The third annual Highlights of the Resident and Fellow Section: 2010
A REPRESENTATIVE COLLECTION OF PREVIOUSLY PUBLISHED ARTICLES

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Mitchell S.V. Elkind

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ANNOUNCEMENT

Neurology® Resident and Fellow Section Writing Award

The winner of the 2010 Award is: H. Aitken, G. Gorman, R. McFarland, M. Roberts, R. W. Taylor, and D. M. Turnbull

Clinical Reasoning: Blurred vision and dancing feet: Restless legs syndrome presenting in mitochondrial disease


The trainee authors will be honored at the 2010 AAN awards luncheon.

The Neurology® Resident and 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 and 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 currently in a neurology residency program or in fellowship training in one of the neurological subspecialties. All authors will be considered equal recipients of the award in order to recognize and encourage collaborative work among trainees. The next award will be announced in early 2011 and will be awarded for a paper published in 2010.

No formal application process is required. All manuscripts submitted to the section will be considered. Manuscripts should be submitted online at www.neurology.org. Please direct any questions to kpieper@neurology.org.
Welcome to this third edition of the Highlights of the Resident and Fellow Section of Neurology!

The Highlights of the Resident and Fellow Section provides representative examples of some of the finest articles written for the Section by neurology trainees in the past year.

The Resident and Fellow Section (RFS) began in January 2004 to both serve the trainee readership of the journal and to provide a forum for resident writing. The Section is trainee-run: a nationally representative team of 12 residents and fellows, each of whom serves for three years and has responsibility for writing, reviewing, editing, and publishing articles of interest to trainees. Photographs and brief biographies of the RFS Editorial Team follow this introduction.

Publications of the RFS have grown tremendously over the years. The number of submissions to the section has increased dramatically (from 12 in 2004 to 143 in 2008), and the quality of published manuscripts has improved (represented by an acceptance rate of about 50 percent in 2008). We published 86 manuscripts in 2009, more than were published in the years 2004–2007 combined!

The RFS has several different subsections, as well, which are represented by the articles in this booklet. These include Emerging Subspecialties in Neurology, Clinical Reasoning, Right Brain, Child Neurology, Pearls and Oy-sters, International Issues, Education Research and Initiatives, Teaching Neuroimages (including both static images and videos), and Book Reviews. The descriptions of the subsections appear before each sample article.

The group also initiates and develops other unique projects, including podcasts, weekly electronic communications, an annual writing award, Mystery Cases, and new subsection ideas. Podcasts related to articles published in the RFS began in December 2007, for example, and weekly E-Pearls, or email “pearls,” have been sent to residents nationwide since July 2008. An archive of E-Pearls can be found at www.aan.com/go/education/residents/epearl. The first annual RFS writing award was awarded in April 2009. Our first Mystery Case was published in August 2009 (see page 11), and it generated 23 responses from individuals and residency programs around the world.

The RFS is strongly supported by Neurology’s Editor-in-Chief, Robert A. Gross, MD, PhD, FAAN; the associate editors; the journal staff; the American Academy of Neurology; and the publishers Lippincott Williams and Wilkins. 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.

We anticipate further developments for the RFS in the future, limited only by the imagination of the students, residents, fellows, and others who are interested in neurology education. We hope to have an interactive website, for example, where residents can sign up to write articles and become involved in the peer review of manuscripts submitted to the journal. Through these efforts, we hope that the RFS can play a role in helping trainees to meet requirements for core competencies related to practice-based learning and improvement, communication skills, and professionalism.

We welcome submission of manuscripts for the Resident and Fellow Section, and author instructions can be found at www.neurology.org. Papers submitted for this RFS 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 RFS will carry the same academic weight, whether online or in print, as papers published elsewhere in Neurology. 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 Mitchell Elkind or Kathy Pieper at kpieper@neurology.org.

We hope you enjoy this special third edition of Highlights of the Resident and Fellow Section of Neurology.

Mitchell Elkind, Resident and Fellow Section Editor

Disclosures: Dr. Elkind has no disclosures.
**Section Editor**

**Resident & Fellow Section**

Mitchell S.V. Elkind, MD, MS, FAAN

Dr. Elkind graduated from Harvard Medical School in 1992, interned at Brigham and Women's Hospital, and completed neurology residency at Massachusetts General Hospital. He then obtained a Masters degree in Epidemiology from Columbia University while doing his clinical stroke fellowship. Currently, Dr. Elkind is an Associate Professor of Neurology at Columbia University in the Division of Stroke and the Associate Chair for Clinical Research and Training. His research is focused on inflammatory and infectious biomarkers in stroke risk prediction, as well as acute-stroke therapy. Dr. Elkind is a Principal Investigator of 3 NINDS independent investigator awards. These include NeuSTART (Neuroprotection with Statin Therapy for Acute Recovery Trial), a clinical trial evaluating short-term high-dose statin therapy in acute-stroke; Levels of Inflammatory Markers in the Treatment of Stroke(LIMITS), a multi-center blood biomarker study among lacunar stroke patients participating in the SPS3 trial; and the Northern Manhattan Study, a prospective cohort study of stroke risk factors. He is the former Neurology Residency Program Director at Columbia University in the Division of Stroke and the Associate Chair for Clinical Research and Training. Dr. Elkind is a Principal Investigator of 3 NINDS independent investigator awards. These include NeuSTART (Neuroprotection with Statin Therapy for Acute Recovery Trial), a clinical trial evaluating short-term high-dose statin therapy in acute-stroke; Levels of Inflammatory Markers in the Treatment of Stroke(LIMITS), a multi-center blood biomarker study among lacunar stroke patients participating in the SPS3 trial; and the Northern Manhattan Study, a prospective cohort study of stroke risk factors. He is the former Neurology Residency Program Director at Columbia University in the Division of Stroke and the American Neurological Association and the Stroke Council of the American Heart Association. He has mentored several residents and fellows in neurology and clinical research.

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**Deputy Section Editor**

Ryan Overman, MD

Dr. Overman graduated from Indiana University School of Medicine in 2004. He completed internship at Methodist Hospital in Indianapolis and neurology residency at Indiana University School of Medicine. He is now Assistant Professor of Clinical Neurology at Indiana University School of Medicine. He serves a busy outpatient practice and as neurohospitalist at Methodist Hospital in Indianapolis. He is a member of the American Academy of Neurology. He serves as a member of the Neurology Podcasting Committee.

**James Berry earned his medical doctorate and master’s degree in public health from Northwestern University. During that time, he spent a year as a Doris Duke Clinical Research Fellow at UCSF, where he studied the effect of gabapentin on acute herpes zoster pain. Last year, he was a chief resident in the Harvard Partners Neurology Residency, and he is now a neuromuscular fellow. He plans to develop a career in ALS clinical research.**

**Stacey Clardy is currently a neurology resident at Penn State University in the flexible neurology residency program, pursuing an entwined fellowship in pain and anesthesiology. She received her MD and PhD degrees from the Pennsylvania State University in Hershey, PA. Her research interests include the contribution of ion channel pathology to neurological disease, especially in restless legs syndrome and amyotrophic lateral sclerosis. She is also interested in government policy as it applies to neurological disease.**

**Jennifer Fugate, DO**

Jennifer Fugate is currently a neurology resident at Mayo Clinic in Rochester, MN. She studied molecular biology at Grove City College and subsequently completed medical school at the Philadelphia College of Osteopathic Medicine. She plans to pursue fellowship training in neurocritical care starting in July 2011. Academic interests include critical care neurology, intracerebral hemorrhage, and posterior reversible encephalopathy syndrome.

**Amy Gelbrand, MD**

Amy Gelbrand is a child neurology fellow at the University of California, San Francisco. She is a graduate of Harvard Medical School and Dartmouth College. Her academic interests include headaches in children and pediatric movement disorders. She also has an interest in issues related to parenting during residency.
Chafic Karam is a neurology resident at Beth Israel Medical Center of the Albert Einstein College of Medicine in New York. He completed his medical studies at Saint Joseph University in Beirut. He has first-authored several peer-reviewed articles. He has received several awards during his residency for his research and teaching. He plans to pursue a career in the neuromuscular subspecialty. For leisure, he enjoys travel, biking, wine, and photography.

Sarah Song graduated with Honors in English and Women’s Studies from Williams College. She received her MD and MPH from the University of Illinois College of Medicine in Peoria. She served as Chief Resident of the Georgetown University Neurology residency program. Currently, she is a neurovascular fellow at UCLA. Her academic research interests include stroke prevention and stroke outcomes research. She was a 2009 participant in Neurology on the Hill, and is a graduate of the 2009 Donald M. Palatucci Advocacy Leadership Forum.

Christine Ulane received her MD and PhD from Mount Sinai School of Medicine of New York University in Manhattan. For her thesis she studied how viruses block the Interferon cytokine signal transduction pathway. She completed her internship at Columbia University Medical Center where she is currently in her second year of neurology residency.

Holly Yancy is a PGY-3 neurology resident at the University of Arizona. She studied English, journalism, and photography as an undergraduate at the University of Arizona and completed medical school at Midwestern University in Phoenix. In between undergraduate school and medical school she spent several years editing children’s books and fitness publications.

Keith Ridel is a pediatric neurology fellow at Cincinnati Children’s Hospital Medical Center. He completed his undergraduate studies in the classics at the University of Cincinnati and attended the University of Cincinnati College of Medicine. His academic interests include movement disorders and neuroanatomy.
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.
Clinical Reasoning:
A 62-year-old woman with deafness, unilateral visual loss, and episodes of numbness

SECTION 1
In May 2007, a 62-year-old woman presented with two episodes of right-hand numbness. The episodes were accompanied by profound fatigue. Each event lasted 5 minutes, and both occurred within a 2-week period. She also recalled an episode of right-sided numbness 30 years previously. She had a past medical history of hypothyroidism, hypertension, hypercholesterolemia, and multiple miscarriages. About 15 years ago, she began losing hearing in her left and then right ear, and she had been completely deaf for the last 8 years. Prior testing had revealed that the patient had sensorineural hearing loss, but the etiology could not be determined. Family and social history were unremarkable.

Questions for consideration:
1. What is the differential diagnosis for episodic neurologic abnormalities?
2. What diagnostic testing would you perform?

SECTION 2
The differential diagnosis of transient sensory dysfunction is broad and includes TIA, complicated migraine, seizure, metabolic derangement, peripheral nerve compression, compressive myelopathy, multiple sclerosis (MS), and conversion disorder. Particularly in patients over the age 55, transient neurologic attacks that are focal, nonfocal, or a mixture of both are associated with an increased risk of stroke. Therefore, an evaluation of our patient should include carotid ultrasound, transthoracic echocardiogram, and head CT or MRI of the brain. The history of multiple miscarriages raises the suspicion for antiphospholipid syndrome, which may cause a hypercoagulable state. Anticardiolipin antibodies, anti beta-2 glycoprotein antibodies, and lupus anticoagulant assays could be performed to investigate this possibility. An EEG may be considered to identify epileptiform discharges, especially given the patient’s post-event fatigue.

A diagnostic evaluation for the cause of her two episodes of numbness was unrevealing. Then, in January 2008, the patient noted blurred vision in her left eye that progressed over 3 days. She denied pain on eye movements, photopsia, metamorphopsia, or other neurologic deficit. Initial eye examination showed a left relative afferent defect and a normal-appearing left optic nerve head. An MRI of the brain was performed and revealed T2 and fluid-attenuated inversion recovery (FLAIR) signal abnormality in the subcortical and deep white matter, without enhancement with gadolinium. A diagnosis of optic neuritis was made and the patient received high-dose IV steroids for 5 days. However, her visual function did not improve over the next 2 months. At this time she came under our care.

Question for consideration:
1. What is the differential diagnosis for the constellation of episodic numbness, new visual loss, and progressive hearing loss?
SECTION 3
Our patient has had episodes of transient neurologic dysfunction, visual loss, and a past history of sensorineural deafness. Few conditions can completely account for this symptom complex. Wolfram syndrome is a rare, heterogeneous, inherited neurodegenerative disorder characterized by diabetes insipidus, diabetes mellitus, optic atrophy, and sensorineural deafness. While this syndrome would tie together visual and sensorineural hearing loss, it would not account for her transient numbness. Furthermore, she had no evidence of diabetes, and there was no family history of a similar disorder. Late onset MS was also considered but the clinical course of the visual loss was atypical for optic neuritis given the absence of pain and the lack of subsequent visual improvement. Bilateral hearing loss is also rare in MS. Another possibility was vitamin B1 deficiency. This condition can cause optic neuropathy and sensorineural hearing loss, but usually in combination with confusion, ataxia, and nystagmus, which our patient did not demonstrate. We also considered Susac syndrome, which consists of the triad of encephalopathy, branch retinal artery occlusions, and hearing loss. This condition is due to a microangiopathy affecting the precapillary arterioles of the brain, retina, and inner ear. However, an interval of 30 years between the onset of her progressive hearing loss and her current symptoms would be uncharacteristic of this disorder.

Several mitochondrial disorders can account for her major symptoms and would be highest on the differential at this point. Mitochondrial disorders in general have clinical heterogeneity, in part due to heteroplasmy (differential amounts of mutated DNA and normal DNA within each tissue). Also, each tissue has a different threshold at which the proportion of mutant mitochondrial (mt) DNA causes symptoms. Mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), myoclonic epilepsy with ragged-red fibers (MERRF), and chronic progressive external ophthalmoplegia often include sensorineural hearing loss; on the other hand, Leber hereditary optic neuropathy, neuropathy, ataxia, and retinitis pigmentosa are more commonly inherited Leigh syndrome often involve vision, but not hearing (table). Given the history of sudden onset numbness, MELAS stands out as a possible culprit. This disorder can present with a wide range of clinical symptoms including seizures, ataxia, stroke-like episodes, neuropathy, myopathy, sensorineural hearing loss, and encephalopathy. Although our patient is older than the typical age at presentation, with greater than 90% of patients presenting with a severe course before the age of 40, there are many reports of patients with MELAS and other mitochondrial disorders presenting later in life.

Physical examination revealed that the patient was cachectic and had short stature. She weighed 65 pounds. Her blood pressure and heart rate were

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Table: Clinical features of mitochondrial diseases

<table>
<thead>
<tr>
<th>Features</th>
<th>LHON</th>
<th>MELAS</th>
<th>MERRF</th>
<th>CPEO</th>
<th>Pearson</th>
<th>NARP</th>
<th>MILS</th>
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<td>Short stature</td>
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<td>Fanconi syndrome</td>
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<td>Ragged-red fibers (muscle biopsy)</td>
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LHON = Leber hereditary optic neuropathy; MELAS = mitochondrial encephalopathy with lactic acidosis and stroke-like episodes; MERRF = myoclonic epilepsy with ragged-red fibers; CPEO = chronic progressive external ophthalmoplegia; NARP = neuropathy, ataxia, and retinitis pigmentosa; MILS = maternally inherited Leigh syndrome.
visual fields were normal in the right eye, and revealed a central scotoma and inferior altitudinal defect in the left eye (figure 1). The pupillary light response was brisk on the right and sluggish in the left eye, and there was a left relative afferent pupil defect. Her ocular motility examination revealed mildly restricted upgaze for saccades, pursuit, and oculocephalic movements. Ductions were otherwise full. Funduscopic examination revealed myopic changes bilaterally and optic atrophy in the left eye. There was subtle right optic nerve atrophy. She was deaf bilaterally. She had dysarthric speech, but facial strength and sensation were normal. She had 4/5 strength proximally and 5/5 strength distally. On sensory examination, she had evidence of a length-dependent neuropathy with decreased vibration and temperature sensation up to her elbows and mid-thighs. There was no dysmetria. She had slight difficulty with tandem walk. There was no Romberg sign. Her deep tendon reflexes were absent.

**Question for consideration:**
1. Which features of the examination aid in narrowing the differential diagnosis?
Magnetic resonance imaging (MRI) of the brain showed prominent symmetric T2 and FLAIR signal abnormality in the subcortical and deep white matter and stippling of the basal ganglia. There was no enhancement with gadolinium. The pons had significant T2 and FLAIR abnormality as well.

SECTION 4

Three features of this examination are particularly important. First, short stature is seen in many mitochondrial disorders and suggests a longstanding disorder affecting growth and development. Second, the patient has proximal weakness, fitting a myopathic pattern. Mitochondrial disorders commonly involve multiple organ systems, and are particularly likely to cause myopathy. Finally, she has absent reflexes and length-dependent sensory loss indicative of neuropathy. Among disorders that cause concomitant neuropathy and myopathy, mitochondrial disease is on a fairly short list which also includes rheumatologic conditions such as Sjögren syndrome, sarcoidosis, toxicity from agents such as colchicine, amyloidosis, thyroid disease, or critical illness.

The patient’s brain MRI was reviewed at our institution and revealed prominent, symmetric T2 and FLAIR signal abnormality in the subcortical and deep white matter and stippling of the basal ganglia. There was no enhancement with gadolinium (figure 2).

Electromyography revealed excessive low amplitude, short duration, polyphasic motor units with a decreased recruitment ratio and early interference pattern consistent with a mild myopathy. There was also evidence of a mild axonal polyneuropathy on nerve conduction studies.

Optical coherence tomography (OCT) (figure 3) showed a retinal nerve fiber layer thickness of 80.03 µm in the right eye and 54.79 µm in the left eye (normal, 104 µm ± 12). An electroretinogram (ERG) had normal results.

Questions for consideration:
1. How does the MRI of the brain change the differential diagnosis?
2. Why is the electromyography important?
3. What does the combination of the OCT and ERG tell us about the localization of the patient’s visual loss?
4. What additional diagnostic tests would you order?

GO TO SECTION 5

Figure 3  Ocular coherence tomography showing a retinal nerve fiber layer (RNFL) thickness of 80.03 µm in the right eye and 54.79 µm in the left eye (normal, 104 µm ± 12)

The retinal nerve fiber layer in the left eye is thinnest in the superior, inferior, and temporal regions. TEMP = temporal, SUP = superior, NAS = nasal, INF = inferior.
SECTION 5

The brain MRI revealed diffuse and symmetric abnormality in the white matter with pathologic changes in the basal ganglia. This patient was treated for optic neuritis earlier in her clinical course but it should be noted that the white matter abnormalities on the MRI were atypical for MS. Symmetric, non-enhancing lesions of the subcortical and deep white matter without enhancement of the optic nerves would be unusual for a patient with MS and acute optic neuritis. This fact underscores the importance not only of brain imaging in the diagnosis of MS but also the proper interpretation of the scan results. Furthermore, the patient was treated with 5 days of IV steroids, whereas the current standard of care based on the Optic Neuritis Treatment Trial is 3 days of IV steroids followed by an oral prednisone taper. On the other hand, the combination of the MRI abnormalities might suggest the diagnosis of cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), which results from a NOTCH3 gene mutation. Patients with CADASIL typically present with multiple subcortical infarcts, migraines, dementia, and psychiatric symptoms. The MRI abnormality in this condition reveals T2 FLAIR abnormalities in the subcortical and deep white matter including the anterior temporal lobe and external capsule. Although our patient’s MRI suggested this condition, other clinical features such as optic nerve and cochlear nerve dysfunction did not.

In MELAS, there can be a wide variety of MRI abnormalities. Classically, the prominent abnormality is in the corticospinal gray matter, extending across vascular territories, without restricted diffusion. In addition, there is high T1 signal in the basal ganglia. However, there have been several reports where the MRI abnormality was limited to the white matter.

Our patient’s electromyography and nerve conduction studies confirmed the coexistence of myopathy and neuropathy, in keeping with a mitochondrial disorder with multiorgan involvement. One study found that almost all patients with MELAS had clinical findings suggestive of neuropathy, with confirmation on nerve conduction studies in 77%.

The OCT and ERG results confirmed that our patient has dysfunction of the left optic nerve with normal retinal function. OCT measures the thickness of the retinal nerve fiber layer to quantify the extent of axonal loss. ERG measures the electrical responses of photoreceptors in the retina and therefore provides an indication of retinal integrity and function.

There are a few ancillary tests that can be helpful in the diagnosis of MELAS. Magnetic resonance spectroscopy of the brain can identify lactate peaks when considering mitochondrial disorders. Serum lactic acid levels are often abnormal in MELAS. Our patient had a lactate level of 16 mg/dL (normal range, 4–16) and a pyruvate level of 0.14 mg/dL (range, 0.3–0.7). Her lactate was at the high end of normal and her lactate/pyruvate ratio was elevated. These values are consistent with the metabolic disturbance found when mitochondrial oxidative phosphorylation is not functioning properly. For definitive diagnosis, a test was sent for the common MELAS mutations and she was found to have the A3243G mt DNA mutation.

Although there is no established treatment for MELAS, rational therapeutic approaches based upon the associated biochemical abnormalities include supplementation with leucovorine, coenzyme Q10, and vitamin B complex. MELAS causes dysfunction of complex I of the respiratory chain and, therefore, decreased beta oxidation of long-chain fatty acids. Leucovorine aids in the transport of long-chain fatty acids into the mitochondria, and supplementation may help increase fatty acid oxidation. Coenzyme Q10 transfers electrons from complexes I and II to complex III and also stabilizes these complexes within the mitochondrion membrane. These functions may provide a beneficial antioxidant effect. Vitamin B complex contains thiamine, riboflavin, and nicotinamide, which all have proposed biochemical mechanisms to aid in repairing oxidative phosphorylation. Additionally, there are new data suggesting that arginine therapy may also benefit these patients, possibly by increasing nitric oxide levels and thereby reversing the impairment of vasodilation in this disorder. In a controlled clinical trial, arginine therapy reduced the severity, frequency, and disability resulting from stroke-like episodes in MELAS. Side effects of arginine therapy, however, may include severe hypotension. Therefore, more data are clearly needed to propose this treatment in all patients.

Patients with MELAS must also receive appropriate genetic counseling. Typically, there is a maternal inheritance pattern, in which all children of an affected mother are also affected. Given the clinical heterogeneity in mitochondrial disorders, these affected children can have a wide spectrum of phenotypes. In addition, there are rare autosomal mutations that can also cause the MELAS phenotype. Our patient had the most common mitochondrial mutation. As a result, all of her children would be expected to be carriers and she should be counseled appropriately. Since her parents were not affected, she most likely had a de novo mutation in her mitochondrial DNA.

Our patient had bilateral sensorineural deafness, acute optic neuropathy, and transient episodes of numbness. These clinical features coupled with her
ancillary testing including the MRI of the brain, electromyography, and ocular testing allowed for the final diagnosis of MELAS. Genetic testing confirmed this hypothesis.

REFERENCES

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Clinical Reasoning: A 35-year-old man with a right hemiplegia and a cerebral mass

SECTION 1
A 35-year-old man presented with progressive right face, arm, and leg weakness, and diffuse headache. He lived in rural northwest Argentina. He had no past medical history of sexually transmitted diseases. On examination, he was alert and fully oriented, and had a right hemiparesis with hyperreflexia and an extensor plantar reflex. Apart from low grade fever, the rest of the physical examination was unremarkable. The complete blood count revealed leukopenia (3,300 leukocytes/mL); renal function, liver tests, electrolytes, erythrocyte sedimentation rate, and glucose level were normal. He tested positive for HIV with a CD4 count of 18 cells/mm³ and viral load of 133,400 copies/mm³. Brain CT showed a nonenhancing left temporoparietal lesion with surrounding edema and midline shift.

Questions for consideration:
1. What are the possible etiologies of this intracerebral lesion?
2. What additional diagnostic testing would you consider at this point?

GO TO SECTION 2

SECTION 2
The patient was started on empirical treatment for toxoplasmosis without clinical improvement. A brain MRI with gadolinium performed days later showed a left temporoparietal mass with a ring-like enhancement pattern and marked perilesional edema (figure). Serologies for hepatitis B virus, hepatitis C virus, VDRL, and Toxoplasma (immunoglobulin G, immunoglobulin M, and immunoglobulin A subtypes) were negative. Blood cultures for bacteria, fungi, and mycobacteria were also negative. Since the patient lived in an endemic area, a search for Chagas disease was performed. The serology confirmed chronic Chagas disease (both indirect immunofluorescence and indirect hemagglutination tests were positive). Blood parasitological tests like microconcentration and Giemsa staining of thin and thick blood smears were also performed. Neither of these revealed the presence of the trypomastigote form of Trypanosoma cruzi.

Questions for consideration:
1. What is your differential diagnosis at this point?
2. What additional diagnostic tests would you consider at this point?

GO TO SECTION 3

SECTION 3
A lumbar puncture was performed. The CSF analysis showed 5 cells/mm³, glucose 48 mg/dL (serum glucose: 97 mg/dL), Cl⁻ 121 mEq/L, and protein 0.44 g/dL. PCR testing was negative for Toxoplasma, JC virus, and Epstein-Barr virus. A negative result for Cryptococcus neoformans was obtained with both India ink stain and antigen testing. A Giemsa-stained CSF smear revealed the presence of the trypomastigote form of T cruzi.

Questions for consideration:
1. How would you manage the treatment of an HIV-positive patient with cerebral tumor-like Chagas disease?
2. How long would you extend treatment?
3. What is the prognosis?

GO TO SECTION 4
SECTION 4
As soon as the diagnosis of cerebral tumor-like Chagas disease was made (approximately 10 days after admission), the patient was started on benznidazole 5–7 mg/kg/d and he resumed highly active antiretroviral therapy. In the course of treatment, seizures appeared and were partially controlled with lamotrigine. The patient developed neutropenia later in the course of his treatment, which was attributed to benznidazole, which was then replaced by nifurtimox 8–10 mg/kg/d. After 3 months of treatment, the patient exhibited improvement in both his neurologic condition and his immune status.

A new MRI showed a remarkable reduction in both the size of the lesion and its corresponding edema.

DISCUSSION
Chagas disease, also known as American trypanosomiasis, is an endemic parasitosis of Central and South America caused by the flagellated protozoan Trypanosoma cruzi. Although uncommon in the United States, its prevalence is expected to increase due to immigration from endemic areas. It is transmitted to humans by hematophagous Triatoma insects, and occasionally by other routes (blood transfusions, IV drug use, and congenitally).

The disease course can be divided into 3 phases: acute, indeterminate, and chronic. The chronic phase is characterized by prominent cardiac and gastrointestinal involvement (10%–30%), but often it can remain asymptomatic. In AIDS and other severe immunodeficient states, there is an increased risk of disease reactivation, with a particular predilection for the CNS (75% of cases) both in the form of meningencephalitis and intracranial mass lesions. This is especially true for patients with AIDS with CD4 counts <200 cells/mm³. Cerebral Chagas disease presenting as a tumor-like lesion is often clinically and radiologically indistinguishable from other more prevalent opportunistic diseases, like toxoplasmosis and lymphoma, and should be included in the differential diagnosis of patients with AIDS from endemic areas.

Diagnostic tests like CSF direct examination (Giemsa stain) and PCR techniques could provide a prompt diagnosis, avoiding the need for a brain biopsy.

The antiparasitic drugs benznidazole and nifurtimox are considered standard treatment. Even though there is a lack of agreement regarding treatment duration, it would be wise to maintain antiparasitic therapy until a CD4 count >200 cells/mm³ has been reached.

Cerebral Chagas disease has a poor prognosis, often leading to death within weeks of diagnosis. A high level of suspicion, coupled with early diagnosis and treatment, is the only way to achieve a better prognosis.

REFERENCES
tailed, including several alternative diagnoses and extensive descriptions of the respondent's approach to the diagnosis and management of this patient.

All respondents considered the fact that the patient had HIV and was immunocompromised in their differential diagnosis. All respondents included toxoplasmosis and CNS lymphoma at the top of their differential. All described many of the other most common considerations, and most outlined appropriate courses of diagnosis and management. Six respondents considered the patient's area of residence in South America as relevant to the diagnosis, most discussing the possibility of neurocysticercosis. Only 2 respondents, however, included the diagnosis of trypanosomiasis—infection with T. cruzi, or Chagas disease—in the differential: Kate Ahmad, The Canberra Hospital, Canberra, Australia, and Peter Armanas, Walter Reed Army Medical Center, Washington, DC. Additional considerations, in descending order of the number of times which they were cited, included bacterial abscess, cryptococcus and other fungal infections, viral infections, neurocysticercosis, glioma, metastases, tuberculosis, syphilis, progressive multifocal leukoencephalopathy, infarction, and tumefactive multiple sclerosis.

Half of the respondents recommended starting empiric therapy for toxoplasmosis, followed by brain biopsy if there were no response after several weeks. All suggested measuring serologies against many infectious organisms, though several expressed concerns about performing lumbar puncture due to the presence of the mass lesion. Seven suggested magnetic resonance spectroscopy as a way to distinguish tumor, infection, and vascular lesions.

This first Resident & Fellow Section Mystery Case points to the importance of considering diagnoses of infections uncommonly seen in the United States when evaluating immunocompromised patients from other countries. It is likely that with the increase in international travel we will all see more patients like this one.

Mitchell S.V. Elkind, MD, MS
Resident & Fellow Section Editor

From the Department of Neurology (G.M., J.P.P., M.P.G., M.E.T., P.A.L., M.E.B., S.C., J.L.F.), Department of Internal Medicine (J.P., O.M., A.D.V.), Department of Clinical Biochemistry, Clinical Immunology Division (M.A.), and Parasitology Division (C.M.), Hospital de Clínicas, Buenos Aires, Argentina.

Disclosure: The authors report no disclosures.
Clinical Reasoning:
Blurred vision and dancing feet
Restless legs syndrome presenting in mitochondrial disease

SECTION 1
A 58-year-old woman presented to a neuro-ophthalmologist with a 5-year history of progressively blurred vision, diplopia, and longstanding bilateral ptosis. She described occasional choking episodes after eating as well as fatigue and shortness of breath after minimal exertion. Her older sibling had received corrective eyelid surgery for ptosis and two nieces had ptosis and proximal myopathy and were being investigated in another center.

Direct and consensual pupillary light reflexes were normal with no rapid alternating pupillary defect.

Visual acuity was 20/20 on the right and 20/30 on the left. She had bilateral symmetric ptosis obscuring two-thirds of the pupil and restriction of eye movements below 60% of normal in all directions of gaze. Lower limb examination revealed symmetric proximal limb weakness (Medical Research Council grade 4+) with reduced reflexes and flexor plantars. Tandem gait was hesitant.

Questions for consideration:
1. What are the possible diagnoses?
2. What initial investigations would you recommend?

From Mitochondrial Research Group (H.A., G.G., R.M., R.W.T., D.M.T.), The Medical School, Newcastle University, Newcastle upon Tyne; and Department of Neurology (M.R.), Hope Hospital, Salford, UK.
Disclosure: The authors report no disclosures.
Figure 1  
Histochemical and mitochondrial genetic investigations in patient muscle

(A) Sequential cytochrome c oxidase (COX)/succinate dehydrogenase (SDH) histochemistry in the muscle biopsy from our patient reveals significant numbers (13%) of COX-deficient fibers, some of which show clear subsarcolemmal accumulation of abnormal mitochondria (marked with an asterisk). (B) Long-range PCR clearly demonstrates the presence of multiple mitochondrial DNA (mtDNA) deletions in patient muscle DNA (lane 4) compared to muscle DNA extracted from two age-matched controls (lanes 1 and 2); lane 3 shows muscle DNA amplified from a patient with a single large-scale mtDNA deletion for comparison. M = size marker.

SECTION 2
The initial differential diagnosis included Graves thyroid eye disease, a neuromuscular junction disorder (myasthenia gravis or botulism), oculopharyngeal muscular dystrophy, Miller Fisher variant of Guillain-Barré syndrome, and progressive muscular dystrophy.

Free thyroxin and thyroid stimulating hormone levels were normal. Thyroid antibodies were negative. Acetylcholine receptor antibody assay was negative and repetitive nerve stimulation to exclude a neuromuscular junction disorder was normal. Electromyography of proximal upper limb muscles revealed an increased number of short duration motor units consistent with borderline myopathy. Nerve conduction velocities were normal, reducing the likelihood of an immune-mediated inflammatory neuropathy.

Due to the chronicity of symptoms, presence of gaze paresis, myopathic findings on neurophysiologic assessment, and family history of ocular complications suggestive of dominant inheritance, a muscle biopsy was performed. Polyadenylate binding-protein nuclear 1 (PABPN1) gene mutation analysis to exclude oculopharyngeal muscular dystrophy was deferred pending muscle biopsy analysis.

The muscle biopsy showed 13% cytochrome c oxidase (COX)-deficient fibers, significant numbers of ragged red fibers but no excess of lipid or glycogen accumulation, and subsarcolemmal accumulation of abnormal mitochondria suggestive of a mitochondrial cytopathy (figure 1A). Testing for common mitochondrial DNA (mtDNA) point mutations (MELAS m.3243A>G [mitochondrial encephalopathy, lactic acidosis and stroke-like episodes], MERRF m.8344A>G [myoclonic epilepsy with ragged red fibers], and NARP m.8993T>G/C [neuropathy, ataxia, and retinitis pigmentosa]) did not reveal any abnormalities. Long-range PCR, however, revealed multiple mtDNA deletions in muscle (figure 1B).

Questions for consideration:

1. What is your differential diagnosis at this point?
2. What additional diagnostic tests would you consider at this time?

GO TO SECTION 3
The Resident and Fellow Section is a primarily online feature that serves the resident and fellow readership. Residents and fellows are expected to be the primary authors for most submissions, but those highly involved in graduate medical education (e.g., program directors) may also contribute submissions on appropriate topics.

Submissions for all article categories should be no more than 2,500 words; permission for longer articles will be needed from the editors. The number of references should be 10 or less and one to two tables or figures may be incorporated. The topic must be mentioned in the cover letter of the submission. Potential article topics include: teaching, ethics, practice, career choices, residency training, editorial, international education, research, historical, opinion, book review, training videos, or teaching NeuroImages. Teaching NeuroImages has the same requirements as NeuroImages but is especially valuable to the trainee audience and will be published in the online Resident and Fellow Section. A number of new categories were added in 2007. Queries and comments should be addressed to Mitchell Elkind, MD, MS, FAAN, or Kathy Pieper at kpieper@neurology.org.

The patient presented 10 months later with an uncomfortable “jumping” sensation in her feet when at rest which was relieved by movement. Symptoms were worse at night and she also described sudden involuntary movements of her lower limbs. These symptoms did not subjectively impact on sleep hygiene. Family history was negative for these symptoms.

Questions for consideration:
1. What condition is this patient describing?
2. What additional tests would you consider at this time?
SECTION 4

This patient’s symptoms were consistent with restless legs syndrome (RLS) and periodic limb movements of sleep. Medications included ubiquinone only. Initial blood tests including full blood count, iron, ferritin, glucose, renal and liver profiles, thyroid function tests, and vitamin B12 levels were normal. Nerve conduction studies were normal excluding a peripheral neuropathy. Due to the risks associated with developing a dopamine deficient syndrome with POLG mutations, 123-I Ioflupane DaTSCAN imaging was performed.

This showed asymmetric uptake of tracer in the putamen with relative reduced uptake in the right putamen compared to the left side (figure 2) consistent with impairment of the dopamine transporter mechanism suggestive of parkinsonism. She declined pharmacologic intervention for symptom control. The results of POLG1 gene analysis in the affected relatives revealed the same heterozygous mutations.

DISCUSSION 

Mutations of the POLG1 gene are thought to account for up to 25% of adult mitochondriodisease presentations. This patient presented with gaze paresis, multiple mtDNA deletions in skeletal muscle, and a family history of ptosis. It is widely accepted that this constellation of symptoms warrants consideration of POLG1 as a possible diagnosis. Autosomal dominant progressive external ophthalmoplegia (adPEO) caused by a mutation in POLG1 was first described in 2001. Pathogenic mutations in the genes encoding POLG, the enzyme that synthesizes mitochondrial DNA, have been described in patients with dominant, recessive, and sporadic PEO, as well as in patients presenting with parkinsonism, neuropathy, late onset ataxia, and Alpers syndrome. Mitochondrial dysfunction has been linked to Parkinson disease (PD) with mtDNA deletions and rearrangements found in the substantia nigra of patients with PD and individuals with POLG mutations.

RLS is a common yet underdiagnosed condition with multiple causes. Secondary causes excluded in this patient include iron deficiency, pregnancy, and end-stage renal failure. The patient fulfilled the essential criteria for RLS: the urge to move the legs which is initiated or worsened by inactivity, relieved by movement and worse at night. High prevalence of RLS is reported in this patient’s age group and gender (women, aged 50–59 years). Associated features are a family history of RLS, a positive therapeutic response to dopaminergic drugs, periodic limb movements in sleep, and sleep disturbance.

Pathophysiologic concepts for RLS include dysfunction of the dopaminergic system based on clinical observation and response to dopamine and dopamine agonists. RLS symptoms may be prevalent in PD; however, an etiologic link has not been shown. Unlike PD, RLS is not a degenerative disorder and there is little evidence of degeneration of dopaminergic neurons, although neuroimaging shows a subtle functional impairment of the dopaminergic system with reduced dopamine binding in the caudate and putamen. Although extrapyramidal features have been described in POLG1 mutations, moreover, an association with RLS has yet to be reported.

The patient we describe has an unusual presentation of a commonly occurring syndrome, RLS, and extends the ever-evolving spectrum of clinical phenotypes attributable to mutation of the POLG1 gene.

REFERENCES

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Child Neurology:
Dravet syndrome
When to suspect the diagnosis

John J. Millichap, MD
Sook-young Koh, MD, PhD
Linda C. Laux, MD
Douglas R. Nordli, Jr., MD

Address correspondence and reprint requests to Dr. John J. Millichap, Division of Neurology, Children’s Memorial Hospital, 2300 Children’s Plaza, Box 51, Chicago, IL 60614 jmillichap@childrensmemorial.org

ABSTRACT
Dravet syndrome (DS), previously known as severe myoclonic epilepsy in infancy (SMEI), is an epileptic encephalopathy that presents with prolonged seizures in the first year of life. The seizures often occur with fever or illness, and are frequently initially categorized as febrile seizures. The correct diagnosis of DS and appropriate follow-up are typically delayed. The EEG is normal at onset, and neuroimaging reveals no structural lesion. Early development is normal, but signs of regression appear in the second year of life and are often accompanied by compulsive status epilepticus, alternating hemiconvulsions, and myoclonic seizures. Diagnosis can be confirmed by genetic testing that is now available, and shows mutations within the SCN1A gene. Early recognition and diagnosis of DS and management with appropriate anticonvulsants and treatment plan may reduce the seizure burden and improve long-term developmental outcome. Neurology® 2009; 73:e59-e62

GLOSSARY
BME = benign myoclonic epilepsy; DS = Dravet syndrome; ED = epileptiform discharges; FS = febrile seizures; ILAE = International League Against Epilepsy; LGS = Lennox-Gastaut syndrome; MAE = myoclonic-astatic epilepsy; SIMFE = severe infantile multifocal epilepsy; SMEB = borderline severe myoclonic epilepsy; SMEI = severe myoclonic epilepsy in infancy.

Severe myoclonic epilepsy in infancy (SMEI) was first described by Dravet in 1982 and was added to the International League Against Epilepsy (ILAE) classification in 1989. Dravet syndrome (DS), proposed in the 2001 ILAE report, encompassed SMEI and “borderline” SMEI (SMEB). SMEB represents SMEI with less frequent seizures and atypical features. The discovery of associated specific mutations within the SCN1A gene, in 2001, sparked an interest in DS among pediatric epileptologists. Outside specialty circles, however, DS remains relatively unknown. This review should increase the index of suspicion for DS among neurologists in training and practitioners.

CLINICAL CASE
An 8-month-old girl presented with a right-sided hemiconvulsion without alteration of consciousness for 40 minutes. She was previously healthy, except for recent symptoms of upper respiratory infection. She was born as twin B at 37 weeks’ gestation without complications. Her family history was remarkable for a maternal cousin with benign childhood occipital epilepsy. There was no fever, and general and neurologic examinations were normal. Results of serum studies, brain MRI, and routine EEG were normal. The parents were counseled regarding status epilepticus and rectal diazepam prescribed.

At age 11 months, she had a right-sided hemiconvulsion for 22 minutes refractory to rectal diazepam. Days later, she had a prolonged left-sided hemiconvulsion, followed by Todd paralysis. Levetiracetam was initiated. Alternating hemiconvulsions or generalized convulsions occurred 1 to 2 per month despite escalating doses of the anticonvulsant. Triggers for seizures included fever, illness, vaccinations, sleep deprivation, and missed medication doses. Overnight video EEG monitoring at age 13 months revealed polymorphic right-sided frontal-central spikes maximal during sleep, and asymmetry of the posterior dominant rhythm. At age 18 months, she presented in status epilepticus refractory to 2 doses of rectal diazepam and fosphenytoin. Valproic acid was added. At age 2 years, she has normal development and neurologic examination and has not

From the Division of Neurology (J.J.M.) and Epilepsy Center (S.K.; L.C.L.; D.R.N.), Children’s Memorial Hospital, Northwestern University Medical School, Chicago, IL.

Disclosure: Author disclosures are provided at the end of the article.
Table: Differential diagnosis of Dravet syndrome

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>DS</th>
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DS = Dravet syndrome; FS = febrile seizures; SIMFE = severe infantile multifocal epilepsy; BME = benign myoclonic epilepsy; LGS = Lennox–Gastaut syndrome; MAE = myoclonic atactic epilepsy; ED = epileptiform discharges; + = usually present; +/− = maybe present; − = usually absent.

Discussed: Epidemiology. DS is found in 1 per 20,000 to 1 per 40,000 members of the population, with a male-to-female ratio of 2 to 1. Three percent to 8% of patients with their first seizure before age 1 year have DS.

Clinical characteristics. Diagnosis is based on age at onset, seizure types, and clinical course. Seizures begin in the first year of life in all cases, followed by a variable course that includes different seizure types, developmental regression, and seizure intractability. Certain typical features are required for DS, whereas other manifestations are more variable, leading to the expansion of the syndrome to include SMEB.1–5

The first seizure occurs at 5 to 6 months of age, with a range of 2 to 10 months, and is characterized by a generalized or unilateral convulsion.1–3 Early seizures are typically prolonged and associated with fever or infection. By age 2 years, polymorphic seizure semiology emerges and may include focal and generalized myoclonus, atypical absence, complex partial (atonic, automatisms), and “obtundation status.” Obtundation status is a special seizure type in DS and consists of subjective alteration of consciousness with reduced postural tone and myoclonic jerks. Seizure triggers include fever, infectious illness, increased body temperature (e.g., hot bath water), and photic or pattern stimulation.3–5

Development is always normal at onset, with a plateau and progressive decline between 1 and 4 years of age, typically in the second year of life.7 The degree of neurobehavioral impairment is reported to range from minor learning difficulty to global developmental delay.8 Patients with SMEB have a slightly better developmental outcome.5 Ataxia and increased reflexes are sometimes found, but their presence is not necessary for diagnosis.3

Genetics. Family history of epilepsy or febrile seizures is reported in approximately 25% of cases.3 Mutations within the gene for the α subunit of the spike and wave on EEG. MAE may have an onset similar to DS but is differentiated by the eventual presence of drop attacks.1,3 SCN1A mutations can be present in these epileptic encephalopathies.4

Given this clinical course, DS was suspected, and DNA sequence analysis of the SCN1A gene showed a de novo (parental testing negative) frameshift mutation (deletion GTTT at nucleotide position 5010–5013 at codon 1670) that is previously reported with the classic SMEI phenotype.6 The lack of myoclonic seizures or multifocal epileptiform discharges suggests that our patient’s condition is best classified as a borderline variant of DS, previously known as SMEB.3–5

Differential diagnosis. The first episode of convulsive focal status epilepticus in an otherwise normal infant with normal neuroimaging has many potential etiologies. Children with DS are frequently initially diagnosed with febrile seizures or febrile status epilepticus.1,3 Focal epilepsy due to an occult structural lesion should be excluded by serial neuroimaging. Subsequent alternating hemiconvulsions make a structural lesion improbable in our patient. Progressive myoclonic epilepsies due to metabolic disorders, such as neuronal ceroid lipofuscinosis, are excluded by the absence of typical clinical features.1–3 Family history of benign childhood occipital epilepsy in our patient supported the initial diagnosis of diaphasic focal epilepsy at presentation.

The differential diagnosis of DS includes severe infantile multifocal epilepsy (SIMFE), benign myoclonic epilepsy (BME), Lennox–Gastaut syndrome (LGS), and myoclonic-atatic epilepsy (MAE).1–3 (table) SIMFE is a severe variant of cryptogenic focal epilepsy, not listed by ILAE, with onset in the first year of life, multiple seizure types including complex partial and hemiconvulsive, and multifocal epileptiform discharges. Unlike DS, SIMFE does not exhibit myoclonic seizures, absence seizures, or generalized epileptiform discharges. Developmental regression has a later onset, but with the same poor long-term outcome.4 Our patient has characteristics of SIMFE. BME is excluded by the presence of other seizure types and an abnormal EEG. LGS has a later onset, seizures that are more tonic and atonic, and slow
voltage-gated sodium channel 1.1, SCN1A, are found in 67% to 86% of patients from larger studies with DS (SMEI and SMEB) and 5% to 11.5% of those with generalized epilepsy with febrile seizures plus.3,4,7,8 In a recent report of 359 different SCN1A mutations, DS was the most common (86%) associated phenotype.3 Mutations are found with other epilepsies, nonepileptic disorders, and febrile seizures.4,9 SMEI is sometimes considered the severe form of a continuous spectrum associated with the SCN1A.4,6 Mutations found in classic SMEI patients were previously reported with a cryptogenic focal epilepsy phenotype.4,7 Most mutations occur de novo, but inherited cases and parental mosaicism are also described.3,4,6,7 Because approximately 20% of DS patients do not have a detectable SCN1A mutation, the significance of mutations in other genes will need to be determined.3,7,9,10

Pathogenesis. The voltage-gated sodium channel is responsible for the initiation of action potentials and, therefore, is involved in neuronal excitability.5,6,7,9,10 The α subunit has 4 homologous domains, with 6 transmembrane segments each, that form the voltage sensor and ion-conducting pore.10 Mutations cause either a gain or a loss of function. Initially, researchers could not explain how loss-of-function mutations could lead to seizures. A mouse model of DS showed selective loss of sodium current in the hippocampal γ-aminobutyric acid–mediated inhibitory interneurons. Failure of inhibition leading to excitation is a proposed pathogenesis of this mutation in DS.10

Diagnosis. The clinical diagnosis is supported by EEG, neuroimaging, and SCN1A mutation.5 EEG is typically normal at onset, but often progresses to generalized spike-and-wave discharges. Like the seizure semiology, a variety of interictal EEG findings is more common.1,3,5,6,8 Some patients may have persistently normal interictal records.3 Neuroimaging is normal. In the United States, testing for SCN1A is commercially available. Athena Diagnostics Inc. (Worcester, MA) offers DNA sequencing to detect mutations within the coding regions and multiplex ligation-dependent probe amplification to uncover genomic deletions/duplications. Transgenic Molecular Laboratory (Omaha, NE) scans for mutations with denaturing high-performance liquid chromatography, and then abnormal profiles are subjected to DNA sequencing. Parents are tested to establish inheritance and clinical significance.

Treatment. Intractable seizures are a hallmark of DS. Experience with carbamazepine and lamotrigine in DS show exacerbation of seizures and should be avoided.3 Efficacy of other anticonvulsants is variable. Valproate and topiramate are the most promising agents available in the United States; levetiracetam is also used.3,4 In Europe, stiripentol, an inhibitor of cytochrome P450, is added to the combination of valproate and clobazam and is particularly effective against status epilepticus.5 Ketogenic diet is another option.3,8

Counseling regarding avoidance of triggers is very important. Preventive measures include avoiding hot baths or using cooling vests in hot weather if hyperthermia sensitive, or wearing sunglasses if photosensitive. Emergency benzodiazepine should be used in the home to prevent status epilepticus. Resources for parents are available from the International Dravet syndrome Epilepsy Action League (www.idea-league.org).

Prognosis. Outcome is poor and, after 4 years of age, patients usually reach a steady state of intractable seizures, intellectual impairment, behavioral disorders, and neurologic abnormalities. Myoclonic seizures usually cease and are replaced with nocturnal generalized clonic or absence seizures.3 The number of seizures is a risk factor for the degree of developmental regression. The mortality rate is approximately 16% and is related to prolonged convulsive seizures, drowning, and sudden unexpected death.5

CONCLUSIONS DS is a severe epileptic encephalopathy that is difficult to recognize at the time of onset. Early recognition and diagnosis of DS and management with appropriate anticonvulsants and treatment plan may reduce the seizure burden and improve long-term developmental outcome. The diagnosis should also be considered in adults with infantile-onset refractory epilepsy, by reevaluation of childhood history and SCN1A testing.

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REFERENCES
The Resident and Fellow Section is a primarily online feature that serves the resident and fellow readership. Residents and fellows are expected to be the primary authors for most submissions, but those highly involved in graduate medical education (e.g., program directors) may also contribute submissions on appropriate topics. Submissions for all article categories should be no more than 2,500 words; permission for longer articles will be needed from the editors. The number of references should be 10 or less and one to two tables or figures may be incorporated. The topic must be mentioned in the cover letter of the submission. Potential article topics include: teaching, ethics, practice, career choices, residency training, editorial, international education, research, historical, opinion, book review, training videos, or teaching NeuroImages. Teaching NeuroImages has the same requirements as NeuroImages but is especially valuable to the trainee audience and will be published in the online Resident and Fellow Section. A number of new categories were added in 2007. Queries and comments should be addressed to Mitchell Elkind, MD, MS, FAAN, or Kathy Pieper at kpieper@neurology.org.
Child Neurology: Autism as a model
Considerations for advanced training in behavioral child neurology

ABSTRACT
In this article, we advocate for advanced training for child neurologists in behavior and development in order to facilitate the investigation of childhood behavioral and neurodevelopmental disabilities, with autism serving as a model disorder. We explore the current training options and then propose alternative subspecialty training options that focus on behavior and development, with appreciation that most developmental disabilities are not static encephalopathies but, rather, dynamic processes representing the influence of genetics and environment on neural circuitry.

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Both the incidence and recognition of developmental disabilities are growing, with an estimated 9 million children and adolescents affected with autism spectrum disorders, global developmental delay, or mental retardation.1 Due in large part to increased awareness and earlier diagnosis, the incidence of autism has risen substantially in the past decade, with current estimates being 1 in 150 children.2 As evidenced by the increase in NIH funding and media coverage, autism has become a major public health issue. Extensive efforts are being made to understand its neurobiology in order to create informed therapies.

As a new generation of child neurologists is trained, the autism field is turning heavily toward advanced neuroimaging and genetics. Such technological advances, while invaluable, must be matched with sophisticated phenotyping grounded in behavior and development. We submit that well-trained child neurologists with a solid foundation in behavioral neurology would be well-equipped to develop this type of rigorous phenotyping. Coupling clinical observation with an understanding of functional neuroanatomy, behavior, and normal brain development, child neurologists could define phenotypes informed by functional neural networks, which, in turn, would enable us to design effective therapies for these children.

In this article, we advocate for advanced training for child neurologists in behavioral child neurology in order to facilitate the investigation of childhood behavioral and developmental disabilities, with autism serving as a model disorder.

BACKGROUND: THE NEUROLOGY OF AUTISM The concept of approaching autism from a neurologic perspective is by no means a novel one. In the 1970s, Damasio and Maurer3 took a traditional, lesion-based approach in their analysis of the behavioral and motor disturbances in children with autism. Based on their observations, they wrote a seminal paper in Archives of Neurology entitled “A neurological model for childhood autism.”

An elegant example of their approach lies in their account of the motor disturbances, characterized as “dystonia, bradykinesia and hyperkinesias and involuntary movements,” many of which, they concluded, seemed rooted in the striatum and its connections to the frontal lobe. They provided critical observation that the areas affected “constitute the entire area of termination of the dopaminergic neurons arising in the mesencephalon.”4
Since the localization efforts of Maurer and Damasio, several clinicians and scientists have investigated autism from a child neurology perspective. Through their work, and that of their contemporaries, we have learned much more about the neurologic comorbidities of autism, such as epilepsy, and have better defined autistic regression as distinguished from Landau-Kleffner syndrome. We also have learned that several neurologic disorders are associated with a higher incidence of autism, such as tuberous sclerosis complex and fragile X.4 and that behavioral syndromes, such as obsessive compulsive disorder and attention deficit hyperactivity disorder, occur at higher rates in children with autism.5 Since 2000, 30 original articles about autism have been published in *Neurology*, and over 200 in the *Journal of Child Neurology and Pediatric Neurology*.

**LOOKING TO THE FUTURE** Clearly, the precedent has been set for child neurologists to take initiative in the investigation and care of autism spectrum disorders, but our training must expand upon these efforts. We propose 3 areas of investigation in which child neurologists can make contributions to this field: 1) creation of neurologically based endophenotypes; 2) analysis of early behavioral markers that precede a formal diagnosis; and 3) understanding of the developmental trajectory of autism, focusing on late sequelae.

Several examples of neurologic endophenotypes can be given. First, neuropathologic and imaging studies have indicated abnormalities in cerebellar volume and structure in children with autism.6 In this subgroup, one could ask whether there is evidence of hypotonia, ataxia, or speech impairments attributable to cerebellar circuits. Second, per Maurer and Damasio, one could ask whether children with more prominent movement disorders show evidence of abnormalities in dorsal striatal circuitry as visualized in functional or structural imaging. Perhaps dopamine receptor or transporter genes show mutations that could further refine this clinical profile. Finally, one could ask whether children with autism with specific EEG abnormalities share a common behavioral phenotype, thereby providing insight into common aberrant neural circuitry.

The 2 other areas of investigation (early markers and late sequelae) speak to the importance of understanding autism from a developmental perspective. Autism is not a static encephalopathy, but, rather, a dynamic process that begins in early brain development and continues throughout childhood and possibly later. Observational studies reveal that children with autism can exhibit deficits in social interaction, language, and motor skills in the first year of life, well before a formal diagnosis is made.7 Adults with autism often cannot live or work independently, and have a high rate of comorbid psychiatric and behavioral disorders. Furthermore, early childhood language ability is an important predictor of independent functioning in adults with autism.8 This dynamic process is substantiated by studies showing dysregulation of brain growth based on head circumference measurements in children with autism.9

Child neurologists who can understand behavior in the context of development can investigate autism across a lifetime, from early infancy into adulthood. Through this process, one could ask questions about early precursors of autism, predictors of specific phenotypes, and association of early behavioral and neural markers with late life prognosis. This approach could facilitate the creation of interventions that might modify the developmental progression of autism.

We are using autism as a model disorder, but these suggestions could easily be applied to other, later-onset neurobehavioral disorders, such as schizophrenia, in which early childhood behavioral or cognitive markers may exist.

**CURRENT TRAINING OPTIONS** Currently, child neurology training consists of 2 years of general pediatrics, 1 year of adult neurology, and 2 years of child neurology. There is a required elective in child and adolescent psychiatry, and most programs offer electives in neuropathology and neuroimaging. While residents gain some exposure to behavioral disorders through outpatient clinics and didactics, there is no formal training in behavioral disorders, psychopathology, or development. In order to gain formal advanced training in behavioral disorders, child neurologists must pursue a fellowship in adult behavioral neurology, for which there is an American Board of Psychiatry and Neurology (ABPN) board certification.

There also exists an accredited Neurodevelopmental Disabilities (NDD) residency which focuses on the longitudinal management of patients with neurodevelopmental disorders. This 6-year residency program was created through joint efforts of the American Board of Pediatrics and the ABPN and consists of 2 years of pediatrics, 1 year of adult neurology, 18 months of clinical child neurology and developmental disabilities, and 18 months of “clinical and basic science” including electives in child psychiatry, neurosurgery, neuropsychiatry, and dedicated research time. Residents are eligible for certification in Pediatrics, Neurology with Special Competence in Child Neurology, and Neurodevelopmental Disabilities.10 This training is limited to 7 established NDD programs across the country (www.aacme.org).
PROPOSAL FOR TRAINING  We envision 2 viable options for training in behavior and development. The ABPN currently provides no mechanism for child neurologists to integrate into the NDD training. Therefore, one advanced training option would be to allow those who have completed their child neurology residency to spend 12–18 months in an NDD program completing its training requirements, with focus on research and clinical electives relevant to developmental and behavioral disorders. This option would be particularly relevant for those who decide to pursue this area of interest after beginning child neurology training. These neurologists could sit for both Neurology and NDD boards.

An alternative option would be to create an accredited fellowship in behavioral child neurology, ultimately with board certification. A 1-year fellowship in behavioral child neurology would include a clinical, didactic, and research component, promoting the understanding of behavior from a developmental perspective. Clinical focus would be placed on children with behavioral and developmental disabilities. As with NDD training, fellows would be given clinical instruction in advanced neuropsychological assessments. Didactics would include lectures on normal child development, psychopathology, childhood behavioral disorders, and psychopharmacology. Advanced instruction in neuroimaging, electrophysiology, or genetics would be provided based on an individual’s interests.

Both of these training options would differ from the Developmental Behavioral Pediatric fellowship training, as the latter is a pediatrics subspecialty not focused on neurology or neuroscience. Some of the behavioral issues emphasized in the DBP training, such as encopresis and attachment disorders, are not basic to neurology training and would not be a focus in our proposed training paths.

Finally, we emphasize that all child neurology trainees would benefit from some additional training in neurodevelopmental disorders, particularly as these disorders become more widely recognized and diagnosed. Our proposed training options would provide added benefits to all child neurology residents because of stronger available clinical programs and faculty involvement in development and behavioral child neurology programs.

CONCLUSION  It is time for child neurologists to make scientific contributions to this growing field of neurobehavioral and developmental disorders, with rigorous training opportunities to be able to do so. Armed with knowledge of development, behavior, and clinical neurology, behavioral child neurologists and their NDD counterparts can make innovative, clinically relevant contributions to the assessment and care of children with developmental disabilities and, in the process, regain expertise in the neurology of behavior.

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REFERENCES
PEARLS AND OY-STERS

Pearls and Oy-sters focuses on fundamental clinical neurology. Each article should address a specific niche of neurologic 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 neurologic disease, such as localization, elaboration of a differential diagnosis, evaluation, or treatment. The article should 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:
The orbital bruit
A poor man’s angiogram

CLINICAL PEARLS

1. An orbital bruit represents increased blood flow through the collateral arterial system and intracranial arterial supply. In the correct clinical context, the presence of an orbital bruit should make the examiner suspect either a severe stenosis or occlusion of either the ipsilateral or the contralateral internal carotid artery (ICA).

2. Orbital bruits can represent compensated perfusion to the contralateral hemisphere. This occurs as flow velocity increases through the ipsilateral ICA and through the anterior communicating artery. Thus, blood flow moves from the asymptomatic side to the occluded vascular territory.

3. When listening for an orbital bruit, auscultate by placing the bell of the stethoscope over the patient’s closed eye. In an effort to eliminate the noise of rhythmic eyelid flutter, the patient should then be instructed to open both eyes and gaze at a point across the room. If necessary, the eyelid can be passively shut using the bell of the stethoscope.

4. Although not featured on many popular stethoscopes, a deep and narrow bell (i.e., the Ford-Bowles stethoscope) is ideal for the purpose of ocular and arterial auscultation.

CLINICAL OY-STERS Orbital bruits are also found in systemic illness (severe anemia, thyrotoxicosis) and vascular anomaly (carotid-cavernous fistula, arterial vascular malformation).

CASE REPORT An 83-year-old right-handed man presented with increasing episodes of right limb shaking over a 9-month period. Each episode lasted several minutes and was brought on by both exertion and orthostatic intolerance. Medical history was significant for metabolic syndrome complicated by coronary artery disease and dialysis-dependent end-stage renal disease. One month prior to presentation, these limb-shaking episodes increased in frequency and were also noted during dialysis. Over this same time interval, routine blood pressure assessment revealed a decrease of 10 to 20 mm Hg in systolic pressure.

At presentation, he was diagnosed with probable limb-shaking transient ischemic attacks. While his neurologic examination was essentially unremarkable, cerebrovascular examination identified a high-pitched systolic left cervical bruit at the level of the carotid bifurcation, and a right orbital bruit. MRI did not demonstrate any acute or chronic infarcts. Carotid ultrasound revealed high-grade left internal carotid artery (ICA) stenosis. Cerebral angiogram demonstrated an estimated 95% focal, short-segment stenosis with calcifications at the left carotid bifurcation (figure A). Collateralization to the left anterior and middle cerebral arteries was provided by flow through the anterior communicating artery, in addition to collateral flow from the left external carotid artery (ECA) (figure 1B and C). The latter results were anticipated on the basis of the cerebrovascular examination.

DISCUSSION In 1928, Harvey Cushing referred to cephalic auscultation as a “forgotten practice,” commenting that it was “the one thing most likely to be neglected in a routine neurologic examination.” Utilizing the bell of the stethoscope, proper auscultation of the skull involves listening to the orbits, frontal region, temporal region (including the mastoid process), and atlanto-occipital region. Generally speaking, bruits are a consequence of increased blood velocity or turbulence, and result from a spectrum of both benign and pathologic conditions. As described by C. Miller Fisher in 1957, the physical finding of an orbital bruit can sometimes provide evidence for the presence of contralateral internal carotid occlusion or stenosis. In our patient, the presence of an orbital bruit provided valuable clinical information regarding collateralization, carotid occlusion, and a robust anterior cerebral circulation.

Collateralization is an important process in stroke physiology, and can influence both ischemic localization and size of infarct. Regarding collateralization
Cerebral angiogram findings in a patient with an orbital bruit

Left carotid angiogram (A) reveals high grade, short segment carotid stenosis (white arrow) at the bifurcation. Left carotid angiogram (B) demonstrates retrograde flow across the ophthalmic artery (white arrow) to the supraclinoid internal carotid artery from the left external carotid artery (black arrow). Cerebral angiogram performed from the right carotid artery (C) shows collateral filling of the left anterior and middle cerebral arteries (white arrow).

and intracerebral blood flow, primary collateralization results from an acute vascular occlusion, while secondary collateralization develops over longer periods of time. In primary collateralization, blood flow redistribution occurs primarily within the circle of Willis. Secondary collateralization can occur via both leptomeningeal collaterals and external carotid arterial flow. Compensatory ECA flow occurs in a retrograde manner via the ophthalmic artery.

Compensatory increased flow through the nonoccluded carotid may account for the bruit occurring over the eyeball contralateral to the stenosis. However, carotid siphon stenosis ipsilateral to the ocular bruit has also been demonstrated to be a very common occurrence. With this in mind, the finding of a unilateral carotid bruit or a lateralizing neurologic deficit can further aid in the interpretation of an ocular bruit. Importantly, the significance of a carotid bruit can be judged by the findings of increasing focality and duration, along with a higher pitch.

An additional clinical sign of increased ophthalmic arterial flow is the presence of dilated episcleral arteries, which have been reported as a manifestation of secondary collateralization from progressive ICA stenosis. Palpation of the branches of the facial artery can be useful in assessing a hyperdynamic external carotid system ipsilateral to a high-grade ICA lesion. However, common carotid disease will result in decreased pulsations ipsilateral to the lesion. Several branches may be palpated, including the angular arteries on the sides of the nose, and the superficial temporal arteries, anterior to the tragus. Retrograde ophthalmic artery flow may be inferred by a loss of the supraborital pulsation upon compression of the superficial temporal artery, as ophthalmic arterial flow is dependent on ECA flow through the superficial temporal artery. Retrograde supraorbital arterial flow may also be demonstrated by ultrasound Doppler, which can be a useful extension of the bedside examination.

In this patient, the presence of orbital bruits informed the examiner of both vascular disease and compensatory collateralization. The patient’s severe carotid stenosis manifested clinically as limb-shaking transient ischemic attacks. The history and neurovascular examination guided the diagnostic evaluation strongly away from a pursuit off ocular motor seizures and toward a vascular etiology.

If multifocal cranial bruits are identified, the examiner should consider additional diagnoses. For instance, hyperdynamic states such as thyrotoxicosis and anemia, in addition to structural lesions, such as an arteriovenous fistula or carotid-cavernous sinus fistula, may also be identified by an ocular bruit. This again emphasizes the importance of a thorough history and physical examination.

DISCLOSURE
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REFERENCES
EMERGING SUBSPECIALTIES IN NEUROLOGY

These manuscripts will review the history and development of emerging subspecialties in neurology, including fields such as Pain Medicine, Headache, Neurocritical Care, Interventional Neurology, and others. The focus should be on educating residents with a possible interest in this subspecialty. Those interested in writing these manuscripts should contact the Resident and Fellow Section Editor before submission to inquire about the need for an article on a particular topic.
Emerging Subspecialties in Neurology: Neuro-oncology
A developing subspecialty with many opportunities

NEURO-ONCOLOGY: EXCITING OPPORTUNITIES

Neuro-oncology is a unique, developing neurologic subspecialty that combines many aspects of neurology with those of cancer biology. The neuro-oncologist is expert in both the diagnosis and management of primary brain tumors and neurologic complications of cancer. A career in neuro-oncology presents opportunities to utilize a multidisciplinary team approach and the application of cutting-edge technology toward patient treatment while providing compassionate patient care.

Neuro-oncology can trace its modern origins to the 1970s, when the first therapeutic trials were begun. The treatment and management of primary brain tumors is now a rapidly evolving field. The World Health Organization recognizes approximately 100 different types of primary and secondary brain tumors. Glioblastoma, which is the most common and aggressive type of primary brain tumor, has an incidence of 4 to 5 cases per 100,000. For patients with glioblastoma, life expectancies are measured in months rather than years, with median survival after diagnosis of only 12 to 14 months. In the past, surgical resection and radiation therapy were the main treatment options offered to these patients. In the last several years, studies have shown that chemotherapy provides a significant clinical benefit for patients with malignant brain tumors. More recently, molecular markers that predict response to treatment are beginning to be identified in glioblastoma. Clinical trials that incorporate biologic endpoints and correlative studies are improving our understanding of the mechanisms of disease and tumor response to treatment. This greater knowledge will lead to the development of more effective agents and individualized treatments based on specific tumor profiles. In addition to glioblastoma, the neuro-oncologist manages less common tumors, including other types of glioma, germ cell tumors, meningiomas, medulloblastomas, and primary CNS lymphomas, and becomes familiar with the cancers’ different biologic and molecular profiles, and treatment approaches. Despite the often poor prognosis of patients with brain and spinal tumors, long-term successes are possible. Patient care focuses not only on improving survival but also on preserving quality of life for these patients and providing support for their families.

The neuro-oncologist also specializes in the care of patients with challenging neurologic complications associated with systemic cancers. A common complication of systemic cancer is metastasis to the brain. It is the most common type of brain tumor, with up to 170,000 cases a year in the United States. The neuro-oncologist is proficient in the management of seizures, cerebral edema, stroke, peripheral nerve disorders, and demyelinating disease, which often present unique diagnostic dilemmas and require complex management decisions in patients with cancer. Altered mental status is a common reason for neurologic consultation, and hospitalized patients with cancer usually have multiple causes of delirium, which requires a detailed history and neurologic examination to determine the accurate diagnosis.

Neuro-oncologists sharpen their skills in lesion localization by observing neurologic deficits in the presurgical and postsurgical setting. This acumen is also vitally important in identifying the early signs and symptoms of spinal and leptomeningeal metastasis. Radiation therapy and chemotherapy can produce a variety of complications involving the nervous system, including strokes, seizures, demyelination, and focal necrosis. The challenging and complex nature of patient care makes neuro-oncology an interesting and exciting subspecialty.

Neuro-oncologists play a unique role by coordinating the care of each patient in collaboration with a wide variety of specialists, including neurosurgeons, radiation oncologists, neuropathologists, psychiatrists, and rehabilitation physicians. In this role, the neuro-oncologist has broad knowledge of these other specialties and the role they play in patient management. In academic settings, tumor boards are a core teaching venue and foster camaraderie and collaboration between neuro-oncologists and other subspecialty groups in an effort to develop...
optimal treatment plans for individual patients. Additionally, neuro-oncologists work closely with medical oncologists in coordinating care of patients with systemic cancers and brain metastases. Advances in neuro-oncology will require teamwork among clinicians and clinical and translational research programs so that the expertise from the myriad offshoots involved can be integrated into the development of cohesive patient-oriented treatment plans. Opportunities exist for neuro-oncologists to collaborate with other physicians on cooperative cancer group and multi-institutional clinical trials. Effective communication skills are essential in neuro-oncology, especially because this neurologic subspecialty includes the discussion of complex medical issues and terminal diagnoses.

**ADVANCES IN NEURO-ONCOLOGY** With the explosion of our understanding of the molecular biology of cancer, neuro-oncology offers numerous opportunities for clinician-scientists to participate in the development and clinical testing of novel molecularly targeted agents. Glioblastoma is likely a heterogeneous disease, and thus not all types should be treated uniformly. With the proper training, a neuro-oncologist can utilize tools from cellular and molecular biology to design and evaluate the next generation of clinical trials. In the future, neuro-oncologists will integrate newly identified molecular biomarkers into clinical trials in an effort to develop individualized patient treatments. Biologic agents targeting proangiogenic factors, such as the vascular endothelial growth factor, and kinases, such as Src, epidermal growth factor receptor, and PI3 kinase, are promising treatment options as adjuncts to cytotoxic chemotherapies. The future holds promise that one day the molecular profile of a patient’s tumor may predict tumor response to therapy and guide management decisions. The Cancer Genome Atlas project (http://cancergenome.nih.gov) is systematically exploring the genomic changes involved in selected human cancers including glioblastoma, and the information it provides on molecular derangements in glioblastoma may be used to discover new targets for therapy. Neuro-oncologists will spearhead the future integration of these molecular discoveries into clinical trials in the effort to develop more effective treatments for brain tumors.

Another rapidly developing area of focus in neuro-oncology is the use of noninvasive methods of detecting tumor proliferation, invasion, and angiogenesis within the brain. Dynamic contrast-enhanced MRI, which can assess aspects of the tumor vasculature, and PET, which can be used to evaluate tumor proliferation, hypoxia, and metabolism, are two of the many exciting advances in neuroradiology that may help change the way in which patients with gliomas are treated in the future. Functional MRI studies such as blood oxygenation level-dependent MRI and intraoperative MRI allow the neurosurgeon to precisely excise brain tumors with minimal injury to normal brain tissue, helping to maximize surgical resection and patient outcome while simultaneously preventing devastating neurologic sequelae. In the future, neurogeneticists and epidemiologists will assist in the determination of a patient’s pharmacogenetic profile to predict response to, and toxicity from, specific treatments. Neuro-oncology is based on a multidisciplinary approach that seeks to incorporate these novel technologies, making it an exciting and rapidly evolving field.

**TRAINING OPPORTUNITIES IN NEURO-ONCOLOGY** At the resident level, there are several ways to gain exposure to neuro-oncology. If a neuro-oncology service exists in the resident’s neurology department, then one could easily spend time with that service. However, some neurology departments may not have such a service. The interested resident could do an away rotation at an outside institution with a neuro-oncology service. Alternatively, the American Academy of Neurology (AAN) offers the Consortium of Neurology Residents and Fellows Mentorship Program, which allows one-on-one guidance and counseling to trainees interested in subspecialties such as neuro-oncology (http://www.aan.com/education/mentors/).

Neuro-oncology offers multiple training opportunities for fellows to prepare for a career in either clinical practice or academic neuro-oncology. Pediatric and adult neurologists, as well as medical oncologists, may choose to subspecialize in neuro-oncology by completing various training programs. The Society for Neuro-oncology lists almost 300 neurology-trained, about 100 medical oncology-trained, and slightly greater than 100 pediatrics-trained physicians in its membership. One- and 2-year programs offer specialized training in the management of primary brain tumors, brain metastasis, and the neurologic complications of systemic cancers. Typically, in the first year of a 2-year program, the candidate is dedicated to clinical neuro-oncology training; however, in the second year, the candidate may pursue clinical or basic science research interests in conjunction with more independent patient care management training. Fellows also will become comfortable administering intrathecal chemotherapy via lumbar puncture or Ommaya reservoir and managing related complications. Core curriculum guidelines have been established by the United Council for Neurologic Subspecialties (UCNS), which recently established
an accreditation mechanism for neuro-oncology fellowship programs (http://www.ucns.org). The UCNS has also defined the eligibility criteria for subspecialty certification in neuro-oncology. Interested trainees can find listings of current fellowships on the AAN Web site (http://www.aan.com). Currently, more than 15 neuro-oncology training programs are listed in the AAN section on fellowship training programs (http://www.aan.com/education/fellowships/index.cfm), each offering one to four positions per year. Additional resources and information about the field of neuro-oncology can be found on the Society for Neuro-oncology Web site (http://www.socneuro-onc.org).

As with other neurology subspecialties, applicants should identify the training programs in neuro-oncology that are best suited to their particular interests. Some programs concentrate on preparing the fellow to practice clinical neuro-oncology, while others focus on training the fellow for a career in academics. Programs can provide specialized training in molecular and stem cell biology, novel targeted therapies, functional neuroimaging, biomarker development, and patient care research, which includes the areas of neurocognitive outcomes and quality of life. Other programs may provide additional training in pediatric oncology, radiation oncology, and palliative care. Combined training in multiple subspecialties will prepare the neuro-oncology trainee for the challenges frequently encountered in the field.

CAREER PROSPECTS IN NEURO-ONCOLOGY

Multiple career tracks are available to aspiring neuro-oncologists. Some neuro-oncologists choose a private clinical practice in a major metropolitan area, typically with some general or cancer neurology patients integrated into the practice. Given the relative rarity of primary brain tumors, neuro-oncology practice is not suited for rural areas. Many neuro-oncologists choose an academic setting because it provides a wide patient base, easy access to diverse CNS tumor subspecialties, and facile integration of clinical and translational as well as basic research. In addition to supporting basic research related to neuro-oncology, many academic centers provide numerous opportunities for neuro-oncologists to concentrate on clinical trial development and the translation of new ideas from the laboratory to the clinical setting. Opportunities exist to integrate electrophysiology expertise with a career in neuro-oncology. Intraoperative monitoring is frequently used in tumor surgeries of the brain and spine, and neuro-oncologists frequently utilize EEG and EMG/nerve conduction studies in the clinical evaluation and management of their patients. Additional procedures such as intrathecal administration of chemotherapy via lumbar puncture and Ommaya reservoir are frequently performed in the clinic for patients with leptomeningeal metastasis. Finally, one could consider employment in the biotechnology or pharmaceutical industry. Although there are no readily available data on jobs in industry, many medical oncologists and neurologists have had successful careers in this setting. Currently, there is a need for formally trained neuro-oncologists across the country; for example, at the time of this writing, 15 academic job listings were posted on the Society for Neuro-oncology Web site.

DISCUSSION

The future of neuro-oncology is promising and offers an exciting opportunity to advance the treatment of patients with brain tumors and neurologic complications of cancer. The goal to personalize cancer therapy based on an individual patient’s tumor drives research into the genetic and epigenetic factors that are important to tumor cell growth and survival and those that predict treatment response. Newer agents targeting growth factor signaling, angiogenesis, and cell cycle pathways are expanding treatment options for patients with brain tumors. Neuro-oncology provides an excellent opportunity to work as a neurologist with an expertise in oncology. Because of the small number of neuro-oncologists in the nation, they are a close-knit, collegial group, with many employment opportunities available to them. Subspecialization in neuro-oncology allows the neurologist to treat challenging diseases affecting the nervous system while simultaneously expanding the boundaries and defining the future of a young field.

REFERENCES

INTERNATIONAL ISSUES

More than 85 percent of the world’s population lives in low- and middle-income countries, where the burden of neurologic disease is the largest. Relatively little is known, however, about patients and practitioners of neurology in most countries. This section aims to explore international issues in neurology education. We welcome manuscripts describing international educational exchanges, personal rotations and experiences in low- and middle-income countries, and work by neurology trainees from around the globe. Descriptions of notable differences in training between countries are of interest. Inclusion of practical information regarding how interested residents might get involved in international programs would also be of use.
Standing at the top of Humayun’s Tomb (figure 1), I had a wonderful view over Delhi. It was the end of February. Spring had suddenly struck and the thermometer climbed. Kites in the hundreds rode the thermals and green parrots filled the air with their screeches. It was a peaceful scene of a building on which the Taj Mahal was modeled and is the final resting place of the 16th century Moghul ruler Humayun, who fell to his death while descending the steps of his library.

It was the perfect place to stand back, think about a fascinating month, and distance myself from a sense of being overwhelmed by sheer numbers of people, impressions, and contrasts.

A resident, halfway through my 3-year neurology residency, I had come to India to spend an elective rotation in neurology at the All India Institute of Medical Sciences in Delhi, known to the locals as AIIMS (figure 2). It is considered to be one of India’s finest government medical institutions, serving not only the citizens of a multi-million bustling metropolis but also those in search of a cure from all over India. Battling through the dust and traffic on my 1-hour drive to the hospital in the morning, I pass a daily repeating scene: small Suzuki Marutis jostling for space with motor scooters, cycle rickshaws, cyclists, pedestrians, and the occasional tractor or elephant; cows munching on rubbish in the middle of the road, the barber shaving a man at his roadside stand, throngs of small uniformed children on their way to school. A cyclist with a monkey perched calmly on the cycle rack, a man with a red turban on a scooter, a young lady balancing herself elegantly on the back and adjusting her flowing dress in the wind.

I would arrive to dozens of people, young and old, crouching in the dust in front of the hospital building, lying on pieces of cardboard, wrapped in woolen shawls, cotton wool in their ears to fend off the morning chill. Whole family scenes unfolded here: food was eaten from metal tiffin carriers, children were washed and wounds dressed, monkeys and stray dogs joining this organic melange.

Patients would come from all over India, perhaps as far as 3 days’ journey away, to seek help from an AIIMS doctor, revered as among the most knowledgeable and dedicated in the country. Our postgraduate education might be considered to be long but theirs is even longer: after medical school, a year’s internship, and 3 years in internal medicine, a specialty training position is awarded usually based on rankings in national examinations (AIIMS has a separate entrance examination). It is a highly competitive process and medical specialties, such as cardiology and radiology, I was told, were currently more sought after than surgical ones.

There were around a dozen residents spread over a 3-year program. Split into two teams and supervised by around 10 rotating attendings, they covered roughly 70 inpatients and 200 outpatients per day. The residents usually had 10- to 12-hour days and Saturday was considered a normal working day, as it seemed to be for most other professions in India. Overnight calls were split evenly between the residents, and usually a junior and a senior resident took calls together to cover the wards, new admissions, emergency room, and ward consultations. Communication was entirely by cell phone and pagers had been relegated to history.

On a bad call day, they might admit 10 patients, see up to 30 emergency room patients, and get another 20 consults in addition to attending their own ward rounds, teaching rounds, and outpatient clinic.

And all this with only one computer dedicated to the residents.

How do they do it, I wondered. Over the next few weeks, I had a chance to see and learn how they coped in a system so very different from what I was used to.

Being a government hospital, care is free, though tests and medications have to be paid for and procured by the patient.

Hardly anybody has health insurance and an interesting mix of schemes and offers has developed: there are government hospitals, essentially free but usually underfunded; private hospitals,
such as the Apollo hospital chain, whose marbled corridors cater to the local rich as well as international medical “tourists” (traveling from Kenya for cardiac bypass surgery or from the United Kingdom for a knee replacement); and then there are private clinics.

Most tend to prefer these smaller private clinics, found in plenty in all neighborhoods, advertising their services with gleaming white boards and neon colors. These small clinics might be run by a husband and wife team, have a few nurses, a dietician, perhaps a social worker and physical therapist, such as the clinic run by a couple I met who came from an entire medical family. Off the sisters, all were doctors married to doctors of a specialty complementary to theirs. 

Back at AIIMS, the waiting room is full. I barely manage to squeeze through roughly 200 people who fill the large atrium in front of the clinic corridors. They stand in lines, divided into old and new patients, and have to register before 10:30 AM so that their files can be pulled for the day’s clinic. Everybody seems preoccupied with their own worries and thoughts and despite the crowds there is a hushed silence.

There are two residents, in white coats, holding simultaneous reign over one small clinic room. It is still quite cold this morning but there are no provisions for heating. The paint is peeling from the walls in large strips and the tap drips a steady rhythm. There is a metal stretcher in one corner of the room, a blood pressure cuff, and a scale. The doctors sit on opposite sides of a table, stacks of notes between them.

The patients’ names are huddled into the waiting room, the cry taken up by all those waiting to try and spur the lucky next patient into the consultation room. A few patients just walk in without being asked, standing by the door patiently until they can catch the doctor’s eye to ask for a signature, a repeat prescription, or a consultation. With great concentration and gurso the two residents dive into their pile of notes and start seeing patients. There is no privacy. No curtain to hide the
wasted leg which one man reveals, dropping his trousers (he has wasted leg syndrome, a tropical form of anterior horn cell disease), or to conceal the depigmented lesions on another man’s torso (he has leprosy). Histories are taken in Hindi in front of a large audience of relatives, other patients, and drug reps, who keep coming into the room unsolicited. The notes are then written in English into the cardboard bound paper charts and communication among the doctors themselves is a curious mix of English and Hindi. They are kind to include me by translating snippets of the conversation into English.

A young woman, threatened with marriage by her parents, comes with difficulty walking but without objective neurologic deficits, and the mother confirms that she will have the girl married “as soon as she can walk again.”

A 22-year-old woman complains of sudden early morning jerking preceding generalized seizures: juvenile myoclonic epilepsy. She is started on valproate and can choose to come for follow-up on Tuesday, Thursday, or Saturday, the clinic days of this particular team.

A 27-year-old man comes with a first seizure; his neurologic examination is non-focal. He, like so many other patients, clutches an old plastic bag containing all his notes and a CT scan. This shows multiple small, calcified lesions with minimal edema. He has neurocysticercosis. The scan cost him around 200 rupees ($5 or about 2 days’ earnings for taxi drivers, such as mine). An MRI would cost around 2,000 rupees ($50), the IV contrast another 800 rupees.

There is no routine handwashing but there is alcohol hand rub in the room, which is used rarely.

The tea lady interrupts us and brings small paper cups filled with fragrant cardamon chai, which she carries in an old sugar box.

That day, we also see tuberculomas, more epilepsy, Parkinson disease, carpal tunnel syndrome, headache, conversion disorder, strokes, and intracranial abscess, but no brain tumor (these go directly to neurosurgery).

Occasionally, I partake in inpatient teaching rounds; they are quite an experience. Three attendings preside over case presentations and one resident gets picked to discuss the case and then has to answer a barrage of questions on the presumed pathophysiology, anatomy, differential diagnosis, and the merits and shortcomings of chosen investigations. If he fails to provide acceptable answers, the Socratic baton gets passed to the next victim. Perhaps this is not the most comfortable way off earning but it certainly seems to be effective.

On the wards, men and women share the same rooms. There are no curtains to pretend that there is even a modicum of privacy. Each patient has a relative by the bedside who helps with daily care, and goes to fetch any devices or medications which might be needed. Few medications are in stock on the ward, so if IV fluids or medications are required, the doctor hands the relative a piece of paper with the name of the desired medication and the relative then disappears, to return a few minutes later with the required goods, miraculously procured from the local bazaar. Although some medications might be expensive, most families will do their utmost to scrape together what they have to help.

We see meningococcal meningitis, subacute sclerosing panencephalitis, severe Parkinson disease, multisystem atrophy, tuberculous meningitis (sputum is not tested routinely to see whether there is lung tuberculosis), subacute stroke, varicella zoster encephalitis, and intracerebral hemorrhage with intraventricular extension. None of these patients is in the intensive care unit. They have a high dependency unit in which ventilated and nonventilated patients are monitored more closely. Only one bed has a monitor, but I see no pulse oximeter for the ventilated patients.

It is still light outside as I wander out of the hospital. Groups of huddled waiting patients are getting ready to spend another night in front of the hospital or to go and visit one of the saints that so many people in Delhi revere and seek help from in times of need. One such tomb, that of Nizamuddin, lies in a marble complex at the end of a winding street in the old town. A fascinating mix of people, religions, and classes rub shoulders there, among them some of my patients. Around this area, too, some of the traditional medicine doctors, practicing Unani medicine in the ancient Greek tradition or Ayurvedic medicine, are also found, but on this visit, I do not get a chance to see one in action. I only hear patients’ accounts who combine the advice of a traditional healer with that of the AIIMS doctor in an attempt to cover all bases.

I learned a lot during my Delhi medical travels: a lot of medicine and neurology, but also how doctors and patients cope in a very different medical system. These talented doctors could easily choose to work at higher paid institutions elsewhere. Instead they choose to dedicate themselves to caring for the underprivileged and often illiterate groups of society. Their rewards are a rich clinical experience: in numbers, in diagnoses, and in human encounters. This unique combination of efficiently delivered technology at reasonably affordable cost and dedicated physicians and health care workers is a great example of providing extraordinary care in extraordinarily challenging circumstances.

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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.
Right Brain: My first tPA

It is the ultimate rite of passage for the 21st century junior neurology resident: administering IV tissue plasminogen activator (tPA) for an acute ischemic stroke for the first time.

It was only a few months into residency, but the telephone number that glowed on my pager, accompanied by the repetitive shrill “beep,” had become an all-too-familiar experience. However, the dreaded “911” was affixed to the emergency department’s telephone extension, indicating a “stroke code,” and signifying that dinner would unceremoniously conclude—3 bites into my slice of cold pizza.

I ran to the emergency department (ED) and was given a brief history by the ED physician, who said, “This lady is in her 70s, is demented and living in a nursing home, and comes in with slurred speech and altered mental status that started an hour ago.” I was concerned but skeptical, unsure if this was truly an acute ischemic stroke worthy of that 911 suffix.

The IV lines were placed, the bloodwork was sent to the lab, and I helped push the patient in her stretcher to the CT scanner, introducing myself and taking a quick history along the way. She immediately told me her name, extending her right hand out to shake mine. This woman did not seem to have altered mental status. The nurse agreed with me. When I moved to the left side of her stretcher, however, she did not seem to respond to my questioning. “Aha,” I said to myself, knowing that the ED physician must have talked to the patient from the left side of her stretcher, as she had hemispatial neglect. I moved back to her right side, and took a history. She told me that she was eating dinner at her subacute nursing facility, a place that she actually didn’t mind so much, and suddenly had difficulty swallowing her food, speaking clearly, and holding up her fork with her left hand. The staff there attended to her quickly, and called 911.

As she told me the events of the evening rather eloquently, although obviously dysarthric, I knew that this was a person who could be helped. She told me that she was a great Scrabble player, and read the newspaper cover-to-cover daily. I asked her why she lived in such a facility, and she pointed to her knees. She was quite obese, and had had debilitating osteoarthritis for years.

After examining the patient, we discussed the risks and benefits of tPA, and she told me that she would only agree to it if her daughter also approved of the intervention. I complied with her request and made the phone call. Her daughter confirmed that her mother was quite intelligent, was a retired teacher, and that she would trust her to make the right decision.

I felt proud. This woman, mislabeled as “demented,” was truly enjoying her life despite her physical misfortunes. After dutifully calculating the National Institute of Health Stroke Scale score and confirming her lack of contraindications, I phoned the attending stroke physician on call. After a brief discussion, we agreed that giving tPA was the appropriate next step. However, he was unable to come to the ED prior to the infusion as he was involved with another neurologic emergency at a sister hospital.

As the infusion began, the patient and I stared wondrously at the tPA bottle, and were mutually optimistic. I sat down to write my note within eyesight of the patient, and as the infusion completed, I went to the neurology floor to write the admission orders. Before I was even able to reach the floor I received a frantic page from the ED, stating that the patient was being intubated. I ran down the 10 flights of stairs back to the ED, and from 50 feet away I could see that my patient’s lips, face, and eyelids were markedly swollen, although much better than 5 minutes prior, according to the ED attending physician. “She had an allergic reaction to the tPA, so we gave her IV diphenhydramine, methylprednisolone, and subcutaneous epinephrine, and had to intubate her to protect her airway.”

As we helped transfer the patient to the intensive care unit, I was quite distraught. Here I was, a fresh, relatively new, optimistic neurology resident, who had the best intentions. Had I done no harm? Appar-
ently not. I knew that tPA carried the uncommon but potential risk of angioedema, and that risk was magnified in patients taking angiotensin converting enzyme inhibitors; my patient was on lisinopril.¹

She recovered quite well, and was extubated the next morning. Neurologically she improved enough so that in the evening prior to her discharge, I walked into her room and witnessed a heartwarming experience: I found her playing Scrabble with her daughter, and she was trouncing her, with a smile on her face.

As a resident I gave tPA dozens of times, but as in other experiences in medicine or life, the first time may be the most memorable. For every patient eligible for tPA, I always remember that first patient, and aim to get everyone back to playing Scrabble.

REFERENCE


New Neurology® Resident & Fellow Website

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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: Bias and poor interrater reliability in evaluating the neurology clinical skills examination

ABSTRACT

Objective: The American Board of Psychiatry and Neurology (ABPN) has recently replaced the traditional, centralized oral examination with the locally administered Neurology Clinical Skills Examination (NEX). The ABPN postulated the experience with the NEX would be similar to the Mini-Clinical Evaluation Exercise, a reliable and valid assessment tool. The reliability and validity of the NEX has not been established.

Methods: NEX encounters were videotaped at 4 neurology programs. Local faculty and ABPN examiners graded the encounters using 2 different evaluation forms: an ABPN form and one with a contracted rating scale. Some NEX encounters were purposely failed by residents. Cohen’s kappa and intraclass correlation coefficients (ICC) were calculated for local vs ABPN examiners.

Results: Ninety-eight videotaped NEX encounters of 32 residents were evaluated by 20 local faculty evaluators and 18 ABPN examiners. The interrater reliability for a determination of pass vs fail for each encounter was poor (kappa 0.32; 95% confidence interval [CI] = 0.11, 0.53). ICC between local faculty and ABPN examiners for each performance rating on the ABPN NEX form was poor to moderate (ICC range 0.14 – 0.44), and did not improve with the contracted rating form (ICC range 0.09 – 0.36). ABPN examiners were more likely than local examiners to fail residents.

Conclusions: There is poor interrater reliability between local faculty and American Board of Psychiatry and Neurology examiners. A bias was detected for favorable assessment locally, which is concerning for the validity of the examination. Further study is needed to assess whether training can improve interrater reliability and offset bias. Neurology® 2009;73:904 –908

GLOSSARY

ABIM = American Board of Internal Medicine; ABPN = American Board of Psychiatry and Neurology; CI = confidence interval; HFH = Henry Ford Hospital; ICC = intraclass correlation coefficients; IM = internal medicine; mini-CEX = Mini-Clinical Evaluation Exercise; NEX = Neurology Clinical Skills Examination; RITE = residency in-service training examination; UC = University of Cincinnati; UM = University of Michigan; USF = University of South Florida.

The American Board of Psychiatry and Neurology (ABPN) eliminated its centralized oral examination for several reasons. First, the encounters were not standardized. Second, a single high-stakes, high-stress encounter is not necessarily representative of a candidate’s performance. Third, deficiencies were difficult to remediate for failed candidates as they had already completed training. To replace the centralized oral examination, the ABPN Neurology Council voted to require residency programs to administer a set of clinical skills examinations called the Neurology Evaluation Exercise (NEX) to all residents entering training as of July 1, 2005, and document every graduating resident’s satisfactory performance on these. The ABPN proposed this approach after reviewing the American Board of Internal Medicine (ABIM) experience with clinical skills evaluation in internal medicine (IM) residency using the Mini-Clinical...
Evaluation Exercise (mini-CEX), which had also been developed to replace a single bedside oral examination that was felt to be poorly generalizable.1-3

The mini-CEX was designed to assess residents with respect to clinical skills, attitudes, and behaviors that are essential in providing high-quality patient care. In a study of 421 PGY-1 IM residents from 21 programs, evaluated by 316 physicians, the 7 components of competence were highly correlated and reliable.4 Four encounters per resident produced acceptable confidence intervals (CIs) for residents with aggregate scores at the midpoint (marginal/satisfactory performance) or higher on the evaluation scale. Other investigators, using scripted videotapes of standardized patients and standardized residents, demonstrated construct validity (degree to which a test measures the theoretical concept it intends to measure) of the mini-CEX, with faculty evaluators demonstrating discrimination among unsatisfactory, satisfactory, and superior clinical skills by standardized residents.5 Concurrent validity, or the degree to which a measurement instrument produces the same results as another proven instrument measuring the same variable, has also been demonstrated with the mini-CEX, but only in one residency program with correlations between monthly evaluation forms and in-service training examination scores.6

In contrast to the mini-CEX, no validation studies have been performed on the NEX. The ABPN selected 5 clinical evaluations as the minimum needed based on extrapolation from the mini-CEX studies, but the neurologic and general medical examinations differ, so it is not clear how many examinations are needed for reliable results. The need for evaluation and validation of the NEX is urgent. If the process is flawed, this must be learned quickly to prevent wasted effort from program directors, minimize inconvenience to residents, and protect the public by maintaining high standards for neurology board certification. Furthermore, the mini-CEX studies did not address the potential for bias from local evaluating faculty. The reliability and validity studies of the mini-CEX were performed long after the live patient examination had been eliminated from the ABIM certifying examination, so comparison to gold standard ABIM board examiners was not possible. Neurology has a unique opportunity to address how presumptive gold standard ABPN examiners would grade NEX encounters.

The primary aim of this study was to study interrater reliability and bias in the NEX comparing untrained local faculty to trained, unaffiliated ABPN examiners. The secondary aims were to study the concurrent validity of resident NEX evaluations with neurology residency in-service training examination (RITE) scores and to study the number of examinations needed for reliable testing and a passing score.

METHODS Residency program directors were offered an opportunity to participate in multicenter educational research at the 2006 Consortium of Neurology Program Director’s Meeting. Our goal was to enroll a variety of programs from across the United States, with differing levels of academic achievement as demonstrated by 2006 RITE scores of PGY-2 residents. Ultimately, 4 programs participated, 3 in the Midwest and 1 in the Southeast: Henry Ford Hospital (HHF), University of Michigan (UM), University of Cincinnati (UC), and University of South Florida (USF). Three of these programs are university-based, and one is an urban community-based residency program.

Current ABPN board examiners were recruited through a mail posting and announcement describing the study at an examination. Local faculty evaluators were voluntarily recruited by study co-investigators at each site.

Demographic data were collected on each participating resident, ABPN evaluator, and faculty evaluator. Demographic data on residents included months of training in all residencies, months of training in neurology, age, and sex. Demographic data on ABPN and faculty evaluators included age, sex, years of teaching experience, academic rank, number of ABPN examination service, and status as program director or associate program director.

Patients were offered compensation with parking reimbursement and a small gift card. ABPN examiners were offered compensation with a small honorarium. Residents and local faculty were not compensated.

Each site’s local Institutional Review Board approved the study. Resident informed consent was obtained prior to participation in this study. Patient consent for videotaping was obtained. Local faculty evaluators and ABPN examiners were exempted from informed consent. We preferentially recruited PGY-2 residents, given the greater likelihood of variable and unsatisfactory performances in less senior trainees. Of the 5 required settings for NEX encounters (child neurology, ambulatory/episodic disorders, neuromuscular disorders, critical care, and neurodegenerative/movement disorders), we excluded critical care and pediatric encounters for technical reasons. At 2 sites (HHF and UC), residents knew which faculty were evaluating them. Lack of anonymity could conceivably bias local faculty in favor of passing their residents. We attempted to minimize this ef-
fect by informing faculty that residents would sometimes be intentionally performing at a failing level. A standardized patient encounter was developed in which residents were coached to perform at a failing level in a specific manner. Residents were limited to 45 minutes for each encounter, an ABPN requirement. Two evaluation forms were used in each encounter: the ABPN sanctioned NEX 1 form with an 8-point grading scale, and a modified form with a 3-point rating scale (appendix e-1 on the Neurology® Web site at www.neurology.org). Residents must pass each section (medical interviewing skills, examination skills, and humanistic/professionalism skills) for an overall passing score.

To standardize encounters, written instructions for performing and evaluating the NEX were developed and distributed to all participants (appendix e-2). ABPN grading instructions were distributed to local faculty and ABPN examiners. Each local faculty and ABPN examiner viewed no more than one purposely failed encounter. Encounters were de-identified as much as possible to minimize potential evaluator bias and protect confidentiality. Aliases were used by residents and patients. Residents were instructed to avoid questions that might identify the location of the encounter, but this was divulged on rare occasion.

The NEX encounters were videotaped by the co-investigator or designee. One local faculty evaluator and ABPN examiner reviewed each DVD NEX encounter and completed the NEX 1 and modified form. All data were entered into a database by the statistician investigator.

Descriptive statistics were computed for the demographic information for residents, local faculty examiners, and ABPN examiners. Kappa statistics were computed to assess the interrater agreement between faculty and ABPN examiners for pass/fail responses. Kappa statistics greater than 0.75 represent excellent agreement, 0.4 to 0.75 good agreement, and less than 0.4 poor agreement. Intraclass correlation coefficients (ICC) were computed to assess the agreement between faculty and ABPN examiners for each performance rating component on the NEX form.

Wilcoxon 2-sample t tests were used to evaluate the relationship between RITE scores and the individual resident’s performance. Residents were separated into 2 groups for this analysis, based on whether they passed their first NEX encounter.

Generalized estimating equations methods were used to assess the passing evaluation rate with increasing number of encounters. This method was selected to take into account multiple encounters from the same resident. In addition, the number of encounters was grouped into first encounter, second encounter, and 3 or more encounters. For these analyses, only residents with encounters performed ever time and provided feedback between encounters were included.

**RESULTS** Thirty-two residents (21 men, 11 women) participated. The majority (63%) were PGY-2 residents. Pre-study performance on the 2006 RITE was variable among these programs with a mean of 31.5% (range 0%–60%) of PGY-2 residents at these programs scoring above the 75th percentile among residents in the same year of training. Twenty-two local faculty with a mean of 7.9 ± 8.5 years of teaching experience participated. Most (68%) were assistant professor rank or lower and only 2 local faculty evaluators had ever served as ABPN examiners. Individuals participated as a local faculty evaluator or ABPN examiner, not both. Eighteen ABPN examiners were recruited with a mean of 21.1 ± 10.6 years of teaching. The majority (78%) were associate professor rank or higher. A total of 98 NEX encounters (20 neurodegenerative, 29 neuromuscular, and 49 ambulatory) were reviewed by both local faculty and ABPN examiners. Twelve encounters were intentional failures. Thirty-three encounters were from HFH, 25 from UM, 20 from UC, and 20 from USF.

Table 1 presents the concordant and discordant results between ABPN and local faculty examiners for all encounters, as well as for true encounters and intentional failure encounters, separately. The interrater reliability for a determination of pass vs fail for each encounter was poor (kappa = 0.32; 95% CI = 0.11, 0.53). For all encounters in which ABPN examiners failed a performance, local faculty agreed 40.7% of the time (individual program agreement ranged from 14.3%–60%). When ABPN examiners passed a performance, local faculty agreed 88.7% of the time for all encounters (individual program agreement ranged from 76.9% to 100%). There was no relationship between local faculty years of teaching experience and grading correlation with ABPN examiners. No difference was seen when the 2 local faculty who had served as ABPN examiners were excluded from the analysis (kappa = 0.32; 95% CI = 0.10, 0.54). Faculty at the sites where residents were blinded to the identity of their evaluators did not have a higher concordance with ABPN examiners than faculty at the non-anonymous sites. In fact, there was a trend for faculty from the non-anonymous sites to agree more closely with ABPN examiners (non-anonymous kappa = 0.49 vs anonymous kappa = 0.12, p = 0.07).

<table>
<thead>
<tr>
<th>Table 1</th>
<th>ABPN and local examiners</th>
<th>Encounter results</th>
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<tr>
<td></td>
<td>Local examiners</td>
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<td></td>
<td>Pass</td>
<td>Fail</td>
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<tr>
<td>All encounters</td>
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<tr>
<td>ABPN</td>
<td>Pass</td>
<td>63</td>
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<td>Examiners</td>
<td>Fail</td>
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<td>True encounters</td>
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<td>Examiners</td>
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<td>Intentional failure encounters</td>
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<td>Examiners</td>
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</table>

ABPN = American Board of Psychiatry and Neurology.
ICCs between local faculty and ABPN examiners for each performance rating on the NEX 1 form were poor to moderate, ranging 0.14—0.44 for each rating. The ICC did not improve with the use of a contracted 3-point rating form (ICC range: 0.09—0.36). RITE examination scores from 2008 were available for 28 residents. One resident completed only a single intentional failure and was not included in the RITE analysis. Of the remaining 27, 20 passed their first encounter. This group of passing residents had higher median RITE scores than the 7 residents with a failed first encounter, but none of these differences was significant (median percentile RITE score vs same year in training 46 vs 31 and median percent correct 55.5 vs 48).

Residents at UM and HFH performed examinations over a period of time and were given feedback following each examination. There were 20 residents with 50 true encounters. There was a positive trend in the ABPN examiner assessed rate of passing NEX evaluations with later encounters (table 2: 65% for first encounter, 88.9% for second encounters, and 91.7% for 3 or more encounters). There was improvement between the first and second encounters ($p = 0.033$) and a strong trend between the first encounter and 3 or more encounters ($p = 0.05$). No improvement was seen between the second encounter and 3 or more encounters ($p = 0.442$).

**DISCUSSION** If the ABPN examiner’s evaluations are a gold standard, these results suggest local faculty may be biased in assessing their own resident’s NEX performance. Local faculty were twice as likely to concur with ABPN examiners on a passing vs failing grade. This result did not depend on whether residents knew who was evaluating them. Some of the difference in grading may be due to stratification of grading by local faculty. Local faculty knew the training level of the resident and may have assessed performance based on the expected performance for that year of training (e.g., PGY-2), rather than on the expected performance of a neurology residency graduate, as ABPN examiners have been trained to do. Local examiners might be more likely to forgive unsatisfactory performance among residents they know well, while ABPN examiners might consider these behaviors grounds for failure. Local faculty may consider the daily clinical performance of a resident, and not just the performance in this staged situation. Therefore, even if bias exists among local faculty, it does not necessarily follow that this bias invalidates the results of determining clinical competence. In fact, local results may be more valid than ABPN-based results, where truly competent neurologists could have failed for performance errors under pressure in an artificial situation.

Even though this study demonstrated poor interrater reliability between local faculty and ABPN examiners, there was agreement between both about 75% of the time on the essential issue of overall pass/fail performance. With multiple resident observations, this may still represent an improvement over the single high stakes observation of the traditional centralized live patient examination. The ABPN maintains that the hurdle to neurology board certification is not passing the oral examination, but the written examination. The NEX therefore may be sufficient to the needs of board certification even if it is not a strongly reliable tool.

It might be possible to design a faculty development course to improve assessment of neurology resident clinical skills. One group of investigators found that 11 of 40 faculty inaccurately rated taped mini-CEX performances as satisfactory when they were not.$^7$ In a follow-up study, the investigators used videotapes in a 4-day faculty development course with lectures and a variety of interactive evaluation exercises with standardized residents and patients.$^8$ Eight months later, those randomized to the educational intervention rated videotaped encounters between standardized residents and patients more stringently than control faculty who did not take the course. It is not known whether the same result could be accomplished with less training. Earlier studies with short duration faculty training did not improve faculty rating skills.$^9$ It would be very difficult for programs to find and fund faculty to attend a 4-day-long course to become NEX evaluators. Any requirement of prior faculty training to serve as a NEX evaluator could pose logistical difficulties, and could negate one of the express purposes of the NEX: to have multiple observers evaluate each resident. From a logistic standpoint, a Web-based training and assessment program would be preferred, but any faculty development tool must be studied for effectiveness and ability to mitigate bias.

Concern about interrater reliability is mitigated by improvement in ABPN examiners’ ratings of resident performance with increasing number of examinations. Reliable resident performance was obtained.
after only 2 NEX encounters. Reducing the number of completed NEX encounters from 5 to a lower number may reduce stress on residents and programs without reducing the reliability of the NEX, although one reason to retain all 5 is that they each require demonstration of unique history and examination skills.

One limitation of this study is the limited number of participating neurology programs, residents, and NEX encounters. Another limitation is that each NEX encounter was evaluated by only one ABPN examiner, so the interrater reliability among ABPN examiners was not assessed. Before making decisions based on the gold standard of ABPN examiners, their interrater reliability should be evaluated. If their interrater reliability is good, then the NEX process might be strengthened by routinely sending videotapes to ABPN examiners for review. Given that the supply of ABPN examiners will diminish with time, an alternate would be to send the videotapes to faculty outside the local program. Thus, another possible follow-up study may be to evaluate the interrater reliability between outside faculty and ABPN examiners.

Follow-up studies are essential. We must first address the interrater reliability between 2 groups of ABPN examiners to determine if the NEX tool is reliable. If there is good interrater reliability between ABPN examiners, we should address the interrater reliability between unaffiliated faculty and ABPN examiners. If a faculty development tool is developed for assessing resident skills in the NEX, it is essential that the effectiveness of that tool be rigorously studied to make certain it is accomplishing its stated goals. We cannot assume that training local faculty will eliminate bias.

AUTHOR CONTRIBUTIONS
Statistical analysis was completed by Lonni Schultz, PhD, Henry Ford Hospital.

ACKNOWLEDGMENT
The NEX Study Group thanks the neurology residents and faculty from Henry Ford Hospital, University of Michigan, University of Cincinnati, and University of South Florida, and the ABPN Examiners who contributed to this work.

DISCLOSURE
This study was funded by an American Academy of Neurology Education Research Grant. Dr. Schuh has received funding for travel from the ACGME and the AAN and has received an honorarium from the ACGME (Park Caplan Award). Dr. London serves as an editor for Medlink Neurology online. Dr. Noel reports no disclosures. Dr. Brock services as Book Review Editor for the Journal of Neuroimaging and serves on a speakers’ bureau for Serono. Dr. Kinsela has served as an ABPN examiner and is a current member of the ACGME Neurology Review Committee, has served on a scientific advisory board for Neurirbr Neurosciences and a speakers’ bureau for Boehringer-Ingelheim; serves on the Neurology Residency Review Committee; has served as an expert witness in medicolegal cases related to stroke that performed chart reviews and been deposed once; and receives research support from the NIH (Principal Investigator: NIH-NINDS R-01 NS0678) and the Executive Committee at St. P’s. NIH-NINDS R-01 NS039987; NIH-NINDS U-01 NS045548). Dr. Schulte reports no disclosures. Dr. Gelf has served as an ABPN examiner; serves as an editor for Current Opinion in Internal Medicine; receives royalties from the publication of Introduction to Clinical Neurology (Elsevier 1995). UpToDate (chapter author, 2001-2009), and MedLink Neurology (chapter author, 1998-2009); and has received speakers honoraria from Washington University, Mayo Clinic, the American University of the Caribbean, and the University of Pennsylvania.

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REFERENCES
TEACHING NEUROIMAGES

Teaching NeuroImages are interesting, previously unpublished photomicrographs, patient photographs, neuroradiologic images, or other pictorial material. They should be particularly clear examples of established observations intended for the trainee audience.
Teaching NeuroImages: Reversible bilateral thalamic lesions in vein of Galen thrombosis

Rou-Chen Jee, MD
Sheng-Huang Lin, MD, MSc

Address correspondence and reprint requests to Dr. Sheng-Huang Lin, Department of Neurology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan, No. 707, Sec. 3, Chung-Yang Rd., Hualien City, Hualien County 970, Taiwan, Republic of China
shlin355@gmail.com

T2-weighted MRI (A) revealed high-signal lesions in bilateral thalami and right caudate nucleus. Magnetic resonance venography (B) showed thrombus formation in vein of Galen (arrow). After treatment, the lesions of bilateral thalami and right caudate nucleus disappeared (C), and the vein of Galen was patent (D).

A 51-year-old woman was admitted with 2 days of progressive drowsiness and bradyphrenia. On examination, she had blood pressure of 125/75 mm Hg and a pulse of 68 beats/minute. She aroused to verbal stimuli, and her answers were correct but slow. There was no focal weakness or numbness, and reflexes were normal. Brain MRI revealed lesions in bilateral thalami and right caudate nucleus (figure, A) and vein of Galen thrombosis (figure, B). There was no evidence of dehydration, coagulopathy, autoimmune dysfunction, or infection. She recovered completely on heparin. Follow-up brain images were normal (figure, C and D). Early detection and treatment of deep cerebral venous thrombosis lowers the risk of permanent neurologic deficits.1,2

REFERENCES

From the Department of Neurology, Buddhist Tzu Chi General Hospital, Hualien, Taiwan.
Disclosure: The authors report no disclosures.
BOOK REVIEWS

The trainee book review section assesses the usefulness of books developed for use by neurology residents and fellows. Reviews will be written primarily by upper-level residents, fellows, or program directors that have appropriate perspectives on the potential value of the book at various levels of training.
THE NEUROLOGICAL MANIFESTATIONS OF PEDIATRIC INFECTIOUS DISEASES AND IMMUNODEFICIENCY SYNDROMES  
edited by L.L. Barton and N.R. Friedman, 421 pp., Totowa, NJ, Humana Press, 2008, $139

Pediatric neuroinfectious diseases is an evolving and important neurologic subspecialty. The Neurological Manifestations of Pediatric Infectious Diseases and Immunodeficiency Syndromes is the only available text focused primarily on this subject. Doctors Leslie L. Barton, a pediatric infectious diseases specialist, and Neil R. Friedman, a pediatric neurologist, produced a complete reference with a target audience that includes residents, general pediatricians, pediatric critical care specialists, pediatric infectious disease specialists, and pediatric neurologists.

The book is organized into 8 sections. The first 6 refer to all major classes of infectious agents, while the last 2 include immunodeficiencies and general clinical management principles. Each neuropathogen is covered with a common format that provides both basic information for the generalist as well as specific evidence-based management for the pediatric neuroinfectious diseases specialist. There is a complete list of references at the end of each chapter. Important data are plentiful and displayed in 27 tables and multiple figures (8 MRIs, 7 photographs, 4 CTs, and 2 EEGs). There is a complete index for reference use, but the writing style also facilitates a cover-to-cover overview of the subspecialty.

The editors, and contributing authors, succeeded in fulfilling the needs of interested readers with variable backgrounds and expertise who encounter pediatric neuroinfectious diseases. Organization of the book by neuropathogen favors the perspective of the infectious disease specialist rather than that of the neurologist, who may categorize by diseases instead. Neurology residents and fellows will find this book useful for managing patients, but it is too detailed to be an appropriate resource for board review. The Neurological Manifestations of Pediatric Infectious Diseases and Immunodeficiency Syndromes will endure as the seminal text of the emerging subspecialty of pediatric neuroinfectious diseases.

Reviewed by John J. Millichap, MD

Disclosure: Dr. Millichap serves on the Neurology® Resident & Fellow Section editorial team.

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E-PEARLS

E-Pearls are listed only on our website and sent out on a weekly basis to Residents and Fellows. They are composed to be read and absorbed within a few minutes. The editorial team of the Resident & Fellow Section invites E-Pearl submissions. The length should be 85 words or less and include one reference, if applicable. Please submit your E-Pearl to Ryan Overman at rtoverma@iupui.edu.
The monocular temporal crescent

Pop quiz:
Can you get a monocular field cut from an occipital lesion?

Answer:
You betcha!

A lesion in the anterior medial occipital lobe can cause a loss of the far temporal visual field (temporal crescent) of the contralateral eye without involvement of the ipsilateral eye. There is no representation of the far nasal segment of the visual field in the retina of the ipsilateral eye, presumably because of the presence of the nose where that field would otherwise be. This is an example of monocular vision loss in which the responsible lesion can be retrochiasmal. This phenomenon is rare (only 1 of 904 cases of hemianopia in one series), but illustrates an important neuroanatomic principle.

Reference:
Zhang X, Kedar S, Lynn MJ, Newman NJ, Biousse V. Homonymous Hemian

The lumbar puncture in Guillain-Barre syndrome

The lumbar puncture in Guillain-Barre syndrome (GBS) demonstrates an elevated CSF protein level only two-thirds of the time in the first week of symptoms. So in one-third of cases the initial LP in GBS will be normal. An early LP in GBS is thus most helpful in evaluating for the presence or absence of cells. If a patient has more than 10 or 15 white cells—assuming the CSF doesn't demonstrate lots of red cells too—then the physician needs to consider rare GBS mimics, such as infections or lymphomatous or carcinomatous disease.

Disclosure:
Dr. Burns receives a stipend as Podcast Editor for Neurology®, performs EMG studies in his neuromuscular practice (30% effort), and received compensation for a presentation on MG-QOL15, given to study investigators of eculizumab in myasthenia gravis.

Submitted by Ted Burns, MD
Anticipation

“Anticipation” is more than the title of her hit song. It’s part of Carly Simon’s life with migraine: anticipating when the next migraine will strike, and when relief will set in.
20 MINUTES
Pack a Punch

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