2021 ANNUAL HIGHLIGHTS OF THE RESIDENT & FELLOW SECTION
HOW CAN I CONTRIBUTE?

The Neurology® Resident & Fellow (R&F) Section provides countless opportunities for trainees to make an introductory contribution to the field. We have over 12 categories of manuscripts, from Global and Community Health to Clinical Reasoning cases. Every year, the R&F team develops innovative submission opportunities and new ways to engage our readers and users.

EXPLORE THE R&F SITE
Access NPub.org/RF for the latest blogs, articles, e-Pearls, Mystery Cases, and other trainee resources. The print issue also features “Resident & Fellow Rounds”—a monthly summary of the R&F Section articles.

SUBMIT AN E-PEARL
These brief educational points often tie in to a Neurology article, podcast, or item on the website. Each should consist of 85 words or less and one reference.

BECOME A PEER REVIEWER
Create an account at submit.neurology.org and include any expertise terms that interest you. After your profile is complete, contact the editorial office at rfsection@neurology.org and you will be added to the database of available reviewers.

FOLLOW NEUROLOGY ON SOCIAL MEDIA
Receive the R&F Section alerts including e-Pearls, Mystery Cases, and recently published article alerts.

@AANResidentsAndFellows
@greenjournal
#NeurologyRF
#NeurologyRF

ANSWER OUR MYSTERY CASE QUESTIONS
Disseminated via our social media sites, emails, and our website, these mini-cases pose fascinating questions for the reader and provide instructions for submitting your answers.

CHECK OUT A TOPIC
The R&F team members have compiled a list of prospective topics for authors under the following subcategories: Child Neurology, Opinion & Special Articles, and Emerging Subspecialties.

ACCESS THE AUTHOR GUIDES
The R&F Author Center provides pictorial guides on writing Clinical Reasoning, Pearls & Oy-sters, and Teaching NeuroImages at NPub.org/rfsections.

HAVE MORE QUESTIONS? HAVE AN IDEA?
Contact the editorial office at rfsection@neurology.org.
CT angiography

Coronal (A) and axial (B, C) CT angiography done by right side antecubital vein injection reveals jugular and cervical veins reflux (blue arrows) reaching the parotid tumor (orange arrow), with opacification of carotid and vertebral arteries (red arrows) and enhancement of intracranial compartment (yellow arrow). Also note hemithyroid contrast reflux (green arrow).
Neurology® Resident & Fellow Section

Roy E. Strowd III, MD, MS, MEd, FAAN, and Whitley Aamodt, MD, MPH

The mission of the Resident & Fellow Section (RFS) is to keep our readers up to date on issues relevant to trainees, educators, and others interested in the training and practice of neurology. The RFS was launched in 2004 by Robert "Berch" Griggs, MD, FAAN, then the editor-in-chief of Neurology, and Karen C. Johnston, MD, MSC, associate editor. The RFS is a trainee-run editorial team of more than 20 neurology residents and fellows who are responsible for reviewing, editing, and publishing articles. Residents are selected for a three-year term annually through a competitive process that attracts many dozens of applicants. The board attracts a diverse applicant pool and currently 45 percent of editorial team members are women and 25 percent are international members from Italy, Philippines, Mexico, United Kingdom, and Canada. Past editorial team members have gone on to other important editorial activities at Neurology and elsewhere, and they have found the experience a formative part of their careers. This past year, Roy E. Strowd, MD, MEd, MS, FAAN, the RFS associate editor, assumed leadership of the section from John J. Millichap, MD, FAAN. He is joined by Deputy Section Editor Whitley Aamodt, MD, MPH, another former editorial team member. Photographs and brief biographies of the current Resident & Fellow Section editorial team can be found in this Highlights booklet.

The number of submissions to the section has grown considerably from 481 submissions in 2013 to 1,133 in 2020 (Figure 1). This represents a 235-percent increase from 2013 and a 139-percent increase from 2019. The RFS publishes primarily case reports and opinion pieces, with scientific research articles limited to education research. The subsections are curated by the RFS Editorial Team members and focus on (1) case-based clinical neurologic education, including Clinical Reasoning, Pearls & Oy-sters, Child Neurology, Teaching NeurolImages, and Mystery Cases; (2) graduate medical education, including Journal Club, Global and Community Health, and Education Research; and (3) career issues, including Emerging Subspecialties in Neurology. Descriptions of these subsections appear in this Highlights booklet and include the top representative articles published in the past year as selected by the RFS Editorial Team members.

Over the past year, the RFS responded to the considerable challenges presented by the COVID-19 pandemic with a call for papers on the impact of COVID-19 on training in neurology. Of the 73 Neurology articles published on the COVID-19 pandemic, 14 (19 percent) were published in the RFS including nine case-based publications describing neurological manifestations in patients with COVID-19 and five articles relating to adaptation of training in response to the pandemic. The RFS has also expanded its blog site to provide a forum for resident and fellow dialogue on the pandemic as well as health equity, anti-racism, and virtual learning.

Education is central to the mission of the RFS. In 2020, Neurology received 87 education articles which is up from 11 in 2012 and 49 in 2019. The Education Research subsection publishes research articles on new teaching, learning, and assessment methods. Training in Neurology describes innovative approaches to teaching at all levels of training. These two submission types in addition to Contemporary Issues—Innovations in Education accept a range of manuscripts describing best practices and new innovations in education within neurology.

In addition to publishing, writing, and reviewing for the journal, the RFS Editorial Team members have initiated and developed multiple unique projects over the years, including podcasts (beginning in 2007), weekly e-Pearls (2008), an annual Writing Award (first given in 2009), a mentored peer review training program (2016), social media presence to disseminate journal content (2019), and the publication of two books, Clinical Reasoning and Child Neurology, with previously published cases compiled to provide an educational resource for trainees and program directors. One of the greatest accomplishments of the RFS is the mentor-mentee program designed to pair new RFS team members with recent graduates of the section. This past year, the program was expanded under the direction of former team member Ariel M. Lyons-Warren, MD, PhD, to serve as a structured model for bringing new, young peer reviewers into the process, even outside the RFS itself.

The RFS webpage has exciting features such as the blog, special e-Pearls formatting, listings of the latest RFS articles, and online survey platform for the Mystery Cases. There are also links to other resident and fellow resources on the Neurology website and at AAN.com. We publish one RFS article in every print issue of Neurology, and the "Resident and Fellow Rounds” commentary written monthly by the RFS section editors provides summaries of RFS articles published with each issue. The RFS editorial team members are proud of the additional exposure through print distribution and expect that this will undoubtedly encourage the continued submission of high-quality manuscripts. Recognizing the role of social media in medicine and daily life, the RFS delivers regular Instagram, Twitter, and Facebook posts and is involved in the Neurology Minute™ daily briefing as well.

Neurology recognizes that the future of the journal, and the future of the field of neurology itself, depends on the interest and commitment of its readers and writers. This journal is one of the most important records of our profession, and current trainees are the profession’s most valuable resource. Accordingly, the RFS is strongly supported by Neurology’s current Editor-in-Chief José G. Merino, MD, MPHIL, FAHA, FAAN; Executive Editor Patty Baskin; editorial staff; the AAN; and publisher Wolters Kluwer. In particular, Managing Editor Kathy Pieper has provided continual assistance and encouragement without which the section could not have survived. We welcome submission of manuscripts for the Resident & Fellow Section, and author instructions can be found at Neurology.org. Papers submitted for this section will undergo the same thorough peer-review process as all Neurology submissions, and it is anticipated they will reflect the same high level of quality. It is further expected that manuscripts published in the section will carry the same academic weight, whether online or in print, as papers published elsewhere in the Neurology journals. We also continue to welcome input from our readers, including program directors and other educators, on features that will be most valuable. Questions and comments should be addressed to Roy Strowd, Whitley Aamodt, or Kathy Pieper at rfssection@neurology.org. We hope you enjoy this year’s edition of the Highlights of the Resident & Fellow Section!

Roy E. Strowd III, MD, MS, MEd, FAAN, Section Editor Resident &Fellow Section

Whitley Aamodt, MD, MPH, Deputy Section Editor Resident & Fellow Section
2021 Resident & Fellow Section Writing Award

Education Research
Effect of the COVID-19 pandemic on neurology trainees in Italy: A resident-driven survey
Elena Abati and Gianluca Costamagna
Neurology 2020;95;1061-1066

The Neurology Resident & Fellow Section Writing Award is intended to recognize the extraordinary writing abilities of those currently in training in neurology. Eligible manuscripts will include any submitted to and published in the Neurology Resident & Fellow Section, whether online or in print. Submissions on any topic of interest to trainees and in any subcategory of the section will be eligible. The main criteria for selection will be educational value, novelty, depth of exposition, and clarity of writing. At least one author of the manuscript must be a resident or fellow in one of the neurologic subspecialties. All authors will be considered equal recipients of the award in order to recognize and encourage collaborative work among trainees. The award will be announced in early 2022 and will be awarded for a paper published in 2021.

No formal application process is required. All manuscripts submitted to the section will be considered. Manuscripts should be submitted online at NPub.org/submit. Please direct any questions to rfsection@neurology.org.

PAST RECIPIENTS

2020 Award Winner
Right brain: Art and the restoration of identity in dementia
Bryan J. Neth, MD, PhD
Neurology 2019; 93:719-721

2019 Award Winner
Emerging Subspecialties in Neurology: Pain medicine
Nathaniel M. Schuster, MD, and Jacob R. Hascalovici, MD, PhD
Neurology 2018;91;1025-1028

2018 Award Winner
Clinical Reasoning: An 82-year-old man with worsening gait
Sheena Chew, MD; Ivana Vodopivec, MD, PhD; and Aaron L. Berkowitz, MD, PhD
Neurology November 21, 2018, 89:21e246-e252

2017 Award Winner
Pearls & Oysters: Episodic ataxia type 2: Case report and review of the literature
Elan L. Guterman, MD; Brian Yurgionas, MD, MS; and Alexandra B. Nelson, MD, PhD
Neurology June 7, 2016, 86:23. e239-e241

2016 Award Winner
Emerging Subspecialties in Neurology: Telestroke and teleneurology
Sunil A. Mutgi, MD; Alicia M. Zha, MD; and Reza Behrouz, DO
Neurology June 2, 2015, 84:191-e193

2015 Award Winner
Clinical Reasoning: An unusual cause of transverse myelitis?
Pavan Bhargava, MD, and Rodger J. Elble, MD, PhD
Neurology February 11, 2014, 82: e46-e50

2014 Award Winner
Right Brain: A reading specialist with alexia without agraphia: Teacher interrupted
Jason Cuomo, MA; Murray Flaster, MD, PhD; and José Biller, MD
Neurology January 7, 2014, 82:e5-e7

2013 Award Winner
Clinical Reasoning: A 55-year-old woman with vertigo: A dizzying conundrum
Daniel R. Gold, DO, and Stephen G. Reich, MD
Neurology October 23, 2012, 79:e146-e152

2012 Award Winner
Child Neurology: Brachial plexus birth injury: What every neurologist needs to know
Christina B. Pham, MD; Johannes R. Kratz, MD; Angie C. Jelin, MD; and Amy Gelfand, MD
Neurology August 16, 2011, 77:695-697
Shashank Agarwal, MD

Shashank Agarwal is an adult neurology resident at NYU Langone Health-Brooklyn. He received his medical degree from Kasturba Medical College, Manipal University, in India. Prior to starting his neurology residency, he worked as a research scientist at the Marlene and Paolo Fresco Institute for Parkinson and Movement Disorders at NYU Langone Health. During residency, Shashank developed interest particularly in caring for neurovascular and neuro-critical care patients. He is actively engaged in research projects with mechanism of stroke treatments and headache management in subarachnoid hemorrhage patients. Shashank is passionate about medical education and enjoys teaching medical students and residents. Outside of medicine, Shashank loves photography and enjoys cooking and kayaking in his free time.

Mehdi Bouslama, MD

Mehdi Bouslama is an adult neurology resident at Emory University. Originally from Tunisia, he completed medical school at Faculté de Medecine de Tunis. After graduation, he spent two years working as a clinical research fellow at Grady Memorial Hospital in Atlanta investigating ways to enlarge the scope of stroke endovascular therapies and developing new imaging paradigms and tools to improve stroke care systems, under the mentorship of Raul Nogueira, MD. His research interests include "big data", AI, and machine learning in neuroimaging. After residency, Mehdi will pursue stroke and neuroendovascular fellowships. In his spare time, he enjoys playing the "oud," tennis, exploring the Atlanta food scene, and spending time with his wife and son.

Sarah Brooker, MD, PhD

Sarah Brooker is an adult neurology resident at Northwestern Memorial Hospital of Northwestern University. She is originally from Minnesota and completed her undergraduate education at Yale University in 2010. She then joined the Medical Scientist Training Program at Northwestern where she earned her MD and PhD degrees. Her PhD research focused on signaling pathways modulating adult hippocampal neurogenesis. Her current research interests include investigating genetic and inflammatory mechanisms of neurodegenerative movement disorders. Outside of medicine, she enjoys figure skating, spending time with family, and exploring the Chicago food scene.

Gianluca Costamagna, MD

Gianluca Costamagna is a neurology resident at the University of Milan, Ospedale Maggiore Policlinico, Italy. During medical school, he studied for one year in Bonn, Germany, while completing his medical degree at the University of Pavia, Italy. Prior to neurology residency, he was awarded the Armenise Harvard Summer Fellowship and worked at Weimer’s lab, Harvard Medical School and Brigham and Women’s Hospital, investigating the role of microbota in modulating multiple sclerosis in mice. Gianluca truly enjoys medical education, having served as a microbiology, tropical medicine, and human physiology teaching assistant in medical school. As a neurology resident, he has broad research interests within the field of neuromuscular disorders, with emphasis on motor neuron diseases and stem cell-based 3D models of amyotrophic lateral sclerosis. Outside of neurology, Gianluca loves running, exploring Italian boroughs, and hiking in the Alps.

Guillermo Delgado-García, MD, MSc

Guillermo Delgado-García is a clinical fellow in epilepsy and EEG at the University of Calgary in Canada. Originally from Mexico, he received his medical degree from the Universidad Autónoma de Nuevo León. After graduating medical school, Guillermo spent one year at the Instituto Nacional de Ciencias Médicas y Nutrición, Mexico, as a research assistant. He completed residency in internal medicine at the UANL University Hospital, and then in clinical neurology at the Instituto Nacional de Neurologia y Neurocirugia in Mexico City. Guillermo earned a master’s degree in neurobiology and biotechnology at the Université de Bordeaux, and recently completed a second master’s degree, this time in medical sciences, at the Universidad Nacional Autónoma de México. He is an Open Medical Institute Fellow and was recently appointed as a Level-1 National Researcher by the National System of Researchers in Mexico. After fellowship, Guillermo plans to pursue a career in academic neurology. Outside of medicine, he enjoys literature, cinema, amateur genealogy, and spending time with his wife.

Katherine Fu, MD

Katherine Fu is an adult neurology resident at the University of California, Los Angeles (UCLA). She graduated with degrees in biological sciences and neuroscience with honors from the University of Southern California (USC) and obtained her medical degree from the Keck School of Medicine of USC. Her research interests include investigating neuroimaging biomarkers of neurodegenerative diseases. She also has an interest in medical education; she is engaged in the Medical Education Fellowship Certificate Program in Curriculum Design at UCLA and has contributed to the Neurology Minute daily briefing. She is also a senior director for Camp Neuro, a summer day camp for high school students interested in careers in medicine and neuroscience. Her hobbies include creative writing, shao-lin kung fu, and playing viola and ukulele. After residency, she will remain at UCLA to pursue a fellowship in movement disorders, with a particular interest in deep brain stimulation and neuroregeneration.

Whitley Aamodt, MD, MPH

Whitley Aamodt is a second year Edmond J. Safra Fellow in Movement Disorders at the University of Pennsylvania. She graduated with a degree in neuroscience from the College of William and Mary and completed dual degrees in medicine and public health at the University of Texas School of Medicine at San Antonio. She also completed her adult neurology residency at the University of Pennsylvania in 2019. Aamodt is currently the recipient of an NIH T32 grant in neuroepidemiology and recently began a postdoctoral fellowship and master’s degree program in clinical epidemiology (MSCE). She is passionate about medical education, global health, and the practice of neurology in resource-limited settings. Her research interests also include topics in health care disparities, neurological outcomes, and end-of-life care for patients with Parkinson’s disease and related disorders.

Regan Jo Lemley, MD, MS

Regan Lemley is an epilepsy fellow in neurology at Brigham and Women’s Hospital in Boston. Previously, she was a chief adult neurology resident at Wake Forest School of Medicine. She graduated from...
Fábio Nascimento, MD
Fábio Nascimento is a EEG/Epilepsy Clinical Fellow at Massachusetts General Hospital-Harvard Medical School. Originally from Brazil, he completed medical school at the Universidade Federal do Paraná and then spent two years at the University of Toronto working as a research fellow in epilepsy genetics. Subsequently, he moved to Houston, TX, to train as an adult neurologist. Outside of neurology, Fábio enjoys listening and dancing to sertanejo (a Brazilian music style), going to the movies, eating lots of sushi, and working out.

Behnam Sabayan, MD, PhD
Behnam Sabayan is an adult neurology resident at Northwestern Memorial Hospital, Northwestern University, Chicago. He will start his fellowship in vascular neurology at Massachusetts General Hospital, Harvard University. Behnam has an established interest in brain aging and in particular the vascular contribution to brain structural and functional integrity. After medical school he received a Master of Science in aging and vitality and his PhD in clinical neuroscience from Leiden University in the Netherlands. He has been a close collaborator with neuro-epidemiology and population science lab at NIA/NIH and has published more than 60 peer-reviewed papers mainly through multi-disciplinary research projects. Behnam is passionate about medical journalism and evidence-based neurology practice and would like to pursue his academic career in vascular neurology with focuses on brain health and cognitive brain aging.

Jens Witsch, MD
Jens Witsch is an adult neurology resident at Yale University. He is originally from Freiburg, Germany, and studied medicine at the University of Heidelberg. Before graduating from medical school, he engaged in a one-year research thesis in electrophysiology at the Max Planck Institute for Medical Research in Heidelberg investigating in-vivo neuronal physiology in an epilepsy mouse model. He then completed neurology residency at the Charité in Berlin under the mentorship of Matthias Endres, Christoph Pöner, and Eric Jüttler, followed by a neurocritical care research fellowship in Jan Claassen’s group at Columbia University. Jens is interested in mechanisms leading to secondary injury as well as prognosis after intracranial hemorrhages.

Alison G. Zea Vera, MD
Alison G. Zea Vera is a child neurology resident at Cincinnati Children’s Hospital Medical Center. He received his medical degree from the Universidad Peruana Cayetano Heredia. His research interests include neurology, movement disorders, and cognitive neuroscience. Outside of medicine, he enjoys playing soccer and spending time with his dog.

Adina Wise, MD
Adina Wise is an adult neurology resident at Mount Sinai Beth Israel, New York. As an undergraduate, she studied comparative literature and philosophy at NYU, where she went on to obtain a master’s degree in creative writing and psychology. She completed post-baccalaureate studies at Columbia University and earned her MD from Sidney Kimmel Medical College at Thomas Jefferson University. Adina is passionate about medical education; she has spearheaded curriculum design and trainee wellness initiatives throughout medical school and residency, and has published several essays and editorials about medical training and the practice of modern medicine. In 2019, she attended the Harvard Macy Program for Future Academic Clinician-Educators and currently serves on Mount Sinai’s Graduate Medical Education Subcommittee.
Top 10 Ways Program Directors Can Use the Resident & Fellow Section

By Alonso G. Zea Vera, MD, and Denise Xu, MD

1. Encourage your trainees to submit a blog commentary that shares their experiences with trainees and educators around the world. The Resident & Fellow Section (RFS) is interested in showcasing trainees’ ideas and experiences. Our blog publishes commentaries from trainees on multiple topics, from recently published articles to challenges during the COVID-19 pandemic. This platform allows trainees to express opinions and ideas in a less formal and restrictive format. To submit an inquiry for your commentary, email rfsection@neurology.org with a brief description of the topic you will discuss.

2. Encourage trainees to join our editorial team. Are your trainees interested in the editorial process? Encourage them to join our RFS editorial board. Annually we offer three-year positions to adult and pediatric neurology residents from around the world. Team members peer review manuscripts, assist in writing and editing blogs, implement new projects for the section, and participate in monthly conference calls. Keep an eye out for our call for applications around May to June. If trainees are looking for a less time-consuming option, they can also apply to become reviewers for the section.

3. Send clinical pearls to your trainees. Residency and fellowship are busy times, but education remains the foundation of training. Our e-Pearls provide essential insight into a neurologic topic in fewer than 85 words. Incorporate information from these weekly submissions into daily rounds, or include the e-Pearls themselves in your email announcements to trainees. Pearls & Oysters submissions also feature longer case vignettes that begin with a list of clinical pearls and red flag “oy-sters” that are great for an email, Tweet, or communication to your trainees.

4. Learn and share new educational initiatives. The RFS publishes new educational innovations and programs that you may want to implement in your program. Training in Neurology is an article type that highlights topics related to training neurologists at all stages of their careers. From practical career guides to changes in workflow precipitated by the COVID-19 pandemic, this subsection provides a wide-ranging view of neurologic education and emphasizes how lessons and ideas can be translated to other institutions. Learn from these initiatives, and share your own. Find the submission guidelines on Neurology.org.

5. Discuss a teaching case with your trainees. The Resident & Fellow Section publishes instructive cases from submissions around the world. Published cases are chosen for their significant teaching value or originality and provide an opportunity to reinforce clinical reasoning skills. Our reviewers and editors work with the authors to improve the educational value of all cases in our section. Use our Clinical Reasoning and Child Neurology subsections to discuss the presentation, differential diagnosis, and management of challenging patients. Also, explore two free PDF books with selected cases from the clinical reasoning and child neurology sections on the RFS website.

6. Demonstrate exam and neuroimaging findings (virtually!). Expand your trainees’ repertoire of bedside clinical and exam skills. Teaching Neurolmage and Teaching Video Neurolimage are brief case reports with an associated image or video. Cases feature classic presentations of uncommon disorders and rare manifestations of common conditions. In comparison to text-based instruction, these graphics allow learners to make their own observations and independently describe deficits before developing interpretations and differentials. Did we mention that the cases are easily accessible in PowerPoint format?

7. Learn about new career paths in neurology. The field of neurology is expanding at a vertiginous rate with several new and exciting subspecialties. Our subsection, Emerging Subspecialties in Neurology, highlights these new career options and provides guidance to interested trainees. Our “Cortical Careers” project is potentiating this effort. Listen to our episodes in the Neurology Minute daily briefing, review our articles with your trainees, or share your experience in a new area of neurology by submitting a manuscript to this section.

8. Challenge your trainees with our polls. In addition to the Neurology Question of the Day app and the AAN online trivia sessions, the Resident & Fellow Section provides several opportunities to challenge yourself. Our Mystery Cases guide readers through a case with an undisclosed diagnosis, revealing new information as participants answer multiple-choice questions. At the end, respondents can compare their answers to those from people around the world. The answers are summarized and published in the next issue of Neurology. We also frequently post short polls on social media.

9. Write up a case with your trainees. The Resident & Fellow Section publishes educational case reports in several different formats, offering trainees an opportunity to engage with academic writing. Explore our visual author guides (Neurology.org/rf/author_guides) to quickly learn how to structure submissions, avoid common pitfalls in writing, and increase the chance of publication. The Author Center includes a more in-depth explanation of the requirements and expectations of each subsection. After submission, our team of trainee and faculty reviewers works hard to provide detailed feedback to authors.

10. Follow and engage with us on social media. To keep up to date on the latest publications, find us on Twitter (@GreenJournal), Instagram (@aanbrain), and Facebook (@AANResidentsandFellows), where we link to articles and studies from the Resident & Fellow Section, as well as news and resources about the field of neurology as a whole. Look out for an interesting Teaching Neurolimage case weekly and a challenging clinical conundrum every other week. Share our posts using #NeurologyRFS.
Child Neurology

The Child Neurology section in the Resident & Fellow Section of Neurology focuses on contemporary educational issues in child neurology. The goal of the section is to provide up-to-date reviews on important topics in child neurology that are relevant to all neurologists, both adult and child, particularly those still in their training. Examples include management of acute stroke in children, childhood demyelinating disease, neuroimaging in metabolic disorders, and the neurobiology of autism. Each piece will begin with a patient case, followed by a brief discussion about the differential diagnosis and a detailed discussion about the topic of focus. Submissions are welcome from residents and fellows in either child or adult neurology. Ideally, submissions will include the patient case as well as the discussion, but submission of timely review articles without an accompanying case will also be considered. In this situation, the editors of this section may supply an appropriate patient case.
Child Neurology: Genetically determined dystonias with childhood onset

Travis Larsh, MD, Neil Friedman, MBChB, and Hubert Fernandez, MD


A previously healthy 10-year-old girl of Croatian descent presented to the pediatric neurology clinic with an abnormal gait. She first noted symptoms 1.5 years prior to presentation, which included flexion–inversion posturing of her left foot while playing soccer. She would drag her left foot, leading to excessive falling. Her family noted that she did not seem to have much difficulty ambulating at the beginning of the day and they did not notice any abnormal posturing of the foot when she woke up in the morning. However, by the evening, they noted her left foot, and occasionally her right foot, would develop a flexion–inversion posture. Her symptoms seemed to be worse when she was tired or after activity. She had previously been evaluated by 2 orthopedic surgeons and a pediatric neurologist and was most recently seen in an emergency department for this problem, with no diagnosis being provided. Workup included a normal lumbar spine MRI and X-rays of both legs.

Physical examination was notable for subtle equinovarus posturing of the patient’s left foot only but was otherwise unremarkable. There was no family history of dystonia or parkinsonism. She was started on 100 mg/d of levodopa, with complete resolution of the dystonic posturing, and she was able to return to playing sports without difficulty. A dystonia gene panel was sent and revealed a heterozygous pathogenic variant in the GTP cyclohydrolase 1 gene (GCH1), diagnostic of DYT5a (Segawa disease), a form of autosomal dominant dopa-responsive dystonia (DRD).

Differential diagnosis

Dramatic and sustained response to low doses of levodopa distinguishes DRD from the other genetic dystonias (including DYT1) and other conditions such as cerebral palsy and hereditary spastic paraplegias. Other DRDs, including DYT-5b and DYT-SPR, tend to present earlier and have a more severe phenotype in comparison to DYT-5a. Early-onset Parkinson disease (PD) (PINK1, PRKN) can also initially present as gait disturbance due to foot dystonia. Development of motor fluctuations and dyskinesias from chronic levodopa therapy would be atypical in DRD, which can be helpful in distinguishing from PD. Improvement with sleep may be seen in early-onset PD, but typically not as dramatic or sustained as in DRD. Genetic testing is widely available to confirm the diagnosis of the most common forms of genetic dystonias.

Discussion

The term dystonia was first used in 1911 by Hermann Oppenheim in “About a peculiar cramping sickness in children and adolescents (dysbasia lordotica progressive, dystonia muscularum deformans).”1 Even in this early description, there was speculation of a genetic etiology.1 The first dystonia gene was discovered in 1994 (GCH1), and since then numerous dystonia genes have been identified.2 There are 14 confirmed genetic forms that have typical childhood onset (table). Recently, classification of genetic dystonia by inheritance pattern or associated features (isolated dystonia i.e., simple vs combined) with another movement...
sleep may be seen in early-onset PD, but typically not as dramatic or sustained as in DRD. Improvement with dyskinesias and fluctuations from chronic levodopa therapy would be atypical in DRD, which can be helpful in distinguishing from PD. Improvement with 1.5 years prior to presentation, which was otherwise unremarkable. There was no family history of dystonia or parkinsonism. She had previously been seen in the emergency department for this problem, with no diagnosis being provided. Workup included a normal lumbar spine MRI and X-rays of both legs.

The term dystonia was first used in 1911 by Hermann Oppenheim in a case presentation. The dystonia spreads to involve other limbs and the trunk muscles by the teenage years and patients may develop parkinsonian features. In rare cases, parkinsonian features may be the only sign of the condition. Early in the course, symptoms show a diurnal fluctuation, with symptoms becoming worse over the course of a day and improving with sleep. Symptoms become static by early adulthood. There is often considerable diagnostic delay of about 13 years.2 Despite being a highly treatable medical condition, there is often considerable diagnostic delay of about 13 years.2

Isolated dystonias

DYT1 is the most common hereditary dystonia. It is inherited in an autosomal dominant fashion, with reduced penetrance and variable expressivity. It is particularly common among patients of Ashkenazi Jewish descent. Symptoms typically start before 6 years of age as a focal dystonia in an extremity (more often lower extremity), with spread to other extremities and trunk muscles by the early teens.4 The face and neck are not typically involved.2 Whereas pharmacologic therapies, including levodopa and anticholinergic drugs, may show variability in therapeutic benefit, deep brain stimulation (DBS) of the globus pallidus pars interna (GPI) has more consistently produced favorable outcomes.5

DYT6 shares some similarities with DYT1, but tends to have a later age at onset (average age at onset 19 years), and has prominent cranial involvement.2 Dysphonia is often a prominent feature. Treatment is similar to DYT1, with the caveat that GPI DBS has marginal effect on speech.6

Combined dystonias

Dystonia with parkinsonism

DYT5a is a result of a heterozygous mutation in the GCH1 gene. Most individuals with DYT5a present in childhood with gait disturbance due to lower extremity dystonia, often a rigid pes equinovarus deformity of 1 foot, such as the patient in the case presentation. The dystonia spreads to involve other limbs and the trunk muscles by the teenage years and patients may develop parkinsonian features.4 In rare cases, parkinsonian features may be the only sign of the condition.2 Early in the course, symptoms show a diurnal fluctuation, with symptoms becoming worse over the course of a day and improving with sleep.4 Symptoms become static by early adulthood. There is a female predominance, with possibly a higher prevalence in patients of Eastern European descent. DYT5a is exquisitely responsive to levodopa therapy, with a complete, or near complete, response of symptoms at relatively low doses. Despite being a highly treatable medical condition, there is often considerable diagnostic delay of about 13 years.2

DYT5b and DYT-SPR are both inherited in an autosomal recessive fashion (SPR gene mutations can be inherited in an autosomal dominant manner as well, although less commonly). As DRDs, they are exquisitely responsive to levodopa. These

<table>
<thead>
<tr>
<th>Symbol</th>
<th>Gene</th>
<th>Gene locus</th>
<th>Inheritance</th>
<th>Phenotype</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>DYT1</td>
<td>TOR1A</td>
<td>9q32-q34</td>
<td>AD</td>
<td>Early-onset generalized dystonia</td>
<td>Most common</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ashkenazi Jewish</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Good response to GPI DBS</td>
</tr>
<tr>
<td>DYT5a</td>
<td>GCH1</td>
<td>14q22.1-22.2</td>
<td>AD</td>
<td>Dopa-responsive dystonia</td>
<td>Clinical case</td>
</tr>
<tr>
<td>DYT5b</td>
<td>TH</td>
<td>11p15.5</td>
<td>AR</td>
<td>Dopa-responsive dystonia</td>
<td>More severe phenotype than DYT5a</td>
</tr>
<tr>
<td></td>
<td>SPR</td>
<td>2p14-p12</td>
<td>AR</td>
<td>Dopa-responsive dystonia</td>
<td>More severe phenotype than DYT5a</td>
</tr>
<tr>
<td>DYT6</td>
<td>THAP1</td>
<td>8p11.1</td>
<td>AD</td>
<td>Adolescent onset mixed phenotype</td>
<td>Later age at onset than DYT1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prominent cranial involvement</td>
</tr>
<tr>
<td>DYT7</td>
<td>MRT1</td>
<td>2p35</td>
<td>AD</td>
<td>Paroxysmal nonkinesigenic dyskinesia 1</td>
<td></td>
</tr>
<tr>
<td>DYT8</td>
<td>PRRT2</td>
<td>16p11.2-q12.1</td>
<td>AD</td>
<td>Paroxysmal kinesigenic dyskinesia</td>
<td></td>
</tr>
<tr>
<td>DYT10</td>
<td>SGCE</td>
<td>7q21.3</td>
<td>AD</td>
<td>Myoclonus-dystonia</td>
<td>Responsive to alcohol</td>
</tr>
<tr>
<td>DYT11</td>
<td>ATP1A3</td>
<td>19q13.2</td>
<td>AD</td>
<td>Rapid onset dystonia-parkinsonism</td>
<td>Poor response to levodopa and DBS</td>
</tr>
<tr>
<td>DYT12</td>
<td>SLC2A1</td>
<td>1p34.2</td>
<td>AD</td>
<td>Paroxysmal exertion-induced dyskinesia 2</td>
<td></td>
</tr>
<tr>
<td>DYT18</td>
<td>KCTD17</td>
<td>22q12.3</td>
<td>AD</td>
<td>Myoclonus-dystonia</td>
<td>Dystonia more disabling than DYT11</td>
</tr>
<tr>
<td>DYT26</td>
<td>KMT2B</td>
<td>19q13.12</td>
<td>AD</td>
<td>Generalized dystonia</td>
<td>Prominent cranial, cervical, and laryngeal involvement</td>
</tr>
<tr>
<td>DYT28</td>
<td>ADCYS</td>
<td>3q21.1</td>
<td>AD</td>
<td>Chorea, dystonia, and myoclonus</td>
<td>Diurnal paroxysms</td>
</tr>
<tr>
<td></td>
<td>GNAO1</td>
<td>16q13</td>
<td>AD</td>
<td>Hyperkinetic movement disorder</td>
<td>Good response to GPI DBS</td>
</tr>
</tbody>
</table>

Abbreviations: AD = autosomal dominant; AR = autosomal recessive; DBS = deep brain stimulation; GPI = globus pallidus pars interna.
disorders often have a much more severe phenotype resembling homozygous \textit{GCH1} mutations, and may manifest as an infantile movement disorder with developmental delay.\textsuperscript{7}

\textbf{DYT12} is due to a mutation in the \textit{ATP1A3} gene, and is inherited in an autosomal dominant pattern with reduced penetrance. It typically presents in teenagers or young adults with rapid-onset dystonia-parkinsonism (RDP). This is characterized by a sudden onset (hours to weeks) of dystonic spasms (usually the upper limbs), orofacial dystonia, and bulbar symptoms, and is sometimes accompanied by parkinsonian features.\textsuperscript{2} It is often triggered by stressful events such as fever, prolonged exercise, or childbirth. Levodopa and DBS are not effective. In addition to RDP, mutations in \textit{ATP1A3} are also known to cause alternating hemiplegia of childhood and CAPOS syndrome (cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss).\textsuperscript{8}

\textbf{Dystonia with other dyskinetic movements}

Paroxysmal nonkinesigenic dyskinesia (DYT8) is caused by 2 missense mutations in the myofibrillogenesis regulator 1 (\textit{MR1}) gene. There is a 2:1 female predominance, and average age at onset is 4 years. Symptoms include attacks consisting of a combination of dystonia and chorea. Attacks last from minutes to hours, but may occur a few times daily in severe cases.\textsuperscript{2} Attacks may be precipitated by alcohol, caffeine, stress, hunger, fatigue, and tobacco. The frequency of attacks tends to decrease with age. Management involves avoidance of precipitating factors; clonazepam may also be beneficial.

The inherited form of paroxysmal kinesigenic dyskinesia (PKD, DYT10) is caused by missense and truncating mutations in the \textit{PRRT2} gene.\textsuperscript{2} Age at onset is between 5 and 15 years, and boys are more commonly affected. Attacks consist of combinations of dystonia and chorea lasting a few seconds to minutes, during voluntary movements, several times daily. They are precipitated by startle or making a sudden voluntary movement after a period of rest. PKD responds well to carbamazepine, phenytoin, levetiracetam, and phenobarbital. Attacks diminish with age regardless of treatment.

Mutations in the \textit{SLC2A1} gene can cause paroxysmal exertion-induced dyskinesias (DYT18). Attacks consisting of dystonia, chorea, and athetosis are triggered by sustained exercise. Attacks typically last 5–30 minutes. Management involves avoidance of prolonged exercise. Ketogenic diet may also be helpful.

\textit{KMT2B}-related dystonia (DYT28) is characterized by a progressive disease course that evolves from a focal lower limb dystonia into a generalized dystonia with prominent cervical, cranial, and laryngeal involvement.\textsuperscript{9} Mean age at onset is 7 years. Additional features include developmental delay, choreoathetosis, myoclonus, seizures, eye movement abnormalities, psychiatric comorbidities, spasticity, and sensorineural hearing loss. GPI DBS may be beneficial, particularly in younger patients.\textsuperscript{9}

ADCYS5-related dyskinesia presents as a childhood-onset hyperkinetic movement disorder featuring a combination of chorea, myoclonus, and dystonia.\textsuperscript{10} Distinguishing features include diurnal paroxysms with nocturnal attacks of chorea and dystonia.\textsuperscript{10} Treatment with clonazepam or clonazepam may be helpful.\textsuperscript{11}

In addition to an epileptic encephalopathy, mutations in the GNAO1 gene can cause a childhood-onset progressive movement disorder. Described phenotypic features include chorea, athetosis, dystonia, myoclonus, and stereotypes.\textsuperscript{12} GPI DBS appears to be the most effective treatment for GNAO1-related movement disorders.\textsuperscript{13}

\textbf{Dystonia with myoclonus}

DYT11 involves a mutation in the \textit{SGCE} gene causing myoclonus-dystonia syndrome (MDS). Inheritance may involve maternal imprinting as paternal inheritance results in almost 100% symptom expression and maternal inheritance only results in 10%.\textsuperscript{14} Symptoms typically begin in childhood or early adolescence and consist of myoclonus and dystonia that preferentially involves the upper body. Treatment is with valproate and benzodiazepines. DBS has been consistently reported to improve both myoclonus and dystonia in DYT11. There are reports that \textgamma\textsubscript{-}hydroxybutytrate may be helpful.\textsuperscript{14} Symptoms are also very responsive to alcohol, which can lead to dependence in adults.

DYT26 is a more recently described cause of MDS that is a result of heterozygous mutations in the \textit{KCTD17} gene. Range of onset is 3–10 years.\textsuperscript{15} Differentiating factors from DYT11 include that the myoclonus associated with DYT26 tends to be less pronounced in the neck and upper extremities, and the dystonia tends to be more disabling.\textsuperscript{15} There is no improvement with alcohol. GPI DBS may be beneficial.\textsuperscript{15}

\textbf{Study funding}

No targeted funding reported.

\textbf{Disclosure}

T. Larsh and N. Friedman report no disclosures relevant to the manuscript. H. Fernandez has received honoraria from Prime Education, Inc., International Parkinson and Movement Disorders Society, Carling Communications, Medscape (speaker in CME events), AbbVie, Biogen, GE Health Care, Inventiv, Kyowa Hakko Kirin, Lundbeck, Merz Pharmaceuticals, Voyager, Sunovion, and Pfizer Pharmaceuticals (as a consultant); has received grant and research support from AbbVie, Acadia, Teva, Biotie/Acorda Therapeutics, Civitas, Kyowa/Prostrakan, Michael J. Fox Foundation, Movement Disorders Society, NIH/NINDS, Parkinson Study Group, Rhythm, and Synosia; has no owner interest in any pharmaceutical company; has received royalties from Demos Publishing (serving as a book author/editor); The Cleveland Clinic has a contract with Teva for his role as a co–principal investigator in SD-809 tardive dyskinesia global studies; serves as a member of the publication committee for Acorda Pharmaceuticals but does not receive any personal
compensation for this; and receives a stipend from the International Parkinson and Movement Disorders Society for serving as Medical Editor of the MDS Web Site. Go to Neurology.org/N for full disclosures.

Appendix Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Travis Larsh, MD</td>
<td>Cleveland Clinic, OH</td>
<td>Design and conceptualization of manuscript, drafting and revision of manuscript</td>
</tr>
<tr>
<td>Neil Friedman, MBChB</td>
<td>Cleveland Clinic, OH</td>
<td>Drafting and revision of manuscript</td>
</tr>
<tr>
<td>Hubert Fernandez, MD</td>
<td>Cleveland Clinic, OH</td>
<td>Drafting and revision of manuscript</td>
</tr>
</tbody>
</table>

References

15. Mencacci NE, Brüggemann N. KCND17 is a confirmed new gene for dystonia, but is it responsible for SGCE-negative myoclonus-dystonia? Parkinsonism Relat Disord 2019;61:1–3.

Disputes & Debates: Rapid online correspondence

The editors encourage comments on recent articles through Disputes & Debates:

Access an article at Neurology.org/N and click on “COMMENT” beneath the article header.

Responses will be posted within three business days.

Before submitting a comment to Disputes & Debates, remember the following:

- Disputes & Debates is restricted to comments about studies published in Neurology within the last eight weeks
- Read previously posted comments; redundant comments will not be posted
- Your submission must be 200 words or less and have a maximum of five references; reference one must be the article on which you are commenting
- You can include a maximum of five authors (including yourself)
Clinical Reasoning

Clinical Reasoning focuses on case presentations with the aim of developing clinical reasoning skills among trainees. Appropriate cases for publication would include uncommon presentations of common neurological disorders and also typical presentations of more exotic disorders. The emphasis of the case presentation should be on generating a sound, thorough differential diagnosis; logically arriving at the correct diagnosis; and thoughtfully discussing the teaching points of the case. Cases discussed in the section should utilize data presented serially in two to four segments that could be opened sequentially by the reader, allowing them to challenge themselves by thinking through the differential diagnosis or treatment options at each step. The manuscript should indicate where each break would occur, with specific questions for the reader to consider as they work their way through the case. The final section should provide the experienced clinician’s discussion (or resident author’s literature review). Ideally the individual sections will also include visually presented data, such as radiology, EEG, EMG, or other studies. See published samples as examples.
Clinical Reasoning: Bilateral ptosis, dysphagia, and progressive weakness in a patient of French-Canadian background

Pritikanta Paul, MD, Reem Alhammad, MD, and Elie Naddaf, MD

Neurology® 2020;95:933-938. doi:10.1212/WNL.0000000000010613

Correspondence
Dr. Naddaf
Naddaf.Elie@mayo.edu

Section 1

A 40-year-old man presented with slowly progressive weakness and eyelid droopiness. His symptoms began in his early 30s as increased fatigue with exertion. In his mid 30s, he developed droopy eyelids without double vision. About 3 years before presentation, he started having progressive difficulty swallowing, initially with solid food but later with both solid and liquid consistencies. He also reported the food getting stuck in his throat. He had been treated for aspiration pneumonia once. A year later, he noticed slowly progressive limb weakness affecting his hands and proximal lower limbs, described as difficulty holding a tablet at church, frequently dropping objects from his hands, and difficulty with standing up from a seated position. More recently, he started experiencing dyspnea on exertion and mild orthopnea. He occasionally experienced blurry vision without diplopia, mild head drop, and hoarseness of voice, mainly towards the end of the day or when he was tired. He was diagnosed with seronegative myasthenia gravis at a local facility, with negative acetylcholine receptor, muscle-specific kinase, and low-density lipoprotein receptor-related protein 4 antibodies. His medical and social history were otherwise unremarkable. The patient’s father was French Canadian. The patient also had Native American and African American ancestry. There was no family history of myopathy or any neuromuscular disorder. Neurologic examination was significant for moderate bilateral ptosis, bilateral ophthalmoparesis with limited upward gaze and to a lesser extent horizontal gaze (both eye abduction and adduction), mild weakness of both upper and lower facial muscles, moderate weakness of the proximal lower extremities most prominent at the hip abductors (Medical Research Council [MRC] grade 3 to 4/5), and mild (MRC grade 4) weakness of finger extensors and intrinsic hand muscles. He had no demonstrable fatigable weakness on examination in any of the affected muscles. He had a mildly waddling gait and absent ankle jerks bilaterally. Sensory and coordination evaluations were unremarkable.

Questions for consideration:
1. What is the localization for the patient’s symptoms and examination findings?
2. What investigations would you perform?

GO TO SECTION 2
Section 2

The pattern of weakness manifesting with bilateral symmetric distal upper and proximal lower limb weakness, without any upper motor neuron signs, and the presence of marked bilateral ptosis would be unusual for a CNS etiology and indicates a peripheral nervous system disorder. While any defect along the motor pathways can result in dysphagia and dyspnea, especially at advanced stages, the predominant ptosis and extraocular muscle involvement are more suggestive of a neuromuscular transmission defect or a myopathy, rather than a motor neuropathy or neuropathy. With no evidence of demonstrable fatigability on examination, the patient-reported fluctuation of the weakness with diurnal variation is not necessarily specific for a neuromuscular transmission defect, and hence a myopathy should be considered. Furthermore, patients with myopathy can have a component of muscle fatigue. It is noteworthy that the presence of ophthalmoparesis without diplopia would be unusual for myasthenia gravis, and is more likely to be due to a slowly developing process such as a hereditary myopathy. The slow progression rate and the clinical phenotype with ptosis and ophthalmoparesis would make an acquired myopathy, such as an inflammatory myopathy, less likely.

To further refine the localization, electrodiagnostic testing was performed. Upper and lower limbs and sensory and motor nerve conduction studies were normal except for a borderline low sural sensory nerve action potential amplitude of 6 μV (normal >6 μV). Two-Hz repetitive nerve stimulation of the facial, spinal accessory, and ulnar nerves, at rest and after exercise, were normal. Needle EMG showed early recruitment of short duration, low-amplitude motor unit potentials, often with increased phases and turns, in proximal and distal, upper, and lower limb muscles as well as in cranial muscles. Fibrillation potentials were present in cranial muscles, proximal upper limb muscles, and tibialis anterior. These electrodiagnostic findings were consistent with a myopathic process.

Laboratory workup was remarkable for an elevated creatine kinase of 550 (normal 52–336 U/L). Blood tests including liver function, renal function, thyroid-stimulating hormone, and lactate level were normal. Myositis autoantibody panel and acetylcholine receptor binding antibodies were normal as well. A video swallow study showed moderate oropharyngeal dysphagia with marked prominence of the cricopharyngeus muscle, in a patient of French Canadian background, we had strong suspicion for OPMD. Subsequently, the patient was tested for this condition but had no GCN repeat expansions in the polyadenine binding protein nuclear (PABPN1) gene. Questions for consideration:

1. Based on these results, what types of myopathy would you consider on the top of your differential?

Figure 1 Barium video-swallow evaluation

Barium video-swallow showing significant prominence of the cricopharyngeus, which covers well over half of the luminal diameter (left), markedly improved after cricopharyngeal myotomy (right).

GO TO SECTION 3
Section 3

The electrodiagnostic testing confirmed the presence of a myopathy. The slowly progressive clinical course is suggestive of a hereditary myopathy. With the absence of other affected family members, the mode of inheritance remains unclear. While the pattern of weakness predominantly affecting hip girdle muscle can be seen with a wide spectrum of hereditary myopathies, the marked ptosis and ophthalmoplegia help narrow down the differential diagnosis to include oculopharyngeal muscular dystrophy (OPMD), mitochondrial myopathy, or a congenital myopathy. Among the congenital myopathies, RYR1-related myopathy can have prominent ptosis with or without ophthalmoplegia. In its classical form, RYR1-related myopathy is usually associated with central core disease on muscle histopathology and is inherited in an autosomal dominant pattern. However, autosomal recessive forms, which can be associated with multiminicore disease or centronuclear myohistopathology, can have more prominent ptosis. Interestingly, mutations in other genes associated with a centronuclear myopathy, such as MTM and DNM2, and congenital fiber type disproportion or a cap myopathy such as TPM2 or TPM3, can also cause a myopathy with neuromuscular transmission defect, associated with prominent ptosis with or without ophthalmoplegia. On the other hand, marked ptosis is relatively common in congenital myasthenic syndromes, and the presence of a myopathy with fibrillation potentials does not rule out such conditions, as many of the genes such as ALG2, ALG14, DPAGT1, GMPPB, PLEC, and GFPT1 can cause both a myasthenic syndrome and a myopathy. Furthermore, congenital myasthenic syndromes can rarely present with normal repetitive nerve stimulation. Based on the clinical phenotype with the prominent dysphagia and the markedly prominent cricopharyngeus muscle, in a patient of French Canadian–Native American background, we had strong suspicion for OPMD. Subsequently, the patient was tested for this condition but had no GCN repeat expansions in the polyadenine binding protein nuclear (PABPN1) gene.

Questions for consideration:
1. Is the possibility of OPMD ruled out?
2. What will be your next step?

Visit the Neurology Resident & Fellow Website

Click on the Resident & Fellow Section menu dropdown at Neurology.org or visit NPub.org/rf directly.

Now offering:
- Blogs of interest to trainees and educators
- Neurology Resident & Fellow Editorial team information
- “Search by Subcategory” option
- E-pearl of the Week
- Mystery Case surveys
- RSS Feed
- Direct links to AAN resources
- Recently published Resident & Fellow articles
Section 4

OPMD is an autosomal dominant condition secondary to expansion of a GCN trinucleotide repeat in exon 1 of the PABPN1 gene. However, point mutations have also been reported and had to be ruled out. Therefore, sequencing of the PABPN1 gene was performed in our patient but showed no mutations. At this point, we decided to pursue a left gluteus medius muscle biopsy to guide further genetic testing. It showed frequent ragged-red, ragged-blue, and cytochrome C oxidase–negative fibers with rare atrophic and regenerating fibers indicating a mitochondrial myopathy (figure 2). Subsequently, we performed mitochondrial genome analysis on the muscle specimen, which was normal with no mutations or deletions. Thereafter, we obtained a mitochondrial nuclear gene panel, which showed 2 mutations in polymerase γ (POLG): (1) p.Arg1096His (c.3287G>A), an established pathogenic mutation; and (2) p.Arg953Cys (c.2857C>T), a likely pathogenic mutation. The patient’s asymptomatic mother and brother both were tested and carried the p.Arg1096His mutation, indicating that the 2 mutations were heteroallelic.

Discussion

Mitochondrial myopathies can be caused by mutations in either mitochondrial DNA (mtDNA) or nuclear genes. Mutations in mtDNA may affect only a proportion of the multiple copies of mtDNA within each cell, and result in the presence of both normal and mutant mtDNA, a phenomenon known as heteroplasmy. The degree of heteroplasmy can vary between cells in the same tissue or organ, between different organs within the same individual, and also between individuals in the same family. Therefore, manifestations of a mitochondrial disorder reflect tissue-specific mutation load, and hence it is essential that analysis of mtDNA is performed from the muscle tissue when myopathy is suspected. Progressive external ophthalmoplegia (PEO) with or without associated limb myopathy can be seen with both primary mitochondrial and nuclear DNA defects. Primary mtDNA defects can be due to point mutations or a single large mtDNA deletion. Among single large-deletion disorders, patients can have a spectrum of clinical manifestations ranging from a pure myopathic presentation (i.e., pure PEO) to multisystem involvement as seen in Kearns-Sayre syndrome, with associated pigmentary retinopathy, hearing loss, short stature, or cardiac conduction abnormalities. A growing list of nuclear genes encoding proteins involved in maintenance, transcription, or translation of mtDNA have been reported in mitochondrial disorders, including POLG. POLG encodes the catalytic subunit of POLG, the sole DNA polymerase enzyme responsible for mtDNA replication and repair. Mutations in POLG can be associated with a wide spectrum of clinical manifestations ranging from encephalopathy and epilepsy to sensory ataxia and myopathy, presenting from neonatal period to late adult life. From a myopathy standpoint, patients may present with PEO with or without an associated limb myopathy, in an autosomal dominant or recessive pattern of inheritance. Patients may also present with limb weakness without extraocular muscle involvement. The 2 mutations detected in our patient have been described in association with progressive external ophthalmoplegia.

The cricopharyngeus muscle is an essential part of the upper esophageal sphincter and its relaxation allows forward passage of food bolus during the oropharyngeal phase of swallowing. Failure to relax or early closure can cause dysphagia symptoms and imaging studies may show a posterior indentation on the pharyngeal wall, described as “prominent cricopharyngeus” or a cricopharyngeal bar. It is noteworthy that this can also be an asymptomatic incidental finding associated with aging. Nevertheless, this is not a specific finding for OPMD as it can also be seen in myotonic dystrophy and inflammatory myopathies, especially inclusion body myositis, sometimes requiring dilation or

Figure 2 Muscle biopsy findings

Left gluteus medius muscle biopsy. (A) Modified Gomori trichrome–stained section showing scattered ragged-red fibers, most prominent in the fibers indicated by a star. (B) Cytochrome C oxidase–stained section showing multiple fibers (stars) with absent enzyme reactivity (cytochrome C oxidase–negative fibers).
Mitochondrial Myopathy: A Blurred Case of Ptosis, Dysphagia, and Progressive Weakness

A 40-year-old French Canadian man with unremarkable family history presented with progressive symptoms of difficulty rising from a seated position, droopy eyelids without diplopia, difficulty in swallowing, fatigue, shortness of breath, and difficulty in holding objects. He was previously diagnosed with seronegative myasthenia gravis. Further investigation revealed negative antibodies for acetylcholine receptor, muscle-specific kinase, and low density lipoprotein receptor-related protein 4. 

We reported a case of progressive ptosis, dysphagia, and limb weakness, with marked cricopharyngeus prominence, due to 2 heterozygous mutations in POLG. Even though OPMD is more common in people with French Canadian origin, alternative etiologies, such as a mitochondrial myopathy, may present with similar phenotype, and should also be considered.

Study funding
No targeted funding reported.

Disclosure
The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Appendix Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pritikanta</td>
<td>Department of Neurology, Mayo</td>
<td>Study concept and design, acquisition of data, drafting of the manuscript,</td>
</tr>
<tr>
<td>Paul, MD</td>
<td>Clinic, Rochester, MN</td>
<td>critical revision of the manuscript for important intellectual content</td>
</tr>
<tr>
<td>Reem Alhammad,</td>
<td>Department of Neurology, King</td>
<td>Study concept and design, critical revision of the manuscript for important</td>
</tr>
<tr>
<td>MD</td>
<td>Saud University, Riyadh, Saudi</td>
<td>intellectual content</td>
</tr>
<tr>
<td></td>
<td>Arabia</td>
<td></td>
</tr>
</tbody>
</table>

References
Call for Voices: Lived Experiences

The editors of the Neurology specialty site Equity, Diversity, & Inclusion encourage you to submit short first-person accounts (1,000 words or less) of experiences lived within the realm of equity, diversity, and inclusion (EDI) with the goal of informing and enlightening our community on these critical issues. Some topics to consider include, but are not limited to:

- Descriptions of personal experiences that shaped your views of EDI.
- Reflections on the intersection between personal identity and career.
- Discussions at the intersection of EDI and neurology patient care, research, education, advocacy, or policy.

Submit your contributions to journal@neurology.org and include “Voices Submission” in the subject line.

Disputes & Debates: Rapid online correspondence

The editors encourage comments on recent articles through Disputes & Debates:

Access an article at Neurology.org/N and click on “COMMENT” beneath the article header.

Responses will be posted within three business days.

Before submitting a comment to Disputes & Debates, remember the following:

- Disputes & Debates is restricted to comments about studies published in Neurology within the last eight weeks.
- Read previously posted comments; redundant comments will not be posted.
- Your submission must be 200 words or less and have a maximum of five references; reference one must be the article on which you are commenting.
- You can include a maximum of five authors (including yourself).
Education Research

As the central mission of Neurology, education is a top priority. This is a section for interventional educational studies, as well as more traditional educational research, such as surveys. This section will examine the way neurologists not only practice, but also the way we teach and approach education. Neurologists have traditionally been respected, perhaps above all other specialties, for their scholarship and teaching. Educational issues will therefore continue to be at the center of the mission of Neurology.
Education Research: Neurology Resident EEG Education

Survey of US Neurology Residency Program Directors

Fábio A. Nascimento, MD, and Jay R. Gavvala, MD, MSCI

Abstract

Objective
To better understand the EEG education provided to adult neurology residents by surveying program directors of adult neurology residency programs in the United States.

Methods
An online survey focused on characteristics of neurology residency programs and their EEG teaching systems was distributed to the 161 adult neurology residency program directors listed in the Accreditation Council for Graduate Medical Education website at the time of the study.

Results
Forty-seven (29%) out of the 161 program directors completed the survey. Most of the participating programs (89%) were academic. The mean number of 1-month EEG rotations required to graduate was 1.7 (range 0–4, median 1.75). EEG rotations involved the inpatient and outpatient setting in 91% and 70% of programs, respectively. The average number of EEGs read during a typical EEG rotation varied from more than 40, in about one-third of programs, to 0–10, in about 14% of programs. There was significant variability in the requirements for successful completion of EEG rotations, and most program directors (64%) reported not utilizing objective measures to assess EEG milestones. The most commonly used educational methods were didactics throughout the year (95%) and EEG teaching during EEG rotations (93%). The most commonly reported barriers to EEG education were insufficient EEG exposure (32%) and ineffective didactics (11%); possible solutions are summarized.

Conclusion
Our study identified a lack of consistency in teaching and evaluating residents during residency and presented EEG education barriers alongside possible solutions. We encourage program directors across the country to re-evaluate their EEG teaching systems in order to optimize EEG education.
Glossary

AAN = American Academy of Neurology; ACGME = Accreditation Council for Graduate Medical Education; AES = American Epilepsy Society; ICU = intensive care unit; PGY = postgraduate year; RITE = Residency In-service Training Examination.

In accordance with the Accreditation Council for Graduate Medical Education (ACGME) neurology milestones project, adult neurology residents, by graduation, should be able to “interpret common EEG abnormalities, recognize normal EEG variants, and create a report.” This milestone is of utmost importance as EEGs are often read by general neurologists. Nonetheless, published literature has shown that a significant portion of graduating neurology residents do not feel confident interpreting EEGs independently. In this context, we sought to better understand the EEG education provided to residents as well as possible educational barriers by surveying program directors of adult neurology residency programs in the United States.

Methods

We evaluated multiple aspects of EEG education during adult neurology residency training utilizing an online survey directed at program directors. The survey consisted of 18 questions that focused on characteristics of neurology residency programs and their respective EEG teaching systems (e-survey available from Dryad: doi.org/10.5061/dryad.wdbrv15mm). The survey was conducted electronically via SurveyMonkey, and links to the survey were emailed to program directors or program coordinators of all 161 adult neurology residency programs listed on the ACGME website at the time of the study. Their contact information was obtained from both the ACGME website and the online American Academy of Neurology (AAN) member directory. In addition to the first email inviting program directors to participate in this research project, 4 weekly reminders were sent to nonrespondent centers. This study was approved by the Baylor College of Medicine institutional review board and was performed in April to May 2020. No financial compensation was offered to respondents. All data are available upon request.

Results

Survey Results

Forty-seven (29%) out of the 161 program directors of adult neurology residency programs completed the survey. Forty-two programs were purely academic, 3 community, and the remaining 2 mixed. The mean number of residents in each center varied significantly (range 10–49).

EEG Rotation Characteristics

The mean number of 1-month EEG rotations required to graduate was 1.7 (range 0–4, median 1.75). EEG rotations were typically completed by residents in their second year of residency (postgraduate year [PGY] 2), in 50% of programs, and PGY3s, in 41% of programs. PGY1s and PGY4s typically rotated through EEG in 2% and 7% of programs, respectively. EEG rotations involved the inpatient setting (including epilepsy monitoring unit) in 91% of programs and outpatient setting in 70% of programs. The average number of EEGs read during a typical EEG rotation was more than 40 in about one-third of programs. In the other two-thirds, responses included 0–10 (14%), 11–20 (20%), 21–30 (20%), and 31–40 (11%).

EEG Education: Resident Evaluation

In terms of requirements for successful completion of EEG rotations, program directors’ answers varied significantly and ranged from completion of rotation to oral examination and evaluation and interpretation of 30 EEGs. More than half of program directors (55%) reported that 81%–100% of their residents met EEG level 4 milestones by graduation. Roughly a quarter (27%) of program directors reported that 61%–80% met level 4 milestones and 18% of program directors reported fewer than 61% of residents meeting level 4 milestones. Most programs (64%) reported not utilizing objective measures to assess EEG milestones. In those programs where objective measures were used, these varied significantly and included EEG tests/quizzes, oral examinations, Residency In-service Training Examination (RITE), Self-Assessment Examination, American Epilepsy Society (AES) examination, direct assessment from faculty, evaluation of EEGs logged by residents, and number of EEGs read during the rotation.

EEG Education: Teaching Methods, Barriers, and Solutions

The 2 educational methods utilized most frequently by residency programs were (1) didactics given by attending, fellows, or residents throughout the year and (2) teaching EEG during EEG rotations by fellows or attendings. These methods were utilized by 95% and 93% of programs, respectively. Additional educational methods comprised teaching during epilepsy clinic (66%), bedside teaching during inpatient rounds (52%), and didactics given by attendings, fellows, or residents that are concentrated in a 1-to-2 months protected course directed at residents (30%). Other methods were reported by 16% of program directors and included overnight EEG reading on senior night float and utilizing online EEG teaching platforms.

Almost half of program directors (41%) reported an absence of any barriers to teaching EEG to residents. Insufficient EEG exposure and ineffective didactics were reported by 32% and 11% of program directors, respectively. Other barriers listed...
Possible Solutions to Most Commonly Reported Barriers to EEG Education During Adult Neurology Residency (Number of Respondents = 25)

<table>
<thead>
<tr>
<th>Increase exposure</th>
<th>1. Increase length/number of rotations</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2. Create rotation devoted exclusively to EEG, without clinical duties</td>
</tr>
<tr>
<td></td>
<td>3. Implement EMU rotation</td>
</tr>
<tr>
<td>Optimize teaching and learning</td>
<td>1. Increase supervision/oversight</td>
</tr>
<tr>
<td></td>
<td>2. Increase reading time with faculty</td>
</tr>
<tr>
<td></td>
<td>3. Increase responsibility/accountability to read EEGs during rotation</td>
</tr>
<tr>
<td></td>
<td>4. Utilize online modules to supplement education</td>
</tr>
<tr>
<td></td>
<td>5. Utilize case-based teaching—online and/or in-person</td>
</tr>
<tr>
<td></td>
<td>6. Encourage independent reading throughout residency</td>
</tr>
<tr>
<td></td>
<td>7. Ensure that faculty has time to read EEGs and teach</td>
</tr>
<tr>
<td></td>
<td>8. Implement regular EEG conferences</td>
</tr>
<tr>
<td></td>
<td>9. Increase EEG emphasis on inpatient services</td>
</tr>
<tr>
<td>Optimize measures of learning and evaluation</td>
<td>1. Require minimum numbers of EEGs read during rotation</td>
</tr>
<tr>
<td></td>
<td>2. Implement tests/quizzes, written and/or oral, online, and/or in-person</td>
</tr>
</tbody>
</table>

Abbreviation: EMU = epilepsy monitoring unit.

include excessive inpatient workload and necessity for more residents, low/absent resident interest, and insufficient time to teach from faculty standpoint. Possible solutions to these barriers, submitted by roughly half of program directors, are summarized in the table. Survey results are summarized in e-table 2 available from Dryad (doi.org/10.5061/dryad.wdbrv15mm).

Discussion

Our study evaluated EEG education practices in roughly 30% of American adult neurology residency programs, most of which were purely academic. On average, the mean number of 1-month EEG rotations required to graduate was 1.7 (median 1.75, range 0–4) and most programs had EEG rotations completed by PGY2s and PGY3s. EEG rotations were noted to take place both in inpatient and outpatient settings: in 91% and 70% of programs, respectively.

The time devoted to EEG during residency training seems to have remained grossly unchanged over time. Survey data from 1999 to 2000 involving more than 100 adult neurology program directors showed that the mean number of EEG months required to graduate was 2 (range 0 to 4). A similar survey study, conducted in 2007 and also involving more than 100 adult neurology program directors, showed that the typical length of EEG and epilepsy unit rotations was 1.5 (range 0–4) and 0.5 (range 0–3), respectively.

Our survey data also highlighted the lack of consistency in evaluation of residents during their EEG rotations. Almost two-thirds of program directors reported not using objective measures to assess for ACGME-recommended EEG milestones. Even in programs that utilized objective measures, there was significant variability in criteria measured.

We suspect the above leads to variations in the resident education experience—for example, the number of EEGs read by residents during EEG rotations among different residency programs. Limited published data demonstrate the educational value of increased EEG review in trainees who interpreted 20 vs 10 EEGs. Due to institutional variability, it is difficult to compare resident performance across institutions—for example, the percentage of residents meeting level 4 EEG milestones by graduation across various programs. In our study, more than half of program directors (55%) reported that more than 80% of their residents meet level 4 EEG milestones upon graduation. In the literature, the median of residents who meet level 4 EEG milestones was identified as 85%.

Published resident perception data, however, does not align with program director perceptions. In fact, it appears that adult neurology residents are graduating without becoming comfortable reading EEGs independently. According to the last triannual AAN survey, only 37.3% of graduating adult neurology residents felt confident performing or interpreting EEG in an independent fashion. An additional survey-based study that involved 55 adult neurology residents from different programs asked these residents how confident they were, on a scale of 0%–100%, in terms of their EEG skills. For graduating PGY4s, the median was 67% for interpreting common EEG abnormalities and creating a report and 60% for recognizing normal EEG variants.

As far as weaknesses, our study was limited by inherent aspects of its methodology. The response rate to our survey (29%) lies within the typical response rate linked with academic surveys. The respondents in our study were mainly program directors from academic institutions. We suspect that EEG education experiences in community-based programs may differ due to differences in EEG types (less continuous EEG in intensive care unit [ICU] and epilepsy monitoring unit environments) and program structure (fewer epilepsy and clinical neurophysiology fellows, which in turn may increase resident EEG exposure). Further, we examined PD perspectives only and did not study objective measures of the quality of EEG education such as residency in-service training examination (RITE) and neurology certification scores. Lastly, our survey did not investigate resident exposure...
to ICU EEG. Given its significant clinical and educational importance, this specific category within EEG education should be explored in future studies. All these factors need to be accounted for when analyzing our results and caution is needed upon extrapolation of our data to a national level.

Our study revealed intrinsic issues related to EEG education in residency. We identified a lack of consistent and objective measures associated both with teaching and evaluating residents. Moreover, we learned that over half of programs reported barriers to effective EEG education including insufficient EEG exposure and ineffective didactics. While program directors seem to believe most residents are able to read EEGs independently by graduation, graduating residents repeatedly report low levels of confidence in doing so.

Minimal quality standards are necessary to ensure competency in EEG interpretation by residents. However, current practice is largely guided by nonobjective measures. As a result, on a national level, resident EEG education and EEG exposure are varied. Guidelines outlining minimum training requirements for EEG education in residency are clearly needed to standardize the resident experience nationwide. This need was also identified in the realm of electrocardiogram education, leading to many experts advocating for the use of guidelines based on objective measures associated with teaching and assessment. The production and implementation of EEG education guidelines may require support from national organizations such as the AAN, AES, and the American Clinical Neurophysiology Society.

In current EEG practice in the United States, general neurologists without any neurophysiology fellowship training often read EEGs. This model of practice mandates that all neurologists should be competent in reading EEGs since EEG misinterpretation has significant negative implications to patients and health care systems. Unless this model is switched in a way that neurologists who read EEGs are required to undergo a clinical neurophysiology or epilepsy fellowship after residency, EEG education in residency must be improved. Current milestones assessing resident “EEG competency” may be a poor metric for defining residents who are capable of reading EEGs independently. The milestones lack any guidance on assessing the accuracy and quality of EEG report, for example, which is an essential component of the EEG interpretation process. A level 4 EEG milestone requires ability to identify “common EEG abnormalities” without specifying which abnormalities are included. The first step in ensuring that graduating residents are able to successfully review and interpret an EEG study is to establish specific learning expectations and rewrite clear and objective evaluation measures.

We encourage program directors across the country to re-evaluate their EEG teaching systems in light of the EEG education barriers presented in this study as well as possible solutions. Increasing EEG exposure, optimizing EEG teaching, and establishing objective measures to teach and evaluate residents are avenues through which EEG education can be improved.

Study Funding
No targeted funding reported.

Disclosure
F.A. Nascimento is a member of the Neurology Resident & Fellow Section editorial team. J.R. Gavvala reports no disclosures relevant to the manuscript. Both authors accept responsibility for conduct of the research. Go to Neurology.org/N for full disclosures.

Appendix Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fábio A. Nascimento, MD</td>
<td>Baylor College of Medicine, Houston, TX</td>
<td>Conceptualized and designed study, analyzed and interpreted data, drafted manuscript</td>
</tr>
<tr>
<td>Jay R. Gavvala, MD, MSCI</td>
<td>Baylor College of Medicine, Houston, TX</td>
<td>Conceptualized and designed study, analyzed and interpreted data, reviewed manuscript, supervised study</td>
</tr>
</tbody>
</table>

References
Emerging Subspecialties in Neurology

Emerging Subspecialties explores the diverse array of fellowship and career opportunities available for neurology trainees. Manuscripts can fall into one of two categories. First, traditional submissions may review the history and development of emerging subspecialties in neurology training, such as Interventional Neurology, Neurodevelopmental Disabilities, and Autonomic Disorders, and provide guidance on how to pursue these fields or incorporate new opportunities into existing training programs. Second, as part of the “Cortical Careers” series, papers should focus on career pathways outside of clinical neurology, including neuro-informatics, health services research, and global health. Through an interview-based format, manuscripts should summarize advice from senior leaders on how to pursue a particular career pathway and provide concrete, actionable steps that trainees can take to develop the skills needed to succeed in this area. Find detailed information about submission guidelines for this series at: NPub.org/emsu. Those interested in writing manuscripts for this subsection should contact the Resident & Fellow Section Editor prior to submission at rfsection@neurology.org to inquire about the need for an article on a particular topic.
Emerging Subspecialties in Neurology: Neurodevelopmental disabilities

Nicolas J. Abreu, MD, David K. Urion, MD, and Miya R. Asato, MD


Approaching clinical neurology through the lens of child development and behavior is an old and well-established concept. Take for example Sir William Osler’s 1894 description of the breadth of symptoms of what is now known as Sydenham chorea extending far beyond hyperkinetic movements: “The entire disposition may be changed, and the child becomes irritable, cross and unmanageable. Emotional disturbances are common, the child crying on the least provocation.”1 He demonstrates that adequate characterization of a child’s neurologic status requires a thoughtful review of behavioral functioning compared to age-referenced norms. Through specific and systematic training in the variation of typical child development, neurologists may then begin to diagnose and manage the entire scope of neurologic disease and its impact across the lifespan. Osler drew upon 410 cases of chorea to develop his expertise; in 2001, the American Board of Psychiatry and Neurology and the American Board of Pediatrics created the subspecialty training program in neurodevelopmental disabilities (NDD) to create the future generation of neurologically trained pediatric specialists to provide comprehensive assessment, personalized treatment, and superior outcomes for children and youth with complex conditions affecting the developing nervous system.

The long path to an NDD training program recognized by the American College of Graduate Medical Education began with the creation of a distinct specialty certificate for child neurology by the American Board of Psychiatry and Neurology in 1969. In the early years of the Child Neurology Society, members recognized there was limited training and understanding of developmental disorders such as intellectual disability, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), and cerebral palsy, so in 1978 the Child Neurology Society established a standing committee on developmental disabilities.2 This group aimed to promote education of child neurologists in this area given the discrepancy between the sizeable volume of patients seen with these conditions and the limited formal didactic exposure over the course of training. Within the field of pediatrics, the Society for Developmental Pediatrics (SDP) was founded that same year with Arnold Capute as its first president. Dr. Capute played a fundamental role in shaping the conceptualization of current NDD training. He trained in and eventually led the developmental pediatrics program at the Kennedy Krieger Institute at Johns Hopkins University School of Medicine in Baltimore.3

With growing expertise among pediatricians across the United States in development and behavior, private funding through the W.T. Grant Foundation supported behavioral pediatrics training during pediatrics residency. These program directors formed the Society for Behavioral Pediatrics in 1982, which evolved into the Society for Developmental and Behavioral Pediatrics (SDBP) in 1994.4 Their mission focused on clinical care, research, teaching, and child advocacy across children’s cognitive, social, emotional, and physical development in the framework of their family, school, and community system.

The SDP and SDBP worked in parallel in the 1990s and by 1997, the SDP had worked with the American Board of Psychiatry and Neurology (ABPN) and the American Board of Pediatrics (ABP) to submit a proposal for the NDD subspecialty. Collaborating extensively with the ABP, the SDBP created the subspecialty of developmental–behavioral pediatrics, distinct as a
pediatric subspecialty from NDD, which were both simultaneously recognized by the American Board of Medical Subspecialties on March 18, 1999. The ABP and ABPN jointly sponsored NDD, with the examination overseen by the ABPN. In contrast, the ABP oversees board certification in developmental and behavioral pediatrics (DBP).

The “2 + 4” NDD training model extends the “2 + 3” model of child neurology such that residents complete a minimum of 2 years of general pediatrics and then over 4 years of advanced postgraduate education, they develop proficiency in neurology with additional expertise in NDD across inpatient and outpatient settings. The latter 4 years integrate 12 months of adult neurology, 18 months of clinical child neurology and NDD training, and 18 months of clinical and basic science education. Required advanced rotations include at least one full-time equivalent month in child and adolescent psychiatry, neurosurgery, and neurorehabilitation. In addition, longitudinal care of both children and adults with disabilities is required, as is working in multidisciplinary teams. Scholarly activity is expected and more protected research time is typically offered compared to child neurology residency.

In contrast, DBP fellowship follows a “3 + 3” training model of 3 years of general pediatrics and 3 years of primarily outpatient subspecialty training. Fellowship must include at least 12 months of clinical care and 12 months of scholarly activity. There are no requirements for clinical neurology or adult care.

To become a board-certified NDD specialist, physicians are expected to sit for 3 board examinations. NDD trainees are required to obtain pediatrics certification and may apply to the ABP in their penultimate year of training. Application for initial certification in neurology with special qualification in child neurology

Table Neurodevelopmental disabilities (NDD) programs as of March 8, 2020, with compiled results from personal communications with NDD program directors

<table>
<thead>
<tr>
<th>Institution</th>
<th>Number of categorical positions</th>
<th>Number of advanced positions</th>
<th>MS4</th>
<th>Program focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>Children’s National Medical Center/ George Washington University</td>
<td>0</td>
<td>1</td>
<td>Yes</td>
<td>A rigorous program with a strong focus on building skills in child neurology and developmental pediatrics intermixed throughout training; trainees gain mastery in diagnostics and family-based care and receive substantial support for mentored research at Children’s National Medical Center or one of many local collaborating institutions</td>
</tr>
<tr>
<td>Indiana University School of Medicine</td>
<td>1</td>
<td>0</td>
<td>Yes</td>
<td>Integrated NDD training across the full spectrum of NDD; a tradition of collaborative training in combined residencies; categorical program with broad, intensive inpatient and outpatient clinical, teaching, and leadership experience along with mentored opportunities in basic, translational, and systems research; multiple faculty board certified by ABP and ABPN</td>
</tr>
<tr>
<td>Johns Hopkins University</td>
<td>0</td>
<td>2</td>
<td>Yes</td>
<td>Commitment to developing clinical expertise and positioning the graduate to assume leadership in academic training, research, and advocacy</td>
</tr>
<tr>
<td>Boston Children’s Hospital/Beth Israel Deaconess Medical Center/Harvard Medical School</td>
<td>0</td>
<td>1</td>
<td>Yes</td>
<td>Skill on skill spiral of training in both child neurology and developmental pediatrics intermixed throughout the 4 years; 6 months of research time is expected</td>
</tr>
<tr>
<td>Oregon Health &amp; Sciences University</td>
<td>1</td>
<td>0</td>
<td>Yes</td>
<td>Training physicians to become clinical, educational, and research leaders for children with NDD through a collaborative 6-year program integrated with child neurology and pediatrics</td>
</tr>
<tr>
<td>UPMC/Children’s Hospital of Pittsburgh</td>
<td>1</td>
<td>0</td>
<td>Yes</td>
<td>Individually tailored clinical exposure and mentored research experiences are an integral component of the NDD program, with 12 months of contiguous research time</td>
</tr>
<tr>
<td>University of Texas Southwestern Medical Center</td>
<td>1</td>
<td>0</td>
<td>Yes</td>
<td>Seeking to train NDD residents to not only be astute clinical scholars, but also advocates and thought leaders in the field of neurodevelopment</td>
</tr>
<tr>
<td>Baylor College of Medicine/Texas Children’s Hospital</td>
<td>2</td>
<td>0</td>
<td>Yes</td>
<td>A rigorous program combining pediatrics, neurology, and development supplemented by genetics, rehabilitation, psychoeducational, psychiatric, and social work training; program fosters the neurodevelopmental mindset throughout training, supporting development of clinical expertise and scholarly activity as well as advocacy and teaching skills</td>
</tr>
</tbody>
</table>

Abbreviations: ABP = American Board of Pediatrics; ABPN = American Board of Psychiatry and Neurology; MS4 = presence of NDD elective experiences for 4th-year medical students. Categorical positions offer full residency training required for board certification in NDD; advanced positions in NDD begin 2 years after the match and require a separate application to 2-year preliminary general pediatrics programs. All programs offer elective experiences in NDD for interested medical students.
may be done in the physician’s final year of NDD training. The NDD boards may only be taken once the individual has obtained these 2 certifications. However, there was a grandparenting period between 2001 and 2007 where any board-certified pediatrician or child neurologist with sufficient NDD clinical experience could take the NDD boards. In the first 2 years of offering the NDD boards, 88% of the 270 examinees were pediatricians with a special interest in NDD.5

Interested medical students apply through the Electronic Residency Application Service (ERAS) in their final year of medical school for both 2-year preliminary pediatrics programs as well as the 4-year advanced NDD programs. The majority of training sites have moved to a categorical match, such that the application process is streamlined across pediatrics and NDD, and residents work at nearby institutions throughout all 6 years. Another pathway into NDD training includes finding an open or “reserved” position in ERAS upon completion of a 3-year pediatrics residency program. While there is considerable variation in curricula and areas of focus across NDD programs across the country (table), all share a common foundation of education on developmental assessment, translational neuroscience, and neurodiagnostics in the context of a multidisciplinary team for children with complex health care needs. Within the framework of a neurobiologic model of illness, evidence-based interventions spanning behavioral therapies and novel biomedical technologies are harnessed to best care for patients. NDD graduates are expected to have greater fluency with screening, evaluation, neuropsychological testing interpretation, and management of conditions like ASD, intellectual disability, specific learning disorder, and ADHD than their child neurology colleagues, unless the latter seek additional training themselves. An NDD training program will instill competency in performing a detailed neurologic examination, analyzing laboratory results, reading neuroimaging and neurophysiologic studies, understanding molecular and anatomic pathophysiology, and interpreting complex genetic tests in the postgenomic era. Yet NDD physicians are taught to bring attention to often overlooked issues in a general child neurology practice, like medical comorbidities, care coordination, transition of care to adulthood, and systems-level problem-solving. Finally, mentored research is strongly encouraged throughout NDD education, and the additional year of training compared to child neurology allows for protected research time to explore academic interests.

There are diverse and exciting career opportunities after NDD residency. Previous residents have chosen to practice in a variety of locations, from outpatient clinics to inpatient neurology consult services. Private practice may be tailored to the physician’s areas of interest, and within academic medical centers, NDD faculty have been hired within neurology, developmental medicine, pediatrics, psychiatry, or rehabilitation divisions or departments. NDD specialists are leading multidisciplinary programs in areas like traumatic brain injury, spina bifida, and cerebral palsy, as well as directing clinics with integrated clinical research on single gene disorders such as Down syndrome and PTEN hamartoma tumor syndrome. They are championing neurodevelopmental evaluation and management of children with congenital heart disease and sickle cell anemia, building transition clinics for adults with developmental disabilities, developing novel gene therapies for neurodegenerative conditions, and transforming ASD screening best practices. None of this work is done in isolation. An NDD physician’s work is by necessity one that relies on close collaboration with therapists, psychologists, psychiatrists, social workers, genetic counselors, physical medicine specialists, and other medical subspecialties in order to provide the best possible care for patients. Whether at the laboratory bench or speaking to Congressional representatives, NDD specialists have made it their life’s mission to pioneer and advocate for the best possible care for patients with these disorders.

Across the United States, there is a great need for more NDD specialists, as 15% of children are living with a developmental disability.6 Yet there is also a demand for clinically informed investigators who will address the outstanding questions in basic science and translational medicine in order to move this field further. NDD training programs provide the clinical rigor and mentored research to meet both requirements, and provides a deeply fulfilling career path for young physicians.

Study funding
No targeted funding reported.

Disclosure
The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Appendix Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicolas J. Abreu, MD</td>
<td>Nationwide Children's Hospital, Columbus, OH</td>
<td>Designed and conceptualized study, drafted and revised the manuscript</td>
</tr>
<tr>
<td>David K. Urion, MD</td>
<td>Boston Children's Hospital, MA</td>
<td>Designed and conceptualized study, revised the manuscript, including for intellectual content</td>
</tr>
<tr>
<td>Miya R. Asato, MD</td>
<td>Children's Hospital of Pittsburgh at UPMC, PA</td>
<td>Design and conceptualized study, revised the manuscript, including for intellectual content</td>
</tr>
</tbody>
</table>

References
Neurons on Wheels (NOW) is a team of 2 neurologists with tools in our backpacks, roaming the streets of downtown Ottawa to see our homeless patients in shelters, on the streets, and in supportive housing units.

How we started

I was a second-year neurology resident doing a general internal medicine elective with Ottawa Inner City Health (OICH), learning to work as a resident physician in the shelter system. I went to see a patient who was inexplicably falling, causing her to be relocated from independent living in a supportive housing unit to a shelter-based palliative care unit with more support staff.

Supportive housing units are old hotels converted to studio apartments with staff supervision for medication administration and meals. The palliative care unit is a unique setting in which street-involved patients toward their end of life can be housed and cared for by experienced staff around the clock. I quickly realized I did not have the neurology expertise needed to make a diagnosis or recommend any treatment. Help was needed, and this was when NOW was born.

Before NOW, homeless patients did not have access to outpatient neurology expertise for various reasons. Some of these included not having a phone number to receive appointment times, lack of transportation, inability to keep an appointment that is months away while living in the shelters, being unable to remain for a prolonged period of time in the waiting room, and addictions to alcohol or drugs. All of these result in no-shows to outpatient appointments; eventually the patient is lost to follow-up or "fired" from physicians’ care. Homeless patients usually are only seen by neurologists in the hospital once they have deteriorated to having decreased level of consciousness or complete inability to care for themselves, at which point emergency medical services are alerted. They may also have acute neurologic deteriorations such as seizures or stroke that bring them into the hospital. While they are in the hospital, they may experience stigma from healthcare providers, other patients, or their families. Some of our homeless patients tell us that they feel judged and uncomfortable while in the hospital, or their cravings for their addictions arise, and often as soon as they are able, they leave the hospital against medical advice. This cycle continues as they miss their outpatient follow-up appointments. Ultimately, patients end up on the streets without neurology follow-up for seizures, acute strokes, subdural hemorrhage, or whatever medical problems they may have.

There is a need for neurologists in outreach medicine to bridge the gap in care for homeless patients, as well as to reduce costly emergency department assessments and repeated admissions to the hospital.

NOW is an outreach neurology clinic to bridge this gap. We go into the shelters to see patients in the early stages of their diseases so we can perform an appropriate workup and prevent or treat them before deterioration requires hospitalization. Importantly, this approach may reduce the stigma that our patients experience, helps us understand where they have come from and their background.

Global and Community Health

More than 85 percent of the world’s population lives in low and middle income countries, where the burden of neurologic disease is greatest. In addition, more than 50 million Americans live in medically underserved communities. Despite these figures, relatively little is known about patients and practitioners of neurology in resource-limited settings. This section aims to explore global and community health topics in neurology education. We welcome manuscripts describing international educational exchanges, personal rotations in low- and middle-income countries, and work by neurology trainees from around the world. We also welcome manuscripts that discuss community health initiatives and volunteer experiences in underserved regions of the United States. Inclusion of practical information on local or international volunteer opportunities would also be of use.
Global & Community Health: Bringing neurologists into shelters for better patient care

Neurons on Wheels

Joy Zhuo Ding, MD, Jeff Turnbull, MD, Med, and Chris Skinner, MD

Neurons on Wheels (NOW) is a team of 2 neurologists with tools in our backpacks, roaming the streets of downtown Ottawa to see our homeless patients in shelters, on the streets, and in supportive housing units.

How we started

I was a second-year neurology resident doing a general internal medicine elective with Ottawa Inner City Health (OICH), learning to work as a resident physician in the shelter system. I went to see a patient who was inexplicably falling, causing her to be relocated from independent living in a supportive housing unit to a shelter-based palliative care unit with more support staff. Supportive housing units are old hotels converted to studio apartments with staff supervision for medication administration and meals. The palliative care unit is a unique setting in which street-involved patients toward their end of life can be housed and cared for by experienced staff around the clock. I quickly realized I did not have the neurology expertise needed to make a diagnosis or recommend any treatment. Help was needed, and this was when NOW was born.

Before NOW, homeless patients did not have access to outpatient neurology expertise for various reasons. Some of these included not having a phone number to receive appointment times, lack of transportation, inability to keep an appointment that is months away while living in the shelters, being unable to remain for a prolonged period of time in the waiting room, and addictions to alcohol or drugs. All of these result in no-shows to outpatient appointments; eventually the patient is lost to follow-up or “fired” from physicians’ care. Homeless patients usually are only seen by neurologists in the hospital once they have deteriorated to having decreased level of consciousness or complete inability to care for themselves, at which point emergency medical services are alerted. They may also have acute neurologic deteriorations such as seizures or stroke that bring them into the hospital. While they are in the hospital, they may experience stigma from health care providers, other patients, or their families. Some of our homeless patients tell us that they feel judged and uncomfortable while in the hospital, or their cravings for their addictions arise, and often as soon as they are able, they leave the hospital against medical advice. This cycle continues as they miss their outpatient follow-up appointments. Ultimately, patients end up on the streets without neurology follow-up for seizures, acute strokes, subdural hemorrhage, or whatever medical problems they may have.

There is a need for neurologists in outreach medicine to bridge the gap in care for homeless patients, as well as to reduce costly emergency department assessments and repeated admissions to the hospital.

NOW is an outreach neurology clinic to bridge this gap. We go into the shelters to see patients in the early stages of their diseases so we can perform an appropriate workup and prevent or treat them before deterioration requires hospitalization. Importantly, this approach may reduce the stigma that our patients experience, helps us understand where they have come from and their

Correspondence
Dr. Ding
joy.ding@medportal.ca
unique issues, and starts to heal the broken patient–physician relationship with our homeless patients.

**Ottawa Inner City Health**

Ottawa, the capital of Canada, has a total population of 1 million people. Of these, 7,530 are homeless.1 OICH is an organization that provides health care to the homeless and street-involved communities in Ottawa. OICH was created and is led by Dr. Jeff Turnbull (Medical Director) and Wendy Mucke (Executive Director). OICH comprises a team of 16 registered nurses and 100 client care workers, looking after approximately 1,500 homeless patients throughout the Ottawa region. Each nurse follows more than 15 patients in the shelters. They know these homeless patients as people, the ins and outs of what they are using, the obstacles to getting housed, and much more than we could ever learn from a single social work consultation in the hospital. Patients are able to move among shelters and as long as they remain in Ottawa, they will continue to be followed by OICH.

Our referrals come from the OICH team. We act as a consultation service. As we move from shelter to shelter, we bring bedside neurologic tools (reflex hammer, ophthalmoscope, tuning fork, et cetera) with us. After we have seen the patient, our recommendations including further workup (bloodwork, imaging, neurophysiology) or treatment interventions are followed up by the OICH team. Vital signs are taken as needed; medications are administered with documentation kept up to date in an electronic medical record. Bloodwork can be done on site by the patient’s nurse and is picked up by a community laboratory on a daily basis. Imaging and neurophysiology (EEG, EMG) are done in the hospital and often require the patient to be accompanied by a client care worker (CCW). CCWs are support staff who can accompany patients to and from their appointments. This helps to ensure that patients make it to appointments and investigations offsite. Decisions to pursue investigations that require hospital visits are discussed with the patient (“Are they able to walk to and willing to wait in the hospital?”) and nurse (“Will they stay for the appointment, be compliant with testing, and be sober enough to go to the hospital?”). Frequently, we have to adjust our expectations of best care to what the patient is ready to do. Sometimes this means not pursuing further invasive testing before initiating empiric treatments. After the initial consultation, we are asked to reassess patients by OICH as needed.

What we have seen in the shelters in 2 years

We have maintained monthly NOW clinics since November 2015.

In our first 2 years, from November 2015 to September 2017, we have seen 34 new consultations. The average age overall was 55 years and 74% were men. The most common reasons for referrals were for seizures, movement disorders, and falls (figure). The most common diagnoses after consultation were focal seizures, essential tremor, cerebellar degeneration, and polyneuropathy. Patients lost to follow-up comprised 10% of our consultations. These included patients who underwent prolonged hospitalizations with extensive medical interventions including tissue plasminogen activator, craniotomy for subdural hemorrhages, and status epilepticus. Management was changed for 94% of the patients we saw. This included further investigations or initiating treatment.

Some rare conditions that we have encountered included patients with HIV/AIDS associated progressive multifocal leukoencephalopathy, progressive external ophthalmoplegia due to SPG7 mutation, severe drug-induced reversible cerebral vasocostriction syndrome requiring intra-arterial milrinone,2 and Pisa syndrome.

Over the years, we have seen patients in countless makeshift offices, shared bunk bed shelter rooms, shelter-based primary care clinics, supportive housing units, patients’ boarding rooms in the community, and curbside encounters close to the shelters where the patients had been expected to be found. These curbside encounters are necessarily brief. We make sure the patient feels comfortable with our interactions in a public place, perform an appropriately abbreviated examination, inform them of the plan, as well as update their registered nurse. After each patient encounter, an electronic medical record is created with details of the history, examination, assessment, and plan. Typically, we see the patients with at least 2 people present (staff, resident, with or without their registered nurse). We have not had any problems with safety over the years.

As of 2019, NOW clinics have been incorporated into the Division of Neurology at The Ottawa Hospital. A staff neurologist attends each monthly outreach clinic. All senior neurology residents attend NOW clinics, similar to other scheduled clinics when they are rotating through the ambulatory clinic rotation.

**Figure** Reasons for referral

![Reasons for referral](image)

- Seizure (n = 9)
- Movement disorder (n = 8)
- Falls/syncope (n = 6)
- Lost to follow-up (n = 4)
- Headache (n = 3)
- Neuro-ophtalmologic (n = 3)
- Confusion/cognitive (n = 2)
- Abnormal gait (n = 2)
- Muscle spasm (n = 1)

*Patients may be referred for more than one reason.*
Clinical pearls we have learned

In a large retrospective cross-sectional study published in 2019, Rosendale et al. found that homeless patients are at increased risk of 30-day readmission compared to housed patients. One of the most common reasons for homeless patients to be admitted to hospital was seizures. We recommend that seizures should generally be treated in homeless patients, regardless of their substance use status, especially if they have known focal brain abnormalities. This may help reduce readmission rates, especially when patients can be monitored in the shelters by a team like OICH.

Most of the patients with seizures we saw had focal seizures, diagnosed based on history, semiology, or electrophysiology. Reasons for focal seizures include a variety of lesions confirmed by CT head, including old stroke, intracerebral hemorrhage, traumatic brain injury with encephalomalacia, subdural hemorrhage, and subarachnoid hemorrhage. These homeless patients are at greater risk of recurrent seizures when they use substances that lower seizure threshold. We have been using antiepileptic medications in these patients to prevent further brain injury from seizures such as anoxia, falls, and traumatic brain injury. Given multiple comorbidities such as liver dysfunction, psychiatric disease, and noncompliance, choosing the right antiepileptic medication can be a challenge in this population. Levetiracetam is not ideal as it is twice a day and may worsen baseline psychiatric and mood disorders. We have found that once daily medications such as eslicarbazepine or phenytoin confer the best compliance. However, phenytoin may worsen cerebellar degeneration in this population, therefore increasingly we have been using eslicarbazepine. Hyponatremia and elevated enzymes are possible side effects, but we have not had significant trouble with this.

Future studies of interest include review of prevalence of neurologic diseases in homeless patients followed by OICH, prevalence of Wernicke encephalopathy, number of patients lost to follow-up who are homeless in our division of neurology, and whether the NOW clinic makes a difference in patient hospitalizations and patient engagement for investigations and treatments.

Reflections

Shelter neurology is interesting, empowering, and meaningful for those who like doing off-the-beaten-path medicine. Our homeless patients are kind and grateful when we make the effort to come see them in their temporary homes. Neurology consultation service within shelters is feasible when there is a primary care team to collaborate with. The front-line workers who are faced with patients with complex neurologic issues are very appreciative of having access to neurology consultants in the shelters. This is especially helpful for patients who do not present to hospital until end-stage disease is present.

Monthly or bimonthly consultations are sufficient to make an effect in our patient care. When conducted at an academic institution, this mobile clinic can be incorporated into residency programs to help build mutual respect, reduce stigma, and develop an understanding of our systemic pitfalls and the difficult problems of addictions and mental health. For those who are interested in global health, seeing our own homeless patients may be the first step to improving health care access in the world.

Shelter neurology is a different kind of medicine that requires an open mind and heart. It requires a harm reduction approach and ultimately doing what is right for the patient—perhaps the epitome of patient-centered care.

Acknowledgment

The authors thank their patients; the Ottawa Inner City Health team, including Wendy Muckle, Louise Beaudoin, Amanda MacNaughtan, Amy Towle, Anne Marie Hopkins, Beth Lusk, Kari Tomalin, Kim Van Herk, Lorraine Brownrigg, Lynn Burnett, Nora Chernier, Sophie Wheeler, Tammy Paterson, Wen Lin, and Yolanda Dare; neurology residency program director Dr. Christine De Meulemeester for her help with getting NOW started; Dr. Danny Lelli for support in maintaining resident involvement in NOW clinics; Orma Lester for helping with NOW organization; and Dr. Grant Stotts for continuing NOW’s work.

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Appendix Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Joy Zhuo Ding, MD</td>
<td>The Ottawa Hospital, Canada</td>
<td>Major role in initiation of the mobile clinic; manuscript concept, design, and draft; data analysis</td>
</tr>
<tr>
<td>Jeff Turnbull, MD, Med</td>
<td>Ottawa Inner City Health, Canada</td>
<td>Major role in initiation of mobile clinic, revised the manuscript</td>
</tr>
<tr>
<td>Chris Skinner, MD</td>
<td>The Ottawa Hospital, Canada</td>
<td>Major role in initiation of the mobile clinic, revised the manuscript</td>
</tr>
</tbody>
</table>

References

Journal Club

*Neurology* Journal Club submissions are structured evaluations of recent *Neurology* research articles. The aim is to enhance the training of residents and fellows by instruction in the critical appraisal of medical literature. Residents or fellows interested in submitting a *Neurology* Journal Club article should review the e-Publication Ahead of Print articles at NPub.org/aheadofprint for the most recently published material and email *Neurology* with their selection for prior approval. Selections will aim to represent the major categories of research methodology over the course of a three-year residency cycle. Submissions should be timely and are requested no longer than four weeks following the original e-publication date of the subject article. These Journal Club critiques, written by neurology residents and fellows with faculty supervision, should follow a specific outline and contain subtitles for background and significance, hypothesis and design, methods, results, and interpretation. Rather than a critical correspondence or editorial, this feature will highlight methods for the critical appraisal of medical literature. This online feature could be used as an adjunct to traditional institutional journal clubs and promote discussion among neurologists, including trainees and those in practice.
Journal Club: Scoping review of prevalence of neurologic comorbidities in patients hospitalized for COVID-19

Guillermo Delgado-García, MD, Antonio Arauz, MD, PhD, and Teresa Corona, MD, MSc


Correspondence
Dr. Delgado-García
guillermo.delgadogr@comunidad.unam.mx


Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

Coronavirus disease 2019 (COVID-19) is a global pandemic. As COVID-19 cases rise in different countries, neurologists and neurologists-in-training will be increasingly involved in the care of these patients from both a general medical and neurologic perspective. In the same way, patients with preexisting neurologic conditions are in no way exempt from acquiring this infection. On the other hand, new-onset neurologic manifestations have also been recently reported in previously healthy people infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). It is essential for neurologists and neurologists-in-training to be aware of the repercussions that COVID-19 may have in our daily practice.

Herman et al. recently reported a scoping review on COVID-19 and neurologic practice. This review displayed the current panorama in brief and simple terms. Its concise results are one way to continue caring for these patients in a better-informed way. Syntheses like this one are vital when evidence is rapidly changing, especially during this season when many neurologists are directly treating patients with COVID-19 and they do not have enough time to read all relevant articles coming out daily. Therefore, this Journal Club highlights 2 main teaching goals: (1) to present a summary and interpretation of this relevant article; and (2) to discuss the methodology and value of a relatively new approach to evidence synthesis (i.e., scoping review), particularly contrasting this method with that performed in a systematic review.

Hypotheses and design

The authors detailed 2 different but related aims: (1) to evaluate the frequency of preexisting neurologic conditions in adult inpatients with COVID-19 and (2) to estimate the frequency of new neurologic manifestations in adult inpatients infected with SARS-CoV-2. The authors chose the scoping review as synthesis methodology. As recommended for systematic reviews, in this particular type of strategy, rather than simply describing their hypotheses, authors are advised to unambiguously state the purposes that will be addressed in their synthesis.

Scoping reviews are one of the many methodologic approaches to knowledge synthesis. This tool is ideal to explore the scope and nature of a body of literature and provide clear indication of the studies available as well as an overview of their focus. Compared to systematic reviews, the most popular evidence synthesis strategy in evidence-based medicine, scoping reviews answer broader questions (e.g., extent, range, or nature of available evidence). Meta-analysis or meta-synthesis are not typically conducted as a part of scoping reviews. Additional differences between scoping and systematic reviews are summarized in the table.

Choosing the scoping review method as a means to navigate the sea of COVID-19–related evidence may reflect the diversity of the field, as COVID-19 is a continuously changing research
topic. This strategy is often applied in emerging fields where it aims to map evidence on a particular topic.

Methods

The article by Herman et al. followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR) in general terms. PRISMA-ScR is intended to foster a wider understanding of key elements (such as basic terms and concepts) while reporting scoping reviews. Herman et al. systematically searched the literature using the following databases as information sources: MEDLINE, Cumulative Index to Nursing and Allied Health Literature, and Scopus. Although it may seem confusing at first glance that both systematic and scoping reviews systematically explore the specialized literature, some methodologic particularities allow us to discern between these 2 methods. For instance, compared to systematic reviews, scoping reviews have less restrictive inclusion criteria. In addition, specialized frameworks other than population, intervention, comparison, and outcome may also be used in scoping reviews (e.g., population, concept, and context) when developing research questions. Furthermore, this synthesis methodology is not restricted to any specific study design, including qualitative studies. However, the opposite is not always true, and reviewers working on a scoping review may decide to focus on a specific study design as in the case of Herman et al., who only included quantitative studies.

Additional reports were retrieved by the authors through a Google-based gray literature search and snowballing. Versions of articles that precede formal peer review (i.e., preprints) are usually considered gray literature and were allowed by their prespecified eligibility criteria. Theses, dissertations, research, committee and government reports, conference papers, and ongoing research are also considered gray literature. Inclusion of this type of documents in a knowledge synthesis may decrease publication bias, boost timeliness and comprehensiveness, and promote a fair overview of available evidence.

Snowballing is a manual method of scanning the reference lists of articles or pursuing references of references.

Articles reporting adult inpatients with COVID-19 and pre-existing neurologic conditions or new-onset neurologic manifestations during the course of this infection were included in this scoping review but only if they were published in English. This language restriction is especially relevant in the present case because, at the beginning, the pandemic primarily affected non-English-speaking countries (such as China and Italy). In any evidence synthesis, exclusion of non–English language articles may decrease the generalizability and applicability of the results. It may in addition preclude the performance of future sensitivity analyses, especially those focused on assessing geographical bias. In this context, non–English language reports could also be regarded as a quality indicator. If, during the course of the review, it is not feasible to extract the information of interest from one of these non–English language reports, the most recent edition of the Cochrane Handbook for Systematic Reviews of Interventions recommends classifying this article in the PRISMA flow diagram as “studies awaiting classification” rather than “excluded studies,” thus informing readers about other potentially pertinent reports. Focusing on scoping reviews, the JBI Reviewer’s Manual also disapproves restrictions on evidence source selection by language unless a valid rationale is provided (e.g., feasibility).

A primary literature search was designed by the authors and then at least 2 reviewers independently screened all publications (including title and abstract). If an article met inclusion criteria, one reviewer independently extracted data on comorbidity and clinical variables. A dual independent review of search results is associated with the identification of a higher number of relevant studies. An increase in the precision of study selection seems to be also linked with greater involvement of a second reviewer throughout the review process.

The risk of bias across studies was not assessed by Herman et al. because, unlike what is recommended for systematic reviews, a risk of bias assessment is not typically conducted in

---

Table: Two different knowledge syntheses: scoping vs systematic reviews

<table>
<thead>
<tr>
<th>A priori review protocol</th>
<th>Sometimes</th>
<th>Yes</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROSPERO registration of the review protocol</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Explicit, transparent, peer-reviewed search strategy</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Standardized data extraction forms</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Mandatory critical appraisal (risk of bias assessment)</td>
<td>No*</td>
<td>Yes</td>
</tr>
<tr>
<td>Synthesis of findings from individual studies and the generation of “summary” finding</td>
<td>No*</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Abbreviation: PROSPERO = International Prospective Register of Systematic Reviews. Modified from reference 3.

* Some scoping reviews are followed by a quantitative synthesis.

---

34
scoping reviews. In general, this assessment is not performed since scoping reviews are not intended to be used to critically appraise a cumulative body of evidence. Therefore, practical implications arising from this type of knowledge syntheses are utterly distinct in comparison to those from systematic reviews. If provided, as in the present study, these implications may be limited in terms of providing advice from a clinical point of view. In short, scoping reviews are not customarily carried out for upholding the making of authoritative clinical guidelines but for advancing an overview of the nature and assortment of the evidence available.

At the end of their Methods, Herman et al. stated that a meta-analysis will not be performed. However, they focused their analysis on pooling disease frequencies. If an included article reported continuous data as medians and interquartile ranges, means and SDs were estimated according to the method described by Wan et al. As the expert panel did not consider this item to be applicable for scoping reviews, PRISMA-ScR did not include summary measures in its checklist. Additional methods for quantitative synthesis have also been proposed. Furthermore, statistical methods for quantitative analysis of noncomparative series have already been described.

Results

The authors screened 643 citations and excluded 288 (45%) due to duplication. The remaining 355 citations were reviewed by title and abstract and 274 (77%) did not meet eligibility criteria. From the 81 articles reviewed in full text, 49 (60%) were excluded for different reasons (including outpatient setting and language restrictions, both n = 2). A total of 32 reports were considered for this scoping review. According to the prespecified aims, 22 and 11 articles were included in the final analyses of the first and second objectives, respectively. Of these articles, one was included in both analyses. This description was depicted succinctly by the authors using a flow diagram, as recommended by the PRISMA-ScR reporting guidelines. The characteristics of evidence sources were displayed in detail using 2 tables.

Regarding the first aim, this analysis included 20 retrospective studies, 1 prospective observational study, and 1 randomized controlled trial. Of these, most studies were conducted in China (n = 20 [90.9%]). Altogether, in this analysis, 4,014 patients (mean age 55.6 ± 8.4 years) were included; 43% were women. The pooled frequency of preexisting neurologic conditions in adult inpatients with COVID-19 was 8.0% (n = 322/4,014 [range 0%–40%] for individual studies). Among secondary outcomes, the authors also found that cerebrovascular disease (CVD) as a comorbidity was more likely in critically ill patients. Likewise, a history of CVD was more common in inpatients who did not improve or remit in the first 10 days. Acute respiratory distress syndrome was also more likely in patients with a history of CVD. Finally, a univariate analysis from a prospective cohort of patients with COVID-19 pneumonia showed that those with preexisting cardiovascular conditions (including CVD) had higher odds of death (odds ratio, 11; 95% confidence interval, 4–30).

Regarding the second aim, no pooled frequency of new-onset neurologic manifestations in adult inpatients infected with SARS-CoV-2 was reported. Among secondary outcomes, the authors also found that, in one retrospective study conducted in Wuhan, more than one-third (36%) of patients (n = 214) developed a new neurologic symptom or event. Another retrospective study from Wuhan reported that 6% of inpatients with COVID-19 (n = 221) had an acute cerebrovascular event (including infarction, venous thrombosis, and hemorrhage). In a third retrospective study also conducted in Wuhan, hypoxic-ischemic encephalopathy was described in one-fifth of patients. In addition, delirium was reported in almost two-thirds (65%) of critically ill patients in Strasbourg, France. Finally, the authors reported that additional new-onset neurologic manifestations, such as acute necrotizing encephalopathy, seizures, Guillain-Barré syndrome, and meningocencephalitis, had been reported in isolated case reports.

Interpretation: scoping vs systematic reviews

One of the major findings from this scoping review is that 8% of adult inpatients with COVID-19 had at least one preexisting neurologic condition. This knowledge synthesis in addition suggested that patients with preexisting neurologic conditions (especially those with CVD) are prone to severe clinical courses when infected with SARS-CoV-2. It also indicated that more than one-third of inpatients with COVID-19 may have a new-onset neurologic manifestation during their admissions. Herman et al. concluded that a coordinated undertaking by the neurologic community is required to restructure clinical practices and thus serve the medical needs of patients during this season.

The main strength of this article is its selected methodology: scoping review. This method is especially fitting for examining emerging evidence, particularly when the prospect is still fuzzy and asking specific questions is challenging, which hinders the conduction of a proper systematic review. The scoping review methodology is therefore perfectly suitable to our current situation during this pandemic. Another strength of this article is the organization of studies included in the scoping review into 2 separate categories for synthesis: preexisting neurologic conditions and new-onset neurologic manifestations, respectively, both in adult inpatients with COVID-19. This step is termed grouping and its rational use in this evidence synthesis facilitates the understanding of both analyses and results.

Herman et al. identified several limitations of their scoping review, including small sample sizes, study designs, and overlapping publications. Nevertheless, most of these limitations are related to the nature and way of generating evidence.
during the pandemic. The acuity of this pandemic also limits the amount and quality of available neurologic information (including history, physical examination, and neuroimaging studies) in primary studies. Including only patients with COVID-19 who received inpatient treatment may also be a limitation in the scope of this synthesis, as this inclusion criterion excludes those who might have had either preexisting neurologic conditions or developed new neurologic complications but did not meet admission criteria. Another potential limitation is the lack of reporting of the method used to estimate the pooling disease frequencies. As the use of PRISMA-ScR is recommended for researchers, editors, and journals, an incomplete adherence to PRISMA-ScR reporting guidelines may be also regarded as a limitation of this scoping review.

Given the methodology used, the clinical implications of this review are not immediate. As a whole, this study informs our practice by providing us a brief synthesis of the latest evidence on COVID-19 and neurology, and likewise it will help us to manage, in a better and more informed way, the challenges we currently endure worldwide.

Study funding
Guillermo Delgado-Garcia was supported by a full national scholarship from the Consejo Nacional de Ciencia y Tecnologia (Conacyt) to pursue his MSc degree (CVU: 613905).

Disclosure
G. Delgado-Garcia is an editorial team member of the Neurology® Resident & Fellow Section. A. Arauz and T. Corona report no disclosures relevant to the article. Go to Neurology.org/N for full disclosures.

Appendix Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guillermo Delgado-Garcia, MD</td>
<td>Instituto Nacional de Neurologia y Neurocirugia, Mexico</td>
<td>Designed and conceptualized study, analyzed the data, interpreted the data, drafted the manuscript for intellectual content</td>
</tr>
<tr>
<td>Antonio Arauz, MD, PhD</td>
<td>Instituto Nacional de Neurologia y Neurocirugia, Mexico</td>
<td>Analyzed the data, interpreted the data, revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Teresa Corona, MD, MSc</td>
<td>Instituto Nacional de Neurologia y Neurocirugia, Mexico</td>
<td>Analyzed the data, interpreted the data, revised the manuscript for intellectual content</td>
</tr>
</tbody>
</table>

References
Mystery Case

Interesting teaching cases submitted to the Resident & Fellow Section are chosen by the editors to be published under the new Mystery Case subcategory. The Neurology editorial office disseminates a teaser through social media before the case is published. This usually includes a short description of the case, video or partial figure, and one to three questions. Responses are compiled and then published with the full case.
Mystery Case: Clinical Reasoning
Recurrent cerebral ischemia during pregnancies

Zachary Bulwa, MD, Laura P. Dresser, MD, Jamie Clarke, MS, and Scott Mendelson, MD, PhD

Neurology® 2020;95:e2453-e2457. doi:10.1212/WNL.0000000000010829

Section 1

A 29-year-old G6P3023, left-handed woman presented with acute onset left-sided weakness and expressive aphasia. She was in her normal state of health while driving home from work when her mother noted symptom onset. She was taken immediately to the emergency department for further evaluation. On presentation, she was afebrile with blood pressure 136/99 mm Hg, regular heart and respiratory rates, and oxygen saturation 88% on room air. Neurologic examination was notable for left-sided hemiparesis and sensory disturbance. The aphasia had resolved. Emergent head CT did not demonstrate any abnormalities.

The patient reported that 4 years ago, during her previous term pregnancy, she developed transient neurologic symptoms characterized by right-sided weakness lasting less than 24 hours. She was not offered tissue plasminogen activator (tPA) during that encounter, as she presented outside the time window, and exhibited no residual deficits thereafter. She was sexually active and denied use of contraception. She denied headache, loss of consciousness or trauma, changes in vision, chest pain, or shortness of breath at this time.

The patient did not have any contraindications to and was thus offered recombinant tPA. However, she and her family refused administration of tPA due to a family history of intracranial hemorrhage status post tPA administration in her maternal aunt. To help guide further diagnostic decision-making, she underwent a pregnancy test. Her pregnancy test result was positive (β-hCG 39.5 units/mL).

Questions for consideration:
1. Is pregnancy alone a contraindication for IV tPA administration?
2. What diagnostic considerations should be considered in pregnant patients?
3. What additional laboratory evaluation is indicated in pregnant patients with recurrent cerebrovascular events?
4. What additional risk factors may predispose the patient to recurrent cerebral ischemia during pregnancy?

GO TO SECTION 2
Section 2

Recombinant tPA is categorized as pregnancy class 3 and does not cross the placenta.1 Current guidelines recommend that tPA should not be categorically withheld in pregnancy-associated ischemic stroke, but a risk–benefit analysis, including the risks of uterine bleeding, should be discussed with each patient.1,2

Ischemic stroke during pregnancy is rare and is typically associated with the same risk factors as stroke in the general population. However, pregnancy is associated with an increased risk of stroke, highest in the peripartum and postpartum periods due to a progressing hypercoagulable state. Concentrations of factors VIII, IX, and X and von Willebrand factor increase, while concentrations of antithrombin III and protein S decrease, augmented by protein C resistance.1 Physiologic changes in blood volume, cardiac output, autonomic tone, and hormones during pregnancy may interfere with atrial electrical mechanics, predisposing to atrial fibrillation. Other predisposing factors include structural heart disease and the use of tocolytics during delivery.3 Laboratory testing may include a hypercoagulability panel as well as studies of infectious and noninfectious inflammatory etiologies.1

Diagnostic and treatment decisions can be challenging because of exposure to the fetus. Noncontrast MRI and ultrasonography are considered safe during pregnancy and the imaging techniques of choice. The use of gadolinium contrast for MRI should be limited as it can cross the placenta and may have teratogenic effects.4 CT may be used in the diagnostic evaluation as expected radiation exposure is often less than the exposure known to cause fetal harm. However, iodinated contrast agents for CT can cross the placenta, and despite a lack of studies demonstrating teratogenic effects, should be employed only if determined to be categorically critical for treatment purposes.4

Our patient underwent emergent brain MRI, which demonstrated bihemispheric punctate lesions of restricted diffusion (figure). Brain magnetic resonance angiography (MRA) and carotid ultrasound revealed no abnormalities, including no large vessel occlusion or hemodynamically significant stenoses. Her deficits resolved during the first 24 hours of hospitalization.

A more detailed family history was obtained following emergent evaluation. Our patient reported a family history of bleeding, including her mother’s recurrent epistaxis and her maternal aunt’s postthrombolysis fatal intracranial hemorrhage. She reported a history of spontaneous epistaxis, occurring 3–4 times per year, never requiring hospitalizations nor transfusions. She denied any additional sites of bleeding. She had never been formally tested for hereditary coagulation disorders and none of her children had demonstrated spontaneous bleeding.

Figure Brain and lung imaging

(A, B) MRI brain with evidence of bihemispheric ischemic stroke (yellow arrows demonstrate areas of restricted diffusion). (C) CT chest coronal view with evidence of a pulmonary arteriovenous malformation (AVM) (red arrow). (D, E) Digital subtraction angiography of the chest demonstrates a pulmonary AVM (D; red arrow) and the embolization of the AVM (E; red arrow).
Cardiac evaluation, including a 12-lead ECG, continuous cardiac telemetry, and transthoracic and transesophageal echocardiogram, was unrevealing for sources of embolism; however, no contrast agent was used, consistent with our institution's policy for pregnant patients. Lower extremity Doppler studies were negative. Blood counts, electrolytes, liver and renal function, lipid profile, and hemoglobin A1C were within normal limits. Additional serum laboratories were negative including hypercoagulability panel, inflammatory markers, rheumatologic panel, and infectious panel following the recommendations of Singhal et al.5 Thus this young woman presented with cerebral ischemic attacks during sequential pregnancies, with a history significant for epistaxis and a familial bleeding disorder, with borderline hypoxia and unremarkable laboratory, cardiac, and cerebrovascular evaluations.

Questions for consideration:
1. What diagnosis would you suspect based on the clinical history?
2. What additional screening tests should be considered?

---

Call for Voices: Lived Experiences

The editors of the Neurology specialty site Equity, Diversity, & Inclusion (EDI) encourage you to submit short first-person accounts (1,000 words or less) of experiences lived within the realm of equity, diversity, and inclusion with the goal of informing and enlightening our community on these critical issues. Some topics to consider include, but are not limited to:

- Descriptions of personal experiences that shaped your views of EDI.
- Reflections on the intersection between personal identity and career.
- Discussions at the intersection of EDI and neurology patient care, research, education, advocacy, or policy.

Submit your contributions to journal@neurology.org and include “Voices Submission” in the subject line.
Section 3

After meeting with the patient and her family to discuss the risks and benefits of further evaluation and possible treatment indications, she underwent chest CT angiography (CTA), liver MRI, and complete spine MRI to evaluate for arteriovenous malformations (AVMs) as a source of paradoxical embolism. Liver and spine MRIs were unremarkable. Chest CTA demonstrated multiple bilateral pulmonary AVMs. She underwent urgent and successful embolization of 7 pulmonary AVMs (figure).

Given the history of epistaxis, pulmonary AVMs, and family history of bleeding, we counseled the patient on the suspected diagnosis of hereditary hemorrhagic telangiectasia (HHT). Genetic testing revealed she had a 1429-1G>A sequence change in the ENG gene consistent with a diagnosis of HHT type 1.

Discussion

HHT is also known by the eponyms Osler-Weber-Rendu syndrome for their descriptions in the late 19th and early 20th centuries. HHT is now known to be an autosomal dominant disease with a prevalence of at least 1/5,000 persons, although estimates vary by region.

Early diagnosis of HHT relies upon clinical features including a history of epistaxis (spontaneous and recurrent) as well as telangiectasias of the lips, buccal mucosa, face, and hands. Epistaxis is the most common manifestation of HHT, typically presenting in the early teenage years, affecting nearly all individuals by age 40. Roughly two-thirds of telangiectases occur before age 40. Diagnosis of HHT should be considered in a patient presenting with this constellation of symptoms, enhanced by a known family history of bleeding or a diagnosis of an AVM. In 2000, Shovlin et al. published the Curaçao Criteria for the diagnosis of HHT, which includes epistaxis, telangiectases and visceral lesions (at characteristic sites: gastrointestinal, pulmonary, hepatic, spinal, and cerebral), and a family history of HHT. The diagnosis of HHT is considered definite when 3 or more criteria are met, suspected when 2 criteria are present, and unlikely if fewer than 2 criteria are present. Genetic testing can be used to establish the diagnosis in inconclusive clinical presentations.

Genetic testing can begin with sequence analysis for a heterozygous pathogenic variant of ENG (HHT type 1) or ACVR1 (HHT type 2) or a multigene panel including the rarer mutant genes SMAD4 and GDF2. ENG and ACVR1 encode endoglin and activin A receptor type II-like 1, respectively, 2 proteins involved in the transforming growth factor β family, which mediate vascular remodeling. Mutations in ENG are associated with a higher prevalence of pulmonary AVMs, whereas mutations in ACVR1 have a higher prevalence of hepatic AVMs and a more benign clinical course. Genetic counseling remains a significant aspect in the care of families with HHT including family planning as well as screening at-risk family members.

Screening is directed at visceral AVMs, which can lead to substantial morbidity and mortality if undiagnosed. The evaluation and management of pulmonary AVMs, gastrointestinal telangiectasias, and liver AVMs should be individualized. Detection of cerebral AVMs may be achieved with a combination of MRI and MRA, but CTA is more sensitive to detect associated aneurysms and digital subtraction angiography remains the gold standard. Investigational therapies aimed at disrupting the development and progression of these abnormal vascular connections lack controlled trials.

CNS manifestations of HHT include cerebral abscesses, intracranial hemorrhage, and ischemic stroke. Ischemic stroke is usually the result of paradoxical thromboemboli passing through pulmonary AVMs, but may also be caused by hyperviscosity due to chronic hypoxemia.

Most women with HHT proceed with normal pregnancies, although those with pulmonary AVMs should be aware of life-threatening complications such as AVM hemorrhage, ischemic stroke, and maternal death. Most complications are the result of the complex hemodynamic changes associated with increased maternal blood volume and cardiac output and decreased systemic vascular resistance occurring in the second and third trimesters. Women with HHT should be screened prior to pregnancy for pulmonary AVMs and treated accordingly.

Upon discharge, our patient was referred to our high-risk pregnancy care and family birth center, where she received care through the delivery of her baby girl. She continues to be followed at our University’s HHT Center of Excellence.

Study funding

No targeted funding reported.

Disclosure

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Appendix Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zachary Bulwa, MD</td>
<td>University of Chicago</td>
<td>Manuscript drafting/revision, literature review, data analysis and interpretation, formatting of figures, patient care</td>
</tr>
</tbody>
</table>
Appendix (continued)

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laura P. Dresser, MD</td>
<td>University of Chicago</td>
<td>Manuscript drafting/revision, literature review, data analysis and interpretation, patient care</td>
</tr>
<tr>
<td>Jamie Clarke, MS</td>
<td>Leonard M. Miller School of Medicine</td>
<td>Manuscript drafting/revision, literature review</td>
</tr>
<tr>
<td>Scott Mendelson, MD, PhD</td>
<td>University of Chicago</td>
<td>Manuscript revision</td>
</tr>
</tbody>
</table>

References


Mystery Case responses

The Mystery Case series was initiated by the Neurology® Resident & Fellow Section to develop the clinical reasoning skills of trainees. Residency programs, medical student preceptors, and individuals were invited to use this Mystery Case as an educational tool. Responses were solicited through a group email sent to the American Academy of Neurology Consortium of Neurology Residents and Fellows and through social media.

A total of 278 individuals submitted complete responses to the Mystery Case. Of these, 9 respondents answered all questions correctly. The majority of respondents (85.1%) were correct that pregnancy is not a contraindication for tPA. However, only 23.2% recognized that tPA is a class 3 drug that does not cross the placenta.

Most of the respondents (68.2%) correctly diagnosed the patient with HHT. In one study, stroke was the first presentation of HHT in 26% of patients with HHT and pulmonary AVMs. The key to this case was that the patient had an oxygen saturation of 88% with regular heart and respiratory rates. This should raise concern for pulmonary vasculature abnormalities and 29.5% of respondents correctly selected CTA chest as an evaluation tool. Fifteen to fifty percent of patients with HHT will have pulmonary AVMs. The additional clue of a history of spontaneous epistaxis in this patient raises specific concern for HHT and prompts imaging of the liver (selected by 7.3% of respondents) and spine (selected by 7.6% of respondents). A total of 30% to 75% of patients with HHT will have liver AVMs, although fewer than 10% will have symptomatic liver disease. The final correct imaging choice was lower extremity Dopplers, which are indicated to look for sources of clotting, not specific to HHT. Interestingly, the most common imaging choice selected by respondents (52%) was CTA head, which is not indicated in this case. MRI is recommended to evaluate for intracranial AVMs.

The final question of this Mystery Case asked about genetic etiology. Only 15.6% of respondents identified ENG as the most common gene associated with HHT. ENG, or endoglin, causes HHT1 and accounts for about 60% of cases of HHT. A total of 34.4% of respondents selected ACVRL1 (also known as ALK1), which is associated with HHT2 and is the second most common mutation, accounting for 37% of cases.

This Mystery Case illustrates a rare but important etiology for stroke that can be identified with a thorough clinical history.

Ariel M. Lyons-Warren, MD, PhD
Baylor College of Medicine, Texas Children’s Hospital

References

Pearls & Oy-sters

“Pearls and Oy-sters” is a feature focusing on fundamental clinical neurology. Each article addresses a specific niche of neurological disease and provide expertise in the form of clinical insights and tips, i.e., “pearls,” as well as advice for avoiding mistakes, or “oy-sters.” The author may choose to address a particular facet of the approach to neurological disease such as localization, elaboration of a differential diagnosis, evaluation, or treatment. These articles concentrate on what may be found in a textbook and/or provide what textbooks cannot, in the form of knowledge rendered from clinical experience. The target audience consists of those in training; however, the subject matter should be of interest to all in the world of clinical neurology.
Pearls & Oy-sters: Fatal brain edema is a rare complication of severe CACNA1A-related disorder

Laurence Gauquelin, MD, FRCPC, Cynthia Hawkins, MD, PhD, FRCPC, Emily W.Y. Tam, MDCM, MAS, FRCPC, Steven P. Miller, MDCM, MAS, FRCPC, and Grace Yoon, MD, FRCPC

Neurology® 2020;94:631-634. doi:10.1212/WNL.0000000000009223

Pearls

- Heterozygous pathogenic variants in CACNA1A are associated with 3 classic phenotypes, with variable expression and significant overlap: familial hemiplegic migraine 1, spinocerebellar ataxia 6, and episodic ataxia type 2.
- In addition to the 3 classic phenotypes, there is a more recently described fourth rare and severe presentation characterized by early-onset permanent cerebellar ataxia, developmental delays, seizures, and episodic attacks resembling hemiplegic migraine.
- The severe subtype of CACNA1A-related disorder can be associated with refractory, fatal brain edema.

Oy-sters

- CACNA1A-related disorder should be considered in the differential diagnosis of childhood-onset ataxia associated with isolated cerebellar atrophy on brain imaging, even in the absence of episodic clinical manifestations.
- CACNA1A-related disorder can mimic an immune-mediated process and should be considered in cases of acute refractory brain edema of unclear etiology.
- A timely and accurate diagnosis of CACNA1A-related disorder has treatment implications; corticosteroids are beneficial during the acute phase of cerebral edema, and attacks may potentially be prevented by early treatment with acetazolamide.

A 5-year-old girl initially presented in the first months of life with hypotonia and eye movement abnormalities. She had instability of primary gaze and saccadic smooth pursuit, and there was evidence of ocular motor apraxia. She then developed cerebellar ataxia, dysarthria, and generalized dystonia. Posturing was most noticeable in the lower extremities. Ataxia was severe, and the patient never walked independently. She did not have any type of headache, and her family history was noncontributory. Brain MRI revealed isolated cerebellar vermis atrophy (figure).

At age 3 years, the patient had a first episode of decreased level of consciousness in the context of fever. She was diagnosed with focal seizures, with left temporal epileptiform interictal discharges on EEG, and signal changes in the left hippocampus on brain MRI. She was treated with levetiracetam, which was later weaned after 2 years of seizure freedom.

The patient was admitted to the intensive care unit at our hospital at age 5 years with a second episode of altered mental status following a minor fall. She was found to be comatose, with prolonged seizures, exacerbated generalized dystonia, and unexplained fevers. CSF studies were unremarkable. Creatine kinase increased to 4,939 U/L (laboratory reference range 75–230) and then returned to normal within 48 hours. EEG revealed right temporal as well as generalized periodic discharges, superimposed on diffuse background slowing. Levetiracetam was...
restarted, and dystonia was treated with baclofen. Brain imaging was repeated and showed new findings of T2 and fluid-attenuated inversion recovery hypersignal, increased size of the right hippocampus, and multiple foci of cortical diffusion restriction involving both hemispheres, with a frontoparietal predominance (figure, B–D). There was mild interhemispheric pachymeningeal enhancement, but no definitive leptomeningeal enhancement and no parenchymal enhancement. Magnetic resonance spectroscopy was normal.

Despite complete seizure control, the patient remained encephalopathic and continued to require significant ventilatory support. She received pulse steroids (methylprednisolone 30 mg/kg/dose) from day 5 until day 9 of admission. On day 8, she was found to have a fixed dilated right pupil. Repeat brain imaging showed diffuse edema and bilateral uncal herniation, with low N-acetylaspartate peak and a probable lactate peak on spectroscopy. Intracranial pressure monitoring revealed an initial pressure of 31 mm Hg (normal 3–7 mm Hg in young children). The patient received multiple doses of mannitol in addition to continuous infusion of hypertonic saline over days 8, 9, and 10 of admission. A trial of IV immunoglobulins was started on day 9 given the possibility of an immune-mediated process. On day 10, while on maximal medical treatment for intracranial hypertension, the patient was found to have bilateral fixed dilated pupils with persistent global swelling on repeat brain imaging. A decision was made to withdraw life-sustaining measures, and she died on day 10 of admission.

Chromosomal microarray, metabolic investigations, and a comprehensive brain malformation gene panel had all previously been normal. Skin and muscle biopsy were obtained during the admission at our hospital and were normal. Whole exome sequencing was also pursued and revealed a de novo heterozygous pathogenic variant in the CACNA1A gene (c.5000G>C, p.R1667P) after death.

Postmortem brain biopsy and neuropathologic examination were performed (figure, E–H). The cerebellar vermis and hemispheres appeared atrophic without any other focal lesion within the brainstem. There was complete loss of Purkinje cells. Hemorrhagic lesions involving the cerebral cortex were seen in the right occipital lobe.

**Discussion**

Heterozygous pathogenic variants in CACNA1A, encoding the α1A subunit of the neuronal P/Q-type voltage-gated calcium channel, are associated with 3 classic phenotypes, with variable expression and significant overlap: familial hemiplegic migraine 1, spinocerebellar ataxia 6, and episodic ataxia type 2. More recently, a fourth rare and severe presentation was described,
characterized by early-onset permanent cerebellar ataxia, developmental delays, seizures, and episodic attacks resembling hemiplegic migraine.\textsuperscript{2–6}

It is well-established that episodes of CACNA1A-related hemiplegic migraine can be triggered by minor head trauma and can be associated with altered mental status.\textsuperscript{1,6} In addition, there are a few reports in the literature of severe CACNA1A-related disorder presenting with episodes of prolonged coma, with reversible cerebral edema.\textsuperscript{4,5,7} These dramatic attacks were previously thought to be specific to the S218L variant but have now been associated with several other CACNA1A pathogenic variants.\textsuperscript{3} Our patient carried a de novo missense variant (c.5000G>C, p.R1667P) that has not previously been reported, but is absent from large population databases.

This is the second report of fatal delayed cerebral edema associated with CACNA1A-related disorder.\textsuperscript{3} This phenotype likely represents the most severe end of the disease spectrum. The mechanisms for brain edema in CACNA1A-related disorder are hypothesized to include a cytotoxic response through dysfunction of the neuronal voltage-gated calcium channels.\textsuperscript{3,8} Aberrant neurotransmitter release has also been described.\textsuperscript{9}

During the most recent acute attack, the clinical features of our patient included fever and seizures. Together with the imaging findings of hippocampal signal changes and cerebral edema, the clinical picture was believed to be suspicious for inflammatory/immune-mediated causes, prompting trials of pulse steroids and IV immunoglobulins. The genetic diagnosis was not known at the time. It appears that severe CACNA1A-related disorder can mimic immune-mediated processes or even stroke-like episodes, and should be considered in cases of acute refractory brain edema of unclear etiology.

In addition to intracranial hypertension management (e.g., hypertonic saline, mannitol), treatment with corticosteroids has been reported to be beneficial in a few cases of cerebral edema associated with acute attacks in CACNA1A-related disorder.\textsuperscript{2,4,6} The effect of corticosteroids may be through indirect inhibition of the voltage-dependent calcium channels and by reducing cortical spreading depression.\textsuperscript{4} However, despite pulse methylprednisolone and aggressive intracranial hypertension management, the edema and mass effect progressed rapidly in our patient.

In episodic ataxia type 2, acetazolamide was previously found to be effective in reducing attack frequency.\textsuperscript{1} Familial hemiplegic migraine is also reported to respond to acetazolamide, flunarizine, verapamil, sodium valproate, or lamotrigine.\textsuperscript{10} In the severe phenotypic subtype of CACNA1A-related disorder, results have been inconsistent, with only a few case reports suggesting a benefit of verapamil or acetazolamide.\textsuperscript{5,7}

Our patient had initially presented several years before the fatal episode with hypotonia and prominent cerebellar signs, with evidence on brain MRI of isolated cerebellar vermis atrophy. CACNA1A-related disorder is known to be associated with isolated cerebellar atrophy, and should be considered in the differential diagnosis of childhood-onset ataxia with this brain imaging finding, even in the absence of episodic clinical manifestations. An early diagnosis of CACNA1A-related disorder could allow clinicians to consider a trial of preventative medication. Although there is no evidence that such medication would change the outcome, a trial appears reasonable given the severity of acute attacks in patients with the severe phenotypic subtype.

This report illustrates an atypical and severe presentation of a rare genetic disorder. The phenotypic spectrum of CACNA1A-related disorder is broad, and this diagnosis carries important management implications.

Acknowledgment
L. Gauquelin has received grants from the Canadian Gene Cure Advanced Therapies for Rare Disease (Can-GARD) and from the R.S. McLaughlin and Teva Canada Innovation funds from the Faculty of Medicine, Université Laval. S.P. Miller is supported by the Bloorview Children’s Hospital Chair in Paediatric Neuroscience.

Study funding
No targeted funding reported.

Disclosure
L. Gauquelin, C. Hawkins, and E.W.Y. Tam report no disclosures. S.P. Miller is supported by the Bloorview Children’s Hospital Chair in Paediatric Neuroscience. G. Yoon reports no disclosures. Go to Neurology.org/N for full disclosures.

Appendix Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laurence Gauquelin, MD, FRCPC</td>
<td>University of Toronto, Ontario</td>
<td>Designed and conceptualized the study, analyzed the data, drafted the manuscript for intellectual content</td>
</tr>
<tr>
<td>Cynthia Hawkins, MD, PhD, FRCPC</td>
<td>University of Toronto, Ontario</td>
<td>Major role in the acquisition of the data, interpreted the data, revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Emily W.Y. Tam, MDCM, MAS, FRCPC</td>
<td>University of Toronto, Ontario</td>
<td>Interpreted the data, revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Steven P. Miller, MDCM, MAS, FRCPC</td>
<td>University of Toronto, Ontario</td>
<td>Interpreted the data, revised the manuscript for intellectual content</td>
</tr>
<tr>
<td>Grace Yoon, MD, FRCPC</td>
<td>University of Toronto, Ontario</td>
<td>Designed and conceptualized the study, analyzed the data, revised the manuscript for intellectual content, overall study supervision</td>
</tr>
</tbody>
</table>
Visit the Neurology Resident & Fellow Website

Click on the Resident & Fellow Section menu dropdown at Neurology.org or visit NPub.org/rf directly.

Now offering:
- Blogs of interest to trainees and educators
- Neurology Resident & Fellow Editorial team information
- “Search by Subcategory” option
- E-pearl of the Week
- Mystery Case surveys
- RSS Feed
- Direct links to AAN resources
- Recently published Resident & Fellow articles

References
Right Brain

Right Brain is a feature devoted to the relationship between neurology and the medical humanities, with submissions either written by trainees or with a focus on the experience of the trainee. Appropriate submissions include articles, commentaries, and reflections on the interaction between neurology and history, literature, ethics, theology, sociology, anthropology, philosophy, poetry, theater, film, fine arts, or the media. Right Brain also will publish original works of fiction, poetry, and reflection written by residents and fellows relating to the practice of neurology or neurology training.
It was a slow night at the end of a week of slow nights, which felt like a blessing. A blessing you don’t want to talk about too loud in case you jinx yourself, but a blessing all the same. I was in the call room starting to consider a nap when my pager went off with the special tone that indicates a stroke code. Patient K, floor 8 West, onset now. I recognized the room number as belonging to the stem cell transplant unit. I took the elevator, congratulating myself on not having gone to bed earlier; it is hard to get on full functioning mode after being woken up suddenly.

The room’s door had every kind of isolation sign on display, which always feels somewhat ominous on a hematology floor. I started gowning up while the intern in the primary team briefed me on the story: “He is 32. He is on a medication that can cause intracranial bleeds, defibrotide.” Isolation gown open. “We have not seen him tonight, but per his dad he was talking normally earlier in the night and now he is barely saying anything and he is not following commands.” Gown wrapped around me and tied. “When was the last time anybody saw him fine?” Right glove on. “11 PM.” Left glove on. Pause to look up at the intern.

“Why is he is in the hospital?”

“Relapsed ALL.”

I will admit that based on the floor we were in, the multiresistant pathogens that my yellow gown and purple gloves portended, and the relatively nonspecific symptoms at a late hour at night, my suspicion for an acute stroke was dwindling. I opened the door resolutely. My first thought upon seeing Mr. K was, “Why is it that they never mention the jaundice?” My neurologist brain had missed the connection between defibrotide and hepatic failure. He was the shade of yellow that comes with a bilirubin over 15 and had his eyes closed and his head bent down, as somebody who is trying to retreat into themselves would do. “Hey, there,” I said. He opened his eyes, but he still appeared to be gazing up from a very distant place. “What’s your name?” He mouthed an answer but no words came out. “Can you hold this arm up in the air for me?” He did, well enough that I had no doubt that his strength was full despite the violent asterixis that shook his entire body. The same thing happened when I tested the other arm.

“That trembling has been there for a while,” offered a voice at the foot of the bed. I turned around to find Dad, a heavyset man in his 60s who appeared much calmer than what I, for some reason, was anticipating. “He did a similar thing the other night. I was here and he started talking out of his mind, but then got better after a couple of hours.”

“I heard you saw him acting normally at around 11 tonight? Show me 2 fingers with your left hand, Mr. K.”

Tremulous and ashen, 2 fingers came out of his left fist.

“Yes, I was here at 11 and he was fine. I then left for the hotel I’m staying at, and he called me on my cell half an hour ago. He was scared; he did not know where he was. But he had the presence of mind to know I was the one on for tonight.”
“What do you mean? Now smile really big for me, Mr. K.”

Effortful but symmetric grimace.

“My wife and I have been alternating spending the night here. Before we leave for the night we tell him which one of us to call if something happens.” He pointed at the whiteboard next to him, where 2 phone numbers preceded by “Mom” and “Dad” were written in a corner. “He knew to call me and not my wife.” He beamed and looked sideways at Mr. K, so very proud that his son, in the midst of this distorted nightmare, had retained that scrap of common sense.

I stopped going through my NIH Stroke Scale motions and for the first time gave my full attention to the gentleman standing next to me. The meaning of that calm demeanor that had bothered me upon entering the room suddenly sunk in: Dad’s composure was unsettling because it clashed dramatically with the reality of that hospital bed. Because Mr. K, with his multiresistant pathogens, his jaundice, his hands flapping downwards a good 3 inches at a time, and above all, his way of looking at us as if peering from the very center of his being, was dying. And his dad, as the pride in that smile betrayed, did not know or did not want to know.

I allowed myself 5 seconds of looking at this man straight in the eye, of wondering what it must be having your son crumble in front of you a little bit more every day, how on earth you keep entering this room with a straight face. For a moment, I envisioned an alternative reality in which it was not 1 in the morning and I was not a stranger to Mr. K, with his multiresistant pathogens, his jaundice, his hands flapping downwards a good 3 inches at a time, and above all, his way of looking at us as if peering from the very center of his being, was dying. And his dad, as the pride in that smile betrayed, did not know or did not want to know.

And then I turned back around and asked Mr. K to touch his nose with his right pointer finger, because it was indeed 1 in the morning and I was just here for the stroke code.

Common sense tells us that death is an absolute state, defined as “a permanent cessation of all vital functions.” But then we become doctors, and that very clear line separating the living from the departed blurs. We bring people back from cardiac arrests. We transition sick patients to comfort measures knowing that we are committing them to an unavoidable outcome for the greater good. We diagnose them with brain death and have to explain to a grieving family how this is death too, regardless of the green line beeping on the cardiac monitor. Mr. K was very much alive when I saw him, yet in the imaginary spectrum extending from “completely healthy” to “deceased,” he was not in the same category as the rest of us in his room. He was not, by any means, the most far gone of the patients I have seen, but he stuck with me because of the disconnect between his place in that spectrum and our approach: me, barging in his room and asking him to comply with my seemingly random requests, and Dad, focusing on the small victories instead of on the disheartening big picture.

On the way down to the CT scanner, when Mr. K was out of earshot, the primary resident confided that he had been dodging a transfer to the ICU for several days, because his hematologist was worried that he would be made comfort care as soon as he arrived in the unit. After the head CT showed no bleed and we were all satisfied with encephalopathy as the cause of Mr. K’s decline, I returned to the call room thinking about hope. Of all the human feelings that, as physicians, we have to navigate, hope is one of the most difficult to control. When should we put a limit to it? Is it wrong if we fall prey to hope ourselves, if we try to delay the inevitable? I could not help wondering how many hours of lucidity Mr. K had left, and if, in the name of hope, we had denied him the opportunity to use them to say goodbye.

I checked his electronic chart a few hours later, as the hospital was waking up around me while the day shift started to come in. By then he had been transferred to the medical ICU. After a small paragraph describing his mental status on transfer, the ICU resident’s note mentioned that when she was leaving the room Mr. K had asked her if she was on her way to talk to the grim reaper. I recalled his sunken eyes and suddenly noticed in them what, trying to focus on his pupillary function, I was not aware of during the stroke code: fear. Mr. K was less oblivious to his fate than he appeared, and he was terrified. That is when I understood that Dad’s composure was nothing more than a brilliant performance, not coming from hope as much as it was coming from love. He was just showing me how you keep entering your dying son’s hospital room with a straight face, day after day: by shielding yourself in a determined hope, so that when his demons come to haunt him, he can at least find comfort in his dad’s proud smile.

**Author contributions**
M. Diaz, composition of the manuscript.

**Study funding**
No targeted funding reported.

**Disclosure**
M. Diaz reports no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.
Teaching NeuroImages

Teaching NeuroImages are interesting, previously unpublished photomicrographs, patient photographs, neuroradiologic images, or other pictorial material. They are clear examples of established observations intended for the trainee audience. Educational videos may also be submitted under this category (Teaching Video NeuroImages). Teaching NeuroImages and Teaching Video NeuroImages now feature accompanying “Teaching Slides.” These slides are available online with the article as a teaching tool for trainees and program directors.
Teaching NeuroImages: Pupil-sparing compression of oculomotor nerve by posterior cerebral artery vessel

Anfei Li, Anika Tandon, MD, Apostolos J. Tsiouris, MD, Marc J. Dinkin, MD, and Cristiano Oliveira, MD

Neurology® 2020;94:e1450-e1451. doi:10.1212/WNL.0000000000009181

Correspondence
Dr. Oliveira
cro9004@med.cornell.edu

Figure 1 Compression of the left CNIII nerve by left posterior cerebral artery

(A, B) Isolated asymmetric atrophy of the left superior rectus muscle (arrows). (C) Left posterior cerebral artery in cross-section (arrow) impinges upon the left CNIII (arrowhead). (D, E) Asymmetric flattening of the left CNIII (arrowheads) by the left posterior cerebral artery (arrows).

A 54-year-old woman presented with a 30-year history of worsening left blepharoptosis. Neuro-ophthalmic examination was significant for blepharoptosis, limited levator function, and supraduction in the left eye with left hypotropia, and normal pupils without diplopia. MRI brain/orbits revealed subtle atrophy of the left superior rectus (figure 1, A and B), without any orbital pathology. Superior compression of the left oculomotor nerve by the posterior cerebral artery (PCA) was observed (figure 1, C–E). Given the microanatomy of oculomotor nerve in the cistern space, this is a rare selective compression of the superolateral oculomotor nerve by the PCA vessel (figure 2), sparing the superomedial parasympathetic limb.
Lesson Title: Pupil-sparing compression of oculomotor nerve by posterior cerebral artery vessel

A 54-year-old woman presented with a 30-year history of worsening left blepharoptosis. Neuro-ophthalmic examination was significant for blepharoptosis, limited levator function, and supraduction in the left eye with left hypotropia, and normal pupils without diplopia. MRI brain/orbits revealed subtle atrophy of the left superior rectus (figure 1, A and B), without any orbital pathology. Superior compression of the left oculomotor nerve by the posterior cerebral artery (PCA) was observed (figure 1, C–E). Given the microanatomy of oculomotor nerve in the cistern space,¹,² this is a rare selective compression of the superolateral oculomotor nerve by the PCA vessel (figure 2), sparing the superomedial parasympathetic limb.

Image is constructed based on similar images in Brazis.¹

**Figure 2** Illustration of the CNIII microanatomy (not to scale)

**Appendix Authors**

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anfei Li</td>
<td>Weill Cornell Medicine, New York, NY</td>
<td>Interpretation of data and drafting of the manuscript</td>
</tr>
<tr>
<td>Anika Tandon, MD</td>
<td>Weill Cornell Medicine, New York, NY</td>
<td>Interpretation of the data and revision of the manuscript</td>
</tr>
<tr>
<td>Apostolos J. Tsiouris, MD</td>
<td>Weill Cornell Medicine, New York, NY</td>
<td>Generation of imaging data</td>
</tr>
<tr>
<td>Marc J. Dinkin, MD</td>
<td>Weill Cornell Medicine, New York, NY</td>
<td>Design of the study, interpretation of the data, and revision of the manuscript</td>
</tr>
<tr>
<td>Cristiano Oliveira, MD</td>
<td>Weill Cornell Medicine, New York, NY</td>
<td>Design of the study, interpretation of the data, and revision of the manuscript</td>
</tr>
</tbody>
</table>

**References**


**Study funding**

No targeted funding reported.

**Disclosure**

The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

---

**Disputes & Debates: Rapid online correspondence**

The editors encourage comments on recent articles through Disputes & Debates:

Access an article at Neurology.org/N and click on “COMMENT” beneath the article header.

Responses will be posted within three business days.

Before submitting a comment to Disputes & Debates, remember the following:

- Disputes & Debates is restricted to comments about studies published in Neurology within the last eight weeks
- Read previously posted comments; redundant comments will not be posted
- Your submission must be 200 words or less and have a maximum of five references; reference one must be the article on which you are commenting
- You can include a maximum of five authors (including yourself)
A 59-year-old woman was admitted with acute left hemichorea-hemiballism. Blood glucose level was 87 mg/dL. Head CT scan showed old infarcts (Figure). The patient underwent thrombolysis with IV alteplase (0.9 mg/kg) within 86 minutes of symptom onset, evolving with partial improvement after 2 hours (video) and complete resolution after 24 hours without other treatments. Brain MRI showed an acute stroke in the right insula (Figure), known to be functionally connected to the posterolateral putamen.1 Hemichorea-hemiballism is an uncommon presentation of stroke and may be caused by insular, putaminal, and various other lesions connected to the same network.1,2

Study funding
No targeted funding reported.

Disclosure
The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

References
Teaching Video NeuroImages: Acute hemichorea-hemiballism reverted after IV thrombolysis

Caio Disserol, MD, Bárbara Alencar, MD, Jacy Parmera, MD, Adriana Bastos Conforto, MD, PhD, and Lécio Figueira Pinto, MD, PhD

Neurology® 2020;94:e121-e122. doi:10.1212/WNL.0000000000008706

Correspondence
Dr. Disserol
ciao.disserol@hc.fm.usp.br

Figure Imaging

Head CT scan shows old infarcts (A) and brain MRI shows an acute stroke involving the right insular cortex and capsula extrema on diffusion-weighted (B), apparent diffusion coefficient map (C), and fluid-attenuated inversion recovery (D) images.

A 59-year-old woman was admitted with acute left hemichorea-hemiballism. Blood glucose level was 87 mg/dL. Head CT scan showed old infarcts (figure). The patient underwent thrombolysis with IV alteplase (0.9 mg/kg) within 86 minutes of symptom onset, evolving with partial improvement after 2 hours (video) and complete resolution after 24 hours without other treatments. Brain MRI showed an acute stroke in the right insula (figure), known to be functionally connected to the posterolateral putamen.1 Hemichorea-hemiballism is an uncommon presentation of stroke and may be caused by insular, putaminal, and various other lesions connected to the same network.1,2

Study funding
No targeted funding reported.

Disclosure
The authors report no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

References
Appendix  Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Role</th>
<th>Contribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caio Disserol, MD</td>
<td>Hospital das Clínicas, University of São Paulo Medical School</td>
<td>Author</td>
<td>Wrote the manuscript, data collection, analysis, and interpretation</td>
</tr>
<tr>
<td>Barbara Alencar, MD</td>
<td>Hospital das Clínicas, University of São Paulo Medical School</td>
<td>Author</td>
<td>Data collection, analysis, and interpretation</td>
</tr>
<tr>
<td>Jacy Parmera, MD</td>
<td>Hospital das Clínicas, University of São Paulo Medical School</td>
<td>Author</td>
<td>Conceptualization of the study, interpretation of the data, revision of the manuscript</td>
</tr>
<tr>
<td>Adriana Bastos Conforto, MD, PhD</td>
<td>Hospital das Clínicas, University of São Paulo Medical School</td>
<td>Author</td>
<td>Interpretation of the data, revision of the manuscript</td>
</tr>
<tr>
<td>Lécio Figueira Pinto, MD, PhD</td>
<td>Hospital das Clínicas, University of São Paulo Medical School</td>
<td>Author</td>
<td>Conceptualization of the study, interpretation of the data, revision of the manuscript</td>
</tr>
</tbody>
</table>

Visit the Neurology Resident & Fellow Website

Click on the Resident & Fellow Section menu dropdown at Neurology.org or visit NPub.org/rf directly.

Now offering:

- Blogs of interest to trainees and educators
- Neurology Resident & Fellow Editorial team information
- “Search by Subcategory” option
- E-pearl of the Week
- Mystery Case surveys
- RSS Feed
- Direct links to AAN resources
- Recently published Resident & Fellow articles

Call for Voices: Lived Experiences

The editors of the Neurology specialty site Equity, Diversity, & Inclusion encourage you to submit short first-person accounts (1,000 words or less) of experiences lived within the realm of equity, diversity, and inclusion (EDI) with the goal of informing and enlightening our community on these critical issues. Some topics to consider include, but are not limited to:

- Descriptions of personal experiences that shaped your views of EDI.
- Reflections on the intersection between personal identity and career.
- Discussions at the intersection of EDI and neurology patient care, research, education, advocacy, or policy.

Submit your contributions to journal@neurology.org and include “Voices Submission” in the subject line.
Training in Neurology

This subsection features structured descriptions of novel training programs and personal experiences or expert opinion on critical gaps in neurology training across all stages of learning, from pre-collegiate preparation to fellowship and beyond. Manuscripts should provide descriptions of detailed training initiatives and interpret these initiatives within the context of existing literature, teaching, and practice. Authors should thoroughly review the literature to identify an important knowledge gap related to neurology training. Strong submissions will also outline why the educational program was created and provide data on assessments or evaluations. Conclusions should be supported by study findings and provide guidance around how best practices can be translated to other training institutions or generalized for additional learner groups. Note that educational research studies should be submitted to the main journal. Find detailed information about the submission guidelines for this subsection at: NPub.org/train.
Training in Neurology: Adoption of resident teleneurology training in the wake of COVID-19

Telemedicine crash course

Alicia M. Zha, MD, Lee S. Chung, MD, Shlee S. Song, MD, Jennifer J. Majersik, MD, MS, and Amanda L. Jagolino-Cole, MD


Abstract

The coronavirus disease 2019 pandemic has changed the way we engage patient care, with a move toward telemedicine-based health care encounters. Teleneurology is now being rapidly embraced by neurologists in clinics and hospitals nationwide but for many, this paradigm of care is unfamiliar. Exposure to telemedicine in neurology training programs is scarce despite previous calls to expand teleneurology education. Programs that provide a teleneurology curriculum have demonstrated increased proficiency, accuracy, and post-training utilization among their trainees. With the current changes in health care, broad incorporation of teleneurology education in resident and fellow training after this pandemic dissipates will only serve to improve trainee preparedness for independent practice.

Introduction

The coronavirus disease 2019 (COVID-19) pandemic is forcing a reckoning of current health care delivery and expediting a rapid transition to telemedicine-based care. In 2017, the Telemedicine Work Group of the American Academy of Neurology (AAN) recommended a teleneurology curriculum as an elective rotation for trainees.1 How long ago 2017 seems now as we all hastily work to create operational teleneurology infrastructure in our clinics and hospitals. Although prior exposure in teleneurology is advantageous in tackling the complexities of moving to telehealth-based care, most of the neurology workforce is not formally trained in telemedicine. While we are far from fully understanding the long-term sequelae of this pandemic on our health care systems, broader exposure and increased comfort with teleneurology is imperative to prepare our trainees for the new world of medicine they will face after the current pandemic dissipates.

Contemporary teleneurology practice

Neurology has long recognized the power of telemedicine in addressing gaps in access to care. Telestroke became an established practice among stroke centers in the mid-2000s, prompted by the STRoKe DOC2 trial demonstrating diagnostic accuracy in acute stroke care. In the outpatient setting, teleneurology is an alternative for some patients with chronic conditions and disability that make an in-person trip to a subspecialty clinic difficult. Teleneurology support for outpatient neurology care is well-described in the recent update by the Telemedicine Work Group,3 whose comprehensive review outlines the importance of teleneurology in improving patient satisfaction, patient-associated costs, and caregiver burden, without sacrificing quality of care.

However, teleneurology is far from universally embraced. Limitations in the neurologic examination over camera, dissatisfaction with potential technical failures, and a sense of

From the Department of Neurology (A.M.Z., A.L.J.-C.), Institute of Stroke and Cerebrovascular Disease, University of Texas Health Science Center, Houston; Department of Neurology (L.S.C., J.J.M.), University of Utah, Salt Lake City; and Department of Neurology (S.S.S.), Cedars-Sinai Medical Center, Los Angeles, CA.

Go to Neurology.org/N for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.
depersonalization from a lack of physical interaction with patients contribute to slow acceptance of this care modality. Perhaps the greatest barrier to broader adoption of practice was the lack of infrastructure for reimbursement prior to our current public health crisis. Because the Centers for Medicare and Medicaid Services (CMS) relaxed billing regulations and privacy guidelines temporarily to allow providers to continue caring for their patients remotely,4 neurologists have the ability to prove the utility and importance of teleneurology.

While current CMS reimbursement for teleneurology is intended for use only during the pandemic, routine teleneurology care—once shown feasible and effective—will become a standard tool for facilitating physician–patient interactions.

Are we preparing our trainees for this new world of health care? Regardless of reimbursement, the need for teleneurology is not going away after this crisis passes. Telestroke is already ubiquitous among vascular neurology divisions. Many academic departments are establishing tele-neurohospitalist capabilities for community hospitals. Five telehealth companies already provide nationwide teleneurology services. Setting up a teleneurology curriculum for trainees requires investment in time, effort, and finances from faculty and departments; however, decreased overhead costs, improved patient satisfaction, and decreased patient attrition could potentially offset that cost.

Existing models of teleneurology training

Dedicated teleneurology training is rare in neurology residencies. A literature search identified 1 fellowship and 2 resident training programs that describe formalized education in teleneurology. The University of California San Francisco implemented a teleneurology rotation for their postgraduate year 3 and 4 residents.5 After 2 nonconsecutive 2-week blocks of didactics and rotating in telemedicine-based neurology outpatient clinics, residents had improved telemedicine knowledge, more favorable impression regarding teleneurology, and fewer perceived challenges in conducting the neurologic examination over a camera. The Mayo Clinic at Jacksonville, Florida, instituted a telestroke education program for their residents with didactics, simulation training, and real-time clinical practice. Residents now train to conduct prehospital assessments of potential stroke patients via telemedicine-enabled ambulances prior to arrival to their comprehensive stroke center,6 and their study on the effects of this training on door-to-needle times is ongoing.

Vascular neurology training programs incorporating telestroke education illustrate the real-world effects of formalized telemedicine training. The University of Texas Health Science Center in Houston (UTHSC), Cedars-Sinai Medical Center, and University of Utah Medical Center provide dedicated telestroke education in their respective stroke fellowships and track door-to-needle times for fellows and faculty as a training metric. A survey of graduates from UTHSC reported exposure to telemedicine as fellows led to proficiency in telestroke care, and almost a third of graduates from that program went on to start telemedicine networks in their respective practices. Review of thrombolytic metrics at the UTHSC telestroke network revealed that fellows took 9 minutes longer to administer alteplase from page time compared to attendings. This lag gradually decreased with increasing fellow experience and proficiency in performing teleconsultations, improving page-to-needle time by 1 minute for every 14 consults.7 Data from the University of Utah linked training and experience with more appropriate deployment of teleconsultations and avoidance of unnecessary utilization.8 Familiarity and repetition can clearly improve teleneurology competency and efficiency.

The AAN recognized the need to incorporate telemedicine in neurology training in 2013 and multiple subsequent publications outline recommended curricula.1,5,6,9 provide data on implemented programs,7,9,10 and demonstrate the real-world benefits of systematic telemedicine training.7–9 Anecdotally, the residents at our 3 institutions have expressed increasing interest and curiosity regarding additional teleneurology exposure, which is magnified by the emergent changes in clinical practice implemented in response to the COVID-19 pandemic. The lack of mandated education in this area has led to slow adoption of training in teleneurology. Vascular neurology fellowships are increasingly incorporating telestroke training, but even in centers with robust telestroke networks and training programs, resident exposure pre-pandemic was scarce.

Towards broad adoption of teleneurology education

Trainees would most effectively benefit from a teleneurology rotation, or other clinical exposure to teleneurology, midtraining, after mastering the in-person neurology encounter. The AAN Telemedicine Work Group recommends comprehensive training in clinical bedside neurology for the safe practice of teleneurology.7 Accreditation Council for Graduate Medical Education (ACGME) neurology milestones or the Neurology Clinical Evaluation Exercise can guide evaluation for teleneurology competency. Adapted from our institutions’ programs, the table offers an example of potential competencies and milestones for a teleneurology curriculum. Training can help hone skills such as “webside” manner; communication with telepresenters, both novice and experienced; interpretation of remote neurologic examinations; accuracy of diagnosis and treatment plans; efficient consultations/evaluations; and recognition of the limitations of teleneurology. Multiuser teleneurology software can provide trainees direct supervision by an attending physician, albeit
sometimes at increased cost. Bringing residents and fellows to community hospitals for site visits, especially when activating a new site, can teach how to be a valued partner with local nurses and physicians and help better understand the patient experience. Faculty with experience in telenurology and curated from a broad spectrum of subspecialties should assist in teaching skills. Inherent differences in conducting visits with patients with movement disorders vs dementia vs stroke should be highlighted during training. Posttraining and lifelong learning of telenurology can take the form of board examination questions and Maintenance of Certification Program activities.

Embedding trainees in telenurology consultations provided by senior neurology staff may not be straightforward. Each institution must tackle local barriers in licensing and credentialing. For programs servicing sites in multiple states, the new
interstate licensure compact does not circumvent difficulties in licensing for fellows. Community hospitals do not lend themselves naturally to a teaching environment and many sites may hesitate to allow trainees on camera. Contractual educational agreements may alleviate some of this concern by assuring appropriate supervision and expectations. With these concerns in mind, teleneurology training should always begin with trainee observation of seasoned teleneurologists before graduating to more trainee-driven consultations. Initial encounters may be more manageable in less urgent, outpatient settings as residents and fellows gain familiarity with teleneurology skills. Standardized patients and simulation-based training may also provide some of the requisite experiences if live patient encounters are not feasible. The University of Utah uses SimLearn curricula to design telestroke simulations for new providers and have started to extend this to residents.

The COVID-19 pandemic necessitates novel and flexible vehicles for emergency and longitudinal care and provides a unique opportunity to expand education and adoption of telemedicine as a routine form of health care delivery. The ACGME should request telemedicine curricula in accredited neurology residencies and fellowships to reflect this real-world transition towards remote teleneurology consultations. Omitting teleneurology didactics leaves our trainees unprepared for the realities of modern-day neurology independent practice. It is time for us to shed our teleneurophobia and implement the changes necessary for programs to adequately prepare our future neurologists.

Study funding
No targeted funding reported.

Disclosure
A.M. Zha, L.S. Chung, and S.S. Song report no disclosures relevant to the manuscript. J.J. Majersik reports NIH/National Institute of Neurological Disorders and Stroke funding 1U24NS107228; is Associate Editor for Stroke; reports consulting fees for Foldax scientific advisory board; and is an editorial board member of Neurology®. A.L. Jagolinco-Cole reports no disclosures relevant to the manuscript. Go to Neurology.org/N for full disclosures.

Appendix Authors

<table>
<thead>
<tr>
<th>Name</th>
<th>Location</th>
<th>Contributions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alicia M. Zha, MD</td>
<td>Department of Neurology Institute of Stroke and Cerebrovascular Disease, University of Texas Health Science Center, Houston</td>
<td>Drafted the manuscript for intellectual content, major role in acquisition of data, design and conceptualization of editorial</td>
</tr>
<tr>
<td>Lee S. Chung, MD</td>
<td>Department of Neurology, University of Utah, Salt Lake City</td>
<td>Revised the manuscript for intellectual content, major role in acquisition of data</td>
</tr>
<tr>
<td>Shlee S. Song, MD</td>
<td>Department of Neurology, Cedars-Sinai Medical Center, Los Angeles, CA</td>
<td>Revised the manuscript for intellectual content, major role in acquisition of data</td>
</tr>
<tr>
<td>Jennifer J. Majersik, MD, MS</td>
<td>Department of Neurology, University of Utah, Salt Lake City</td>
<td>Revised the manuscript for intellectual content, major role in acquisition of data</td>
</tr>
<tr>
<td>Amanda L. Jagolinco-Cole, MD</td>
<td>Department of Neurology Institute of Stroke and Cerebrovascular Disease, University of Texas Health Science Center, Houston</td>
<td>Revised the manuscript for intellectual content, major role in acquisition of data, design and conceptualization of editorial</td>
</tr>
</tbody>
</table>

References
8. de Havenon A, Chung LS, Smith J, Taylor K, Majersik JJ, Chauhan N. Less experienced telestroke consultants are more likely to go on-camera, but less likely to give tPA. Stroke Res Treat 2019;2019:1059369.
**May 6, 2020: Rhythmic Ictal Nonclonic Hand (RINCH)**

Rhythmic ictal nonclonic hand (RINCH) motion is an ictal phenomenon that has been reported in patients with temporal lobe epilepsy. It is a “low-amplitude, milking, grasping, fist clenching, or pill rolling” movement in the hand contralateral to the seizure focus, distinguishable from ictal dystonic posture which usually lacks rhythmicity.\(^1\)

RINCH motions are believed to occur as a result of ictal spreading to the contralateral frontal lobe, i.e., orbitofrontal cortex and anterior cingulate gyrus. The incidence of RINCH ranges from 20-40 percent in patients with temporal lobe epilepsy and has an estimated lateralizing predictive value of 80-90 percent making it a useful sign for seizure focus localization and presurgical evaluation.\(^2\)

**References**


Submitted by: Mohanad AlGaeed MD, Epilepsy Fellow at Beth Israel Deaconess Medical Center, Boston.

AlGaeed reports no disclosures.

**August 31, 2020: Cogan’s Lid Twitch Sign**

In 1965, Cogan described his eponymous characteristic sign of myasthenia gravis (MG), elicited by asking the patient to gaze downward for 10–15 seconds and then returning to primary gaze.\(^1\) Cogan’s sign is present when the affected lid briefly “twitches” upward on returning to primary gaze. A variation on this technique—holding downgaze for 15 seconds then looking up and then returning to primary gaze—is often employed.\(^2\) The precise physiologic mechanisms are unknown. However, the twitch has been proposed to relate to initial fatigability, followed by rapid recovery of the levator muscle. One study found the sign to have a sensitivity of 75 percent and specificity of 99 percent for MG.\(^2\) However, given that the clinical suspicion for myasthenia was high in this cohort, these figures are potentially confounded by selection bias. Importantly, Cogan’s lid twitch is not pathognomonic for MG. The sign has also been reported in association with Miller-Fisher syndrome, myopathic disease, and dorsal midbrain lesions.\(^3,4\)

**References**


Submitted by: Conor Fearon, MB, PhD, Department of Neurology, Beaumont Hospital, Dublin.

Fearon reports no disclosures.