Christopher	S167	Galleguillos, Danny	S283
Engel, Andrew G.	M286	Findley, J. Chase	S206	Galvez-Jimenez, Nestor	M108
Engel, Jerome	K-M105	Finley, Daniel P.	S289	Galvis, Martha E.	S222
Engel, Patti A.	M247	Fino, Peter	K-M117	Gandelman, Stephanie	S192
Engel, Priya V.	LB-M102	Fischer, David	M263	Gandhi, Jason	M277, S316
Enriquez, Ana	S237	Fischer, Tanya Z.	M247	Gandhi, Sunil	M175
Enstrom, Amanda	M135	Fish, Sarah	S251	Ganesh, Aishwarya	M171
Epstein, Mark	M195	Fitzsimons, Stephen	S108	Ganguly, Taneeta	M208
Erler, Jacqueline	S310, S312	Flagstad, Peter	M299	Ganzman, Adam	S127
Erler, Jacqueline A.	S280, S296	Flanagan, Eoin	M124	Gao, Virginia	S214
Eslinger, Paul	S215	Flanagan, Eoin P.	LB-M101, M131, M147	Garabedian, Meghan	S192
España-Irla, Goreti	M243	Flores, Gladys	M213	Garcia-Mesa, Yoelvis	M118
Espinosa-Garcia, Claudia	S276	Flores-Mendez, Marco	LB-S119	Gardener, Hannah	S125
Esquenazi, Yoshua	S263	Foote, Kelly	S255	Gardiner, Joseph	K-M112
Essam, Dina	M257	Forman, Rachel	S152	Garofalo, Gabriela	S234, M314
Estes, Raja	S251	Formanowski, Brielle	S296	Garton, Thomas	M142, S283
Etienne, Mill	S188, S194, S195, M253, S262	Forner, Sven	M174	Garzon, Jenny P.	M232
Eymard, Bruno	M293	Foroud, Tatiana	M185, S207	Gatchoff, Philion	M106, M193
Ezzeddine, Mustapha	M250	Fragapane, Lauren	S257	Gatchoff, Philion L.	S139
Facco, Francesca L.	S342	Franceschi, Ana M.	M163	Gatto, Rodolfo G.	LB-M103
Factor-Litvak, Pam	K-M119, M291	Franceschini, Simone	M176	Gauna, Jeilo	S313
Fadda, Giulia	M124	Franco, Camarlin	M258	Gautam, Mukesh	M280
Fadiran, Babyosimi	K-S101	Franco, Stefan	S158, S334	Gautam, Shiva	S268
Fagan, Anne M.	M170	Fraser, Jamie	S293, S310	Gavazzi, Francesco	S280, S293, S294, S296, S298, S299, S302, S305, S310, S312
Falcone, Guido	S152	Fraser, Jamie L.	S307, S309	Ge, Connie	M258
Fallah, Aria	K-M105	Frawley, Rebecca	M312	Gee, James	M201
Famakin, Bolanle	K-S101	Fregni, Felipe	LB-S127	Gee, James C.	M186
Fang, Lynn	M181	French, Jacqueline	M209	Geisler, Stefanie	M317
Fang, Xiang	S167	Freundlich, Robert	S201, S277	Gelaye, Bizu	LB-S104, LB-M114
Fanning, Kristina	LB-S105	Fridriksson, Julius	S104	Gelb, Michael	K-S113
Fara, Michael	S199	Friedman, Benjamin W.	LB-S105	Gelfand, Jeffery	LB-M106
Farid, Hasan	M276	Frimpong, Smith K.	M211, M302	Genkil, Jessica	M214
Farrar, Michelle A.	M292	Frontera, Jennifer	M189	George, Alexis	LB-S105
Farrell, Kathleen	LB-S108	Frydman, Judith	S289	George, Alfred L.	LB-M113
Farrell, Nathan	S272	Fukada, Toshinori	K-M115	George, Donna K.	S150
Fasano, Alfonso	S213	Fukihara, Kazuo	M124	George, Joshy	LB-S115
Fatemi, Ali	M231	Fuller, Ryan	S192	Gerard, Elizabeth E.	M219, M241
Fatemi, S. Ali	S313	Fumihiko, Takahashi	M301	Gervais, Catherine	M192
Fathali, Iman	S144, S160	Fung, Steve	LB-M100	Geschwind, Daniel	LB-M105
Faulhaber, Lila	K-S118	Funk, Adrian T.	K-S106	Geschwind, Michael D.	S124, S137, S144, S160, M170, M174, M178, M203
Fecteau, Shirley	M179, M202	Fureman, Brandy	LB-S108	Ghabra, Nora F.	LB-M113
Fedman, Eva	M276	Furie, Karen	S133	Ghaith, Hazem	S123, M257
Feichtenbiner, Alicia	K-S119	Furlan, Julio C.	S335, S336, S348	Ghaly, George	S195
Feigin, Andrew	S232	Furr Stimming, Erin	S204	Gharagozloo, Marjan	M142, S283
Feldman, Eva	M169, M238, M242, S326	Furusawa, Yoshihiko	S218		
Feldman, Eva L.	K-M121, M177	Gabel, Maya	M211, M246, M302, S323		
Ferguson, Adam R.	S108				

Ghassemian, Jordan J.	LB-S121	Griggs, Robert C.	M292	Hamedani, Ali	M297, S304
Ghobrial, Anthony	M281	Grobman, William A.	S342	Hamel, Alexander	S132
Giler, Gema	M139	Groechel, Renée	M156	Hamid, Umair	M270
Giles, James A.	S107	Groeneveld, Geert J.	M299	Hamidianjahromi, Anahid	M304
Giliberto, Luca	M163	Groff, Karenna	M228	Hamilton, Eline	S312
Gill, Alexander J.	M142	Grogan, James	M278	Hampton, Stephen	M263
Gill, Christine	M127	Gronnebak, Thomas S.	M299	Han, Xia	K-M104, LB-M105
Gill, Kamaljot	K-S117, LB-S123	Gropman, Andrea	S309	Handy, Marcus	M225
Gillani, Syed	M315	Gross, Robert E.	M227	Hanlon, Alexandra	S182, S341
Gilligan, Michael	M111, M147	Grossman, Murray	M186, M191, M194, M199, M201, S245	Hao, Qing	S143
Gilsrud, Alexandra	M313	Grossman, Scott	M262	Haque, Deena	S190
Giraldo, Elias	LB-M102	Groth, Christopher L.	M162	Harazeen, Ahmed	S167
Glanzman, Allan M.	S296	Grove, Nathan	S274	Harish, Shruthi	LB-S101
Glieber, G. P.	S291	Grundmeier, Robert W	S313	Harmin, David	K-S112
Goate, Alison	M185	Gu, Xin	K-S112	Harms, Matthew	M283
Godoy, Daniel	M235	Gudeman, Jennifer	S340, S343, S345, S349	Harrington, Ann	S296
Goldberg, Emily B.	S104	Guez-Barber, Danielle	LB-S122	Harsh, John	S343, S345
Goldstein, Eric	S133	Gugger, James J.	M210	Harvey, Jessica	LB-M104
Goldstein, Jody	S204, S232	Guido, Giorgio	M176	Hasan, Abigail C.	S147
Golubjatnikov, Aili	M203	Gulergun, Zachary S.	S164	Hasbun, Rodrigo	M120, S332
Gomes-Osman, Joyce	M179, M202	Gulraiz, Azouba	S128, S142, S155, M285, M288, M296, M303	Hassan, Asim A.	K-S106
Gomez-Galvez, Yolanda	S106	Gunasekaran, Tamil	M185	Hassoon, Ahmed	S272
Gonzalez, Christopher	LB-S110	Gunduz, Aysegul	S255	Hatanaka, Ken	S347
Gonzalez, David A.	S230	Gunel, Murat	M217	Hatchwell, Eli	S315
Gonzalez Alegre, Pedro	S304	Gunturu, Manasa	S224	Hattori, Nobutaka	S218
Gonzalez-Alegre, Pedro	M311	Guo, Kai	S326	Haubenberger, Dietrich	S204
Gonzalez-Giraldo, Ernesto	M215	Guo, Michael	M188	Hawkins, Trevor	S187
Gonzalez-Manrique, Guillermo	M232	Gupta, Ashish	K-S109	Hayes, John	M169, M242, S326
Gooden, Matthew J.	M237	Gupta, Ashish O.	S281	Hayes, John M.	M177
Goodman, Jordan	S313	Gupta, Nishtha	M228	Healey, Molly A.	LB-M108
Gooneratne, Nalaka	S182, S337, S341	Gupta, Rajesh	M120	Heckman, Michael	LB-S109
Gootee, Emma	S115, S120	Gupta, Rajesh K.	M101, M105, M145, S270, S314, S332	Heemels, Robin	LB-S127
Gordon, Cameron	LB-S110	Gurin, Lindsey	M189	Heffner, Aaron	S264
Gordon, David Lee	S173	Gusdon, Aaron M.	K-M118	Hefnawy, Mahmoud	S123
Gordon, Marc L.	M163	Gust, Julianne	K-S118	Hefti, Marco	M165
Gottesman, Rebecca	S117, S162	Guthrie, Bart	LB-S110	Heide, Sara K.	M253
Gottesman, Rebecca F.	S115, K-M116, S120, S129, M155, M156, M210, M252, M259	Gutierrez, Dave R.	M308	Heinzen, Erin L.	M224
Goudy, Yomna	S123, M257	Gutierrez, Jose	S125, S144, S160	Helagalli	Paramashivaiah,
Gourmaud, Sarah	M197	Gutierrez Quiceno, Laura	S127	Sushma	M117
Goutman, Stephen	M276	Gutmann, David H.	LB-S116	Heller, Laura	M247
Gowda, Ram	S127	Guzik, Amy K.	M140	Helman, Guy	S312
Goyal, Manu	K-M100	Gygi, Steven P.	S289	Hemingway, Cheryl	M124
Graff-Radford, Neill R.	M166, M170, M178	Hacker, Julia	S248	Hemond, Christopher C	K-M102
Grant, Natalie	S228	Hackett, Ashley Nicole	S313	Henchcliffe, Claire	S213, S214
Grant, Natalie Rose	S313	Hacohen, Yael	M293	Henderson, Lisa	S282
Grau Chaves, Adriana Graciela	M108	Hady, Mariam	M257	Henkel, Julia	S212
Graves, Jennifer	M124	Hahn, Andreas	M293	Henn, Rosemary	S326
Gray, Gabrielle	S230	Haines, Jonathan	M185	Henninger, Nils	M260
Green, Ilana	M107	Hajjar, Ihab	S144, S160	Henriquez-Rojas, Paulina	LB-S101
Greenberg, Michael	K-S112	Halfdanarson, Thorvardur R.	M131	Herbst, Zackary (Ari) M.	K-S113
Greenfield, Julie	M247	Hallacli, Erinc	S279	Hernandez, Dena	LB-S109
Greve, Hendrik J.	S107	Hally, Alyson	M194	Hernandez, Jason	S137
Griebachov, Arthur	M282	Halpern, Casey H.	S255	Hernandez-Jones, Amanda	M287
Griffith, Eric	K-S112	Hamad, Abdullah	S123	Hernandez Silva, Yaimara	S122
				Herren, Cherie	S109
				Herrmann, David N.	K-M112
				Hess, David C.	M180
				Heuberger, Jules	M306

Heuberger, Jules A.	M299	Hurst, Rebecca	S257	Jaywant, Abhishek	M190
Hicks, Caitlin	M252	Hussain, Shaun A.	K-M105	Je, Goun	S247
Higgins, Connor	M179, M202	Hussein, Mohammad	M106	Jellen, Leslie C.	S222
Hildebrand, Michael	M224	Hutchison, John	M299	Jensen, Frances E.	S131, S175, M197, M225
Hill, Jacob	S169	Hutten, Samantha	S207	Jensen, Ivar	M144
Hillis, Argye E.	S104	Huttner, Anita	M224	Jensen, Klaus G.	M299
Hindsley, Heidi	S134	Hwang, Wenke	S119	Ji, Sung	S338
Hiniker, Annie	S278	Hyman, Bradley T.	LB-M108	Jia, Dan Tong	S189
Hinson, H. E.	K-M115	Hyman, Sara	M262	Jie, Xiaobo	M293
Hintze, John	K-S116	Iacovitti, Lorraine	S106	Jimenez-Arango, Jorge A.	M232
Hirai, Manabu	M301	Iadecola, Costantino	M190	Jimenez Giraldo, Sandra	S299
Hirsch, Alan R.	LB-S102, LB-M107, M157, M161, S233, S320	Ianelli, Mallory	M190	Johansen, Michelle	S115
Hirschey, Jacqueline	S333	Ibrahim, Nada	M257	Johansen, Michelle C.	S120
Hirschrift, Matthew E.	M154	Ibrahim, Sally	S343	Johnson, Caroline	S311
Hitzig, Sander L.	S348	Ikenaga, Chiseko	LB-M120	Johnson, Dawn	S192
Ho, King Chung	S218	Imamura, Tomohiro	M121	Johnson, Emily	M215
Ho, Peggy P.	LB-S125	Imperioli, Matthew	M104	Johnson, Emily L.	M210
Ho, Quan	S268	Inoue, Ken	S299	Johnson, Grace	S257
Hobson, Grace	S299	Insuasti, Walter E.	S234, M314	Johnson, Kelsey	S304, M311
Hoche, Franziska	S184	Irwin, David	LB-S111, M191, S243, S245	Johnson, Kevin M.	S124, S137
Hodics, Timea	LB-M100	Irwin, David J.	M186, M194, M197, M199, M201, S207	Johnson, Patrick	LB-S109
Hodics, Timea M.	S118, S153	Isaacs, David	S293, S294	Johnson, Teshawn	S319
Hoke, Ahmet	M308	Ishac, George	M132, S174, S185	Johnson, Vanessa	M195
Holland, Marshall	LB-S110	Ishida, Koto	M189	Johny, Paul	S151
Holland, Steven M.	S282	Ishikura, Teruyuki	M275	Joo, Yuyoung	K-M101, M126
Hollender, Kimberly	S127	Isobe, Noriko	M121	Jordan, Justin T.	S265
Hollenhorst, Cecilia	M271	Ittyerah, Ranjit	M201	Joseph, Donald	S295
Holloway, Robert	S178	Ivashkevich, Yana	S111	Josephs, Keith A.	LB-M103, LB- M103, M205
Holmes, Brandon B.	K-S108	Iyer, Keshav	S215	Judge, Bradley	K-M100
Honavar, Vasant	M216	Izda, Aleksandar	K-S114, S308	Jumani, Laraib	S128, S142, S155, M285, M288, M296, M303
Hong, Jinpyo	S126	Jack, Clifford R.	LB-M103, M205	Jung, Keun-Hwa	M223
Horng, Sam	M107	Jackson, Phyllis	S178	Jung, Ki-Young	M229
Horsnell, Matthew	S349	Jackson, Skyler	M247	Jungbluth, Heinz	M293
Horton, Kevin	M267	Jacobs, Dina	S192	Juraschek, Stephen P.	M252
Hosamath, Abhishek	S232	Jacobson, Leslie	M293	Juul, Halvor	M118
Hosein-Woodley, Rasheed	M253	Jafri, Neda	S103	Juvinao-Quintero, Diana	LB-M114
Hossain, Nadia	S242	Jagolino, Amanda	S130	Kabeel, Marwa	M257
Houlden, Henry	S310	Jagolino, Melanie	S140	Kaden, Alyssa	S311
Housri, Nadine	S180	Jagolino-Cole, Amanda	S140	Kadipasaoglu, Mehmet C.	M269
Howard, James F.	M294	Jahan, Nusrath	K-S105	Kafaie, Jafar	LB-M119
Howie, Kenneth	M144	Jain, Rishabh	M209	Kahle, Kristopher T.	M224
Hsu, Ming	LB-M109	Jaisa-aad, Methasit	LB-M108	Kaiser, Eric A.	S175
Hu, Bo	S229	Jaisil, Pongrat	M242	Kakara, Mihir	S192, S197
Hu, Youhong	S320	Jalilzadeh, Shapour	S315	Kakawand, Soroush	S109, S157, S173
Huang, August Yue	M224	Jamal Omidi, Shirin	M120	Kala, Narendra	S133
Huang, Brendan	M163	James, Sandra	M274	Kalb, Robert G.	M304
Huang, Juebin	M210, S224	Jan, Amanda K.	S293	Kalia, Suneil	S213
Huang, Weiliang	K-M101, M126	Jang, Dae Gyu	S326	Kamel, Hooman	M190
Huang, Xiaoping	M313	Jang, Dae-Gyu	M276	Kammeyer, Ryan M.	M112
Huang, Xuemei	S222	Jang, Yoonhyuk	M110, M222, M223, M229, S306, S325	Kampmann, Martin	K-S108
Huff, Hanalise V.	M240	Janku, Cynthia	LB-M102	Kan, Hirohito	S292
Hughes, Amber R.	LB-M115, LB-S121	Jannati, Ali	M179, M202	Kanakura, Minami	M275
Huntley, Mikayla L.	S278	Jarmol, Mitchell	M262	Kandawasvika, Gwendoline	M292
Hunzinger, Katherine J.	M252	Jayadev, Suman	S160	Kane, Maureen	K-M101, M126
Huppert, Theodore	K-S103	Jayaraman, Keshav	K-S102	Kang, Ju Hee	S207
Hur, Junguk	S326				

Kannarkat, George T.	LB-S111	Kihara, Keigo	M275	Kumar, Harendra	S145
Kapapa, Musambo	K-M112	Killoran, Annie	S205	Kumar, Prateek	S276
Kapoor, Anil	M221	Kim, Dae-Seong	M293	Kumar, Sonal	M190
Kapoor, Gaurav	S112	Kim, Erin	S192	Kummer, Benjamin	LB-S129
Kappler, Martin	M231	Kim, Ho Jin	M124	Kuntzer, Thierry	M293
Kapur, Ritu	S218	Kim, Hope B.	S255	Kus, Sumeyye	M104
Karachentsev, Dmitry	S284	Kim, Jennifer A.	K-M109	Kushida, Clete A.	S340
Karakis, Ioannis	M227	Kim, Jung G.	S177	Kvalsund, Michelle	K-M112
Karakoleva, Ema V.	S191	Kim, Minjee	S342	Kvalsund, Michelle P.	K-M121
Karam, Alvina	S128, S142	Kim, Yongmoo	M110, M222, M223, M229, S306, S325	Kvantaliani, Nino	S114
Karawya, Fardous	S285	Kim, Yongya	S278	Kwentus, Jacquelin F.	M177
Karp, Adam M.	S199	Kinel, Shari	S232	Kymes, Steven	S170, S171
Karvelas, Nikolaos	S108	King, Alexa	M241	Labounek, Rene	K-S109, S281
Kasarskis, Edward	K-M119	Kinker Mishra, Ram	S237	Lachner, Christian	M166
Kasarskis, Edward J.	M291	Kinoshita, Makoto	M275	Lacoursiere, Christopher M.	K-M111
Kasner, Scott E.	S114, S154	Kira, Jun-ichi	M121	Lah, James J.	M168, S183, M196
Katoch, Avinsh	M216	Kirkpatrick, Laura	M219	Lai, Eugene	LB-M100
Katz-Lichtenstein, Hilla	S262	Kiziltug, Emre	M224	Lam, Isabel	S279
Kaufman, Jacob	M212	Klaiman, Tamar	M172	Lam, Keng	S177
Kaur, Manmeet	M132	Klein, Christine	S212	Lam, Tukiet	M217
Kaur, Rmneek	S134	Klepitskaya, Olga	S204	Lambert, Clare	S119
Kay, Richard	M231	Klinge, Petra	S211	Lampron, Antoine	S213
Kayser, Andrew	LB-M109	Koda, Toru	M275	Lancaster, Eunjoo	M225
Kayson, Elise	S204, S232	Koga, Shunsuke	LB-M103, LB-S118	Landes, Reid	S244
Kearns, Gerry	M293	Köhler, Wolfgang	M231	Landsness, Eric	S107
Keator, Lynsey M.	S104	Kohli, Shaun	LB-S129	Landsness, Eric C.	K-S120
Keller, Jonah	S108	Kölbel, Heike	M293	Larson, Theodore	M267
Keller, Stephanie	S293, S310	Kollmorgen, Gwendlyn	S207	Lasker, Aaron	S209
Keller, Stephanie R	S313	Kolson, Dennis L.	M118	La Spada, Albert R.	LB-M118
Kelly, Catherine	S104	Komer, Lauren	S214	Laswi, Ibrahim	M234, M244
Kelly, Jeffery W.	S289	Komisarow, Jordan	K-M114	Latchman, Kumarie	M283
Kelly, Sean	M189	Kong, Lan	S222	Lauzon, Julie	M293
Kelly-Hedrick, Margot	K-M114	Kong, Sandra	S115	Lavender, Maggie	S349
Kendroud, Sarah	M102	Kong, Wenna	M224	Lavu, Venkat S.	M149
Keough, Kathleen	K-S117, LB-S123	Koopmans, Ingrid W.	M299	Law, Connor	M265
Keri, Vishakh C.	M256	Korn, Ronald	M300	Law, Connor A.	M252
Kern, Kyle C.	S129	Kornafel, Tracy	S296	Lawson, Michael	M164
Kessler, John A.	M249	Kornberg, Michael D.	K-M103	Lazar, Adam	M141
Khadilkar, Satish	M292	Kornblum, Cornelia	M293	Lazar, Evelyn B.	M170
Khaksari, Kosar	S309	Korobko, Denis	M294	Le, Khoi	S215
Khalid, Khalid E.	LB-S128	Korthauer, Laura E.	S211	Leadley, Deja	M134
Khan, Amina N	S313	Kotes, Emma	S302, S313	Lee, Andrea	S214
Khan, Erum I.	LB-S126	Koton, Silvia	M259	Lee, Caleb J.	M250
Khandelwal, Pulkit	S110, M201	Koubeissi, Mohamad Z.	LB-M112	Lee, Edward	M191, S245
Khawaja, Uzzam A.	S128, S142, S155, M285, M288, M296, M303	KP, Abdurehiman	S151	Lee, Edward B.	LB-S111, M186, M199, M201
Khera, Arnav	S251	Krahn, Lois	S349	Lee, Eunjung Alice	M224
Khodadadi-Chamgordani, Hesamoldin	M180	Krainc, Dimitri	S203, S286, S290	Lee, Han Sang	M110, M222, S306
Khongbantabam, Nikhil	M209	Kraus, Allison	S278	Lee, Han-Sang	M223, M229, S325
Khosa, Gurveer S.	M138, S201, M207, S277	Kremer, Philip	M306	Lee, Ikjae	K-M119, M291
Khosa, Shaweta	M138, M149, S201, M207, S277	Krencik, Robert	S223	Lee, Janice	S192
Khoshkhoo, Sattar	M224	Krishnaiah, Balaji	S122, S148, S275	Lee, Jessica	S163
Khurana, Shikhar	M117	Krishnamoorthy, Vijay	K-M114	Lee, Jin Moo	K-S120
Khurana, Vikram	S279	Krumholz, Harlan	S152	Lee, Kiwon	S127
Kiebertz, Karl	S207	Krzyzanowski, Brittany	S210	Lee, Mark	M156
		Kucharska-Newton, Anna M.	M210	Lee, Nadine	M224
		Kuchenbecker, Lindsey A.	M170	Lee, Paul B.	M256
		Kulick-Soper, Catherine V.	M263	Lee, Sang Kun	M222, M223, M229

Lee, Seolah	M110, M222, M223, M229, S306, S325	Lin, Jean Pierre	M293	Mace, Jackson W.	S283
Lee, Seonjoo	K-M119, M291	Linares, Anthony	M181	Mac Grory, Brian	S133
Lee, Seungil	S313	Lingam, Sneha	M140	Machulda, Mary M. LB-M103, M205	
Lee, Soon-Tae	M222, M223, M229	Lipton, Richard B.	LB-S105, S169	Madde, Pranathi	M279
Lee, Ting-Ting	S289	Little, Jessica N.	S114, S154	Madera, Ashley V.	S187
Lee, Virginia M.	LB-S111	Litvan, Irene	S240	Madigan, Nicolas N.	M279
Lee, Wan-Ping	M188	Litvin, Amy	M203	Magdamo, Colin	S330
Leibowitz, Lee	S192	Liu, Andy	M192	Magrinelli, Francesca	S296
Leigh, Richard	S129	Liu, Ashley	S268	Mah, Jean K.	M292
Leite, M Isabel	M293	Liu, Feilin	LB-S120	Mahadevan, Sangeetha	M171
Lekoubou, Alain	S126, M216	Liu, Lawrence	K-M105	Mahajan, Abhimanyu	S230
Lekoubou Looti, Alain Zingraff	S135	Liu, Li	M294	Mailman, Richard	S222
Lemanski, Elise	M167, M204	Liu, Meizi	K-S102	Maimaitijiang, Guzailiayi	M121
Lenchur, Peter	S262	Liu, Qiang	M113	Majersik, Jennifer J.	S160
Lennon, Vanda A.	M131	Liu, Siyuan C.	M249	Major, Eugene O.	S315
Lenzi, Kerry	S192	Liu, Ying	M307	Makhoul, Karim	LB-M115
Lequang, Timothy Q.	S328	Lizarazo-Nino, Jairo F.	M232	Makke, Yamane	LB-M112
Lesnick, Connie E.	M147	LK, Sreevidya	S151	Malavia, Tulsi	S189, M271
Lessard, Darleen	S132	Llanos, Mario	M232	Maldonado, Dalynah	S262
Letcher, Austin R.	M247	Lloyd, Thomas	LB-M120	Maldonado, Jose	LB-S115
Letendre, Scott L.	S172	Lockard, Blake S.	M195	Maldonado, Jose	LB-S114
Leu, Jia-Shiun	LB-S114	Loebel, Emma M.	S121	Malik, Athar	S211
Levchenko, Oksana	S134	Loh, Eldon	S335	Maltepe, Emin	K-S100
Levesque, Justine	S324	Lohana, Paneeni	S327	Mamarabadi, Mansoureh	M278, S328
Levey, Allan I.	M168	Lokan, Julie	M224	Manca, Matteo	S278
Levine, Joshua	M263, M264	Lomen-Hoerth, Cathy	M300	Mandrekar, Jay	M279
Levine, Steven R.	S114	Loo, Hannah	M119	Mangioris, Georgios	M131
Lewis, Ariane	M189	Loo, Hannah K.	S319	Manjarrez, Kristi	M135
Lewis, Katherine E.	M135	Lopez, Reydmir	M232	Manning, Sara	M194
Lewis, Mechelle M.	S222	Lord, Aaron	M189	Mannyam, Chandra	M150, S159
Li, George	M294	Loring, David W.	M227	Manohar, Nivethitha	M122
Li, Handong	M113	Los, Oleksandra	S139	Mantegazza, Renato	M135, M294
Li, Jiang	S119	Louvi, Angeliki	M217	Maqsood, Hamza	S128, S142, S155, M285, M288, M296, M303
Li, Jun	S229	Lowden, Max	S193	Marcus, Huda	K-M121
Li, Peter	K-M115	Lowden, Max R.	S191	Marczak, Izabela	S114
Li, Rui	S307	Lowe, Makayla	S245	Marek, Kenneth	S207
Li, Wei	LB-M118	Lowe, Mallory C.	S317	Margolis, Seth A.	S211
Li, Xiaofan	M197, M225	Lowe, Val J.	LB-M103	Maricich, Stephen M.	M300
Li, Xiaoyang	LB-M101	Lozano, Alicia	S182, S337, S341	Marignier, Romain	M124
Li, Yan	M313	Lozano, Andres	S213	Marini-Bettolo, Chiara	M292
Li, Yedda	M152, M184	Lu, Hannah	M132, S174, S185	Markantone, Desiree	S121
Li, Yuebing	M294	Lu, Ruijin	M168	Markowitz, Clyde	S192
Li, Yuhua A.	LB-S117	Lucas, John A.	M166	Marks, William J.	S218
Liang, Dan	M217	Luchembe, Musisye	S117	Marsh, Andrew	M151
Liang, Grace	S204	Ludolph, Albert C.	M301	Marsh, Eric	S248, S295
Liang, Yini	M228	Luk, Kelvin	LB-S111	Martens, Yuka	M178
Liao, Bing	M103, M146, M268, M269	Luna, Esteban	S246	Martens, Yuka A.	M170
Libon, David	M202	Lund, Troy	K-S109, M231	Martin, Holly	S200
Lickliter, Jason D.	M135	Lund, Troy C.	S281	Martin, Nicholas B.	LB-S118
Liebeskind, David S.	S124, S137, S160	Luo, Jian	S289	Martin, Sandra B.	M237
Lieberman, Kenneth	S291	Lutsep, Helmi L.	S160	Martin, Sandy	S196
Lildar, Taikchan	M221	Lutsey, Pamela L.	M156	Martin-Aguilar, Lorena	M287
Lima, Joao A.	S120	Ly, Anh M.	LB-S120	Martinell, Marc	M231
Lin, Alice	M206	Lynch, David	S237	Martinez, Carla S.	M141
Lin, Hsin-Pin	M313	Lyons, Hannah	LB-S100	Martinez, Juan M.	LB-S128
		Lyu, Xiru	S254	Martinez-Arellano, Emma	M132, S174, S185
		Ma, Yidan	S265		
		Ma, Yilong	S231		



Maryala, Shashi	M102	Mencacci, Niccolò E.	S203	Moon, Jangsup	M110, M222, M223,
Masaki, Katsuhisa	M121	Mendelson, Faye	S326		M229, S306, S325
Masdeu, Joseph	LB-M100	Mendelson, Faye E.	M177	Moon, Joon-Shik	S139
Masi, Gianvito	M287	Mendelson, Robert	S147	Moonis, Majaz	S132
Masi, Paul J.	M163	Mendizabal, Adys	S236	Moore, Lauren	M247
Mas Monteys, Alejandro	K-S114, S308	Mendlik, Matthew T.	M263	Moradi, Babak	M157, M161
Masnada, Silvia	S299	Menon, Uma	LB-S107	Moradi, Farshad	M300
Mason, Shayna N.	M177	Meraj, Shazeb	M258	Moran-Losada, Patricia	S289
Massabki, Ivana	LB-M119	Mercurio, Ann	S262	Morency, Jason A.	M253
Massimo, Lauren	M186, M194, M199	Mercial, Brandon	M264	Morganroth, Jennifer	M297
Masud, Amenah	M293	Merker, Vanessa L.	S265	Morimoto, Bruce	M306
Mataa, Moses	S117, S162	Messé, Steven R.	S114	Morley, James F.	LB-S111
Mateos, Gonzalo	M233	Mesulam, Marsel	M153	Morris, Jennifer	S182
Mathew, Alex	S341	Metcalfe, Stacy	M203	Morris, John C.	M168, M170, M176, M178
Mathias, Sally	M230	Meyers, Keya R.	M307	Morse, Anne Marie	S349
Matsukawa, Noriyuki	S292	Mezic, Matea	S262	Mortel, Dominique	S100, S117, S162
Matthews, Elizabeth	S317	Miao, Hanyang	K-S120	Moshayedi, Pouria	S147
Matys, Benjamin	LB-M106	Michels, Sebastian	LB-M118	Mosley, Thomas	M156
Maurer, Maya	K-S103	Midha, Rajiv K.	LB-S121	Mosley, Thomas H.	K-M116, M259
May, Jasmine	S189, M271	Miele, Andrew	S147	Moss, Kathryn R.	M308
Mayasi, Yunis	M282	Miglietti, Martina	M135	Moukheiber, Emile	M114
Mayeux, Richard	M185	Mike, Jana	K-S100	Moura, Lidia	LB-S108
McCabe, Kristin	S192	Mikhail, Fadi	M208	Moury, Luana	S108
McCann, Jacob	S313	Miller, Beckley	M144	Mowafi, Samar	K-S113
McDonald, Tanya J.	M226	Mills, John R.	M147	Moyano, Martha	M232
McDonnell, Lisa	S108	Mills, Kelly A.	S256	Mozes, Julie	S192
McElrath, Thomas F.	M219	Minakaki, Georgia	S203	Muddasani, Varsha	S136, S138
McGarvey, Michael L.	M251	Minen, Mia	S169	Muehlschlegel, Susanne	M258
McGinley, Lisa M.	M177	Minen, Mia T.	LB-S105	Mueller, Andreas	M293
McGinley, Marisa	S198	Mirchi, Amytice	S299	Mueller, Bryon	K-S109
McGraw, Christopher M.	K-M111	Misago, Gamaliel	K-M112	Mueller, Bryon A.	S281
McGuire, Tammy	M249	Mishra, Shri K.	M138, S201, M207, S277	Muirhead, Kayla	S280, S293, S299, S310, S312, S313
McKenzie, Emma	S296	Mishra, Shrikant	M149	Mukhija, Sasha	S330
McKeon, Andrew	M131, M147	Mistry, Arun	M231	Mula, Manasa	S182, S341
McLendon, Kristi	M135	Mitchell, Cassie S.	M196	Mulatu, Yohannes	S114
McManus, David D.	S132	Mitchell, Minnie	LB-S107	Mulenga, Chilando	S100
McMillan, Corey	M191, S243, S245	Mitchell, Oscar J.	M263	Mullen, Bryan	S215
McMillan, Corey T.	M186, M194, M199, M201, M233	Mitsumoto, Hiroshi	K-M119, M291	Muller, Ashley	M226
McMillan, Julia	M172	Mizenko, Christopher	M112	Munkombwe, Dickson	S100, S117, S162
McMinimy, Rachael	LB-S115	Mizsei, Gabor	M201	Munoz, Katrina	M227
McNaughton, Bruce	M175	Mobley, William C.	S284	Muñoz-Castro, Clara	LB-M108
McVicker, Benita	M164	Mochel, Fanny	M231	Muqarram, Sayera	M167
Meador, Kimford J.	M219	Mochizuki, Hideki	M275	Murdock, Benjamin	S226
Mehawej, Jordy	S132	Moderer, Dmytro	LB-S120	Murin, Peyton	LB-M119, M317
Mehta, Deviyani	S127	Modesti, Nicholson	S280, S305	Murphy, Geoffrey	S326
Mehta, Paul	M267	Modesti, Nicholson B.	S293	Mushannen, Malik	M234
Mehta, Shreya	M251	Moelter, Stephen	S182	Musiek, Erik S.	S347
Mehta, Tapan	S101	Moelter, Stephen T.	S341	Mutete, Frighton	S100, S117, S162
Meier, Andreas	LB-M106, M151	Mohammed, Eman	S285	Mutua, Sylvia	S280, S298
Meili, Zachary	S329	Moline, Margaret	S347	Muzyka, Iryna	M279
Melbourne, Jillian A.	S247	Mollenhauer, Brit	S207	Mwendaweli, Naluca	S100, S117, S162
Melendez-Perez, Ashley J.	S297	Monday, Lea	M256	Myers, Laura	S200
Mellinghoff, Ingo	S263	Money, Kelli M.	M112, M134, S317	Nabil, Amir	S123
Melmed, Kara	M189	Monsoor, Tonmoy	K-M105	Nader, Remi	S167
Memar Ardestani, Poonch	M214	Montero, Marcelo	S260		
		Montes-Rivera, Jose	LB-S106		

Naeini, Sahar E.	M180	Nolan, Amber	K-S119	Otabil, Edith M.	S132
Nagano, Seiichi	M275	Noon, Alison	S192	Otero-Millan, Jorge	S272
Nagata, Satoshi	M121	Norato, Gina	S196, M237	Oveisitorik, Sarah	S164
Naik, Sahil	M214	Norris, Scott A.	K-S107, S235	Owens, Gregory	M112
Nair, Kavita V.	M112	Norwood, Fiona	M293	Oyama, Genko	S218
Nakajima, Tsuneo	M275	Notarangelo, Luigi D.	S282	Oyegbile-Chidi, Temitayo	K-M106
Nakalule, Juliet	S184	Noukens, Jan	M294	Ozdemir, Ezgi	M121
Nakamura, Yuri	M121	Noureldein, Mohamed	M169, M238, S326	Ozdinler, Pembe Hande	M280
Nakano, Yoshikazu	LB-S112	Noureldein, Mohamed H.	M177	Ozel, Osman	LB-M100, M146, M315
Nakhmani, Arie	LB-S110	Nowak, Richard J.	M284, M287	Pacheco-Barrios, Kevin	LB-S104, LB-M114, LB-S127
Nall, Caroline	M150	Nutakki, Aparna	S117	Pack, Alison M.	M219
Namangala, Coolwe	S117	Oana, Shingo	K-M105	Pacut, Crystal	M242
Nanavati, Payal	M306	Obaid, Abeer H.	M287	Padawer-Curry, Jonah	K-S120
Napit, Prabhat	S248	O'Boyle, Ryan	K-S119	Padiath, Quasar	S248
Narayanan, Anand	M217	O'Connor, Kevin C.	M287	Page, Nicole	S313
Narechania, Aditi	S200	Odama, Caesar A.	S184	Paik, Jihye	LB-S114
Narendra, Derek	M313	Oguno, Bella	M300	Pak, Victoria M.	S346
Nariai, Hiroki	K-M105	Oh, Bradley	S108	Palace, Jacqueline	M124, M293
Narva, Aliza M.	M263	Ohashi, Sarah	M287	Palesh, Oxana	K-S104
Nascene, David	K-S109, S281	Ohlemacher, Timothy	LB-S100	Pallanck, Leo	S251
Nasrallah, Ilya M.	S341	Ohm, Daniel	S245	Palta, Priya	M252
Nasrallah, McLean	M208	Ohm, Daniel T.	M191	Palumbo, Joseph M.	M183
Natarajan, Sivaraman	LB-S115	Ohnuma, Tetsu	K-M114	Pandit, Lekha	M124
Natera-de Benito, Daniel	M293	Oishi, Kenichi	S292	Pandit, Maya	S262
Nath, Avindra	M237, S282	Ojha, Ajitesh	M272	Pang, Francis	M144
Natteru, Prashant	M127, S205	Okere, Samantha C.	S138	Panta, Nisha	S145
Natteru, Prashant A.	M162	Okun, Michael S.	S255	Papapetropoulos, Spyros	LB-M106, M151
Navarro-Flores, Alba	LB-S104	Okuno, Tatsusada	M275	Pappalardo, Laura W.	M259
Naveed, Sadiq	S155	O'Leary, Kelly	M174	Pappolla, Miguel	S167
Navratilova, Zaneta	M175	O'Leary, Kelly L.	M203	Pappolla, Sean	S167
Nazam, Imtiaz	S128, S142, M285, M288, M303	Oliver, Brant	M122	Pardieck, Zachary	S261
Nazeen, Sumaiya	S279	Olivera, Anlys	M189	Pardo-Villamizar, Carlos A.	M232
Neelon, Kelly	M151	Olm, Christopher A.	M186	Parent, Rachel	S326
Negida, Ahmed	S123, M257	Olson, James	LB-S115	Parikh, Neal S.	M190
Nelson, Caroline	LB-S113	Olson, Joseph	LB-S110	Park, Elena	S182, S337
Nelson, Ruth S.	S276	O'Mara, Ryan	M151	Park, Kyung-Il	M223, M229
Nelson, Shareen	K-S114, S308	Onda, Kengo	S292	Park, Lina	K-S118
Nelson-Williams, Carol	M224	Opere-Addo, Priscilla A.	S149	Park, Ryan	S108
Nestrasil, Igor	K-S109, S281	O'Rahelly, Mark	M293	Parker, T. M.	S272
Neumann, Anne	M247	Orchard, Paul	K-S109, K-S113	Parra-Patino, Beatriz	M232
Neumeyer, Ann M.	S184	Orchard, Paul J.	S281	Parwani, Jashank	S329
Neuteboom, Rinze	M124	Orjuela, Karen D.	S160	Pascual, María	M231
Newman-Toker, David E.	S272	Orthmann-Murphy, Jennifer	M130, S192, S304, S307, S319	Pascual, Sílvia	M231
Newsome, Scott	M114, M128	Orthmann-Murphy, Jennifer L.	M119	Pascual-Leone, Alvaro	M179, M202, M243
Newton, Michael A.	S124, S225, S238	Ortiz, Juan F.	S234	Pasquali, Marzia	K-S113
Ngo, Jacqueline P.	K-M105	Ortiz, Juan Fernando	M314	Pastula, Daniel M.	S317
Nguyen, Bao	M316	Ortiz, Luis	S349	Patel, Anisha M.	S198, S219
Nguyen, Cam-Tu Emilie	M293	Ortiz-Gonzalez, Xilma R.	LB-S119	Patel, Juhi R.	S242
Nguyen, Thao	S223	Osgood, Thomas	M279	Patel, Kajol N.	M250
Nicita, Francesco	S299, S312	Osipovich, Maria	M228	Patel, Kisan	LB-M102
Nicolayevsky, Sofia E.	LB-S122	Oskarsson, Bjorn	M279	Patel, Megh	S223
Niethammer, Martin	LB-S112	Oskoui, Maryam	M293	Patel, Payal	S338
Nieto, Alejandra	S301	Osorio-Amaya, Lyda	M232	Patel, Shivam	S101, S111, S112
Nieves, Jeri	M291	Osredkar, Damjan	M292	Patel, Virali	S296, S310, S312
Nieves, Jeri W.	K-M119	Osterhaus, Emma	M209	Patil, Gauri	K-M113
Nix, Kerry	K-M110, K-M110				
Nkromah, Kodwo	M246				

Patil, Parag	S254	Piecuch, Caroline	M276	Racette, Brad A.	S210
Patnaik, Jennifer	S274	Pierce, Samuel R.	S296, S302	Radabaugh, Hannah	S108
Patterson, Bruce W.	M200	Pierpont, Elizabeth I.	K-S109, S281	Radhakrishnan, Karthikeyan	K-S113
Paul, Friedemann	M124	Pike, James R.	K-M116	Radtke, Heather B.	S265
Paul, Rachel	S304	Pileckyte, Indre	M243	Rafferty, John	S205
Paul, Rachel A.	M311	Pileggi, Caitlin	S192	Raghib, Muhammad F.	M141
Paulk, Angelique C.	S339	Pillai, Lakshmi	S244	Rahimi, Narges	M115, M214
Paulo, Joao A.	S289	Pillai, Nishitha	K-S113	Rahmani, Benjamin	S291
Paulsen, Jane S.	S124, S137, S144, S160, S225, S238, S263	Pina, Guillem	M231	Rainaldi, Erin	S218
Paulson, Amy	K-S109, S281	Pino, William	M263	Raj, Aiswarya	S151
Pedersen, Thomas H.	M299	Pinto, Alex	S225	Rajagovindan, Raj	LB-M106, M151
Pekyi-Boateng, Patrick D.	M211, M302, S323	Piquet, Amanda L.	M112, M134, S317	Rakolle, Keamogetswe	S188, S194
Pekyi-Boateng, Prince K.	M211, M246, M302, S323	Pisano, Tom J.	M264	Ramalingam, Nirmala D.	M154
Pelak, Victoria S.	S274	Pitarch Castellano, Inmaculada	M292	Ramanan, Vijay	LB-S109
Pelc, Emily	M141	Pitter, Britney	LB-S107	Ramanathan, Sudarshini	M124
Pellinen, Jacob	LB-S108	Pittock, Sean	M124	Ramaswamy, Srinath	S114
Pelo, Ryan	K-M117	Pittock, Sean J.	M131, M147	Ramdas, Sithara	M293
Peng, Chian-Yu	M249	Pizzino, Amy	S280, S293, S299, S310, S312, S313	Ramirez-Zamora, Adolfo	S255
Peng, Junmin	S143	Plotkin, Scott R.	S265	Ramos, Gustavo	M232
Peng, Shichun	S231	Podhorna, Jana	M294	Ramos, Maria F.	M232
Peng, Stanford	M135	Poduri, Annapurna	K-M111, M224	Ramos, Mark Jason O	S313
Peng, Wesley	S286, S290	Pollock, Jeffrey M.	K-M115	Ramos-Rodriguez, Leonardo	LB-S119
Pennell, Page	M209	Polydefkis, Michael J.	M307	Ramphul, Kamleshun	M211, M246, M302, S323
Pennell, Page B.	M219	Polymeropoulos, Christos M.	S311	Ramy, Maya	LB-M100, M315
Perellón-Alfonso, Ruben	M243	Polymeropoulos, Mihael H.	S311	Rana, Maheen	S133
Perelstein, Elizabeth	S133	Poston, Kathleen	LB-S112	Rana, Sandeep	M281
Perez Davila, Mauricio X.	S260, S301	Poston, Kathleen L.	S207	Rana, Shehroz	M244
Perez-Davila, Mauricio X.	S267	Potashman, Michele	M247	Ranasinghe, Tamra	S161, M250, S324, S327
Pericak-Vance, Margaret A.	M185	Poudel, Sujana	S145	Ranasinghe, Tamra I.	M140
Perlman, Susan	S236	Powers, Scott W.	LB-S105	Rangaraju, Srikant	S276
Perlmutter, Joel S.	K-S107, S235	Prabhakaran, Karthik	M201	Ransom, Christopher	K-S119
Pernal, Sebastian	S229	Prabhu, Aparna	S136, M214	Rao, Laya	S270, S332
Perrone, Chris	S192	Prabhu, Aparna M.	M117, S202	Raoof, Ameer	M234, M244
Perrone, Erin	S192	Prado, Miguel A.	S289	Rashid, Mehak	S128, S142, S155, M285, M288
Persico, Michele	S216, S221	Prakash, Prarthana	S211	Rasool, Sohaib	S128, S142, S155, M285, M288, M296, M303
Pervin, Saniya	M230	Prasuhn, Jannik	S212	Rastall, David	S272
Peterman, Kelli	M154	Price, Ray	S192	Rau, Naraharisetty A.	M214
Petersen, Ronald C.	LB-M103	Priyadarshini, Shubadra	M271	Ravi, Samyuktha	S215
Petersen, Thomas K.	M299	Proano, Ana C.	S301	Rawley, Nicole	S211
Peterson, Claire S.	M186	Prudencio, Mercedes	LB-M111	Rayaprolu, Sruti	S276
Petrocelli, Jillian	K-S112	Przychodzen, Bart	S311	Raymond, Jaime	M267
Petropoulos, Helen	S124, S137	Przydzial, Paulina	S127	Raymond, Mirasol	S127
Petrucelli, Leonard	LB-M103	Pu, Cunfeng	S222	Razzaque, Joyeta	S215
Petrykowski, Ben	LB-S100	Pucci, Kristy	S302	Reading, Christopher L.	M183
Petucci, Justin	M216	Puckett, Meaghan	S161	Reandean, Cassidy	S337
Pfeffer, Gerald	M292	Purdon, Patrick L.	S339	Reda, Eman	S123
Pham, Nha Trang Thu	LB-M103, M205	Pylypyuk, Caroline	S230	Redondo-Camós, María	M243
Pham, Truc	K-S115, M218	Qi, Wendy	K-M110	Reeder, Annie Kate	S169
Phillips, H. Westley	M224	Qiu, Enchao	S165, S166	Reich, Daniel S.	K-M102
Phillips, Jeffrey	M191, S243	Querol, Luis	M287	Reichard, R. Ross	LB-M103
Phillips, Jeffrey S.	M199, S207, S245	Quicksall, Zachary	LB-S109	Reid, Kathryn J.	S342
Phillips-Cremens, Jennifer	M188	Quijano-Roy, Susana	M292	Reid, Robert	M210
Phinney, Brett S.	LB-S120	Quinlan, Miriam	S134	Reider-Demer, Melissa M.	S181
Piazzon, Flavia	M292	Quinn, Colin	S304, M311	Reilly, Cavan	M240
		Quinn, Nathaniel	LB-S100		
		Quiroz, Jorge A.	M299		

Reilmann, Ralf D.	M203	Roy, Asim	S340, S343, S345	Sarwat, Zoha	S101, S111, S112
Reimann, Jens	M293	Roy, Bhaskar	M284, M287, M292	Sasaki, Tsutomu	M275
Reindl, Markus	M124	Roychowdhury, Vwani	K-M105	Sase, Sunetra	S248
Ren, Yingxue	LB-S109	Rube, Jacob	M141	Sasso, Nicholas E.	S261, S333
Reoma, Lauren	S196	Rubinos, Clio	M235	Satari, Anas	S285
Reoma, Lauren B.	M237	Ruch, Kristina	S104	Sato, Douglas	M124
Rexach, Jessica E.	K-M104, LB-M105	Rudrud, Maria	S225	Satyadev, Nihal	M170, M178
Reyes, Dolly	M185	Ruiz, Juan	K-S115, M218	Savarraj, Jude P.	K-M118
Reyes-Esteves, Sahily	S150	Rundek, Tatjana	S125	Savelieff, Masha G.	M177
Rezk, Ayman	S307	Russell, Katherine L.	M245, S346	Sawa, Mariko	S284
Rhodes, Emma	S207, S243	Russo, Delia J.	LB-S122	Saylor, Deanna	S100, S117, S162, M241
Ribeiro, Alejandro	M233	Rybinnik, Igor	S127	Scannevin, Robert H.	M306
Ribeiro, Estevao	M106, M160, M193	Ryneerson, Kevin D.	S284	Schara -Schmidt, Ulrike	M293
Richards, Kathy	S182, S337, S341	Saadi, Altaf	K-S105, S190	Scharf, Jodi	S169
Richardson, R. Mark	S339	Saber Tehrani, Ali S.	S272	Scheffer, Ingrid	M224
Rieder, Emily	S119	Saccà, Francesco	M294	Schellenberg, Gerard	M188
Rieiro, Hector	S272	Sachdev, Aradhana	K-S117, LB-S123	Scherer, Steven	S304
Rigan, Diana	M169, M238, M242, S326	Saczynski, Jane	S132	Scherer, Steven S.	M311
Rigan, Diana M.	M177	Sadaghiani, Shokufeh	S110	Schindlbeck, Katharina	LB-S112
Riggins, Nina	S176	Sadiq, Zuhair	M244	Schindler, Matthew	S192
Rigler, Nicole	S176	Sadjadi, Reza	M231	Schindler, Suzanne	M168
Rinaldi, Elena	M135	Saeed, Mujtaba	M103	Schindler, Suzanne E.	M170
Ringheim, Garth E.	S347	Saez Calveras, Nil	S227	Schjoldager, Katrine	K-S116
Ristori, Giovanni	M247	Safavi, Farinaz	S282	Schlotawa, Lars	K-S113, S294
Ritchie, Alanna	M112	Safren, Nathaniel	S203	Schmidt, Johanna	S293, S299, S312, S313
Ritt, Elissa	M294	Sahin, Mustafa	K-S115, M218, M228	Schmidt, Johanna L.	S280, S310
Rivera-Torres, Noellie	S192	Sahu, Malya	S271	Schneck, Michael J.	S144
Rivier, Cyprien	S152	Saito, Kayoko	M292	Schneider, Andrea L.	K-M116, M156, M210, M252, M259, M265
Robbins, Ashley	K-S114, S308	Sakata, Takeshi	M301	Schneider, Beth	S349
Robens, Barbara	K-M111	Sakoda, Ayako	M121	Schneider-Gold, Christiane	M293
Robert, Stephanie M.	M224	Sakthivel, Hemamalini	M211, M302, S323	Schreiber, Martin	K-M115
Roberts, Amanda J.	S284	Sakurai, Keita	S292	Schreiber, Steven	S200
Roberts, William H.	S266	Sakuru, Ragha	S159	Schröder, Leonie F.	S286, S290
Robitsek, Jonathan	S147	Salah, Alejandro	M301	Schubert, Robin	M203
Roccaforte, Zachary	S206	Salarda, Erika	LB-S128	Schuldt, Robert	S198
Rodman, Hillary R.	S346	Saleem, Amna	S128, S142, S155, M285, M288, M296, M303	Schumacher, Hermann C.	S103
Rodriguez, Bianca	S295	Saleem, Arshaq	M127	Schwake, Michael	S290
Rodriguez, Maria C.	M287	Salemi, Michelle	LB-S120	Schwarz, Christopher G.	M205
Roefke, Kathrin	M293	Salles, Evila L.	M180	Schwarz, Heidi	S178
Rogalski, Emily	M153	Salley, Jacey	S266	Sckaff, Maria	K-S117, LB-S123
Rojas, Juan P.	M232	Salloway, Stephen	S160	Scott, Thomas	M277
Rojas, Maria D.	S138	Samkutty, Danny	M193	Sebastian, Rajani	S104
Rojas-Ceron, Christian A.	M232	Sampson, Jacinda	M231	Seeberger, Lauren C.	M247
Roman, Samantha	M100, M114, M128	Samudralwar, Rohini	S192, S271	Seeley, William	LB-M105
Rosales, Raymond L.	S212	Samuelson, Annika G.	S138	Segall, Hailey	M283
Rose, Deborah	M192	Sanders, Katherine	S183	Sehgal, Amita	K-M108
Rosenbaum, Michael	K-M119, M291	Sanderson, Russell J.	M135	Sekella, Nora	S192
Rosenberg, Roger	M185	Sands, Stephen	S263	Selcen, Duygu	M286
Ross, Jennifer	S291	Sankar, Raman	K-M105	Selness, Daniel	M301
Ross, Owen	LB-S109	Sankar, Sujata	M306	Selva, Sean	M112
Rosso, Michela	S114, S154	Santhosh, Sarayu	S122	Sen, Kuntal	S309
Rossoll, Wilfried	LB-S120	Saouda, Christopher	LB-M112	Seng, Elizabeth	LB-S105, S169
Rostasy, Kevin	M124	Sapantzi, Styliani	K-M107, M206	Seog, Daniel	M153
Rothstein, Jeffrey	M301	Sarfo, Fred S.	S149	Serrano-Pozo, Alberto	LB-M108
Roussi, Abdurrahman	M250	Sarva, Harini	S213	Seshadri, Sudha	S160
Rowell, Susan	K-M115				

Seth, Arjun	M271	Shu, Liqi	S133	Sriwastava, Shitiz K.	S314
Sevagamoorthy, Anjana	S280, S293, S298, S299, S305	Shuhaiber, Hans	M231	Staba, Richard J.	K-M105
Seyedroudbari, Sara	M129	Shults, Justine	S280, S293, S296, S298	Staff, Nathan P.	M279
Sgobbi, Paulo	M231	Shvartsur, Anna	M154	Staikova, Ekaterina	M227
Shafian, Neeva	M163	Siderowf, Andrew	S207	Starling, Amaal J.	S170, S171
Shah, Bhavya	S227	Siderowf, Andrew D.	S245	Stebbins, Glenn	S230
Shah, Kajol	S153	Sihag, Saurabh	M233	Steeland, Sophie	M294
Shah, Shrenik	LB-S102, LB-M107	Sikandar, Morgan	M263	Stein, Laura	S192
Shah, Syed	M102	Sillau, Stefan	M112, M134	Stein, Laura K.	S121, S199
Shah, Vinil	M300	Silvestri, Jasmine A.	M172	Steinberg, Kathy	S170, S171
Shahjouei, Shima	S156	Simon, David K.	S216, S221	Steiner, Joe	S282
Shahrivari, Mahan	S130	Simonson, Donald C.	M183	Steinhardt, Julia	S212
Shaik, Fathima	M157, M161	Simuni, Tanya	S207	Steinman, Lawrence	LB-S125
Shaik, Noor F.	M265	Simushi, Faith	S100, S117, S162	Stellingwerff, Menno	S312
Shaikh, Marwan	S105	Sine, Kathryn	S211	Stephen, Chris	LB-S113
Shakeel, Hassan Abdullah	M277, S316	Singh, Raman	S157	Stephen, Christopher	S228
Shakibajhromi, Banafsheh	S110	Singh, Romil	M277	Sterling-Angus, Oliver	K-M120
Shallcross, Amanda	S169	Singh, Savdeep	S122	Stern, Thomas	S340, S343, S345
Shannon, Kathleen M.	S225, S238	Singla, Ramit	S122, S148, S275	Stern-Nezer, Sara J.	S107
Shapiro, Colin M.	S343	Sinha, Saurabh R.	M263	Stewart, Alistair	M306
Sharet, A. R.	M155	Sintini, Irene	LB-M103	Stiles, David	LB-M106, M151
Sharkus, Robert	M133	Sinyagovskiy, Pavel	S179	Stinnett, Sandra	M212
Sharma, Ashish	S347	Sirsi, Deepa	LB-S108	Stockbridge, Melissa D.	S104
Sharma, Nutan	K-S106, LB-S113, S228	Sisniega, Daniella	S121	Stopschinski, Barbara	S227
Sharma, Pranav	M129	Sivakumar, Shravan	M258	Stoub, Travis	S230
Sharma, Richa	S152	Skjeie, Vivian	S231	Stout, Jacob M.	M140
Sharma, Sameer	S159	Skolarus, Lesli E.	K-M121	Stretz, Christoph	S133
Sharma, Sandeep	S170, S171	Skrinak, R T.	LB-S111	Stronge, Edward	M224
Sharrief, Anjail	S130	Smieszek, Sandra	S311	Stutterd, Chloe	S299
Shaw, Leslie M.	M168, S207	Smilowski, Marek	M294	Subramanian, Megha P.	S215
She, Xiwei	K-M110	Smirnov, Denis	S278	Subramanian, Thyagarajan	S215
Sheikh	Andalibi,	Smith, Alicia R.	K-S114, S308	Sudhakaran Lissy, Akshara	M274
Mohammadsobhan	S172	Smith, Alina	M135	Sudilovsky, Gabrielle M.	S280, S299
Sheinberg, Nurit	M195	Smith, Edward B.	S315	Sugar, Dana	S230
Shen, Ting	M199	Smith, Matthew	M142, S283	Sugimoto, Tomoyuki	M275
Shen, Xin-Ming	M286	Smits, Lars	M306	Sugiyama, Yasuko	M275
Sheppard, Shannon M.	S104	Snyder, Amanda M.	S222	Suh, EunRan	M194
Sherbini, Omar	S280	So, Yuen	M300	Suhana, Salma	M117
Sherma, Arun	M256	Sobue, Gen	M301	Sullivan, Kevin	M156
Sheth, Kevin N.	S152	Solana Sánchez, Javier	M243	Sumi, Hisae	M275
Shetty, Namrata	S201, S277	Solanky, Riya	S337	Sun, Ruiqing	M132, M132, S185
Shi, Yiwen	S256	Somal, Aneetinder	LB-S102, LB-M107	Sun, Ruiqing L.	S174
Shibuya, Yohei	S289	Sombans, Shaheen	M211, M246, M302, S323	Supnet, Melanie L.	S228
Shih, Andy	K-S118	Song, Pingping	S286	Suresh, Surya	M274
Shimizu, Mikito	M275	Sotirchos, Elias	M100	Suridjan, Ivonne	S219
Shin, Jin-Hong	M292	Speier, William	K-M105	Sutton, Erica	LB-S107
Shin, Yong-Won	M110, M222, M223, M229, S306, S325	Spell, Leigh Ann	S104	Svokos, Konstantina	S211
Shin, Yongjoon	LB-S117	Spencer, Dennis	M224	Swan, Matthew	S199
Shiplett, Emily	K-S116	Sperling, Reisa A.	M168	Swed, Sarya	S285
Shiraishi, Naoyuki	M275	Spinale, Charlie	S170, S171	Sweet, Robert A.	M185
Shivaprasad, Akhil	M103	Spindler, Meredith	S245	Swenson, Rod	M202
Shook, Brian	M306	Spinner, Warren	S158, S334	Sytsma, Karinn	K-S119
Shoulson, Ira	S232	Squatruto, Massimo	LB-S114	Tabar, Viviane	S213
Showalter, John	M179, M202	Srichawla, Bahadar S.	S132	Tackett, William	S110
Shroff, Sheetal	M273, M315	Sriwastava, Shitiz	LB-S126	Tada, Satoru	M275
				Tager, Dale	M227
				Taghvaei, Mohammad	S110
				Taha, Hash Brown	S217

Tahanis, Aboud	S223	Tiiti, Pamela	S184	Vallejo, Catalina	M232
Takada, Koji	S292	Tintos-Hernandez, Jesus A.	LB-S119	Van Deerlin, Vivian M.	M194
Takanohashi, Asako	S248, S312	Tippett, Donna C.	S104	Van Den Bergh, Peter VK	M293
Takeda, Shuko	M275	Tipton, Philip W.	M170, M178	van der Knaap, Marjo	S296, S310, S312
Talmasov, Daniel	M189	Tisdall, M. Dylan	M201	Vanderver, Adeline	K-S113, S248, S280, S293, S296, S298, S299, S305, S310, S312, S313
Talos, Delia	M225	Titia, Ruijs Q.	M299	Van Haren, Keith	S293, S313
Talos, Delia M.	S131, M197	Tobi, Martin	M164	Van Hoorick, Benjamin	M294
Talwar, Harvinder	M164	Tobi, Yosef	M164	Van Ryn, Collin	M240
Tan, Irene	S138	Tobyne, Sean	M179, M202	Vardarajan, Badri	M185, M188
Tandon, Raghav	M196	Tochen, Laura	S307	Vargas-Manotas, Jose E.	M232
Tang, Bin	S172	Todorovic, Vesna	M301	Vasileiou, Eleni	M100
Tang, Chris C.	LB-S112	Toga, Arthur W.	S207	Vasireddy, Rani Priyanka	S163
Tang, Michelle	K-S120	Tokala, Janaki	M270	Vassallo, Melanie	S262
Tang, Rui	S269	Toledano, Michel	LB-M101	Vassar, Robert	M200
Tang, Yunshuo	LB-S116	Tonduti, Davide	S296, S299, S310, S312	Vasu, Reshma	S233
Tannemaat, Martijn	M299	Tong, Han	M159	Vaswani, Pavan	S255
Tanner, Caroline M.	S207	Tormos, Josep M.	M243	Vaziri, Ashkan	S237
Tanzi, Rudolph E.	S284	Toro-Serey, Claudio	M179, M202	Vázquez-Costa, Juan F.	M292
Tapia, Christopher	M190	Torres, Jose	M189	Velasco, Margarita	K-S105, S190
Tarasaria, Karan	S111	Tran, Han Nhat	LB-S114, LB-S115	Venkateswaran, Kala	S215
Taravella, Michael	S274	Treiman, Scott	S108	Vera Silva, Maria Andreina	M108
Tarfeh-Burnette, Helen	M240	Tremoulis, Jacob	LB-S100	Vershuuren, Jan	M299
Tassiopoulos, Karina	M215	Trescher, William	LB-S108	Vest, Ryan	S289
Taylor, Elena	M114	Trikamji, Bhavesh	M149	Vettleson-Trutza, Sara	LB-S120
Taylor, Stanley	S200	Trojanowski, John Q.	M186	Vijaywargiya, Darshana	M305
Teaney, Nicole	K-S115, M218	Tropea, Thomas	S245	Villasante-Tezanos, Alejandro	S167
Teener, Samuel	M169, M238, M276	Tropea, Thomas F.	LB-S111, S207	Vincent, Angela	M293
Teertam, Sireesh Kumar	K-S101	Trotman, Winifred	M191	Vincent, Ariel	S280, S310
Teklehaimanot, Abeba	S104	Trowbridge, Sara K.	K-S112	Vindel Zuñiga, Carlos	S267
Temraz, Heba	S123	Trujillo, Jacquelyn E.	M280	Virmani, Tuhin	S244
Tenembaum, Silvia	M124	Tsai, Anne	S109	Virtucio, James	S337
Teng, Michelle	S296	Tsai, Annie	K-S118	Visvanathan, Pallavi	S169
Terranova, Michael	S144, M174, M203	Tsai, Chih-Wei	LB-S120	Viswanathan, Neena	M274
Tessema, Sophia	M141	Tseng, Bertrand	M284	Vithayathil, Joseph	S131
Testa, Claudia	M283	Tsuang, Debby W.	M185	Vitti, Emilia	S104
Testa, Marcia A.	M183	Tucci, Carl	S216	Vivanco, Ricardo A.	S234, S260, M314
Thackaberry, Evan	M151	Tulu, Bengisu	M258	Vo, An	S231
Thakkar, Richa	M133	Turfah, Ali	S326	Vogel, Jacob W.	M199
Thakur, Nivedita	S298, S302	Turner, Michelle	M279	Vollmer, Timothy L.	M112, M134
Thaliath, Andrew	M102	Tyner, Christina	S311	Vorasoot, Nisa	M147
Thangavel, Ramasamy	M165	Tzoulis, Charalampos	S231	Vranceanu, Ana-Maria	K-S105
Thaxton, Colby S.	M280	Uchida, Yuto	S292	Vu, Tuan	M294
Thaxton, Courtney	M283	Uchil, Alpa	S272	VV, Ashraf	S151
Thebault, Simon	S307	Uebergang, Eloise	S299	Wagner, Daymond	S215
Theyel, Brian	K-M107	Uhl, George R.	LB-S103	Wagoner, Ngan	LB-S116
Theyel, Brian B.	M206	Uitti, Ryan J.	LB-S109	Wahbeh, Farah	M190
Thieme, Andrea	M293	Ullrich, Nicole J.	S265	Waite, Shelley R.	S184
Thomas, Mary Ann	M293	Undavia, Anishee	M312	Waldman, Genna J.	M263
Thomas, Olivia R.	S278	Unnithan, Shakthi	M192	Walker, Harrison	LB-S110
Thomas, Rachel	M251	Urban, Alexandra	M212	Walker, Keenan A.	M155
Thompson, Christopher H.	LB-M113	Urrego, Jonathan	M232	Wallace, Gerald C.	S266
Thon, Jesse M.	M133	Uter, Jan	S212	Walsh, Christopher A.	M224
Thon, Olga R.	M133	Utianski, Rene L.	M205	Walter, Alexa E.	M210, M252
Thorn, Jakob	LB-M104	Utsugisawa, Kimiaki	M294	Walter, Maggie C.	M292
Thorson, Justin	S327	Uzel, Gulbu	S282		
Thuro, Lisa	M279	Vakhrushev, Sergey Y.	K-S116		
Tian, Fangyun	S339	Valdez, Brooke	M134		

Walz, Markus	M144	Windham, B. G.	M252	Younus, Shifa	S155, M303
Wamil, Art	M301	Witkowski, Tom	M224	Youssefi, Julie	M230
Wan, Hoi-Shan	M293	Woidill, Sarah	S280, S293, S296, S298, S299, S305, S310, S312, S313	Yu, Emily	S280, S294, S298
Wang, Caiyi	LB-S114	Wold, Barbara	M181	Yu, Kenneth	S213
Wang, Chanung	S347	Woldeamanuel, Yohannes W.	K-S104	Yu, Mandy	S230
Wang, Erming	S143	Wolf, Michael S.	S342	Yu, Melody	K-S116
Wang, Ju	S143	Wolf, Nicole I.	S296, S299, S310, S312	Yu, Selina	S251
Wang, Lei P.	M180	Wolk, David	S110, M168, S182, M191, S243, S245, S337	Yu, Shengyuan	S165
Wang, Xinyuan	S279	Wolk, David A.	M201, S341	Yu, Zheming	S224
Wang, Yilan	M224	Wong, Brad	M306	Yuan, Hsiangkuo	S166
Wang, Zehui	M264	Wong, Dean	M156	Yuan, Yang	S109
Wanigasinghe, Jithangi	M292	Wong, Dean F.	M155	Yun, Jina	M181
Ware, Jeffrey B.	M263	Wong, Eric T.	S268	Yun, Kyuson	LB-S114, LB-S115
WarnerRosen, Tila	S230	Wong, Katherine	M174	Yushkevich, Paul	S110, M201, S243
Wasan, Ajay	K-S103	Wong, Katherine S.	M203	Yuskaitis, Christopher	M228
Wassmer, Evangeline	S296, S310, S312	Wong, Phil	LB-M120	Zack, Rebecca	LB-S111
Watanabe, Mitsuru	M121	Wong, Yvette C.	S286, S290	Zafar, Sahar	LB-S108
Waters, Patrick	M124	Wozniak, Jeffrey	K-S109	Zafar, Saman	LB-S101, M214
Watson, Heidi	S200	Wozniak, Jeffrey R.	S281	Zagorulk, Alsu	S179
Waugh, Jeff L.	K-S106	Wright, Clinton B.	S125, S129	Zahid, Anza	M103
Weaver, Meredith	M283	Wright-Jin, Elizabeth	M167, M204	Zahid, Manahel	S196
Webb, Conor	LB-M105	Wszolek, Zbigniew	LB-M106, LB-S109	Zaky, Andrew	S134
Webber-Davis, Ian	S326	Wu, Dee H	S109	Zamore, Hannah H.	S278
Webster, Katherine	S178	Wu, Sienna	M101	Zand, Ramin	S119
Weeks, Katie	S224	Wu, Sienna L.	S332	Zarrinnegar, Donya	S295
Wei, Brandon	M268	Wu, Zhiping	S143	Zayed, Hany	M135
Weigand, Stephen D.	M205	Wuni, Nadia I.	M211	Zeccardi, Sara	S192
Weintraub, Daniel	LB-S111, S207, S243, S245	Wyss-Coray, Tony	S289	Zedan, Esraa	M257
Wells, Jim A.	K-S108	Xiao, Hailian	S276	Zee, Phyllis C.	S342
Wells, McKenzie	S237	Xie, Emily	M191	Zeiler, Steven R.	S272
Wells, Rebecca E.	S169	Xing, Bo	M225	Zekeridou, Anastasia	LB-M101, M131, M147
Wernig, Marius	S289	Xing, Xinbo	S166	Zelmann, Rina	S339
Westenberger, Ana	S212	Xiong, Chengjie	M168	Zeni, Cristian	S206
White, Charles	S178	Xiong, Hui	M292	Zerbe, Christa S.	S282
Whiteman, Katherine	K-S114, S308	Xu, Elizabeth	S268	Zetterberg, Henrik	M243
Whittington, Jeanne Ann	M122	Xu, He	M118	Zhang, Bin	S143
Whitwell, Jennifer L.	LB-M103, M205	Xu, Jiaqiong	S153	Zhang, Ce	M217
Wiendl, Heinz	M294	Xu, Ping	S279	Zhang, Cen	M189
Wigodski, Karina	S261, S318, S333	Yaghi, Shadi	S133	Zhang, Guoqi	K-M111
Wilkins, Kevin B.	S247	Yamasaki, Ryo	M121	Zhang, Hui	S204
Wilkinson, Jayne	S200	Yamashita, Toshihide	M275	Zhang, Jordan	M175
Williams, James	M253	Yang, Binxia	M147	Zhang, Lidan	M258
Williams, Linda	S200	Yang, Edward	M224	Zhang, Qiang	M165
Williams, Nicole	S115	Yang, Jimmy C.	M227	Zhang, Xu	M121
Williams, Ziv	S339	Yang Liu, Sunny	K-M114	Zhang, Yan	LB-S101, S136
Williamson, Rebecca L.	M201	Yasen, Noha	M257	Zhang, Yipeng	K-M105
Willie, Jon T.	M227	Ye, Zimeng	M224	Zhang, Yizhen	K-M107
Willis, Mary	M150	Yeppez, Geovanna	S301	Zhang, Yizhen S.	M206
Wilson, Andrew	LB-M120	Ying, Chunwei	K-M100	Zhang, Yun	K-S108
Wilson, Cara	S317	Yohay, Kaleb	S265	Zhang, Zhihao	LB-M109
Wilson-Grady, Joshua	S289	Younce, John R.	K-S107, S235	Zhang Fang, Tracy Shi	S216, S221
Wiltshire, Timothy	M279	Young, Jessica	S251	Zhao, Lili	S326
Win, Nikki	S198, S219	Young, Robert	S263	Zhou, Guoyu	M174, M203
Winch, Peter J.	K-M121	Yountz, Marcus	S213, S213	Zhou, Zhaolan	K-S116
Windebank, Anthony	M279			Zhou, Zitao	K-S113
Winden, Kellen	K-S115, M218				

Zhu, Guangya	M224	Zinman, Lorne	M301	Zubair, Adeel S.	S180, M284
Zhu, Jidong	M224	Zipfel, Gregory J.	K-S102	Zuchner, Stephan	M283
Zielinski, Dina	S279	Zitser, Jennifer	S144	Zuluaga-Lotero, Daniela	M232
Zimba, Stanley	K-M112, S117, S162	Zizzi, Christine	S178	Zuroff, Leah	M130, M297



## ANA 2023 Keyword Index

### A

**Addiction** M161, M250, S157  
**Alzheimer's Disease** M155, M166, M168, M172, M176, M177, M178, M179, M181, M183, M185, M188, M192, M196, M197, M200, M202, M233, S183, S207, S245, S276, S278, S284, S288, S289, S347  
**Amyotrophic Lateral Sclerosis** M267, M274, M275, M276, M279, M280, M291, M300, M301, M302, M303, M304, M306, S180, S226, S272, S308  
**ANA-AHS Headache** LB-M114, LB-S100, LB-S103, LB-S104, LB-S105  
**Animal Model** M135, M142, M167, M175, M228, M260, M304, M308, M313, S106, S175, S229, S246, S248, S276, S287, S308, S319  
**Artificial Intelligence** M196, M216, M239, M317, S145, S163, S218, S232, S238  
**Ataxia** M111, M247, S205, S224, S228, S233, S237, S241

### B

**Behavioral Neurology and Dementia** LB-M100, LB-M102, LB-M103, LB-M104, LB-M106, LB-M107, LB-M108, LB-M109, LB-M111, LB-M118, LB-S102, LB-S120, LB-S121, LB-S123  
**Biomarkers** M103, M111, M112, M121, M129, M147, M155, M156, M164, M168, M170, M174, M180, M196, M200, M203, M222, M243, M284, M296, S108, S110, S124, S137, S142, S143, S149, S172, S183, S207, S214, S215, S217, S219, S225, S227, S231, S278, S285, S337  
**Brain Imaging** M100, M128, M141, M150, M186, M199, M201, M205, M210, M244, M245, M250, M256, M300, S110, S112, S115, S122, S129, S136, S137, S138, S151, S189, S224, S230, S235, S243, S256, S257, S260, S263, S267, S271, S275, S281, S291, S292, S301, S328, S341  
**Brain Tumor** M244, M277, S111, S262, S263, S264, S265, S266, S267  
**Brain-Machine Interface** M227

### C

**Cerebrovascular Disease** LB-S100, LB-S101, LB-S129  
**Child Neurology** M167, M195, M228, M240, M246, M286, M293, S109, S131, S134, S164, S184, S188, S194, S265, S280, S281, S293, S298, S299, S309, S312, S313  
**Clinical Logic** M108, M170, M221, M237, M251, M263, M316, S163, S167, S180, S185, S189, S191, S193, S195, S199, S202, S267, S282, S304  
**Clinical Trials** M135, M151, M183, M237, M257, M279, M294, M299, M301, M306, S115, S123, S150, S196, S204, S213, S218, S262, S263, S348  
**Cognitive Dysfunction** M101, M110, M122, M157, M159, M160, M161, M162, M163, M165, M166, M169, M171,

M175, M179, M190, M192, M202, M227, M246, M253, S115, S118, S129, S132, S197, S215, S264, S274, S288, S326

**Coma** M258, M263  
**Complex Genetic Disorders** M144, M185, M208, M228, S135, S205, S280, S293, S294, S304, S305, S307, S313  
**Computational Neuroscience** M233

### D

**Dementia** M156, M162, M163, M164, M165, M166, M168, M169, M170, M171, M172, M174, M178, M179, M180, M184, M192, M193, M200, M202, M203, M221, S110, S124, S132, S137, S144, S152, S160, S211, S222, S227, S240, S285, S337, S341  
**Demyelination** M100, M103, M106, M113, M117, M119, M121, M124, M130, M132, M138, M141, M146, M148, M150, M268, M277, M281, M287, M308, M312, S192, S228, S229, S277, S313, S319  
**Developmental Disorders** M195, M198, M217, M218, M293, S136, S184, S197, S291, S295, S296, S297, S298, S299, S302, S305, S310, S312  
**Diagnostic Errors** M110, M138, M230, M256, S157, S164, S167, S168, S189, S217

### E

**EEG** M120, M127, M207, M208, M211, M213, M214, M215, M219, M230, M235, M239, M241, M243, S339  
**EMG** M104, M271, M272, M273, M278, M282, M285, M312  
**Epilepsy** LB-M112, LB-M113, LB-S108

### F

**Frontotemporal Dementia** M186, M191, M194, M199, M201, M205, M280  
**Functional Neuroimaging** M153, M175, M186, M234, M244, S124, S165, S166

### G

**Gene Expression** M129, M164, M181, M188, M199, M204, M313, S241, S295  
**Gene Therapy** M296, S248, S308, S311  
**Global Neurology** LB-M107, LB-M114, LB-S102, LB-S104

### H

**Health services and Health Equity research** LB-S107, LB-S108, LB-S113  
**Huntington's Disease** M246, S204, S209, S225, S232, S236, S238

**I**

**Intracerebral Hemorrhage** M189, S101, S109, S122, S142, S149

**L**

**Language** M153, M221, S290  
**Lewy Body Dementia** M165, S240, S243, S245, S278

**M**

**Metabolic Disorders** M144, M152, M159, M169, M171, M184, M190, M231, M238, M242, M264, M307, M314, S135, S139, S223, S326, S342  
**Migraine** M253, S164, S165, S168, S169, S170, S171, S173, S174, S175, S176  
**Monogenic Disorders** M152, M184, M203, S108, S209, S282  
**Motor Neuron Disease** M267, M270, M271, M282, M283, M292, M301, M303, M304, M311, M315, S226  
**Movement disorders** LB-S109, LB-S110, LB-S111, LB-S112, LB-S113, LB-S117, LB-S118  
**MS and Autoimmune Neurology** LB-M100, LB-M101, LB-S125  
**Myopathies** M104, M208, M269, M283, M288, M293, M296, M311, M313

**N**

**Neuro-Ophthalmology/Neuro-Otology** M148, M297, S133, S156, S269, S270, S271, S272, S274, S275, S324, S328  
**Neurocritical Care and Traumatic Brain injury** LB-M115, LB-M116, LB-S121  
**Neurodegeneration** M100, M112, M127, M141, M142, M144, M151, M153, M162, M163, M174, M181, M191, M205, M210, M231, M233, M252, M274, M275, M276, M280, M291, M303, S108, S203, S211, S212, S216, S219, S221, S224, S227, S228, S234, S240, S246, S247, S251, S276, S279, S281, S282, S283, S284, S286, S287, S288, S289, S290, S294, S311  
**Neurodegeneration and Cell Death** LB-M103, LB-M105, LB-M106, LB-M108, LB-M115, LB-M118, LB-M120, LB-S111, LB-S116, LB-S117, LB-S118, LB-S119, LB-S120, LB-S121, LB-S123, LB-S124, LB-S125  
**Neurodevelopment** LB-S115, LB-S119, LB-S122, M167, M195, M198, M204, M217, M218, S184, S197, S206, S248, S260, S280, S291, S292, S293, S294, S295, S296, S297, S298, S299, S302, S305, S310  
**Neurogenetics** M130, M152, M185, M188, M194, M217, M218, M224, M247, M286, M311, M314, S109, S144, S160, S205, S212, S236, S237, S251, S265, S296, S302, S304, S306, S307, S309, S310, S312, S315

**Neurogenetics and gene therapy** LB-M105, LB-S109, LB-S114, LB-S119, LB-S123, LB-S124  
**Neuroinfectious Disease** M102, M107, M118, M139, M232, M240, M256, S112, S172, S315, S317, S318, S320, S323, S325, S328, S329, S332, S333, S338  
**Neuroinflammation** M101, M102, M103, M104, M105, M106, M107, M108, M111, M112, M113, M114, M115, M117, M119, M120, M121, M122, M124, M126, M127, M128, M129, M131, M132, M133, M134, M138, M139, M140, M142, M145, M146, M147, M148, M150, M177, M178, M183, M197, M198, M207, M222, M231, M232, M249, M250, M268, M271, M284, M287, M300, M314, M315, S132, S167, S192, S222, S223, S226, S234, S256, S270, S283, S287, S307, S314, S315, S316, S317, S319, S320, S324, S326, S327, S330, S332, S333  
**Neuroinflammation and Neuroinfection** LB-M100, LB-M105, LB-M106, LB-S103, LB-S114, LB-S115, LB-S117, LB-S122, LB-S124, LB-S125, LB-S126  
**Neuromodulation** M212, M225, M227, M243, M268, S104, S235, S247, S254, S255, S339  
**Neuromuscular Disease** LB-M118, LB-M119, LB-M120, LB-S120  
**Neurooncology** LB-S114, LB-S115, LB-S116  
**Neuroophthalmology and Neurovestibular disease** LB-S116  
**Neuropathy** M105, M106, M132, M146, M149, M157, M238, M242, M245, M272, M273, M278, M281, M283, M284, M285, M307, M308, M312, M316, M317, S172, S173, S257, S268, S320, S333, S334  
**Neurophysiology** M108, M120, M157, M206, M209, M211, M225, M230, M235, M239, M245, M273, M278, M285, M287, M288, S185, S234, S261, S274, S309, S339  
**Neuroprotection** M118, M119, M191, M257, M307, S106, S131, S150, S178, S216, S221, S283, S285, S289, S297, S330  
**Neurorecovery and Neuroplasticity** LB-M115, LB-S102, LB-S122, LB-S127

**O**

**Other** LB-M101, LB-M103, LB-M107, LB-S100, LB-S103, LB-S106, LB-S108, LB-S128

**P**

**Parkinson's Disease** M154, S203, S207, S210, S213, S214, S215, S216, S217, S218, S221, S222, S223, S231, S233, S235, S242, S243, S244, S245, S246, S247, S251, S254, S255, S256, S279, S286, S290, S314

**R**

**Regenerative Medicine** M177, M279, S213  
**Rehabilitation** M211, M252, M262, M263, M302, S118, S120, S153, S155, S323, S335, S336, S348

**Risk Factors** M105, M156, M159, M161, M176, M189, M190, M226, M237, M252, M257, M259, M262, M265, M276, M288, M302, M315, S119, S120, S128, S140, S152, S155, S159, S173, S176, S177, S178, S187, S192, S203, S210, S261, S269, S277, S279, S323, S332, S335, S342

## S

**Sleep Disorders** M117, S182, S335, S337, S338, S340, S341, S342, S343, S345, S346, S347, S348, S349

**Sleep Disorders and Circadian Rhythms** LB-S112

**Stroke** M140, M155, M180, M216, M251, M258, M259, S100, S101, S103, S104, S105, S106, S111, S112, S114, S117, S118, S119, S120, S121, S122, S123, S125, S126, S127, S128, S129, S130, S131, S133, S134, S135, S136, S138, S139, S140, S142, S143, S144, S145, S147, S148,

S149, S150, S151, S152, S153, S154, S155, S156, S157, S158, S159, S160, S161, S162, S163, S179, S180, S181, S270, S275, S327, S329

**Subarachnoid Hemorrhage** M189, S123, S174, S269

## T

**Teleneurology/Mobile Health Technology** M122, M213, M258, S107, S140, S153, S182, S190, S198, S200, S232, S237, S238, S272

**Therapeutics** M107, M113, M114, M118, M135, M149, M151, M207, M223, M226, M229, M249, M281, M291, M305, M306, S101, S127, S133, S139, S148, S156, S176, S185, S201, S209, S231, S257, S284, S311, S347

## V

**Vertigo** M253