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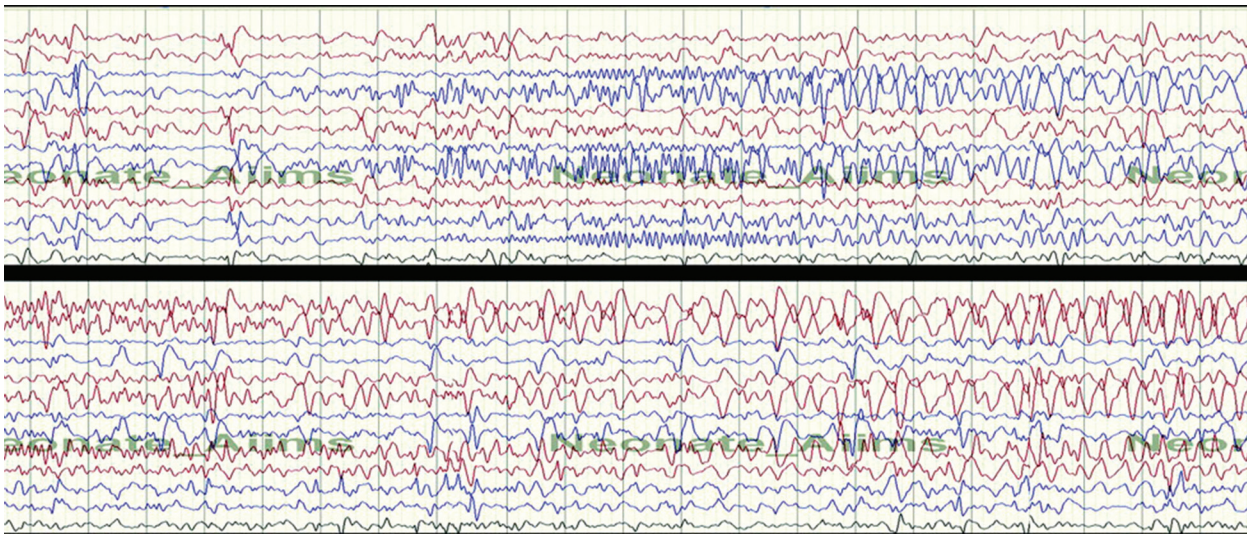

Child Neurology: A Case-Based Approach

Cases from the *Neurology*® Resident & Fellow Section

CHILD NEUROLOGY SOCIETY

Child Neurology: A Case-Based Approach

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Editors

John J. Millichap, MD
Attending Epileptologist
Ann & Robert H. Lurie Children's Hospital of Chicago
Associate Professor of Pediatrics and Neurology
Northwestern University Feinberg School of Medicine
Chicago, IL

Jonathan W. Mink, MD, PhD
Frederick A. Horner, MD Endowed Professor in Pediatric Neurology
Professor of Neurology, Neuroscience, and Pediatrics
Chief, Division of Child Neurology
Vice Chair, Department of Neurology
University of Rochester Medical Center
Rochester, NY

Phillip L. Pearl, MD
Director of Epilepsy and Clinical Neurophysiology
William G. Lennox Chair, Boston Children's Hospital
Professor of Neurology
Harvard Medical School
Boston, MA

Roy E. Strowd III, MEd, MD
Assistant Professor
Neurology and Oncology
Wake Forest School of Medicine
Winston Salem, NC

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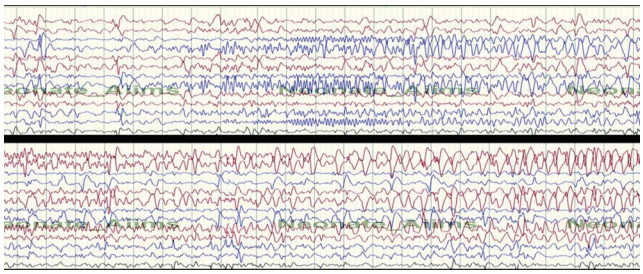

Cover image

Note seizure onset with α range activity over the right central and temporal leads later evolving into delta activity (top). Ictal EEG after 5 minutes shows seizure onset from the left central and temporal leads (bottom). The child had tonic posturing of the right upper limb during this period.

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Introduction

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Introduction

John J. Millichap, MD, Roy E. Strowd, III, MEd, MD, Jonathan W. Mink, MD, PhD, and Phillip L. Pearl, MD

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Correspondence
Dr. Millichap
j-millichap@
northwestern.edu

Child Neurology: A Case-Based Approach

Cases from the Neurology Resident & Fellow Section

The *Neurology*® Resident & Fellow Section (RFS) Editorial Team, founded in 2004, is composed of over 20 neurology trainees recruited worldwide and supported by faculty Editors and editorial staff. During the past 15 years, more than 130 pediatric clinical cases were published that span all the child neurology subspecialties. All of these cases are freely available online and organized according to the specific subsection to which they were submitted. Despite the variety of formatting, each case presentation includes important educational material of value to neurologists-in-training and practicing neurologists alike.

These case reports describe patients with both rare and common diseases that are presented in a variety of formats based on the RFS subcategory to which they were submitted. The "Child Neurology" subsection is perhaps the most straightforward case report format. A patient case is followed by structured discussion about the final diagnosis with the goal of providing an up-to-date review of the pediatric neurology topic. "Clinical Reasoning" is another popular case-based article category. Published cases include uncommon presentations of common diseases and also typical presentations of rare neurologic disorders. The goal is logically arriving at the correct diagnosis through a series of 2–4 steps laid out for the reader. "Pearls and Oy-sters" is a subsection with cases focused on a disease that includes both clinical insights and tips, that is, "pearls," as well as advice for avoiding mistakes, or "oy-sters." Finally, "Teaching NeuroImages" and "Teaching Video NeuroImages" are interesting images associated with a succinct case description that emphasizes the teaching point.

This book is intended to be a resource to both adult and pediatric neurologists and trainees. It is a collaborative project between the Child Neurology Society (CNS) and the American Academy of Neurology (AAN). Cases are organized by child neurology discipline (e.g., epilepsy, stroke). Each chapter begins with an introduction co-authored by RFS Editorial Team members and faculty expert members from the CNS and AAN. There are 2 separate introductions targeted to adult and child practitioners which provide a brief discussion of the relevance of the cases to each group in clinical practice and understanding of pathophysiology. Pediatric practitioners will benefit from a review of the evaluation and management of major childhood neurologic diseases as well as considering how to hand off adolescent patients who become adults. Adult practitioners will benefit from considering pediatric diseases that can present in adults, from late complication of childhood diseases that occur in adulthood, and from how to receive adolescents who age out of pediatric care. The final chapter specifically addresses the transition from pediatric to adult providers, an important and applicable purpose of such a compilation of cases.

The Editors and the current and past members of the RFS Editorial Team hope that readers will consider the organization of compiled child neurology cases included here as a unique educational resource for use by clinicians at any stage of training or practicing.

From the Departments of Pediatrics and Neurology (J.J.M.), Ann & Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, IL; Neurology and Oncology Departments (R.E.S.), Wake Forest School of Medicine, Winston Salem, NC; Division of Child Neurology and Department of Neurology (J.W.M.) University of Rochester Medical Center, NY; and Epilepsy and Clinical Neurophysiology (P.L.P.) Boston Children's Hospital, Department of Neurology, Harvard Medical School, MA.

For disclosures, please contact the *Neurology*® Resident & Fellow Section at rfsection@neurology.org.

Introduction

Pediatric Perspective

By Ittai Bushlin, MD, PhD, and Phillip L. Pearl, MD

The following collection of cases highlights the diversity and difficulties that accompany the diagnosis and treatment of pediatric epilepsy. Although the most common pediatric epilepsy syndrome—such as childhood absence and benign Rolandic epilepsy—are recognizable by the general neurologist, the breadth and depth of the breathtaking syndromes presented will enlighten the most experienced pediatric neurologist and epileptologist. Vagaries and unique aspects of Dravet syndrome, GLUT1 deficiency, Epilepsy of Infancy with Migrating Focal Seizures (EIMFS), Hemiconvulsion-hemiplegia-epilepsy (HHE), and Foix-Chavany-Marie syndrome (FCMS) are contained in these succinct presentations. These cases highlight a foundational aspect of seizures—that they reflect a dysfunctional or injured brain, and that an appropriate evaluation is required to identify the etiology of this dysfunction. The underlying cause may be genetic (e.g., Dravet syndrome, EIMFS, or GLUT1 deficiency), inflammatory (e.g., HHE), or structural (e.g., FCMS).

The discussions present a real case, with guidance as to the differential diagnosis, and demonstrate the results of investigations ranging from imaging (pivotal in FCMS and HHE), neurophysiology (highlighted in EIMFS), and targeted genetic/metabolic testing to evaluate for treatable disorders (with specific results in Dravet syndrome and GLUT1 deficiency). Each case provides a welcome historical perspective, citing and discussing the seminal descriptions, and then explains how new technologies, from high-resolution MRI to next-generation genetic sequencing, have been used to yield greater precision.

The time-honored electroclinical syndromes of pediatric epilepsy combined with modern diagnostic and treatment approaches provide rich material for learners of all levels. One does not want to skip… or miss… these cases!

From the Department of Neurology (I.B.), Boston Children's Hospital, MA; and Director of Epilepsy and Clinical Neurophysiology (P.L.P.), Harvard Medical School, Boston, MA.
Correspondence Dr. Bushlin ittaibushlin@gmail.com

Adult Perspective

By Fábio A. Nascimento, MD, and Robert A. Gross, MD, PhD, FAAN

Epilepsy is one of the most common chronic conditions in neurology, affecting over 70 million people worldwide. Because of its high incidence and bimodal age distribution, with the highest risk in young individuals and the elderly, both pediatric and adult neurologists frequently care for patients with epilepsy. In the adult clinic, these patients comprise not only those with adulthood-onset seizures but also children with epilepsy who transition to the adult healthcare.

Among children with epilepsy, it is estimated that roughly half will become adults with epilepsy. This population tends to keep growing as medical advances continue to allow children with complex disorders to survive longer. As a result, adult neurologists are required to have a theoretical and practical up-to-date knowledge of pediatric epilepsy disorders to provide optimal care for this particular patient population.

From an adult neurology perspective, having a sound understanding of pediatric epilepsy syndromes becomes essential in at least 2 scenarios. The first would be when a child with an established epilepsy diagnosis enters the adult system. The clinician would have to know how to treat, counsel, and screen for late complications that are characteristic of that diagnosis. For instance, it would be of paramount importance to be aware that sodium channel blockers should be avoided in patients with Dravet syndrome and that ketogenic diet is the primary treatment modality for those with GLUT1 deficiency syndrome. The second scenario would be when meeting an adult with long-standing childhood-onset seizures who remains undiagnosed. The adult provider would have to be familiar with pediatric epilepsy syndromes that are either difficult to diagnose, hence underrecognized, or associated with late-onset forms. Of course, if epilepsy is intractable, a referral to an epilepsy center is warranted, as resective surgery or devices might be appropriate and beneficial.

In this section, we intend to provide the readers with current, evidence-based knowledge in pediatric epilepsy using a case-based approach. We hope that by using clinical cases as the substrate for our discussion, the bridge between theory and practice is shortened—ultimately leading to improved care for children with epilepsy.

From the Department of Neurology (F.N.), Baylor College of Medicine, Houston, TX; and Neurology (R.G.), Strong Epilepsy Center, University of Rochester Medical Center, NY.
Correspondence Dr. Nascimento nascimento.fabio.a@gmail.com

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Child Neurology: Hemiconvulsion-hemiplegia-epilepsy syndrome

Jeffrey R. Tenney, MD, PhD
Mark B. Schapiro, MD

Correspondence & reprint requests to Dr. Tenney: jeffrey.tenney@cchmc.org

ABSTRACT

Hemiconvulsion-hemiplegia-epilepsy (HHE) syndrome is an uncommon outcome of prolonged focal status epilepticus in childhood. The prolonged focal motor seizure usually occurs during the course of a febrile illness and is followed by hemiplegia ipsilateral to the side of convulsions. This is accompanied by radiologic evidence of acute cytotoxic edema in the affected hemisphere followed by chronic atrophy. Intractable epilepsy may develop at a time remote from the initial presentation. The clinical features of HHE syndrome were first described more than 5 decades ago but its pathophysiology remains poorly understood and the long-term cognitive outcomes are unclear. Early recognition of the syndrome may help provide patients and families with an accurate prognosis regarding the subsequent development of epilepsy. ***Neurology*® 2012;79:e1–e4**

GLOSSARY

FIRES = fever-induced refractory epileptic encephalopathy in school-aged children; **HH** = hemiconvulsion-hemiplegia; **HHE** = hemiconvulsion-hemiplegia-epilepsy; **HHS** = hemiconvulsion-hemiplegia syndrome; **MR** = magnetic resonance; **NORSE** = new-onset refractory status epilepticus.

CLINICAL CASE, PART I A 21-month-old boy, former 25-week premature infant, with a history of bilateral grade III/IV intraventricular hemorrhages and hydrocephalus with ventriculo-peritoneal shunt, presented with a likely prolonged period of right-sided jerking. There was no prior history of seizures and his motor and language development was age-appropriate. His parents stated that he was in his usual state of health and acting normally on the day prior to presentation but he did have a tactile fever. He was last seen normal at midnight when he was checked on by his parents. His mother found him 6 hours later with right face, arm, and leg jerking but he had no impaired consciousness or eye deviation. During transport he had continuous right-sided jerking but was conscious and moving the left side normally. He was febrile upon arrival to the emergency room and he initially received IV lorazepam and IV valproic acid with no effect. At that point he developed gaze deviation to the right and mental status deterioration. He received IV fosphenytoin, was intubated, and was admitted to the intensive care unit. The right-sided face, arm, and leg jerking continued so a pentobarbital infusion was started. The total duration of the seizure was approximately 10 hours. The patient remained in a pentobarbital coma for 48 hours before it was weaned and levetiracetam was started as a maintenance antiepileptic medication. On hospital day 5 his mental status improved but he was noted to have a right facial droop, right visual field deficit, right hemiparesis, right hyperreflexia, and no spontaneous speech.

Differential diagnosis. Acute focal weakness following a seizure in a child has many serious etiologies that must be investigated (table). The evaluation is focused on excluding serious or treatable causes. Evaluation should begin with MRI and magnetic resonance (MR) angiography to exclude structural lesions such as neoplasms, intracerebral abscesses, acute disseminated encephalomyelitis, developmental brain malformations, or signs of trauma and vascular disorders such as ischemic or hemorrhagic infarctions. In the case presented it was also important to evaluate for ventriculo-peritoneal shunt malfunction causing increased intracranial pressure with funduscopic examination, MRI, and shunt externalization, if needed. Other testing should include EEG, serum glucose, and CSF analysis.

CLINICAL CASE, PART II Following resolution of burst suppression the EEG became severely suppressed over the entire left hemisphere. MRI brain done on hospital day 5 showed restricted diffusion with apparent diffusion coefficient correlation throughout the left hemisphere (figure, A). This progressed over the next

From the Department of Neurology, Cincinnati Childrens Hospital Medical Center, Cincinnati, OH.
Go to Neurology.org for full disclosures. Disclosures deemed relevant by the authors, if any, are provided at the end of this article.
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Table Differential diagnosis of postictal focal weakness in childhood

Seizure with postictal paralysis
Stroke
Ischemic
Hemorrhagic
Neoplasm
Infectious
Encephalitis
Meningitis
Intracranial abscess
Acute disseminated encephalomyelitis
Metabolic
Hypoglycemia
Mitochondrial disorder (mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes)
Developmental brain malformation
Trauma
Psychogenic

month to more pervasive signal abnormalities and volume loss of the entire left hemisphere that were likely consistent with diffuse cortical necrosis (figure, B). Routine electrolytes and CSF analysis at the time of presentation were within normal limits.

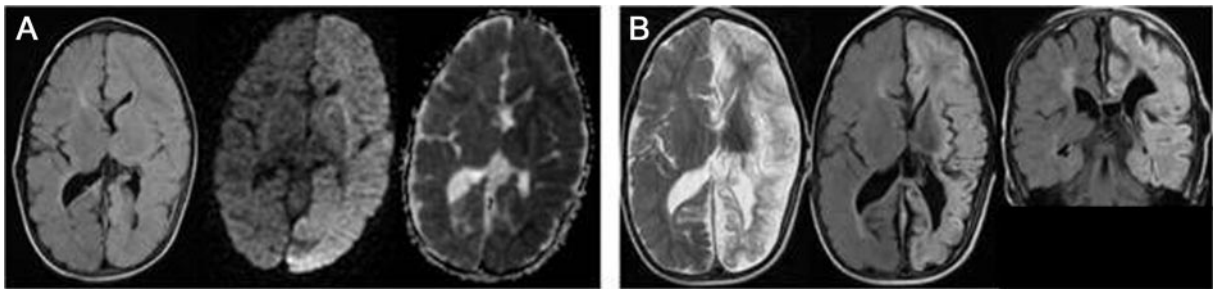
At the last follow-up (16 months posthospitalization) the patient remained seizure- free on levetiracetam. The presenting symptoms, hospital course, and imaging were most consistent with hemiconvulsion-hemiplegia (HH) syndrome since he has not developed subsequent epilepsy. His motor functioning improved with weekly physical therapy/occupational therapy and he was taking some steps independently. He continued to have limited use of the right upper extremity, especially with fine motor movements of the hand. Speech progressed well and he was speaking in sentences, counting, and identifying some letters.

DISCUSSION

Epidemiology. HHE syndrome was first reported by Gastaut and colleagues[1] approximately 50 years ago. The specific incidence is unknown but it has been reported that it is declining in developed countries.[2,3] This could be due to improved and more rapid treatment of status epilepticus as well as the wider availability of rectal and IV benzodiazepines. A decrease in the incidence of febrile status epilepticus due to increased rates of childhood immunizations is another possible explanation.

Clinical characteristics. The first report in the English literature of HHE syndrome (1960) described the clinical, electrographic, radiologic, and pathologic features of 150 children identified with the syndrome.[1] Children are usually less than 4 years of age at the time of presentation and a concurrent febrile illness should be present. The initial stage is referred to as HH syndrome (HHS) since epilepsy has not yet developed. HHS is characterized by prolonged (hours), unilateral, and clonic convulsions that are often initially unrecognized and many times the child is found having the convulsions in his or her bed.[4] The hemiconvulsion has the following characteristics that have been described by Chauvel and Dravet[4]: 1) duration of hours and at times more than 24 hours, 2) variable location of the jerking, with a possibility of contralateral seizures if it is prolonged, 3) inconstancy of impairment of consciousness, 4) variable onset with possible head/eye deviation, unilateral jerking, or bilateral jerks evolving to unilateral jerks, and 5) the possibility of severe autonomic symptoms such as hypersalivation, respiratory disorders, and cyanosis. HHE syndrome can be divided into 2 groups based on known etiologies. Idiopathic HHE syndrome is only associated with fever and pre-

Figure MRI brain



MRI brain done on hospital day 5 shows fluid-attenuated inversion recovery (FLAIR) (left), diffusion-weighted imaging (middle), and apparent diffusion coefficient (right) signal abnormalities throughout the left hemisphere (A). These abnormalities are not consistent with any vascular territories. This progressed over the next month to more pervasive signal abnormalities and volume loss of the entire left hemisphere that were likely consistent with diffuse cortical necrosis as seen on the T2-weighted (left) and FLAIR axial (middle) and coronal (right) images (B).

sumed extracranial infection while the symptomatic type is associated with fever as well as some identified, predisposing factor (head trauma, intracranial infection, or cerebral vascular disease).

Unilateral hemispheric swelling occurs during the time of convulsive status epilepticus. The earliest changes seen are edema of the subcortical white matter in the affected hemisphere.[5] This is followed by the development of global cerebral hemiatrophy over weeks to months.[6] An important distinguishing feature from stroke is that these abnormalities are independent of any vascular territory. In addition, in HHE syndrome the MRI often shows prominent diffusion restriction within the internal capsule, basal ganglia, and portions of the thalamus initially, as it did in this case. MR angiography in this case was normal and is consistent with data from larger case series of HHE syndrome that have shown normal vascular imaging.[7] The radiologic abnormalities correspond with clinical changes such as hemiplegia, visual field deficit, or aphasia.

Pathogenesis. The etiology of HHE syndrome remains unclear, but it is likely the result of multiple factors. Radiologic findings indicate that there is a relationship between a sequence of events including early repetitive seizures, brain edema, cortical and subcortical atrophy, and chronic epilepsy in many of the cases.[4] It is clear from pathologic examinations that the hemispheric swelling is related to cytotoxic edema.[8] Other reported pathologic features are spongiosis and disruption of the normal cellular architecture. It has been proposed that these changes could be related to the primary, presumed viral, infection with resultant inflammatory cytokine damage.[2] There has also been speculation that the syndrome is directly related to the prolonged ictal activity. The young age seen at the time of onset is possibly related to the propensity of the immature brain to develop unilateral ictal discharges. This prolonged, unilateral ictal activity could cause excessive neuronal excitation via *N*-methyl-D-aspartic acid (NMDA) glutamate receptors. This could lead to a cascade of increased intracellular calcium causing cytotoxic edema and eventual necrosis and apoptosis. Most likely is that there is a synergistic relationship between inflammation and seizures that potentiates status epilepticus and cellular damage. It has been proposed that HHE syndrome, along with fever-induced refractory epileptic encephalopathy in school-aged children (FIRES) and new-onset refractory status epilepticus (NORSE), may be part of the same spectrum of inflammatory mediated encephalopathy and status epilepticus syndromes with the difference in clinical expression related to the stage of brain maturation.[9] There are no known underlying genetic factors associated in children with HHE syndrome; however, a recent report has linked it with CACNA1A mutation and possible cerebral vasospasm.[10]

Much of the data related to the pathogenesis of HHE syndrome support the existence of a "febrile idiopathic HHE syndrome" that shares some commonalities with simple febrile seizures. However, the relative rarity of HHE syndrome has caused some authors to question this connection and raise the possibility that children who develop HHE syndrome may have a preexisting cerebral lesion which transforms what would have been a simple febrile seizure into focal status epilepticus.[4]

Treatment and prognosis. Treatment for HHE syndrome during the early acute phase of the illness is mainly supportive and in the short term most children do well once the initial status epilepticus is controlled. However, it has been proposed, based on radiologic and pathologic findings, that the use of anti-edema agents and NMDA-type glutamate receptor antagonists during the acute period could help to stop neuronal injury.[2]

After some variable period (months to years) of seizure freedom, approximately two-thirds of patients will develop epilepsy that is in many cases intractable.[11] Making a distinction between idiopathic and symptomatic types of HHE is important because the 2 types differ in long-term prognosis.[12] Patients with the idiopathic type tend to develop temporal lobe epilepsy whereas those in the symptomatic group have an earlier onset of epilepsy and it is a symptomatic generalized type. No guidelines exist as to whether children with HHE syndrome should be on chronic anticonvulsant medication to prevent the remote seizures. There is evidence that surgical treatment of delayed intractable epilepsy in HHE syndrome is beneficial.[12]

The motor deficits associated with HHE syndrome have a variable course with some patients having persistent hemiplegia and others with complete resolution.[1] Physical and occupational therapy can be useful in the acute and chronic periods of the syndrome in order to maximize motor function. Long-term cognitive and language outcomes associated with HHE syndrome are poorly understood. Chauvel and Dravet have reported mental retardation as a feature in one-third of the patients with intractable epilepsy referred for epilepsy surgery, but a more recent study demonstrated that outcome can vary depending on which hemisphere is affected and mental retardation is not universal.[4,13] Patients with retained language in the affected hemisphere tended to have a better cognitive outcome.

Based on this literature, the prognosis for our patient can be made. His focal status epilepticus seemed to be related to a prolonged febrile seizure as in many of the idiopathic cases. However, he had preexisting

neuronal injury which places him in the symptomatic HH category making early, symptomatic generalized epilepsy more likely. Long-term language outcome may be dependent upon whether the functional cortex was reorganized following cerebral injury. Future fMRI for language function could help to establish the prognosis in this regard more accurately.

FUTURE PERSPECTIVES HHE syndrome is a rare but serious disorder in the pediatric population. It can greatly impact the quality of life for patients and their families. Health care dollars spent on patients with this disorder could be substantial given the remote development of medically intractable epilepsy and possibly lifelong hemiplegia.

HHE syndrome should be preventable by continued advances related to the rapid resolution of seizures. The severe impairments associated with HHE syndrome makes it imperative that continued research into the pathophysiology and treatment of the disorder is performed. It would be reasonable to pursue research related to preventing cytotoxic damage acutely with the use of NMDA antagonists or aggressive, early treatment of cerebral edema.

AUTHOR CONTRIBUTIONS

J. Tenney qualifies as an author based on the following contributions: drafting/revising the manuscript for content and analysis/interpretation of diagnostic testing. M. Schapiro qualifies as an author based on the following contributions: drafting/revising the manuscript for content and analysis/interpretation of diagnostic testing.

DISCLOSURE

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

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Child Neurology: Epilepsy of infancy with migrating focal seizures

Suvasini Sharma, DM*
Naveen Sankhyan, DM*
Konanki Ramesh, MD
Sheffali Gulati, MD

Address correspondence and reprint requests to Dr. Sheffali Gulati, Division of Pediatric Neurology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, 110029, India
sheffaligulati@gmail.com

Epilepsy of infancy with migrating focal seizures is a rare, infantile epileptic encephalopathy characterized by normal early development, refractory focal seizures arising independently from both hemispheres, and severe psychomotor retardation. In the revised terminology by the International League Against Epilepsy, it has been classified as an "electro-clinical syndrome" of "unknown cause" with onset in infancy.[1] Affected infants have progressive psychomotor retardation and decline of head circumference percentile. We present a 6-month-old boy diagnosed with this entity and discuss the approach to an infant with unexplained refractory seizures.

CLINICAL CASE, PART I A 6-month-old boy presented with developmental delay and focal seizures. He was the second child born to a third-degree consanguineous couple. His perinatal period had been uneventful and he had attained social smile by the age of 6 weeks. He started having seizures at the age of 2 months. The seizures consisted of deviation of eyes and head along with tonic posturing of arm or leg of either side and associated flushing. The seizures usually lasted for 1–2 minutes. The initial frequency was 2–3 per day but gradually over the next 4 months, it increased to 50–60 per day. He had been treated with phenobarbitone, phenytoin, carbamazepine, topiramate, and levetiracetam without success. He had lost social smile, and not gained any new developmental milestones. Family history was not significant.

Examination revealed a well-thriving baby with head circumference of 40 cm (<−2 SD). There were no neurocutaneous markers or dysmorphic features. The neurologic examination revealed reduced interaction and alertness, normal cranial nerves including fundus, and normal tone with brisk tendon reflexes and extensor plantar responses. Systemic examination was unremarkable.

Differential diagnosis. Important causes for refractory seizures in infancy include malformations of cortical development, acquired structural brain lesions such as sequelae of intrauterine or perinatal brain injury, pyridoxine dependence, glucose transporter type 1 deficiency syndrome, neurocutaneous syndromes, some metabolic/degenerative disorders, and epileptic syndromes (table). Hence the evaluation begins with a comprehensive history and examination to look for features of perinatal insult, dysmorphism (suggesting a chromosomal abnormality), and neurocutaneous markers. A brain MRI must be obtained to look for structural causes (e.g., malformations, sequelae of previous insults, features of tuberous sclerosis). Metabolic screening tests such as blood ammonia, arterial lactate, blood acylcarnitine profile, and urine organic acid studies are then performed to exclude organic acidemias, aminoacidopathies, and urea cycle defects. If all these investigations are normal, therapeutic trials of pyridoxine, pyridoxal phosphate, and folinic acid must be given sequentially. Another treatable metabolic cause of refractory infantile epilepsy is glucose transporter defect, which is diagnosed by the presence of CSF hypoglycorrhachia (CSF/blood sugar ratio <0.4). An EEG should be performed to look for localization of seizure focus, and for diagnosis of infantile epileptic encephalopathies such as Ohtahara syndrome and epilepsy of infancy with migrating focal seizures. Other rare causes of refractory infantile seizures include Alpers disease, some chromosomal abnormalities (e.g., ring chromosome 20), and SCN1A mutation–related epilepsy.[2,3]

CLINICAL CASE, PART II MRI of the brain, arterial blood gas, blood lactate and ammonia levels, urine ketones, plasma acylcarnitine profile, urine gas chromatography–mass spectrometry for organic acids, hair microscopy, serum copper and ceruloplasmin levels, thyroid profile, CSF examination (including glucose and lactate), and the karyotype were normal. The EEG revealed multifocal spikes and ictal rhythms arising variably from the right or left hemispheres (figure). The patient's seizures were uncontrolled despite treatment with sodium valproate, clobazam, pyridoxine, biotin, and folinic

*These authors contributed equally to this work.

From the Division of Pediatric Neurology, Department of Pediatrics, All India Institute of Medical Sciences, New Delhi, India.

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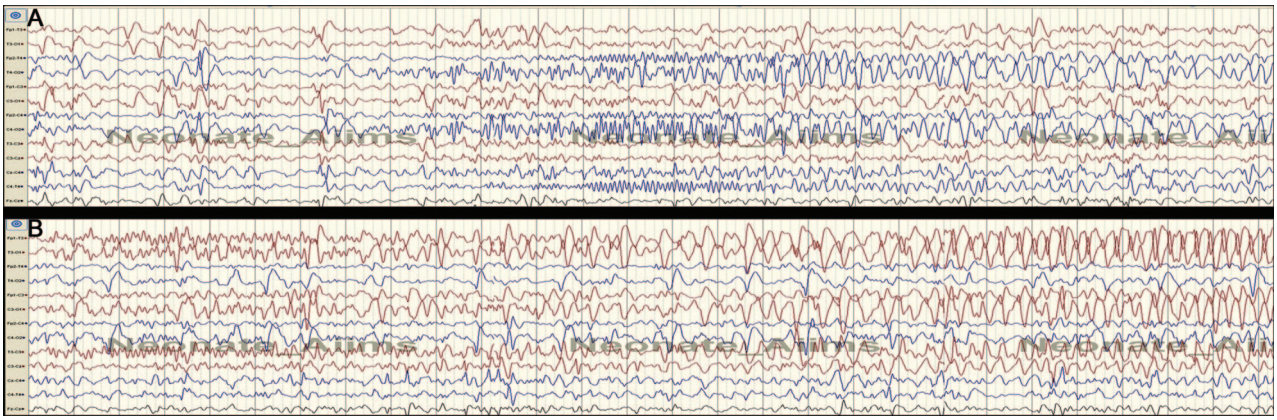
Table Selected causes of refractory seizures in infancy

Condition	Commonly seen features	Diagnosis
Malformations of cortical development	Seizures, developmental delay, microcephaly	MRI brain
Acquired structural brain lesions	History of perinatal asphyxia, hypoglycemia; neuroinfections, trauma	MRI brain
Neurocutaneous syndromes: tuberous sclerosis and Sturge-Weber syndrome	Tuberous sclerosis: ash leaf macules, adenoma sebaceum; Sturge-Weber syndrome: port wine stain, glaucoma	CT/MRI brain; mutation in *TSC1*, *TSC2*
Pyridoxine dependence	Seizures with onset in prenatal or neonatal period, refractory to conventional antiepileptic drugs	Response to therapeutic trial of pyridoxine; elevated α-aminoadipate semialdehyde (AASA) and pipecolic acid in CSF; mutation in *ALDH7A1* (Antiquitin protein)
Pyridoxal phosphate-dependent seizures	Prematurity, in utero and postnatal seizures, encephalopathy, burst suppression pattern on EEG	Therapeutic trial of oral pyridoxal phosphate (30 mg/kg/d); CSF: elevated glycine, threonine, L-dopa, 3-methoxytyrosine, and decreased homovanillic acid, 5-hydroxyindole acetic acid; *PNPO* mutation
Glucose transporter 1 (GLUT 1) deficiency syndrome	Infantile onset epilepsy, developmental delay, and acquired microcephaly; treatment of choice: ketogenic diet	CSF hypoglycorrhachia (CSF/blood sugar ratio < 0.4); mutation in *SLC2A1* gene (Glut1 protein)
Folinic acid responsive seizures	Neonatal-onset seizures, variable response to pyridoxine, and rapid response on addition of folinic acid and lysine-restricted diet	Response to therapeutic trial of oral folinic acid (3–5 mg/kg/d); elevated α-aminoadipate semialdehyde and pipecolic acid in CSF
Disorders of biotin metabolism (biotinidase deficiency, holocarboxylase deficiency)	Symptoms within first weeks of life, seizures, breathing abnormalities, hypo/hypertonia, lethargy, vomiting, skin rash, occasionally alopecia; treatment with biotin (10 mg/d) is usually beneficial	Ketoacidosis, organic aciduria, hyperammonemia; *BTD* and *HLCS* gene mutations
Sulfite oxidase/molybdenum cofactor deficiency	Seizure onset in first week of life, feeding problems, hypomotility, pyramidal signs, lens dislocation, severe neuromotor impairment	Imaging: cystic cavities in white matter and cortical atrophy; elevated urine sulfite; *SUOX*, *MOCS1*, *MOCS2*, and *GPHN* mutations
Glycine encephalopathy	Onset in neonatal period, myoclonic seizures, lethargy/stupor, breathing difficulties, hiccups, rapidly fatal	Glycine levels elevated in urine, plasma, and CSF; *GLDC*, *AMT*, *GCSH*, and other mutations
Disorders of γ-aminobutyric acid (GABA) metabolism	Frequent seizures, diffuse, generally nonprogressive encephalopathy, hypotonia, extrapyramidal signs, ocular abnormalities	MRI may reveal signal changes in globus pallidi, white matter, dentate nuclei; 4-hydroxybutyric acid in urine, plasma, and CSF; free GABA and homocarnosine are usually high in CSF *ALDH5A1* gene mutation
Menkes disease	X-linked disorder, rapidly progressive neurodegeneration, seizures, hair changes, hypothermia, arterial degeneration, osteoporosis and other skeletal changes	Pili torti on hair microscopy; low serum copper and ceruloplasmin; *ATP 7A* gene mutation on Xq
Alpers syndrome	Familial rapidly progressive encephalopathy with onset in infancy, intractable seizures, liver disease, progressive cerebral atrophy	Genetic testing for *POLG1* mutation (DNA polymerase γ)
Early infantile epileptic encephalopathy (Ohtahara syndrome)	Frequent, refractory tonic spasms with onset in first few months of life; frequent association with brain malformations; high mortality and very poor neurodevelopmental outcome in survivors	Suppression-burst pattern on EEG; MRI may demonstrate brain malformations
Early myoclonic encephalopathy	Early-onset, frequent myoclonias and partial seizures; association with genetic and metabolic causes; poor prognosis for psychomotor development	Suppression-burst pattern on EEG
Epilepsy of infancy with migrating focal seizures	See discussion	

acid. The final diagnosis of epilepsy of infancy with migrating focal seizures was concluded based on the electroclinical findings and exclusion of known etiologies. When followed up at 16 months of age, he continued to have 1–2 seizures per week, severe psychomotor retardation, and a head circumference below the first percentile.

DISCUSSION Epilepsy of infancy with migrating focal seizures (earlier known as malignant migrating partial seizures in infancy) was first reported in 1995 by Coppola et al., who described 14 infants with a severe epileptic disorder characterized by refractory multifocal seizures involving both hemispheres and severe psychomotor developmental delay.[2] The diag-

Figure Ictal EEG during a seizure manifested by gaze deviation to the left



Note seizure onset with α range activity over the right central and temporal leads later evolving into delta activity (A). Ictal EEG after 5 minutes shows seizure onset from the left central and temporal leads (B). The child had tonic posturing of the right upper limb during this period.

nostic criteria include the presence of 1) normal development before seizure onset, 2) onset before 6 months, 3) migrating focal motor seizures at onset, 4) multifocal seizures becoming intractable, 5) intractable to conventional antiepileptic drugs, 6) no identified etiology, and 7) profound psychomotor delay.[4] It is a rare syndrome and has been reported in approximately 50 patients.

Clinical features. Three distinct phases are described in the natural history of this syndrome.[4,5] Seizures appear after an uneventful perinatal period and normal early development. The first phase is heralded by seizures beginning in the first few months. The seizures are mainly focal motor with frequent secondary generalization. Autonomic manifestations such as apnea, cyanosis, or flushing are common. This phase usually lasts a few weeks or months. The second phase (also called the stormy phase) starts variably between 1 and 12 months of age. It is characterized by very frequent polymorphous focal seizures. They occur in multiple clusters in a day or nearly continuously. Long-term video EEG recordings frequently reveal subclinical ictal manifestations during this phase. The third phase begins between 1 and 5 years of age. It is a relatively seizure-free period with severe psychomotor retardation. This phase may be frequently complicated by seizure recurrences during intercurrent illnesses and further developmental regression.

Etiology. The exact etiology of this syndrome is not known. A role of channelopathies or metabolic disorders is suspected and is the focus of ongoing research. Neuroimaging has been normal in all reported patients. No familial occurrence or consanguinity has been reported. No metabolic abnormalities have been identified. In those cases that were examined postmortem, no cortical dysplasia or neuronal migration defects have been found.[4]

Sodium channel (*SCN1A*) mutations have been identified in patients with infantile-onset cryptogenic focal epilepsy with variable intellectual disabilities.[3] However, no mutations of potassium (*KCNQ2, KCNQ3*), sodium (*SCN1A, SCN2A*), or chloride (*CLCN2*) ion channels were identified in a study of 3 patients with epilepsy of infancy with migrating focal seizures.[6] Recently, a submicroscopic duplication 16p11.2 was found in an infant with this phenotype, raising the possibility that such chromosomal rearrangements may play an etiologic role.[7]

EEG. The EEG patterns in migrating partial seizures in infancy evolve over time.[8] The interictal EEG initially shows diffuse slowing of background activity and frequent slow waves, which often shift from one hemisphere to the other. Multifocal discharges originating from both hemispheres are also frequently noted. The ictal EEGs display paroxysmal discharges occurring in various regions in consecutive seizures in a given patient. The area of ictal onset shifts from one region to another and from one hemisphere to the other, with occasional overlapping of consecutive seizures. The migratory feature of ictal discharges is not pathognomonic of the disorder and may be seen in benign partial epilepsy of infancy.[9]

Treatment. Therapies including conventional antiepileptic drugs, pyridoxine, biotin, folinic acid, ketogenic diet, steroids, and adrenocorticotropic hormone have proved ineffective. Vigabatrin and carbamazepine may worsen the seizures. Some improvement has been reported with the use of bromides and stiripentol.[10,11]

Prognosis. The long-term outcome is dismal in most cases. Most children have severe psychomotor retardation and acquired microcephaly along with continuing seizures. A few children whose seizures are controlled may acquire the ability to reach for objects and walk, but do not develop language. A number of patients die before the end of the first year of age or later, mainly because of intercurrent infections and respiratory failure.[5]

AUTHOR CONTRIBUTIONS

All authors contributed to the content of the manuscript. S.S., N.S., and R.K. performed the clinical and diagnostic evaluation of the child, reviewed the literature, and prepared the manuscript. S.G. was in charge of the case and approved the final version of the manuscript.

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Child Neurology: Dravet syndrome

When to suspect the diagnosis

John J. Millichap, MD
Sookyong 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 convulsive 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.[1,2] "Dravet syndrome" (DS), proposed in the 2001 ILAE report, encompassed SMEI and "borderline" SMEI (SMEB).[2] SMEB represents SMEI with less frequent seizures and atypical features.[1-5] The discovery of associated specific mutations within the *SCN1A* gene, in 2001, sparked an interest in DS among pediatric epileptologists.[6] 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 frontocentral 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.

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Table Differential diagnosis of Dravet syndrome[1,3,4]

Clinical feature	DS	FS	SIMFE	BME	LGS	MAE
Onset <1 y	+	+/−	+/−	+/−	−	−
Fever-sensitive seizures	+	+	+/−	−	−	+/−
Hemiconvulsion	+	−	+/−	−	−	−
Generalized convulsion	+	+/−	+/−	−	+/−	+
Partial seizures	+	+/−	+	−	+/−	−
Myoclonic seizures	+/−	−	−	+	+/−	+
Tonic seizures	−	+/−	−	−	+	−
Atypical absence seizures	+/−	−	−	−	+	+
Generalized ED	+/−	−	−	+	+	+
Multifocal ED	+/−	−	+	−	−	−
Photosensitivity	+	−	−	−	−	−
Abnormal development	+	−	+	−	+	+
Abnormal brain MRI	−	−	−	−	+/−	−

DS = Dravet syndrome; FS = febrile seizures; SIMFE = severe infantile multifocal epilepsy; BME = benign myoclonic epilepsy; LGS = Lennox-Gastaut syndrome; MAE = myoclonic astatic epilepsy; ED = epileptiform discharges; + = usually present; +/− = maybe present; − = usually absent.

experienced any unprovoked seizures during valproate monotherapy.

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 idiopathic 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-astatic 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 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]

DISCUSSION

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.[3]

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.[1,3-5,7]

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, autonomic, automatisms), and "obtundation status." Obtundation status is a special seizure type in DS and consists of fluctuating 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.[3] 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

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.[9] 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.[3,4] 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.[3,4,6,7,9,10] 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.[9] 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.[3] 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.[1,3,5,8] Some patients may have persistently normal interictal records.[8] 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. Transgenomic 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.[3,8] In Europe, stiripentol, an inhibitor of cytochrome P450, is added to the combination of valproate and clobazam and is particularly effective against status epilepticus.[3] 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.[3]

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.

DISCLOSURE

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Clinical Reasoning: Novel GLUT1-DS mutation

Refractory seizures and ataxia

Sonali Sen, MD
Karen Keough, MD
James Gibson, MD, PhD

Correspondence to Dr. Sen: stsen@seton.org

ABSTRACT

Intractable epilepsy is a common diagnosis among child neurology practitioners with medical management remaining unsatisfactory in many cases. GLUT1 deficiency syndrome (GLUT1-DS) is a disorder that should be considered in such situations. Evaluation by comparing serum to CSF glucose levels is a fast and relatively easy test, with hypoglycorrhachia being highly suggestive of GLUT1-DS. Furthermore, treatment with the ketogenic diet is well-established and can result in significant improvement in quality of life for these patients. The following case report outlines the presentation of one such patient and highlights common features that can be seen with GLUT1-DS. Of interest, she was found to have a spontaneous, novel mutation that has not been reported previously. Her case allows us to expand on the present literature and demonstrate the improvements that can be seen in a child with appropriate treatment. *Neurology®* 2015;84:e111–e114

SECTION 1

An 18-month-old girl with intermittent paroxysmal events was brought to our clinic for workup. Medical history revealed recurrent 1- to 2-minute episodes of unresponsiveness, head rolling, and disconjugate gaze beginning around 3 months of age. Distinct from these events, she also had occasional dystonic posturing of her left arm. Prior MRI and 2 4-hour video EEGs were normal; medication had not been started due to the uncertain etiology of her episodes.

Brief unresponsive episodes were present in the setting of mild developmental delay; she sat at 7 months, walked at 16 months, and had 1 word and followed 2-step commands at 18 months. She had low muscle tone and poor coordination but her motor examination was symmetric.

Questions for consideration:

1. What should be included in the differential diagnosis?
2. Is further workup necessary at this time?

The differential diagnosis of paroxysmal neurologic events in infancy includes benign paroxysmal torticollis of infancy, benign paroxysmal vertigo, syncope, dyskinesias, migraines, Sandifer syndrome, and seizures. Persistent reports of stereotyped events, particularly in light of developmental delay, warrant prolonged EEG studies for spell characterization.

GO TO SECTION 2

From UT Southwestern, Austin, TX. All authors are currently with UT Austin, TX.

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SECTION 2

Just before her first visit to our office, the patient had a more prominent episode that began with a fall followed by apnea and cyanosis. As observed in prior events, there was a 2- to 3-minute period of unresponsiveness; however, distinct from others, this event was followed by a 10-minute recovery period. A 3-day EEG at this time revealed rare but obvious 150–200 μV bursts of 2–2.5 Hz generalized spike and wave activity during sleep; no clinical events were captured. The suspicious nature of this event along with interictal epileptiform activity prompted treatment with lamotrigine (Lamictal; GlaxoSmithKline, Research Triangle Park, NC). Her family reported that after starting lamotrigine the child was more alert, attentive, and made developmental gains, more notably in expressive than receptive language skills. The family reported that milder episodes of unresponsiveness and dystonic posturing continued intermittently. In addition to presumed seizures, the mother described transient episodes of poor balance and slightly unstable gait that self-resolved within hours to days.

Questions for consideration:

1. How does the differential diagnosis broaden in an ataxic toddler with a history of seizures and dystonic posturing?
2. Is there a unifying diagnosis?
3. What further workup should be performed?

It is important to recognize the evolution of symptoms as a child develops. Previously reported poor coordination has now become a more obvious intermittent ataxia. With the addition of episodic, reversible ataxia, the diagnostic considerations broaden to include vitamin deficiencies, neuroblastoma, various metabolic disorders, and genetic ataxias.

GO TO SECTION 3

At 3 years old, the patient was hospitalized during a severe ataxic episode that gradually resolved over 10 days. Repeat MRI was normal and EEG showed the same interictal generalized spike and wave activity during sleep. Lactate, ammonia, vitamins B_{12} and E, urine organic acids, urine catecholamines, and α-fetoprotein were all within normal limits. Workup for hereditary ataxias was negative. Lumbar puncture was performed to collect CSF neurotransmitters and a glucose level. Studies revealed normal levels of neurotransmitters and a low CSF glucose of 28 (normal 45–80 mg/dL) compared to near simultaneous serum glucose of 89.

Sequence analysis of the *SLC2A1* gene coding region revealed an in-frame deletion, confirming the diagnosis of GLUT1 deficiency syndrome. One of the characteristic features of the GLUT-1 transporter is a 5-residue motif RXGRR (where X is any amino acid) present in the cytoplasmic loops that connect transmembrane (TM) domains 8 and 9.[1] The mutation seen in our patient occurs on the boundary of TM domain 8 and the cytoplasmic loop. Considering the location of the deletion within this highly conserved sequence, this mutation likely alters the function of the transporter, resulting in the symptoms noted in our patient.

This is a novel mutation not previously reported. Both parents' *GLUT1* genes were sequenced, with normal results confirming the de novo occurrence of the mutation in the patient. Review of the literature and listed genetic mutations to date indicate no other reported pathogenic in-frame deletions within *SLC2A1*.

Table Common symptoms associated with GLUT1-DS phenotypes

GLUT1-DS phenotypes	Symptoms
Classical	Seizures (focal, apneic/cyanotic, abnormal eye movements, absence); may transform or generalize over time
Early onset (<2 y)	Mild to severe developmental delay (primarily speech, dysarthria)
Late onset (>2 y)	Ataxia (C/P)
	Dystonia (C/P)
	Chorea (C/P)
Nonclassical	Mild to severe developmental delay
≥3 y	Ataxia (C/P)
	Dystonia (C/P)
	Chorea (C/P)
Adult onset	Mild/infrequent seizures (myoclonic or generalized tonic-clonic)
Adolescence/early adulthood	Paroxysmal exercise-induced dyskinesia

Abbreviation: C/P = continuous or paroxysmal (some patients have continuous symptoms with paroxysmal worsening).
The table outlines the known phenotypes of GLUT1 deficiency syndrome (GLUT1-DS). The classical presentation is the most common, with the majority of patients presenting before 2 years of age. There is a late-onset form wherein patients develop symptoms after 2 years and have been noted to have less severe developmental delay than their younger counterparts. The nonclassical and adult-onset types are significantly less common.[4] In adult-onset GLUT1-DS, symptoms are typically brought on by stress, fatigue, and fasting.[10] Column 2 is presented in descending order of reported frequency.[4]

DISCUSSION Classic GLUT1 deficiency syndrome (GLUT1-DS) can present with a variety of symptoms including infantile seizures, developmental delay, movement disorders, or ataxia.[2] The table illustrates many of the features associated with the 3 known phenotypes of GLUT1-DS. The symptoms result from decreased CSF glucose due to a mutation in the *SLC2A1* gene, which encodes a membrane-spanning protein that transports glucose across the blood–brain barrier.

GLUT1-DS frequently does not present until the later part of infancy, which may be due to the fact that in the neonatal period ketones are more readily available as a source for energy metabolism in the brain. As cerebral glucose uptake increases during childhood, it is postulated that inadequate glucose transport to neurons results in impaired cerebral metabolism and disruption of thalamocortical development.[3] In one retrospective study of 46 patients with early-onset, classical GLUT1-DS, average CSF glucose was 1.7 mmol/L (30 mg/dL) with a CSF: serum glucose ratio of 0.35.[4] The average time to diagnosis of patients in this study was 6 1/2 years after the onset of symptoms. Seizure presentation varies greatly, including cyanotic spells, atypical absence, atonic, and generalized tonic-clonic seizures, among others.[2] Extent of intellectual disability correlates with the severity of hypoglycorrhachia.[4]

Since the identification of the syndrome in 1991, approximately 200 patients have been reported, of whom 70%–80% have one of a variety of mutations within the *SLC2A1* gene.[5] In a 2005 review,[6] 14 of 16 patients in whom genetic analysis was performed had novel genetic mutations within *SLC2A1*. In that article, Wang et al.[6] proposed 5 different phenotypes based on the extent of residual function of GLUT1, ranging from minimal to lethal. In 2010, Leen et al.[3] expanded upon this hypothesis by demonstrating that patients with nonsense, frameshift, and multiple exon deletions had lower CSF glucose concentrations and frequently more severe presentation than those with missense mutations. To date, however, no exact correlation between genotype and phenotype has been discerned. Even among patients with identical mutations, there remains significant phenotypic variance. This variability in presentation and severity likely reflects influence of other genes related to the function of *SLC2A1*.[5]

In GLUT1-DS, neurons utilize ketones as a source of energy instead of glucose. The ketogenic diet (KD) functions by limiting carbohydrates and

increasing fat content, thereby promoting ketone body formation. A variety of ketogenic dietary regimens exist, several of which have been shown to be effective. The KD is frequently used as supplementary or second-line treatment for intractable epilepsy; however, in GLUT1-DS it is the primary treatment since an alternate source of fuel for the brain is necessary to prevent symptoms.

As long as adequate ketosis is maintained, seizure control can frequently be achieved without anticonvulsants.[7] In one retrospective study of 37 patients with GLUT1-DS with epilepsy, 62% acquired complete seizure control and another 24% had a reduction in frequency.[4] The KD has also been shown to be effective in decreasing the frequency/severity of movement disorders.[4] Although a baseline level of delay is expected in all children, adequate treatment with the KD allows for greater developmental progress. Early recognition of GLUT1-DS optimizes this possibility. Of significance, the KD in rat models has been shown to decrease brain growth and impair visual-spatial learning compared to controls.[8] Studies in humans are necessary to further understand the potential effects on memory. Additional long-term complications of the diet are currently being investigated, including dyslipidemia due to high fat content and poor growth due to limited protein intake.[9] The extent of seizure control is highly dependent on the patient's compliance with the diet. The difference in fat: carbohydrate + protein ratio affects the palatability of the diet, which can influence adherence.

Our patient, now 5 ½ years old, has been seizure-free for 22 months since starting on a KD. She was initially weaned off lamotrigine but became irritable, so was restarted on a lower dose for mood stability. During this time, she has had noticeable improvement in her language and motor skills. Recent neuropsychological evaluation using the Adaptive Behavior Assessment System–II suggested a developmental functioning in the 3–5 years range, with most simple tasks being age-appropriate. She displayed weakness with complex tasks involving memory, long-term attention, and multimodal learning.

The presentation of GLUT1 deficiency syndrome can often be subtle. Developmental delay may be mild, and other associated signs/symptoms are highly variable. Detection of seizures may be difficult; therefore, prolonged EEG may be helpful in confirming ictal events. CSF studies with concurrent serum glucose levels should be obtained to establish a diagnosis. It is important to consider this metabolic disorder in infants and children with a constellation of refractory paroxysmal events, gait disturbance, and involuntary movements, especially when symptoms worsen with illness or fasting. Early recognition of GLUT1-DS and appropriate treatment can allow for a much higher quality of life.

AUTHOR CONTRIBUTIONS

Sonali T. Sen: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Karen Keough: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, study supervision. James Gibson: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval.

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DISCLOSURE

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Clinical Reasoning: An 11-year-old boy with language disorder and epilepsy

Liling Dong, MD
Xiang-qin Zhou, MD

Correspondence to Dr. Zhou: zwypumc@126.com

SECTION 1

An 11-year-old boy with recurrent seizure attacks and expressive language disorder was referred to our clinic. His initial attack was at the age of 2, when he had a sudden facial twitching, followed by a generalized tonic convulsion together with loss of consciousness, lasting a few minutes. The episode recurred every few months thereafter. In addition, he could never utter any verbal language, although he could understand what others said, as well as follow their commands.

Further questioning revealed that he was born after a full-term difficult delivery. The Apgar score was 5 at birth. He could walk at 14 months. He was in the third grade of elementary school at the initial visit, with a poor intellectual performance in contrast to his normal motor development. He was able to conduct most daily activities, including eating, dressing, bathing, etc.

On physical examination, although his hearing and comprehension were normal, he had no verbal response and could only follow commands by nonverbal means. He had some difficulties in chewing and swallowing solid food. He presented with an inexpressive face with a half-open and drooling mouth (figure 1). Moreover, he was unable to show his teeth, close his eyes, or protrude his tongue on command, yet he could smile at a joke, yawn, close eyes during sleep, and move the tongue unconsciously. There was no atrophy of tongue muscle or fasciculation. The pupillary, corneal, gag, and jaw reflexes were normal, and a right Babinski sign was elicited. His other motor and sensory systems were normal, as well as his coordination and gait.

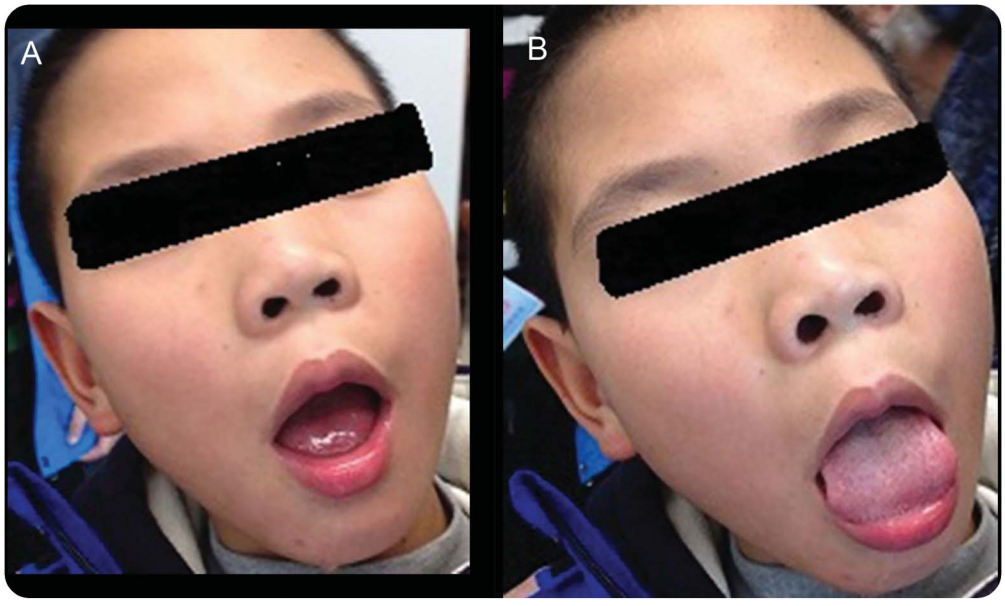
The interictal EEG displayed scattered slow wave from posterior leads (figure 2). No epileptic discharge was recognized.

After the administration of 400 mg carbamazepine a day, he was free of seizures, but all the other symptoms remained.

Questions for consideration:

1. What is the differential diagnosis at this stage?
2. What is the probable topical diagnosis?

Figure 1 Facial features



The boy presented with an inexpressive face with a half-open and excessively drooling mouth (A). He had difficulties in protruding his tongue, without tongue muscle atrophy (B).

From the Department of Neurology, Peking Union Medical College Hospital, Beijing, China.

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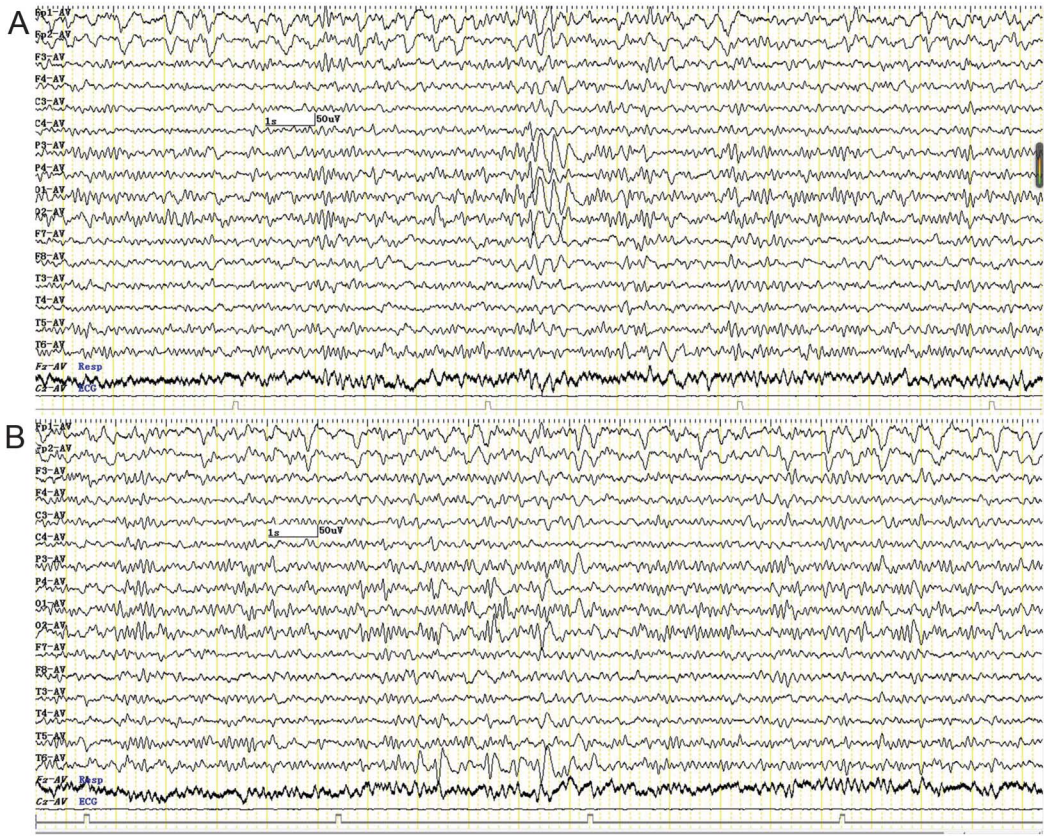
Figure 2 Interictal EEG



The interictal EEG displayed scattered θ wave with low to medium amplitude (A) and slow wave at 2 to 3 Hz (B) from posterior leads.

GO TO SECTION 2

SECTION 2

The differential diagnosis at this stage might consist of the following common diseases:

1. Landau–Kleffner syndrome (LKS): since the combination of epileptic disorder and language disorder are chief complaints of the boy, the differential diagnosis might come to epilepsy-aphasia spectrum, especially LKS, which is an acquired verbal auditory agnosia combined with a subsequent disruption of expressive language due to prominent epileptiform activity. It usually occurs in children who are between the ages of 3 and 10 years with previous normal age-appropriate speech, and mostly a spontaneous remission in adolescence in parallel to the EEG improvement. Our boy has never developed speech ability and his auditory language comprehension is excellent, which do not support the diagnosis of LKS.
2. Congenital vocal organ diseases, such as ankyloglossia: these might contribute to loss of expressive language ability, but they cannot cover all the symptoms of the patient. Furthermore, the boy has undergone ear, nose, and throat examinations repeatedly without positive findings.

The boy's distinctive symptoms are persistent movement disorders of facial, lingual, pharyngeal, masticatory, and laryngeal muscles, with preserved brainstem reflexes, normal tongue muscle bulk, absent tongue fasciculation, and pathologic laughter. These suggest that the location of neurologic impairment is at the supranuclear level such as cortical or subcortical area, instead of the lower motor neurons, such as motor nuclei in brainstem, cranial nerve, neuromuscular junction, muscle, etc.

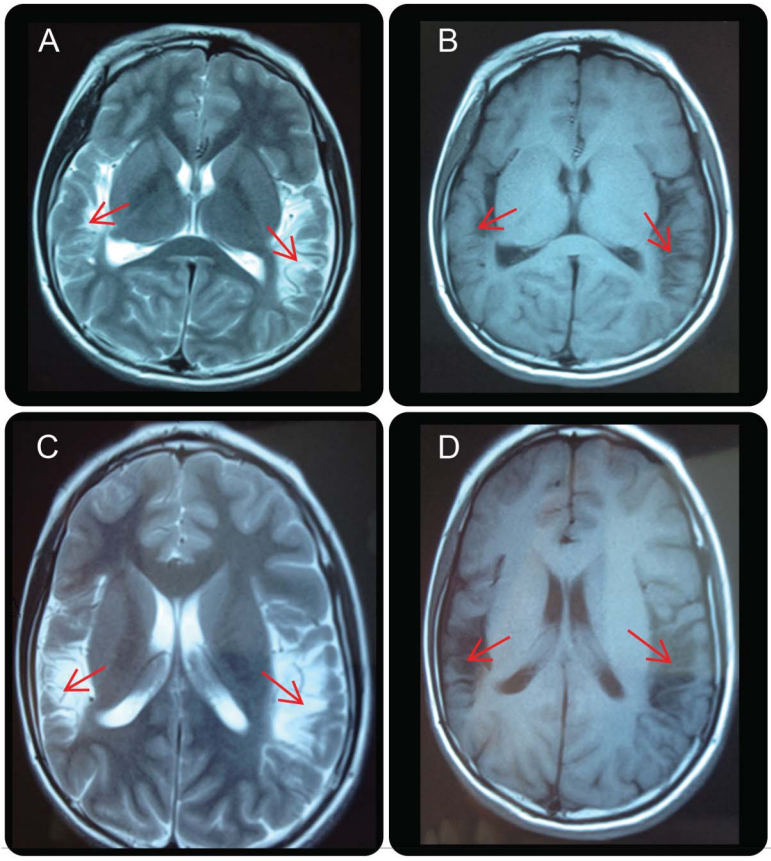
There seems to be a paradox in the clinical symptomatology of the boy. He has lost the voluntary movement of orofacial muscles, while the reflexive or involuntary movement is unaffected, which makes the topical diagnosis more confusing.

Questions for consideration:

1. What should be done next to disclose the topical diagnosis?
2. Can the lesion detected be responsible for all the symptoms?

GO TO SECTION 3

Figure 3 Brain MRI



(A, B) T2- and T1-weighted MRIs show prominent symmetrical atrophy or shrinking of bilateral insular and temporal lobes. Ulegyric cortex is shown in bilateral temporal lobes (arrows) with mushroom-shaped gyri and diminished subcortical white matter, which was hypointense on T1-weighted image and hyperintense on T2-weighted image. (C, D) T2- and T1-weighted MRIs show atrophy of bilateral insular and parietal lobes, as well as ulegyric cortex in bilateral parietal lobes (arrows).

SECTION 3

Cranial MRI revealed abnormal signal intensity and significant symmetrical atrophy in bilateral temporal, parietal, and insular lobes. The abnormal signal intensity was mainly located in subcortical white matter, which was hypointense on T1-weighted imaging and hyperintense on T2-weighted imaging, consistent with leukomalacia and gliosis. The deeper sulcal portions showed more prominent volume loss than the superficial parts, making a mushroom-shaped lesion (figure 3).

With the assistance of MRI, topical diagnosis could easily be achieved. The symptoms of the boy should be attributed to bilateral opercular lesions. Operculum comprises the cerebral cortices from frontal, parietal, and temporal lobes overlying the insula. The motor nuclei of the 5th, 7th, 9th, and 10th cranial nerves in brainstem are innervated by bilateral corticonuclear tracts descending from motor cortices, and the 12th cranial nerve is controlled by the opposite corticobulbar tract.[1] Therefore, a bilateral interruption between motor cortices and cranial motor nuclei of brainstem can lead to the suprabulbar palsy. In contrast, the spontaneous and reflexive controls are regulated by thalamus, hypothalamus, and extrapyramidal tract,[2] which are not involved in this case confirmed by MRI, resulting in the normal reflexive movement.

Questions for consideration:

1. What is the probable final diagnosis?
2. What is the differential etiologic diagnosis?
3. Does epileptic attack have a role in the pathogenesis of the disease?

GO TO SECTION 4

SECTION 4

Foix-Chavany-Marie syndrome (FCMS), first described in neurologic literature by Foix, Chavany, and Marie in 1926, is a rare cortical type of pseudobulbar palsy, usually resulting from damages in the anterior part of the operculum. Clinical manifestations mainly consist of facial diplegia, hypersalivation, dysarthria, and dysphagia.[3] FCMS could link language disorder, orofacial movement disorder, and bilateral opercular lesions in the boy. The selective paralysis of voluntary fasciopharyngo-glosso-masticatory movements with preservation of reflexive and automatic functions is referred to as "autonomic-voluntary dissociation," which is a distinctive feature of FCMS.[3]

The etiologic spectrum of FCMS includes, among others, CNS infections, congenital abnormality, epileptic disorder, stroke, vasculitis, head trauma, tumor, and neurodegenerative disease.[4] Based on the supplemental medical history and MRI manifestation, CNS infections, head trauma, and stroke could be ruled out. The persistent clinical course, neither progressive nor reversible, is not in favor of the diagnosis of tumor, neurodegenerative disease, or vasculitis.

The differential diagnosis at this stage includes:

1. Perinatal hypoxic-ischemic encephalopathy–related FCMS: considering the history of asphyxia at delivery, along with the ulegyric pattern of MRI, we infer that all the symptoms might be secondary to perinatal hypoxic-ischemic encephalopathy, which might be a new etiology never covered in the previous literature.
2. Congenital FCMS: the patients with congenital type could have extra developmental abnormalities such as developmental delay, arthrogryposis, pectus excavatum, micrognathia, hearing loss, hemiparesis, or paraparesis.[5] MRI and pathologic examination could reveal perisylvian polymicrogyria or schizencephaly, failure of opercular closure, periventricular gray matter heterotopias, or absence of the septum pellucidum.[5] There is no obvious evidence in support of the congenital FCMS in our case.
3. Acquired epileptiform opercular syndrome: it was first proposed by Shafrir and Prensky.[6] When strong, persistent epileptic discharge spreads to bilateral opercular cortices, interfering with the cortical function in perisylvian regions, seizure patients can develop FCMS symptoms, which will disappear with EEG improvement.[6] However, the operculum syndrome in the present case is supposed to be irrelevant to epileptic discharge or seizure episode. The explanations are as follows: the paralysis of orofacial muscles precedes seizure; the symptoms are persistent, do not fluctuate, and are not relieved with seizure remission; and no epileptic discharge has been detected in the symptoms.

DISCUSSION In the differential diagnosis of children with difficulties in speech output and epileptic attack, especially those with autonomic-voluntary dissociation, FCMS should be considered.

The clinical course, treatment, and prognosis of FCMS are diverse, depending on the heterogeneous underlying etiologies. In adults, FCMS is mostly induced by multiple successive strokes involving bilateral anterior opercula.[4] In children, meningoencephalitis, epilepsy, and congenital malformation are the most frequent etiologies.[7]

Although it is usually called "anterior operculum syndrome," the lesions of FCMS are not limited to operculum. Most patients have bilateral opercular lesions, while some show a single opercular lesion and a coexistent contralateral subcortical lesion, or bilateral subcortical lesions without opercular involvement.[8] Some even result from the lesions verified by SPECT, which are invisible on MRI. Thus, if the opercular lesions are negative on MRI in those with suspected FCMS, the subcortical lesions involving corticobulbar tracts should be explored. And if there are no structural lesions on MRI, SPECT should be performed to identify the possible functional lesions.[9]

On the basis of anatomical knowledge, it is generally believed that a unilateral lesion does not result in FCMS and a bilateral structural or functional impairment between motor cortices and brainstem cranial motor nuclei is necessary. However, Giraldo-Chica et al.[10] have reported an FCMS case caused by unilateral right opercular ischemia affirmed by both brain MRI and SPECT, which proposes whether a unilateral structural and functional lesion is sufficient for FCMS. Further research is needed to investigate whether the contralateral lesion is invisible because of the limitation of technique, or because there is an anatomical variant that the corticonuclear tract is predominantly unilateral.

AUTHOR CONTRIBUTIONS

Dr. Dong drafted and revised the manuscript, including medical writing. Dr. Zhou critically revised the manuscript for important intellectual content.

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Introduction

Pediatric Perspective

By Robert Hurford, MSc, MRCP, and Laura L. Lehman, MD

Stroke is a condition of the elderly in the minds of many. Pediatric stroke differs in nearly every aspect when compared with stroke in adults. However, it is not rare; the incidence of ischemic and hemorrhagic stroke combined is between 2.3 to 13 per 100,000 children per year and features among the top 10 causes of death. Furthermore, insults to the developing brain can cause lifelong disability such as epilepsy, as in the case presented by Zamora et al.

Whereas modifiable risk factors and atherosclerotic disease are common in adults with arterial ischemic stroke, these are rarely present in children. Nonatherosclerotic cerebral arteriopathies such as parainfectious focal cerebral arteriopathy are detected in about half of pediatric patients with ischemic stroke. The Suter et al. case reminds us that arterial dissection occurs in young patients and can be nontraumatic. The Siegler et al. case also highlights the role of congenital cardiac disease and hematologic disorders such as sickle cell disease as important causes of pediatric ischemic stroke.

As in adults, clinicians begin with an accurate history and good clinical examination, which help localize the lesion. The Franssanito et al. case underscores the value of this clinical examination when working up a pediatric stroke patient. Pediatric ischemic stroke presents several diagnostic challenges, including higher rates of seizures at onset and stroke mimics, such as migraine aura and Todd paralysis. As few as 7% of pediatric patients presenting with acute neurologic symptoms have a cerebrovascular cause compared with 3 quarters of adults. These factors make streamlined pathways, which have revolutionized the prognosis of adult patients with ischemic stroke, more difficult to replicate for children.

The full spectrum of cerebrovascular disease seen in adults is also found in children, including arteriovenous malformations and fistulas, cavernomas, and aneurysms. As demonstrated in the case by Aw-Zoretic et al., sometimes these can be the only clue to a wider genetic diagnosis.

From the Nuffield Department of Clinical Neurosciences (R.H.), University of Oxford, United Kingdom; and Department of Neurology (L.L.L.), Stroke and Cerebrovascular Center, Boston Children's Hospital, MA.
Correspondence Dr. Hurford robert.hurford@ndcn.ox.ac.uk
For disclosures, please contact the *Neurology*® Resident & Fellow Section at rfsection@neurology.org.

Adult Perspective

By Behnam Sabayan, MD, PhD, and Mitchell S.V. Elkind, MD, MS, MPhil

Stroke is among the top 10 causes of mortality in children. Some reports indicate that the number of children with stroke has increased in the recent years. It is estimated that 1 of 2,700 live births has either ischemic or hemorrhagic stroke, and the risk of stroke from birth through age 19 years is nearly 5 per 100,000 children per year. The increase in stroke among children has been attributed to a variety of factors, including improvements in availability of neuroimaging studies and awareness of physicians and families about this clinical entity.

More than half of pediatric patients with stroke have long-term motor, functional, and cognitive outcomes. Epilepsy, speech or language disorders, visual impairments, behavioral abnormalities, poor attention, and lower school performance are commonly seen among pediatric patients with stroke. Children with cerebrovascular events are at significantly higher risk of recurrent stroke as well. The financial and psychosocial burden of stroke in infants and children is substantial. Health care costs in children with stroke are 15 times higher than in children of the same age without stroke. This burden can be decreased with earlier diagnosis, customized acute interventions, and multimodal rehabilitation soon after the insult.

Over the past several decades, case fatality from pediatric stroke has fallen consistently, meaning that a growing proportion of children with stroke survive into adulthood. Adult neurologists may not be as equipped as pediatricians to take care of some of the challenges posed by these survivors. Risk factors for childhood stroke differ from those in adult stroke; this could have implications for secondary prevention of stroke in this population. There is therefore a need for increasing awareness and education among pediatric and adult neurologists to ensure a safe transition of care over the life course.

The cases contained in this chapter focus on clinical features of pediatric stroke and discuss short- and long-term strategies to decrease the neurocognitive consequences of stroke in children. These cases help the adult neurologist understand important differences in pediatric stroke evaluation, management, and rehabilitation.

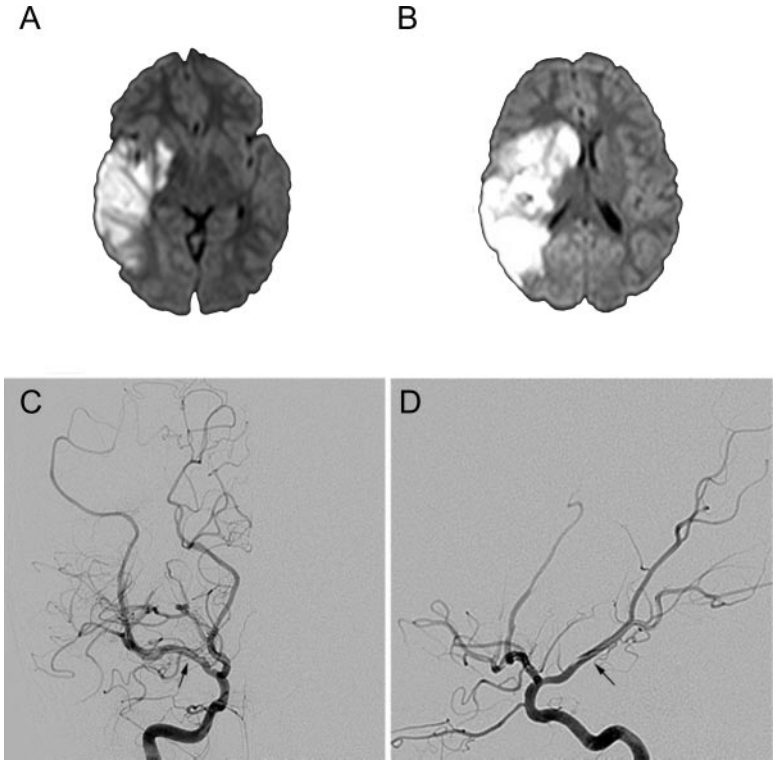
From the Department of Neurology (B.S.), Northwestern, Feinberg School of Medicine, Chicago, IL; and the Division of Neurology Clinical Outcomes Research and Population Sciences (NeuroCORPS) (M.S.V.E.), Columbia University, New York.
Correspondence Dr. Sabayan behnam.sabayan@northwestern.edu
For disclosures, please contact the *Neurology*® Resident & Fellow Section at rfsection@neurology.org.

Child Neurology: Stroke due to nontraumatic intracranial dissection in a child

Bernhard Suter, MD
Lisa Michael El-Hakam, MD

Address correspondence and reprint requests to Dr. Lisa Michael El-Hakam, Department of Pediatric Neurology, Baylor College of Medicine, Texas Children's Hospital, 6621 Fannin St. CC 1250, Houston, TX 77030-2399
hakam@bcm.edu

Figure MRI and catheter angiography



(A, B) Diffusion-weighted sequence of MRI of the brain shows acute infarction in the right middle cerebral artery (MCA) territory. (C, D) Catheter angiography showed irregularities of the right supraclinoid internal carotid artery, extending into the M1 segment of the right MCA. An intimal flap (arrow) indicates dissection.

A 9-year-old girl without prior trauma presented with weakness and headache. Examination showed profound left hemiplegia. MRI demonstrated a right middle cerebral artery (MCA) territory infarction. Magnetic resonance angiography showed proximal right MCA irregularity. Conventional angiography revealed an intracranial dissection (figure).

Intracranial dissections are frequently spontaneous (nontraumatic) and are associated with stroke in the young, comprising 60% of anterior circulation dissections in childhood.[1] Exclusion of intracranial dissections is challenging using magnetic resonance angiography; cerebral angiography must be considered.[2] Potential treatments include anticoagulation and antiplatelet therapies; Class III recommendations discourage anticoagulation because of the association of subarachnoid hemorrhage with intracranial dissection.[2]

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From the Department of Pediatric Neurology, Texas Children's Hospital, Baylor College of Medicine, Houston.
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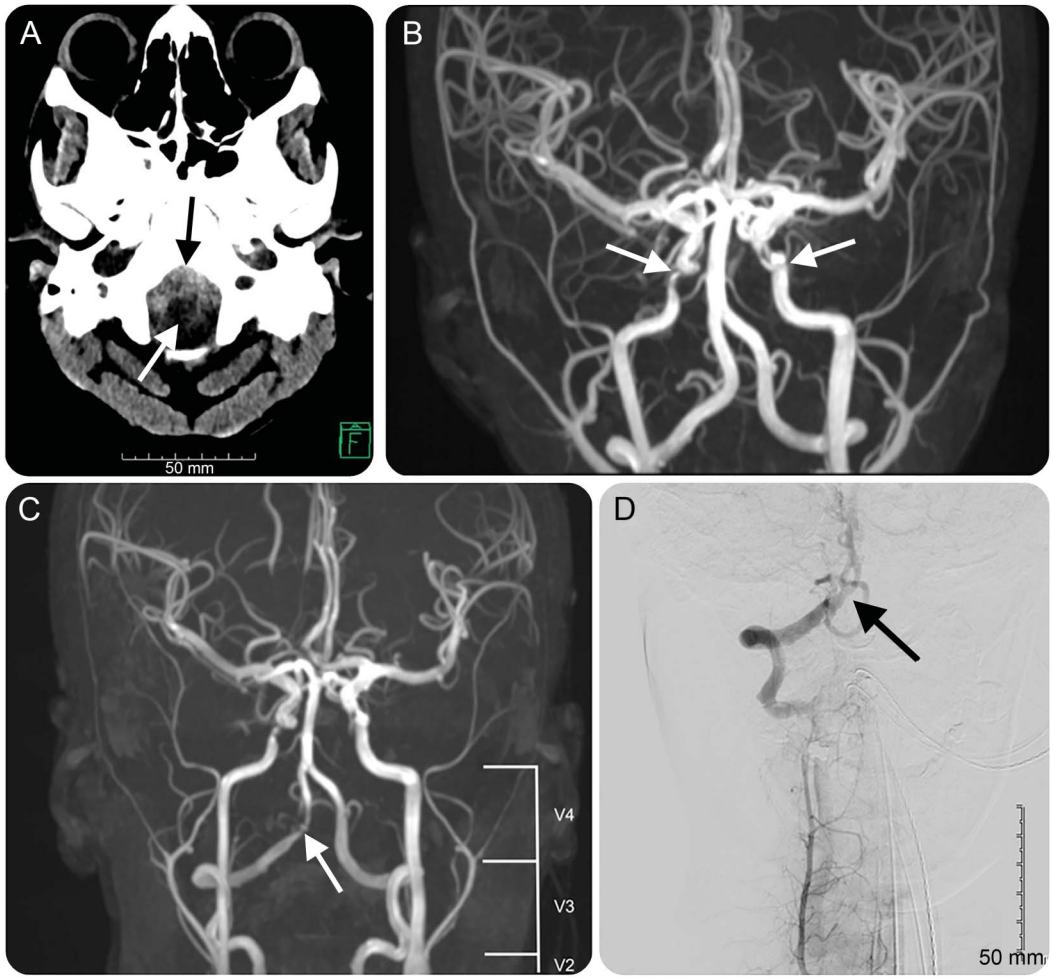
Teaching Neuro*Images*: Intracranial vertebral dissection in a 15-year-old boy with sickle cell disease

James E. Siegler, MD
Brenda Banwell, MD
Rebecca N. Ichord, MD

Correspondence to
Dr. Siegler:
james.siegler@uphs.upenn.edu

A 15-year-old boy with sickle cell disease became unresponsive after sudden-onset headache. There was no antecedent trauma. A head CT scan demonstrated subarachnoid hemorrhage at the medulla (figure). Magnetic resonance angiography of the head and neck identified the patient's known bilateral internal carotid artery stenosis (a moyamoya-like arteriopathy associated with stroke in sickle cell disease)

Figure Imaging



(A) Head CT at time of presentation. The black arrow indicates a hyperdense signal surrounding dark spinal cord (white arrow) in subarachnoid space, concerning for subarachnoid hemorrhage. (B) Magnetic resonance angiogram (MRA) of the head and neck 2 years prior to presentation. Arrows indicate bilateral internal carotid stenosis. (C) MRA of the head and neck during hospitalization identifies tapered appearance of the V4 segment of the right vertebral artery (arrow), consistent with dissection. Other segments of the vertebral artery are also labeled: V2 (pars transversaria) and V3 (atlas loop). (D) Digital subtraction angiogram of a right vertebral injection with arrow indicating the luminal narrowing corresponding to the region of dissection.

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From the Department of Neurology (J.E.S.), Hospital of the University of Pennsylvania; and Department of Pediatric Neurology (B.B., R.N.I.), Children's Hospital of Philadelphia, PA.

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and a new right vertebral artery dissection, which was confirmed on conventional angiography (figure). Prior MRI performed as part of routine cerebral monitoring did not reveal any preexisting abnormality of the vertebral artery.

The V4 segment of the vertebral artery has the lowest risk of dissection compared to other segments. However, due to its intracranial location, dissection at V4 can cause subarachnoid hemorrhage and mimic aneurysmal rupture.[1]

AUTHOR CONTRIBUTIONS

Dr. Siegler: conception of the idea of the manuscript, drafting of the original manuscript, preparation of images, and critical revisions to the manuscript for important intellectual content. Dr. Banwell: drafting of the manuscript and critical revisions to the manuscript for important intellectual content. Dr. Ichord: drafting of the manuscript and critical revisions to the manuscript for important intellectual content.

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DISCLOSURE

J. Siegler is a member of the *Neurology*® Resident & Fellow Section. He reports no competing financial interests. B. Banwell reports no disclosures relevant to the manuscript. R. Ichord receives grant support from the NIH. Go to Neurology.org for full disclosures.

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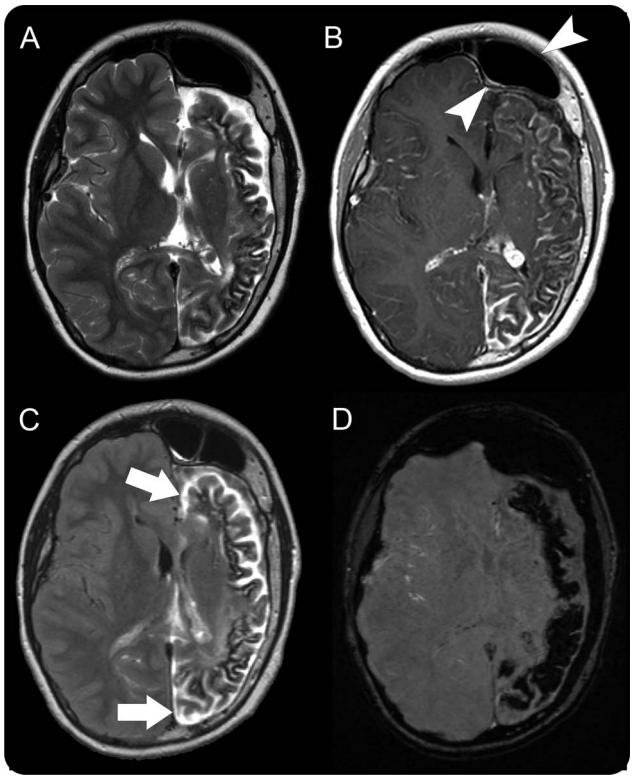
Teaching Neuro*Images*: Dyke-Davidoff-Masson in Sturge-Weber syndrome

Carlos A. Zamora, MD, PhD
Marinos Kontzialis, MD

Correspondence to
Dr. Zamora:
carlos_zamora@med.unc.edu

Figure MRI findings in Dyke-Davidoff-Masson syndrome and Sturge-Weber syndrome



(A) T2 and (B) contrast-enhanced T1 and (C) fluid-attenuated inversion recovery images show marked left hemispheric atrophy with engorgement of ipsilateral choroid plexus and extensive leptomeningeal enhancement (arrows, C). Note calvarial thickening with marked expansion of the left frontal sinus (arrowheads, B) and extensive susceptibility due to cortical calcification on susceptibility-weighted imaging (D).

A 13-year-old boy with long-standing seizures presented with a port wine stain involving the left V1 trigeminal distribution, right hemiparesis, and left-sided glaucoma. MRI showed typical manifestations of Sturge-Weber syndrome (SWS) with cerebral atrophy and extensive pial angiomatosis[1] (figure). Images also demonstrated findings of Dyke-Davidoff-Masson syndrome (DDMS) with compensatory calvarial expansion as a consequence of long-standing cerebral hemiatrophy.[2] DDMS usually results from early insults to the developing brain. Symptoms reflect the underlying injury and include seizures, mental retardation, hemiparesis, and facial asymmetry. Seizure management in SWS is challenging and may include medical therapy or surgery in refractory cases.

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AUTHOR CONTRIBUTIONS

Carlos Zamora: study concept, analysis of MRI data, revising the manuscript, and final approval. Marinos Kontzialis: analysis of MRI data, drafting and revising the manuscript, and final approval.

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From the Division of Neuroradiology, The Russell H. Morgan Department of Radiology and Radiological Science, Johns Hopkins University School of Medicine, Baltimore, MD.

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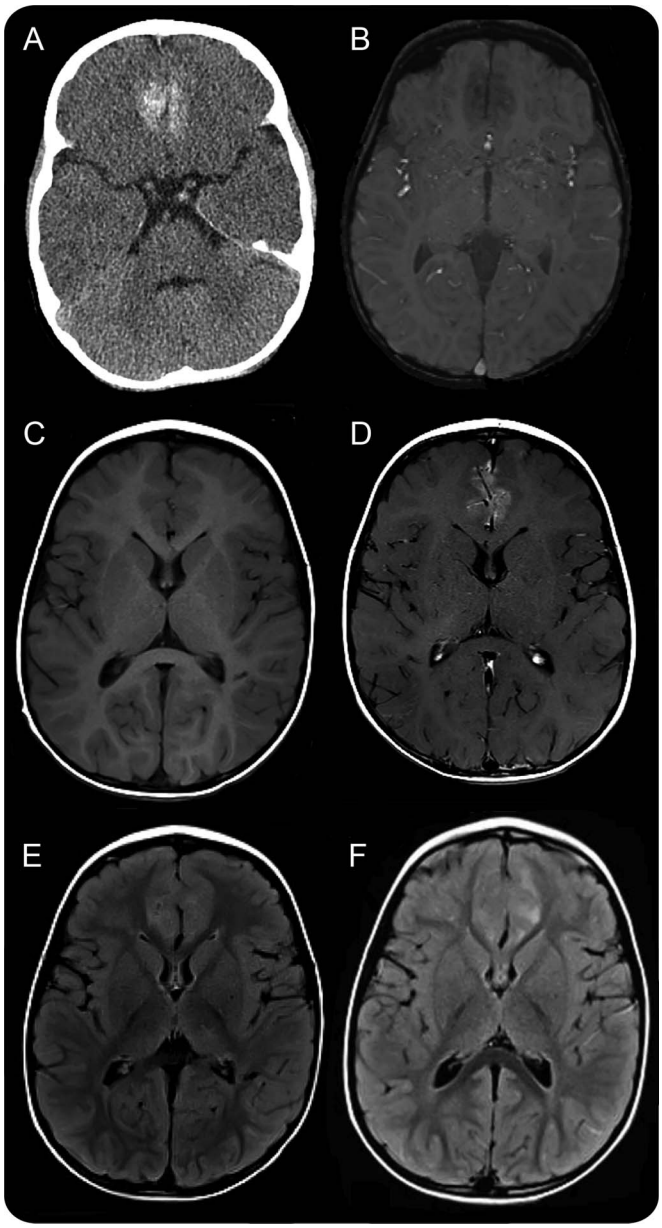
Teaching NeuroImages: Meningioangiomatosis

Jessie Aw-Zoretic, MB, ChB
Delilah Burrowes, MD
Nitin Wadhwani, MD
Maura Ryan, MD

Correspondence to Dr. Aw-Zoretic: jawdoc3@gmail.com

Figure 1 CT and MRI of bifrontal parasagittal lesion noncontrast axial CT



(A) Amorphous high density indicative of mineralization with corresponding subtle low signal on susceptibility MRI (B). (C) Precontrast T1 shows isointense but thickened cortex. (D) Postcontrast T1 shows robust leptomeningeal enhancement, presumably due to vascular proliferation, and subtle nonspecific cortical enhancement. Subcortical white matter signal changes, characteristic of meningioangiomatosis, were initially difficult to appreciate (E) but were more apparent on follow up T2-fluid-attenuated inversion recovery image (F).

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From the Departments of Medical Imaging (J.A.-Z., D.B., M.R.) and Pathology (N.W.), Ann & Robert H. Lurie Children's Hospital of Chicago, IL.
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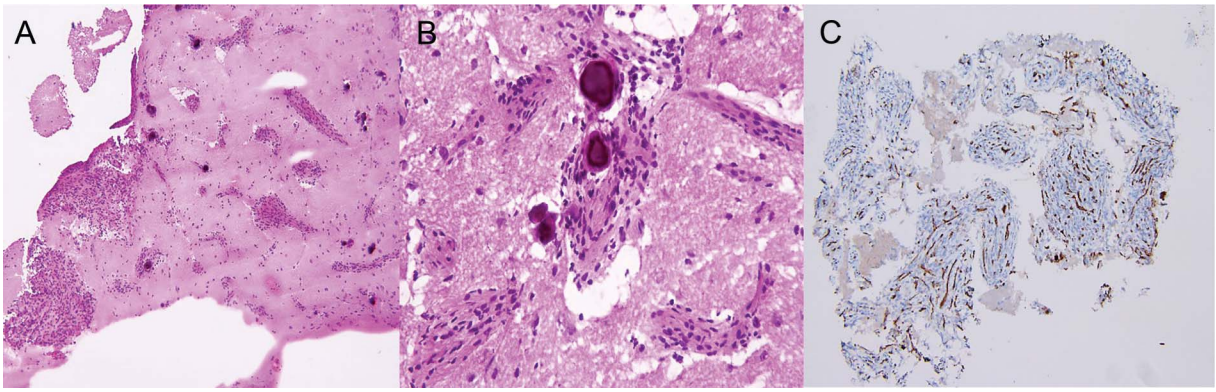
Figure 2 Histology of meningioangiomatosis



Hematoxylin & eosin staining at 4× (A) and 20× (B) magnification shows whorls of meningothelial-like spindle cells proliferating around blood vessels with numerous calcified psammoma bodies. CD31 staining (C) highlights the numerous blood vessels around which the meningothelial-like cells proliferate.

A 23-month-old full-term boy presented with tonic-clonic seizures. Lumbar puncture and routine laboratory tests were unremarkable. CT (figure 1A) showed bifrontal parasagittal calcification. Brain MRI revealed corresponding signal abnormalities with gradient susceptibility (figure 1D) and enhancement (figure 1F). Differential diagnoses included prior infection, vascular malformation, and tumor. Biopsy (figure 2) was consistent with meningioangiomatosis.

Meningioangiomatosis is a rare epileptogenic lesion involving the meninges and cortex characterized by vascular proliferation and calcifications. Meningioangiomatosis occurs sporadically or in association with neurofibromatosis 2 (NF2).[1,2] Testing for NF2 proved positive in this patient, despite no other clinical stigmata.

AUTHOR CONTRIBUTIONS

Jessie Aw-Zoretic: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data, image processing. Delilah Burrowes: study concept or design, accepts responsibility for conduct of research and final approval, study supervision. Nitin Wadhwani: drafting/revising the manuscript, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Maura Ryan: drafting/revising the manuscript, study concept or design, accepts responsibility for conduct of research and final approval.

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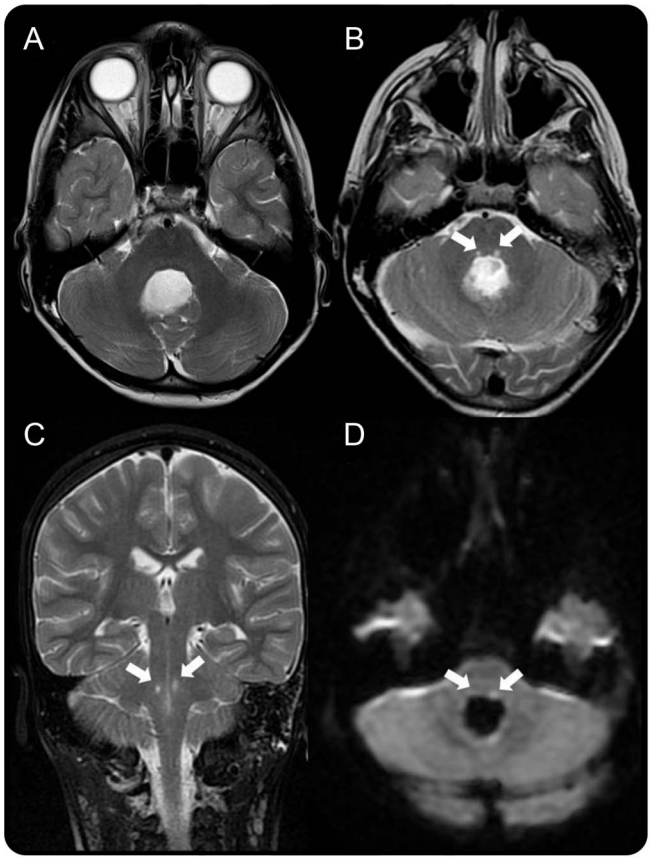
Teaching Neuro*Images*: Postoperative bifocal stroke of the pontine tegmentum

Why don't you smile anymore?

Paolo Frassanito, MD
Luca Massimi, PhD
Gianpiero Tamburrini, MD
Concezio Di Rocco, MD
Massimo Caldarelli, MD

Correspondence to Dr. Frassanito: paolo.frassanito@gmail.com

Figure Radiologic findings



(A) Preoperative T2-weighted axial MRI sequence shows a tumor of the fourth ventricle. (B, C) Postoperative T2-weighted axial and coronal MRI sequences demonstrate hyperintense lesions bilaterally in the pontine tegmentum (arrows). (D) Diffusion-weighted imaging documents 2 areas of restricted diffusion, suggestive of infarction (arrows).

A 7-year-old boy underwent resection of a posterior fossa medulloblastoma. Two days later, he developed facial diplegia, left abducens nerve palsy, and mild hypalgesia below the neck. MRI documented 2 dot-like ischemic foci in the pons (figure). We diagnosed the unusual bilateral occurrence of Gasperini syndrome, a lesion of the sixth and seventh cranial nerve nuclei and the lateral spinothalamic tract that produces ipsilateral cranial nerve palsies with contralateral hemisensory deficits.[1] We hypothesized a mechanism of postoperative spasm of long circumferential branches of the basilar artery. This mechanism should be considered in cases of postoperative neurologic deficits with delayed onset.[2]

AUTHOR CONTRIBUTIONS

Paolo Frassanito: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, accepts responsibility for conduct of research and final approval, acquisition of data. Luca Massimi: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval. Gianpiero Tamburrini: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, study supervision. Concezio Di Rocco: analysis or interpretation of data, accepts responsibility for conduct of research and final approval. Massimo Caldarelli: drafting/revising the manuscript, accepts responsibility for conduct of research and final approval, study supervision.

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From Pediatric Neurosurgery, Catholic University Medical School, Rome, Italy.

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Introduction

Pediatric Perspective

By Jeffrey Russ, MD, PhD, and Nancy L. Kuntz, MD

The following cases present an array of pediatric neuromuscular disorders ranging from common entities encountered by general practitioners—neonatal brachial plexus injury—to unusual disorders rarely seen by specialists—pediatric Lambert-Eaton myasthenic syndrome (LEMS).

A key diagnostic challenge in these cases is localizing weakness within the motor unit: anterior horn cell, nerve root, plexus, nerve, neuromuscular junction (NMJ), or muscle. As always, a careful history and neurologic examination can identify distinguishing features that guide next steps.

For example, neonates whose delivery is complicated by shoulder dystocia may stretch or rupture the brachial plexus. Examination may reveal the classic "waiter's tip" hand or other patterns of brachial plexus involvement. However, key findings, such as Horner syndrome, winged scapula, or hemidiaphragm paralysis, are highly suggestive of root avulsion, which would benefit from early referral for surgical repair.

The history and examination are also paramount in tick paralysis, a motor neuropathy that presents as acute flaccid paralysis. Distinct from tick-borne bacterial infections, tick paralysis involves the direct effect of a neurotoxin on motor axons. The exposure history and offending tick are easily overlooked, leading to extensive workup and therapy, although the treatment is simply tick removal.

NMJ disorders and myopathies may be more difficult to diagnose in pediatrics because rare genetic etiologies are often identified. Certain constellations suggest specific syndromes; Andersen-Tawil, for example, involves a triad of periodic paralysis, cardiac arrhythmias, and dysmorphic facies. However, less specific presentations—such as weakness—require serum and electrodiagnostic studies. In pediatric LEMS, for example, antibodies against the P/Q-type voltage-gated calcium channel may be present, and EMG demonstrates an increment of compound motor action potential amplitude with high-frequency repetitive stimulation.

Ultimately, genetic testing may be required. Congenital myasthenic syndromes are a group of disorders that affect the NMJ. Genetic testing can reveal one of many mutations affecting acetylcholine synthesis and metabolism, acetylcholine receptor subunits, or other NMJ proteins such as MuSK, agrin, or rapsyn.

Together, these cases illustrate a range of pediatric neuromuscular disorders. A stepwise pursuit of the history, examination, serum and electrodiagnostic studies, and genetics can reveal hallmark features to aid diagnosis.

From the Department of Neurology (J.R.), University of California San Francisco; and Pediatrics and Neurology (N.L.K), Northwestern University Feinberg School of Medicine, Ann and Robert H. Lurie Children's Hospital, Chicago, IL.
Correspondence Dr. Russ jeffrey.russ@ucsf.edu

Adult Perspective

By Kwo Wei David Ho, MD, PhD, and Clifton Gooch, MD

In this chapter, we showcase 5 of the finest cases from the *Neurology* Resident & Fellow Section, which present interesting and important concepts relevant to the practice of both adult and pediatric neurology.

Two of these cases detail rare but fascinating disorders, which can occur at any age (Lambert-Eaton myasthenic syndrome and tick paralysis), whereas another reviews a birth injury, which has important implications for adult function and which involves structures (brachial plexus and the cervical roots) often also traumatized in adults during motor vehicle accidents, falls, and sports injuries, among others.

Another case presents Andersen-Tawil syndrome (ATS), which causes both periodic paralysis and potentially fatal ventricular arrythmias; this rare diagnosis is often missed until patients are well into young adulthood, with potentially catastrophic results.

A final case is presented as an unknown (no spoilers in this introduction!) and includes a characteristic set of clinical symptoms and signs due to dysfunction of a particular part of the nervous system affected by a variety of both adult and pediatric diseases.

The essential principles of clinical neurology are the same in children and adults, and these cases illustrate the continuing, critical importance of a careful neurologic history and physical examination in patients of all ages.

We live in an exciting era of diagnostic and therapeutic revolution in neurology, but the growing array of ever more advanced (and often, highly expensive) tools at our disposal requires us to have a clear clinical direction. Our human skills in cognitive reasoning and our expertise in the neurologic examination provide this critical guidance, helping us to choose wisely the path to proper diagnosis and to sometimes life-saving therapies.

Outstanding case reviews, such as those presented here, are an excellent tool to hone such expertise in both pediatric and adult neurologists.

From the Department of Anesthesiology (K.W.D.H.), Stanford University, CA; and Department of Neurology (C.G.), University of South Florida Morsani College of Medicine, Tampa.
Correspondence Dr. Ho kwoweiho@stanford.edu

RESIDENT & FELLOW SECTION

Section Editor
Mitchell S.V. Elkind, MD, MS

Child Neurology: Brachial plexus birth injury

What every neurologist needs to know

Christina B. Pham, MD
Johannes R. Kratz, MD
Angie C. Jelin, MD
Amy A. Gelfand, MD

Address correspondence and reprint requests to Dr. Amy A. Gelfand, UCSF Department of Neurology, Box 0114, 505 Parnassus Ave, M-798, San Francisco, CA 94143-0114
GelfandA@neuropeds.ucsf.edu

ABSTRACT

While most often transient, brachial plexus birth injury can cause permanent neurologic injury. The major risk factors for brachial plexus birth injury are fetal macrosomia and shoulder dystocia. The degree of injury to the brachial plexus should be determined in the neonatal nursery, as those infants with the most severe injury—root avulsion—should be referred early for surgical evaluation so that microsurgical repair of the plexus can occur by 3 months of life. Microsurgical repair options include nerve grafts and nerve transfers. All children with brachial plexus birth injury require ongoing physical and occupational therapy and close follow-up to monitor progress. *Neurology*® 2011;77:695-697

CASE PART 1 A term male infant was delivered to a gravida 3 parity 3 mother after an uncomplicated pregnancy. Labor was uneventful; however, delivery was complicated by shoulder dystocia. An episiotomy was performed and the infant's posterior shoulder (left) was grasped and delivered, followed by the anterior shoulder (right). The infant weighed 4,750 g, >97th percentile for age. In the delivery room he was noted to have a left upper extremity palsy, with an asymmetric Moro reflex.

Differential diagnosis. Brachial plexus injury is the most common etiology of a plegic arm in the neonatal period. Other considerations include a clavicular or humeral fracture, with pain limiting limb movement. Fractures can be diagnosed by feeling for "step-offs," crepitus, or pain along the bone and obtaining plain films. Central causes, such as a focal cortical dysplasia selectively affecting the arm area of motor cortex, are rare. Poland syndrome, the absence or hypoplasia of the pectoralis muscles, can cause monomelic arm weakness; however, the structural abnormality is visibly apparent. A perinatal stroke typically does not cause hemiparesis in the neonatal period, but rather later in infancy.

CASE PART 2 On examination, there were no clavicular or humeral step-offs or crepitus, and a chest x-ray was normal. The parents were counseled that the brachial plexus injury would fully resolve. In pediatric follow-up at 2 months, however, the infant held the arm adducted and internally rotated at the shoulder. His forearm was pronated, his elbow extended, and his wrist and fingers were flexed in the "waiter's tip" posture, consistent with injury affecting the C5-C7 root levels. There was no Horner syndrome. He was referred for neurologic and surgical evaluation.

Epidemiology. Brachial plexus birth injury occurs in 0.4 to 4 per 1,000 live births.[1] It is most commonly associated with shoulder dystocia, an impaction of the infant's anterior shoulder behind the maternal symphysis pubis. Lateral traction on the head, as part of the corrective maneuvers to deliver the infant, stretches the brachial plexus, leading to injury 4%–40% of the time.[2]

The strongest fetal risk factor for shoulder dystocia is macrosomia—birth weight greater than 4,000 g.[2] Maternal risk factors for brachial plexus birth injury include diabetes or gestational diabetes, obesity, or a history of shoulder dystocia during a previous birth. A prolonged second stage of labor (pushing) and operative vaginal delivery also increase the risk.[1–3] However, half of the cases have no identifiable risk factor.[2]

While the risk factors for shoulder dystocia are well recognized, they have poor predictive value.[3,4] C-section decreases, but does not eliminate, the risk of brachial plexus injury, and introduces additional maternal morbidity.[1,2]

See page 698

From the School of Medicine (C.B.P.), Department of Obstetrics and Gynecology (A.C.J.), Department of Genetics (A.C.J.), Department of Neurology, Division of Child Neurology (A.A.G.), University of California, San Francisco; and Department of Surgery (J.R.K.), Massachusetts General Hospital, Boston.

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Neuroanatomy and prognosis. The ventral rami of the C5 through T1 spinal nerves form the roots of the brachial plexus. Children with brachial plexus birth palsy have traditionally been classified clinically into 4 groups. The largest group (50% of cases) involves C5-C6 injury, classic Erb palsy, and generally has the best prognosis. The next group (25%) involves C5-C7 injury and has an intermediate prognosis. Children in these 2 groups hold the arm in adduction and internal rotation at the shoulder due to relative sparing of the shoulder adductor and internal rotation muscles. The imbalance of push-pull muscular forces across the glenohumeral joint at the shoulder causes the joint itself to develop abnormally, with increasing deformity as the child grows.[1] Involvement of C7 is suggested by the presence of a wrist drop.

The third and fourth groups (together 25%) involve injury to the entire plexus. The arm is held in a neutral position with little to no movement. The fourth group is the most severely affected and can be distinguished by the presence of an ipsilateral Horner syndrome (miosis, ptosis, and anhidrosis) due to concurrent injury to the sympathetic chain as it exits the spinal cord.[5] Isolated lower root injury (C8-T1), Klumpke palsy, is extremely rare.[6]

Brachial plexus injuries can also be classified by the type of neuropathologic injury. The least severe is neurapraxia, or stretch injury, causing conduction block, but no permanent structural damage to the nerve. Conduction block can last for hours to weeks, but ultimately fully recovers. Axonotmesis injury involves damage to axons, as well as supporting blood vessels and connective tissue, including perineurium and epineurium. If only the axons are disrupted, they regrow with full recovery. If the perineurium or epineurium are also disrupted, the likelihood of complete recovery decreases significantly. Neurotmesis injury indicates complete nerve rupture. Scar tissue forms between the proximal and distal ends of the nerve to become a neuroma. Recovery is limited because it is difficult for axons to regenerate through the neuroma. Root avulsion is the most severe injury, usually occurring at the nerve rootlets at or near the spinal cord.[7] Avulsion injuries do not spontaneously recover so it is essential that these patients be identified for early intervention.[6,8]

When examining the brachial plexus in a neonate, the emphasis should be on looking for signs of injury to proximal nerve structures as these are highly suggestive of avulsion. Given the proximity of the sympathetic chain to the spinal cord, the presence of Horner's almost always implies a root avulsion injury. Additional signs of avulsion include winging of the scapula, indicating long thoracic nerve injury, and asymmetry in chest wall excursion, indicating phrenic nerve injury. In cases of complete plexus palsy, a chest x-ray should be performed to rule out hemidiaphragm paralysis.

Diagnostics. The diagnosis of brachial plexus birth injury and the assessment of severity are both made clinically based on history and examination findings.

Some groups support the routine use of EMG/NCS or MRI for diagnosis early in the patient's course to confirm the presence of avulsion-type injuries[9]; however, as the decision to intervene surgically is exclusively based on whether there is adequate recovery on physical examination over time, these studies typically do not aid clinical decision-making.

Therapeutics. In the first few days of life, the patient's arm can be temporarily immobilized via swaddling if there is pain from an accompanying fracture. Caregivers should be instructed in appropriate positioning to avoid contractures, pressure ulcers, and unnecessary traction.[10] If the patient tolerates it, gentle range of motion exercises may be started either immediately or at latest by 7 to 10 days of life. Physical therapy should be continued until the child's brachial plexus injury recovers.[1,6] For cases that result in permanent functional deficit, therapy should be tailored to the patient's age and developmental stage.[10]

Ideally, infants with brachial plexus injuries should be referred to a multidisciplinary specialty clinic for treatment. Teams at these clinics include pediatric neurologists, orthopedic surgeons, neurosurgeons, physical and occupational therapists, and social workers. If this is not possible, the infant should be followed closely by a neurologist to monitor the pace and extent of neurologic recovery. If antigravity biceps function does not return before 6 weeks of age, a referral to surgery is appropriate, as a subset of these infants will require microsurgical reconstruction of the plexus. In cases of suspected avulsion or rupture injuries where spontaneous recovery is impossible or unlikely, it is generally agreed the infant should undergo microsurgical reconstruction by age 3 months for avulsions and by 6 months for nerve ruptures.[1] Early surgery minimizes motor endplate loss and maximizes recovery time.

In less severe injuries, the indications for, and timing of, surgical interventions remain controversial. Most groups agree that lack of antigravity biceps function by 3 to 6 months is an indication for surgical intervention, while others continue to observe and operate as late as 9 or 10 months of age.[1]

Surgical intervention for brachial plexus palsy includes early microsurgical repair of the brachial plexus using nerve grafts or nerve transfers. In both

cases, the neuronal scar tissue (neuroma) is resected. For rupture injuries, a donor nerve, most often the sural nerve, is inserted into the area of discontinuity.[6] Nerve transfers, in contrast, redirect an uninvolved healthy nerve, such as the spinal accessory nerve (CN XI), to the distal site of nerve injury and rely on neuroplasticity for adoption of functional control by the transferred nerve.[1]

Outcomes. Most children with brachial plexus birth palsy recover well. A recent prospective study demonstrated full recovery in 50% of patients by 3 months of age, and 82% by 18 months.[11] However, roughly one in 5 affected infants have some degree of permanent nerve damage.[12]

While patients with permanent injury have lower functional scores than their peers, these children have equivalent rates of individual and team sports participation as their peers.[13] Most children with persistent injury can manage their activities of daily living, albeit with varying degrees of difficulty.[11]

CASE PART 3 The infant regained gravity-assisted biceps function at 3 months of age and antigravity biceps function at 5 months. Now 18 months old, he is able to use his left hand and arm, though still with weakness and range of motion limitations. He continues with intensive physical and occupational therapy and his ultimate outcome is not yet determined.

DISCUSSION Brachial plexus birth injuries are usually transient, but can result in permanent functional deficits. Signs of nerve root avulsion, indicating severe injury that will not recover spontaneously, include a total plexopathy (complete arm paralysis), Horner syndrome, or phrenic nerve involvement. These infants should be referred for microsurgical evaluation immediately so that reconstruction of the plexus, if indicated, can be performed by 3 to 6 months. All infants with brachial plexus nerve injuries need close follow-up to monitor progress, and early and ongoing physical and occupational therapy to maintain range of motion, prevent glenohumeral joint deformity, and maximize function.

AUTHOR CONTRIBUTIONS

Dr. Pham: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Kratz: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Jelin: drafting/revising the manuscript. Dr. Gelfand: drafting/revising the manuscript.

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DISCLOSURE

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Child Neurology: Andersen-Tawil syndrome

Mohammed Almuqbil, MD
Myriam Srour, MD, FRCPC

Correspondence to Dr. Srour: myriam.srour@mcgill.ca

Andersen-Tawil syndrome (ATS) is one of the periodic paralyses. This autosomal dominant disorder was initially named after Andersen, who in 1971 reported the case of a young boy presenting with intermittent muscle weakness, ventricular arrhythmias, and other developmental abnormalities. It was subsequently renamed Andersen-Tawil syndrome following the additional work of Dr. Rabi Tawil. Periodic paralysis, cardiac arrhythmias, and dysmorphic features are now recognized as the 3 characteristic features in patients with ATS.[1,2]

CLINICAL CASE The proband is a 14-year-old boy who presented at the age of 9 years with recurrent episodes of leg weakness lasting several days. These episodes became more frequent, occurring at least once a month. The severity of the weakness during the episodes varied from mild weakness to inability to walk unassisted (2-3/5 weakness of proximal leg muscles). There were no clear triggers. Serum potassium levels measured during episodes of weakness were normal. Neurologic examination between episodes demonstrated proximal weakness (4/5) in the lower and upper extremities and a positive Gower sign. Treatment with potassium supplementation and acetazolamide resulted in mild clinical improvement. Family history revealed that his mother had had similar episodes that began during adolescence, improved with age, and resolved in her 40s. Potassium levels were reported to be low during her acute episodes. Sequencing of *CACN1AS* and *SCN4A* in the proband did not reveal any abnormalities. Several years after presentation, the proband's 14-year-old brother developed a ventricular tachycardia. He had no history of weakness and his neurologic examination was normal. The combination of periodic paralysis and family history of cardiac arrhythmia prompted the testing of *KCNJ2* for ATS. A pathogenic heterozygous missense c.652C>T (p.R216W) mutation was identified that segregated with the phenotype in the family. In retrospect, the proband, his brother, and his mother were noted to have mild dysmorphic features (micrognathia [figure], clinodactyly of the 5th fingers of the hands, and syndactyly of the 2nd and 3rd digits of the left foot). ECG and cardiac Holter monitoring of the proband did not reveal any abnormalities.

DISCUSSION **Clinical features.** ATS is one of the first known channelopathies; causal mutations have been identified in *KCNJ2* on chromosome 17q24, which encodes the inward rectifier potassium channel 2 protein, Kir2.1.[3] The dominant mutations in the Kir2.1 channel have a dominant negative effect on the potassium current (i.e., the mutated protein loses its normal function and adversely affects the function of the normal protein), resulting in prolonged depolarization of the action potential, thereby accounting for the cardiac and muscular symptoms.[2] Autosomal recessive mutations in Kir2.1 have also been reported.[4] Recently, a mutation in *KCJN5*, which encodes the Kir3.4 subunit, has been linked to ATS and is thought to exert an inhibitory effect on the inward rectifier potassium current.[5]

In ATS, episodes of periodic paralysis first develop during childhood or adolescence and typically last between several hours and several days. Serum potassium levels during the episodes may be normal, elevated, or reduced. Although most cases seem to be associated with hypokalemia, several recent studies suggest normal potassium levels in patients with ATS.[1,6] Triggers of the paralytic episodes mainly include prolonged exercise, prolonged rest, rest after exercise, and emotional stress. Patients usually present with mild permanent proximal weakness.

Cardiac manifestations include ventricular arrhythmias as well as electrocardiogram abnormalities such as long QT interval, pronounced U waves, and long QTU interval.[2] Patients may develop fainting spells or, in some cases, present with cardiac arrest leading to sudden death. ATS is also classified as "long QT syndrome type 7" (LQTS7), although the QT interval is either normal or only slightly prolonged in most cases.[7]

From the Division of Pediatric Neurology (M.A., M.S.), Montreal Children's Hospital-McGill University Health Center, Montreal, Canada; and Division of Pediatric Neurology (M.A.), King Saud bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia.

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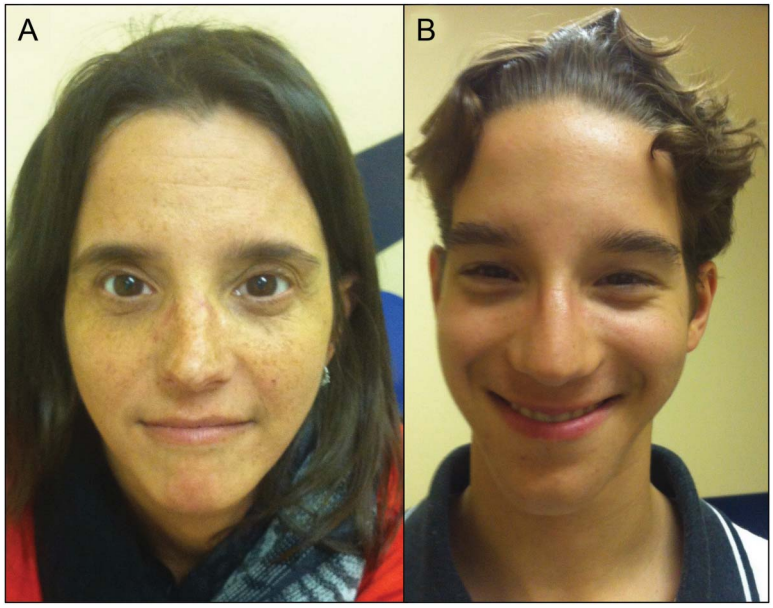
Figure Mother (A) and proband (B) with Andersen-Tawil syndrome



Note the subtle characteristic facial features such as the broad forehead, pointed chin, and small mandible.

In addition to skeletal and cardiac muscle abnormalities, patients with ATS have dysmorphic features that are usually subtle. In fact, the use of the term "distinctive facial features" may be more appropriate.[2] Dysmorphisms include broad forehead, hypoplastic mandible, hypotelorism, short palpebral fissures, short nose with fullness along the bridge and bulbous tip, thin upper lip, high arched or cleft palate, triangular facies, digit clinodactyly, syndactyly of the 2nd and 3rd toes, and short stature.[2,8]

Patients with ATS have a distinct neurocognitive phenotype characterized by deficits in executive function and abstract reasoning.[9]

ATS is a syndrome with a very high degree of phenotypic variability and is therefore very difficult to diagnose. The characteristic triad of clinical features (ventricular arrhythmias, periodic paralysis, and dysmorphic features) is present in 58%–78% of patients with *KCNJ2* mutations, whereas between 32% and 81% present with involvement of only 2 of the 3 organ systems.[10] Approximately 60% of the patients with a clinical diagnosis of ATS have causal mutations identified in *KCNJ2*.[9] About 6%–20% of mutation-positive individuals do not exhibit any of the associated features, indicating that this disorder has incomplete penetrance.[8]

Differential diagnosis. The diagnosis of ATS should be considered in any individual who displays at least 2 of the characteristic triad of symptoms, i.e., periodic paralysis, cardiac abnormalities, and facial dysmorphism. The differential diagnosis of ATS includes other periodic paralyses, namely hypokalemic periodic paralysis, hyperkalemic periodic paralysis, and thyrotoxic periodic paralysis.

The onset, duration, and severity of attacks in patients with hypokalemic or hyperkalemic paralysis are similar to those in ATS.[2] Hypokalemic paralysis is associated with low serum potassium levels, whereas patients with hyperkalemic periodic paralysis generally have increased levels of serum potassium. In patients with ATS, periodic paralysis can occur with normokalemia, hyperkalemia, or hypokalemia. Nevertheless, the absence of the other typical features present in ATS (cardiac abnormalities and mild dysmorphic features) generally distinguishes patients with both hyperkalemia and hypokalemia from those with ATS. The presence of myotonia is characteristic of hyperkalemic periodic paralysis, and a majority of the patients with hypokalemic paralysis have mutations in the *CACNA1S* or *SCN4A* genes.[11]

Management. Treatment strategies for ATS are generally directed toward the management of the periodic paralysis and cardiac arrhythmias. A thorough examination involving blood chemistry, including serum potassium concentration and thyroid function, should be done at baseline and during attacks. Cardiac evaluation including ECG and Holter monitoring should be performed, and patients should be followed by a cardiologist. Characteristic abnormalities of the heart, including prominent U waves, prolonged Q-U intervals, premature ventricular contractions, and bidirectional ventricular tachycardia, may be noted on ECG. Similarly, the use of 24-hour Holter monitoring will aid in examining the presence, frequency, and duration of ventricular tachycardia. Carbonic anhydrase inhibitors (such as acetazolamide 250–1,500 mg/day and dichlorphenamide 50–200 mg/day) have been used to reduce recurrent attacks of paralysis.[2] Daily potassium supplements may be used in cases in which attacks are associated with hypokalemia. This can be an attractive option since elevated potassium levels shorten the QTc interval and decrease cardiac arrhythmogenecity.[2] Cardiac pacemaker or defibrillators may be required in some patients.

Analysis of mutations in *KCNJ2* is the only confirmatory genetic test so far. Genetic counseling, including thorough screening of family history, must be conducted, as it enables early treatment and prevention, especially of cardiac complications.

CONCLUSION ATS should be considered in the differential diagnosis of patients with periodic paralysis. The clinical triad of ATS consists of periodic paralysis, cardiac arrhythmias, and dysmorphic features. However, due to its phenotypic heterogeneity and subtle physical findings, ATS can be difficult to diagnose. Because some of the cardiac manifestations

of ATS can be dangerous and life-threatening, establishing the accurate diagnosis of ATS is critical.

AUTHOR CONTRIBUTIONS

Mohammed Almuqbil drafted and revised the manuscript for intellectual content. Myriam Srour drafted and revised the manuscript for intellectual content.

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RESIDENT & FELLOW SECTION

Section Editor
Mitchell S.V. Elkind, MD, MS

Child Neurology: Tick paralysis

A diagnosis not to miss

Sarah L. Chagnon, MD
Monica Naik, MD
Hoda Abdel-Hamid, MD

Correspondence to Dr. Chagnon: sarah.chagnon@chp.edu

A 4-year-old girl presented to our tertiary care hospital with a complaint of lower extremity weakness and unsteady gait for 2 days. She was able to pull herself to stand but could not stand unsupported. She had no sensory symptoms or pain. She did not complain of any weakness in her arms, trunk, face, or neck. She had no bowel or bladder incontinence or retention. On presentation to the emergency department, she had minimal antigravity strength of the lower extremities but normal strength elsewhere. In addition, she was areflexic in both lower extremities and had a wide-based, unsteady gait but no appendicular dysmetria or titubation. Sensory examination was normal.

After consultation by the neurology service, MRI of the brain and total spine were completed and a plan was made for subsequent lumbar puncture. Lyme disease antibodies were drawn because of exposure to a wooded area in West Virginia; these were negative. MRI of the spine showed syringomyelia extending from T5 to T8 and an extramedullary, intradural cystic lesion dorsal to the spinal cord from T1 to T4, which was believed to be consistent with an arachnoid cyst. Due to this unexpected finding, the neurosurgical service was consulted, who believed that this cyst and the associated syrinx were the source of her paralysis. The following day, she was taken to the operating room for fenestration. Subsequent to the fenestration, repeat imaging showed resolution of syringomyelia.

The following night, the patient developed increasing respiratory distress, requiring mechanical ventilation. Over the subsequent postoperative period, she failed multiple attempts at extubation. Extensive evaluation including infectious workup, chest x-ray, ultrasonography of the diaphragm, and upper airway endoscopy revealed no reason for her ongoing breathing difficulties. In addition, it was noted that the patient had not been able to move her upper extremities at any point during the day of surgery or in the following days.

The neurology service was consulted again for further evaluation. Seven days after the initial surgery, the patient's neurologic examination revealed flaccid paralysis of all 4 extremities, bifacial weakness, minimal gag reflex, and complete areflexia. She had full extraocular movements and normal pupillary response to light. Bulbar function was difficult to evaluate due to intubation. Repeat MRI of the brain and cervical spine revealed continued resolution of syringomyelia and no new abnormalities. A lumbar puncture showed mild albuminocytologic dissociation with protein of 90, 2 leukocytes, and 1 erythrocyte. IV immunoglobulin (IVIg) therapy was instituted for presumed acute inflammatory demyelinating polyneuropathy.

On postoperative day 8, EMG and nerve conduction studies were completed. Nerve conduction studies revealed low compound motor action potentials in multiple nerves with preserved sensory nerve action potentials. There was no prolonged conduction velocity seen and normal F-wave responses were noted. EMG/needle study revealed increased insertional activity and positive sharp waves. The summation of these results suggested a possible diffuse motor axonal neuropathy or a presynaptic neuromuscular junction disturbance. Moreover, it did not fulfill criteria for a primary demyelinating neuropathy.

Based on EMG results, we performed a thorough evaluation of the patient's skin and scalp. Along the superior retroauricular scalp, a 3-cm engorged tick was found and removed. This tick was identified by an infectious disease specialist as a gravid female *Dermacentor* species tick.

DISCUSSION Tick paralysis (TP) is a rare and easily reversible condition that if missed can lead to significant morbidity and mortality. In one series of children with TP between 1946 and 1906, 6% died.[1] However, in the modern era of respiratory support and intensive care, survival may be higher. TP in the United States is more common in girls younger than 8 years with long hair, presumably due to the ability of the tick to go unnoticed on the scalp.[2,3]

Most cases reported in the literature have been identified in Australia, where the causative species is *Ixodes holyclus*. In North America, most cases reported in the Rocky Mountain region, US Pacific Northwest, and Southwestern Canada are transmitted by *Dermacentor andersoni* species and in the Southeast region are transmitted by *Dermacentor variabilis*.[4]

From the Children's Hospital of Pittsburgh of UPMC, PA.

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These distinctions are relevant due to the differences in clinical presentation produced by the 2 species. Pupillary changes and focal weakness are more common in Australian cases (i.e., *Ixodes* cases). In addition, symptoms tend to remit immediately upon removal of a *Dermacentor* tick, whereas they persist for a day or two after removal of an *Ixodes* tick. Duration of recovery is more prolonged in Australian cases, often lasting days to weeks.[1]

TP is thought to be caused by a neurotoxin produced in the insect's salivary glands. The toxin is thought to decrease presynaptic acetylcholine release at the neuromuscular junction, similar to botulinum toxin. It is possible that variations in the toxin of *Dermacentor* ticks compared to *Ixodes* ticks may account for the variation in clinical features.[1]

The classic clinical presentation of TP is an acute symmetric, ascending flaccid paralysis occurring over hours to days. There can be a prodrome of restlessness, irritability, fatigue, and myalgias, but fever is noticeably absent. Weakness usually begins in the lower extremity, and as the tick continues to feed, the weakness ascends from the legs to the arms and then to the muscles supplied by the cranial nerves, causing dysphagia, dysphonia, and facial weakness. Deep tendon reflexes are diminished or absent.[1,5] A case series reported from Australia noted frequent pupillary involvement and external ophthalmoplegia in 2 of their patients, although this has not been the case in the United States.[6] Respiratory involvement and requirement for mechanical ventilation occur invariably if the tick remains in place, though in some patients the tick may have fallen off, accounting for those patients who recover without assisted ventilation.[1] Atypical presentations have been reported, including lower motor neuron facial nerve palsy, in which ticks were identified in the external auditory canal,[7] and left-sided arm weakness in a brachial plexus distribution, which resolved after an engorged tick was removed from the subclavian fossa.[8]

TP presents as an acute-onset flaccid paralysis of the lower extremities with hyporeflexia or areflexia. Therefore, the differential diagnosis typically includes pathologies of the lower motor neuron or neuromuscular junction. See the table for full differential diagnosis.

Table **Differential diagnosis of tick paralysis[1,9]**

Guillain-Barré syndrome (acute inflammatory demyelinating polyneuropathy or acute motor axonal neuropathy)	Spinal cord compression	Transverse myelitis
Cerebellar ataxia	Poliomyelitis	Myasthenia gravis
Botulism	Organophosphate ingestion	Lambert-Eaton syndrome
Encephalomyelitis	Periodic paralysis	Diphtheria
Porphyria	Electrolyte imbalance	Heavy metal poisoning

The diagnosis of TP is made by finding the engorged tick on a patient with symptoms that correlate clinically. The importance of a complete skin evaluation including the scalp, external ear canals, groin, and axillae is irrefutable. Neuroimaging studies including CT and MRI are normal, although on closer inspection they may show the embedded tick if located on the scalp. CSF should also be normal.[9] The albuminocytologic dissociation in our patient was believed to be postsurgical. If performed, electrophysiologic tests show a diffuse reduction in the compound muscle action potentials (CMAPs) with preserved sensory nerve action potentials. The low CMAPs are not usually accompanied by any abnormality of neuromuscular transmission with repetitive nerve stimulation testing. Published cases have proved that the function is reversible after removal of the tick.[10]

Despite attention to other tickborne diseases such as Lyme disease and Rocky Mountain spotted fever, TP remains a frequently misdiagnosed entity. A recent meta-analysis reviewed 50 cases of TP in the United States between 1946 and 2006 and revealed that 11 (22%) of these cases were initially misdiagnosed, with mean time to correct diagnosis of 2.16 days. Of these 11 cases, 9 were initially diagnosed as Guillain-Barré syndrome (GBS), 1 as chronic polyneuropathy, and 1 as postinfectious polyneuritis. In this analysis, preparations for invasive IV therapy for GBS were initiated in 4 patients before tick attachment was discovered and 3 patients received IVIg, while 1 case was discovered during the process of placing a central catheter to prepare for plasmapheresis.[4]

The definitive treatment of TP is removal of the offending tick, after which symptoms rapidly resolve. Careful inspection of the rest of the body for additional ticks is mandatory. The tick should be carefully removed by grasping it as closely as possible to the attachment site and using steady traction to avoid leaving the head or mouthparts engaged.[5] During paralysis, standard supportive therapy should be utilized, including mechanical ventilation when necessary for respiratory support.[9] Antitoxin, a hyperimmune dog serum used in veterinary medicine, has been used in severe cases but carries a high risk of adverse reaction.[6]

CASE SUMMARY Within 24 hours after removal of the tick, our patient started to regain some movement in her upper and lower extremities. Within 48 hours, reflexes were elicited in the patella, ankles, biceps, and brachioradialis bilaterally. By 3 days after removal, she was extubated. She had normal facial strength but continued to have some weakness, primarily in the upper extremities, likely due in part to deconditioning. The patient was able to sit independently, feed

herself, and walk with minimal assistance 6 days after tick removal and was discharged home.

AUTHOR CONTRIBUTIONS

Sarah L. Chagnon: corresponding author responsible for case report, literature review, and primary content of the manuscript. Monica Naik: coauthor responsible for revision of the manuscript. Hoda Abdel-Hamid: coauthor responsible for revision of the manuscript and execution and interpretation of EMG and nerve conduction studies.

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Section Editor
Mitchell S.V. Elkind, MD, MS

Child Neurology: Diagnosis of Lambert-Eaton myasthenic syndrome in children

Bethanie Morgan-Followell, MD
Emily de los Reyes, MD

Correspondence to Dr. Morgan-Followell: bethanie.morgan@nationwidechildrens.org

ABSTRACT

Objective: To report a case of Lambert-Eaton myasthenic syndrome (LEMS) in a child and review the existing literature of LEMS in children.

Methods: We report a pediatric case of LEMS with the classic clinical triad of proximal weakness, autonomic dysfunction, and areflexia; the characteristic increment in compound motor action potential on high-frequency repetitive nerve stimulation; and positive serum P/Q-type voltage-gated calcium channel antibodies. Only 11 pediatric cases of LEMS have been reported in the literature.

Results: The patient's presentation with LEMS led to the diagnosis of occult neuroblastoma. Based on review of the existing pediatric literature, no consistent clinical or electrodiagnostic criteria exist to diagnose LEMS in children.

Conclusions: There exists a need for consistent clinical criteria and electrodiagnostic testing for prompt diagnosis of LEMS in children. Prompt identification of LEMS will alert the physician to search for malignancy or another immune-mediated process. *Neurology*® 2013;80:e220–e222

GLOSSARY

CMAP = compound motor action potential; **LEMS** = Lambert-Eaton myasthenic syndrome.

Paraneoplastic syndromes are immune-mediated phenomena that occur in a location remote to the primary neoplasm. The incidence of these syndromes is rare in adult cancers. The incidence is unknown in the pediatric population.

Lambert-Eaton myasthenic syndrome (LEMS) is an immune-mediated disorder of neuromuscular transmission. The classic clinical presentation is proximal weakness, areflexia, and autonomic dysfunction. Antibodies to the P/Q-type voltage-gated calcium channel are present in 85%–90% of adult patients with LEMS.[1] These antibodies interfere with quantal acetylcholine release from the presynaptic terminal of the neuromuscular junction and functional loss of voltage-gated calcium channels. Thus, less calcium enters the presynaptic terminal with the action potential, resulting in decreased release of acetylcholine. Nerve conduction studies characteristically show low compound motor action potential (CMAP) amplitudes.[1] Facilitation, or an incremental increase in the amplitude of the CMAP, is seen upon high-frequency repetitive stimulation or following exercise testing. This is a finding highly specific for LEMS.[1]

LEMS is a rare disorder in adults, most often seen as a paraneoplastic process with small-cell lung cancer. LEMS is even rarer in children, and only 11 pediatric cases have been reported in the literature (table).[2–10] Neoplasm was associated with 4 of these cases.[4,6]

We present the case of a 3-year-old boy with LEMS, supported by the clinical presentation, characteristic findings on EMG, and elevated serum P/Q-type voltage-gated calcium channel antibodies.

Case report. A previously healthy 3-year-old boy was admitted for evaluation of proximal weakness and ptosis, and for treatment of severe constipation that developed over a 4- to 5-month period. CSF was normal. MRI of the brain was unremarkable. The child's ptosis and extremity weakness improved without treatment over several days and he was discharged home. He returned approximately 1 week later with quadriparesis, worsened ptosis, and areflexia in the lower extremities.

From the Division of Child Neurology, Nationwide Children's Hospital, The Ohio State University, Columbus.

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Table Pediatric LEMS cases reported in the literature

Reference	Age	Symptoms	Underlying disease	CMAP	Low-frequency RNS	High-frequency RNS or postexercise testing	Antibodies	Follow-up
2	11 y	Proximal weakness, areflexia	None	Low	Decrement at 3 Hz	82% increment postexercise	VGCC Ab present	3.5 y
3	7 y	Proximal weakness, areflexia, ptosis, ophthalmoplegia	Burkitt lymphoma	"Compatible with LEMS"	"Compatible with LEMS"	"Compatible with LEMS"	No VGCC antibodies	3 mo
4	3 y	Ptosis, ophthalmoplegia	Neuroblastoma	Not stated	Normal	Normal	VGCC not tested	1 y
4	2 y	Ptosis	Neuroblastoma	Normal	Not performed	Not performed	VGCC not tested	2 mo
5	10 y	Proximal weakness	Autoimmune disease	Low	Not stated	Increment postexercise	VGCC Ab present	Not stated
6	13 mo	Proximal weakness, constipation, ptosis, ophthalmoplegia	Neuroblastoma	Normal	Not performed	Not performed	No Ach receptor Ab; VGCC Ab not stated	2 mo
7	10 y	Proximal weakness, hyporeflexia	None	Low	Decrement at 3 Hz	>200% increment at 50 Hz	P/Q VGCC Ab present	"Months"
7	10 y	Proximal weakness	None	Low	Not performed	62% increment postexercise; 124% increment at 50 Hz	P/Q VGCC Ab present	2 y
8	13 y	Proximal weakness	None	Normal	45% decrement at 3 Hz	42% increment at 50 Hz	Not stated	1 y
9	9 y	Proximal weakness, hyporeflexia	None	Normal	Not stated	Increment at 20 Hz	Not stated	8 mo
10	4 y	Hypotonia, areflexia	None	Low peroneal	33% decrement at 1 Hz	>2000% increment at 20–50 Hz	Not stated	Not stated

Abbreviations: Ab = antibody; Ach = acetylcholine; CMAP = compound motor action potential; LEMS = Lambert-Eaton myasthenic syndrome; RNS = repetitive nerve stimulation; VGCC = voltage-gated calcium channel.

Initial nerve conduction studies and EMG were normal. Plasma exchange was initiated as the evaluation continued due to suspicion of an immune-mediated process. The child had notable improvement in clinical symptoms following the first 2 plasma exchanges.

Repeat EMG with repetitive nerve stimulation showed 31% decrement in CMAP with low-frequency stimulation and 278% increment with high-frequency stimulation. Paraneoplastic antibody panel was positive for P/Q-type voltage-gated calcium channel antibodies. No other autoantibodies were present.

CT of the chest and thorax showed a small paraspinal mass. MRI of the chest and abdomen confirmed the presence of a small left paraspinal mass at L3-L4 extending into the neural foramina. The mass was resected and pathologic examination was consistent with a neuroblastoma with favorable histopathology. Following 7 plasma exchanges and resection of the tumor, the patient's strength improved and ptosis resolved. At 3 years post presentation, the patient is well and without any neurologic deficits.

DISCUSSION The incidence of LEMS is unknown in children. Its incidence in adults is 0.48 per million.[1] The incidence of LEMS in adults is rising, most likely related to recognition of the syndrome. The cancer most commonly associated with LEMS is small-cell lung cancer. Other malignancies associated with LEMS may have characteristics similar to small-cell lung cancer, including neuroendocrine origin.[1] In addition to our case, 3 other cases of LEMS related to neuroblastoma have been reported.[4,6] In non-tumor-associated LEMS, there may be a genetic predisposition to an autoimmune phenotype. A correlation with HLAB8 and HLADR3 and non-tumor-associated LEMS has been shown in adults.[1] No such associations have been reported in children.

There is no single confirmatory test for LEMS. Diagnosis is based on clinical signs and symptoms, electrophysiologic studies, and testing for serum P/Q-type voltage-gated calcium channels. The classic clinical triad for LEMS consists of proximal muscle weakness, hyporeflexia, and autonomic dysfunction.[1] Proximal muscle weakness is commonly seen in the lower extremities. As opposed to myasthenia gravis, weakness typically progresses in a proximal to distal and caudal to cranial fashion.[1] In contrast to Guillain-Barré syndrome, no sensory changes are present and weakness progresses proximally to distally as opposed to beginning distally and ascending.[1] It is unclear whether autonomic dysfunction was not a prominent feature or was an underrecognized feature of LEMS as reported in the pediatric literature.

One confounding factor in the diagnosis of LEMS is that postexercise facilitation may allow transient return of deep tendon reflexes and an improvement in proximal strength.[1] Nerve conduction studies characteristically show low CMAP amplitude. In addition, facilitation may not be seen initially. A low CMAP is nonspecific and may be seen clinically in combination with areflexia or hyporeflexia in polyneuropathies such as Guillain-Barré syndrome.

On repetitive nerve stimulation, a decrement in CMAP amplitude of ≥10% at low-frequency stimulation and an increment in CMAP amplitude of ≥100% at either high-frequency stimulation or postexercise testing are sensitive and specific for LEMS. Postexercise CMAP amplitude increment at high frequency of stimulation is perhaps more specific for LEMS than is repetitive nerve stimulation.[1]

Testing for serum P/Q-type voltage-gated calcium channel antibodies is being done with increasing frequency in suspected cases of LEMS in adults. In adults, 85%–90% of patients with LEMS have serum P/Q-type voltage-gated calcium channel antibodies. This number is higher in cases with underlying small-cell lung cancer.[1] Antibody testing was not routinely performed in the cases of LEMS in the pediatric literature. Of the 11 cases reported, however, 4 of these had positive voltage-gated calcium channel antibodies.[2,5,7] Thus, the value of testing for P/Q-type voltage-gated calcium channel antibodies in children with suspected LEMS is unclear but may be helpful in circumstances where the diagnosis is unclear.

No uniform set of criteria exists for diagnosis of LEMS in children. Most of the reported cases used the combination of clinical signs and symptoms and electrophysiologic testing as the basis for diagnosis. However, in 2 cases, the EMG was suggestive of a myasthenic syndrome and one was normal.[4] Another case showed normal nerve conduction.[6] It is not stated whether repetitive nerve stimulation or exercise testing was performed in these cases. Due to the high sensitivity and specificity of the characteristic findings of LEMS in adults on electrophysiologic testing, it seems appropriate that repetitive nerve stimulation or exercise testing should be incorporated into the pediatric diagnostic algorithm for LEMS. The utility of testing for P/Q-type voltage-gated calcium channel antibodies for suspected LEMS in children is unclear due to the small number of cases reported.

The association of LEMS in children with cancer is unclear. Malignancy appears to be less common in pediatric patients with LEMS (4 of 11 cases).[3,4,6] However, due to the short follow-up in these cases (mean 13 months), one cannot exclude the possibility of later development of cancer. In a study of 100 consecutive adults diagnosed with LEMS and subsequently small-cell lung carcinoma, 96% were diagnosed with cancer within the first year of symptoms.[11] Current guidelines for tumor screening in paraneoplastic syndromes state that screening for 2 years postdiagnosis of LEMS in adults is sufficient.[12] There are insufficient data in the pediatric literature to make any such recommendations; however, based on adult literature, a screening period of at least 2 years for neoplasm in children with LEMS is prudent. In addition, screening for autoimmune disorders is reasonable given the adult literature on nontumor LEMS and a pediatric case report of LEMS in the setting of autoimmune disease.[5]

LEMS is an immune-mediated syndrome that rarely affects children. Diagnosis of LEMS in children should be based on the characteristic clinical presentation and on electrodiagnostic studies. The presence of serum P/Q-type calcium channel antibodies is supportive of the diagnosis of LEMS. LEMS may be associated with malignancy and autoimmune disease in children. In children without identifiable malignancy at presentation, screening for autoimmune disease and close surveillance for development of cancer for at least 2 years should be performed.

AUTHOR CONTRIBUTIONS

Dr. Morgan-Followell is the primary author of the manuscript. Dr. de los Reyes was involved in the drafting and revision of the manuscript.

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RESIDENT & FELLOW SECTION

Section Editor
John J. Millichap, MD

Clinical Reasoning: A child with delayed motor milestones and ptosis

Partha S. Ghosh, MD

Correspondence to Dr. Ghosh: partha.ghosh@childrens.harvard.edu

SECTION 1

A 6-year-old boy was evaluated for delayed motor milestones and ptosis. He was born at term without complications. He walked at 14 months; he was slow in running, jumping, and climbing compared to his peers. He fatigued easily. He had early-onset (within the first 3 months) bilateral ptosis. Some members on the maternal side of the family (male and female) had varying degree of weakness and ptosis (details unknown as the mother migrated from her home country). On examination, the patient had fatigable bilateral ptosis, horizontal and vertical ophthalmoparesis, facial weakness, nasal dysarthria, proximal muscle weakness (lower limbs > upper limbs), and neck flexor weakness. Tendon reflexes were preserved and sensory and cerebellar functions were normal.

Questions for consideration:

1. What is the differential diagnosis in this case?
2. What tests would you consider to help narrow your differential diagnosis in this case?

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SECTION 2

The differential diagnoses in this case are broad and most likely involve lower motor neuron disorders. Lower motor neuron unit includes anterior horn cells, peripheral nerves, neuromuscular junction (NMJ), and muscles. Anterior horn cell disorders (spinal muscular atrophy in children) can present with motor delays and proximal weakness but presence of ptosis, facial weakness, and preservation of tendon reflexes go against that diagnosis. Peripheral neuropathies seem unlikely given lack of distal weakness, preserved reflexes, and no sensory findings. There are several features that point to an NMJ disorder: oculobulbar weakness, prominent fatigability, and proximal limb weakness. Among the NMJ disorders, autoimmune myasthenia gravis (MG) and congenital myasthenic syndrome (CMS) should be considered. Insidious onset of symptoms presenting within the first year of life and positive family history favors CMS.[1,2] Myopathies associated with ptosis ± ophthalmoplegia include congenital myopathies, mitochondrial myopathies, myotonic dystrophy, and oculopharyngeal muscular dystrophy (does not present in children).[3]

Creatine kinase (CK) was normal. EMG showed normal motor and sensory responses. Repetitive nerve stimulation (RNS) could not be performed due to poor tolerance. Needle EMG showed myopathic motor unit potentials; there were no myotonic discharges. A muscle biopsy showed some variation in fiber size and prominent type 2 fiber atrophy. There was no evidence of mitochondrial pathology on muscle biopsy.

Question for consideration:

1. What further testing would you consider to obtain a diagnosis?

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SECTION 3

Based on normal CK, myopathic muscle biopsy, and EMG findings, a congenital myopathy was considered. Genetic testing for centronuclear myopathies (*MTM1*, *DYNM2*, *BIN1*) as well as *RYR1* gene and mitochondrial DNA sequencing were negative. As there was no unifying diagnosis, whole exome sequencing was performed, which revealed homozygous mutation of acetylcholine receptor ε gene (*CHRNE*) confirming the diagnosis of CMS.

GO TO SECTION 4

In retrospect, RNS could have provided diagnostic clues for NMJ disorder. The child was started on pyridostigmine, which was gradually titrated up to 7 $mg \cdot kg^{-1} \cdot d^{-1}$ in 4 divided doses. His muscle weakness stabilized, fatigue improved, and he was able to participate in gymnastics and play soccer. There was some improvement of ptosis, but ophthalmoplegia persisted.

DISCUSSION Congenital myasthenic syndromes are a group of rare disorders that are genetically heterogeneous, resulting from more than 20 gene mutations affecting the NMJ.[1] A brief review of the normal function of NMJ will help to better understand the pathophysiology of CMS. At the presynaptic terminal, acetylcholine (ACh) is formed from choline and acetyl CoA with the help of enzyme cholineacetyl transferase (ChAT) and packaged into synaptic vesicles. A nerve impulse triggers release of Ach into the synaptic cleft. ACh diffuses and binds to the AChR receptors clustered on the crest of the postsynaptic membrane. This results in opening of central ion channel pore leading to depolarization of the muscle membrane through voltage-gated sodium channels located at the bottom of postsynaptic junction folds. ACh dissociates rapidly and is cleared from the synaptic cleft via the enzyme acetylcholine esterase (AChE).

General overview of CMS. ***Clinical features.*** CMS typically presents at birth or early childhood. However, milder phenotypes can present later in life or are unrecognized.[1] CMS is a great mimicker (table e-1 at Neurology.org) and should always be considered when a child presents with oculobulbar or respiratory symptoms, hypotonia, gross motor delays, weakness of the limb and axial muscles, along with diurnal variation of symptoms and fatigability. It should also be considered in patients with seronegative MG with poor response to immunotherapy.

Electrophysiologic studies. Routine motor studies can show repetitive compound muscle action potentials (CMAPs) in AChE deficiency and slow channel CMS after single stimulus. On low frequency (2–3 Hz) RNS, most CMS demonstrate decrement with post-tetanic repair and fatigue. At subtetanic stimulation (10 Hz), most CMS demonstrate decrement after 1–5 minutes; however, in ChAT deficiency, decrement is evident after 5 minutes with very slow recovery.[1] Single-fiber EMG is the most sensitive technique, which shows increased jitter and blocking in CMS.[2]

Genetic studies. Single gene tests are useful if there is a characteristic phenotype, family history, and EMG findings. As there is considerable phenotypic overlap, a commercially available panel of CMS genes may be most cost-effective. Whole exome sequencing is emerging as a powerful tool in the diagnosis of novel syndromes or undiagnosed cases.[1]

Treatment strategies. Unlike autoimmune MG, there is no immunologic abnormality in CMS, so immunotherapies are not effective. The mainstay of therapy in most CMS is AChE inhibitor (pyridostigmine most commonly used), which prolongs the action of ACh at the endplate (typical daily dose: 7 $mg \cdot kg^{-1} \cdot d^{-1}$).[2] Pyridostigmine is contraindicated in AChE deficiency, slow channel syndrome, and may worsen symptoms in Dok-7 myasthenia.[1,2] 3,4-Diaminopyridine (3,4-DAP) is a potassium channel blocker that acts on the presynaptic ending and increases release of ACh (maximum daily dose: 80 mg/d). Oral albuterol and ephedrine are β2 agonists that improve neuromuscular transmission by stabilizing the postsynaptic membrane.[2] They are the mainstay of therapy in Dok-7 and AChE deficiency. Open-channel blockers (fluoxetine and quinidine) are effective in slow channel syndrome. Patients with CMS should be cared for in a multidisciplinary setting with a neuromuscular specialist, pulmonologist, gastrointestinal/nutrition specialist, genetic counselor, and physical/occupational therapist.

Common specific subtypes of CMS. ***Presynaptic.*** *Choline acetyltransferase deficiency.* The hallmark of this syndrome is development of sudden apneas in the first year of life, which can be triggered by infection or stressors or without any apparent reasons.[1,2,4] Patients with severe phenotype may never breathe spontaneously and develop cerebral atrophy from hypoxemia.[5] A characteristic electrophysiologic finding consists of marked decrement after subtetanic stimulation followed by slow recovery over 5–10 minutes.[1] Pyridostigmine is helpful; 3,4-DAP also gives symptomatic relief.[2] Patients with recurrent apneas should have apnea monitor and home ventilator therapy (table 1).[6]

Synaptic basal lamina. *AChE deficiency.* Due to enzymatic deficiency, ACh stays in the synaptic cleft for a prolonged time, leading to depolarization blockade.[2] Prolonged end-plate potentials cause excitotoxic myopathy.[2] Children typically present with severe weakness since early life. About 25% of children show delayed pupillary dilation following constriction to light.[1] EMG classically shows repetitive CMAPs after single stimulus.[1,2,4] Treatment is with albuterol or ephedrine.[2] Pyridostigmine is contraindicated.[1]

Postsynaptic. Postsynaptic mutations affecting AChR account for the majority of CMS.[1] AChR deficiency due to ε subunit (*CHRNE*) mutation is the most common subtype (as presented in this vignette).[1,2] The ϵ subunit found in adult AChR replaces the γ subunit in fetal AChR. The high frequency of *CHRNE* mutations compared to other subunits is attributable to the

Table 1 Characteristic clinical and electrophysiologic features and treatment options of common congenital myasthenic syndrome (CMS) subtypes

CMS subtype	Site of defect	Characteristic clinical features	Electrophysiologic characteristics	Treatment
Choline acetyltransferase deficiency	Presynaptic	Sudden apneas	Marked decrement of CMAP amplitude after subtetanic stimulation followed by slow recovery	AChE inhibitors
				Apnea monitors ± home ventilator
Acetylcholine receptor deficiency due to ε subunit (*CHRNE*)	Postsynaptic	Most common CMS		AChE inhibitors ± 3,4-DAP ± albuterol
Slow Channel syndrome	Postsynaptic	Autosomal dominant	Repetitive CMAPs after single stimulus	AChE inhibitors and 3,4-DAP contraindicated
		Selective cervical and distal upper limb involvement		Fluoxetine and quinidine helpful
Acetylcholine esterase deficiency (*COLQ*)	Synaptic lamina	Delayed pupillary dilation (25%)	Repetitive CMAPs after single stimulus	Albuterol or ephedrine
				AChE inhibitors contraindicated
Dok-7 deficiency	Development and maintenance of endplate	Limb girdle phenotype		Albuterol or ephedrine
		Stridor in neonatal-infantile period		AChE inhibitors worsen symptoms
Rapsyn deficiency	Development and maintenance of endplate	Arthrogryposis and other congenital malformations (1/3)		AChE inhibitors and 3,4-DAP

Abbreviations: 3,4-DAP = 3,4-diaminopyridine; AChE = acetylcholine esterase; CMAP = compound muscle action potential.

phenomenon of phenotypic rescue.[1] AChR in the postsynaptic membrane is reduced to about 10% of normal.[1] These children present with ptosis and feeding difficulties within the first year of life.[2] Ophthalmoplegia develops within the first year of life and is often fixed.[1,2] These patients also have varying degree of limb weakness.[1] They usually do not experience acute crises and are stable in the long term.[2] They typically respond to pyridostigmine. 3,4-DAP and albuterol can be used as adjuvant therapies.[2,7]

Kinetic defects in AChR. ***Slow channel syndrome.*** This is inherited as autosomal dominant, unlike other CMS, which are mostly autosomal recessive. An important clinical clue is selective involvement of the cervical and distal upper limb muscles with relatively mild ocular symptoms.[1,2] The pathophysiology is prolonged ACh channel opening leading to desensitization blockade and cationic overload of the postsynaptic membrane. Pyridostigmine and 3,4-DAP are contraindicated; fluoxetine and quinidine are helpful.[8]

Fast channel syndrome. Fast channel syndrome is a severe form of CMS in which patients experience acute crises on a baseline severe generalized weakness.[2] Many patients require respiratory support and gastrostomy tube due to severe respiratory and bulbar muscle compromise. Pyridostigmine and 3,4-DAP are helpful but effects may decline after initial response.[2]

Endplate development and maintenance. ***Dok-7 deficiency.*** Dok-7 deficiency typically presents with a limb girdle phenotype mimicking myopathy.[1] It can present in the neonatal-infantile period with stridor.[2] Patients respond well with albuterol or ephedrine. Pyridostigmine usually worsens symptoms.[2]

Rapsyn deficiency. Rapsyn deficiency presents as an early-onset form that is severe and late-onset form that is mild. Arthrogryposis and other congenital malformations occur in about one-third.[1] Pyridostigmine and 3,4-DAP are usually helpful.[2]

CMS is a rare but frequently underdiagnosed entity that is potentially treatable, so clinicians should be vigilant about this entity, as seen in our case.

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Introduction

Pediatric Perspective

By Ariel M. Lyons-Warren, MD, PhD, and Jonathan W. Mink, MD, PhD

Pediatric movement disorders include a broad group of conditions ranging from benign to severe, transient to progressive, and rare to common. They can be inherited or acquired. The first step in assessing a pediatric patient with involuntary movements is to define the movement phenomenology. Describing the spatial-temporal properties of the movements helps substantially to focus the differential diagnosis and treatment choices.

The importance of phenomenology is illustrated for dystonia in the accompanying article by Blake et al. and for myoclonus in the patient described by Blackburn et al. Although the terminology is the same as for adult movement disorders, the task may be more difficult in children because the presentations are more heterogeneous. Once the movement has been described, a detailed history is important with an emphasis on timing of the movements. Specifically, at what age the movements started, if the course is progressive, and if the movements are continuous or intermittent.

The clinical reasoning process for movement disorder evaluation in children is described in the article by Kuo et al. Many unusual movements in children, and particularly infants, are benign. As described in the article by Tibussek et al., prompt recognition of these entities is necessary to prevent unnecessary investigation and to provide appropriate reassurance to parents.

Finally, over the past 10 years, numerous genetic causes of movement disorders have been recognized. An important feature of inherited movement disorders is the significant heterogeneity in clinical presentation, even within a family carrying the same mutation. Therefore, as discussed by de Bot et al., a broad differential and high clinical suspicion even in atypical presentations is necessary to make the appropriate genetic diagnosis.

From the Division of Child Neurology in the Department of Pediatrics (A.M.L.-W.), Baylor College of Medicine, Houston, TX; and Division of Child Neurology and Department of Neurology (J.W. M.), University of Rochester Medical Center, NY.
Correspondence Dr. Lyons-Warren lyonswar@bcm.edu

Adult Perspective

By Whitley Aamodt, MD, MPH, and Joel S. Perlmutter, MD

Movement disorders beginning in childhood include various clinical syndromes characterized by involuntary movements, abnormal posturing, or gait dysfunction. These disorders can persist across the lifespan, making them relevant to pediatric and adult neurologists.

Like all neurologic evaluations, assessment of a patient with a movement disorder includes a detailed history and thorough neurologic examination. Yet, unlike most other neurologic disorders, the initial evaluation also involves close observation to determine the phenomenology of the observed movements with many patients exhibiting more than 1 feature. The clinician then classifies each patient based on the predominant phenomenology: ataxia, chorea, dystonia, myoclonus, parkinsonism, tics, tremor, and stereotypies.

Developing a differential diagnosis for potential etiologies must include developmental and family history, age at onset, affected body part, and time course of symptoms. Movement disorders frequently have mixed features or may occur in discrete episodes. Manifestations in children or even young adults may evolve over time as the brain and nervous system develop.

In this section, we describe the clinical approach to 5 pediatric syndromes characterized by abnormal movements or posturing: hereditary spastic paraplegia (HSP), PLA2G6-associated neurodegeneration (PLAN), myoclonus dystonia (DYT11), pantothenate kinase–associated neurodegeneration (PKAN), and benign shuddering attacks in infancy.

These cases also serve as important teaching tools for the adult neurologist. When movement disorders present in childhood, neuroimaging may provide important clues for metabolic disorders, structural abnormalities, or evidence of neurodegeneration commonly seen in leukodystrophies, cerebral palsy, or other genetic syndromes. In addition, genetic testing can confirm diagnosis in those with inherited disorders characterized by a variable age at onset or wide phenotypic spectrum including atypical adult presentations. As the field of movement disorders advances with new therapies, early and accurate diagnosis becomes increasingly important to ensure appropriate and timely symptomatic or disease-modifying treatment.

From the Department of Neurology (W.A.), University of Pennsylvania, Philadelphia; and the Department of Neurology (J.S.P.), Washington University School of Medicine, St. Louis, MO.
Correspondence Dr. Aamodt whitley.aamodt@pennmedicine.upenn.edu

Child Neurology: Hereditary spastic paraplegia in children

S.T. de Bot, MD
B.P.C. van de Warrenburg, MD, PhD
H.P.H. Kremer, MD, PhD
M.A.A.P. Willemsen, MD, PhD

Address correspondence and reprint requests to Dr. S.T. de Bot, Radboud University Nijmegen Medical Centre, Department of Neurology, PO Box 9101, 6500 HB, Nijmegen, the Netherlands
ST.Bot@neuro.umcn.nl

Because the medical literature on hereditary spastic paraplegia (HSP) is dominated by descriptions of adult case series, there is less emphasis on the genetic evaluation in suspected pediatric cases of HSP. The differential diagnosis of progressive spastic paraplegia strongly depends on the age at onset, as well as the accompanying clinical features, possible abnormalities on MRI, and family history. In order to develop a rational diagnostic strategy for pediatric HSP cases, we performed a literature search focusing on presenting signs and symptoms, age at onset, and genotype. We present a case of a young boy with a *REEP1* (SPG31) mutation.

CASE REPORT A 4-year-old boy presented with progressive walking difficulties from the time he started walking at the age of 12 to 13 months. His family history was significant for minimal gait abnormalities with onset after age 35, occurring in the patient's mother, maternal grandfather, and maternal aunt; none of them had ever sought medical attention. Neurologic examination revealed a mildly spastic gait and marked lower limb hyperreflexia with bilateral Babinski signs present. Vibration perception was reduced at the ankles. Neurologic examination of the patient's mother and maternal aunt revealed subtle gait abnormalities with bilateral Babinski signs present.

MRI of the brain and spinal cord and general metabolic screening revealed no abnormalities. Diagnostic genetic testing in both the patient and his mother revealed a pathogenic mutation (c.417 + 1 G>T) in *REEP1* (SPG31) which causes a pure HSP. Mutations in *ATL1* (SPG3A) and *SPAST* (SPG4) had previously been excluded.

DISCUSSION HSP is a genetically and clinically heterogeneous group of disorders in which the main clinical feature is progressive lower limb spasticity secondary to pyramidal tract dysfunction. HSP is classified as pure if neurologic signs are limited to the lower limbs (although urinary urgency and mild impairment of vibration perception in the distal lower extremities may occur). In contrast, complicated forms of HSP display additional neurologic and MRI abnormalities such as ataxia, more significant peripheral neuropathy, mental retardation, or a thin corpus callosum. HSP may be inherited as an autosomal dominant, autosomal recessive, or X-linked disease. Over 40 loci and nearly 20 genes have already been identified.[1] Autosomal dominant transmission is observed in 70% to 80% of all cases and typically results in pure HSP.[2]

Spastic paraplegia is a common problem in the daily practice of pediatric neurologists, generally caused by acquired brain disorders such as perinatal asphyxia or infections early in life resulting in cerebral palsy. In addition, there is a long list of more rare disorders to consider when confronted with spastic paraplegia including structural, infectious, demyelinating, and metabolic disorders (table).[3] Only in a small minority of cases does HSP underlie the spastic syndrome. Many patients with childhood-onset HSP are mistakenly diagnosed with cerebral palsy.[4,5] In children with spastic paraplegia in whom no acquired cause can be identified, HSP should be considered. A positive family history aids with the diagnosis. Our case illustrates the importance of neurologic examination of family members who may be mildly affected.

Since the medical literature on HSP is dominated by adult case series, it is difficult to decide how the genetic evaluation should be structured when a child is suspected to have HSP. In order to develop a rational diagnostic strategy for HSP in children, we per-

GLOSSARY

ATL1 = atlastin (GTPase) 1; *BSCL2* = Berardinelli-Seip congenital lipodystrophy 2 (seipin); *KIF5A* = kinesin family member 5A; *L1CAM* = L1 cell adhesion molecule; *NIPA1* = nonimprinted in Prader-Willi/Angelman syndrome region protein 1; *PLP1* = proteolipid protein 1; *REEP1* = receptor expression-enhancing protein 1; *SPAST* = spastin; SPG = spastic paraplegia gene; *ZFYVE26* = zinc finger FYVE domain-containing protein 26 (spastizin).

From the Departments of Neurology (S.T.d.B., B.P.C.v.d.W.) and Paediatric Neurology (M.A.A.P.W.), Donders Centre for Brain, Cognition, and Behaviour, Radboud University Nijmegen Medical Centre, Nijmegen; and Department Of Neurology (H.P.H.K.), University Medical Centre Groningen, Groningen, the Netherlands.

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Table Differential diagnosis of spastic paraplegia

Abnormalities on MRI	Differential diagnosis of spastic paraplegia with additional abnormalities on MRI of the brain	HSPs
Leukoencephalopathy	Many neurometabolic and other hereditary white matter disorders with characteristic MRI pattern, like Krabbe disease, Alexander disease, X-linked adrenoleukodystrophy, vanishing white matter; inflammatory disorders like multiple sclerosis, acute disseminated encephalomyelitis, neuromyelitis optica	SPG4 (some), SPG11, SPG15, SPG21
Thin corpus callosum	Thin corpus callosum + epilepsy, Andermann syndrome	SPG1, SPG4 (some), SPG11, SPG15, SPG21, SPG32,
Cerebellar atrophy	See cerebellar ataxia (below)	SPG7
Additional clinical features	**Differential diagnosis of spastic paraplegia with additional clinical features**	**HSPs**
Mental retardation	Many neurometabolic or neurogenetic disorders; sometimes recognizable based on MRI abnormalities (see top of table) or further additional features (see below)	SPG1, SPG2, SPG11, SPG14, SPG15, SPG16, SPG20, SPG21, SPG23, SPG27, SPG32, SPG35
Dysmorphisms	Andermann syndrome, hydrocephalus due to congenital stenosis of aqueduct of Sylvius	SPG1, SPG23
Optic atrophy	Cobalamin C disease, biotinidase deficiency, cerebral folate deficiency, SPOAN, ARSACS, type III 3-methylglutaconic aciduria	SPG7
Retinopathy	Cobalamin C disease, Sjögren-Larsson syndrome, homocarnosinosis, abetalipoproteinemia	SPG15
Cataract	Cerebrotendinous xanthomatosis, α-methyl-CoA racemase deficiency	SPG9
Hearing loss/deafness	Biotinidase deficiency, cerebral folate deficiency	SPG29
Neuropathy/amyotrophy	dHMN, HMSN V, cerebrotendinous xanthomatosis, cobalamin C disease, MTHFR deficiency, metachromatic leukodystrophy, Krabbe disease, adrenomyeloneuropathy, polyglucosan body disease, α-methyl-CoA racemase deficiency, biotinidase deficiency, abetalipoproteinemia (posterior column), homocysteine remethylation defects, SPOAN, ARSACS, Andermann syndrome	SPG7, SPG9, SPG10, SPG11, SPG14, SPG17, SPG20, SPG27, SPG38, SPG39
Cerebellar ataxia	Atypical Friedreich ataxia, cerebrotendinous xanthomatosis, triple H syndrome, cerebral folate deficiency, metachromatic leukodystrophy, SAX1, SAX2, ARSACS, ARSAL, Type III 3-methylglutaconic aciduria, Alexander disease	SPG7, SPG15, SPG20, SPG21, SPG27
Extrapyramidal signs/diurnal fluctuations	Dopamine synthesis defects and cerebral folate deficiency (dystonia), amyotrophic dystonic paraplegia (dystonia), polyglucosan body disease, phenylketonuria and cerebrotendinous xanthomatosis (parkinsonism), dopa-responsive dystonia (diurnal fluctuations)	SPG21, SPG23 (tremor)
Epilepsy	Dopamine synthesis defects, α-methyl-CoA racemase deficiency, triple H syndrome, metachromatic leukodystrophy, cerebrotendinous xanthomatosis, arginase deficiency, cerebral folate deficiency, thin corpus callosum + epilepsy, Alexander disease	SPG2, SPG35
Cutaneous signs	Cerebrotendinous xanthomatosis (xanthomas), biotinidase deficiency (alopecia, dermatitis), Sjögren-Larsson (ichthyosis), adrenoleukodystrophy/adrenomyeloneuropathy (melanoderma)	SPG23 (pigmentary abnormalities)
Episodes of confusion, nausea/vomiting, or diarrhea	Cobalamin C disease, MTHFR deficiency, triple H, arginase deficiency, cerebrotendinous xanthomatosis (chronic diarrhea), adrenal insufficiency (adrenomyeloneuropathy, adrenoleukodystrophy), abetalipoproteinemia (diarrhea), homocysteine remethylation defects (confusion)	SPG9 (gastroesophageal reflux), SPG29 (hiatus hernia, hyperbilirubinemia)

Abbreviations: ARSACS = autosomal recessive spastic ataxia of Charlevoix-Saguenay; ARSAL = autosomal recessive spastic ataxia with leukoencephalopathy; dHMN = distal hereditary motor neuropathy; HMSN = hereditary motor and sensory neuropathy; HSP = hereditary spastic paraplegia; MTHFR = 5,10-methylenetetrahydrofolate deficiency; SAX1/SAX2 = spastic ataxia; SPG1 = *L1CAM*; SPG2 = *PLP1*; SPG4 = *SPAST*; SPG10 = *KIF5A;* SPG15 = *ZFYVE26*; SPG17 = *BSCL2*; SPOAN = spastic paraplegia, optic atrophy, and neuropathy; triple H syndrome = hyperornithinemia-hyperammonemia-homocitrullinuria syndrome.

formed a literature search focusing on presenting signs and symptoms, age at symptom onset, and genotype. We also share some of our personal experiences from a clinic-genetic database, as our institution has served as a tertiary referral center for Dutch HSP patients for over 2 decades.

Characteristics. In the medical literature, symptom onset before age 18 has been documented in many HSP cases, particularly in the complicated forms, which show a clear overlap with many metabolic disorders and leukodystrophies. In a series of 23

children with HSP, 15 of 23 (65%) were reported to have a complicated (mostly recessively inherited) HSP, compared to 8 of 23 (35%) with a pure HSP.[6]

In our HSP database, an early age at symptom onset (prior to age 18) was found in 72 of 175 (41%) patients, with a heterogeneous genetic background: 47 of 72 (65%) autosomal dominant cases, 12 of 72 (17%) autosomal recessive cases, and 13 of 72 (18%) sporadic cases. Gait difficulties were the presenting symptom in 81%, with a mean age of 8 years. A complicated phenotype was present in 25%. Of these 72 early-onset HSP patients, at least 20 (28%) had presented in childhood to a pediatrician or pediatric neurologist.

Prior reviews have provided in-depth descriptions and overviews of all known HSP forms.[1,2] In this article, we focus on the most prevalent (>5 families described) forms of HSP with a possible childhood onset.

Autosomal dominant pure HSP. *ATL1* (SPG3A). This is a pure form of HSP, comparable to SPG4, and almost never starts after age 20 years. It is the most frequent cause of HSP (twice as frequent as *SPAST*), with onset before age 10 years.[7] Therefore, *ATL1*, which encodes atlastin (a dynamin-like GTPase), is the first candidate gene that should be tested in patients with a suspected pure autosomal dominant or sporadic HSP with symptom onset before age 10.[2]

***SPAST* (SPG4).** SPG4 is the most prevalent, mostly pure form of HSP with a variable age at onset, varying from infancy through over 70 years of age. *SPAST* encodes spastin with microtubule-severing activity, necessary for axonal transport. In a large study of 172 *SPAST* patients, approximately 30% had an age at onset before 20 years.[8] In our *SPAST* cohort, comparable figures were found, with walking difficulties presenting at a mean age of 7.5 years (range 1–18 years) in this young-onset group. Onset in infancy is unusual. After the description of 5 patients from 1 family,[5] we identified an additional 5 patients from 4 families with symptom onset in infancy. Until that point, such a young onset had been described only in association with co-dominant mutations (genetic modifiers) in the *SPAST* gene. Therefore, *SPAST* is the second candidate gene that should be tested in patients with a pure HSP with symptom onset before age 10, after *ATL1*. With an onset of symptoms between 10 and 20 years, both genes should be tested.

***NIPA1* (SPG6), *KIF5A* (SPG10), *and* SPG12.** SPG6 causes a pure HSP, occasionally with a childhood onset, but more commonly with onset of symptoms in the late teenage to early adult years.[9] SPG10 and SPG12 both lead to an early-onset pure HSP. All 3 are described in fewer than 10 families.[1]

***REEP1* (SPG31).** SPG31, a pure form of HSP, shows a variable age at onset, with an onset before 20 years in 71% of cases.[10] *REEP1* encodes the mitochondrial protein receptor expression-enhancing protein 1. *REEP1* mutations were found in 8.2% of pure autosomal dominant HSP patients (of all ages), in whom *ATL1* or *SPAST* mutations had been excluded.[1]

We encountered 5 SPG31 patients who presented before age 18 years, with gait abnormalities and foot deformities at a mean age of 4 years. *REEP1* mutations can cause a pure HSP in children, but should only be tested after *SPAST* and *ATL1* mutations have been ruled out.

Complicated forms of HSP. *L1CAM* (SPG1) *and PLP1* (SPG2). These are both X-linked and complicated forms of HSP, which may be tested in boys with mental retardation and other clinical features.[1,2]

SPG7. SPG7, an autosomal recessive HSP, causes a spastic paraplegia in combination with cerebellar ataxia, cerebellar atrophy, optic atrophy, and peripheral neuropathy. Age at onset varies from 10 to 42 years in the literature, but mostly adult cases have been reported.

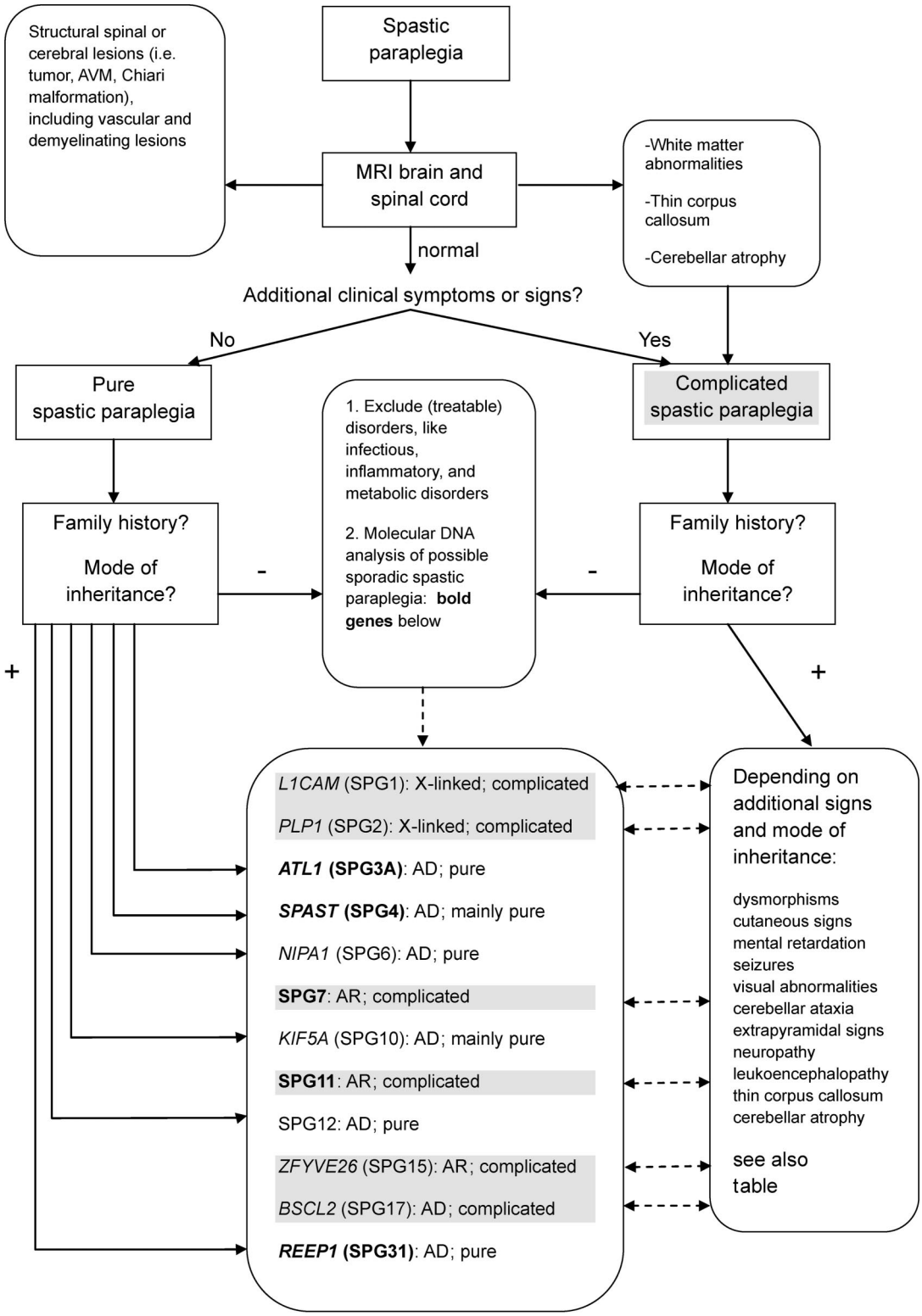
SPG11 *and ZFYVE26* (SPG15). SPG11 is the most frequent form of autosomal recessive HSP with onset typically in childhood (age range 1.5–21 years). It is characterized by a thin corpus callosum, mild leukoencephalopathy, mild mental retardation, and peripheral neuropathy. A comparable autosomal recessive syndrome is SPG15 (Kjellin syndrome), with additional cerebellar signs, maculopathy, and onset between 5 and 19 years.

***BSCL2* (SPG17).** SPG17 (Silver syndrome) has a variable age at onset. Distal amyotrophy affecting upper extremities more than lower extremities accompanies the spastic paraplegia. Inheritance is autosomal dominant.

Four SPG17 patients in our cohort, with onset between 10 and 16 years, presented with weakness of the upper extremities greater than in the lower extremities, and 3 of the 4 had foot or hand deformities.

Genetic testing in children. A formal diagnosis provides a prognosis, prevents additional burdensome and potentially costly diagnostic evaluation, may facilitate the prevention of complications, and allows for potential inclusion in clinical trials. In addition, a genetic diagnosis allows for genetic counseling with regard to the recurrence risk within the family. Ethical, social, and financial considerations, as well as written or verbal informed consent from the parents, according to established guidelines, are necessary before genetic testing in children.

Figure Diagnostic flow chart of hereditary spastic paraplegia in children



The combination of pure or complicated (gray) and the mode of inheritance will help to select the appropriate DNA tests. AD = autosomal dominant; AR = autosomal recessive; AVM = arteriovenous malformation.

Diagnostic approach. When confronted with a child with a pure spastic paraplegia, a thorough family history (of at least 3 generations) is essential. After neurologic examination of the child and the parents, structural lesions and white matter disorders need to be excluded by performing MRI of the brain, with transverse T1, T2,

and sagittal T1 images, and of the entire spinal cord. A positive family history or examination facilitates direct diagnostic genetic testing (figure).

In a pure, autosomal dominant HSP, *ATL1* (SPG3A) and *SPAST* (SPG4) mutation analysis would be the first tests of choice. If negative, *REEP1* (SPG31) could be tested subsequently. In case of a negative family history or examination, ophthalmologic examination, CSF analysis, and metabolic screening should be considered, primarily to look for conditions with disease-modifying therapies available. Finally, a trial of levodopa may be considered, since a dystonic gait and striatal toes as part of a dopa-responsive dystonia syndrome could be mistaken for spastic paraplegia.[3] If these investigations are negative, *ATL1* and *SPAST* mutation analysis should be considered because sporadic cases (due to de novo mutations and incomplete penetrance) have been described in these HSP forms.[4,5]

When confronted with a child with a complicated spastic paraplegia, the accompanying signs and symptoms will lead to a differential diagnosis and the required specific diagnostic evaluation (table).[1,2]

DISCLOSURE

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Child Neurology: Two sisters with dystonia and regression

PLA2G6-associated neurodegeneration

Robert B. Blake, MD
Donald L. Gilbert, MD
Mark B. Schapiro, MD

Correspondence to
Dr. Blake:
robert.blake@cchmc.org

CLINICAL CASE, PART 1 A 19-month-old girl presented for neurologic consultation for delayed walking. She rolled at 6 months, sat unsupported at 8 months, but never walked independently. She babbled only. Her examination was notable for slightly decreased bulk in her legs, mild truncal hypotonia, and decreased deep tendon reflexes. She had difficulty pulling to stand and could only walk with support. She exhibited a steppage gait with hyperextension of her knees, exaggerated lifting of her feet, and out-turning of her ankles. Birth history was unremarkable and parents were not consanguineous. A head CT performed at 13 months for mild head trauma was normal.

The initial diagnostic workup was directed at causes of gait abnormality and developmental delay. Initial metabolic screening labs, including serum lactate/pyruvate, amino acids, creatine phosphokinase, carnitine, lipid panel, and coenzyme Q10 profile, were normal. MRI of the spine was normal. At age 23 months, brain MRI showed new mild to moderate cerebellar atrophy and minimal brainstem volume loss (figure).

By age 26 months, the patient developed pain and dystonia in her legs. On examination, she had striatal toes (spontaneous extensor plantar response without fanning of the toes) and continued decreased deep tendon reflexes. She could no longer stand, although she still crawled. Repeat brain MRI at 29 months showed progressive cerebellar volume loss.

By age 31 months, she developed a mild spastic quadriparesis and continued to have significant painful dystonic posturing of lower extremities. Developmental regression continued. She was no longer able to sit independently or crawl and only made occasional sounds. She developed bilateral optic atrophy and intermittent left esotropia.

Differential diagnosis. Dystonia is a movement disorder characterized by sustained or intermittent muscle contractions causing abnormal, often repetitive, movements, postures, or both.[1] The differential diagnosis for dystonia in children is broad (table e-1 on the *Neurology*® Web site at Neurology.org) but can be narrowed by presence of other neurologic manifestations. Dystonia associated with cerebellar atrophy and developmental delay or regression is concerning for an inherited neurodegenerative process. Etiologies to consider include neurodegeneration with brain iron accumulation (NBIA), neuronal ceroid lipofuscinosis, pontocerebellar hypoplasia, Rett syndrome, Wilson disease, and Leigh syndrome or other mitochondrial diseases.

CLINICAL CASE, PART 2 Genetic testing results included normal karyotype and interstitial duplication of 129 kb of DNA at 17q21.31, likely benign, on chromosomal microarray. The Cerebellar/Pontocerebellar Hypoplasia Sequencing Panel (University of Chicago Genetic Services Laboratory, 2013) detected no pathogenic variants. Copper and ceruloplasmin were normal. Mitochondrial DNA (mtDNA) Deletion/Duplication and mtDNA Common Mutation Panels (Cincinnati Children's Molecular Genetics Laboratory, 2014) showed no abnormalities.

Continued hyporeflexia and pain, and new intermittent episodes of leg flushing, raised concern for peripheral neuropathy. This, in conjunction with regression, dystonia, and MRI findings, prompted sending the NBIA Sequencing Panel (University of Chicago Genetic Services Laboratory, 2014) at age 33 months. The panel showed 2 mutations in the *PLA2G6* gene (*PLA2G6* c.1674del and *PLA2G6* c.2370T>G), both pathogenic variants previously described in *PLA2G6*-related disorders.[2,3] Based on the phenotype (clinical history, neurologic examination, and neuroimaging), the patient was diagnosed with the infantile neuroaxonal dystrophy (INAD) subtype of *PLA2G6*-associated neurodegeneration (PLAN). At the time of diagnosis the patient had 2 younger siblings, one of whom was displaying signs of developmental regression. Given the patient's family history, her classic presentation, and the identification of 2 previously reported pathogenic variants, parental genetic testing was not thought necessary. Genetic counseling was provided.

The patient was prescribed docosahexaenoic acid (DHA) 250 mg per day. During the 18 months following diagnosis, she continued to have dystonia,

Supplemental data at Neurology.org

From the Department of Neurology, Cincinnati Children's Hospital Medical Center, OH.

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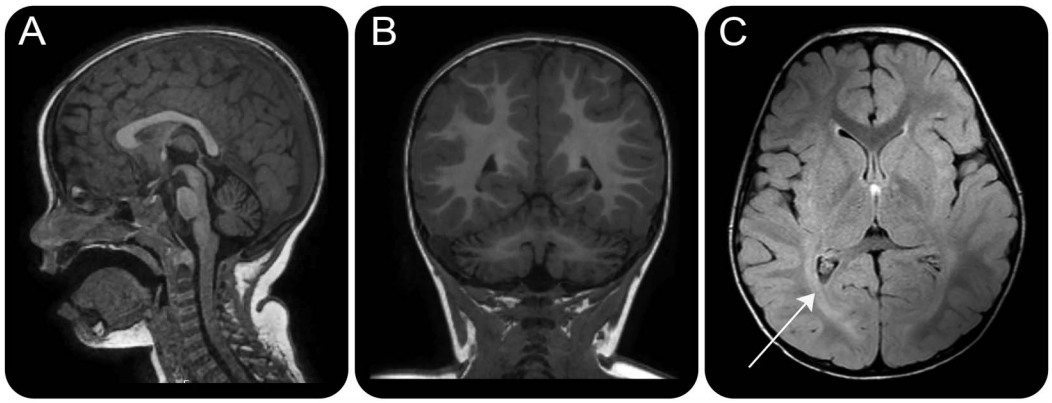
Figure Brain MRIs from patient in case presentation



T1-weighted images at age 23 months in midsagittal (A) and coronal (B) views demonstrate atrophy of vermis and cerebellar hemispheres and minimal brainstem volume loss. Axial fluid-attenuated inversion recovery image at age 33 months (C) shows nonspecific white matter changes (arrow), but no sign of iron deposition or other signal abnormality in basal ganglia.

tight heel cords, and lower extremity pain, which were treated symptomatically with baclofen, trihexyphenidyl, gabapentin, diazepam, and tramadol. After video swallow study showed silent aspiration, a gastrostomy tube was placed. She developed epilepsy with occasional generalized tonic-clonic seizures. Sleep study showed brief central and obstructive sleep apnea, and she was placed on overnight oxygen. Her last brain MRI, performed at age 33 months, showed stable volume loss in the cerebellum and brainstem, subtle nonspecific hyperintense T2/fluid-attenuated inversion recovery signal in the supratentorial white matter, but no radiographic evidence of brain iron accumulation (figure). Palliative services were engaged, and the patient expired at age 4 years from respiratory causes.

The patient's younger sister developed motor delays by age 1 year. By age 2, the younger sister could not walk independently, displayed a steppage gait when supported, and spoke only 2 recognizable words. Over the next few months, she regressed in motor and language skills and developed dystonia in her lower extremities. A brain MRI showed cerebellar volume loss similar to her sister's. Given the similar phenotype, she was given a presumptive diagnosis of PLAN.

DISCUSSION PLAN, also known as NBIA2, is a rare autosomal recessive disorder first reported by Seitelberger[4] in 1952 and later clinically defined by Aicardi and Castelein[5] in 1979. The incidence of PLAN is unknown. It falls in the broader disease category of NBIA. NBIA is a heterogeneous group of rare diseases characterized by progressive extrapyramidal symptoms, intellectual impairment, and excessive iron deposition in the brain, especially the globus pallidus. The 2 most common NBIA diseases are pantothenate kinase–associated neurodegeneration (PKAN, also known as NBIA1), which accounts for approximately 50% of all NBIA cases, and PLAN, which accounts for about 20%.[6] Because of the rarity of NBIA, knowledge of the clinical characteristics, response to treatment, and prognosis are based mostly on case series.

PLAN has 3 distinct clinical phenotypes.[6,7] The first, often referred to as *infantile neuroaxonal dystrophy* or INAD, typically presents between 6 months and 3 years of age with neurodevelopmental arrest and then devastating regression in all domains. Motor symptoms include early truncal hypotonia, limb dystonia, and eventual development of spastic quadriparesis. Many children develop an axonal-type sensorimotor neuropathy with hyporeflexia and paresthesias. Cerebellar ataxia commonly but not invariably develops. Early visual disturbances due to optic atrophy occur in the form of strabismus, nystagmus, and eventual blindness. Seizures occur in up to 17% of patients. Most children with INAD die before age 10 years.

A second phenotype referred to as atypical neuroaxonal dystrophy presents between early childhood and the end of the second decade. It has a slower progression than INAD and presents with heterogeneous clinical features including language difficulties, autism spectrum disorder, eye movement abnormalities, spastic quadriparesis, and progressive dystonia and dysarthria.[6]

A third phenotype called *PLA2G6*-related dystonia-parkinsonism has been described. Patients with this phenotype present between childhood and the third decade of life and experience dystonia, bradykinesia, rigidity, and marked cognitive decline.[6]

In contrast, the more well-known PKAN typically presents in the first decade of life with gait disturbance, dystonia, rigidity, and dysarthria. Slow progression leads to loss of ambulation within 15 years.

PKAN is not typically associated with ataxia or peripheral neuropathy, and visual disturbances occur primarily due to pigmentary retinopathy.[6]

Brain MRI shows cerebellar atrophy in virtually all well-established PLAN cases. Other neuroimaging findings are more variable. Diffuse T2 white matter hyperintensities, thinning of corpus callosum, and thinning of the optic nerves and chiasm are commonly seen. Unlike PKAN, in which the majority of patients will have the classic "eye of the tiger" sign in globus pallidus, the neuroradiologic evidence of iron deposition in PLAN is much more variable. Many patients with advanced PLAN never have clear radiographic evidence of brain iron accumulation. The gold standard for diagnosis of PLAN used to be demonstration of dystrophic axonal spheroids in nerve and conjunctival biopsies. Now most diagnoses are confirmed through the detection of mutations in the *PLA2G6* gene.

The *PLA2G6* gene, located on chromosome 22q13, encodes the protein iPLA2-beta, which is a subunit of the calcium-independent phospholipase A_2 enzyme. Phospholipase A_2 is important in the synthesis of free fatty acids and lysophospholipids. A recent study demonstrated that loss of normal *PLA2G6* activity leads to elevated mitochondrial lipid peroxidation, mitochondrial dysfunction, and subsequent mitochondrial membrane abnormalities.[8] Mouse models of PLAN reveal decreased incorporation of DHA into the brain.[9] DHA is a precursor of anti-inflammatory neuroprotectins, and decreased brain DHA metabolism may increase vulnerability to neuroinflammation. However, it remains unclear how these disturbances lead to brain iron accumulation or the clinical findings seen in PLAN. There is not a clear correlation between specific *PLA2G6* gene mutations and clinical presentation.

The standard of care for PLAN is supportive care and symptomatic treatment of dystonia, spasticity, and epilepsy. There is no disease-specific treatment for PLAN. Some current clinical trials are evaluating treatment of NBIA with iron chelators,[10] but most only enroll patients with PKAN. Some centers have treated individual patients with supplementary DHA, although efficacy is unclear and results have not been published. Multinational consortia will be needed to enroll sufficient numbers of patients for any treatment trials of this rare disease.

CONCLUSION PLAN is a form of NBIA that should be considered in any child with developmental regression, especially when associated with dystonia, truncal hypotonia, peripheral neuropathy, ataxia, visual disturbance, and/or cerebellar atrophy. The lack of radiographic evidence of iron accumulation, especially early in disease course, should not dissuade clinicians from including this rare neurodegenerative disease in their differential.

AUTHOR CONTRIBUTIONS

Robert B. Blake, MD: conceptualized, drafted, and revised the manuscript for intellectual content. Donald L. Gilbert, MD: provided significant revisions of manuscript for intellectual content. Mark B. Schapiro, MD: conceptualized, drafted, and revised the manuscript for intellectual content.

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Clinical Reasoning: A 13-year-old boy presenting with dystonia, myoclonus, and anxiety

Joanna S. Blackburn, MD
Melissa L. Cirillo, MD

Correspondence & reprint requests to Dr. Cirillo: mcirillo@childrensmemorial.org

SECTION 1

A 13-year-old, right-handed boy was referred for movement and speech abnormalities. His mother reports his voice becoming soft and choppy at 8 years of age. Over the past year, he developed head jerking to the right while using his right hand. The patient denied a premonitory urge or ability to suppress these movements. They had become so disabling that he had to eat and write with his left hand. He has no other medical problems, other than a pectus excavatum. His family history is notable for his father being diagnosed with Tourette syndrome as a teen. His father continues to have episodic head jerking to the left at times. The patient's general examination was notable for an anxious teenager with marfanoid features including pectus excavatum and long limbs. The patient's neurologic examination revealed strained, choppy speech, which was present while speaking but not while singing. He had involuntary forced head turn to the right with right tilt and right upper extremity sustained twisting posturing when trying to use his right hand. He had right upper extremity fast jerking movements with attempts to use his right arm. His deep tendon reflexes were brisk, with crossed adductors. The remainder of his neurologic examination was normal.

Question for consideration:

1. What type of movement is being described in the history?

GO TO SECTION 2

From the Department of Pediatrics, Division of Neurology, Children's Memorial Hospital, The Feinberg School of Medicine, Northwestern University, Chicago, IL.

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SECTION 2

Although his father had been diagnosed with Tourette syndrome, the patient's movements were neither suppressible nor preceded by an urge, which are the hallmarks of tics. The strained choppy voice was consistent with spasmodic dysphonia, a form of laryngeal dystonia. His forced head turn to the right and twisting posturing was consistent with cervical dystonia and limb dystonia, respectively. The jerking movements of his arm suggested a dystonic tremor vs myoclonus. On his initial examination it was difficult to differentiate between these 2 involuntary movements.

Questions for consideration:

1. What is the definition of dystonia?
2. What is the differential diagnosis for dystonia with onset in childhood or early adolescence?
3. What diagnostic tests would you order?

GO TO SECTION 3

SECTION 3

Dystonia in childhood has been defined as a movement disorder with involuntary sustained or intermittent muscle contractions which cause twisting and repetitive movements, abnormal postures, or both.[1]

A broad differential diagnosis must be considered in the evaluation of childhood or adolescent onset dystonia, including primary dystonias, dystonia plus syndromes, secondary dystonias, and heredodegenerative disorders.[2,3] Primary dystonias do not have other neurologic or systemic findings. The most common primary dystonia is DYT-1 dystonia, which is typically characterized by childhood onset limb dystonia often with subsequent generalization.[2,3] It is an autosomal dominant disease with a penetrance rate of 30%–40% which is caused by a GAG deletion in the *TOR1A* gene. Dystonia plus syndromes include additional neurologic findings such as parkinsonism and myoclonus.[4] Two dystonia plus syndromes are dopa-responsive dystonia (DYT 5) and myoclonus dystonia (DYT 11). Dopa-responsive dystonia (DYT 5) typically presents in midchildhood with gait dystonia. There is diurnal variation in symptoms in 75% of patients.[2] Other possible associated features include parkinsonism and hyperreflexia.[2,3] A key feature of this condition is a dramatic and sustained response to levodopa.[2,3] It is caused by a mutation in the GTP-cyclohydrolase-I gene. The presence of myoclonus in association with dystonia is characteristic of myoclonus dystonia (DYT 11).[2,3] Secondary and heredodegenerative dystonias typically present with other neurologic and systemic signs and symptoms in addition to dystonia. Secondary dystonia is due to an acquired or exogenous cause including drug exposures, toxins, infections, and focal CNS lesions.[3] Important historical information includes drug or toxin exposure, perinatal injury, encephalitis, or head trauma. A focal structural lesion may present with hemidystonia. Heredodegenerative disorders which have dystonia as a feature are genetic disorders including Huntington disease, Wilson disease, and pantothenate kinase–associated neurodegeneration.[2] These are often associated with other signs including cognitive impairment, seizures, oculomotor dysfunction, retinal abnormalities, neuropathy, spasticity, as well as liver dysfunction and skeletal abnormalities.

Our patient presented with dystonia, a dystonic tremor vs myoclonus, and marfanoid features. In addition, on further examination of the patient's father, his findings were more consistent with myoclonus rather than tics. His father also reported that his head jerking resolved with alcohol use. This suggests the most likely diagnosis was either a primary dystonia or a dystonia plus syndrome. The patient's abnormal movements were unilateral, so a focal etiology was considered. Given the presence of marfanoid features, abnormal vessels leading to a basal ganglia stroke was considered. Marfanoid features are not associated with a primary dystonia or dystonia plus syndrome. The following laboratory testing was normal: complete blood count, complete metabolic panel, copper, ceruloplasmin, zinc, thyroid function testing, and ferritin. He had MRI of the brain and magnetic resonance angiography (MRA) of the head and neck, which showed no evidence of stroke or abnormal vessels to suggest his presentation was related to his marfanoid habitus. He had a normal ophthalmologic examination with no evidence of Kayser-Fleischer rings or retinal detachment. DYT-1 genetic testing was pending.

Question for consideration:

1. Would you treat the patient while awaiting genetic testing results? If so, with what?

GO TO SECTION 4

SECTION 4

It is recommended that patients with early onset dystonia without an alternative diagnosis undergo a levodopa trial.[4] Although our patient's presentation was not typical for dopa-responsive dystonia, he was treated with levodopa while additional genetic testing was pending. There was no clinical response to levodopa, making that an unlikely diagnosis. DYT-1 testing was negative. On repeat examination, his abnormal movements appeared to be consistent with myoclonus in addition to a dystonic tremor.

Question for consideration:

1. What additional diagnostic testing would you send at this time?

GO TO SECTION 5

SECTION 5

Given the constellation of dystonia, myoclonus, anxiety, and his father's history, the patient was evaluated for myoclonus dystonia. Epsilon sarcoglycan gene (*SGCE*) testing revealed a known mutation and a diagnosis of myoclonus dystonia syndrome was made. Our patient was treated with trihexyphenidyl, which resulted in significant improvement of his myoclonus and dystonia. He was able to eat and write with his right hand and was remarkably less anxious.

DISCUSSION Myoclonus dystonia is a rare disorder characterized by myoclonic jerks and dystonia. Presentation is typically in childhood or early adolescence.[5] The most common presenting symptom is myoclonus, but dystonia can be the initial presentation in 20%.[5] Myoclonus typically involves the arm and axial musculature and is responsive to alcohol. Dystonia is usually mild and most often manifests as cervical dystonia or writer's cramp. Psychiatric features are common and include depression, obsessive-compulsive behavior, panic attacks, and attention deficit hyperactivity disorder.[2,5] Severity of symptoms varies. Spontaneous resolution of limb dystonia and improvement of myoclonus occur in 20% and 5%, respectively.[5] Although spontaneous resolution can occur, myoclonus and dystonia can progress at any time during the disease course.[5]

Inheritance is autosomal dominant with reduced maternal inheritance due to maternal imprinting. Paternal inheritance always results in the disease whereas maternal inheritance has a penetrance of 10%–15%.[2] Mutations in the *SGCE* gene, which encodes the protein epsilon sarcoglycan, is located in chromosome region 7q21. Mutations in the *SGCE* gene are found is less than 40% of patients with the clinical phenotype.[5] There are reports of both sporadic cases as well as kindreds with *SGCE*-negative myoclonus dystonia. One notes a kindred presenting with autosomal dominant clinical features of myoclonus dystonia syndrome who was found to have GTP cyclohydrolase I deficiency, which is typically associated with dopa-responsive dystonia.[6] The pathophysiology of myoclonus dystonia is unknown.

Treatment of myoclonus dystonia is symptomatic. Anticholinergic drugs and benzodiazepines may improve dystonia and myoclonus.[5] Antiepileptic drugs including levetiracetam, piracetam, valproic acid, and zonisamide have improved myoclonus in some patients.[5] Levodopa has been shown in isolated cases to improve symptoms.[7] Botulinum toxin is an option to treat focal dystonia. Deep brain stimulation (DBS) of the globus pallidus interna (GPi) and ventral intermediate thalamic nucleus have been shown to improve symptoms in more than 70% of patients with DBS-GPi, having fewer adverse effects.[8,9]

Diagnostic criteria for definite myoclonus dystonia have been proposed and include early onset (<20 years), myoclonus predominating in the upper body either isolated or associated with dystonia, positive family history with paternal transmission when due to *SGCE* mutation or deletion, exclusion of additional neurologic findings such as cerebellar ataxia, spasticity, and dementia, and a normal brain MRI.[5,10]

Myoclonus dystonia is a rare cause of dystonia in childhood but must be considered in the setting of early onset dystonia when myoclonus is present, especially in cases with potential paternal inheritance. Our patient meets the suggested criteria for the diagnosis of myoclonus dystonia as described above. *SGCE* testing in his father confirmed that his father also has a diagnosis of myoclonus dystonia, rather than the previous diagnosis of Tourette syndrome.

AUTHOR CONTRIBUTIONS

Dr. Blackburn qualifies as an author for drafting and revising the manuscript for content including medical writing for content. Dr. Cirillo qualifies as an author for drafting and revising the manuscript for content including medical writing for content.

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Clinical Reasoning: A 16-year-old boy with freezing of gait

Sheng-Han Kuo, MD
Paul Greene, MD

Address correspondence and reprint requests to Dr. Sheng-Han Kuo, Department of Neurology, The Neurological Institute of New York, 710 W. 168th Street, 3rd floor, New York, NY 10032
sk3295@columbia.edu

SECTION 1

A 16-year-old boy had a long history of clumsiness. He had an unremarkable birth history. He walked unassisted at the age of 16 months and ran at age 2. He started running with difficulty at age 10. He performed poorly in physical education classes and was never able to hop. He had normal cognition and good academic performance. His speech difficulty started at age 7. His speech was slurred and nasal and he had difficulty opening his mouth fully while talking or eating. He did not bite his tongue and had no trouble swallowing. His handwriting was tight and slow. He started to fall at age 13. When he was rushed or startled, his feet froze and he fell. He would fall in the middle of the street when the traffic light changed, when he got out of a chair quickly, or at the top of a flight of stairs. He did not have visual symptoms, weakness, sensory change, or bowel or bladder incontinence. He had no other past medical problems and took no medications. His brother had a similar neurologic problem. The pertinent neurologic examination is shown in video 1 on the *Neurology*® Web site at www.neurology.org.

Questions for consideration:

1. What is the phenomenology in this patient?
2. How do you describe the patient's speech?

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From the Department of Neurology, College of Physicians and Surgeons, Columbia University, New York, NY.
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SECTION 2

In video 1, the boy had freezing of gait while getting up from a chair quickly. His speech was strained with voice breaks consistent with adductor spasmodic dystonia. His nasal speech could be attributed to soft palate dystonia whereas the dysarthria could be due to palate, tongue, and facial muscle dystonia with superimposed parkinsonism. His facial expression was hypomimic with a decreased blink rate. He could open his jaw fully to command but could not open it fully while speaking, consistent with task-specific jaw-closing dystonia. He had no tremor or bradykinesia. His gait was wide-based and his toes curled. He had no neck or truncal dystonia. When writing, he did not have dystonia in his hands. In addition to what is shown in video 1, his tone was normal and he was stable on the pull test. Funduscopic examination did not show any abnormalities and he had normal smooth pursuit and saccadic eye movements.

The core features in this boy were generalized dystonia involving vocal cord, tongue, face, jaw, and extremities, accompanied by parkinsonian signs such as hypomimia and freezing of gait without extremity bradykinesia or rest tremor. The clinical course was progressive, and he had a family history of similar neurologic symptoms. The differential diagnosis falls under the category of dystonia-parkinsonism. Lubag disease (DYT3), dopa-responsive dystonia (DYT5), and rapid-onset dystonia parkinsonism (DYT12) present with dystonia and parkinsonism at a young age. Juvenile PD with Parkin mutations (PARK2) can have prominent dystonia and dystonia-parkinsonism associated with PLA2G6 mutation (PARK14) should also be included in the differential diagnosis. Several forms of secondary dystonia due to heredodegenerative diseases (i.e., diseases with evidence of neuronal degeneration, usually of genetic etiology) should be considered such as Wilson disease, pantothenate kinase-associated neurodegeneration (PKAN), and mitochondrial diseases.[1] Non-hereditary causes should also be included such as secondary dystonia-parkinsonism from perinatal insults and tardive dystonia with drug-induced parkinsonism from dopamine receptor blocking drugs. The patient has tongue and jaw dystonia, which occur in tardive dystonia, Lesch-Nyhan syndrome, neuroacanthocytosis, and PKAN.[2]

Question for consideration:

1. What would you do next?

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SECTION 3

We next examined the patient's older brother, a 17-year-old boy with pervasive developmental disorder, impulsivity, and lack of executive planning. He developed twisting of his hand at age 8, and the abnormal postures spread to his left foot and his right side at age 10. He had difficulty eating and speaking because of abnormal movements of his tongue and jaw. The pertinent neurologic examination is shown in video 2.

Question for consideration:

1. What is the phenomenology in the brother?

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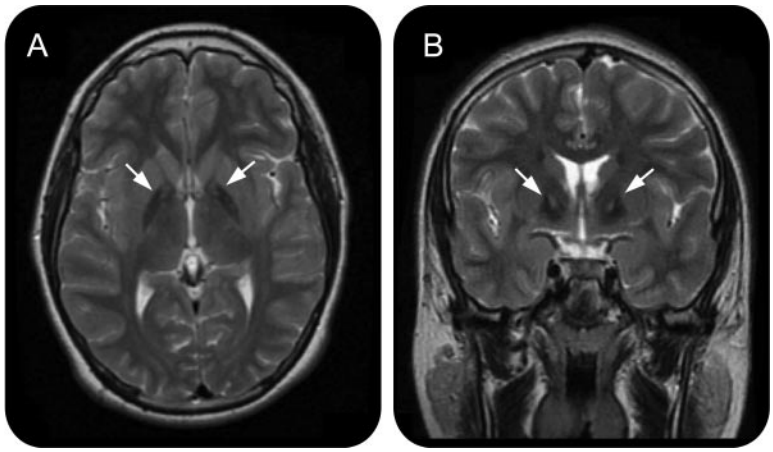
SECTION 4

The neurologic examination (video 2) revealed both facial and tongue dystonia, which were exacerbated with speaking. He had generalized dystonia involving the trunk and all extremities. He walked with a broad and stiff-legged gait. In addition to what was shown on the video, his toes curled while walking. He had mild postural instability on the pull test.

Figure Brain MRI



(A, B) MRI of the brain revealed central hyperintensity in the bilateral globus pallidus surrounded by hypointense signal on T2 sequence, consistent with the eye-of-the-tiger sign.

The patient also had a younger sister, who was healthy. No other family members had dystonia. Therefore, the hereditary pattern is likely to be autosomal recessive or X-linked. Among the hereditary dystonias, dopa-responsive dystonia can be autosomal recessive and DYT3 is X-linked. Wilson disease, Lesch-Nyhan syndrome, neuroacanthocytosis, and PKAN are all inherited in an autosomal recessive manner.[1]

MRI of the brain in the patient and his brother revealed hyperintensity in the bilateral putamen surrounded by hypointensity on the T2 sequence, consistent with the eye-of-the-tiger sign (figure, A and B). Genetic analysis of the patient's brother showed pathogenic homozygous Y117C mutations in the *PANK2* gene. They were diagnosed with PKAN.

Question for consideration:

1. How do you treat freezing of gait?

GO TO SECTION 5

SECTION 5

Freezing of gait is an uncommon presentation in the setting of generalized dystonia. It occurs more frequently in parkinsonian syndromes such as PD and Parkinson plus syndromes, such as progressive supranuclear palsy and corticobasal degeneration. It can also happen in normal pressure hydrocephalus or vascular parkinsonism.[3] Freezing of gait sometimes can respond to levodopa. However, levodopa-unresponsive freezing of gait is very difficult to treat. Motor tricks sometimes can help with freezing of gait, such as walking sideways, redistribution of body weight, marching, and taking long steps. Sensory cueing can also help; for example, walking to music, clapping hands, and stepping over a line.[4] To our knowledge, freezing of gait has been reported in 5 cases of PKAN and may not be levodopa-responsive.[5-8] In one case, the freezing of the gait was responsive to anticholinergics.[8] Therefore, we treated this patient with trihexyphenidyl 5 mg, 3 times a day, and the patient had less freezing and falls.

DISCUSSION Pantothenate kinase–associated neurodegeneration. PKAN, once called Hallervorden-Spatz syndrome, is caused by a mutation in the *PANK2* gene. PKAN belongs to a group of diseases known as neurodegeneration with brain iron accumulation. The clinical presentation of PKAN can be divided into a classic form and atypical presentations.[6] Classic PKAN has age at onset before 6 years and usually presents with postural difficulties. The predominant features are dystonia involving trunk, face, and voice. Patients usually become wheelchair-bound by 15 years after the disease onset. Pigmentary retinal degeneration is associated with classic PKAN. In atypical PKAN, the age at onset is in the second or third decade and the progression is slower. Dystonia and rigidity are less severe than in the classic form. Patients usually have the ability to ambulate in adulthood. Psychiatric symptoms are prominent in atypical cases such as hyperactivity, obsessive-compulsive disorders, and behavioral problems. Extrapyramidal signs such as spasticity and hyperreflexia are common in PKAN. Genotype and phenotype correlation of PKAN is limited but generally, null mutation results in early onset of the disease and missense mutation leads to late-onset presentation.[9]

MRI of the brain in PKAN often shows the eye-of-the-tiger sign; i.e., central hyperintensity surrounded by hypointensity in the bilateral globus pallidus on a T2 sequence (figure, A and B). Occasionally, the hypointensity in T2 sequence can also be observed in the red nucleus, dentate nucleus, putamen, or caudate. This sign is relatively specific for PANK2 mutations.[10] The postmortem examination of patients with PKAN shows iron deposition in the globus pallidus and substantia nigra. Axonal spheroids in the CNS can be observed microscopically.[9]

Dystonia usually requires treatment in PKAN. Benzodiazepines, baclofen, and anticholinergics have been used as therapy for generalized dystonia. Botulinum toxin injections can alleviate focal dystonias such as blepharospasm, cervical dystonia, limb dystonia, or spasmodic dysphonia. Deep brain stimulation targeting the bilateral internal globus pallidus has produced benefit in several patients.[9] Although PKAN is associated with excessive iron accumulation and defective pantothenate metabolism, chelating agents or supplemental pantothenate have not been proven to modify disease progression. Both the patient and his brother received trihexyphenidyl and baclofen and had significant improvement of limb and trunk dystonia. The patient's older brother also received botulinum toxin injections for blepharospasm with a good response.

DISCLOSURE

Dr. Kuo serves on the Resident & Fellow Section editorial team for *Neurology*®. Dr. Greene serves on a scientific advisory board for GE Healthcare and receives research support from the Parkinson's Disease Foundation.

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Clinical Reasoning: Shuddering attacks in infancy

Daniel Tibussek, MD
Michael Karenfort, MD
Ertan Mayatepek, MD
Birgit Assmann, MD

Address correspondence and reprint requests to Dr. Daniel Tibussek, Department of General Pediatrics, Division of Paediatric Neurology, University Children's Hospital, Heinrich-Heine-University Düsseldorf, Moorenstr. 5, D-40225 Düsseldorf, Germany
daniel.tibussek@med.uni-duesseldorf.de

SECTION 1

A 6-month-old boy was brought in by his parents because of a series of paroxysmal shivering episodes. The parents were able to document one attack on video (video 1 on the *Neurology*® Web site at www.neurology.org). The attack began with sudden staring, followed by opening of the mouth, noisy stridulous inspiration, and shivering movements predominantly of his neck and shoulders. This was accompanied by a slight deviation of his eyes, head, and mouth to the right side. The parents reported that these attacks seemed to occur particularly while eating (video 2) and were often preceded by myoclonic jerks of the mouth. The patient was staring but seemed alert. Onset and termination of the events were always abrupt and the child immediately continued his activities. Duration of the episodes was no longer than 5 to 15 seconds.

We were able to observe more than 20 of these episodes within a period of 48 hours while he was hospitalized (example given in video 3).

Questions for consideration:

1. How would you describe these movements?
2. What is your differential diagnosis at this point?
3. What further testing would you recommend?

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From the Department of General Pediatrics, University Children's Hospital, Duesseldorf, Germany.
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SECTION 2

The attacks were initially believed to be focal seizures because the shivering movements were repeatedly preceded by right perioral myoclonic jerks. Repeated video-EEG recordings was performed, but did not reveal any changes in the EEG other than muscle artifacts.

On the basis of published descriptions of similar fits in infancy,[1] the diagnosis of shuddering attacks was suspected. No further diagnostic workup was undertaken.

On follow-up the frequency of the attacks gradually decreased, and they eventually seemed to have ceased after 3 months. However, at the age of 15 months the episodes resumed, and another home video was sent to us. At this time the attacks were provoked by an attempt to stick a fork into a piece of bread (video 4). In addition, the mother had observed shuddering attacks provoked by pressing Lego bricks together. This relapse lasted for less than 1 week and was followed by another uneventful period of 6 months. Again, after that time the parents observed sporadic shuddering attacks (not more than one a day) which were somewhat milder than at original presentation.

At the age of 24 months the parents provided another video documenting a third relapse (video 5). While playing with his mother the child is pretending to wash his hair and in the end is asked to shake his head in order to "dry his hair." However, in attempting to shake his head he provokes another shuddering attack. Again and again the mother could reproduce this phenomenon. At the last follow-up, aged 26 months, the parents reported shuddering attacks frequently occurring just after coming out of the bath.

Questions for consideration:

1. What other information would you request at this time?
2. How would you advise the parents?

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SECTION 3

Regular neurologic examinations during the first 2 years of life have not revealed any additional abnormalities. In addition, at the age of 2 years the child was scored as being within normal limits on the Mental Scale and the Motor Scale of the Bayley Scales of Infant Development, Second Edition (BSID-II), a widely used measure of cognitive and motor development in infancy.[2] The BSID-II comprises three separate scales (the Mental Scale, the Motor Scale, and the Behavior Rating Scale). Performance is measured through Mental Development Index (MDI) and Psychomotor Development Index (PDI) scores. Index scores have a mean of 100 (±15). Scores between 85 and 114 are classified as within normal limits.

No family history of essential tremor was reported.

DISCUSSION Shuddering attacks are benign nonepileptic events that typically begin in infancy. The clinical events consist of rapid shivering of the head, shoulder, and occasionally the trunk. As in our patient, events have been reported as brief, usually lasting not more than a few seconds. Frequency can be up to more than 100 events per day with a great inter- and intraindividual variability.[3,4] In our patient, attacks seemed to be precipitated not only by feeding or eating, which has been interpreted as stimulus overflow by some authors,[3] but also by head movements and certain tasks (pressing toys together or sticking a fork into a piece of bread).

Shuddering attacks are not epileptic in nature. Ictal EEG is normal in this syndrome, and typically no neurologic abnormalities are found. However, confusion with tonic, myoclonic, and absence seizures, and with West syndrome, has been reported. This misdiagnosis may lead to unnecessary anticonvulsive treatment.[5] Therefore, EEG is advocated in all patients and ictal video documentation should always be attempted by caregivers. In cases with unusual clinical presentations, prolonged video EEG monitoring is helpful. Other events which can mimic myoclonic seizures in the infant may also be taken into consideration, mainly benign myoclonus of early infancy or gratification disorder.

The pathophysiology of shuddering attacks is unknown, although a relationship to essential tremor has been postulated.[6,7] This was initially based on the observation of six infants and young children presenting with a history of shuddering attacks who exhibited postural tremor on examination and who had a positive family history of tremor.[6] Successful treatment of shuddering attacks with propanolol, a first line agent in the treatment of essential tremor, was reported years later.[7] Moreover, the EMG pattern during the attacks has been reported to be very similar to that of essential tremor.[8] However, a recent study on essential tremor in 39 patients <18 years did not find any patient with a history of shuddering attacks during infancy or among family members.[9] Accordingly, in more recent cases reports[8,10] no positive family history for essential tremor was reported.

Although the incidence of shuddering attacks has been reported to be low, our personal experience leads us to conclude that the incidence may be underestimated. Since this case presented to our hospital, we were able to diagnose three additional cases within 12 months. In support of this view, a retrospective study of paroxysmal nonepileptic events in 666 pediatric patients found 7% of all events to be shuddering attacks.[11]

Further investigations in affected infants are usually not indicated. Reassurance of parents is crucial since relatives are often frightened by the unexpected appearance and often high frequency of the attacks. Spontaneous remission can be expected according to previous reports.[3]

However, if progression occurs or additional neurologic abnormalities are found on examination, further diagnostic evaluation including cerebral imaging is indicated, as there have been reports of symptomatic shuddering attacks.[8]

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Introduction

Pediatric Perspective

By Ariel M. Lyons-Warren, MD, PhD, and Timothy Lotze, MD

Acquired demyelinating neuroinflammatory disorders occur when abnormal host immune activity leads to destruction of the protective myelin surrounding central or peripheral axons in a monophasic or relapsing pattern.

In the brain or spinal cord, demyelinating lesions—identified on MRI as hyperintense T2 lesions—can be due to multiple sclerosis (MS), transverse myelitis, neuromyelitis optica (NMO), acute demyelinating encephalomyelitis (ADEM), or other rarer diseases such as chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids. The most common of these in pediatrics is MS with an incidence of 0.5 to 1 per 100,000 person-years. Patient age and the clinical presentation, shape, and location of brain lesions on imaging can be useful preliminary considerations in determining the likelihood of a particular disorder.

Making an accurate diagnosis is important because it will affect long-term management. For example, ADEM is most often a monophasic disease requiring only acute treatment, whereas MS and NMO are frequently relapsing and remitting, and thus, patients should be started on lifelong disease-modifying therapy after treatment of acute attack symptoms. Relapsing demyelinating disease in the peripheral nervous system presents as chronic inflammatory demyelinating polyradiculoneuropathy (CIDP).

This chapter describes 2 important pediatric acquired demyelinating neuroinflammatory disorders, NMO and CIDP. NMO has been reported in children as young as 16 months of age, and approximately 4% of all patients with NMO present in the pediatric age group. Most features of pediatric NMO are the same as for adults, except that a larger percentage of patients may have a monophasic course. CIDP, affecting the peripheral nervous system, is very rare in children, occurring in less than 1 in 200,000 individuals. Pediatric CIDP usually presents with slowly progressive lower extremity weakness following an infection with peak disability reached by 2 months. Unlike in adults, 40% of patients will have a relapsing-remitting course for months to years but will ultimately have a favorable outcome with minimal to no weakness.

From the Division of Child Neurology in the Department of Pediatrics (A.M.L.-W., T.L.), Baylor College of Medicine; and Department of Child Neurology (A.M.L.-W., T.L.), Texas Children's Hospital Baylor College of Medicine, Houston, TX.
Correspondence Dr. Lyons-Warren lyonswar@bcm.edu

Adult Perspective

By Regan Jo Lemley, MD, MS, and Josep Dalmau, MD, PhD

Commonly encountered neuroinflammatory diseases such as multiple sclerosis, neuromyelitis optica (NMO), and acute or chronic inflammatory demyelinating polyradiculoneuropathy have largely preserved clinical features in pediatric and adult patients. This chapter includes articles that highlight the age-specific differences in some of these conditions, which are important for adult neurologists to consider when these patients transition into adulthood. For example, the article "Neuromyelitis optica spectrum disorders" discusses how the same criteria are used to diagnose NMO in both children and adults. Importantly, the average age at onset in children is 10–12 years, and the aquaporin-4 antibody may not be detectable until 4 or 5 years after symptom onset, possibly delaying diagnosis until near adulthood. Treatment and outcomes are similar in children and adults, which rely on plasma exchange (PLEX) and IV methylprednisolone for acute exacerbations, followed by initiation of preventive agents.

In "Chronic inflammatory demyelinating polyradiculoneuropathy in children," the authors report that children tend to present with more rapid gait deterioration than adults, leading to earlier disease identification. Of interest, autoantibodies such as anti-GM1 and anti-MAG have not been identified in pediatric cases and thus are not tested. Children may respond better to IV immunoglobulins than to PLEX, and they often achieve complete remission or have minimal deficits after treatment.

Other inflammatory conditions, such as Krabbe disease, are principally diagnosed in childhood but may initially present in adults. "Krabbe disease: A potentially treatable white matter disorder" highlights the use of hematopoietic stem cell transplantation in the disease. This has been shown to increase survivorship in patients with presymptomatic early- or late-infantile onset disease and may greatly improve the neurologic outcome in patients with juvenile- and adult-onset disease.

Lastly, the Teaching NeuroImages cases show the dramatic CNS changes that can occur as a complication of viral infections in children: acute necrotizing encephalopathy after influenza A and bilateral striatal necrosis after *Mycoplasma pneumoniae*. These 2 viral-induced CNS disorders are not seen in adults and show the increased brain vulnerability in the pediatric population to the indicated viral infections.

From the Department of Neurology (R.J.L.), Wake Forest Baptist School of Medicine, Winston Salem, NC; ICREA-IDIBAPS (J.D.), Service of Neurology, Hospital Clínic, Department of Neurology, University of Barcelona, Spain; and University of Pennsylvania (J.D.), Philadelphia.
Correspondence Dr. Lemley rlemley@wakehealth.edu

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John J. Millichap, MD

Child Neurology: Neuromyelitis optica spectrum disorders

Michael J. Bradshaw, MD
NgocHanh Vu, MD
Tracy E. Hunley, MD
Tanuja Chitnis, MD

Correspondence to
Dr. Bradshaw:
Michael.j.bradshaw@vanderbilt.edu

A 3-year-old girl presented with 4 days of progressive bilateral vision loss. Medical history included presumed autoimmune hepatitis at 6 months of age, when she had an extensive evaluation including hepatitis A immunoglobulin G (IgG) detected in her serum, thought to represent maternal antibodies. Liver biopsy suggested autoimmune hepatitis and she was treated with oral prednisolone 2 mg daily for 2 weeks and remained on maintenance 1 mg daily. Family and social histories were unremarkable.

Neurologic examination demonstrated severely decreased central vision in both eyes; pupils were slowly reactive to light without relative afferent pupillary defect. She had a left Babinski sign. The remaining general and neurologic examinations were normal, including funduscopy.

MRI brain, orbits, and spine with contrast demonstrated bilateral optic neuritis (ON; figure) and no other lesions.

CSF contained 0 nucleated cells/μL, 1 erythrocyte/μL, glucose 47, protein 30, no oligoclonal bands, and elevated IgG index at 0.81 (0.28–0.66). The patient had normal folate, cyanocobalamin, and sedimentation rate/C-reactive protein, and was antinuclear antibody (ANA)–positive at 1:640 with a nucleolar pattern; other rheumatologic antibodies were absent. Serum aquaporin-4 IgG (AQP4-IgG) was pending at the time of treatment.

The patient was treated empirically for neuromyelitis optica (NMO) spectrum disorder (NMOSD) with plasma exchange (PLEX) and 20 mg/kg/d IV methylprednisolone (IVMP) on the day of presentation. With 5 sessions of PLEX/IVMP, her vision improved significantly. She was discharged with oral prednisone and serum AQP4-IgG returned positive at 73 units/mL. She was given rituximab 375 mg/m^2 on days 1 and 15, and then every 3 months thereafter. Her vision subjectively improved somewhat after her first cycle of rituximab.

DISCUSSION Eugène Devic first coined "neuromyelitis optica" in 1894 while describing a novel syndrome of acute myelitis and ON. Discovery of the pathogenic AQP4-IgG led to the development of international diagnostic criteria that include AQP4-IgG status.[1] Clinical features include ON (severe/bilateral), longitudinally extensive transverse myelitis (≥3 vertebral segments), and area postrema syndrome (intractable hiccups, nausea/vomiting). Brainstem and diencephalic syndromes such as narcolepsy/hypersomnolence and endocrine dysfunction have also been recognized in NMOSD. It is important to distinguish NMOSD from multiple sclerosis (MS) and other disorders as treatment differs among these and prompt treatment is important for minimizing disability.

The differential diagnosis of ON has recently been reviewed and will not be covered in detail.[2] Infectious etiologies should be considered when there are infectious signs/symptoms or highly inflamed CSF. Deficiencies in cyanocobalamin, folate, and copper should be considered when there is bilateral optic neuropathy, especially in an at-risk patient (e.g., malabsorption syndromes, gastrointestinal surgery). The clinical features and subacute–progressive time course of NMOSD and other demyelinating conditions help to distinguish them from other diagnoses, which may tend to be more hyperacute (vascular) or chronic (genetic/nutritional).

Clinical features of NMOSD in children. In one analysis of children with NMOSD, the most common presenting features included visual, motor, and constitutional syndromes.[3] In the largest report of children with NMO, 83% and 78% of children with AQP4-IgG had at least one episode of ON or transverse myelitis, respectively, while 45% had other symptoms such as encephalopathy, seizures, ophthalmoparesis, ataxia, or area postrema syndrome.[4] Children with NMOSD were older than those with acute disseminated encephalomyelitis (ADEM) (mean 10–12 vs 5 years), but approximately the same age as those with MS (13 years).[3,4] Female patients and non-Caucasians are overrepresented in NMOSD. NMOSD is associated with additional autoimmunity, with 42% and 76% of patients with other autoimmune diagnoses or

From the Department of Neurology (M.J.B., N.V.), Vanderbilt University Medical Center; Division of Nephrology and Hypertension (T.E.H.), Vanderbilt Children's Hospital, Nashville, TN; and Center for Neurologic Diseases (T.C.), Brigham and Women's Hospital/Partners MS Center, Brigham and Women's Hospital/Partners Pediatric MS Center, Massachusetts General Hospital, Boston.

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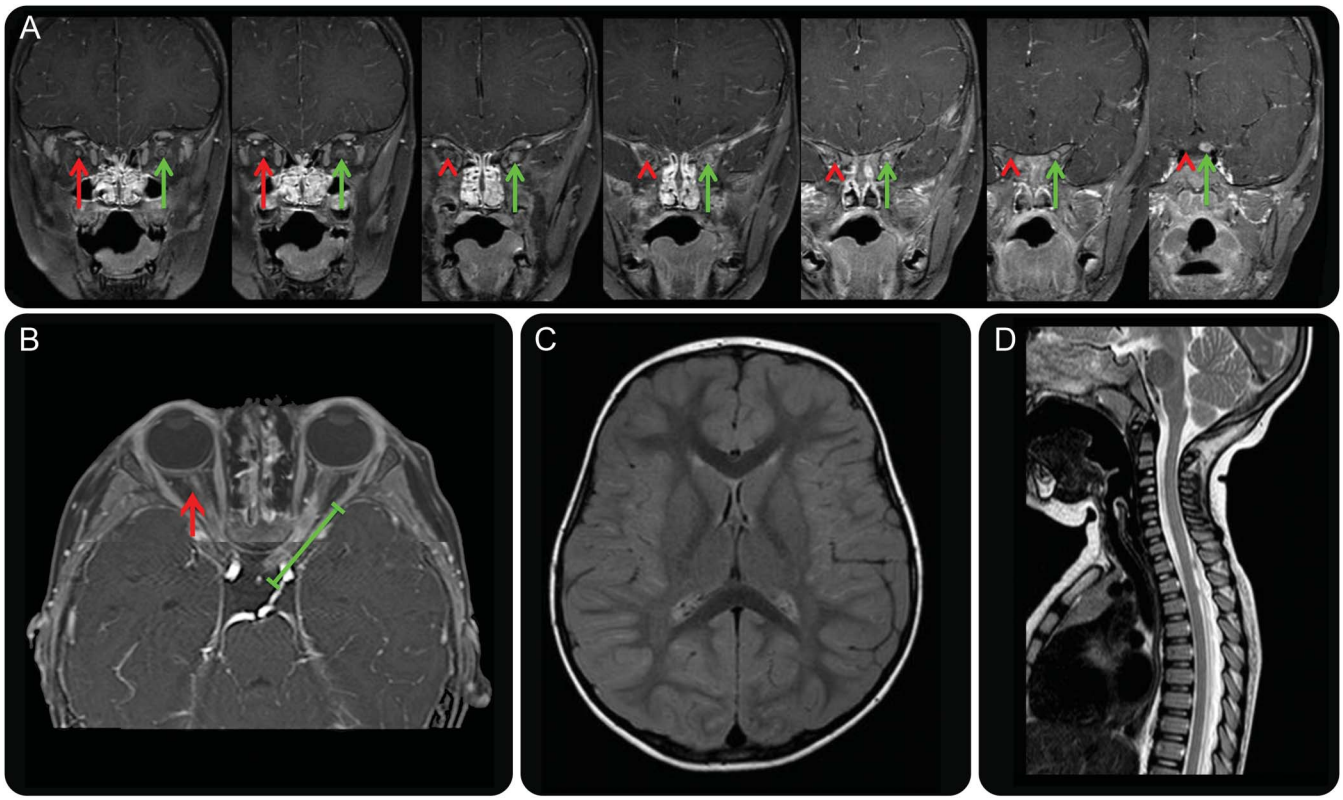
Figure MRI brain, orbits, and spine with and without gadolinium



(A) Coronal T1-weighted postcontrast MRI demonstrates enhancement of both optic nerves. The left optic nerve is indicated with green arrows/arrowheads and the right is indicated with red. The arrows indicate areas of contrast enhancement, while the arrowheads indicate optic nerve without significant contrast enhancement. (B) Axial T1-weighted postcontrast MRI of the orbits demonstrate longitudinally extensive contrast enhancement in the left optic nerve involving the rostral chiasm (green bracket) and a short segment of contrast enhancement in the distal right optic nerve (red arrow; 2 separate MRI, 5 mm apart, are combined in this image in order to demonstrate the length of the optic nerve). There were no other enhancing lesions in the brain or spinal cord. (C) Axial fluid-attenuated inversion recovery MRI of the brain is normal. (D) Sagittal short tau inversion recovery MRI of the spine is normal.

autoantibodies, respectively.[4] Sixty-four percent have a positive ANA, as in our case. There is one other case of autoimmune hepatitis associated with NMO reported in the literature.[5]

Imaging features of NMOSD in children. MRI with gadolinium is the imaging modality of choice for evaluating possible demyelinating disease, although there are no definitive radiologic criteria for NMO in children. MRI brain, orbits, and cervical ± thoracic spinal cord should be imaged as clinically indicated. Among 56 patients with MRI data included in one study, 56% had brain parenchymal abnormalities and 34% had optic nerve contrast enhancement; 5 had involvement of the chiasm and 1 had bilateral ON.[4] ON caused by NMOSD is more likely to be clinically severe, bilateral, and longitudinally extensive, and to involve the optic chiasm, compared to other causes of ON.[6] Features that help distinguish NMOSD myelitis from MS include longitudinally extensive (≥3 spinal segments) myelitis involving the central cord with >50% of the cross-sectional area, compared to the shorter, smaller, and more dorsolateral lesions seen in MS.[6]

Brain lesions are common in pediatric NMOSD and may overlap with MS or ADEM. NMOSD lesions tend to be periependymal T2 hyperintense lesions predominantly. Periventricular NMOSD lesions tend to be longer than the Dawson fingers seen in MS, which are usually shorter and confined to the pericallosum. Lesions in the corpus callosum occur in NMOSD, where they are often large and follow the ependymal lining, while those seen in MS tend to be smaller, ovoid, or flame-shaped and oriented radially to the ventricles.[6] Extensive and confluent predominantly white matter hemispheric lesions, which may be associated with encephalopathy, can make it difficult to distinguish NMOSD from ADEM.[4] In that setting, laboratory features, particularly the presence of AQP4-IgG, can be critical to the diagnosis.

Laboratory features of NMOSD in children. Roughly 65% of children with NMOSD tested positive for AQP4-IgG, rates similar to those observed in adults with NMOSD, but seropositivity may occur up to 4–5 years after onset.[3] Testing for AQP4-IgG is the most sensitive and cost-effective when performed on

serum, which is the source recommended by the Mayo Clinic laboratory.[7] In ON from NMOSD, the CSF may appear bland, while during an episode of myelitis, CSF may be highly inflamed, with pleocytosis >100 cells/μL, commonly with neutrophils or eosinophils. Oligoclonal bands are observed in roughly 25% of patients with NMOSD. This is contrasted with CSF in MS, which commonly contains oligoclonal bands (90%) and only rarely is pleocytosis >50, typically lymphocytic.[6] CSF studies in children with ADEM are variable and often nondiagnostic; however, oligoclonal bands are only rarely present.[3] Children with features of NMOSD but with negative serum AQP4-IgG should have CSF AQP4-IgG testing and may also be tested for myelin-oligodendrocyte glycoprotein antibodies (in the United States, only available through research laboratories). AQP4-IgG may appear up to 4 years after disease onset, and sequential testing should be employed for initially seronegative patients.

Diagnostic criteria in children. The Wingerchuk 2006 criteria were 49% sensitive for a diagnosis of pediatric NMO, while the 2015 updated international panel for NMO diagnosis criteria, which allowed for diagnosis after one attack and the presence of AQP4-IgG, were 97% sensitive and can be applied to children.[3] This is in part due to the lower lesion accrual in pediatric NMO.

Treatment of NMOSD in children. In contrast to MS, in which disability is driven primarily by progressive disease and there is relatively good recovery after acute exacerbations, in NMOSD, acute exacerbations can be severe with little recovery and drive virtually all of the disability. In addition, 93%–95% of children with NMOSD have relapsing disease,[3,4] and there is some evidence that acute exacerbations respond more favorably when the patient is on preventative medicaiton.[8] Therefore, prompt recognition and initiation of acute abortive therapy and preventative medication is critical. Some disease-modifying therapies used in MS (including interferons, fingolimod, and natalizumab) are ineffective and may worsen NMOSD.[6] No randomized controlled trials have been conducted in adult or pediatric NMOSD; therefore, all treatments are considered off-label and based on available literature and expert recommendations.

Acute treatment. Acute exacerbations are commonly treated with IVMP (in children 20 mg/kg/d for 5 days), an approach extrapolated from data on treating other immune-mediated neurologic conditions. We advocate for urgent PLEX as a first-line therapy for NMOSD exacerbations based on evidence demonstrating improved outcomes in patients treated with PLEX and IVMP compared to IVMP alone.[8,9] At Vanderbilt Children's Hospital, we exchange 1.5 volumes of plasma 5 times over 5–8 days. Complications are uncommon in experienced centers, but include those related to the central line, electrolyte abnormalities, and coagulopathy associated with the exchange process and transfusion-related complications. IV immunoglobulin may be beneficial and can be considered when there is a poor response to steroids and contraindication to PLEX exists. Children with NMOSD should be given a prednisone taper over several months.

Preventative therapy. The most common preventative agents include azathioprine, prednisone, mycophenolate mofetil, and rituximab. There is evidence to support the use of rituximab or mycophenolate over azathioprine.[6] The same strategies used to treat adults with NMOSD have been applied to children, and results appear comparable.[3] Studies intended to assist with the dosing and monitoring of rituximab for pediatric NMOSD have begun to emerge in the literature.[10]

As recently demonstrated,[3] the updated international panel for NMO diagnosis criteria are sensitive for the diagnosis of NMOSD in children. Prompt recognition and treatment of exacerbations followed by initiation of preventative agents are critical for minimizing disability. Strong consideration should be given to treating acute exacerbations with urgent PLEX in addition to IVMP, which appears to be more effective than IVMP alone.

AUTHOR CONTRIBUTIONS

Michael J. Bradshaw: treating clinician, literature review, clinical review, imaging review, manuscript preparation, editing. NgocHanh Vu: manuscript review, editing. Tracy E. Hunley: treating clinician, manuscript review. Tanuja Chitnis: manuscript review, editing.

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RESIDENT & FELLOW SECTION

Section Editor
Mitchell S.V. Elkind, MD, MS

Child Neurology: Krabbe disease

A potentially treatable white matter disorder

Jennifer Gelinas, MD, PhD*
Pamela Liao, MD*
Anna Lehman, MD
Sylvia Stockler, MD
Sandra Sirrs, MD

Correspondence & reprint requests to Dr. Gelinas: jgelinas@cw.bc.ca

Krabbe disease (glucocerebrosidase [GALC] deficiency) is an inherited leukodystrophy resulting in altered myelination. Most patients have early-infantile onset of disease (<6 months) characterized by rapid neurologic deterioration and death. Approximately 10%–15% of patients have late onset disease (late-infantile 6 months–3 years; juvenile 4–8 years; adult >8 years) with a milder course. Hematopoietic stem-cell transplantation (HSCT) may be used in some patients to improve outcome. Here we report an untreated patient with early-infantile onset disease and her presymptomatic sibling treated with HSCT to demonstrate the benefit this treatment can have on clinical outcomes. Chart review was approved by BC Children's & Women's Hospital Research Ethics Board (CW09-0290/H09-03031).

CASE REPORTS **Case 1: Untreated infantile-onset Krabbe disease.** After an unremarkable pregnancy and neonatal course, a female infant presented at 6 months of age with regression of motor development and irritability. Neurologic examination showed increased tone and reduced strength in all limbs, with diminished muscle stretch reflexes and extensor plantar responses. Krabbe disease was diagnosed at 8 months of age based on decreased GALC activity (0.5 nmol/h/mg protein). Genetic analysis showed a 30-kB deletion in 1 *GALC* allele (14q31) and a point mutation in the other allele (c.1538 C>T; p.T513M). Neuroimaging showed poor gray–white matter differentiation on CT and T2 hyperintensity of cerebellar white matter on MRI. Nerve conduction studies (NCS) and EEG were not performed. She developed extensor posturing and swallowing difficulties requiring G-tube insertion. She became unresponsive at 12 months of age and died at 22 months from respiratory complications.

Case 2: Treated infantile-onset Krabbe disease. This patient (original case report[1]), the sibling of case 1, was identified prenatally through mutation analysis in chorionic villus sampling. GALC activity was reduced postnatally in white blood cells (0.4 nmol/h/mg protein). Neurologic examination, neuroimaging studies, and EEG were normal. NCS showed a moderate peripheral demyelinating sensorimotor neuropathy. Transplantation of unrelated umbilical cord blood hematopoietic stem cells was performed at 24 days of life, after preparatory myeloablation with busulfan and cyclophosphamide, and graft vs host disease (GVHD) prophylaxis with methylprednisolone, cyclosporine, and antithymocyte globulin. Engraftment was successful, but the patient experienced transplant-related complications including grade 1 GVHD, septicemia, mild hypertension, and transient steroid-related cardiomyopathy.

Post-transplantation, GALC activity normalized. However, persistent peripheral neuropathy was demonstrated on NCS, and evidence of abnormal T2 hyperintensity of centrum semiovale with diffuse calcification was seen on neuroimaging within 6 months of transplantation. Abnormal white matter signal progressed in the periventricular white matter and white matter tracts during the first 12 months post-transplantation, but then stabilized for 3 years.

Development of neurocognitive skills post-transplantation progressed at a delayed rate. She could communicate by 6 months of age, and walked at 22 months. Neuropsychological assessment at 24 months showed normal receptive language and adaptive skills, with expressive language delayed by 7 months. At last clinical assessment (age 5 years), the patient was in kindergarten with a full-time aide. She was able to run, talk in 5-word phrases, color, use scissors, and feed herself. Neurologic examination was remarkable for pale optic discs, sustained ankle clonus, upgoing plantar responses, and a tendency to toe walk.

DIFFERENTIAL DIAGNOSIS The differential diagnosis of psychomotor delay with white matter

Supplemental data at www.neurology.org

*These authors contributed equally to this work.

From the Division of Pediatric Neurology (J.G.), Faculty of Medicine (J.G., P.L.), Department of Medical Genetics (A.L.), and Adult Metabolic Diseases Clinic (S. Sirrs), University of British Columbia; and Division of Biochemical Diseases (S. Stockler), BC Children's Hospital, Vancouver, Canada.

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abnormalities on neuroimaging is broad. An established approach classifies patients by pattern of neuroimaging abnormality and subsequently targets metabolic and genetic testing.[2] Krabbe disease typically shows white matter with confluent, prominent T2 hyperintensity and T1 hypointensity in a parieto-occipital or periventricular predominance. Other white matter disorders with these patterns include 1) parieto-occipital: X-linked adrenoleukodystrophy, Zellweger spectrum disorder, neonatal hypoglycemia; 2) periventricular: metachromatic leukodystrophy, Sjögren-Larsson syndrome, periventricular leukomalacia, HIV encephalopathy, neuronal ceroid lipofuscinosis. Early-infantile onset Krabbe disease has characteristic CT hyperdensities in brainstem, cerebellum, and thalamus, which can also be seen in Sandhoff disease, GM1 and GM2 gangliosidoses.

CRITERIA FOR HSCT There are currently no consensus criteria to evaluate patients with Krabbe disease for HSCT. Transplantation has been tried in patients of all ages, though most reported cases involve patients with infantile-onset disease.[3,4] A staging system based on clinical evaluation of early- and late-infantile onset patients has been developed to guide candidacy for HSCT.[5] Patients are classified into 1 of 4 disease stages. Outcome analysis has demonstrated that patients with minimal to no disease progression at time of HSCT (stages 1 or 2) have 100% survival post-transplant and make developmental gains, whereas patients with more advanced disease (stages 3 or 4) have significantly higher mortality post-transplant with no developmental gains. These studies suggest that HSCT should only be performed in this age group when symptoms are absent or mild.[5,6,e1] Conversely, juvenile or adult-onset patients with substantial cognitive and neurologic dysfunction at the time of transplantation can benefit from treatment.[3,7]

COMPLICATIONS HSCT carries significant morbidity and mortality. Mortality in a group of symptomatic infants with Krabbe disease treated with HSCT was 29% (4/14 patients), though all presymptomatic transplanted infants survived (11/11 patients).[4] Successful HSCTs have been carried out in juvenile and adult-onset patients, but there are also reports of mortality.[8]

Acute or chronic GVHD has been reported in up to 32% of transplanted patients.[4,7] Overall, risk counseling for HSCT in patients with Krabbe disease of any age remains imprecise, but is generally regarded as carrying significant risk of morbidity and mortality.

CLINICAL AND DEVELOPMENTAL OUTCOMES Thus far, no presymptomatic early- or late-infantile onset patients treated with HSCT have died of progressive disease.[4,6] A multicenter cohort of 16 of these infants showed that all had abnormalities of gross motor control and expressive language. Although receptive language and cognition were considered normal, proper assessment of these skills in young children with motor and expressive language abnormalities is difficult, and some children (as in case 2) may require school assistance.[6] These patients also had poor growth, and developed spasticity, loss of motor milestones, and microcephaly.[6] Thus, significant neurologic morbidity may still develop despite presymptomatic transplantation.

Symptomatic early-infantile onset Krabbe disease patients treated with HSCT show gross motor deterioration although they may show gains in language and cognitive development.[5] Several isolated cases of transplanted juvenile or adult-onset patients suggest that HSCT may lead to clinical benefits despite the presence of pretransplant neurologic symptoms. Juvenile- and adult-onset patients have experienced dramatic resolution of ataxia, tremor, motor incoordination, and cognitive difficulties after HSCT.[3,7] However, there are currently few published cases of HSCT in patients with late-onset Krabbe disease, so it is difficult to draw conclusions about the efficacy of transplantation in this population.

BIOCHEMICAL AND NEUROPHYSIOLOGIC OUTCOMES AFTER TRANSPLANTATION There is currently no known biomarker that parallels long-term clinical outcomes post-transplant.[1,6]

HSCT consistently increases, and in some cases normalizes, GALC activity.[1,3,7] CSF protein levels, elevated in most patients with Krabbe disease, decrease but do not reliably normalize after HSCT.[1,7]

In contrast to the consistent improvements in biochemical measures after HSCT, neurophysiologic and neuroimaging findings post-transplant are variable. Krabbe disease is accompanied by a severe demyelinating sensorimotor neuropathy. In one cohort of 12 patients with Krabbe disease, HSCT increased nerve conduction velocity in all patients, with detection of previously absent nerve responses in some.[9] Greater improvements in NCS were observed when HSCT was performed earlier in disease course. Adult-onset patients may experience stability, or even improvement in peripheral neuropathy, but these improvements are not always sustained,[9] and long-term outcome data are not yet available.

Neuroimaging in Krabbe disease shows demyelination involving periventricular white matter, cerebellum, and brainstem, with differences in distribution observed

in early- and late-onset disease.[e2] HSCT has resulted in stabilization of mild neuroimaging abnormalities and developmentally appropriate patterns of myelination in presymptomatic early-infantile onset cases.[4] However, as our case 2 demonstrates, progressive deterioration of neuroimaging can occur post HSCT even in presymptomatically transplanted patients.[1] Most symptomatic infants have significant MRI abnormalities prior to transplantation, and continued deterioration occurs post-transplant.[4] Some limited evidence suggests that in juvenile- and adult-onset patients with preexistent MRI abnormalities, HSCT can halt or even reverse progression of MRI deterioration.[3,7] The effect of HSCT on subsequent neuroimaging results appears to vary with Krabbe phenotype as well as pretransplant MRI abnormalities, and long-term follow-up studies are necessary.

FUTURE DIRECTIONS IN TREATMENT OPTIONS

Recent advances show promise for additional therapeutic options.[10] Pharmacologic chaperones, which protect misfolded proteins that would otherwise be degraded, could increase the activity of mutated GALC.[e3] Injection of recombinant proteins or neural progenitor cells into brains of animal models of Krabbe disease results in decreased neuropathology and some neurologic improvement.[e4,e5] Similar improvements occur when viral vectors are used to increase GALC expression in such models.[e6,e7] Currently, these therapies are not yet sufficiently established for human trials in patients with Krabbe disease.

DISCUSSION Krabbe disease is a rare disorder for which HSCT is a viable, albeit high-risk, therapy. Further studies are necessary to document long-term clinical outcomes post-transplant and establish guidelines for treatment of this severe neurologic disease.

AUTHOR CONTRIBUTIONS

Dr. Gelinas is responsible for case acquisition, article concept and design, and manuscript revisions. Dr. Liao is responsible for the article concept and drafting and revising the current manuscript. Dr. Lehman is responsible for manuscript revision. Dr. Stockler is responsible for developing the manuscript concept and case acquisition. Dr. Sirrs is responsible for drafting and revising the manuscript.

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DISCLOSURE

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Child Neurology: Chronic inflammatory demyelinating polyradiculoneuropathy in children

Jennifer A. Markowitz, MD
Shafali S. Jeste, MD
Peter B. Kang, MD

Address correspondence and reprint requests to Dr. Jennifer A. Markowitz, Department of Neurology, Fegan 11, Children's Hospital Boston, 300 Longwood Avenue, Boston, MA 02115
jennifer.markowitz@childrens.harvard.edu

ABSTRACT

Chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) is an autoimmune disorder characterized by patchy demyelination of nerve roots and distal nerves. The course may be monophasic progressive or relapsing-remitting. CIDP is less common in children than in adults. As in adults, children with CIDP present with proximal and distal weakness and loss of deep tendon reflexes. Children are most often brought to medical attention due to gait disturbance and falling. As in adults, immunomodulatory treatment is the mainstay of therapy. Based on the small number of case series available, children with CIDP seem have a more favorable long-term course than adults. ***Neurology*® 2008;71:e74–e78**

CLINICAL CASE, PART I A 5-year-old previously healthy boy was brought to the Emergency Department for evaluation of difficulty walking. His mother had first noticed a change in his gait 3 months earlier, when he began to limp intermittently after receiving a set of routine immunizations. Two months later in the setting of an upper respiratory infection she noticed that he had trouble running while playing soccer. Within the next 2 weeks he developed persistent difficulty with walking, climbing stairs, arising from a chair, and putting on his pants. He had no sensory complaints and had no change in bowel or bladder function. Neurologic examination was notable for proximal and distal weakness of the lower extremities, diffusely diminished deep tendon reflexes with flexor plantar responses, and mildly decreased vibration sensation in the feet. He used a Gowers maneuver to rise from the floor, was unable to jump, could not walk on his heels, and had a wide-based gait. There were no cranial nerve abnormalities, no weakness of the upper extremities, and other sensory modalities were intact.

Differential diagnosis. In the evaluation of gait difficulty, as with other neurologic complaints, localization based on history and physical examination is the first step. The decreased tendon reflexes, flexor plantar responses, and Gowers maneuver ("walking" the hands up the thighs to arise from a squat) all suggest a lower motor neuron localization. Within this broad category, diseases of the motor neuron and spinal cord, nerve, neuromuscular junction, and muscle should be considered. Among motor neuron and spinal cord etiologies, tethered spinal cord and spinal muscular atrophy type III can both present with depressed or absent reflexes and should be considered. Intrinsic spinal cord processes such as neoplastic, vascular, and demyelinating lesions are also in the differential, although these are less likely to present with hyporeflexia. Inherited and acquired neuropathies are possibilities, and are discussed in more detail below. The lack of fluctuation in his symptoms makes a neuromuscular junction disorder such as myasthenia gravis less likely, although this does not exclude it completely. Inherited and acquired myopathies are also possible, although the patient does not have some of the classic associated symptoms or signs of these disorders, such as the calf hypertrophy of muscular dystrophy, myalgias of infectious myositis, or heliotrope rash of dermatomyositis.

Among polyneuropathies, two key distinctions that assist with the differential diagnosis are inherited vs acquired etiologies and demyelinating vs axonal physiology. The subacute onset suggests that this is more likely to be acquired. The physiology cannot be determined until electrophysiologic testing is performed. Another important distinction is between large and small fiber neuropathies. In this case, the lack of prominent sensory symptoms makes a small fiber neuropathy less likely.

An important class of acquired neuropathy is the autoimmune neuropathies. Among these, acute inflammatory demyelinating polyradiculoneuropathy (AIDP), or Guillain-Barré syndrome, is less likely due to the

From the Department of Neurology, Children's Hospital Boston and Harvard Medical School, Boston, MA.
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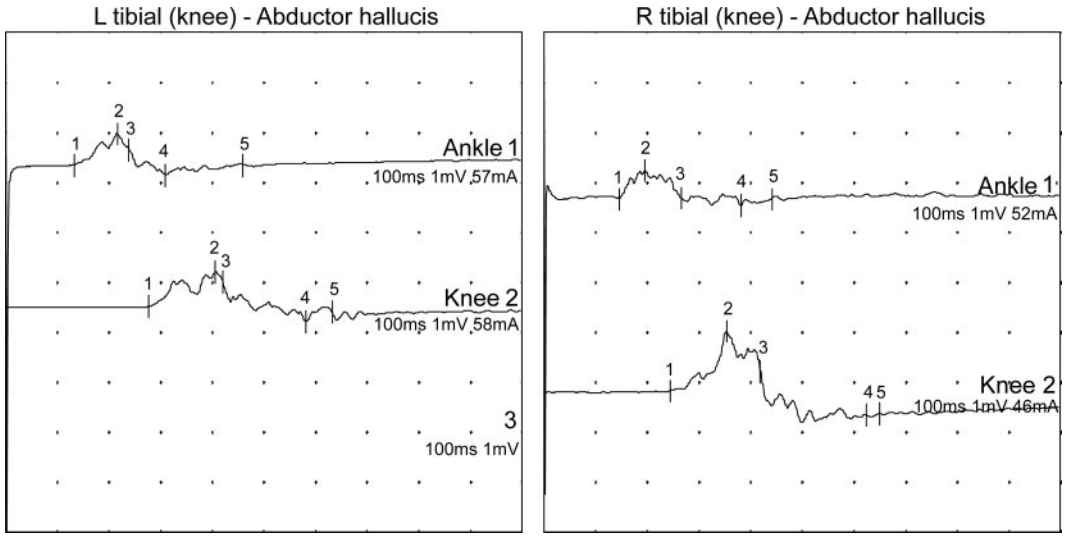
Figure 1 The patient's motor nerve conduction study revealing markedly prolonged latencies and decreased conduction velocities with temporal dispersion, and low amplitudes of bilateral tibial compound motor action potentials



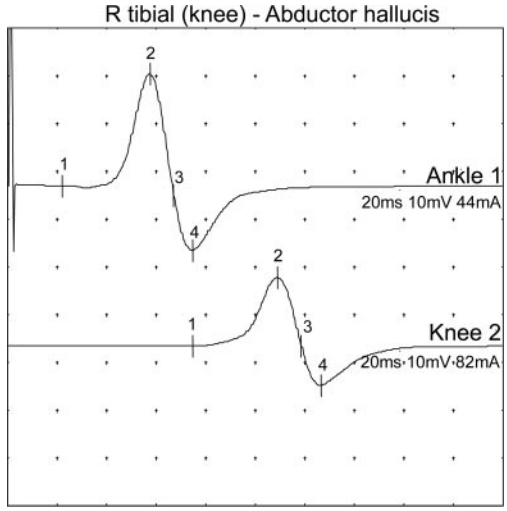
subacute presentation. This patient's clinical course is more consistent with CIDP. CIDP is an autoimmune disorder characterized by proximal and distal weakness that develops over a period of at least 1 month, with a monophasic progressive or relapsing-remitting course. Deep tendon reflexes are diminished or absent. Pathologically, there is patchy demyelination of nerve roots and distal nerves. Although this disease is rare in children, it is important to recognize since children with CIDP often respond favorably to immunomodulatory therapy.[1,10]

Other acquired neuropathies should also be considered in children who present with a subacute to chronic peripheral neuropathy. These include those resulting from infectious causes such as HIV and Lyme disease; metabolic derangements such as uremia, hypothyroidism, or vitamin B12 deficiency; inflammatory causes such as vasculitis; or exposure to toxins, such as lead or heavy metals.[1]

If this patient's course had been more chronic, inherited neuropathies would be more prominent in the differential diagnosis, especially since the onset is typically in childhood. Charcot-Marie-Tooth disease is the most common inherited neuropathy. Other considerations include the neuropathies of more generalized inherited disorders, such as Krabbe disease and metachromatic leukodystrophy. Inherited neuropathies tend to present with uniform rather than patchy involvement of nerves on electrophysiologic testing, with some notable exceptions.[1] Sensory loss may be more prominent than in CIDP. The time course of inherited neuropathies tends to be chronic, rather than subacute or relapsing, so that findings such as pes cavus or contractures are more commonly observed.[1,2]

CLINICAL CASE, PART II The patient was admitted to the Neurology service, where he underwent a lumbar puncture. This revealed four white blood cells per mm^3, 155 red blood cells per mm^3, glucose of 67 mg/dL, and protein of 93 mg/dL. He underwent an MRI of the brain, which was normal, and an MRI of the spinal cord, which revealed enhancement of the anterior nerve roots of the cauda equina. EMG/nerve conduction studies (NCS) revealed severely prolonged distal latencies, decreased conduction velocity (right common peroneal 17.3 m/s [normal ≥44 m/s], right tibial 28.7 m/s, left tibial 17.9 m/s [normal ≥41 m/s]) with temporal dispersion, and low amplitude bilateral tibial and right peroneal compound motor action potentials (figures 1 and 2). Further laboratory workup for infectious, meta-

Figure 2 Normal motor nerve conduction study for comparison



bolic, toxic, and inflammatory causes of neuropathy was normal. Based on the electrophysiologic findings, cytoalbuminologic dissociation, and nerve root enhancement on MRI, he was diagnosed with CIDP.

DISCUSSION **Epidemiology.** CIDP is much less common in children than in adults. In a large population of adults the prevalence of CIDP has been estimated at 1–1.9 per 100,000. In the same population, the prevalence of patients under age 20 with CIDP was 0.48 per 100,000.[5] Since the disease occurs so infrequently in children, knowledge of the clinical characteristics, response to treatment, and prognosis are all based on several small case series, making generalizations difficult.

Clinical characteristics. The most common complaint that brings children with CIDP to medical attention is gait disturbance and falling. This results from symmetric, predominantly motor involvement of the proximal and distal lower extremities. Upper extremity weakness, hand tremor, and ataxia are also present in some cases. Deep tendon reflexes are always reduced or absent.[1,4,9] Some studies indicate that at least one-third of pediatric patients experience sensory symptoms, characterized by paresthesias, dysesthesias, and large fiber sensory loss.[2,4,7,9] Cranial nerve involvement, respiratory muscle weakness, and autonomic dysfunction are all uncommon in childhood CIDP.[9]

Prodromal events, most often upper respiratory infections, have been described in 33–57% of children with CIDP in various series.[3,4,6,8,9] In contrast, as many as 60–80% of children with AIDP (or Guillain-Barré syndrome) have a history of a prodromal event.[9]

The onset of this disease may be insidious over a period of months, or there may be a more acute presentation of symptoms with recurrent episodes.[2] Compared with adults, children present earlier in the course of the disease, exhibit a more rapid progression of neurologic dysfunction, and are more likely to have a relapsing-remitting course.[4,7,9]

It may sometimes be difficult to distinguish CIDP from AIDP initially, especially since patients with both conditions can reach maximal motor disability within 4 weeks.[9] A history of antecedent illness, weakness of facial and respiratory muscles, pain, and autonomic dysfunction are all more common in AIDP.[1,9]

Pathogenesis. CIDP is an autoimmune disorder in which the inflammatory process is mediated by both the cellular and humoral immune systems.[1,2] Demyelination is segmental and occurs anywhere from the nerve roots to the distal portion of nerves. In addition to demyelination, sural nerve biopsy reveals inflammatory infiltrates and subperineural edema. Chronic disease may be associated with "onion bulb" formation, due to concentric proliferation of Schwann cells in the course of repeated demyelination and remyelination.[1,2,6,11] Axonal loss is variably observed, and may correlate with a more severe prognosis.[2]

Diagnostic studies. There are three basic diagnostic studies that help support the diagnosis of CIDP. NCS/EMG provide the most data, and can also provide information about the severity of the disease. Lumbar puncture and spine MRI can provide supportive evidence. Laboratory studies can help exclude other causes of neuropathy.

NCS/EMG in patients with CIDP show evidence of a predominantly demyelinating polyneuropathy, typically in a segmental, or nonuniform pattern (figure 1). Some axonal loss may be present. Demyelinating features include diminished motor and sensory conduction velocities, prolonged distal latencies, and prolonged or absent F waves. Nonuniform features include abnormal temporal dispersion, conduction block, and disparities in nerve conduction slowing between nerves or within a nerve.[1,2,6,9]

CSF analysis in children with CIDP commonly reveals albuminocytologic dissociation, defined as a protein greater than 35 mg/dL and white blood cell count less than 10 per mm^3, similar to that seen in AIDP.[1,2] If there is a significant pleocytosis in the CSF, other conditions should be considered. In two recent case series the mean CSF protein ranged from 194–197 mg/dL.[8,9] However, not all children with CIDP have an elevated CSF protein, and albuminocytologic dissociation is not specific to AIDP or CIDP, although it provides important supportive information.[1]

As observed in AIDP, patients with CIDP may demonstrate enhancement of nerve roots on spine MRI. This enhancement likely relates to disruption of the blood–brain barrier due to the inflammatory process.[1,8]

Adults with CIDP may have identifiable serum autoantibodies (e.g., anti-GM1, anti-MAG, anti-sulfatide), but these have not been observed in children and are thus not commonly tested.[2] Sural nerve biopsy is also no longer routinely performed for the diagnosis of CIDP in children.[1]

CLINICAL CASE, PART III The patient was treated with IV immunoglobulin (IVIg) at a dose of 2 g/kg over 2 days. He was also treated with 5 days of IV methylprednisolone at a dose of 30 mg/kg, then discharged home on a prednisone taper over the next 10

days. His strength and gait returned to normal over the course of the next month.

Four months later he had the first of two relapses of his symptoms. He was again treated with IVIg 2 g/kg over 2 days. He had no improvement in his symptoms, so 1 month later he began oral prednisone 1 mg/kg/day and monthly IVIg infusions of 2 g/kg, with full recovery after 3 weeks. He later relapsed in the setting of adenoviral pneumonia, and this was treated successfully with an increase in his prednisone dose and IVIg. After recovery the prednisone was weaned to an every other day regimen, and he continues on monthly IVIg. He has no residual symptoms and is back to playing soccer.

Treatment. Immunomodulatory therapy is the mainstay of treatment for CIDP. Our approach to therapy is derived from 1) large adult studies, 2) small case series in children, and 3) our own personal experience with a number of such pediatric CIDP patients. One difference in our approach to pediatric CIDP compared to adults is a higher threshold for the use of steroids.

IVIg is more of a first-line therapy for CIDP in children compared to adults. While there have been no randomized controlled trials in children, several case series have indicated that a large proportion of pediatric patients with CIDP show clinical improvement after treatment with IVIg.[8,10,11] Our personal experience with several patients correlates with these findings. The initial dose is 2 g/kg divided over 2 to 5 days, and most patients require maintenance therapy of 1 g/kg/day for 1 to 2 days every 1 to 6 weeks.[11] Drawbacks to the use of IVIg include cost; the need for IV placement; infusion-related side effects such as headache, nausea, rash, fever, chills, and hypotension; risk of infectious exposure; aseptic meningitis; anaphylaxis in IgA deficient individuals when non-IgA depleted IVIg is used; hemolytic anemia; and thromboembolism.

Plasmapheresis is a reasonable alternative in older children, especially those whose peripheral veins are accessible for large-bore IV lines. In adults, plasmapheresis appears to be of equivalent efficacy to IVIg.[2,6] Plasmapheresis may need to be administered more frequently than IVIg, although this has not been clearly established across series.[4] Risks of the treatment include coagulopathy, electrolyte abnormalities, hypotension, and anemia in those treated chronically.

Prednisone was the first agent identified as an effective treatment for CIDP in adults.[1,10] A large proportion of children in several case series responded favorably to prednisone, usually within several weeks.[2-4,6,8,10] Recent studies in children have recommended initiating treatment with prednisone at a dose of 1–2 mg/kg daily or on alternate days, followed by a gradual wean as symptoms improve.[7,10] The side effects of steroids in children must be taken into consideration, such as weight gain, hypertension, hyperglycemia, cataracts, osteopenia, poor wound healing, infection, and growth suppression. The medical and cosmetic complications of steroid therapy have more substantial long-term consequences in children than in adults, thus we prefer not to use them unless the alternatives are not efficacious or tolerated.

There are little data regarding other options for treatment of children with refractory CIDP. Other immunomodulatory agents such as azathioprine, methotrexate, cyclosporine, cyclophosphamide, and interferon have been used, but at present there are no clear data favoring one of these treatments over another.[4,6,8]

Prognosis. Children with CIDP have a more favorable outcome than adults, with complete remission or minimal residual weakness seen in the majority of patients.[3,4,7,8,10] In adults, the relapsing form has a better prognosis than the monophasic form of CIDP, and children are more likely to present with the relapsing form of the disease.[7,10] In children, the number of relapses does not seem to be associated with the severity of prognosis. However, few studies have followed children to adulthood. In one series most children required treatment for at least 1 to 2 years, although in many cases treatment could ultimately be discontinued.[10] Relapses often occur in the setting of intercurrent illness or weaning of immunomodulatory medication.[4,8,10] Most of these relapses occur within the first 2 years after diagnosis, although patients have relapsed after 7–10 years.[8,10]

FUTURE PERSPECTIVES CIDP is an uncommon disorder in the pediatric population. It is a disease that can dramatically affect a child's quality of life, and if left untreated may result in permanent disability. However, if diagnosed properly and treated in a timely fashion, most children with CIDP will respond to immunomodulatory therapy. Children with CIDP typically suffer a relapsing-remitting course and require close monitoring by a neurologist. Nevertheless, the prognosis for remission of neurologic deficits is generally good.

Further research is needed to evaluate the efficacy of different therapies in the pediatric CIDP population, including randomized controlled trials with a sufficient number of patients. The formation of a multicenter consortium could help to pool the experience of different hospitals and enable a large group of patients to be followed over time.

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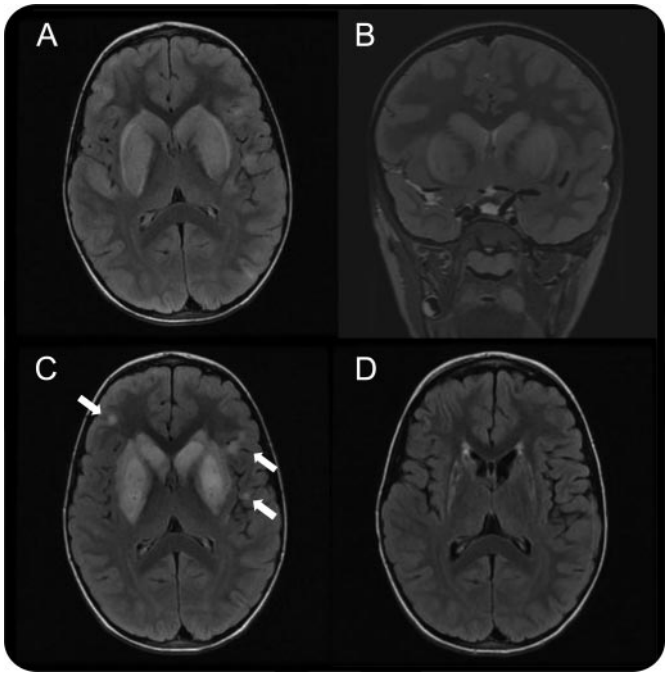
Teaching Neuro*Images*: Call it as you see it

Evolution of bilateral striatal necrosis

Elizabeth A. Coon, MD
Marc C. Patterson, MD

Correspondence & reprint requests to Dr. Coon: coon.elizabeth@mayo.edu

Figure Brain MRI findings at onset, 6 weeks, and 4 months



Axial T2 fluid-attenuated inversion recovery (FLAIR) (A) and coronal CUBE (3-dimensional fast spin echo) images (B) at onset show bilateral hyperintensity of the caudate nucleus and putamen with mass effect. Axial FLAIR images at 6 weeks (C) demonstrate additional cortical and subcortical foci (arrows) with ex vacuo dilation of the frontal horns noted at 4 months (D).

After 2 days of fever, a 5-year-old boy had a partial seizure, then became encephalopathic and anarthric. MRI (figure) was consistent with bilateral striatal necrosis and *Mycoplasma pneumonia* immunoglobulin G and immunoglobulin M serology was positive. He was treated with plasma exchange and IV steroids with improvement in consciousness and speech. One month later he developed oromandibular, limb, and truncal dystonia. Clinical and radiologic improvement was observed after initiating rituximab.

Aptly named, cases of bilateral striatal necrosis were described by Goutiéres and Aicardi[1] in 1982. When attributable to an infectious or parainfectious etiology such as *Mycoplasma*, the prognosis is generally favorable.[2]

AUTHOR CONTRIBUTIONS

Dr. Coon, Dr. Patterson: study concept and design. Dr. Coon: drafting the manuscript. Dr. Patterson: revising the manuscript.

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From the Department of Neurology, Mayo Clinic, Rochester, MN.

Dr. Coon reports no disclosures. Dr. Patterson serves on scientific advisory boards for the World Health Organization, Actelion Pharmaceuticals Ltd., Shire plc, Neuraltus Pharmaceuticals, Inc., and StemCells, Inc; serves on the editorial board of the *Journal of Child Neurology* and as Editor, Pediatric Neurology for *Up-To*-Date; and has received research support from the NIH/NINDS and Actelion Pharmaceuticals Ltd. Go to Neurology.org for full disclosures.

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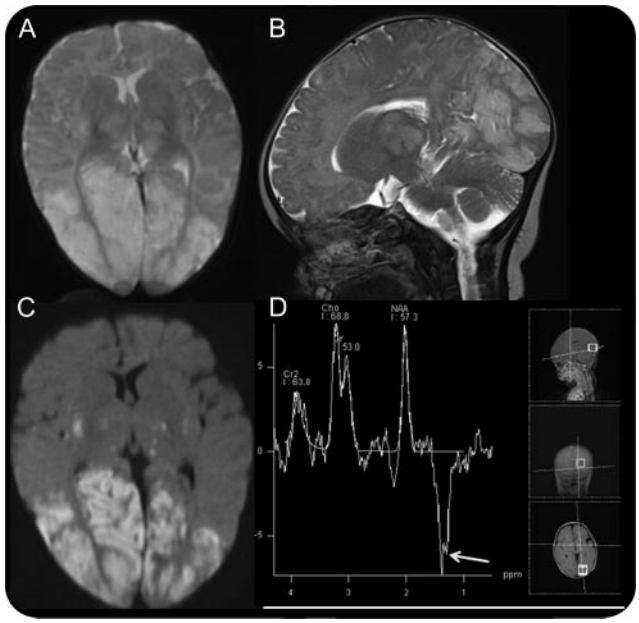
Teaching NeuroImages: Acute necrotizing encephalopathy during novel influenza A (H1N1) virus infection

A. Spalice, MD, PhD
F. Del Balzo, MD
F. Nicita, MD
L. Papetti, MD
F. Ursitti, MD
G. Salvatori, MD
A.M. Zicari, MD
E. Properzi, MD
M. Duse, MD

Address correspondence and reprint requests to Dr. Alberto Spalice, Division of Child Neurology, Department of Pediatrics, University "La Sapienza," Rome, Viale Regina Elena 324, 00161 Rome, Italy childneurology.sapienzaroma@live.it

Figure MRI



Axial (A) and sagittal (B) T2-weighted MRI shows confluent hyperintensity involving the cortical–subcortical regions of the occipital and parietal lobes. There are also several small areas in internal and external capsula, insular cortex, and bilaterally in the thalamus and in the left superior cerebral peduncle (A, B). Axial diffusion-weighted image map shows restricted water diffusion in the corresponding areas mimicking acute ischemic infarction with cytotoxic edema. The lesions are not confined to a certain arterial territory (C). The spectroscopic study (echo time = 144 msec) shows high peaks for lactate (arrow), with normal values for choline, creatine, and NAA (D).

Since the outbreak of novel influenza A (H1N1) in 2009, various neurologic complications have been cited.[1] A 2-month-old girl died of a rapidly progressive encephalopathy after influenza infection. MRI, performed after 12 hours from the onset of symptoms, showed bilateral and symmetric lesions including the thalamus, the cortical–subcortical regions of the occipital and parietal lobes, and brainstem tegmentum (figure). The pathology of necrosis and vasculopathy were in keeping with acute necrotizing encephalopathy, first described in Japan and carrying high mortality and morbidity.[2] A vasculopathy with breakdown of the blood–brain barrier was incriminated but the pathogenesis remained obscure.

AUTHOR CONTRIBUTIONS

Dr. Spalice: drafting/revising the manuscript, study concept or design, acquisition of data. Dr. del Balzo: study concept or design, acquisition of data. Dr. Nicita: study concept or design, acquisition of data. Dr. Papetti: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Ursitti: study concept or design, study supervision. Dr. Salvatori: study concept or design, acquisition of data. Dr. Zicari: study concept or design, acquisition of data. Dr. Properzi: drafting/revising the manuscript, acquisition of data. Dr. Duse: study concept or design, acquisition of data.

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From the Department of Pediatrics Child Neurology Division, University "La Sapienza" Rome, Italy.
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Introduction

Pediatric Perspective

By Aravind Ganesh, MD, DPhil(Oxon), and Christopher B. Oakley, MD

Pediatric headaches can cause considerable pain and frustration for all parties involved—the patient, their family, and even the provider. A specific headache diagnosis can usually be achieved through a detailed history and complete neurologic examination, particularly when it is a primary headache, which often has unique manifestations in children.

When seeing these pediatric patients, it is also important to consider secondary headaches, which have an underlying cause. Potential etiologies may include congenital brain malformations, tumors, or intracranial hemorrhages that require evaluation and if not recognized may lead to significant consequences. Evaluation of secondary headaches involves an appropriate evaluation tailored to the suspected underlying etiology. Neuroimaging, particularly MRI with vessel imaging, is frequently used in assessing for underlying structural lesions. Obtaining the correct diagnosis is crucial to providing disease-specific management that can be more effective and, in some cases, even curative.

This chapter includes a potpourri of pediatric headache diagnoses. First, a Pearls and Oy-sters article points out the intricacies of diagnosing a cough headache due to Chiari malformation type I. Next, a Child Neurology review uses an illustrative case to highlight differences in clinical presentation among hemiplegic migraine, stroke, and Todd paralysis, the approach to diagnostic workup, and key features of migraine with aura and migraine equivalents in children.

Then, a Mystery Case takes readers through the challenge of diagnosing acute obstructive hydrocephalus, including teaching points about localizing the site of obstruction. Subsequently, another Mystery Case explores an intracranial hemorrhage due to a rare congenital vascular malformation, underscoring the importance of interpreting vascular imaging in the context of known anatomy. Finally, a third Mystery Case presents another unusual cause of headache—a rare ventricular tumor.

From the Department of Clinical Neurosciences (A.G.), University of Calgary, AB, Canada; and the Department of Child Neurology (C.B.O.), Johns Hopkins Hospital, Baltimore, MD.
Correspondence Dr. Ganesh aravindganeshy@yahoo.ca

Adult Perspective

By Guillermo Delgado-García, MD, and Rebecca E. Wells, MD, MPH

Similar to a new evaluation of headache in an adult, the key diagnostic approach for evaluating a pediatric patient with headache is determining whether the headache syndrome is a primary or a secondary headache disorder. The prevalence of migraine in children ranges from 3% in those 3–7 years old to 8%–23% in teenagers.

As illustrated with Dr. Gelfand's case, there are several migraine equivalents that also need to be considered in childhood, such as abdominal migraine, cyclical vomiting, and benign paroxysmal vertigo of childhood. Dr. Gelfand's case also demonstrates that clinical diagnoses given to children need to be confirmed with diagnostic testing as in adults. A full history and evaluation met the criteria for abdominal migraine. Children with migraine with prolonged aura also need vascular imaging to rule out ischemia, vasculitis, and moyamoya disease, which is more common in childhood. Migraine treatment approaches in children are similar to those in adults, considering both prophylactic and acute treatment options.

Just as with adults, headaches can also be the presenting symptom for an underlying concerning process in children. The strategy to identify secondary causes in children and adolescents is quite similar to that in adults. A comprehensive history and complete neurologic examination are used to screen for red flags. When present, neuroimaging is indicated. MRI is the favored modality for pediatric patients because of its appropriateness and superior radiation safety.

In the following cases, we will also review 3 examples of unusual secondary headache in pediatric patients. For each case, the authors picked up on an important red flag that led to the testing needed to diagnose the secondary condition. Of interest, sometimes conditions that typically manifest in children may present initially in adulthood, as in the case of the vein of Galen malformation in the 62-year-old woman. Although migraine is prevalent in children, it is critical to fully assess a new headache with red signs/symptoms in a child.

From the Division of Neurology (G.D.-G.), National Institute of Neurology and Neurosurgery, Mexico City; and the Department of Neurology (R.E.W.), Wake Forest Baptist Medical Center, Winston Salem, NC.
Correspondence Dr. Delgado-García guillermo.delgadogr@comunidad.unam.mx

RESIDENT & FELLOW SECTION

Section Editor
Mitchell S.V. Elkind, MD, MS

Pearls & Oy-sters: Cough headache secondary to Chiari malformation type I

James E. Bates, BS
Erika F. Augustine, MD, MS

Correspondence to Dr. Augustine: Erika_Augustine@urmc.rochester.edu

PEARLS

- Cough headache is a rare condition, but its presence should prompt thorough evaluation for intracranial pathology, given a high prevalence of secondary causes of headache in this population.
- Chiari malformation type 1 is a common diagnosis in which many patients are asymptomatic, though headache is the most common neurologic complaint when symptoms are seen.

OY-STER

- Headaches are exceptionally common; the coexistence of headache and Chiari malformation type 1 does not alone implicate the malformation as the cause of the headache. Headache symptoms that are positional or associated with transient increases in intracranial pressure (e.g., cough, Valsalva) may indicate association of the headache with the malformation.

CASE REPORT A 17-year-old girl with migraine headaches and Noonan syndrome presented for neurologic consultation regarding worsened headaches in the setting of a hospitalization for pneumonia. The patient reported a 3-year history of paroxysmal, debilitating, midline headaches typically less than 1 minute in duration, which were increased in frequency and severity at the time of consultation. Pain began at the base of the occiput and then spread anteriorly to the brow line. These brief headaches were associated with coughing, laughing, and neck extension. They were different in nature from her migraine headaches, which were prolonged and associated with photophobia and vomiting. In addition, the patient reported more recent problems with choking while eating. Physical examination was unremarkable with the exception of difficulty with tandem gait. Brain MRI revealed 20 mm of tonsillar herniation below the foramen magnum, with crowding of the foramen magnum, consistent with Chiari malformation type 1 (CM-I) (figure). A diagnosis of cough headache secondary to CM-I was made. Indomethacin was started at a dose of 25 mg twice daily as needed. Upon follow-up 1 month later, headaches had significantly decreased in frequency.

DISCUSSION Headaches directly associated with cough may be primary or secondary. According to International Classification of Headache Disorders (ICHD-2) diagnostic criteria, primary cough headaches are paroxysmal headaches brought on by coughing, straining, or Valsalva, lasting 1 second to 30 minutes, and not attributable to another disorder.[1] Primary cough headache most frequently presents as sudden-onset, bilateral, posterior, explosive pain without associated nausea, vomiting, photophobia, or phonophobia.[2,3] Cough headache with similar clinical characteristics, but caused by another disorder or structural lesion, is referred to as secondary cough headache. Of those with cough headache, the majority are adults with primary cough headache.

Reported secondary causes of cough headache include CM-I, subdural hematoma, acute sphenoid sinusitis, and other posterior fossa structural lesions including primary intracranial malignancy, metastatic malignancy, arachnoid cyst, and os odontoideum.[2,3] Of 7,100 consecutive adult patients in a Taiwanese headache clinic evaluated over a period of 8 years, only 83 (1.2%) were diagnosed with cough headache. Intracranial pathology was found in only 9 of these patients (10.8% of those with cough headache), including 2 with symptoms attributable to CM-I.[2] Similar cough headache prevalence of 1% was found in 6,412 consecutive adult patients from a headache clinic in Spain, though in this cohort, 58.8% of patients with cough headache demonstrated intracranial pathology on MRI. Of these, 80% had CM-I.[3] Similar data regarding the prevalence of cough headache are not available specifically for pediatric populations nor are data available for the incidence of cough headache in patients with CM-I. Overall, epidemiologic studies point to a very low prevalence of cough headache, even within the context of specialty headache clinics.

Differentiation between primary and secondary cough headache (of which headache attributed to CM-I is a subtype) is important as secondary causes may require intervention beyond pain management.

From the School of Medicine and Dentistry (J.E.B.) and the Department of Neurology (E.F.A.), University of Rochester Medical Center, NY.
Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.
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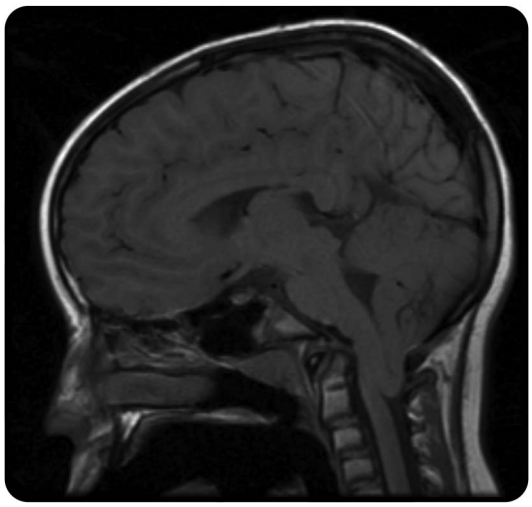
Figure Parasagittal T1-weighted MRI of the head demonstrates 20-mm tonsillar herniation, crowding of the foramen magnum, and compression of the cervicomedullary junction



In the ICHD-2 criteria for CM-I-related headache, one criterion includes improvement of the headache within 3 months following surgery, which presents a challenge for definitive presurgical diagnosis.[1] It can be difficult to differentiate primary from secondary cough headache based on clinical symptoms alone. In the Taiwanese cohort, there were no differences in sex, age at headache onset, pain location, pain characteristics, or associated features between patients with primary and secondary cough headache.[2] In the Spanish cohort, the duration of headache symptoms prior to presentation was greater in those with secondary cough headache (5 years vs 11 months).[3] Common features among patients with cough headache in both cohorts include sudden, severe, posterior headaches lasting less than a minute, most commonly arising in the fifth or sixth decade of life.

Current research suggests that both primary and secondary cough headache are related to paroxysmal increases in intracranial pressure. In the case of secondary cough headache, structural abnormalities may lead to alteration in CSF flow dynamics during cough or Valsalva, resulting in the development of the signs and symptoms of cough headache. The underlying pathophysiology behind primary cough headache is less clear. Lane and Davies[4] reported a modified Valsalva maneuver that was successful in differentiation of primary from secondary cough headache. Sixteen patients with cough headache were asked to exhale into the connecting tube of an aneroid sphygmomanometer to a pressure of 60 mm Hg. This elicited headache in 11 patients, 10 of whom had identifiable intracranial pathology on MRI, 8 of those having CM-I. Further validation of this technique could be helpful in differentiating primary from secondary cough headache without expensive neuroimaging studies.

CM-I itself is an uncommon finding; in a retrospective study of 5,248 pediatric patients receiving MRI of the head or cervical spine, 51 were found to have tonsillar herniation greater than 5 mm below the foramen magnum, consistent with CM-I, or approximately 9.7 per 1,000 children imaged. Of those, 37% were asymptomatic. Headache, found in 55% of patients, was the most common presenting symptom. Distinction between secondary cough headache and other headache types was not reported.[5]

CM-I is typically a stable malformation. A retrospective study of 147 children with CM-I followed for an average of 4.6 years found no change in mean tonsillar herniation or number of symptomatic patients between initial consultation and final follow-up; however, 7 children developed a syrinx during that time.[6] In a patient with cough headache and any other neurologic symptom consistent with CM-I or focal neurologic deficit, suspicion should be elevated for an underlying etiology. Of particular interest to the case presented here, CM-I may be a rare complication of Noonan syndrome.[7]

The optimal treatment of cough headache, whether primary or secondary, is poorly understood. Most patients with primary cough headache have remission of symptoms after 4 years without treatment. Individual episodes, however, can be debilitating despite the brief nature of the headaches, making symptomatic treatment useful. Patients with intracranial pathology may require surgical management for resolution of symptoms. First-line pharmacological therapy is typically indomethacin in a total daily dose of 50–150 mg. The mechanism of action for indomethacin in cough headache is unknown, though its effect may be mediated through decreasing intracranial pressure.[8] Both aforementioned large case series of patients with cough headache have shown that patients with primary cough headache respond more frequently to indomethacin (78%–100%) than do those with a secondary cause (0%–38%).[2,3] Topiramate, methysergide, propranolol, naproxen, and IV metoclopramide have also been shown to be useful for symptomatic relief of cough headache.[8]

Surgical management of CM-I typically involves posterior cranial fossa decompression with an enlargement of the foramen magnum. In a series of 177 adult patients undergoing primary decompression for Chiari malformation, strain-related headache was the second most common presenting symptom (54.2%). Three months postintervention, 98.9% of those with headache had improvement of symptoms, although at 1 year benefit was sustained in only 62.5%. Surgical intervention showed a 0.6% acute (within 7 days of surgery)

complication rate and a 10.1% delayed complication rate. Pseudomeningocele was the most common complication in both the acute and delayed setting.[9] Of note, in a pediatric population of 130 patients surgically treated for CM-I, 83% had postoperative relief of symptoms.[10] The limited evidence available suggests that surgery is the most efficacious treatment for CM-I-associated headache, though due to the nature of the intervention, this should be considered carefully. While the data are mixed regarding the efficacy of indomethacin in patients with CM-I-associated cough headache, we continue to recommend a trial of indomethacin as first-line therapy due to its mild side effect profile in comparison to surgical intervention and due to challenges in distinguishing secondary from primary cough headache, which may demonstrate spontaneous resolution over time without surgical intervention.

AUTHOR CONTRIBUTIONS

J.E. Bates: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Augustine: drafting/revising of manuscript, study concept or design, study supervision or coordination.

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DISCLOSURE

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Child Neurology: Migraine with aura in children

Amy A. Gelfand, MD
Heather J. Fullerton, MD, MAS
Peter J. Goadsby, MD, PhD

Address correspondence and reprint requests to Dr. Amy A. Gelfand, UCSF Department of Neurology, Box 0114, 505 Parnassus Ave, M-798, San Francisco, CA 94143-0114
GelfandA@neuropeds.ucsf.edu

ABSTRACT

The differential diagnosis for an acute hemiparesis in a child includes stroke, Todd paralysis, and hemiplegic migraine. In the context of an illustrative case, this review highlights the differences in clinical presentation among these entities and an approach to the diagnostic workup. Migraine with aura in children is reviewed, including migraine equivalents such as abdominal migraine and the particular presentation of hemiplegic migraine. An approach to the prophylactic and acute treatment for children with migraine with aura is offered. *Neurology*® 2010;75:e16–e19

CASE: PART 1 A 14-year-old boy with Crohn disease was admitted for a presumed flare. On the second hospital day, his abdominal pain acutely increased. Shortly thereafter, he experienced tingling starting in his shoulder and spreading over his left hemibody over 10 seconds. This was accompanied by 7/10 pounding left-sided head pain. Several minutes later, the tingling gave way to diminished sensation and weakness on the left. These symptoms persisted into the next morning, at which time a neurologic consultation was requested.

Now 20 hours into the attack, he had 5/10 pounding head pain. Neurologic examination revealed a left hemiparesis in a pyramidal distribution, with face and arm affected more than leg. Sensation was also diminished over the left face and hemibody. Reflexes were normal and there was no neglect. Complete blood count, electrolytes, erythrocyte sedimentation rate, liver function tests, lactate, amylase, and lipase were normal.

Differential diagnosis. The differential diagnosis for acute onset hemiparesis in a child includes stroke, Todd paralysis, and migraine with aura, specifically hemiplegic migraine. Demyelinating disease, brain tumor, and metabolic disturbances such as hypoglycemia or hypocalcemia should also be considered.

Patients with inflammatory bowel disease are often hypercoagulable, increasing their risk of ischemic stroke.[1] Positive symptoms such as tingling are more suggestive of migraine, while stroke is classically associated with negative symptoms. However, children with ischemic and hemorrhagic stroke can complain of tingling paresthesias.

In this case, there was no witnessed seizure activity or change in mental status. Postictal paralysis is also usually not so prolonged. In a study of adults in an epilepsy monitoring unit, Todd paresis resolved within 22 minutes,[2] though in one pediatric case report it lasted 24 hours.[3]

Migraine with prolonged aura would be a diagnosis of exclusion given this was his first presentation, and that children often complain of headache at the ictus of both hemorrhagic and ischemic strokes.[4]

Recommended workup. Additional history important to elicit includes whether there is a family history of epilepsy, migraine, or hypercoagulability. The presence of migraine markers, such as motion sickness and ice cream headache (throbbing head pain when eating something cold),[5] should also be sought.

Given that migraine with prolonged aura is difficult to differentiate from acute stroke, on first presentation these patients should be imaged with MRI and intracranial magnetic resonance angiography to rule out ischemia. Imaging also rules out vasculitis or moyamoya disease, which may present with headache with a migrainous phenotype, probably as a comorbid activation of the patient's underlying tendency to migraine.

CASE: PART 2 MRI with diffusion-weighted imaging, which is highly sensitive for acute infarction, was normal. Magnetic resonance angiography and venography were also normal. By 26 hours after symptom

From the Division of Child Neurology (A.A.G., H.J.F.), Neurovascular Division (H.J.F.), and Headache Group, Department of Neurology (P.J.G.), University of California, San Francisco, San Francisco, CA.

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onset, the patient's weakness began improving, and by the next morning his neurologic examination was normal.

Further history revealed that the patient experienced monthly headaches which were unilateral, throbbing, and partially relieved by acetaminophen. His mother and older sister had frequent severe headaches, though neither experienced aura. The patient had not experienced aura symptoms with his previous headaches or episodes of abdominal pain.

He did experience motion sickness and frequent abdominal pain and vomiting as a young child. He did not get ice cream headache.

Review of the patient's records revealed that the diagnosis of Crohn disease was purely clinical—he had never had biopsy-proven pathology. He had never experienced bloody or mucous-covered stools, extraintestinal manifestations of Crohn disease, or highly elevated inflammatory makers. His abdominal pain came on more with stress and with nitrite-containing foods, both known migraine triggers. Often the episodes of abdominal pain lasted only 1–2 hours.

A repeat endoscopy and intestinal biopsies were negative for evidence of Crohn disease, raising significant doubts about this diagnosis. His gastrointestinal symptoms were considered to most likely be due to abdominal migraines.

MIGRAINE WITH AURA IN CHILDREN Migraine is common in children.[6] The prevalence is 3% in children aged 3–7 years, 4%–11% in those 7–11 years, and 8%–23% in teenagers.[6] One quarter of patients with migraine experience aura.[7] Aura is thought to be based on cortical spreading depression; a wave of depolarization followed by hyperpolarization spreads across the cortex, precipitating neurologic dysfunction.[8,9] Prognostically, 50%–60% of adolescents with migraine with aura are still symptomatic at 5- to 7-year follow-up.[8]

In migraine with typical aura, visual, sensory, or dysphasic symptoms develop over 5–20 minutes, and resolve within 60 minutes. Headache typically occurs with the aura, or follows within 60 minutes.[10] The headache may be ipsilateral or contralateral to the aura symptoms, usually contralateral.[11] Visual auras are most common, followed by sensory, then language.[12] Motor aura is least common and is a defining feature of hemiplegic migraine.[13]

This patient's hemisensory tingling was most likely a typical aura, even though it came on quickly. The slow, spreading quality of migraine aura is often helpful in distinguishing it from ischemic deficits, which tend to be maximal at onset.[12] Neurologic deficits from aura usually resolve within 20–60 minutes, though this is also often the case in transient ischemic attacks. In migraine aura, positive symptoms such as tingling are often followed minutes later by negative symptoms,[12] as they were in this case when the tingling gave way to diminished sensation. A migratory pattern, or so-called Jacksonian march,[14] can also be seen in seizure.

Migraine with prolonged aura. Aura in migraine is considered prolonged if it lasts more than 1 hour but less than 7 days,[15] with longer aura termed persistent aura.[10] Most patients experience prolonged aura in only a minority of attacks, often experiencing typical length aura with other attacks.[16]

Adult patients with migraine with aura are at greater stroke risk than controls, although the absolute risk remains small, estimated in one study at 12.4 ischemic strokes per 10,000 women per year.[17-19] It is not known whether prolonged aura carries a greater risk for vascular events than typical aura.

Hemiplegic migraine. Hemiplegic migraine can be familial[20] or sporadic.[21] The familial form may be due to mutations in voltage-gated channels *CACNA1A*[22] and *SCN1A*[23] or the Na^+/K^+ pump *ATP1A2* gene.[24] The etiology of the sporadic form, which this patient had, is less clear, although some patients have mutations in the same genes.[25]

The motor aura of hemiplegic migraine is unique. There is no biphasic symptom progression, specifically no jerking before the onset of weakness.[12] While most attacks come on over minutes, 7% of patients experience onset of weakness in under 1 minute,[26] as this patient did. The weakness is twice as likely to affect the arm as the leg.[26] Duration can be hours to days, though most still resolve within an hour.[26,27] Most patients also experience typical aura symptoms during an attack, usually sensory, as this patient did.[26] The hemiplegia is almost always accompanied by head pain, unlike other auras (e.g., visual), which can occur without headache.[27] The pathophysiology of motor aura is now being explored with mouse models as the genes have been identified.[28] Some have hypothesized that the aura in hemiplegic migraine is from vasospasm, not cortical spreading depression. However, there is no evidence for this or for increased stroke risk over other migraines with aura.[29]

Abdominal migraine. Abdominal migraine is one of several childhood migraine equivalents. These syndromes are thought to be developmental manifestations of genes that in adulthood will be expressed as migraine headache. An example of this potential is that benign torticollis of childhood can be linked to the familial hemiplegic migraine gene *CACNA1A.*[30] Children with migraine equivalents make up an estimated 10% of all migraineurs referred to pediatric

neurology clinics.[6] Three migraine equivalent syndromes are recognized in International Classification of Headache Disorders–II: cyclical vomiting, abdominal migraine, and benign paroxysmal vertigo of childhood.[8] Several others are proposed: benign paroxysmal torticollis of infancy,[30,31] acephalgic migraine,[32] and acute confusional migraine.[6,33]

Abdominal migraine presents in school-aged children as periumbilical or midline dull abdominal pain that lasts 1 to 72 hours.[8] There may be associated anorexia, nausea, vomiting, or pallor.[6,8] There is usually a family history of migraine, and about 70% of children also have typical migraines, although it may be several years before these emerge.[6]

TREATMENT OF MIGRAINE WITH AURA IN CHILDREN

Prophylaxis. The decision of when prophylaxis is indicated can only be made in conjunction with the family or caregivers. Even relatively infrequent migraines may merit daily treatment if they are frightening to the child, or likely to trigger repeated unnecessary imaging studies, such as in hemiplegic migraine. In fact, the US Headache Consortium recommends prophylactic therapy for those whose migraines are accompanied by hemiplegia or prolonged aura.[34] Preventive migraine therapies in children and adolescents were recently reviewed[8]; this discussion focuses specifically on treatment of migraine with aura.

There is no proven treatment for migraine with aura. In a survey of adult headache specialists, 55% thought verapamil was most effective, while 18% preferred valproate.[16] Flunarizine is widely used in the United Kingdom and particularly effective in children with hemiplegic migraine.[35] Verapamil may also be effective for hemiplegic migraine,[34,36] lamotrigine for aura in general, and divalproex for persistent aura.[34,37] One open-label study with ketamine suggests that the development of suitable agents with actions at excitatory glutamate receptors may be one way forward.[38,39] Many headache specialists avoid beta-blockers in patients with prolonged aura out of concern that they may limit compensatory vasodilation, although this is more a theoretical concern.[16]

The best prophylactic therapy for migraine with aura remains to be established, and on the individual level often requires trial and error. Calcium-channel blockers are a reasonable first choice. Given the often cyclical nature of migraine, the duration of prophylactic therapy need not be interminable. One approach is to treat for the duration of the school year and wean over the summer.[8]

Acute therapies. With present knowledge, acute aura itself is not treatable. Treatment should therefore focus on the head pain. Acetaminophen and nonsteroidal anti-inflammatory drugs are first-line agents.[8] Almotriptan is approved by the Food and Drug Administration for acute migraine therapy in adolescents.[40] Several other triptans have been studied in adolescents and children and used off-label, most notably nasal spray sumatriptan.[8] In case reports, IV verapamil seems effective for acute hemiplegic migraine.[36] Triptans are contraindicated in hemiplegic migraine because it was wrongly considered when they were developed that vasospasm was an important part of migraine aura, and there are thus insufficient systematic data upon which to base any other recommendation.

CASE CONCLUSION On follow-up 7 weeks later, the patient reported no further episodes of abdominal pain or headache. Given the current infrequency of his symptoms, he and his parents did not desire prophylaxis. The decision was made to treat acute episodes with naproxen. If his migraines become more frequent, he will start verapamil.

DISCLOSURE

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RESIDENT & FELLOW SECTION

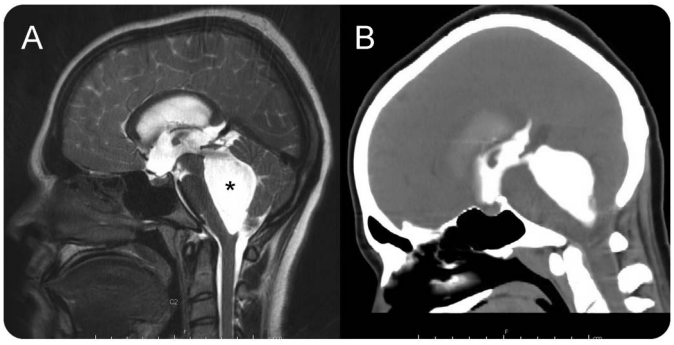
Section Editor
John J. Millichap, MD

Mystery Case: Acute hydrocephalus caused by radiographically occult fourth ventricular outlet obstruction

Daniel Duran, MD*
Muhamed Hadzipasic, MD*
Kristopher T. Kahle, MD, PhD

Correspondence to Dr. Kahle: kristopher.kahle@yale.edu

Figure 1 Acute hydrocephalus associated with functional obstruction of 4th ventricular CSF outflow



(A) Sagittal T2-weighted MRI demonstrates ventriculomegaly. The asterisk highlights prominent fourth ventricular dilation, ventral displacement of the brainstem, and dorsal displacement and thinning of the cerebellum. (B) Sagittal CT ventriculography shows flow of contrast from the 3rd to the 4th ventricle, and absence of flow into the spinal subarachnoid space.

A 19-year-old woman with no history of CNS inflammatory pathology or hemorrhage presented with 5 days of diplopia and headache. Examination revealed papilledema and bilateral sixth nerve palsies. Imaging demonstrated panventricular enlargement and marked 4th ventricular dilation (figure 1). Cine MRI revealed turbulent fourth ventricle CSF flow suggesting outflow obstruction, which was confirmed with contrast ventriculography. A suboccipital craniotomy was then performed, which revealed an arachnoid web (figure 2). Membranous occlusion of the fourth ventricular outlet is a rare cause of obstructive hydrocephalus usually associated with a history of inflammatory conditions or hemorrhage.[1] A small number of idiopathic cases have been reported.[2]

In this case, microsurgical fenestration reconstituted CSF flow and resolved the patient's diplopia. However, she subsequently required ventriculoperitoneal shunting to resolve recrudescence of persistent headache, indicating both obstructive and communicating components to her hydrocephalus syndrome.

AUTHOR CONTRIBUTIONS

Daniel Duran: construction of figures and text. Muhamed Hadzipasic: construction of figures and text. Kristopher T. Kahle: concept and design, performed suboccipital craniotomy, microsurgical fenestration procedure, acquired photographic images, critical revision of text and figures.

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MYSTERY CASE RESPONSES

The Mystery Case series was initiated by the *Neurology*® Resident & Fellow Section to develop the clinical reasoning skills of trainees. Residency programs, medical student preceptors, and individuals were invited to use this Mystery Case as an educational tool. Responses were solicited through a group e-mail sent to the American Academy of Neurology Consortium of Neurology Residents and Fellows and through social media. We received 177 responses. The vast majority of respondents (73%) had been in practice for 1–4 years; 53% were residents/fellows while 32% were faculty/

*These authors contributed equally to this work.

From the Departments of Neurosurgery (D.D., K.T.K.), Pediatrics (K.T.K.), and Cellular and Molecular Physiology (K.T.K.), Yale School of Medicine (M.H.), New Haven, CT.

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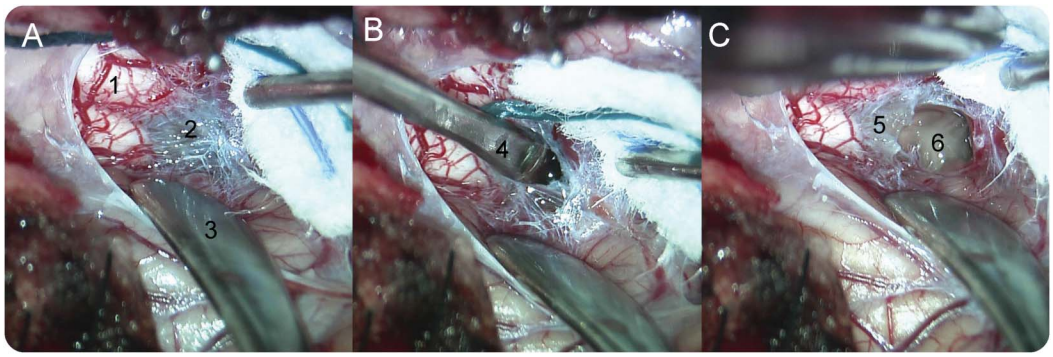
Figure 2 Treatment of acute hydrocephalus by fenestration of an arachnoid web at the 4th ventricular outlet



(A) Arachnoid web at the level of the cerebellomedullary junction (4th ventricular outlet). (B) Fenestration of arachnoid web. (C) Postfenestration. (1) Medulla. (2) Dense arachnoid web obstructing fourth ventricular outlet and obscuring the obex. (3) Dissector retracting the right cerebellar tonsil. (4) Penfield dissector fenestrating the arachnoid web and projecting into the fourth ventricle (5) Remnant of arachnoid web. (6) Area postrema on the floor of the fourth ventricle.

board-certified physicians. Seventy percent resided outside the United States. A wide range of practice settings was represented.

Eighty percent of the respondents correctly identified the basic MRI features of this case, which included dilation of the lateral, third, and fourth ventricles. Fifty-six percent also identified the additional important findings of ventral displacement of the brainstem and dorsal displacement of the cerebellum, which likely contributed to the patient's presenting complaint of diplopia. Twenty-six percent also identified the crucial finding of absent contrast flow in the spinal subarachnoid space on CT ventriculography. However, only 11% correctly identified the most likely diagnosis in this case: an arachnoid web causing obstructive hydrocephalus. The most commonly selected diagnosis was aqueductal stenosis (23%), followed by colloid cyst (19%) and choroid plexus papilloma (15%). While these 3 are important differential diagnoses to consider in a presentation of obstructive hydrocephalus, the key to clinching the diagnosis in this case is the dilation of the patient's fourth ventricle, which means that the obstruction (if any) must be downstream of the fourth ventricle. This rules out a colloid cyst (classically seen in the third ventricle), choroid plexus papilloma (typically in the lateral ventricles), and aqueductal stenosis (which affects the cerebral aqueduct connecting the third and fourth ventricles).[1] Typically, the observation of fourth ventricle dilation simply leads to a diagnosis of communicating hydrocephalus, but in this case, CT ventriculography showed absence of contrast flow into the spinal subarachnoid space, leading to suboccipital craniotomy and an intraoperative diagnosis of an arachnoid web.

This case highlights the importance of interpreting neuroimaging findings of hydrocephalus in the context of the anatomy of the ventricular system.

Aravind Ganesh, MD
Department of Clinical Neurosciences, University of Calgary, Canada; and Centre for Prevention of Stroke & Dementia, Nuffield Department of Clinical Neurosciences, University of Oxford, UK

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RESIDENT & FELLOW SECTION

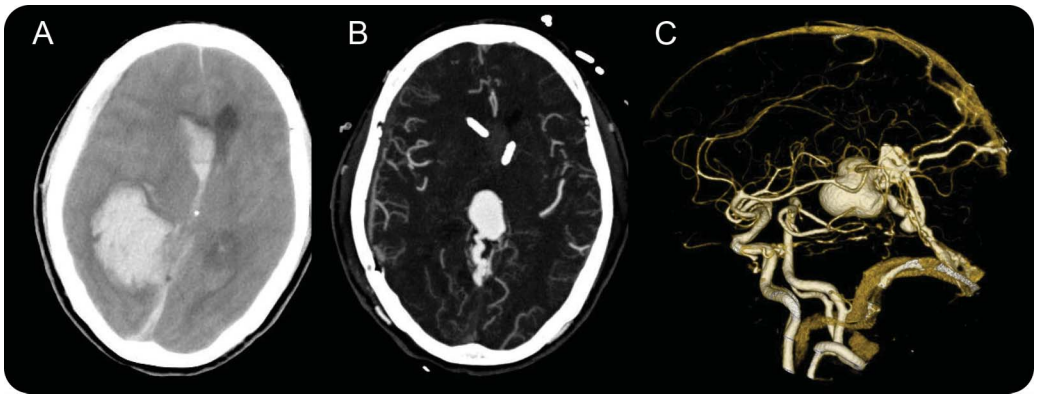
Section Editor
John J. Millichap, MD

Mystery Case: Intracranial hemorrhage in adult vein of Galen malformation

Yi-Shan Tsai, MD
Yen-Rei Chen, MD
Li-Wen Chen, MD

Correspondence to Dr. Chen: muffychen@gmail.com

Figure Intracranial hemorrhage in vein of Galen malformation



(A) Noncontrast brain CT reveals intracranial hemorrhage at right parietotemporal region. (B) Postoperative brain CT angiography shows aneurysm of the great cerebral vein of Galen. (C) Volume rendering reformatted 3D image confirms the diagnosis of vein of Galen malformation.

A 62-year-old woman presented with sudden-onset headache and vomiting followed by loss of consciousness. Brain CT revealed right parietotemporal intracranial hemorrhage (figure, A). Subsequent CT angiography confirmed vein of Galen malformation (figure, B and C). Vein of Galen malformations develop during gestation and usually present in infancy or early childhood with heart failure or hydrocephalus.[1,2] Adult hemorrhagic presentations are rare compared with arteriovenous malformations, considering the slow-flow fistula in adults. However, subarachnoid and intracerebral hemorrhage can occur due to rerouting of blood into the pial veins. For symptomatic patients, surgical closures of the shunt and endovascular interventions are effective treatments.

AUTHOR CONTRIBUTIONS

All authors participated in the neuroimaging examinations and interpretations. The manuscript was drafted by Y.-S.T. and L.-W.C. All the authors made an intellectual contribution to the final manuscript.

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DISCLOSURE

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

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MYSTERY CASE RESPONSES

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

All 25 responses we received came from individuals rather than groups. A total of 76% identified the intracranial hemorrhage in this patient with intraventricular and subarachnoid extension. A total of 68% also recognized the midline vascular abnormality on CT angiography, with 16% correctly identifying this as a vein of Galen malformation. A total of 20% recognized the postoperative

From the Departments of Diagnostic Radiology (Y.-S.T., Y.-R.C.) and Pediatrics (L.-W.C.), National Cheng Kung University Hospital and College of Medicine, Tainan, Taiwan.

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finding of drainage catheters in this patient's ventricles on CT angiography. The most complete answer came from Vinny Montanaro, who recognized all of the radiologic findings and arrived at the diagnosis of vein of Galen aneurysmal malformation. In thinking about the etiology, it is worth noting that this malformation is usually a slow-flow fistula; however, bleeds in this setting likely occur due to rerouting of the blood into the pial veins.

This case underscores the importance of vascular imaging in the setting of intracranial hemorrhage, and of interpreting results in the context of known arterial and venous sinus anatomy.

Aravind Ganesh, MD
Department of Clinical Neurosciences, University of Calgary; Centre for Prevention of Stroke & Dementia; Nuffield Department of Clinical Neurosciences, University of Oxford

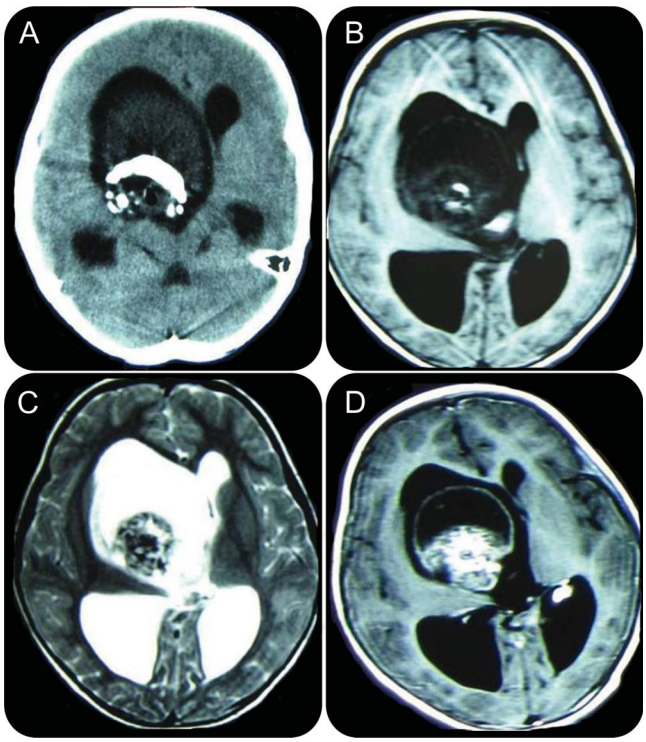
Section Editor
Mitchell S.V. Elkind, MD, MS

Mystery Case: Giant mature teratoma of the lateral ventricle in a child

Jin Li, MD
ZhiGang Lan, MD
JianGuo Xu, MD

Correspondence to Dr. Xu:
hxswjim@163.com

Figure 1 Brain CT and MRI



Axial CT scan shows a mass lesion with heterogeneous density and huge calcification in the right lateral ventricle (A). Cranial MRI, T1-weighted axial (B) and T2-weighed axial (C), shows a mass lesion with low and high signal intensity. Contrast-enhanced images show heterogeneous enhancement of the lesion (D).

A 3-year-old girl was admitted with a 1-month history of headache. Neurologic examination was normal. Cranial CT revealed a mass with huge calcification in the right lateral ventricle (figure 1A). MRI demonstrated a lesion with low and high signal intensity and heterogeneous enhancement (figure 1, B–D). A right frontal craniotomy was performed. The right ventricle was found to be filled with sebaceous glands, hair, fat globules, a full set of teeth, tongue, and gastrointestinal glands (figure 2, A–D). Histologic examination confirmed a mature teratoma. Postoperative MRI demonstrated total tumor resection (figure 2, E and F). A mature teratoma located in the lateral ventricle with a full set of teeth is extremely rare.[1,2]

AUTHOR CONTRIBUTIONS

Dr. Li: data collection, drafting of manuscript. Dr. Lan: data collection, review of literature. Dr. Xu: revision of manuscript, concept of manuscript.

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DISCLOSURE

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

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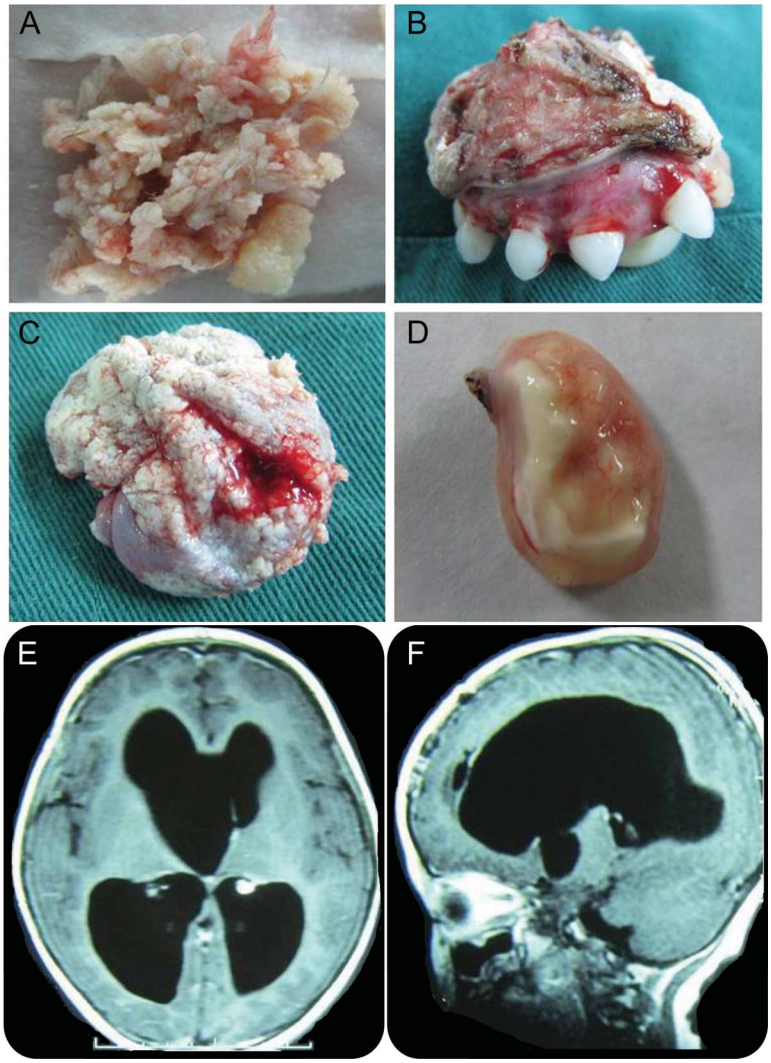
Figure 2 Intraoperative findings and postoperative brain MRI



The resected samples show the sebaceous glands and hair (A), a full set of teeth (B), tongue (C), and gastrointestinal glands (D). Postoperative MRI, contrast axial (E) and sagittal (F) images, shows total tumor resection.

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MYSTERY CASE RESPONSES

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

All the responses we received came from individuals rather than groups. A total of 33% of respondents correctly identified the lesion as a teratoma. The most complete response came from Violet M. Aroon, who pointed out that the heterogeneous lesion likely contains fat and soft tissue based on its signal characteristics on T1 and T2 MRI.

This case highlights the value of MRI in characterizing intraventricular mass lesions, which may be essential in guiding subsequent clinical management.

Andrew Schepmyer, MD
University of British Columbia, Vancouver, Canada

Introduction

Pediatric Perspective

By Alonso G. Zea Vera, MD, and Bruce H. Cohen, MD

Western medicine has aligned the study of health and disease along organ systems. Common to all organ systems are shared biochemical pathways modulated by thousands of transporters, enzymes, and cofactors acting in perfect synchrony. When one of these proteins fails, the effects often affect many organ systems. In the following section, we present 5 articles illustrating the variability and complexity of metabolic disorders.

Inborn errors of metabolism are caused by a mutation in a specific gene resulting in a defective protein, which results in the disruption of a metabolic pathway. This causes energy failure, lack of needed substrates, and/or accumulation of toxic molecules. Because of its high-energy demands and susceptibility to oxidative stress, the brain is especially susceptible. Metabolic diseases commonly present at a young age, although patients of any age can be affected. If the effect of the metabolic abnormality is severe enough, it can present in the neonatal period, as seen in the patient reported by Dhamija et al.

These diseases have very diverse presentations. Often, the main clue for the diagnosis is multiple organ system involvement that includes underscoring the importance of a holistic approach. They require a high index of suspicion, even when the likelihood of these diagnoses seems low. Kranick et al. illustrate this point. Sometimes, a thorough neurologic history and examination reveal characteristic abnormalities narrowing the differential diagnosis, as shown in 2 of the articles in this section. Other times, distinctive findings are seen in auxiliary tests, like the MRI results described by Jain et al.

Expanded newborn screening and the availability of metabolic and genetic testing result in early diagnosis. Early treatment can affect the outcome at times as with the patient presented by Dill et al. Frequently, child neurologists are in the front lines for these diseases. An understanding of these conditions is a crucial part of the practice of child neurology.

From the Department of Neurology (A.G.Z.V.), Cincinnati Children's Hospital Medical Center, OH; and Pediatrics and NeuroDevelopmental Science Center (B.H.C), Children's Hospital Medical Center of Akron, OH.
Correspondence Dr. Zea Vera alonso.zeavera@cchmc.org
For disclosures, please contact the *Neurology*® Resident & Fellow Section at rfsection@neurology.org.

Adult Perspective

By Robert Hurford, MSc, MRCP, and Corrado I. Angelini, MD

Metabolic disorders are characterized by the deficiency or dysfunction of essential metabolites and most commonly manifest with neurologic symptoms due to impaired brain development or functioning. Because of their low incidence and high mortality, metabolic disorders are traditionally the purview of pediatric neurologists; however, some can present in adulthood and increasing numbers of patients' transition into adult services. The inborn errors of metabolism with CNS involvement apply therefore to both pediatric and adult neurologists.

A history of intermittent attacks triggered by feeding, fasting, or stress may raise suspicion of a disorder of the urea cycle, amino acid catabolism, or fatty acid oxidation. Adults may or may not present with the same neurological symptoms as a child. Seizures are one common feature with a broad differential diagnosis. Many childhood epilepsies are also associated with metabolic disorders, and Dhamija et al. provide some useful management tips.

Planning the investigation of an adult or child with a suspected metabolic disorder can be daunting, but the presenting age and clinical history can rationalize the approach. Characteristic examination findings, such as those described in the case by Coorg et al., can help narrow the differential diagnosis. Following initial laboratory panel results, specialist input should be sought for second-line investigations, such as gas chromatography–mass spectrometry or genetic analysis.

Brain imaging is essential early in the diagnostic process. MRI features of metabolic disorders include globus pallidus hyperintensity, cerebellar hypoplasia, agenesis of the corpus callosum, or nonspecific gray and white matter abnormalities. Moreover, many disorders, such as fucosidosis, as described by Jain et al., have characteristic imaging findings.

Consider testing adults with complex presentations for inherited metabolic disorders. Drawing a balance between subjecting a child to extensive investigations, which are likely to be expensive, unpleasant, and potentially unrewarding, and making an accurate diagnosis is a demanding challenge. Yet, diagnostic nihilism should be avoided and regular follow-up should be instituted as there are rare—but critically important—treatable conditions, as described in the accompanying case by Dill et al. Furthermore, as discussed by Kranick et al., a diagnosis provides psychological closure and can have important family planning implications for the parents.

For this anthology, we have compared the clinical signs that cover the major cardinal features of CNS metabolic disorders. We hope that our readers will enjoy each case and appreciate both the general approach and metabolic techniques proposed.

From the Nuffield Department of Clinical Neurosciences (R.H.), University of Oxford, United Kingdom; and Neurosciences Department (C.I.A.), Neuromuscular Center, University of Padova, Italy.
Correspondence Dr. Hurford robert.hurford@ndcn.ox.ac.uk
For disclosures, please contact the *Neurology*® Resident & Fellow Section at rfsection@neurology.org.

RESIDENT & FELLOW SECTION

Section Editor
Mitchell S.V. Elkind, MD, MS

Child Neurology: Paroxysmal stiffening, upward gaze, and hypotonia

Hallmarks of sepiapterin reductase deficiency

P. Dill, MD
M. Wagner, MD
A. Somerville, MD
B. Thöny, PhD
N. Blau, PhD
P. Weber, MD

Correspondence & reprint requests to Dr. Dill: patricia.dill@ukbb.ch

Sepiapterin reductase deficiency (SRD) is a dopa-sensitive neurotransmitter disorder, caused by mutation of the *SPR* gene located on chromosome 2p14-p12.[1] To date, 31 patients with 14 mutations have been diagnosed (BIODEF database, update November 2010, www.biopku.org).

While classic tetrahydrobiopterin deficiencies present with hyperphenylalaninemia and deficiency of monoamine neurotransmitters, SRD is typically associated with normal phenylalanine levels in blood and pterins in urine[2] and not detectable by neonatal screening for phenylketonuria. This implies how important it is to diagnose this condition clinically, in order to provide timely and proper treatment. A summary of the pathophysiology and biochemical pathway is provided by Bonafé et al.[2]

With the following case report and review of 21 published cases,[2–10] we elucidate the clinical features of SRD as well as the diagnostic strategy and therapeutic approach.

CASE REPORT We present a 5-month-old girl, the first and only child born to consanguineous Turkish parents. The parents described the girl's abnormal movements at 3 months of age as sudden stiffening of the whole body, extension of the extremities, upward gaze, and chewing movements lasting for several minutes often after meals, which we also could observe during her hospital stay. Pregnancy and delivery were uneventful. Birthweight, length, and head circumference were within normal ranges. During EEG, a few episodes with chewing movements could be recorded, but no epileptic discharges were evident. The brain MRI was unremarkable. We suspected gastroesophageal reflux and started therapy with omeprazole. The parents reported that the episodes diminished.

At 8 months of age, the patient was readmitted because the crises recurred with an increased frequency and duration of up to 25 minutes. During the episodes, the patient revealed circling movements of the hands and rhythmic tremor of the tongue in addition to the previously mentioned symptoms. Remarkably, the symptoms could be interrupted by voluntary movements. For example, the patient could promptly focus and precisely grab an interesting toy. Yet the abnormal movements resumed immediately when the object was taken away. During these episodes the patient stayed fully conscious, but seemed to be mildly disturbed. Interestingly, the episodes became more severe and lasted longer when the child had an infection or was under emotional stress.

Extensive diagnostic workup revealed an abnormal CSF neurotransmitter pattern with elevated levels of sepiapterin, 15.1 nmol/L (normal range: not detectable), and total biopterin 74 nmol/L (10–50 nmol/L), and low levels of 5-hydroxyindolacetic acid, 10.3 nmol/L (114–336 nmol/L), and homovanillic acid, 84 nmol/L (295–932 nmol/L), indicating a SRD. This could be confirmed by functional enzymatic fibroblast analysis in which the activity of sepiapterin reductase was not detectable (<0.1, normal range 99–185 μU/mg protein). Mutation analysis revealed a novel homozygous mutation in the *SPR* gene allele p.R219X in exon 3 (c.655C>T), resulting in an early stop codon, probably causing an inactive enzyme. In both parents, a heterozygote mutation was confirmed. They are related in both maternal and paternal lines, being concurrently first- and second-degree cousins.

The parents agreed to the patient's treatment at the age of 11 months. We started therapy with L-dopa/benserazide (3.2 mg/kg/day) and 5-hydroxytryptophan (3 mg/kg/day), per os 4 times daily, which resulted in a complete cessation of the episodes 3 weeks after starting therapy. Our patient tolerated the therapy very well and never had any side effects. In the long term the administration 4 times daily was hardly feasible and resulted in sleeping problems and substantial stress to both the child and the parents. Therefore, we extended the ad-

From the Division of Pediatric Neurology and Developmental Medicine (P.D., M.W., P.W.) and Division of Pediatric Emergency Medicine (A.S.), University Children's Hospital, Basel; Division of Clinical Chemistry and Biochemistry (B.T., N.B.), University Children's Hospital, Zurich; Zurich Center for Integrative Human Physiology (ZIHP) (B.T., N.B.), Zurich; and Research Center for Children (RCC) (B.T., N.B.), Zurich, Switzerland.
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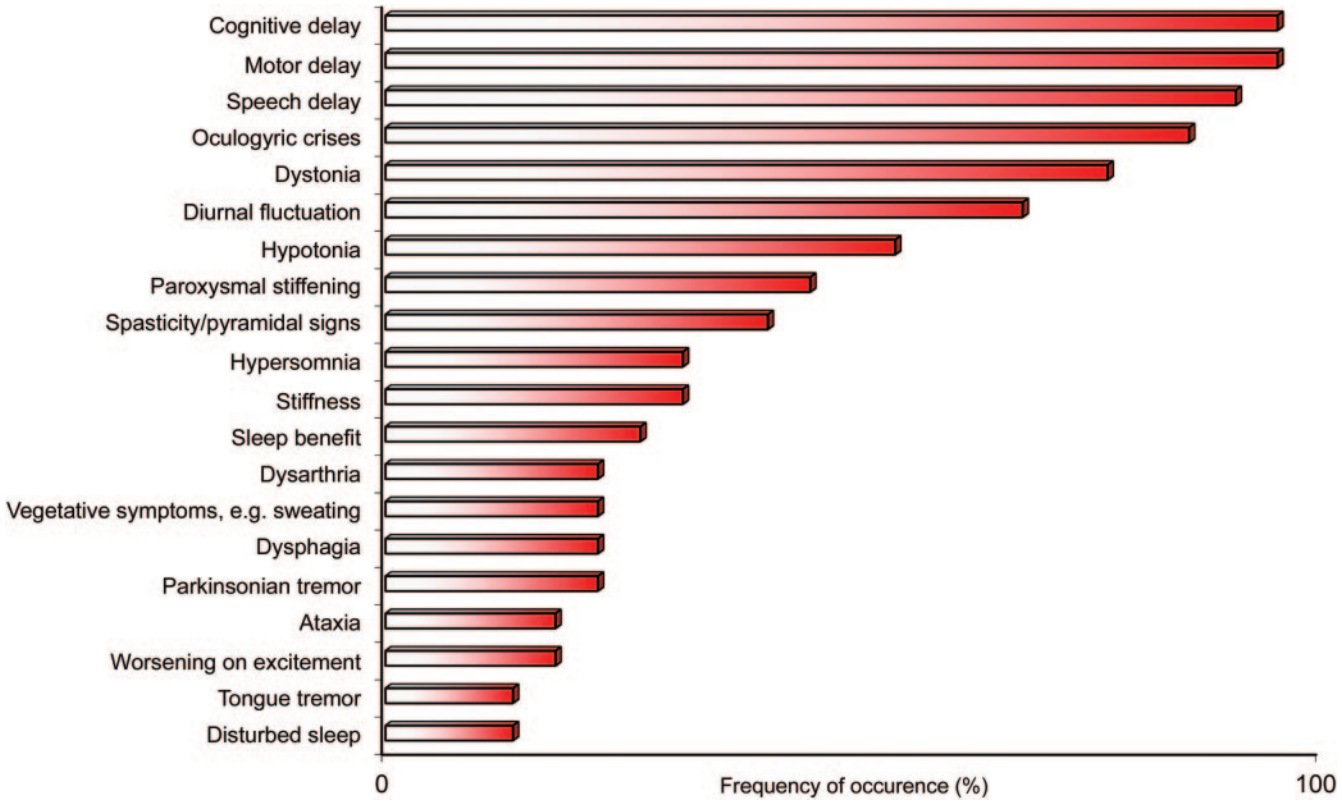
Figure 1 Summary of reported symptoms in patients with sepiapterin reductase deficiency in 22 cases,[2-10] sorted by frequency of occurrence (%)



ministration to 3 times per day, at the age of 17 months, without any problems.

To date, our patient is developing within the normal range. At the age of 21 months, our patient has become a vivid girl with a strong will, who is very clingy to her mother. Worth mentioning are rather sweaty hands and feet, drooling, especially when the girl is focused, and behavioral issues with a tendency toward hyperactivity and distractibility.

DISCUSSION AND REVIEW

Diagnostic workup. The diagnosis of SRD is straightforward via CSF analysis, showing a specific pattern: the levels of the pterins, in particular sepiapterin, are elevated,[1] whereas the 5-hydroxyindolacetic acid and homovanillic acid concentrations are extremely low. This is a consistent finding,[2–5] also in our case.

Additional fibroblast analysis confirms the enzymatic inactivity of sepiapterin reductase.[4] Mutation analysis of the patient and parents is helpful for genetic counseling.

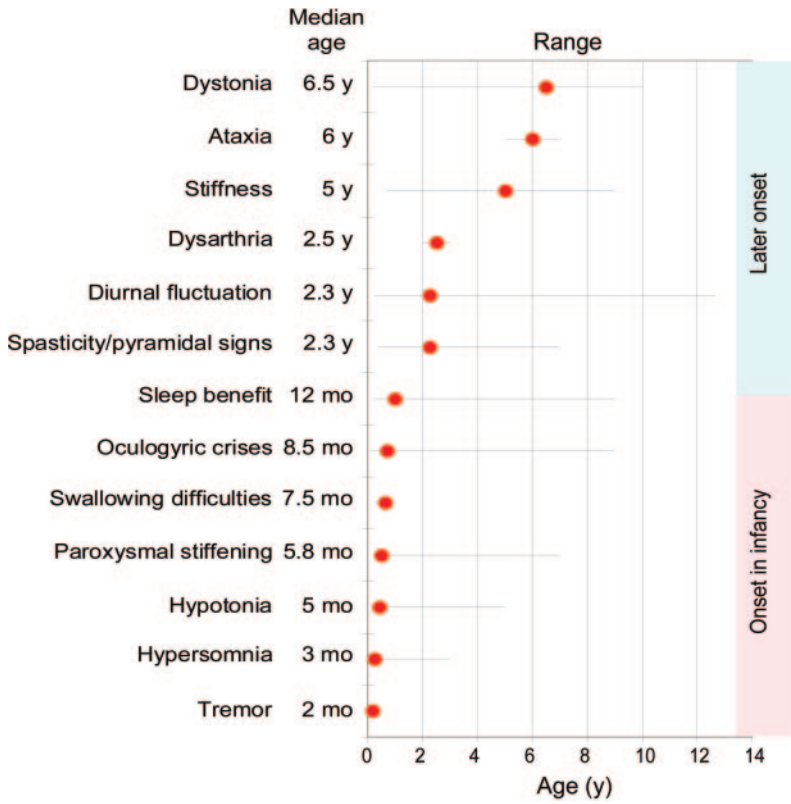
Symptoms. Data were available in all cases. SRD causes symptoms which are related to a disturbed dopamine and serotonin metabolism such as dystonia, speech problems, hypersomnia, and neurocognitive deficits. The spectrum of symptoms is listed in figure 1.

Particular symptoms seem to be age specific. The triad upward gaze (often described as oculogyric crises in previous reports), paroxysmal stiffening, and hypotonia tend to occur early in infancy as one of the first symptoms, which was also the case in our patient, and should be defined as early clinical hallmarks of SRD. Other symptoms requiring higher motor skills and coordination, such as ataxia and dysarthria, can be seen in later course. In adolescents and adults, hypersomnia seems to be one of the main complaints, next to dystonia.[5,6] Figure 2 summarizes the age-related clinical hallmarks of SRD.

One interesting finding, which has not been reported previously, was the interruptability of the symptoms by voluntary movements. This phenomenon can perhaps be explained by the fact that the girl was still young and probably did not yet have significant neuronal damage. We do not have an explanation why, in a few cases, some symptoms like oculogyric crises disappear spontaneously in later course.[4,7]

Therapy. The therapy strategy is straightforward by substituting both precursor substances L-dopa and 5-hydroxytryptophan, enabling a normalization of the CSF profile.

Figure 2 Age-related symptoms in patients with sepiapterin reductase deficiency



Data were available in 20 cases, including our case. In 9/20 cases, a combination therapy with L-dopa/carbidopa or benserazide (median 5 mg/kg/day, range 1.45–20 mg/kg/day) and 5-hydroxytryptophan (median 2.5, range 0.75–16 mg/kg/day) was administered. Eleven of 20 patients were treated with L-dopa/carbidopa (median 2 mg/kg/day, range 0.65–5.9 mg/kg/day) alone. The frequency of application was 2–5 times daily. Rarely, other substances were administered, such as selegiline and sertraline.[2,4] Hypersomnia was treated well with melatonin in one case.[4]

Clinically the therapy provides a significant and rapid improvement (within hours) of the motor deficits, in some cases enabling immediate sitting, walking, and talking in patients who were not able to stand independently and speak more than a single word before treatment.[3,7,8] Fourteen of 20 cases showed partial improvement of motor symptoms, whereas 6/20 cases could achieve a normalization of motor skills. Unfortunately, there are dosage-dependent side effects such as facial and limb dyskinesias which were observed in 5/20 cases and chorea in one case, especially when the dosage of L-dopa was elevated too fast.[7,9] In one case, L-dopa had to be discontinued due to transaminase elevations.[4] Severe vomiting occurred in 2/8 cases with 5-hydroxytryptophan.[2]

The combination therapy is assumed to be the optimal therapeutic strategy, but it has to be noted, especially since 5-hydroxytryptophan is not available everywhere.

Most patients seem to respond to a combination therapy with L-dopa and 5-hydroxytryptophan. Since some patients might easily get side effects, we recommend a very low starting dosage of about 0.5 to 2 mg/kg/day. Because of the short half-life period of L-dopa, the ideal application rate would be at least 3 times daily. For follow-up the analysis of prolactin levels in serum has shown to be a useful surrogate parameter for dopamine metabolism, if it was elevated prior to therapy.[4,8]

Neurodevelopmental outcome. To date, our patient is developing well within normal range. Though we observe a certain hyperactivity and distractibility, at this time it is very difficult to interpret and too early to try to define the neuropsychological profile of affected individuals.

In 18/21 previously reported cases, treatment with L-dopa alone or with 5-hydroxytryptophan did not have any significant influence on cognitive performance.[2–10] The cognitive impairment ranges were defined as mild to severe, with an IQ ranging between 36 and 60 in 4 tested cases.[4,8,10] There are only 2 patients who received treatment under 1 year of age. The first patient from Malta did not show an improvement in cognitive performance.[7] For the other patient from India there were no data regarding the cognitive outcome.[10] Three of 21 cases, 2 Greek siblings[3] and 1 Dutch patient,[9] had minor cognitive delay prior to treatment with L-dopa and were able to attend normal school in later course upon treatment.[3]

SRD shows specific clinical findings which may present in infancy as the triad of paroxysmal stiffening, upward gaze, and hypotonia. Later, childhood and adulthood dystonia with hypersomnia and ataxia may be striking. A combination therapy with L-dopa and 5-hydroxytryptophan improves the motor symptoms significantly in the majority of cases. The cognitive skills seem to be less influenceable if the patients already show significant neurocognitive impairment.

This highlights the importance of early diagnosis and treatment of this disorder as there is a chance of a normal developmental outcome.

AUTHOR CONTRIBUTIONS

Dr. Dill: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data. Dr. Wagner: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data. Dr. Somerville: study concept or design, analysis or interpretation of data, acquisition of data. Dr. Thöny: analysis or interpretation of data, contribution of vital reagents/tools/patients, acquisition of data, study su-

pervision. Dr. Blau: drafting/revising the manuscript, study concept or design, analysis or interpretation of data. Dr. Weber: drafting/revising the manuscript, study concept or design, analysis or interpretation of data.

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DISCLOSURE

Dr. Dill, Dr. Wagner, Dr. Somerville, and Dr. Thöny report no disclosures. Dr. Blau serves on a scientific advisory board for and receives research support from Merck Serono and serves on the editorial board of *Molecular Genetics and Metabolism* and as Communicating Editor for the *Journal of Inherited Metabolic Diseases*. Dr. Weber serves on a scientific advisory board for Eli Lilly and Company; has received funding for travel or speaker honoraria from Eli Lilly and Company and Pfizer Inc; serves on the editorial boards of *Ars medica* and *Pädiatrie*; and receives research support from Mepha (Teva Pharmaceutical Industries, Ltd.), Swiss National Foundation, Marie-Anna-Stfitung, and Stiftung für das kranke kind.

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Child Neurology: A case illustrating the role of imaging in evaluation of sudden infant death

Sarah M. Kranick, MD
Jaya Ganesh, MD
Curtis R. Coughlin II, MS
Daniel J. Licht, MD

Address correspondence and reprint requests to Dr. Sarah Kranick, Human Motor Control Section, National Institute of Neurological Disorders and Stroke, NIH, Bldg. 10, Rm. 7D42, 10 Center Dr., MSC 1428, Bethesda, MD 20892
mattes1@mail.nih.gov

A previously healthy 5-month-old girl was found face down on the bed by her grandmother. Two hours earlier she had acted normally and was placed on her back to nap. She was found to be apneic and pulseless by Emergency Medical Services and regained a pulse after 45 minutes of cardiopulmonary resuscitation.

She was born full-term via spontaneous vaginal delivery to a 30-year-old gravida 1 para 1. Her newborn screen was normal. By maternal report, she was meeting milestones. She had no recent infections and immunizations were up to date. She was breastfed exclusively. Her only medication was Poly-Vi-Sol with iron. There were no smokers or pets in her household. The parents were a mixed race (Asian/Caucasian) couple with no family history of cardiac or neurologic disease or sudden death.

Physical examination revealed reactive pupils but absent oculocephalic and corneal reflexes, gag, and cough. There was no withdrawal from pain or purposeful movement. She was not dysmorphic. Her liver was percussed 4 cm below the costal margin. A dilated ophthalmoscopic examination showed trace optic nerve head pallor but no other abnormality.

DIFFERENTIAL DIAGNOSIS The differential diagnosis of a prolonged arrest in an infant includes respiratory, cardiac, infectious, neurologic, metabolic, and traumatic events. Cultures must be obtained for sepsis or meningoencephalitis. Cardiac conduction anomalies may be detected on EKG, although paroxysmal arrhythmias would not necessarily be detected after the event. While familial arrhythmia syndromes such as long-QT syndrome or Wolff-Parkinson-White syndrome may be revealed by family history, sudden cardiac death in children may also be due to sporadic mutations in cardiac ion channel genes and provoked by fever, as in Brugada syndrome. Structural heart disease, leading to apnea or embolism, can be evaluated by echocardiography. Metabolic or neuromuscular diseases causing respiratory distress may be associated with dysmorphisms, hypotonia, hypoglycemia, metabolic acidosis, ketosis, or hyperammonemia; evaluation should include serum amino acids, urine organic acids, and lactate and pyruvate levels. The newborn screen must be reviewed for inborn errors of metabolism; although not tested in all states, fatty acid oxidation disorders such as very-long-chain acyl-coA dehydrogenase deficiency can present with sudden death when cardiac energy metabolism becomes impaired (Pennsylvania screening information: www.perkinelmergenetics.com/newbornscreening.htm). Toxic screens are warranted even without a known ingestion. While status epilepticus may not be seen on EEG if extensive damage has occurred, neuroimaging may show underlying pathology provoking a seizure, such as strokes or hemorrhages, tumors, or traumatic brain injury. Nonaccidental trauma or smothering (unintentional or intentional) must be suspected in any sudden infant death.

CASE: MEDICAL AND PATHOLOGIC EVALUATION Initial noncontrast head CT showed subtle midbrain hypodensities (figure). Laboratory studies revealed initial arterial pH of 7.03, arterial lactate of 4.2 mg/dL, and albumin of 2.9 mg/dL (norms: lactate 0.5–1.6 mmol/L; albumin 3.1–4.2 g/dL). The initial arterial lactate improved to 1.9 mg/dL prior to the lumbar puncture. CSF showed 8 white blood cells (47% monocytes, 33% lymphocytes), 2 red blood cells, protein 94 mg/dL, glucose 43 mg/dL (serum glucose 61 mg/dL), lactate 2.4 mmol/L (norms: CSF protein 15–40 mg/dL, glucose 32–82 mg/dL or 60% of serum, lactate 0.7–2.0 mmol/L; CSF leukocytes >6/mL is considered abnormal in children older than 3 months[1]). Serum ammonia was 13 μmol/L (norm: 9–33 μmol/L). Blood, urine, and CSF cultures showed no growth. CSF herpes simplex virus and enterovirus PCRs were negative. Serum and urine drug screens were negative for acetaminophen, salicylates, tricyclic antidepressants, ethyl alcohol, cannabinoids, opiates, cocaine, benzodiazepines, barbiturate, amphetamines, phencyclidine, and methadone. Her serum amino acids, urine organic

From the Department of Neurology (S.M.K.), Hospital of the University of Pennsylvania, Philadelphia; Section of Biochemical Genetics (J.G., C.R.C.), Division of Child Development, and Division of Neurology (D.J.L.), Children's Hospital of Philadelphia, PA.

Disclosure: Author disclosures are provided at the end of the article.

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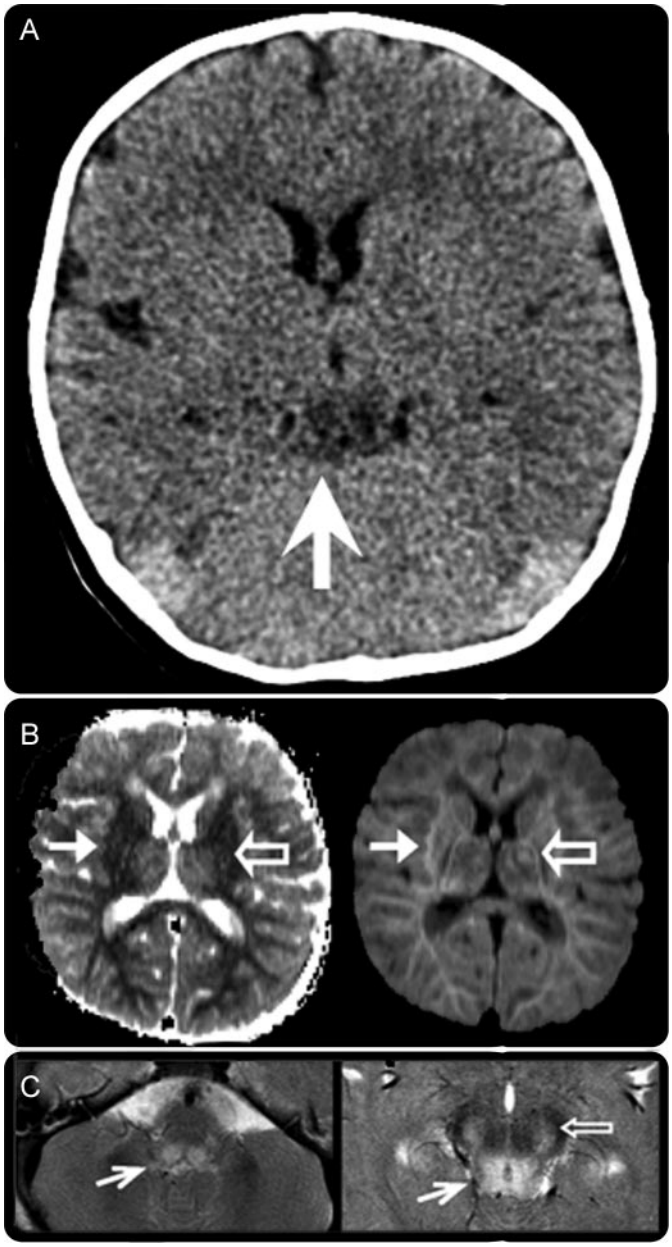
Figure Neuroimaging depicting lesions of different ages



Initial head CT showing hypodensities in the midbrain (white arrow, A). MRI of the brain showing an area of restricted diffusion in the left thalamus (open arrow, right panel, B) not correlating to the apparent diffusion coefficient map (open arrow, left panel, B), implying that this is an older lesion than the acute diffusion-restricting infarcts seen throughout the white matter (white arrows, B). Also seen are T2 hyperintensities in the dorsal midbrain (white arrow, left panel, C), periaqueductal grey matter (white arrow, right panel, C), and substantia nigra (open arrow, C).

acids, and acylcarnitine profile were all normal. Urine ketones were negative.

Her initial EEG was flat with gradual return of some continuous activity over 48 hours. EKG showed no conduction defects and echocardiography revealed a structurally and functionally normal heart. Abdominal ultrasound revealed normal hepatic echotexture.

In addition to the extensive white matter infarcts typically seen after prolonged arrest, her brain MRI performed 3 days after her arrest also revealed infarcts of various ages in the left thalamus and the dorsal brainstem suspicious for a mitochondrial cytopathy (figure). A muscle biopsy was performed. Mitochondrial enzyme activities were within normal range. Quantitative mitochondrial DNA analysis showed a reduced amount of DNA, but the degree of reduction was not sufficient to diagnose a primary mitochondrial depletion syndrome (mtDNA sequencing, MitoMet oligo aCGH: Baylor College of Medicine; quantitative PCR, mitochondrial enzyme activities: Columbia University). Her parents decided to withdraw care, and her heart stopped beating shortly after extubation.

DISCUSSION In the evaluation of an infant who has had a prolonged arrest, neurologists are frequently consulted. Determining the etiology is of critical importance given the risk to future siblings if there is genetically inherited disease or child abuse. The diagnosis of sudden infant death syndrome (SIDS) requires other causes to be ruled out; by definition, SIDS is any sudden unexplained death in an infant less than 1 year old, for which no cause can be found, despite thorough history and examination including autopsy and examination of the scene of death.[2] One recent article proposed that the relative risk of recurrent SIDS, reported between 1.7 and 10.1, has been overestimated in part due to flawed investigations into these deaths.[3] Too frequently the diagnosis of SIDS may be made before appropriate evaluations have been completed, and physicians may feel uncomfortable pursuing autopsies if parents object.

While the evaluation of sudden death in an infant requires autopsy, examination of the scene of death, and detailed history, the evaluation of an infant who has been resuscitated after a prolonged arrest is not clearly defined. More has been written on the diagnostic evaluation of an apparent life-threatening event (ALTE), defined as an acute change in breathing that was frightening to the caretaker including some combination of apnea, color change, change in muscle tone, choking, or gagging. While some SIDS deaths are due to respiratory causes, SIDS and ALTE are differentiated epidemiologically by multiple factors, including the decrease in SIDS, but not ALTE, after the Back to Sleep campaign.[4] The differential diagnosis listed above for prolonged arrest is meant as a guide and is unlikely to be all-encompassing.

While several factors in this case suggested a metabolic disorder, including hepatomegaly, depressed albumin, and elevated lactate, these are nonspecific findings that could follow prolonged arrest. An MRI was obtained not because of any protocol necessitat-

ing neuroimaging after prolonged arrest, but because the family felt that they needed to see more evidence of brain damage before considering withdrawal of care. While profound hypoxia can produce ischemic lesions such as these, the varying ages of the diffusion-weighted imaging abnormalities in this case raised the suspicion of a mitochondrionopathy, especially given the location of these lesions in the dorsal brainstem and periaqueductal gray matter and that hypodensities were seen in the midbrain on CT on arrival.[5]

If resuscitation efforts had failed in our patient, she may have been classified as SIDS. She was found in the prone position, the most significant risk factor for SIDS, although she did not have other risk factors, such as male gender, African American or Native American race, prematurity, or exposure to secondhand smoke.[6] In this case, an MRI that was intended to be prognostic actually widened the differential diagnosis, which had significant implications for genetic counseling. Parents should be informed that the risk of future children being affected, even when a specific genetic or metabolic cause has not been identified, is small but not trivial. This case illustrates that while the evaluation of an infant after prolonged arrest varies widely between institutions and from case to case, there may be a role for neuroimaging.

DISCLOSURE

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RESIDENT & FELLOW SECTION

Section Editor
Mitchell S.V. Elkind, MD, MS

Child Neurology: A case of PMM2-CDG (CDG 1a) presenting with unusual eye movements

Rohini Coorg, MD
Timothy E. Lotze, MD

Correspondence & reprint requests to Dr. Lotze: telotze@texaschildrens.org

Congenital disorders of glycosylation encompass a group of diseases resulting from abnormal protein glycosylation. This group includes more than 20 described diseases.[1] PMM2-CDG, previously referred to as congenital disorder of glycosylation type 1a (CDG 1a), is the most common of the congenital disorders of glycosylation. PMM2-CDG is associated with autosomal recessive inheritance of a mutation in the *PMM2* gene. This mutation causes a deficiency of phosphomannomutase, an enzyme coded by *PMM2*, and results in decreased GDP-mannose production, abnormal glycosylation of N-linked oligosaccharides, and clinical manifestations.

Classically, PMM2-CDG presents in infancy with hypotonia, abnormal fat distribution (accumulation in the buttocks and suprapubic areas), inverted nipples, developmental delay, feeding difficulties, failure to thrive, and esotropia. Infants with PMM2-CDG may have severe multisystemic involvement with up to a 20% mortality rate, but a nonfatal neurologic form has also been observed.[2] Currently, more than 100 different mutations in *PMM2* have been described and may impact the clinical phenotype.[3] We present a patient diagnosed with PMM2-CDG just prior to 4 years of life with primarily neurologic symptoms.

CLINICAL CASE Our patient was born at 37 weeks via spontaneous vaginal delivery with no reported complications. Mother reported normal fetal movement. Birthweight was 4,300 g (97th percentile), length was 48 cm (50th percentile), and head circumference was 34.5 cm (50th percentile). During the newborn period, our patient had a short period of feeding difficulty involving gagging and spitting up which seemed to improve after changing formulas.

Within the first 2 weeks of life, she was observed to have daily episodes consisting of conjugate upward eye movements accompanied with neck extension. At 4 months, she was noted to have jerky eye movements while tracking objects and a resting downbeat nystagmus was observed around 6 months of age. She otherwise continued to have full range of motion in her extraocular muscles. Her episodes of upward gaze resolved around 1 year of age, at which time the parents began observing inward deviation of each eye separately. This failed to correct with patched eye treatment over 6 months.

In addition, she was noted to be hypotonic since infancy. She had difficulty with lifting her head during the first year of life which gradually improved during her second year of life. She first sat unsupported at 13 months and ambulated with assistance at 3 years of age. Her parents felt she had trouble walking due to clumsy and ataxic movements since 31 months of age. By 4 years of age, her receptive language was at age-expected levels, but her expressive language scores were at a 24- to 30-month age level with only 50% of her speech intelligible. She had no history of language or motor regression. The family was not consanguineous and there were no members with known childhood disability, weakness, or similar neurologic disease. A maternal aunt and her son were reported to have juvenile onset epilepsy.

EXAMINATION Physical examination at 45 months of life revealed height and weight to be in the ninth percentile and head circumference was near the fifth percentile. Previously at 30 months, height and weight were at the 15th percentile and head circumference was measured at the 25th percentile, suggesting suboptimal head growth. General examination was unrevealing with no dysmorphology. Neurologic examination revealed a friendly and interactive youngster who was alert and attentive. She played with her dolls during examination. Cranial nerve examination was significant for impaired smooth pursuit and impaired optokinetic nystagmus in vertical and horizontal planes. She had lateral end gaze horizontal nystagmus and bilateral esotropia (video 1 on the *Neurology*® Web site at www.neurology.org). She had mild decreased proximal tone and marked distal hypotonia. She had normal muscle bulk and

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From the University of California at Irvine, Orange.

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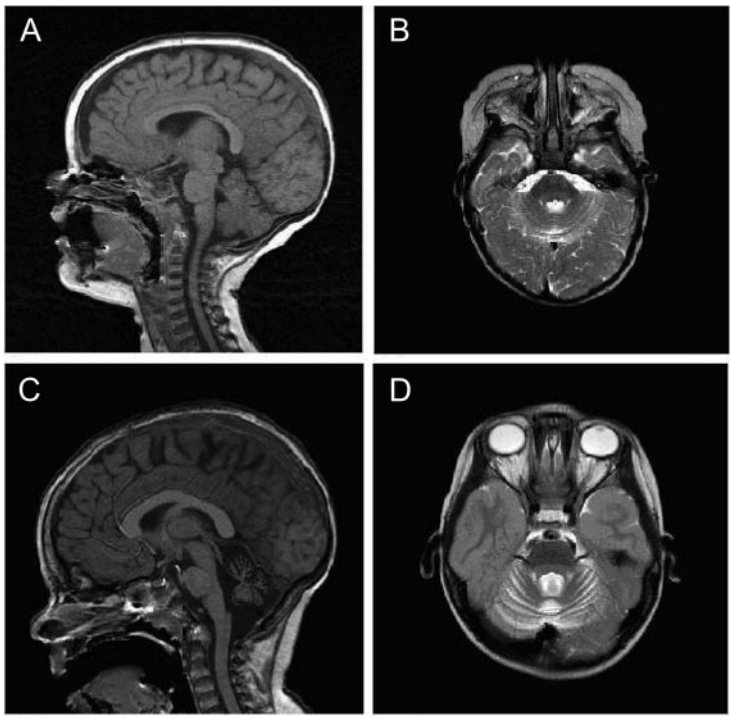
Figure MRI brain



MRI brain with/without contrast at 9 months of age shows slight prominence of cerebellar sulci: (A) sagittal T1, (B) axial T2. Repeat MRI brain at 38 months shows moderate to severe diffuse cerebellar atrophy: (C) sagittal T1, (D) axial T2.

strength. Deep tendon reflexes were normal with downgoing toes bilaterally. She was observed to have truncal titubation while sitting independently, and was dysmetric when reaching for objects bilaterally. Gait was ataxic and broad-based with hyperextension at her knees. She required assistance by her mother, who held her as she walked.

DIAGNOSTIC WORKUP Extensive workup revealed normal complete blood count, chemistry panel, and liver enzymes. Metabolic studies to include ammonia, lactate, plasma amino acids, urine organic acids, acylcarnitine profile, and alpha fetoprotein were normal. Chromosomal microarray (Oligo V8.1) showed no abnormalities. Methylation and DNA sequencing for Angelman syndrome were normal. CSF amino acids and neurotransmitter metabolites were normal. EEG was normal at 10 months in awake and sleep states. MRI of the brain with and without contrast was performed at 9 months of age and showed a slight nonspecific prominence of the cerebral and cerebellar sulci but was otherwise unremarkable. Repeat MRI of the brain performed at 38 months of age showed moderate to severe diffuse cerebellar atrophy with increased T2 hyperintense signal in the cerebellar folia (figure).

Based on MRI findings, a comprehensive spinal cerebellar ataxia panel was obtained and was normal. Testing for Niemann-Pick type C was also negative. Carbohydrate-deficient transferrin panel showed elevated aglycosylated and monoglycosylated transferrins. (Mono-oligosaccharide/di-oligosaccharide transferrin ratio was 0.172 μmol/L, normal range 0–0.100 and a-oligo-/di-oligo-transferrin ratio was 0.082 μmol/L, normal range 0.00–0.05.) N-glycan structural analysis showed small amounts of mannose deficient glycans. *PMM2* gene sequencing resulted in detection of 2 heterozygous missense mutations, c.359T>C (p.I120T) and c.682G>T (p.G228C), and confirmed the diagnosis of PMM2-CDG. Both mother and father were found to be carriers of each mutation.

DISCUSSION Our case demonstrates a typical neurologic presentation of a girl with PMM2-CDG with initial clinical findings of ocular motor abnormalities and hypotonia. Ocular motor findings were also first seen in a 10-month-old boy with PMM2-CDG and cerebellar hypoplasia.[4] He first presented with an ocular motor apraxia, described as jerky, conjugate oscillations of his eyes with awakening or startle. He also had difficulty with initiating voluntary horizontal saccades. It was postulated his eye movements may reflect the diffuse cerebellar hypoplasia seen in PMM2-CDG. Unlike our patient, he was also found to have inverted nipples and abnormal fat distribution.

Three stages of PMM2-CDG have been described: an early infantile stage, late infantile (childhood ataxia-intellectual disability) stage, and adult stable disability stage.[5] The infantile stage contains 2 forms. A well-known multisystem form exists which may include findings illustrated above with the addition of feeding problems, vomiting, diarrhea, failure to thrive, liver or kidney dysfunction, microcephaly, and developmental delay.[6] Within the infantile stage, a second nonfatal neurologic form has also been described with predominant symptoms of hypotonia, strabismus, ataxia, and psychomotor retardation.[2]

The late infantile stage occurs between 3 and 10 years with continued hypotonia, ataxia, delayed language and motor skills, seizures, transient loss of function or stroke-like episodes, retinitis pigmentosa, contractures, and skeletal deformities. Ataxia may initially be progressive and correspond to increasing cerebellar atrophy but may stabilize in early childhood. Additionally, acquired microcephaly may occur.[6] In the adult stage, patients have been described to have stable cognitive ability, skeletal deformities, coagulopathy, osteopenia, premature aging, and peripheral neuropathy. Also, endocrine abnormalities may occur such as hyperprolactinemia, insulin resistance, and failure to develop secondary sexual charac-

teristics.[5] Finally, many patients with PMM2-CDG may become myopic, with half of a genetically homogenous group of patients observed to show signs of retinal degeneration.[7]

Congenital disorders of glycosylation should be suspected based on the presence of any of the above clinical findings, especially in the absence of a known underlying diagnosis. In addition to diffuse cerebellar hypoplasia or atrophy, an enlarged cisterna magna or superior cerebellar cistern may be present on MRI of the brain. Like our patient, cerebellar atrophy may worsen during early childhood but usually stabilizes.[5] Isoelectric focusing of transferrin can show abnormalities in glycosylation and distinguish between types I and II. For example, as in our patient, isoelectric focusing in type I CDG shows an increase in di- or asialotransferrin, reflecting a defect in glycan assembly or transfer. Conversely, type II CDG involves a processing defect and would show increased tri-, dri-, mono-, or asialotransferrin on isoelectric focusing studies.

Isoelectric focusing of transferrin is also abnormal in galactosemia, fructosemia, and alcoholism. It is important to note that children younger than 1 month with PMM2-CDG may show false-negative results initially and develop abnormal results after up to 2 months.[8] Normalization may occur in adulthood or adolescence.[1,5,8] In PMM2-CDG, *PMM2* gene sequencing is diagnostic and has identified more than 800 patients, but genotype–phenotype relationships are still undergoing investigation.[3] A literature search on PubMed failed to reveal a phenotypic description of our patient's genotype.

Upon diagnosis, our patient was sent for further testing to evaluate for any signs of systemic involvement. Ophthalmology follow-up at 46 months confirmed bilateral partially accommodative esotropia and hyperopic astigmatism. Renal ultrasound was negative for microcystic disease. Echo showed a patent foramen ovalewith left-to-right shunting. Random glucose, coagulation studies, liver function tests, and thyroid panel were normal. At this time, the patient exhibits no signs of hormonal or systemic abnormalities. Our patient's disease appears to be limited to neurologic manifestations and will require ongoing monitoring for evolving complications.

DISCLOSURE

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

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RESIDENT & FELLOW SECTION

Section Editor
Mitchell S.V. Elkind, MD, MS

Clinical Reasoning: A 2-day-old baby girl with encephalopathy and burst suppression on EEG

Radhika Dhamija, MD
Kenneth J. Mack, MD, PhD

Address correspondence and reprint requests to Dr. Radhika Dhamija, Department of Pediatric Neurology, Mayo Building, 16th Floor, Mayo Clinic, 200 First Street SW, Rochester, MN 55905
dhamija.radhika@mayo.edu

SECTION 1

A 2-day-old baby girl was transferred to our facility for evaluation and management of seizures. She was born to nonconsanguineous parents from Somalia at 41⅐ weeks of gestation. The pregnancy was uneventful. The mother was group B streptococcus–positive and was appropriately treated with antibiotics during labor. Labor and vaginal delivery were uncomplicated (no history of prolonged rupture of membranes or birth trauma). The baby's Apgar scores were 9 at 1 and 5 minutes. The baby appeared to be well on the first day of life but began having seizures on the second day.

On presentation to our facility, the patient exhibited rhythmic jerking movements of her extremities, consistent with myoclonic seizures. She also had multiple apneic episodes and was therefore intubated and mechanically ventilated. EEG recording showed an asynchronous burst suppression pattern with occasional generalized epileptiform discharges that were associated with body jerking, consistent with severe encephalopathy with seizures. On general physical examination, she was normocephalic and nondysmorphic. There were no abnormal skin findings and no hepatosplenomegaly. Neurologic examination revealed diffuse hypotonia with symmetrically hypoactive reflexes in all 4 extremities. Bedside funduscopic examination revealed normal Moro; suck and rooting reflexes were poor, but palmar grasp reflex was present bilaterally.

There was no family history of neurologic or metabolic disorders (including seizures).

Questions for consideration:

1. What is the differential diagnosis for neonatal seizures?
2. Does the burst suppression pattern on EEG limit the differential diagnosis?
3. Can this infant's presentation be classified as an epilepsy syndrome?

GO TO SECTION 2

Supplemental data at www.neurology.org

From the Department of Pediatric Neurology, Mayo Clinic, Rochester, MN.
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SECTION 2

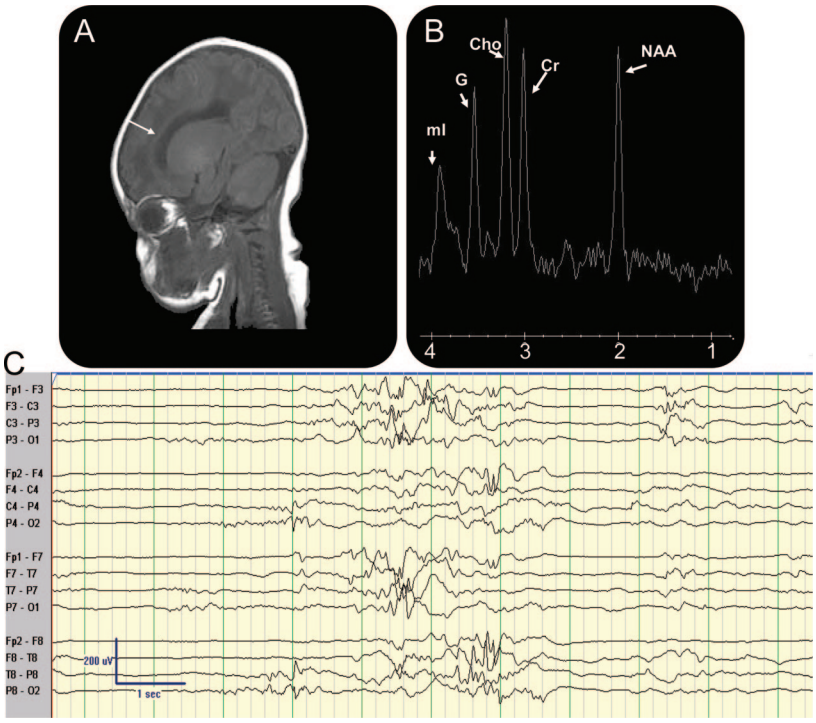
The diagnostic possibilities for neonatal seizures are broad and include common causes such as electrolyte imbalance (hypocalcemia, hypomagnesemia, hyponatremia, or hypoglycemia), hypoxic ischemic encephalopathy, neonatal stroke (ischemic or hemorrhagic), maternal drug withdrawal, benign neonatal seizures, and infectious diseases (e.g., group B streptococcus sepsis or meningitis) and less common but important causes such as metabolic encephalopathies (e.g., mitochondrial disease, organic acid disorders, amino acid disorders, sulfite oxidase deficiency, molybdenum cofactor deficiency, and glucose transporter 1 deficiency), storage diseases (including neuronopathic Gaucher disease, Tay-Sachs disease, and neuronal ceroid lipofuscinosis), CSF tetrahydrobiopterin, folate deficiency, pyridoxine deficiency, and a supratentorial structural lesion (table e-1 on the *Neurology*® Web site at www.neurology.org). The presence of burst suppression on EEG suggests severe encephalopathy and either a significant hypoxic-ischemic insult or a severe metabolic disorder.

The patient's hemoglobin was 15.3 (10–20) g/dL, platelet count was 281 (150–450) × 10^9/L, and leukocyte count was 11.2 (5–20) × 10^9/L. Blood glucose was 102 mg/dL. The patient underwent lumbar puncture for CSF examination; this revealed a white blood cell count of 3 cells/μL, glucose of 54 mg/dL, and protein of 50 mg/dL. Results of blood and CSF cultures were negative. Liver function tests showed that aspartate transaminase, alanine transaminase, and total bilirubin levels within normal limits. Serum ammonia and lactate levels and values for a complete electrolyte panel were normal. Given the initial normal electrolytes and no evidence of hypoxic-ischemic encephalopathy or infection at birth, a metabolic disorder was considered. Urine organic acid levels, serum biotinidase activity, a serum acyl-carnitine panel, a chromosomal microarray, and a serum peroxisomal panel composed of very-long-chain fatty acids, phytanic acid, and pristanic acid were all normal. Serum and CSF amino acid profiles showed markedly elevated glycine, with a CSF/serum ratio of 0.138 (normal <0.03), which was diagnostic for nonketotic hyperglycinemia.

The infant's seizures can be classified as early myoclonic encephalopathy, a symptomatic epilepsy syndrome characterized by seizure onset between birth and the first few weeks of life and burst suppression on EEG. The overall prognosis for this epilepsy syndrome is poor with high mortality in the first few years of life.

Results of a head ultrasound examination were normal. MRI of the brain without gadolinium done at day 3 of life showed agenesis of the corpus callosum and an immature sulcation pattern. There was no evidence of hypoxic-ischemic injury on diffusion-weighted imaging or any evidence of intracranial hemorrhage. Magnetic resonance spectroscopy revealed no elevation of brain lactate or *N*-acetylaspartate and normal creatine but showed an elevated glycine peak (figure).

Figure Brain imaging



(A) MRI (T1 sagittal) shows agenesis of corpus callosum (arrow). (B) Magnetic resonance spectroscopy shows a glycine peak (G), *N*-acetylaspartate (NAA), choline (Cho), creatine (Cr), and myoinositol (mI). (C) EEG shows burst suppression.

Questions for consideration:

1. What are the medications used to treat this condition?
2. Which specific antiepileptic medications should be avoided in this condition?
3. What is the overall prognosis?

GO TO SECTION 3

SECTION 3

The elevated ratio of CSF to serum glycine (>0.08) confirms the diagnosis of nonketotic hyperglycinemia (NKH). Patients with atypical NKH can have ratios between 0.03 and 0.08. A liver biopsy was not performed in our patient for confirmatory enzymatic analysis because the parents did not consent. Our patient's seizures were initially controlled with IV phenobarbital but then recurred. A ketamine (NMDA receptor antagonist) drip and sodium benzoate (an agent that binds excessive glycine in the CSF) were started, which resulted in control of seizures. High doses of sodium benzoate can lower the serum carnitine concentration and thus blood levels of carnitine should be measured and supplemented accordingly.

She was weaned off phenobarbital, given its potential to cause respiratory suppression, and transitioned to topiramate. She was slowly weaned off mechanical ventilation. A gastric tube was placed, given her continued poor feeding.

Valproate should be avoided in infants with NKH because it increases blood and CSF glycine concentrations by further inhibiting the glycine cleavage enzyme and increases seizure frequency.[1] As a general rule, valproate should not be used in any child with an undiagnosed suspected metabolic disorder because it can worsen seizures due to urea cycle disorders, fatty acid oxidation defects, and mitochondrial disorders. Given the higher likelihood of a metabolic disorder being the underlying cause of seizures in younger children, valproate is typically avoided in children younger than 2 years.

The overall prognosis for NKH is dismal. Most patients die in infancy of central apnea, if they are not supported by mechanical ventilation. Intractable seizures and feeding problems are common. Those who survive are left with severe intellectual disability.

At the last follow-up at 4 months of age, our patient continues to have diffuse hypotonia, no social smile, and poorly controlled seizures and is dependent on a gastric tube for feeding.

DISCUSSION NKH, also known as glycine encephalopathy, is an autosomal recessive metabolic disorder characterized by the accumulation of glycine in the brain due to a defect in the glycine cleavage enzyme system. The neonatal form presents in the first few days of life with progressive lethargy, hypotonia, hiccups, and seizures, and progresses to central apnea and often death. Surviving infants often have profound developmental delay and intractable seizures. The infantile form presents in the first few months of life and is also characterized by hypotonia, developmental delay, and seizures. An increased CSF glycine level (typically 20–30 times normal) along with an elevated CSF/plasma glycine ratio suggests the diagnosis. Enzymatic confirmation can be done by measurement of glycine cleavage (GCS) enzyme activity in liver obtained by biopsy and is clinically available. The 3 genes known to be associated with NKH are *GLDC* (encoding the P-protein component of the GCS complex, accounting for 70%–75% of disease), *AMT* (encoding the T-protein component of the GCS complex, accounting for ~20% of disease), and *GCSH* (encoding the H-protein component of the GCS complex, accounting for <1% of disease). Mutations associated with residual enzyme activity seem to be associated with a milder outcome and infantile presentation, and 2 mutations with no residual enzyme activity seem to be associated with severe outcome and neonatal onset.[2–4]

The initial EEG typically shows a burst-suppression pattern that evolves into hypsarrhythmia or multifocal spikes over the next few months. MRI can be normal or show agenesis of the corpus callosum. Delayed myelination can be seen later in life. Agenesis of the corpus callosum is not specific and can be seen in various migrational and structural disorders of the CNS (e.g., Dandy-Walker malformation and lipoma of the interhemispheric fissure).[5] Less common findings include retrocerebellar cysts with subsequent hydrocephalus.[6] A glycine peak on magnetic resonance spectroscopy is seen in the most severely affected infants and carries a poor prognosis.

No effective treatment exists for this disorder. Therapy is focused on managing seizures by using sodium benzoate to reduce the plasma concentration of glycine. NMDA receptor antagonists (ketamine, dextromethorphan, felbamate, and topiramate) are also used in this condition.[7]

AUTHOR CONTRIBUTIONS

R.D. provided the study concept or design. R.D. acquired data. R.D. and K.J.M. drafted/revised the manuscript. K.J.M. supervised the study.

DISCLOSURE

Dr. Dhamija reports no disclosures. Dr. Mack serves on the editorial board of *Pediatric Neurology*, *Journal of Child Neurology*, and *Brain and Development* (2006–present) and is Book Review Editor for *Neurology®*.

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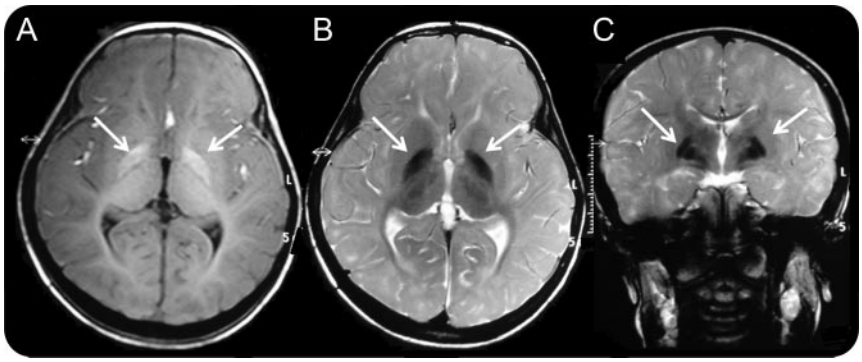
Teaching NeuroImages: Distinct neuroimaging features of fucosidosis

P. Jain, MD
K. Ramesh, MD
A. Mohamed, MD
A. Kumar, MD
S. Gulati, MD

Correspondence & reprint requests to Dr. Gulati: sheffaligulati@gmail.com

Figure Classic MRI findings in fucosidosis



T1-weighted axial (A), T2-weighted axial (B), and coronal (C) MRI of the brain. Bilateral globi pallidi (arrows) show hyperintensity on T1 and marked hypointensity on T2-weighted images. In addition, there is diffuse symmetric hyperintensity of bilateral subcortical and deep white matter on T2-weighted images with normal appearance on T1-weighted image consistent with hypomyelination.

A 5-year-old girl, the product of nonconsanguineous marriage, presented with early-onset intellectual disability and autistic features. There was no regression, seizures, or vision or hearing impairment. She had normal head circumference, coarse facies, angiokeratomas, and lower limb rigidity. She had no cherry-red spot or hepatosplenomegaly. Her 2-year-old brother had similar features with right hemidystonia. The MRI brain findings (figure), positive urine oligosaccharides, and absent α-L-fucosidase activity in plasma and leukocytes confirmed the diagnosis of fucosidosis, an autosomal recessive lysosomal storage disorder with poor cognitive outcome.[1,2] Mucopolysaccharidosis-like phenotype, angiokeratomas, oligosaccharidiuria, and classic MRI findings suggest fucosidosis.

AUTHOR CONTRIBUTIONS

Puneet Jain, Konanki Ramesh, and Akbar Mohamed provided clinical care to the patient and drafted the manuscript. Atin Kumar provided radiologic input. Sheffali Gulati critically reviewed the manuscript.

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From the Division of Pediatric Neurology, Department of Pediatrics (P.J., K.R., A.M., S.G.), and Department of Radio-diagnosis, JPN Apex Trauma Centre (A.K.), All India Institute of Medical Sciences, New Delhi, India.

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Introduction

Pediatric Perspective

By Alonso G. Zea Vera, MD, and Ingo Helbig, MD

Complex and unusual disorders are part of the challenges of child neurology. Pediatric neurogenetics has rapidly advanced in recent decades, and in the following section, we present a series of articles illustrating its evolution. The article by Ghosh et al. reviews one of the most common neurogenetic conditions, neurofibromatosis type I. The authors demonstrate the usefulness of the MRI target sign in a patient with neurofibromatosis type I. This disease was described by von Recklinghausen in 1882, with initial depictions as early as the 13th century. In 1990, more than a hundred years later, the *NF1* gene was finally identified, providing a molecular diagnosis to this common clinical entity.

The first human genome sequencing took 12 years and cost nearly $3 billion. The development of next-generation sequencing resulted in an explosion of gene discoveries in childhood neurologic disorders. The article by Tenney et al. exemplifies this rapid development. The authors present a child with alternating hemiplegia of childhood (AHC) with negative testing for the reported genes at the time of publications in 2010. Only 2 years later, disease-causing variants in *ATP1A3* were identified as the most common genetic etiology in AHC.

Increased genetic testing also resulted in more complexity, including frequent clinical scenarios of genetic heterogeneity, variable expressivity, and pleiotropy. For example, Joubert syndrome, featured in the article by Graber et al., is a condition with more than 30 associated genes. The articles by Abu Libdeh et al. on childhood ataxia and Soni et al. on Waardenburg syndrome type 2 further underscore the importance of these genetic phenomena that are common in child neurology.

Knowledge about the underlying genetic etiologies has already started to guide new therapies. As of 2019, there are 2 FDA-approved medications for spinal muscular atrophy. More gene-based therapies are in the pipeline for rare neurologic disorders in children. With these advances in our diagnosis and management options in neurogenetics, the field may soon be transformed from a primarily diagnostic discipline to a field with promising interventions for conditions that were previously considered untreatable.

From the Department of Neurology (A.G.Z.V.), Cincinnati Children's Hospital Medical Center, OH; and Department of Neurology (I.H.), The Children's Hospital of Philadelphia, PA.
Correspondence Dr. Zea Vera alonso.zeavera@cchmc.org
For disclosures, please contact the *Neurology*® Resident & Fellow Section at rfsection@neurology.org.

Adult Perspective

By Pouya Khankhanian, MD, and Jeffrey Vance, MD, PhD

Neurogenetics is a rapidly growing subspecialty because of the increasing potential to change patients' lives through gene-based therapies. New disorders are being discovered and described monthly. We are also rapidly learning that known deleterious genetic variants can cause a much wider spectrum of phenotypes than we had previously imagined. Identifying genetic disorders can have a profound impact for patients and families. Simply knowing the etiology and mechanism of disease can not only bring peace of mind to patients but can also reduce additional unnecessary testing.

Although approved targeted pharmacologic treatments currently exist for only a small fraction of known neurogenetic disorders, there are many more available today than were available a decade ago, and there will be exponentially more therapies coming through the pipeline in the years to come. As we discover more genetic etiologies, referrals to neurogeneticists will increase. In addition, as more treatments targeted at specific childhood genetic disorders and survival improves to adulthood, the adult neurogeneticist will also see more referrals. Furthermore, as we learn more about the phenotypic spectrum of each genetic disorder and discover milder adult-onset phenotypes, this will also increase referrals to adult neurogenetics. Although not covered in this chapter, research is also making gains on identifying genetic susceptibilities and genetic targets for preventing or slowing common adult disorders such as Alzheimer and Parkinson diseases. Thus, the need for neurogenetics will continue to be a growing subspecialty in neurology.

In this chapter, we review a handful of classic cases of mendelian neurogenetic diseases. This is far from an exhaustive list of neurogenetic disorders, but is intended to be an introduction to the current clinical spectrum of neurogenetics. A Clinical Reasoning case demonstrates the evaluation, diagnosis, and treatment for a patient with a presentation suggestive of an underlying genetic etiology. In particular, we see that the pattern of family history is often very useful in guiding a differential diagnosis, and how options for affordable genetic testing have greatly increased over the past few years, from targeted gene panels and microarrays to whole-genome sequencing. We also feature a few classic cases and images, which demonstrate that specific combinations of phenotypic features can be nearly pathognomonic for some genetic syndromes and also that an accurate diagnosis can aid discussions of prognosis and guide management.

From the Department of Neurology (P.K.), University of Pennsylvania, Philadelphia; and Department of Human Genetics (J.V.), University of Miami, FL.
Correspondence Dr. Khankhanian pouya.khankhanian@uphs.upenn.edu
For disclosures, please contact the *Neurology*® Resident & Fellow Section at rfsection@neurology.org.

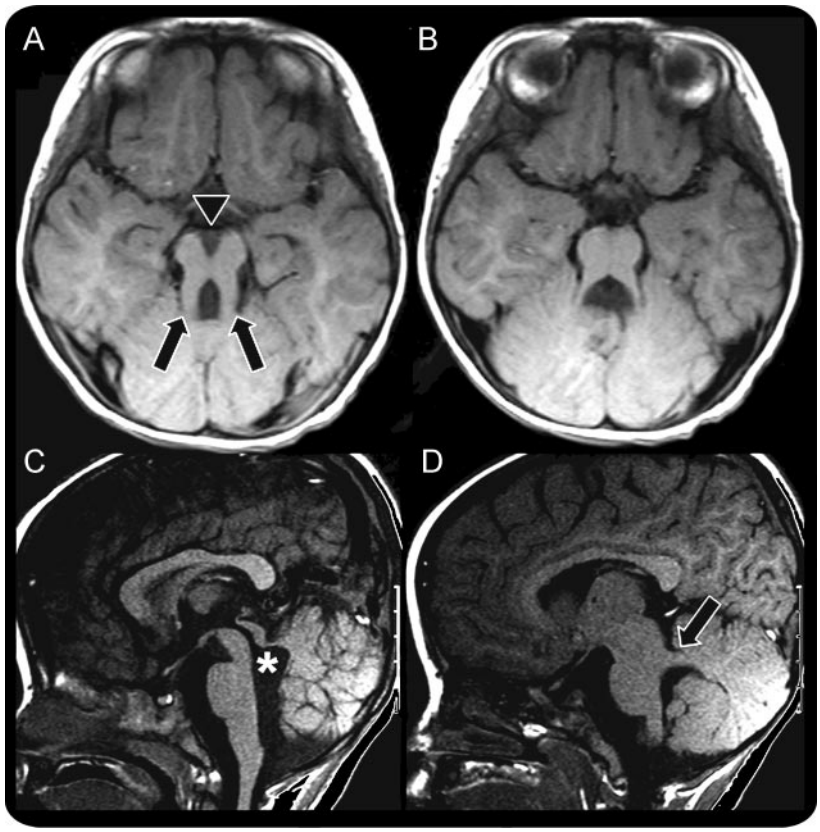
Section Editor
Mitchell S.V. Elkind,
MD, MS

Teaching Neuro*Images*: Molar tooth sign with hypotonia, ataxia, and nystagmus (Joubert syndrome) and hypothyroidism

Jerome J. Graber, MD, MPH
Heather Lau, MD
Swati Sathe, MD

Address correspondence and reprint requests to Dr. Swati Sathe, New York University School of Medicine, Department of Neurology, Division of Neurogenetics, 403 East 34th Street, 2nd Floor, New York, NY 10016
Swati.Sathe@nyumc.org

Figure MRI



Axial (A, B), midsagittal (C), and parasagittal (D) T1-weighted MRI demonstrating deepened interpeduncular fossa (arrowhead, A) and horizontally oriented superior cerebellar peduncles (arrows, A, D) forming the "molar tooth" sign, as well as cerebellar vermis hypoplasia and fourth ventricle enlargement with elevated roof (*, C) and abnormal cerebellar structure (C, D).

A 2-year-old girl with congenital hypothyroidism, diagnosed by neonatal screen, and thyroid dysplasia was referred for developmental delay, hypotonia, ataxia, and nystagmus. She had neonatal episodic hyperpnea and renal cysts. At 3 she understood simple language and signed 6 words. Imaging revealed vermian hypoplasia, the "molar tooth" sign (figure), considered pathognomonic for Joubert syndrome,[1] a heterogeneous group of autosomal recessive disorders linked to several chromosomal loci. Classic features are hypotonia, psychomotor delays, vermian hypoplasia, episodic hyperpnea or apnea, and abnormal eye movement. Joubert variably includes polymicrogyria, retinal, renal, or hepatic abnormalities, as well as polydactyly and orofacial dysmorphisms.[1]

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From the Department of Neurology (J.J.G., H.L.), New York University School of Medicine, New York; and Department of Neurology, Division of Neurogenetics (S.S.), New York University Medical Center, New York, NY.

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RESIDENT & FELLOW SECTION

Section Editor
John J. Millichap, MD

Clinical Reasoning: A 13-year-old boy with chronic ataxia and developmental delay

Amal Abu Libdeh, MBBS
Lauren Talman, MD
Chelsea Chambers, MS, CGC
Radhika Dhamija, MBBS, MD

Correspondence to Dr. Talman: LST8N@hscmail.mcc.virginia.edu

SECTION 1

A 13-year-old boy presented to the neurology clinic for evaluation of ataxia and intellectual disability. He was born at term via vaginal delivery after an uncomplicated pregnancy with no perinatal complications. Newborn screening (Virginia, 2012) was normal. He was first noted to be ataxic at age 6 months (when he began to sit with support) and his symptoms gradually worsened over time. He had global developmental delay. He began to sit at 14 months of age and walked at 20 months. He had his first words around age 2 and received physical and speech therapy early on. He had acute worsening of his symptoms at age 8 months in the setting of a flu-like illness and was admitted to a local hospital. Workup at the time was reportedly unrevealing and included a normal CT and a normal brain MRI with contrast. His ataxia remained fairly stable over time without regression. He had several episodes of acute worsening with febrile illnesses. He continued to have learning problems at school.

His general examination at the time of initial clinic visit was unremarkable. On neurologic examination, he was alert and cooperative. He had dysarthria. He had normal tone and strength with exaggerated muscle stretch reflexes, most notable in the legs. He was observed to have choreoathetoid movements of the face, arms, and legs. He had bilateral dysmetria and dysdiadochokinesia. His gait was unsteady and wide-based.

Questions for consideration:

1. What category of ataxia would you consider in this case?
2. What additional historic details would be important to obtain?

GO TO SECTION 2

From the Department of Neurology, University of Virginia, Charlottesville.

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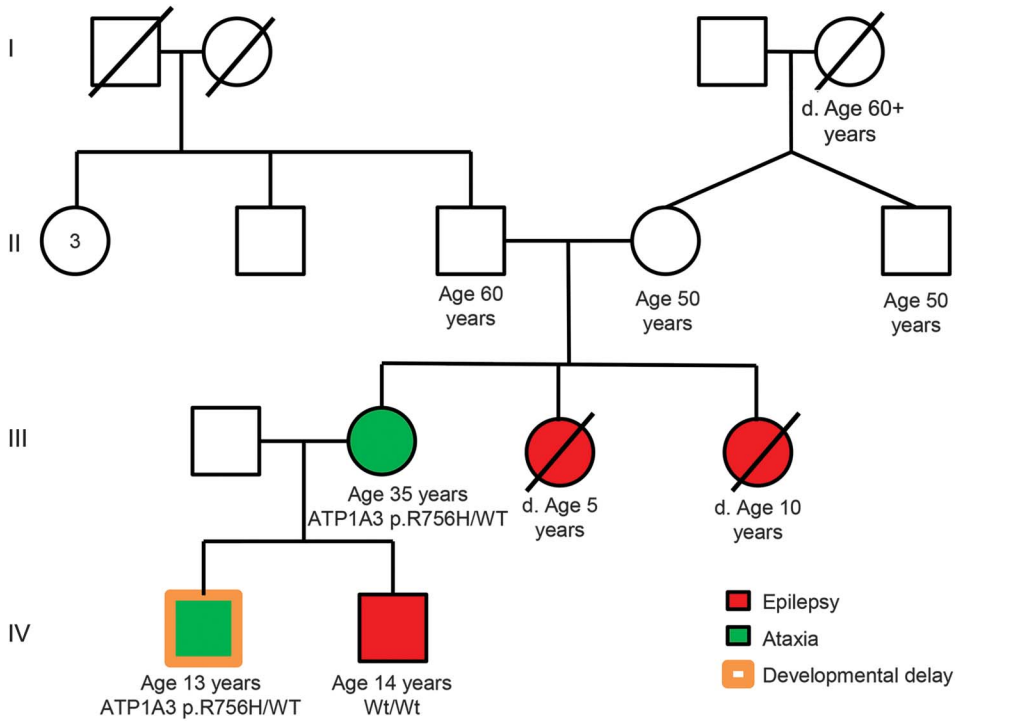
SECTION 2

The patient's presentation is consistent with cerebellar ataxia. Cerebellar ataxias are usually classified based on the duration of symptoms into acute (days), subacute (months), and chronic (years).[1] The most common causes for acute ataxias are toxic (e.g., alcohol ingestion), vascular (e.g., cerebellar hemorrhage or stroke), and infectious etiologies (e.g., varicella). Subacute ataxia usually results from posterior fossa tumors, nutritional deficiencies (e.g., vitamin B12, vitamin E, copper and folate), or autoimmune disorders (e.g., antiglutamic acid decarboxylase). Our patient has chronic ataxia, for which the 2 main categories to consider are hereditary disorders (e.g., spinocerebellar ataxias [SCAs]) and ataxias caused by inborn errors of metabolism (e.g., Refsum disease). Brain MRI, preferably with contrast, is helpful in patients with ataxia.[2] It may show abnormalities in the cerebellum, with or without associated abnormalities in the supratentorial and infratentorial structures, the brainstem (e.g., congenital disorders of glycosylation), or the spinal cord (e.g., Friedreich ataxia). Imaging characteristics can help to narrow the differential diagnosis; for example, contrast enhancement may indicate inflammatory or infective etiologies. Serial imaging is helpful in monitoring changes and detecting new abnormalities. Serial normal imaging could be more suggestive of a genetic disorder such as Rett syndrome.[2] Our patient had a repeat MRI at age 12 that remained unremarkable.

A detailed family history is critical when considering a genetic disorder. Further history obtained for this child revealed that the patient's mother also had ataxia. She initially developed ataxia at age 3 during a febrile illness then had full recovery. The ataxia recurred at age 20 when she was pregnant with her second child (the patient); her symptoms had been slowly progressive since then. She eventually became wheelchair-bound. She was evaluated in the adult neurology clinic, where her examination showed severe truncal and appendicular ataxia, spastic dysarthria, and bilateral dysmetria.

The mother had previously undergone an extensive evaluation including MRI/magnetic resonance angiography of the brain, EMG/nerve conduction studies, muscle biopsy, antineuronal antibody testing, antigliadin and transglutaminase immunoglobulin A and immunoglobulin G, thyroid antibodies, and *CACNA1A* mutation testing for familial hemiplegic migraine. She had an ataxia panel testing for SCAs and episodic ataxia syndromes including SCA1, 2, 3, 6, 7, 8, 10, and 17; dentatorubral-pallidoluysian atrophy; Friedreich ataxia; complete sequence analysis of *APTX* (for ataxia with oculomotor apraxia [AOA]1); *SETX* (for AOA2); *PRKCG* (for SCA14); *SIL1* (for Marinesco-Sjögren syndrome); *TTPA* (for ataxia with vitamin E deficiency); select exon analysis of *POLG1*

Figure **Family pedigree of the patient shows different neurologic presentation in different family members**



Wt = wild-type.

(for 2 mitochondrial recessive ataxia syndrome mutations); *SPBN2* (for 3 known SCA5 mutations); and *KCNC3* (for 2 known SCA13 mutations). All were unrevealing. The patient's 14-year-old brother was diagnosed with generalized epilepsy. He, however, did not have ataxia or developmental delay. Our patient had 2 maternal aunts who died in the first decade of life and had epilepsy. See the pedigree for details (figure).

Questions for consideration:

1. What is your differential diagnosis?
2. What investigations would you order next?

GO TO SECTION 3

SECTION 3

Chronic ataxia with normal MRI raises concern for a genetic disorder, and the family history suggests an inherited syndrome. Based on the family pedigree, the presumed mode of inheritance is autosomal dominant; however, maternally inherited mitochondrial disorders should also be considered. The episodic nature of the symptoms suggests a paroxysmal disorder such as a channelopathy.[3]

Given continued concern for an inherited/genetic disorder, a chromosomal microarray was ordered for our patient and was normal. Whole exome sequencing (WES) was subsequently ordered and showed an *ATP1A3* variant, *c.2267G>A*, *p.R756H* (*NM_152296*), which was maternally inherited. No other variants were noted.

Questions for consideration:

1. What is *ATP1A3*?
2. What are the phenotypes associated with this gene mutation?

GO TO SECTION 4

SECTION 4

The *ATP1A3* gene is located on chromosome 19q13.2 and encodes the α3 subunit of the Na+/K+ transporting ATPase. *ATP1A3* pathogenic variants have been previously associated with rapid-onset dystonia parkinsonism; alternating hemiplegia of childhood; and cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss. More recently, it has been linked to early-onset epileptic encephalopathy and episodic prolonged apnea and to relapsing encephalopathy with cerebellar ataxia.[4] All of these variable phenotypes associated with *ATP1A3* pathogenic variants can occur sporadically as a result of a de novo mutation or can be inherited. Inheritance is autosomal dominant.

The *c.2267G>A*, *p.R756H* (*NM_152296*) variant is located in exon 17 of *ATP1A3.* This alteration results from a G to A substitution at nucleotide position 2267, causing the arginine (A) at the amino acid position 756 to be replaced by a histidine (H). This amino acid change has been observed in affected individuals, including a father and his daughter with rapid-onset dystonia parkinsonism,[5] and a 34-year-old woman with relapsing cerebellar ataxia, generalized dystonia, pyramidal signs, and anger outbursts.[6] Nearby alterations have been reported in patients with alternating hemiplegia of childhood.[7] The alteration cosegregated with disease in the family described here, as it is present in heterozygous form in the patient's mother but not in his father. The altered amino acid is conserved throughout evolution. The alteration is not observed in healthy individuals and is predicted to be deleterious by in silico models. The mutation was therefore determined to be likely pathogenic. The patient's brother was not found to have the same alteration. His epilepsy is likely related to a different etiology.

DISCUSSION This case demonstrates 2 genetic phenomena: variable expressivity and pleiotropy. Variable expressivity measures the extent to which a genotype exhibits its phenotypic expression. The patient and his mother both have ataxia but have differing degrees of severity.

Pleiotropy describes the varying phenotypic traits that can manifest from a single gene mutation.[8] In this case, the same *ATP1A3* gene mutation manifests as ataxia, chorea, and athetosis in the patient and as ataxia in his mother.

There are multiple factors that can lead to pleiotropy and variable expressivity of a phenotype. Perhaps the least understood and most challenging factors to study include environmental and lifestyle factors. Modifier genes, on the other hand, are well-described effectors of phenotype in certain diseases. A modifier gene alters the expression of another gene by influencing transcription of the gene itself or phenotypes at the cellular or organismal level. This can in turn lead to entirely distinct phenotypes as well as varying severity of disease.[8] Modifier genes have been implicated in the phenotypic expression of many neurologic (and non-neurologic) diseases. For example, they are thought to affect severity of renal disease in tuberous sclerosis[9] and café-au-lait macule count in neurofibromatosis type 1.[10] The cause for the phenotypic variance in the case of *ATP1A3* has yet to be studied.

The complexity of genetic inheritance can make diagnosis of a genetic condition challenging, time-consuming, and invasive, as was the case for this patient and his family. WES is a tool that allows for clinicians and researchers alike to solve diagnostic mysteries. In some cases, such as this, WES can be the last available opportunity to provide the patient and family with an answer and arguably should be considered early in the diagnosis process. This testing method not only has allowed for discovery of new diseases but has also defined new phenotypes for a previously described genetic variant. This case provides one example of the many diagnostic odysseys that occur in genetics. Description of this family's phenotypic variants provides evidence to support evaluation for an *ATP1A3* gene mutation in the case of familial cerebellar ataxias.

AUTHOR CONTRIBUTIONS

Dr. Amal Abu Libdeh: chart review, drafting the manuscript, analysis and interpretation of data. Dr. Lauren Talman: chart review, drafting the manuscript, analysis and interpretation of data. Chelsea Chambers: acquisition of data, analysis and interpretation of data. Dr. Radhika Dhamija: acquisition of data, study supervision, and critical revision of the manuscript.

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DISCLOSURE

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

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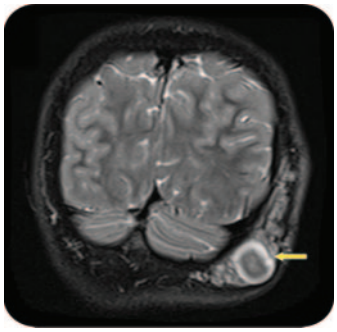
Teaching Neuro*Images*: MRI "target sign" and neurofibromatosis type 1

Partha S. Ghosh, MD
Debabrata Ghosh, MD

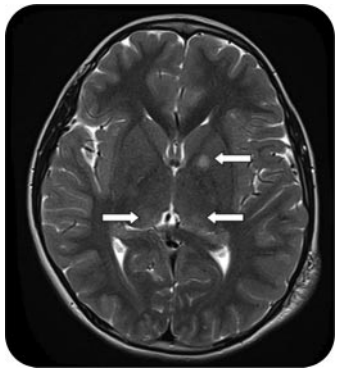
Correspondence & reprint requests to Dr. Partha S. Ghosh: ghoshp3@ccf.org

Figure 1 MRI brain (coronal T2-weighted)



Subcutaneous mass over the left occipito-temporal region with multiple serpiginous lesions and targetoid appearance manifested with peripheral bright and central dark signal (yellow arrow) suggestive of plexiform neurofibroma.

Figure 2 MRI brain (axial T2-weighted)



Hyperintense signals in the left globus pallidus and bilateral posterior aspects of the thalami (white arrows) characteristic of unidentified bright objects seen in neurofibromatosis type 1.

A 9-year-old girl presented with a firm occipital swelling. She had multiple café-au-lait lesions without other clinical features or family history of neurofibromatosis type 1 (NF1). MRI showed subcutaneous soft tissue mass in the left occipito-temporal region with "target sign" suggestive of plexiform neurofibroma (figure 1). There were supra and infratentorial T2-weighted hyperintense lesions, so-called unidentified bright objects characteristic of NF1 (figure 2). MRI target sign helped to confirm plexiform neurofibroma which is one of the clinical criteria for the diagnosis of NF1.[1] Target sign in plexiform neurofibroma is due to central fibrocollagenous core (T2-hypointense) surrounded by myxomatous tissue (T2-hyperintense).[2]

AUTHOR CONTRIBUTIONS

Dr. Partha S. Ghosh collected and organized the data and wrote the first manuscript (including the first draft). Dr. Debabrata Ghosh conceptualized the study and revised the manuscript at all stages.

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From the Pediatric Neurology Center, Cleveland Clinic, OH.
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Child Neurology: Alternating hemiplegia of childhood

Jeffrey R. Tenney, MD, PhD
Mark B. Schapiro, MD

Address correspondence and reprint requests to Dr. Jeffrey R. Tenney, Department of Neurology, Cincinnati Childrens Hospital Medical Center, 3333 Burnet Ave, Cincinnati, OH 45229-3039
jeffrey.tenney@cchmc.org

Alternating hemiplegia of childhood (AHC) is a rare disorder characterized by recurrent attacks of hemiplegia affecting either side of the body, abnormalities of ocular movement, movement disorders, and progressive developmental delay. Children with AHC often have a delay in diagnosis or are misdiagnosed. A broad differential diagnosis is necessary when considering this condition. The clinical features of AHC were first described more than 3 decades ago but its cause remains largely unknown and there is little treatment evidence available. Early diagnosis and multicenter collaboration are necessary to better understand the prognosis of AHC and develop more effective treatments.

CLINICAL CASE, PART I A 12-month-old boy was sent for neurologic consultation after an episode of transient right-sided paralysis. His mother states that during the episode he was fully conscious but half of his body was paralyzed and he appeared to have a stroke. This episode lasted 6 hours and resolved when he slept. He was at his normal baseline upon waking. His mother states that the patient had a similar episode, although occurring on the left side, when he was 4 months old. There was a family history of migraines but no other neurologic disorders. He achieved normal developmental milestones during the first year of life and at 12 months of age was walking independently and had some words. Neurologic examination, done once symptoms had resolved, was normal.

Differential diagnosis. Acute focal weakness in a child has many serious etiologies that must be investigated (table 1). The evaluation is focused on excluding serious or treatable causes. Evaluation should begin with MRI, magnetic resonance angiography (MRA), and magnetic resonance spectroscopy to exclude structural, vascular, and metabolic disorders such as mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke (MELAS) and pyruvate dehydrogenase deficiency. Other testing should include EEG, metabolic screening with urine organic acids, quantitative serum and CSF amino acids, acylcarnitine, lactate/pyruvate (serum and CSF), hypercoagulable studies, erythrocyte sedimentation rate, and transferrin isoelectric focusing.

CLINICAL CASE, PART II On diagnostic testing, brain MRI, MRA, and 2 routine EEGs were normal. Laboratory testing included normal very long chain fatty acids; quantitative serum amino acids, acylcarnitine, ammonia, lactate, and pyruvate; urine organic acids; CSF amino acids; thyroid function studies; and serum transferrin isoelectric focusing assay.

Based on the clinical history, normal neurologic examination between episodes, and negative testing, the patient was given a diagnosis of AHC. Over the next several years, the patient continued to have episodes of alternating hemiplegia and by 2 years old he began to have episodes of quadriplegia. His attacks clustered during the summer months and were triggered by warm ambient temperature and bright sunlight. As he became older, he was able to verbalize that he was having headaches either at the time of his attacks or independent of them. His weakness and headache were frequently relieved by sleep. Analysis of genes that have been associated with AHC, including *SCN1A*, *CACNA1A*, and *ATP1A2*, showed no mutations. The patient was started on nifedipine as prophylaxis for his attacks, but this resulted in only a modest improvement.

DISCUSSION **Epidemiology.** AHC is a rare disorder that was first reported by Verret and Steele[1] in 1971. It has a reported incidence of 1 in 1,000,000 children but this may be an underestimate due to misdiagnosis and variability in the clinical presentation.[2] Since this disease occurs so infrequently and is variable in presentation, knowledge of the clinical characteristics, response to treatment, and prognosis is based on a few small cohort studies.[3,4]

Clinical characteristics. The first report of the disorder in 1971 included 8 children with intermittent hemiparesis of varying severity since infancy. Some

From the Department of Neurology, Cincinnati Childrens Hospital Medical Center, Cincinnati, OH.
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Table 1 Differential diagnosis of acute focal weakness in childhood

Stroke
Vascular abnormality (Moyamoya syndrome, vessel dissection)
Vasculopathy (sickle cell disease)
Embolic
Autoimmune disorders
Vasculitis (infectious, drug-induced, autoimmune)
Hypercoagulable states
Factor V Leiden mutation
Prothrombin gene G20210A mutation
Methylenetetrahydrofolate reductase mutation
Antiphospholipid antibody syndrome
Metabolic disorders
Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes
Pyruvate dehydrogenase deficiency
Congenital disorders of glycosylation
Homocystinuria
Neuromuscular
Polio-like illness
Compression neuropathy
Head trauma
Radiculopathy
Seizure with postictal paralysis
Familial hemiplegic migraine
Alternating hemiplegia of childhood

of these children also had developmental delay, dysarthria, choreoathetosis, or dystonia.[1] Clinical diagnostic criteria of classic AHC have since been established (table 2).[5]

The hemiplegic attacks usually last a few minutes to several days and are associated with slowly progressive neurologic deficits over years.[3] The onset of the syndrome begins with abnormal ocular movements (nystagmus, esotropia, exotropia) or dystonia in a majority of patients by 3 months of age.[3,4] Hemiplegic attacks occur by 6 months of age in more than half of the patients who have been studied.[3,4] Motor findings during an attack have been described as flaccid, areflexic paralysis.[6] Attacks are frequently associated with triggers, most commonly environmental (temperature extremes, odors) but also water exposure, physical activities (exercise, swinging), lights (sunlight, fluorescent bulbs), or foods (chocolate, food dye).[4]

Table 2 Diagnostic criteria for alternating hemiplegia of childhood[5]

1. Symptoms before age 18 months
2. Repeated attacks of hemiplegia that alternate in laterality
3. Episodes of quadriplegia as a separate attack or generalization of a hemiplegic attack
4. Relief from symptoms upon sleeping
5. Other paroxysmal symptoms including dystonic spells, oculomotor abnormalities, or autonomic symptoms either concurrent with attacks or independently
6. Evidence of developmental delay or neurologic findings such as choreoathetosis, dystonia, or ataxia

Pathogenesis. The etiology of AHC remains unclear, but it is likely a symptom complex with multiple causes. Neurophysiologic recordings during an attack have shown impaired brainstem circuits.[7] In contrast, FDG-PET during the interictal period showed low glucose metabolism in the frontal lobes and putamen with normal metabolism in the brainstem which could explain the progressive neurologic symptoms reported with AHC.[8] Microscopic postmortem evaluation of patients with AHC has shown abnormal vascular smooth muscle cells which could result in a functional vascular disorder causing transient small vessel dysfunction in the brain.[9]

The attacks occurring in AHC and familial hemiplegic migraine (FHM) are clinically similar, raising the question of a channelopathy as the underlying dysfunction for both. FHM has been associated with several ion transport genes including *SCN1A* (sodium channel, neuronal type 1, alpha subunit), *CACNA1A* (calcium channel, voltage dependent, P/Q type, alpha-1A subunit), and *ATP1A2* (ATPase, Na+/K+ transporting, alpha-2 polypeptide). AHC, in uncommon familial cases, has been reported to be associated with mutations in *CACNA1A*, a calcium channel gene, and *ATP1A2*, a sodium potassium ATPase gene.[10,11] These gene mutations have yet to be reported with sporadic AHC but given its response to calcium channel blockers a channelopathy is possible.

Treatment. Treatment of AHC is divided into acute management of attacks and episode prophylaxis. Acute management consists of removing known triggers and the early facilitation of sleep. Some authors have advocated the use of buccal midazolam or rectal diazepam to provide rapid sedation.[2]

Episode prophylaxis should consist of avoiding known triggers as well as long-term drug treatment. A wide range of medications has been proposed for AHC but in our experience calcium channel blockers are the most effective. The most commonly used medication is flunarizine, a calcium channel blocker, in a dose of 5 to 20 mg daily.[2,4,6] This has been reported to decrease the frequency and severity of attacks, but not to stop them completely. Other proposed treatments have included beta blockers, an-

ticonvulsants, and other medications such as methysergide, amantadine, aripiprazole, and haloperidol, but these are not frequently used.[2]

Prognosis. The long-term outcome of patients with AHC is frequently poor because of associated developmental delays and stepwise deterioration after severe attacks.[2,4] It is unclear if pharmacologic intervention helps to improve learning, but lessening the severity and frequency of attacks may lead to an improved quality of life.

It has been reported in the largest cohort studies that almost half of children with AHC will develop epilepsy, with seizures that are distinguishable from their attacks.[2,4]

FUTURE PERSPECTIVES AHC is a rare but serious disorder in the pediatric population. It can greatly impact the quality of life for patients and their families. Health care dollars spent on patients with this disorder could be substantial given their frequent emergency room visits, hospitalizations, and broad diagnostic evaluations.

The complex and seemingly progressive nature of AHC makes it imperative that continued research into the pathophysiology and treatment of the disorder is performed. This includes randomized, controlled trials with sufficient numbers of patients. The formation of a multicenter consortium could help to collect the experience of different hospitals and enable a large group of patients to be followed over time.

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Child Neurology: A patient with dissimilar eye color and deafness

Chetan R. Soni, MD, MS, MHA
Gyanendra Kumar, MD

Address correspondence and reprint requests to Dr. Chetan R. Soni, Mason Eye Institute, One Hospital Drive, Columbia, MO 65212
sonic@health.missouri.edu

Waardenburg syndrome (WS) is a rare genetic disorder with developmental anomalies of tissues derived from the neural crest and characterized by auditory and pigmentary findings. Failure of neural crest-derived melanocyte differentiation results in a spectrum of phenotypic presentations that are subdivided into 4 clinical types. We present a case of Waardenburg type 2 and briefly discuss the genetic basis of phenotypic expression of WS.

CASE REPORT An 18-year-old woman undergoing evaluation of intercostal neuralgia was incidentally noted to have one blue and one brown eye (figure). Both pupils reacted equally to light and accommodation. The patient's mother reported that at birth both her eyes were blue but after 2 weeks the left eye changed to brown while the right eye remained blue. At birth she had a tuft of white hair on the frontal area. She had profound sensorineural hearing loss since birth and communicated via sign language. No other family member had this condition. Her mother's eyes were brown and the color of her father's eyes was unknown. The patient was subsequently lost to follow-up.

The differential diagnosis included oculocutaneous albinism, piebaldism, oculocerebral hypopigmentation syndrome, congenital Horner syndrome, neuroblastoma, and WS. Oculocutaneous albinism is characterized by generalized hypopigmentation of skin, hair, and eyes due to defective synthesis of melanin.[1] Since the underlying defect is in pigment production rather than absence of melanocytes, these patients do not have sensorineural hearing loss. Piebaldism is characterized by a white forelock and multiple symmetric hypopigmented or depigmented macules but without developmental anomalies of the cochlea or interocular areas.[2] The oculocerebral hypopigmentation syndrome is an autosomal recessive disorder characterized by the absence of pigmentation of skin and hair, microphthalmia, corneal clouding, and spastic paraplegia.[3] Congenital Horner syndrome and neuroblastoma are rare causes of heterochromia irides, but no ptosis, miosis, or anhidrosis was observed in our patient. Moreover, neither of these conditions is associated with deaf-mutism or hair or skin hypopigmentation anomalies.

Given the presence of auditory and pigmentary findings since birth, a congenital syndrome involving melanocytic dysfunction was considered. The patient met 3 major and 1 minor Waardenburg Consortium diagnostic criteria[4] (table) and a clinical diagnosis of WS type 2 was made.

DISCUSSION WS is a rare condition occurring due to maldevelopment of neural crest-derived tissues resulting in auditory, pigmentary, interocular, limb musculature, and enteric ganglia anomalies.

Clinical features. Four types of WS have been described, although phenotypic presentation may differ due to variable penetrance of the disease traits.[4] WS1 and WS2 are characterized by one or more physical

Figure Heterochromia irides without dystopia canthorum in an 18-year-old woman

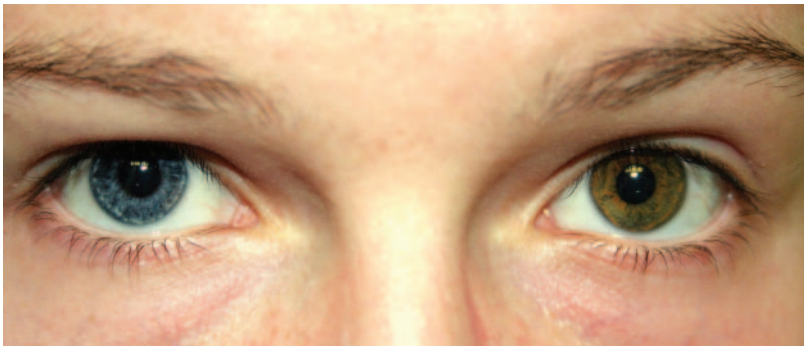

Table Waardenburg Consortium diagnostic criteria[4]

Major	Minor
Congenital sensorineural hearing loss	Congenital leukoderma, synophrys, or medial eyebrow flare
Pigmentary disturbances of the iris	Broad high nasal root
Hair hypopigmentation	Hypoplasia of alae nasi
Affected first-degree relative	Prematurely graying hair
Dystopia canthorum	

From the Mason Eye Institute (C.R.S.), and Department of Neurology (G.K.), University of Missouri-Healthcare, Columbia.
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findings of the disease (table). The distinguishing feature between the 2 types is presence or absence of dystopia canthorum—an unusual facial feature in which the medial canthi of the eyes are spaced farther apart than normal, resulting in an appearance of widely spaced eyes. Ninety-eight percent of patients with WS1 have dystopia canthorum but patients with WS2 do not have this finding.[4] WS3 (Waardenburg-Klein) phenotypes have hypoplasia of limb musculature and/or contractures of elbows and fingers,[5] and WS4 (Waardenburg-Shah) phenotypes have Hirschsprung disease in addition to the other common features of WS.[6]

Etiology. Melanocyte dysfunction may be due to failure of neural crest differentiation, migration, or terminal differentiation and survival in target locations. Neural crest-derived melanocytes are essential to stria vascularis of the cochlea,[7] which explains the sensorineural hearing loss observed in WS and preserved hearing in oculocutaneous albinism. Since retinal melanocytes are not derived from the neural crest but originate from the optic cup of the developing forebrain,[7] they may serve as an important marker for differentiation of melanocyte-specific disorders as opposed to neurocristopathies. The limb muscles, frontal bone, and enteric ganglia are derived from the neural crest, which explains the phenotypic involvement of these structures in WS1, WS3, and WS4.

WS1 and WS3 are transmitted in an autosomal dominant fashion and nearly all cases have mutations in *PAX-3* gene belonging to paired box family of transcription factors.[7] Transcripts of *PAX-3* are expressed in cells of the neural crest between day 8 and 17 of gestation.[7] It is hypothesized that effective levels of PAX-3 protein determine the phenotype variation. Mild reduction in these proteins results in dystopia canthorum, 50% reduction results in melanocyte defects, and severe reduction results in limb anomalies.[7] Hence WS1 and WS3 may actually represent phenotypic variations of the *PAX-3* mutation depending upon the severity of suppression of the transcripts of PAX-3. WS2 is also transmitted in an autosomal dominant fashion, and about 15% of cases have a mutation in the microphthalmia gene *MITF*, while the molecular basis of the remainder of 85% is still unknown.[8] *MITF* appears to be a master gene controlling melanocyte differentiation, and therefore WS2 is, at least in part, melanocyte specific.

WS4 is transmitted in an autosomal recessive manner and results from homozygous mutation of endothelin-3 (*EDN3*), its receptor (*EDNRB*), or *SOX-10* (SRY-related HMG-box).[8] Patients with heterozygous mutation of *EDN3* or *EDNRB* have isolated Hirschsprung disease.[8] The *SOX10* gene directs the activity of other genes that signal neural crest to differentiate into melanocytes and enteric nerves.[8] This explains the presence of Hirschsprung disease in patients with WS4.

Prognosis. Patients with WS have normal intelligence and they perform well on standardized speech tests following cochlear implantation and auditory rehabilitation. Early auditory rehabilitation is essential for normal cognitive development and is associated with excellent prognosis.[9] Given the possibility of neural tube defects in patients with WS, folic acid supplementation is recommended in women with increased risk of having a child with WS.[10]

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Introduction

Pediatric Perspective

By Aaron Rothstein, MD, and Sonia Partap, MD, MS

The prospect of a neuro-oncological diagnosis is an alarming one although it is the most common solid tumor in children and the leading cause of cancer death. Despite existing therapies, there are many CNS malignancies for which treatment is often limited or ineffective. Treatment strategies in pediatric neuro-oncology vary depending on age, pathology, and tumor location. Thus, an accurate diagnosis and understanding of childhood development is essential to guide therapy as well as to advance research in the field. Understanding the differential diagnoses of complicated cases can also prevent undue morbidity and mortality.

This chapter addresses a range of pediatric neuro-oncologic diagnoses and provides the readers with 5 different articles from the Resident & Fellow Section of *Neurology*. The cases of Rosai-Dorfman disease and Pallister-Hall syndrome are both unusual presentations of rare disorders. Ataxia is a common presentation for posterior fossa tumors; however, it is rare for CNS tumors to metastasize outside of the brain and spine. Thus, a thorough investigation was required for the diagnosis. Primary neuro-oncologic diagnoses in the suprasellar region often present with endocrinopathies but rarely cause seizures. These cases emphasize why pediatric neurology requires a detailed history, a full physical and neurologic examination, and appropriate imaging.

This is also illustrated with the case of neurocutaneous melanosis. Neurocutaneous melanosis is a rare entity and recognizing the skin findings as well as distinguishing CNS MRI findings of melanin from pathologic conversion to melanoma can change management and outcome. With today's understanding of adult melanoma, new treatment strategies are being implemented to improve survival in pediatric CNS melanoma.

Finally, the case of multiple brain lesions with edema and the case of bifocal germinoma are great examples of vastly different outcomes in children with more than one lesion. Bifocal germinoma is not considered metastatic disease and has a high cure rate. Current treatments include reducing doses of CNS radiation to prevent long term side effects in adult cancer survivors. We hope these cases will be edifying for the pediatric neurologist as he or she embarks on a career of challenging neuro-oncologic diagnoses.

From the Department of Neurology (A.R.), University of Pennsylvania, Philadelphia; and Neuro-Oncology, Child Neurology and Pediatrics (S.P.), Stanford University & Lucile Packard Children's Hospital, Division of Child Neurology, Palo Alto, CA.
Correspondence Dr. Rothstein aharon.rothstein@gmail.com
For disclosures, please contact the *Neurology*® Resident & Fellow Section at rfsection@neurology.org.

Adult Perspective

By Regan Jo Lemley, MD, MS, and Roy E. Strowd, III., MEd, MD

CNS tumors are the second most common childhood malignancy and the third most common cancer in adolescents and adults aged 15–39 years. Medulloblastoma, glioma, and ependymoma account for the majority of pediatric CNS tumors and are molecularly distinct from those in adults. In contrast, benign meningiomas, pituitary adenomas, and gliomas make up the majority of adult tumors. Although many principles differ for adult and pediatric patients with tumors, pediatric neuro-oncology and the 5 cases that follow can teach the adult neurologist a great deal about the imaging evaluation, differential diagnosis, treatment, and survivorship for patients with brain tumors.

The Rosai-Dorfman disease, neurocutaneous melanosis, and hypothalamic hamartoma cases demonstrate the importance of an imaging differential and histopathologic confirmation for children and adults with new brain lesions. Enhancing mass lesions may be neoplastic, inflammatory, infectious, and at times cerebrovascular in etiology. When noninvasive imaging is unable to establish a diagnosis, definitive tissue evaluation is imperative. In addition, these cases remind the practicing neurologist to inquire about systems not generally investigated in a focused neurologic visit, such as a good dermatologic or endocrine review of systems, which may lead to a diagnosis.

The case of the 8-year-old with multiple brain lesions and cerebral edema discusses the recognition and initial management of neurologic complications of brain tumors, which include cerebral edema, seizures, stroke, hemorrhage, and CNS infections. The tumor described, gliomatosis cerebri, generally presents in adults and has a poor prognosis.

Finally, the case of the 17-year-old emphasizes red flag headache symptoms and the excellent prognosis of germinomas. This case highlights for the adult neurologist the importance of understanding brain tumor treatments and recognizing long-term survivorship care as children become adults.

From the Department of Neurology (R.J.L.) and Neurology and Oncology (R.E.S.), Wake Forest Baptist Medical Center, Winston-Salem, NC.
Correspondence Dr. Lemley rlemley@wakehealth.edu
For disclosures, please contact the *Neurology*® Resident & Fellow Section at rfsection@neurology.org.

Pearls & Oy-sters: Bifocal germinoma of the brain

Review of systems is key to the diagnosis

Partha S. Ghosh, MD
Tanya Tekautz, MD
Sudeshna Mitra, MD

Correspondence & reprint requests to Dr. Ghosh: ghoshp3@ccf.org

PEARLS

- Intracranial germinoma is the most common malignant intracranial germ cell tumor. It usually occurs in children and young adults and with the current therapies, many patients experience long-term survival.
- Suprasellar region germinoma can present with isolated hypothalamic–pituitary axis dysfunction such as diabetes insipidus, delayed growth, menstrual irregularities, or precocious puberty, while pineal region germinoma can present with features of raised intracranial pressure and Parinaud syndrome.
- Pineal and suprasellar region germinomas can coexist in the same patient. Such a combination is called a bifocal germinoma.

OYSTER

- Intracranial germinoma in a child or young adult may be easily missed if careful evaluation of review of systems with reference to endocrine functions is not undertaken.

CASE REPORT A 17-year-old girl presented to the Pediatric Neurology clinic with new onset headache of 8 weeks duration. She experienced a daily headache described as a pressure-like sensation over both the temporal areas, 4/10 in intensity. This baseline headache was interrupted by a few episodes of pounding bitemporal and occipital headache, 10/10 in severity, worse with activity. The severe headaches were associated with dizziness, photophobia, phonophobia, vomiting, and "zig-zag lights" in front of her eyes and often would occur on awakening. She occasionally described "whooshing sounds" associated with the baseline headache. On review of systems it was noted that she had poor energy level. She had polyuria, nocturia, and polydipsia for 3 years. The polydipsia was attributed to psychogenic cause in the context of ongoing serious personal and familial psychosocial stressors. She had menarche at 13 years of age but for the previous 2 years she had had irregular menstrual cycles, occurring once or twice a year. Her appetite was preserved and her weight was stable within 6 months preceding the diagnosis (54.5–55.7 kg). Her general physical as well as the neurologic examinations were normal. The above features were suspicious for an intracranial mass lesion around hypothalamic/suprasellar region. Her evaluation revealed central diabetes insipidus (DI) based on the history, low urine specific gravity (1.002–1.004), and high urine output (>5 mL/kg/hour). Urine osmolality was 51 mOsm/kg, which increased to 251 mOsm/kg after starting oral desmopressin. Follicular stimulating hormone and luteinizing hormone levels were low; prolactin, insulin-like growth factor, thyroid hormone, and cortisol levels were normal. Her pregnancy test was negative. MRI of the brain showed an intra-axial hypothalamic mass with ependymal extension to the right lateral ventricle involving the body and right frontal horn. There was a second mass in the pineal region. Both the masses enhanced intensely and were hypointense on T2-weighted images, suggesting a radiologic diagnosis of germinoma (figure 1). Spine MRI did not reveal any metastases. There was evidence of early onset acute obstructive hydrocephalus. Serum α-fetoprotein (AFP) and β-human chorionic gonadotrophin (β-HCG) were within normal limits. She underwent an endoscopic intraventricular tumor biopsy which confirmed the diagnosis of germinoma. CSF analysis for tumor staging was withheld owing to hydrocephalus. In view of midline tumors she was presumably considered to have CSF+ disease and treated with craniospinal irradiation (CSI) without adjunctive chemotherapy. She got CSI plus posterior fossa boost with a total dose of 4,500 cGy.

At 1-year follow-up she was completely headache free. The polyuria and polydipsia resolved with desmopressin but menstrual cycles did not completely normalize. Follow-up MRI after 9 months showed complete resolution of the tumor masses (figure 2).

From the Pediatric Neurology Center (P.S.G.), Pediatric Hematology-Oncology (T.T.), and Pediatric Neurology Center (S.M.), Children's Hospital, Cleveland Clinic, Cleveland, OH.

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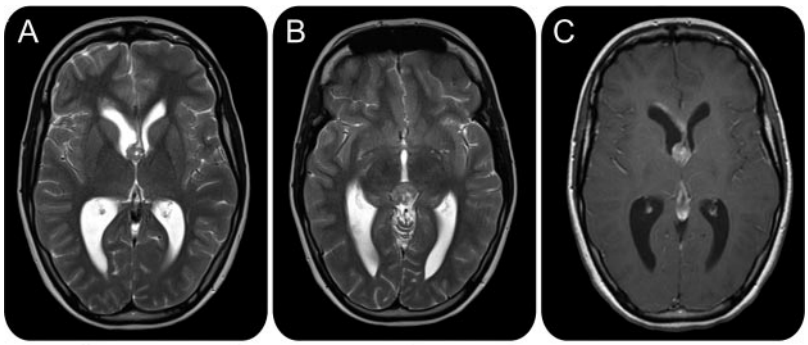
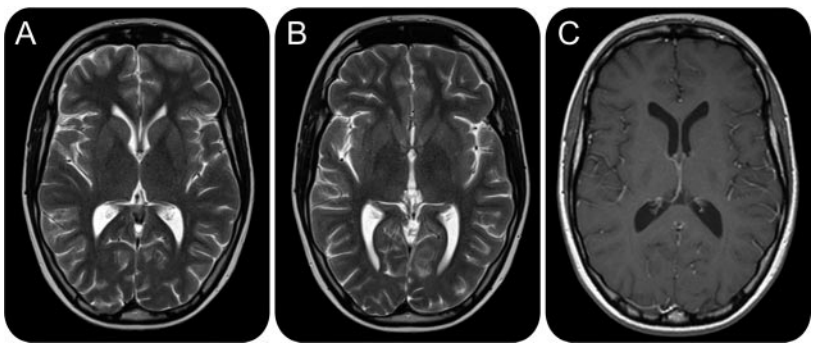
Figure 1 MRI brain (preradiotherapy)



Brain MRI showing (A, B) hypointense mass lesion on T2-weighted image in the hypothalamic and pineal region respectively with early hydrocephalus and (C) intensely enhancing masses on postcontrast T1-weighted image with ependymal extension to the right lateral ventricle involving right frontal horn.

DISCUSSION Intracranial germinoma constitutes 50% to 60% of CNS germ cell tumors (CNSGCT), accounting for 0.5% to 2.0% of all primary intracranial tumors.[1] There is considerable variation in the geographic incidence of intracranial GCT; it is 5–8 times more common in Japan and the far east compared to the western countries.[2] CNSGCT occurs mainly in children and young adults with a peak age at onset between 10 and 18 years. Overall, male patients are affected more than female patients. WHO classifies CNSGCT into pure germinoma, embryonal carcinoma, yolk sac tumor, choriocarcinoma, teratoma, and mixed germ cell tumor.[3] CNSGCT arises from the primordial germ cells. These cells appear in the yolk sac wall by the third gestational week and migrate into the genital ridge by the sixth gestational week. If migration of these primordial germ cells is disrupted, some cells may migrate to the ectopic sites (retroperitoneum, mediastinum, or diencephalon) where they can develop into extragonadal GCT.[4]

Figure 2 MRI brain (postradiotherapy)



Follow-up MRI at 9 months post-treatment showing complete resolution of the hypothalamic, pineal masses and hydrocephalus on T2-weighted images (A, B) and no abnormal contrast enhancement in postcontrast T1-weighetd image (C).

Germinoma usually occurs along the midline of the body, common locations being the pineal and the suprasellar regions, but can also develop in the basal ganglia region. Tumor cells can seed within the ventricular cavity and the CSF and drop metastases have been described in the spinal cord.[5] CSF examination and MRI of the spinal cord are needed for appropriate staging of the disease. At the time of diagnosis, 2%–18% of the intracranial germinomas show bifocal distribution with simultaneous pineal and suprasellar manifestations. It remains unclear whether the bifocal tumors result from simultaneous tumor development or represent metastatic disease.[6]

There is a definite relationship between the clinical presentation and tumor location in cases of germinoma. Lesions in the pineal region can obstruct the cerebral aqueduct and cause hydrocephalus with features of raised intracranial pressure (ICP) as the first presenting symptom; they can also present with Parinaud syndrome.[7] Tumors involving the suprasellar region usually present with hypothalamic–pituitary axis dysfunction such as DI, delayed growth, menstrual irregularities, hypogonadism, or precocious puberty. Patients may also have visual disturbances due to compression of the visual pathways. Interestingly, patients with bifocal germinoma tend to present with symptoms associated with the suprasellar mass initially.[6] The central endocrinopathy associated with suprasellar GCT is thought to be a consequence of direct pressure by the tumor on the critical hypothalamic areas. These endocrine symptoms tend to occur sooner than a similar sized mass in the pineal region. Additionally, in patients with bifocal disease, the suprasellar mass is frequently the larger of the 2 mass lesions in children.[6] Thus the diagnosis may be missed if this possibility in not considered as headache and features of raised ICP may be a late manifestation.

The role of protein markers such as β-HCG and AFP that can be measured in the serum or more preferably in the CSF plays an important part in the diagnosis of CNSGCT.[3] Yolk sac tumor secretes AFP and choriocarcinoma secretes β-HCG. Embryonal carcinoma usually does not secrete tumor markers but it occurs with other GCT-like yolk sac tumors and is considered as a mixed GCT.[8] Pure germinomas do not secrete tumor markers. Ancillary tests with typical neuroimaging findings can aid in the diagnosis of CNSGCT without the need for performing brain biopsy.

Intracranial germinoma is considered as a highly curable brain tumor. Radiotherapy is the standard modality of treatment in such patients. With an irradiation dose of 4,000–5,000 cGy, long-term survival is achieved in more than 90% of patients.[9] Metastatic

intracranial germinoma requires simultaneous radiation to the craniospinal axis.[6] The side effects of CSI, like neurocognitive deficits, pituitary dysfunction, and secondary malignancies, are of real concern, particularly for younger patients. In order to minimize these, combined modality therapy using cisplatin-based chemotherapy regimens with reduced volume and dose irradiation have shown promising results, showing only 9%–14% local failure rate and a salvage rate of over 50%.[10]

There were a number of distractors in the clinical history of this case. Headaches with positive visual phenomena could have been interpreted as migraine with aura. However, our patient had several features which were atypical for migraine, such as bilateral location of the headache, persistent daily headache from the onset, and early morning severe headaches associated with vomiting.

The polydipsia and polyuria were thought to be of psychogenic etiology because there were serious psychosocial issues in the family though the urine specific gravity was clearly low. The differential diagnosis of polydipsia and polyuria should exclude diabetes mellitus and salt-losing nephropathy from end-stage renal disease. In absence of those disorders, one should consider primary polydipsia/psychogenic polydipsia, central DI, and nephrogenic DI. The above disorders can be differentiated based on careful history, checking serum sodium and urine osmolality, performing water deprivation test, and noting the response to exogenous antidiuretic hormone (ADH). In central DI, serum sodium is normal to high with low urine osmolality, and the urine does not become concentrated despite excessively concentrated serum after water deprivation. The urine osmolality increases by more than 50% in response to exogenous ADH as noted in our patient. Oligomenorrhea soon after menarche in our patient was considered to be within normal limits. The combination of new onset headache along with the history of DI and oligomenorrhea pointed to the possibility of intracranial tumor in the suprasellar/hypothalamic region. Endocrine abnormalities and visual field defects are common initial features of pediatric sellar/suprasellar masses. These symptoms may antedate headache and should be thoroughly investigated to look for abnormalities of the hypothalamic-pituitary-gonadal axis. Intracranial germinomas are exquisitely radiosensitive and chemosensitive and thus are highly curable. New therapeutic strategies are focusing on dose reduction of therapy (radiation and chemotherapy) while still achieving the same cure rates we currently experience.

AUTHOR CONTRIBUTIONS

Dr. Ghosh collected and organized the data and wrote the first manuscript (including the first draft). Dr. Mitra conceptualized the study. Dr. Tekautz and Dr. Mitra verified the results and revised the manuscript at all stages.

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RESIDENT & FELLOW SECTION

Section Editor
Mitchell S.V. Elkind, MD, MS

Teaching NeuroImages: Isolated hypothalamic hamartoma vs Pallister-Hall syndrome

Imaging and clinical correlation

Antonio J. da Rocha, PhD
Marcos Rosa Junior, MD
Fernando Norio Arita, PhD

Correspondence & reprint requests to Dr. da Rocha: a.rocha@uol.com.br

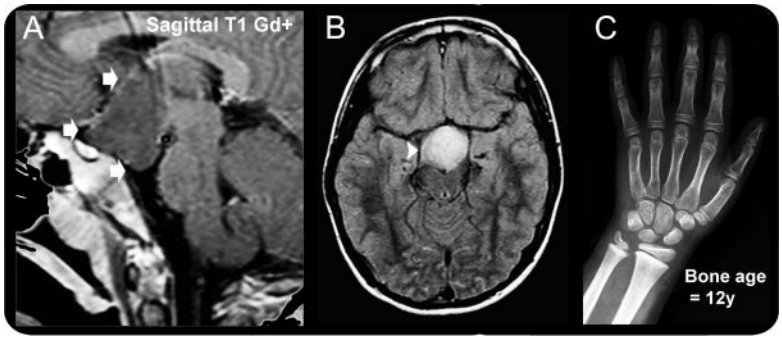
Isolated hypothalamic hamartomas (HH) have a distinct clinical phenotype from that of Pallister-Hall syndrome (PHS), as HH consist of more severe seizures and cognitive, behavioral, and endocrine disorders.[1] The imaging features help one to distinguish these conditions (figures 1 and 2).

Isolated HH are hyperintense on fluid-attenuated inversion recovery and cause precocious puberty (PP) when they are oriented downward (parahypothalamic lesion), while seizures predominate in sessile intrahypothalamic HH.[2] PHS is associated with isointense to gray matter HH, polydactyly, cutaneous syndactyly, bifid epiglottis, imperforate anus, and panhypopituitarism, resulting from GLI3 frameshift mutations (which map to chromosome 7p13) as an autosomal dominant trait.[1]

AUTHOR CONTRIBUTIONS

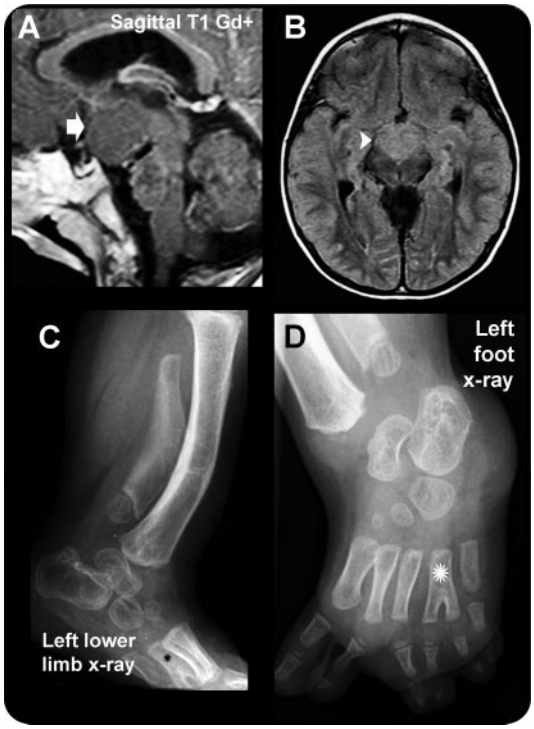
Dr. Rocha was responsible for the study concept, writing the manuscript, and the interpretation of data. Dr. Rosa Jr. was responsible for the interpretation of data and image selection. Dr. Arita was responsible for the clinical study concept and critical revision of the manuscript.

Figure 1 Isolated hypothalamic hamartoma (HH) (3-year-old boy) with gelastic epilepsy and precocious puberty



(A, B) MRI confirmed nonenhancing HH (arrows). Typical hyperintensity on fluid-attenuated inversion recovery (arrowhead). (C) Advanced bone age.

Figure 2 Pallister-Hall syndrome (2-year-old boy)



(A, B) MRI confirmed nonenhancing hypothalamic hamartoma (arrow) that was isointense to gray matter on fluid-attenuated inversion recovery (arrowhead). (C, D) Note the curved long bones, polydactyly, and dysplastic metatarsal (asterisks).

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MYSTERY CASE RESPONSES

The Mystery Case series was initiated by the *Neurology*® Resident & Fellow Section to develop the clinical reasoning skills of trainees. Residency programs, medical student preceptors, and individuals were in-

From the Divisions of Neuroradiology (A.J.d.R., M.R.J.) and Pediatric Neurology (F.N.A.), Santa Casa de Misericórdia de São Paulo, São Paulo, Brazil.
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vited to use this Mystery Case as an education tool. Responses were solicited through a group e-mail sent to the AAN Consortium of Neurology Residents and Fellows and through social media.

All the answers that we received came from individual residents rather than groups and they were all well-reasoned and thoughtful. Three respondents correctly identified the classic appearance of isolated hypothalamic hamartomas (figure 1) and Pallister-Hall syndrome (figure 2). When isolated, hypothalamic hamartomas present with severe epilepsy, more significant neurologic dysfunction, and are more likely to be associated with precocious puberty. Patients with Pallister-Hall syndrome usually have well-controlled seizures and endocrine disturbances other than precocious puberty.

The teaching point of this Mystery Case is that despite similar appearance the exact MRI localization and the T2/fluid-attenuated inversion recovery characteristics may help in differentiating between these 2 entities, and thus the imaging could be used as a prognostic factor for the clinical evolution.

Dragos A. Nita, MD, PhD

Clinical Reasoning: An 8-year-old girl with multifocal brain lesions and cerebral edema

E.S. Seto, MD, PhD
M. Proud, MD
A.M. Adesina, MD, PhD
J. Su, MD, MS
E. Muscal, MD, MS

Correspondence & reprint requests to Dr. Muscal: emuscal@bcm.tmc.edu

SECTION 1

An 8-year-old right-handed girl with a history of declining school performance presented to the emergency center with acute onset altered mental status. For 3 weeks, the former straight A student had been failing classes, but her family noted no changes in her personality or ability to perform activities of daily living. On the night of presentation, the patient was found minimally responsive, lying in vomitus. She aroused briefly with stimulation but was limp.

Her past medical history was significant for a full-term birth without complications, normal acquisition of developmental milestones, and no chronic medical conditions. She took no medications. She had no unusual food or animal exposures and had not traveled overseas. Her family had no history of seizures, strokes, blood clots, cancer, rheumatologic disorders, or recurrent miscarriages. On examination, she was afebrile with normal vital signs. Her examination was significant only for lethargy and bilateral papilledema. Initial workup revealed a normal complete blood count, electrolytes, and blood glucose.

Question for consideration:

1. What is the most appropriate next diagnostic study?

GO TO SECTION 2

From the Department of Pediatrics, Section of Neurology and Developmental Neuroscience (E.S.S., M.P., E.M.), Departments of Pathology (A.M.A.), Immunology (A.M.A.), and Pediatrics (A.M.A.), Department of Pediatrics, Section of Hematology and Oncology (J.S.), and Department of Pediatrics, Section of Pediatric Rheumatology (E.M.), Baylor College of Medicine, Houston, TX.

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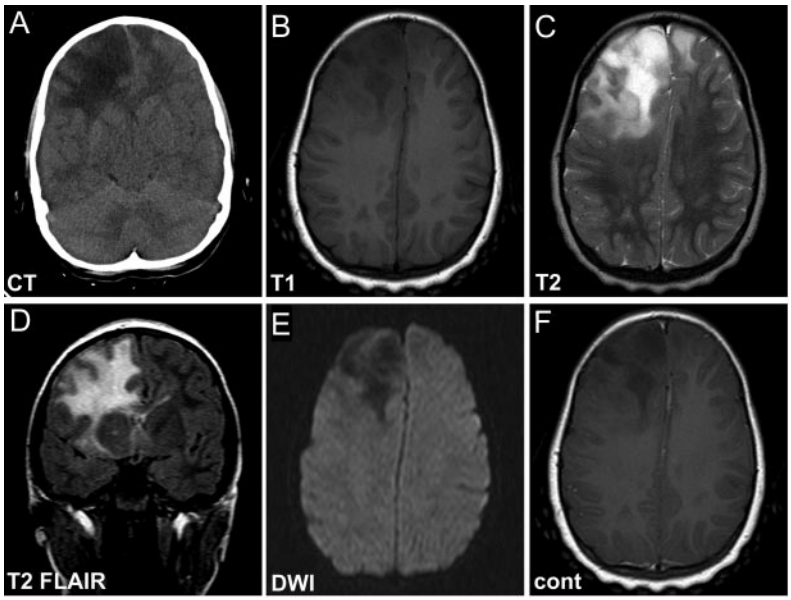
Figure 1 Neuroimaging results



(A) Axial CT head noncontrast image shows right frontal hypodensity with accompanying cerebral edema and midline shift. (B) Axial T1 precontrast image shows right frontal hypointensity. (C) Axial T2 and (D) coronal T2 fluid-attenuated inversion recovery (FLAIR) images show prominent hyperintensity of the right and left frontal lobes, right temporal lobe, right basal ganglia, and corpus callosum. Scattered abnormalities are also present in bilateral parietal lobes and the left temporal lobe. (E) Axial diffusion-weighted imaging (DWI) shows subtle decreased diffusivity of the right frontal lobe. (F) Axial T1 postcontrast image shows subtle bilateral frontal lobe and leptomeningeal enhancement.

SECTION 2

An emergent CT of the head without contrast is indicated since emesis, altered mentation, and papilledema can be signs of elevated intracranial pressure (ICP). Prompt recognition of elevated ICP is critical as it can precipitate brain herniation that compresses vital neural and vascular structures. Early uncal herniation often compresses the oculomotor nerve which manifests as ipsilateral papillary dilatation due to unopposed sympathetic activity. Late herniation affects the brainstem by either direct compression or vascular compromise. This results in ipsilateral hemiparesis, Cushing triad (hypertension, bradycardia, altered respirations), decorticate posturing, and ultimately death.

In this patient, CT showed right frontal cerebral edema (figure 1A). The patient was started on high-dose dexamethasone to reduce any vasogenic edema and returned to baseline mental status within 24 hours. Follow-up MRI demonstrated diffuse cerebral edema with midline shift and tonsillar herniation (figure 1B). Significant T2 prolongation of the right frontal lobe extending into the right basal ganglia, temporal lobe, and corpus callosum was noted as well as smaller changes in the left frontal and bilateral parietal lobes (figure 1, C and D). There was subtle decreased diffusivity and parenchymal and leptomeningeal enhancement (figure 1, E and F).

Question for consideration:

1. What is the differential diagnosis for multifocal gray and white matter lesions with leptomeningeal enhancement?

GO TO SECTION 3

SECTION 3

The differential diagnosis for multifocal gray and white matter lesions is broad and includes meningoencephalitis, metastatic disease, primary CNS tumors, lymphoma, demyelinating disease, and CNS vasculitis. In the next 2 sections, each of these conditions will be discussed in regards to their applicability to this pediatric patient with elevated ICP.

Of these conditions, meningitis and encephalitis have the highest incidence within the pediatric population. Patients with meningoencephalitis often present acutely with altered mentation and meningeal signs such as headache, nuchal rigidity, and nausea. In severe cases, a combination of interstitial, cytotoxic, and vasogenic edema can result in life-threatening elevated ICP. The indolent onset of this patient's symptoms is atypical for most infectious etiologies except for fungi and mycobacterium. In this patient, serum studies were sent to evaluate for infection since lumbar puncture during ICP elevation can precipitate herniation. The patient was empirically treated with acyclovir for herpes simplex virus and azithromycin for a positive mycoplasma immunoglobulin M (IgM), which may be present acutely or persistently following infection. After 8 days of steroids, she underwent a lumbar puncture under neurosurgical supervision. CSF revealed 1 leukocyte, 0 erythrocytes, glucose 68, protein 21, normal immunoglobulin G (IgG) index, indeterminate oligoclonal banding, and cytology without atypia. Infectious studies from the CSF showed no evidence of bacterial, viral, fungal, or mycobacterial infection, arguing against meningoencephalitis.

Neoplasms such as metastases, lymphoma, and primary brain tumors can also cause multifocal brain lesions. Within tumors, abnormal vascular permeability often produces vasogenic edema and elevated ICP. Metastases are the most common cause of CNS tumors in adults but are infrequent in children. Similarly, CNS lymphoma is rare in children, producing multifocal disease more commonly in immunocompromised adults. Lymphoma also exhibits a characteristic T2 hypointensity with homogeneous enhancement not seen in this case. Furthermore, this patient showed no evidence of systemic malignancy such as fever, malaise, weight loss, bleeding diathesis, lymphadenopathy, hepatosplenomegaly, or peripheral smear abnormality. Notably, however, primary brain tumors may lack these systemic features. Primary malignant CNS tumors represent the most common solid malignancy during childhood. The majority arise from glial cells (astrocytes, oligodendrocytes, ependymal cells). Since the patient's initial MRI was consistent with a glioma, repeat neuroimaging was performed on hospital day 13 and a brain biopsy was considered. MRI of the brain showed stable signal abnormalities and enhancement. Magnetic resonance spectroscopy demonstrated moderately decreased *N*-acetylaspartate and increased choline, consistent with neuronal breakdown and increased cell membrane turnover. MRI of the spine showed no abnormalities.

Demyelinating conditions such as multiple sclerosis and acute disseminated encephalomyelitis are common causes of multifocal T2 hyperintense lesions, usually exhibiting enhancement in the acute setting. However, only fulminant demyelination produces elevated ICP. In this case, the lack of significant enhancement and minimal radiologic improvement despite treatment with high-dose steroids argue against a demyelinating process.

Question for consideration:

1. The differential diagnosis for this patient includes CNS vasculitis. What are its radiographic features? What is the diagnostic workup?

GO TO SECTION 4

MRI has 90%–100% sensitivity for CNS vasculitis,[1] showing the effects of vascular inflammation and lumen narrowing. Adults with primary angiitis of the CNS (PACNS) most commonly exhibit infarcts and white matter T2 hyperintensities, often occurring bilaterally.[2,3] Fifteen percent of cases present with mass lesions resembling tumors.[1] Children with PACNS most frequently have multifocal T2 abnormalities with unilateral involvement of the deep gray and deep white matter.[4] Depending on the areas affected, symptoms range from behavioral changes to focal neurologic deficits. Due to vasogenic and cytotoxic edema, symptoms of elevated ICP may be present.

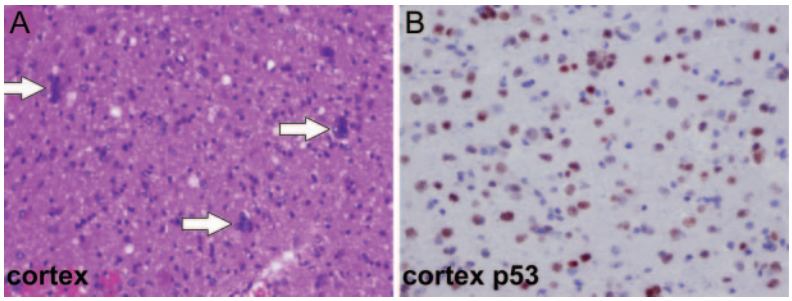
Diagnosis of PACNS is based on the presence of a newly acquired neurologic deficit, angiographic or histologic evidence of CNS angiitis, and absence of a systemic condition that may explain these findings.[5] Since vascular imaging by magnetic resonance angiography has a 14%–40% false-negative rate in adults, 4-vessel conventional angiography is recommended.[4] Given that this patient's presentation and MRI were consistent with vasculitis, a cerebral angiogram was performed, revealing irregularity in the distal branches of the right anterior and middle cerebral arteries, concerning for vasculopathy. While the majority of MRI abnormalities in adult CNS vasculitis have good angiographic correlates,[2] this patient's dense right frontal lobe MRI abnormality and scattered left hemisphere changes were not concordant with the limited angiographic findings. Notably, however, small vessel vasculitis can be difficult to detect angiographically and usually requires brain biopsy for definitive diagnosis and exclusion of infectious or malignant processes.[6]

Having established angiographic evidence for vasculopathy, systemic causes of CNS vasculitis were considered. As previously described, tests for infection including HIV, syphilis, tuberculosis, and fungal disease were negative. Additionally, markers of systemic inflammation (erythrocyte sedimentation rate, C-reactive protein), systemic lupus erythematosus (antinuclear antibodies, anti–double-stranded DNA antibodies, antiphospholipid antibodies, C3, C4, urinalysis), granulomatous polyangiitis (formerly Wegener's granulomatosis), microscopic polyangiitis (antineutrophil cytoplasmic antibodies), and sarcoid (angiotensin converting enzyme, lysozyme) showed no abnormalities. Thus, secondary CNS vasculitis due to infection or systemic rheumatologic disease was unlikely.

To differentiate between neoplasm with secondary vasculopathy and PACNS, the patient underwent a brain biopsy of the affected right frontal lobe and overlying leptomeninges. Histology revealed a diffusely infiltrating neoplasm with elongated cells, nuclear atypia, and p53 positivity consistent with a diagnosis of at least grade III gliomatosis cerebri (GC) (figure 2). The infiltrating pattern and degree of nuclear atypia exceed the characteristics of lower grade gliomas, and the lack of neovascularization and necrosis differentiate GC from grade IV glioblastoma. While angiography was suggestive of vasculopathy, there was no histologic evidence of vessel wall inflammation. These findings may reflect vasculopathy without vasculitis or a sampling bias.

DISCUSSION The World Health Organization defines GC as a malignant neuroepithelial neoplasm of uncertain origin composed of elongated cells resembling astrocytes that diffusely involves at least 2 cerebral lobes.[7] Patients with this rare condition typically present in early adulthood with cognitive/behavioral changes, headaches, or seizures.[8] Later features include focal neurologic deficits and elevated ICP. Radiologically, GC exhibits poorly defined areas of T2 hyperintensity with T1 isointensity or hypointensity. Areas most commonly affected on autopsy include the cerebral white matter, midbrain, pons, and corpus callosum. GC imaging resembles that of demyelinating disease, encephalitis, ischemia, CNS vasculitis, multifocal glioma, and infiltrating astrocytoma. Interestingly, GC can cause vessel irregularity and stenosis due to vascular tumor invasion or reactive inflammation.[9] Since neoplasm and CNS vasculitis can be difficult to differentiate based on clinical presentation and neuroimaging, biopsy is often required for definitive diagnosis. Unfortunately, the prognosis for GC is poor, with a median adult survival of 11.4–38.4 months and median pediatric survival of 27 months.[10] Given the rarity of pediatric GC, optimal treatment protocols are not well-established. This patient participated in an institutional clinical trial including both radiation and chemotherapy. Her tumor responded to therapy for

Figure 2 Histology



Biopsy of right frontal lobe, images taken at 200× magnification. (A) Cortex stained with hematoxylin & eosin shows nuclear pleomorphism and atypia (arrows) indicative of a high-grade tumor. (B) Cortex shows increased p53 positivity characteristic of higher grade tumors.

10 months but then progressed, and she died 18 months after diagnosis.

AUTHOR CONTRIBUTIONS

Drs. Seto, Proud, Adesina, Su, and Muscal all worked on the drafting of this manuscript as well as analysis of data.

DISCLOSURE

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

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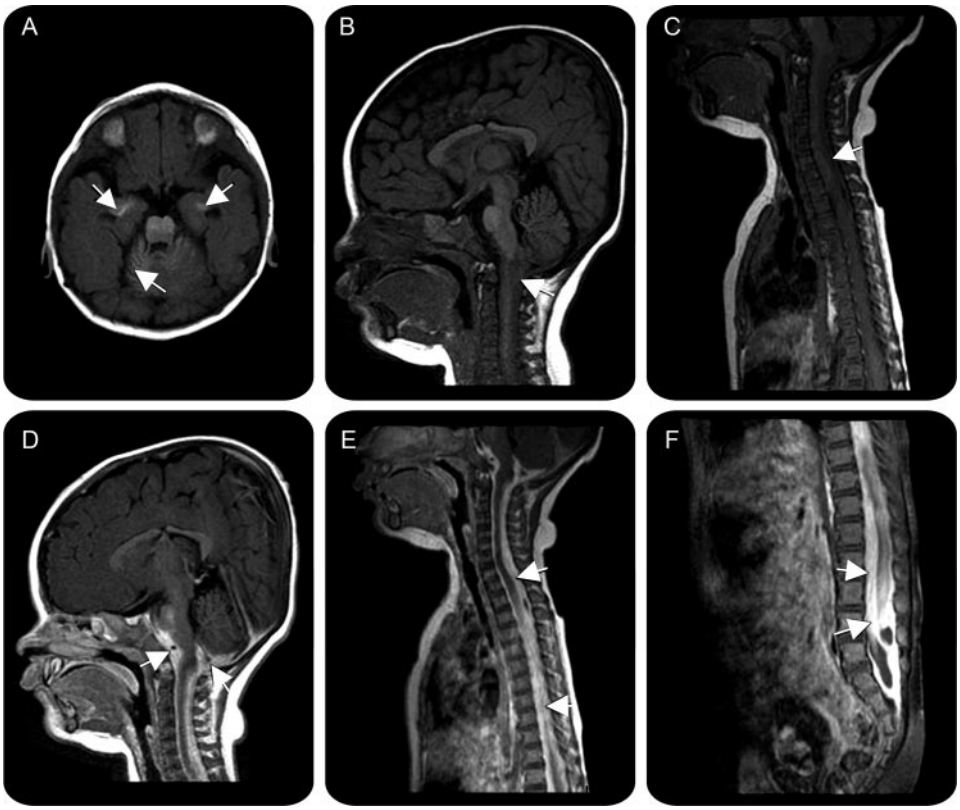
Teaching Neuro*Images*: Neurocutaneous melanosis

Shyamsunder B. Sabat, MD

Address correspondence and reprint requests to
Dr. Shyamsunder B. Sabat,
951, 18 St S, Suite 596,
Birmingham, AL 35205
ssabat@hmc.psu.edu

Figure Unenhanced and contrast-enhanced MRIs



(A–C) Unenhanced T1-weighted MRI showing hyperintense areas consistent with parenchymal melanin in bilateral amygdala, pons, and cerebellar folia (arrows in A) and opacification of CSF spaces around the lower brainstem and cord (arrows in B, C). (D–F) Contrast-enhanced T1-weighted images showing florid enhancement (arrows) obliterating CSF cisterns at the base of brain and around the entire cord consistent with leptomeningeal melanocytic proliferation.

A 4-year-old boy presented with seizures, dysphagia, and weakness in all extremities. Examination revealed large nevi on the trunk which contained benign melanocytes on biopsy. A diagnosis of neurocutaneous melanosis was made on the basis of the MRI (figure) and CSF examination, which showed numerous melanocytes.

Neurocutaneous melanosis is a nonfamilial neurocutaneous syndrome characterized by large melanocytic nevi and excessive proliferation of melanocytes cells in the leptomeninges.[1,2] CNS melanoma develops in about 50%. Patients present with hydrocephalus, seizure, cranial nerve palsies, intracranial hemorrhage, and myelopathy.[1] Prognosis is poor. Treatment is shunting for the hydrocephalus and supportive.

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From the University of Alabama at Birmingham, Birmingham.
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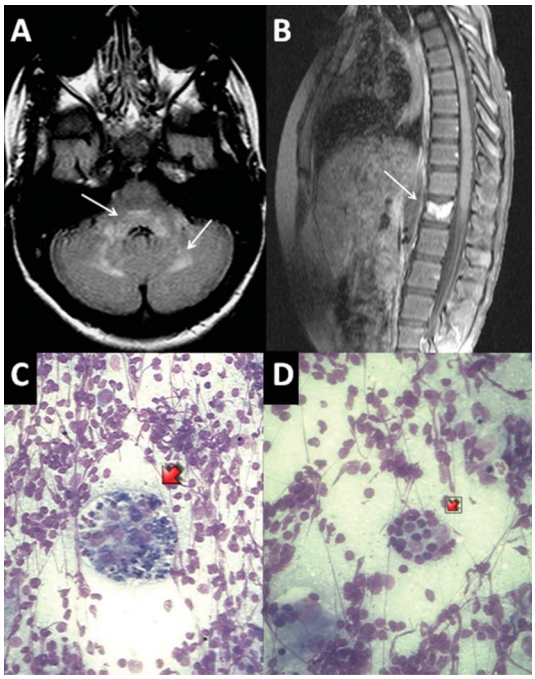
Teaching NeuroImages: Rosai-Dorfman disease presenting with progressive early-onset cerebellar ataxia

Carolina Candeias da Silva, MD
José Luiz Pedroso, MD, PhD
Fabiano Moulin de Moraes, MD
René Leandro M. Rivero, MD, PhD
Fabiano Mesquita Callegari, MD
Francisco Araujo, Jr, MD
Fabio Fieni Toso, MD
João Norberto Stávale, MD, PhD
Orlando Graziani Povoas Barsottini, MD, PhD

Correspondence to Dr. Pedroso: jlpedroso.neuro@gmail.com

Figure Imaging and histopathology



(A) Axial fluid-attenuated inversion recovery–weighted brain MRI shows cerebellar white matter (dentate nucleus), middle cerebellar peduncles, and dorsal pons involvement. (B) Spine MRI discloses a heterogeneous lesion with gadolinium enhancement on T12 vertebral body. (C, D) Cervical lymph node biopsy shows emperipolesis: histiocytes with abundant cytoplasm and engulfed viable lymphocytes, classically seen in Rosai-Dorfman disease.

A 13-year-old girl presented with a 3-year history of progressive gait abnormality. She recently had a self-limited cervical lymphadenopathy. Neurologic examination showed brisk tendon reflexes and moderate ataxia. Brain MRI disclosed hyperintense lesions in the cerebellum and pons (figure, A). Spine MRI showed a heterogeneous lesion in the T12 vertebra (figure, B). Histopathology of the cervical lymph node confirmed Rosai-Dorfman disease (RDD) by showing emperipolesis (figure, C and D). The patient will be followed up in order to determine disease progression and therapy.

RDD is a rare autoimmune histiocytic proliferative disorder first recognized in 1969.[1] The CNS is involved in 5% of cases and generally mimics meningiomas. Bone erosion can be detected in the spine.[2] Herein, we describe a rare CNS manifestation of RDD resembling a neurodegenerative ataxia.

AUTHOR CONTRIBUTIONS

Dr. da Silva: case description conception, neuroimaging conception, pathology conception, writing of the first draft (nothing to disclose). Dr. Pedroso: case description conception, case description organization, case description execution, neuroimaging organization, pathology organization, writing of the first draft, manuscript review and critique (nothing to disclose). Dr. Moraes: case description conception, neuroimaging conception, pathology conception, writing of the first draft. Dr. Rivero: neuroimaging conception, neuroimaging organization, manuscript review and critique. Dr. Callegari:

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From the Department of Neurology, Ataxia Unit (C.C.d.S., J.L.P., F.M.d.M., F.F.T., O.G.P.B.), and Department of Pathology (F.M.C., F.A., J.N.S.), Universidade Federal de São Paulo; and Department of Radiology (R.L.M.R.), Universidade Federal de São Paulo and Delboni Auriemo, Diagnósticos da América, São Paulo, Brazil.

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pathology conception, pathology organization, manuscript review and critique. Dr. Araujo: pathology conception, pathology organization, manuscript review and critique. Dr. Toso: case description conception, neuroimaging conception, pathology conception, writing of the first draft. Dr. Stávale: pathology conception, pathology organization, manuscript review and critique. Dr. Barsottini: case description conception, case description organization, case description execution, writing of the first draft, manuscript review and critique.

STUDY FUNDING

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DISCLOSURE

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

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Introduction

Pediatric Perspective

By Ariel M. Lyons-Warren, MD, PhD, and Anne Tilton, MD

As symptom management improves and new targeted treatments become available, patients are living longer with neurologic disease. Transitioning a pediatric patient with a chronic neurologic condition to adult care presents unique challenges for both patients and providers, which can be overcome through awareness of disease-specific concerns.

Pediatric providers can help improve transition of care for patients by starting the discussion of transitioning early, communicating directly with the accepting provider, and providing a detailed clinical summary in the last clinic note. However, adult neurologists will also benefit from a familiarity with disorders that were traditionally considered pediatric conditions. The articles on Jeavons syndrome and nocturnal seizures discussed in this chapter illustrate the importance of adult management of pediatric neurologic disease.

Furthermore, genetic testing has broadened our understanding of the phenotypic heterogeneity of both rare and common pediatric diseases. It is now clear that some of these diseases, such as described in the articles on Niemann-Pick disease and mitochondrial neurogastrointestinal encephalomyopathy, can manifest in adulthood.

Awareness of the pediatric forms of these diseases will assist the adult neurologist in making a diagnosis and providing patient education. Finally, patients with pediatric neurologic conditions such as childhood-onset epilepsy may experience a continued evolution of their disease process into adulthood. An understanding of the pathophysiology and natural progression of these conditions will greatly benefit the adult provider in identifying adult-onset complications.

From the Division of Child Neurology in the Department of Pediatrics (A.M.L.-W.), Baylor College of Medicine, Houston, TX; and Section of Child Neurology, Department of Neurology (A.T.), Louisiana State University Health Sciences Center, New Orleans.
Correspondence Dr. Lyons-Warren lyonswar@bcm.edu

Adult Perspective

By Fábio A. Nascimento, MD, and Cynthia L. Comella, MD

At first sight, transition and transfer of care may be perceived as synonyms. In reality, however, these processes are significantly different. Transfer refers to switching responsibility of care at a certain time point, whereas transition corresponds to a planned multistage process that ultimately leads to transferring care. Over recent years, transitioning children with chronic neurologic conditions to adult care has become a topic of increasing interest.

Given the inherent contrast between pediatric and adult health care models, it is intuitive to expect undesired outcomes when patients are simply transferred into an adult system. This matter becomes even more relevant in light of the approximately 750,000 pediatric patients who require transition of care yearly in the United States. Based on our current understanding of this topic, there seems to be several barriers to a successful transitioning process—including suboptimal communication between the adult and pediatric providers and unfamiliarity of adult neurologists with pediatric disorders.

Generally, adult neurologists are not experienced with the diagnosis and care of pediatric conditions. These are often either rare or rarely seen by adult providers. Within the field of epilepsy, for instance, there are quite a few syndromes that are associated with childhood-onset seizures but may remain undiagnosed until patients are older. These include conditions such as autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), eyelid myoclonia with absences, and epilepsy due to focal cortical dysplasia (FCD). By making an accurate diagnosis, specific treatments and counseling can be applied—for example, indicating surgery in select cases of FCD and offering genetic counseling for patients with ADNFLE. Therefore, adult neurologists should be familiar with the electroclinical features that are characteristic of these syndromes. This knowledge should ideally derive from both independent learning and continued consultation with pediatric colleagues.

This section highlights the importance of adult neurologists being familiar with disorders that are traditionally viewed as pertaining to the pediatric realm. As discussed above, education of adult providers is an essential avenue to ensure a successful transition of care for those children with chronic neurologic conditions.

From the Department of Neurology (F.A.N.), Baylor College of Medicine, Houston, TX; and Neurological Sciences (C.L.C.) Rush University Medical Center, New Philadelphia, OH.
Correspondence Dr. Nascimento nascimento.fabio.a@gmail.com

RESIDENT & FELLOW SECTION

Section Editor
John J. Millichap, MD

Pearls & Oy-sters: Mitochondrial neurogastrointestinal encephalomyopathy

Diagnosis and response to peritoneal dialysis

Ajith Sivadasan, DM
Karthik Muthusamy, DM
Anil Kumar Patil, DM
Vivek Mathew, DM
Mathew Alexander, DM

Correspondence to
Dr. Alexander:
mathewalex@cmcvellore.ac.in

PEARLS

- The clinical spectrum of mitochondrial neurogastrointestinal encephalomyopathy (MNGIE) is heterogeneous. Atypical presentations are frequently misdiagnosed with adverse prognostic implications.
- Ptosis, ophthalmoparesis, and neuropathy are common findings. Gastrointestinal dysmotility is debilitating and leukoencephalopathy gives a diagnostic clue.
- Buffy coat thymidine phosphorylase (TP) activity is a good screening tool to diagnose MNGIE early in resource crunch settings.
- Peritoneal dialysis provides sustained benefit and should be considered for stabilization prior to definitive restorative therapies like stem cell transplantation (SCT) in advanced illness.

OY-STERS

- Platelet transfusions, enzyme replacement, and SCT, though promising, are limited by transient benefits and high expenses and mortality rates.
- Future studies will help in establishing the efficacy of newer therapeutic interventions in MNGIE.

CASE REPORT A 26-year-old man born to nonconsanguineous parents was admitted with complaints of muscle cramps, fatigue, recurrent abdominal pain, and vomiting since 10 years of age. Since 16 years of age, he noted progressive weakness of the proximal and distal muscles of all 4 limbs with intermittent worsening precipitated by febrile illnesses. He reported dysesthesias of the extremities and gait unsteadiness, which worsened in the dark. There was deterioration of symptoms with progressive dyspnea, orthopnea, dysphagia, early satiety, abdominal pain, and postprandial vomiting associated with a weight loss of 13 kg in the 6 months prior to presentation. Previous treatment received elsewhere included intermittent oral corticosteroids and azathioprine with suboptimal benefit. There was history of proximal weakness, recurrent abdominal pain, and respiratory involvement in his younger sibling (age at onset 20 years), who had died of the illness within 4 years of disease onset.

On examination, the patient was grossly emaciated. Body weight was 42 kg, height 174 cm with body mass index (BMI) of 13.9 kg/m^2 (normal population BMI 18.5–22.9 kg/m^2). He was tachypneic with chest expansion of 1.5 cm and paradoxical breathing. There was bilateral ptosis, horizontal gaze restriction, bifacial weakness, reduced palatal movements, and an impaired gag reflex. Motor examination revealed moderate neck weakness and symmetric weakness in upper and lower limbs (proximal Medical Research Council [MRC] grade 4/5 and distal MRC grade 2/5). There was reduction in pain and temperature perception in a glove-stocking pattern. Joint, position sense, and vibration were impaired in all 4 limbs. All deep tendon reflexes were absent. Romberg sign was positive and there was sensory ataxia.

Routine investigations including blood counts and liver and renal function were normal. Autonomic function testing revealed resting tachycardia and orthostatic hypotension within 3 minutes necessitating termination of tilt table test (figure, A). Other investigations included creatine kinase 349 IU/mL (normal 45–195 IU/mL), venous blood lactate 3.2 mmol/L (normal 0.3–1.3 mmol/L), and arterial blood gas analysis showing hypercapneic respiratory failure needing intermittent noninvasive ventilation (NIV). Pulmonary function testing suggested severe restrictive lung disease. Nerve conduction studies (NCS) showed a mixed axonal-demyelinating polyneuropathy with phrenic nerve involvement. Sympathetic skin response was absent. On needle EMG, there was spontaneous activity in the form of fibrillations and positive sharp waves from the tibialis anterior and vastus lateralis. The motor unit potentials were small amplitude and short duration with increased interference. CSF analysis showed 2 cells with elevated protein (148 gm/dL) and normal sugar (73 mg/dL). MRI of the brain showed patchy leukoencephalopathy. Muscle biopsy revealed myopathic changes without ragged-red fibers. There was evidence of cytochrome *c* oxidase (COX) activity with

From the Department of Neurological Sciences, Christian Medical College, Vellore, India.

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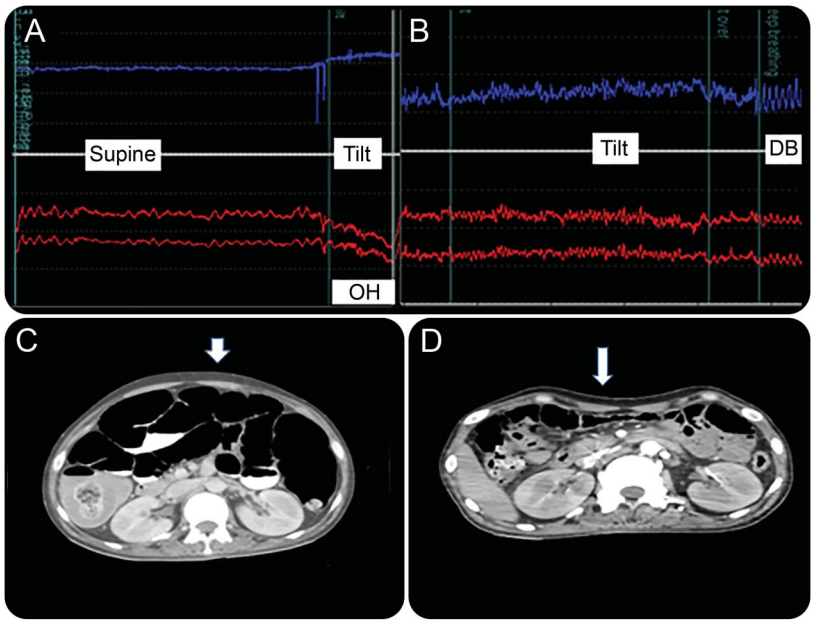
Figure Autonomic functions and CT of abdomen



(A) Autonomic function testing using Finapres shows orthostatic hypotension (OH) within 3 minutes (heart rate blue line, systolic and diastolic blood pressure red line). (B) Posttreatment recording shows no fall in blood pressure even after 10 minutes of tilt with normal heart rate response to deep breathing (DB). (C) CT abdomen during crisis with severe abdominal pain shows distended abdomen and dilated bowel loops with features of intestinal pseudo-obstruction (thick arrow). (D) CT abdomen after initiation of peritoneal dialysis shows improvement in abdominal distension and dilated bowel loops (thick arrow).

COX and COX–succinate dehydrogenase stains. Nerve biopsy showed extensive loss of myelin sheath and axons with myelin ovoid formation without inflammation.

TP assay (expressed as picomoles of thymine formed/cell/h) in leukocytes done by spectrophotometric analysis was 1.24 compared to 18.2 in normal controls (3 controls, SD 4.35). The demonstration of the metabolic defect in the setting of a compatible clinical phenotype and positive family history confirmed the diagnosis of MNGIE.[1] Genetic testing was not done. Hemodialysis was initiated to aid in removal of neurotoxic metabolites. As there was a favorable response to hemodialysis, continuous ambulatory peritoneal dialysis (CAPD) (with 2 L of 1.5% glucose dialysis fluid 3 times a day) was started.

At 3-, 6-, and 9-month follow-up, there was a remarkable improvement in respiratory and neurologic functions. He was weaned off NIV. There was relief from abdominal pain and vomiting with a weight gain of 13 kg. There was improvement in motor power (proximal MRC grade 5 and distal MRC grade 4), dysesthesias, and sensory ataxia, and the patient was ambulant without support. There was significant improvement in autonomic function tests with no orthostatic hypotension and normal heart rate responses to deep breathing and Valsalva maneuver (figure, B). NCS repeated at 9 months revealed improvement in compound motor action potentials. There were no CAPD-related problems like fluid leak or peritonitis.

The patient presented to us at 12 months with relapse of symptoms following temporary discontinuation of CAPD. There was worsening neuromuscular weakness, sensory ataxia, and severe abdominal pain with vomiting and intestinal pseudo-obstruction (figure, C). After clinical stabilization, hemodialysis was started. He improved and CAPD was reinitiated prior to discharge. There was recovery of pseudo-obstruction (figure, D). During subsequent follow-ups at 15, 18, and 24 months, the patient reported steady improvement in his symptoms.

DISCUSSION Challenges in diagnosis and management of MNGIE include phenotypic variability in age at onset, sequence of organ involvement, atypical clinical presentations early in the disease, lack of definite diagnostic tests in resource crunch settings, and limited treatment options.[1,2] Mutations in the *TYMP* gene result in severe deficiency of TP enzyme leading to increased thymidine and deoxyuridine and impaired function of the mitochondrial respiratory chain and DNA.[2] The onset is usually between 15 and 20 years of age.[2] Characteristic features include ptosis, ophthalmoparesis, gastrointestinal dysmotility, cachexia, peripheral neuropathy, and leukoencephalopathy.[2] Extraocular muscle involvement is seen early and parallels disease evolution.[3] The course is invariably fatal, with mortality typically reported between 20 and 40 years of age.[2]

Misdiagnosis is common early in the disease course before all clinical manifestations are apparent.[1] The main differential diagnoses are listed in the table. There is often disproportion between prominent gastrointestinal dysmotility symptoms and mild neurologic involvement (cramps, polyneuropathy). Leukoencephalopathy may be patchy in early illness, eventually becoming confluent and diffuse.[2] Absence of leukoencephalopathy may be seen in MNGIE phenotype associated with RRM2B or POLG mutations, which characteristically have a normal thymidine level.[2]

A decrease in TP activity in leucocytes to <8% of control mean is sufficient for diagnosis.[1] Increased concentrations of thymidine and deoxyuridine are observed. TYMP pathogenic variants are identified in all patients with enzymatically proven disease.[1] DNA sequencing is laborious and expensive in view of the diverse nucleotide changes in the TP gene.[1] However, identification of pathogenic variants in family members will help in assessment of carrier status and prenatal diagnosis.[2,4] In classic cases, homozygous or compound heterozygous mutations cause severe reductions in TP activity[1,5] (<8% of normal).

Table Differential diagnosis of MNGIE with main clinical and laboratory characteristics

Differential diagnosis	Clinical features	Diagnosis
Oxidative phosphorylation and other mitochondrial disorders	Usually childhood onset, broad phenotypic spectrum with ophthalmoparesis, myopathy, neuropathy, sensorineural hearing loss, encephalopathy, seizures, liver, cardiac, and gastrointestinal involvement	High lactate, muscle biopsy showing ragged-red and COX-negative fibers, complex estimations in muscle/skin fibroblast culture; false-negative testing can occur due to heteroplasmy; differentiated from MNGIE by biochemical and genetic studies
Chronic inflammatory demyelinating polyneuropathy	Age at onset variable, subacute to chronic progression, motor predominant proximal weakness, sensory variants known	NCS and nerve biopsy showing demyelinating neuropathy with inflammation and exclusion of other causes
Primary gastrointestinal disorders (gastrointestinal dysmotility, inflammatory bowel disease, celiac disease, irritable bowel syndrome, eating disorders)	Predominant gastrointestinal involvement, though neurologic manifestations can be seen in celiac disease and as a manifestation of nutrient deficiency syndromes due to malabsorption	Endoscopy and biopsies, usually have vitamin and micronutrient deficiencies secondary to malabsorption
Hereditary motor sensory neuropathy: CMTX	Onset in first decade, distal weakness with mild sensory, absent deep tendon reflexes, rarely has hearing loss, transient ataxia, dysarthria, and aphasia, acute worsening with intercurrent illnesses	NCS showing primary axonal neuropathy with demyelinating features, MRI brain showing white matter changes, and genetic studies (*GJB1*)
Leukodystrophies (Krabbe disease, adrenoleukodystrophy, metachromatic leukodystrophy vanishing white matter disease, Alexander disease, Canavan disease)	Usually of childhood onset, gradually progressive nature with central and peripheral nervous system involvement	MRI brain, NCS, enzyme assays, and genetic studies
Merosin-deficient congenital muscular dystrophy	Manifests in infancy with motor developmental delay, generalized hypotonia, rarely seizures and intellectual disability	MRI brain showing neuronal migration disorders and white matter changes, elevated CPK, muscle biopsy with immunohistochemistry for merosin, genetic studies

Abbreviations: CMTX = Charcot-Marie-Tooth disease Type X; COX = cytochrome *c* oxidase; CPK = creatine phosphokinase; MNGIE = mitochondrial neurogastrointestinal encephalomyopathy; NCS = nerve conduction studies.

In late-onset cases, compound heterozygous mutations have been associated with partial loss of TP activity (10%–20% of normal) and milder phenotype.[5] Hence, a diagnostic algorithm should include a joint approach comprising both biochemical testing and genetic sequencing.[4]

Treatment modalities that increase TP activity or decrease thymidine and deoxyuridine have clinical benefits.[2] The renal clearance of thymidine is low due to reabsorption in the proximal tubules attributable to the Na^+/thymidine transporter.[6] The effect of hemodialysis in reducing thymidine concentration (by ultrafiltration) only lasts around 3 hours, necessitating multiple sessions.[6] The transient effect is attributable to the fact that the thymidine production exceeds the clearance by dialysis.[6] The advantages of CAPD in this context include fewer fluctuations in view of its continuous nature combined with the lower costs, greater patient mobility, and lesser need for hospitalization.

Yavuz et al.[7] reported the case of a 16-year-old girl treated with CAPD for 3 years with marked improvement in gastrointestinal symptoms and weight gain. Interestingly, the plasma nucleoside levels were unchanged, suggesting that other metabolic factors in addition to toxic nucleosides were involved in pathogenesis.[7] In addition, plasma nucleoside levels may not have reflected the tissue nucleoside levels that may be reduced by CAPD. Our patient also had substantial and sustained relief from gastrointestinal, autonomic, and neurologic symptoms with recurrence on temporary cessation of CAPD. Plasma nucleoside levels were not done in our patient.

Platelet transfusions can partially restore TP activity, but the effects are transient.[2] The long-term benefit of SCT remains unknown in view of the high mortality rates.[2,8,9] Offering SCT at a younger age, before advanced stage of disease, or stabilizing patients by CAPD prior to SCT as observed by Ariaudo et al.[9] might be future strategies. Erythrocyte-entrapped thymidine phosphorylase can prolong the circulating half-life of enzyme, leading to increased elimination of thymidine.[10] Pharmacologic blockade of the nucleoside carriers responsible for renal reabsorption of thymidine could also have potential benefits.[6]

Early diagnosis is paramount considering the heterogeneity of presentation. Assessment of TP function is a good screening method to confirm MNGIE in resource crunch settings. This case highlights the atypical clinical presentations and the potential of CAPD in treatment. The diagnosis of MNGIE may no longer be associated with a poor prognosis in cases that are diagnosed early and appropriately treated.

AUTHOR CONTRIBUTIONS

All authors agree to the conditions outlined in the authorship and contributorship section. Ajith Sivadasan: data collection, interpretation, and drafting the manuscript. Karthik Muthusamy, Anil Kumar Patil, Vivek Mathew: conceptualization and revision of the manuscript. Mathew Alexander: design, interpretation, and revision of the manuscript.

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DISCLOSURE

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RESIDENT & FELLOW SECTION

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Pearls & Oy-sters: A case of refractory nocturnal seizures

Putting out fires without smoke

Pantelis P. Pavlakis, MD, PhD
Laurie M. Douglass, MD

Correspondence to Dr. Douglass: laurie.douglass@bmc.org

PEARLS

- Autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE) is a hereditary form of epilepsy characterized by multiple seizures during stage 2 sleep. It is caused by several different mutations involving the α2, α4, or β2 neuronal nicotinic acetylcholine receptor (nAChR) subunit genes. The net effect of these mutations is increased activity of the nAChRs, because of an increased sensitivity to ACh.
- Carbamazepine or oxcarbazepine are effective first-line agents. Up to one third of patients, however, have refractory seizures. Nicotine is a potentially effective alternative treatment, which may work by desensitizing AChRs to acetylcholine.
- Genetic testing for ADNFLE should be considered in children with multiple, frequent, brief nocturnal seizures, strong family history, and normal results on interictal EEG.

OY-STERS

- Nicotine has been reported to be effective in a limited number of studies. However, the efficacy, and potential toxicity, of long-term treatment is unknown.

CASE REPORT The patient presented at age 16 years with nocturnal seizures. Her family frequently noticed restless movements during sleep.

In the first few years, the patient's seizures were well-controlled. At age 19 years, she had normal results on routine EEG recording in wakefulness and stage 1 sleep. Brain MRI at age 20 years was normal.

The patient's medical history was notable for glaucoma, which resolved at age 22 years.

The patient's brother and a paternal cousin had similar seizures since their early teens, confirmed by continuous video EEG monitoring (cVEEG). At age 17 years, her brother started smoking and self-discontinued his anticonvulsant. He believed that he was seizure-free, which was confirmed by normal results on cVEEG. Her father, a heavy smoker, was asymptomatic.

The patient had never smoked, used alcohol, or used illicit drugs. Her developmental history was normal and she completed college without difficulty.

Neurologic examination results were normal, except for difficulty in tandem gait that predated the use of phenytoin.

In the following years, the patient had multiple cVEEG admissions because of increased seizure frequency. cVEEGs revealed clinical and electrical seizures arising out of stage 2 sleep every 10–30 minutes and lasting 30–60 seconds each. They were characterized by version of the head to the left, posturing of one or both upper extremities (right upper extremity more than left), fumbling, and lip-smacking. EEG showed abrupt onset of sharply contoured 9 Hz waves increasing slightly in voltage and evolving into medium voltage 5–6 Hz theta activity, without focal onset or discrete spikes. Sometimes slower activity was seen over the frontal and central regions. There was a paucity of slow wave and REM sleep. The awake background was normal. A sleep study at age 20 years showed absence of slow-wave sleep and reduced amounts of REM sleep, without any evidence of central or obstructive apnea.

Between age 16 and 27 years, the patient tried and failed multiple anticonvulsants: oxcarbazepine, lamotrigine, levetiracetam, zonisamide, valproic acid, acetazolamide, pregabalin, phenytoin, clorazepate, and lacosamide. A vagal nerve stimulator was also implanted without success.

The clinical suspicion of ADNFLE was confirmed by genetic testing at age 24 years. DNA sequencing showed the presence of serine 284 to leucine mutation in the *CHRNa4* gene, which has been reported to be a disease-associated mutation in individuals with ADNFLE.[1] This gene encodes the α4 subunit of the nAChR.

The patient underwent cVEEG again at age 26 years (figure) because she believed her seizures were causing increasing memory impairment, anxiety, and fatigue affecting her work. At that time, she was treated with phenytoin, pregabalin, clorazepate, and lacosamide. EEG initially showed multiple events occurring during stage 2 sleep. These occurred on

From the Departments of Neurology (P.P.P., L.M.D.) and Pediatrics (L.M.D.), Boston Medical Center, Boston University, MA.
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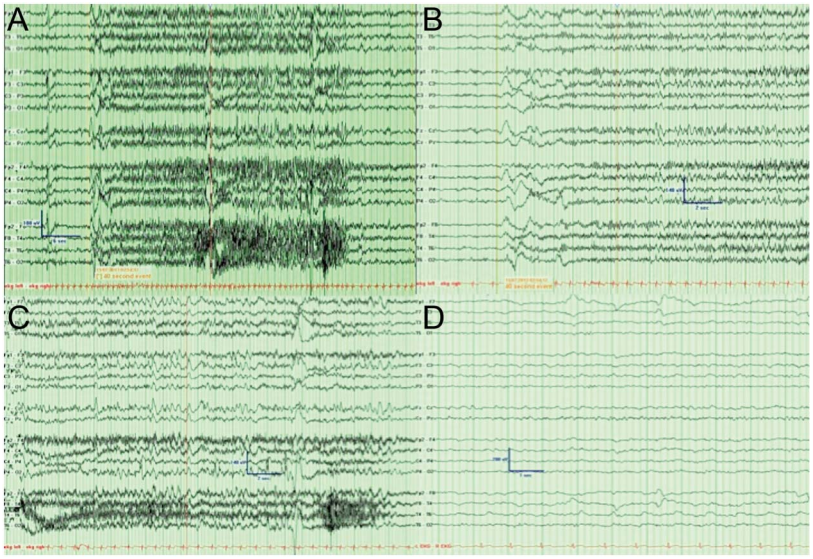
Figure EEG findings during continuous video EEG monitoring at age 26 years



(A) A compressed view of a 40-second seizure prior to nicotine treatment. (B) The first 20 seconds of the same seizure at 30 mm/s. (C) The second 20-second portion of the same seizure at 30 mm/s. (D) REM sleep during treatment with transdermal nicotine. Note the lateral eye movements at F7-8.

average every 60 seconds, lasting on average 6–8 seconds. There were a few seizures lasting up to 60 seconds. The seizures and their electrical correlate were similar to what was seen on prior studies. Due to frequent seizures, there was a paucity of slow-wave sleep and complete absence of REM sleep. On the second day of her hospital admission, a 7-mg nicotine patch was applied about 2–3 hours before bedtime. There was almost complete resolution of clinical and electrical events. The duration of slow-wave sleep increased and REM sleep was recorded. The next morning, the patient felt refreshed and less anxious. A 14-mg patch was tried, but the patient became nauseous. She tolerated transdermal nicotine well, with the exception of myalgia at the site of application, which resolved after the patch was applied to her buttock. She was discharged on a 7-mg nicotine patch, clorazepate, phenytoin, and lacosamide. Two weeks later, she reported that her sleep had improved and her anxiety had resolved. She experienced no side effects from the nicotine patch.

DISCUSSION ADNFLE was first described as a distinct entity in 1995, when 47 patients from 5 families were described.[2] Age at onset ranged between 2 months and 52 years, with a median of 8 years. Patients reported clusters of nocturnal seizures, with a median frequency of 6 per night, ranging up to 70 per night. Median duration was 60 seconds, ranging from 5 seconds to 5 minutes. In 84% of patients, interictal EEG had normal results. Ictal EEG usually demonstrated bilateral slow-sharp wave discharges in the anterior quadrants during stage 2 sleep. Carbamazepine was effective in controlling seizures in most patients.

ADNFLE was the first idiopathic focal epilepsy attributed to a receptor mutation, namely the nAChR. Multiple mutations of the α2, α4, and β2 nAChR subunit genes have been described. Their net in vivo effect is increased cholinergic neurotransmission.[3] Different mutations of the nAChR may exert distinct effects leading to epileptogenesis. In vitro assays of homozygous mutant nAChR subunits lead to decreased ACh-induced currents and increased nAChR desensitization. However, when these receptors were coexpressed with wild-type AChRs, the net effect was increased ACh-induced currents. In vivo studies also show evidence of increased cholinergic neurotransmission.[3–5] The mechanisms of nicotine's beneficial effects are unclear. It is thought to be due to AChR desensitization after prolonged use.[3] Our patient, however, seemed to respond to the nicotine patch after only 1 day of treatment.

Carbamazepine and oxcarbazepine are first-line treatments; however, up to a third of patients have refractory epilepsy.[6] Outcomes of surgery are poor in frontal lobe epilepsy, possibly due to lack of localizing findings on EEG and imaging in most cases.[7] Nicotine is a potentially effective treatment of ADNFLE. The sentinel ADNFLE patient treated with transdermal nicotine remained virtually seizure-free during 9 months of treatment, compared to placebo or no treatment.[8] In another study, tobacco habits of ADNFLE patients from 2 pedigrees were reviewed. Ten out of 14 tobacco users were seizure-free.[4]

Once lesional causes of epilepsy have been excluded, the differential is relatively narrow, including familial partial epilepsy with variable foci, night terrors, periodic limb movement disorder, restless legs syndrome, obstructive sleep apnea, and familial paroxysmal kinesiogenic and nonkinesiogenic dyskinesia. Such findings, and a positive family history, should prompt the consideration of genetic testing.

As seizures in ADNFLE originate from stage 2 sleep, interictal EEG is usually normal if this stage is not captured. Therefore, EEG should include stage 2 sleep to increase its diagnostic yield.

In this article, a case of refractory ADNFLE responding to transdermal nicotine is presented. The first day of treatment there was dramatic symptomatic improvement and almost complete resolution of clinical and electrical events. The patient's brother has also been seizure-free for many years off treatment after starting smoking. Their father, a heavy smoker, is the likely obligatory carrier, as there is a paternal cousin with the same disorder. He has never experienced seizures but has never had cVEEG.

Our patient had prolonged REM sleep deprivation, confirmed by cVEEG. It is well-established that REM sleep deprivation has multiple effects on the CNS, including emotion, memory, and learning.[9] Apart from epilepsy, our patient also had anxiety, which almost immediately resolved with the re-emergence of REM sleep.

Despite the clinical success in this patient, there are some concerns regarding long-term nicotine treatment. Studies have failed to demonstrate an increased risk of cardiovascular adverse events[10] with nicotine treatment, but these studies have looked at short-term treatment for smoking cessation, while the effects of long-term nicotine treatment remain unknown. The potential teratogenic effects, as well as the risk of fetal nicotine exposure, should also be considered, as ADNFLE often affects women of childbearing age.[11] Even though nicotine seems to be an effective treatment, its long-term efficacy has not been studied. Caution is also needed to avoid the perception that smoking is encouraged, particularly given the fact that ADNFLE often affects adolescents.

ADNFLE is a hereditary form of epilepsy characterized by nocturnal seizures arising from stage 2 sleep. ADNFLE can be caused by different mutations of the neuronal nAChR, ultimately leading to increased cholinergic neurotransmission. Although carbamazepine and oxcarbazepine are often effective first-line treatments, here we report a case of ADNFLE refractory to multiple different treatments, including vagal nerve stimulation. Transdermal nicotine, which ultimately alters cholinergic neurotransmission, may be an effective and well-tolerated treatment for ADNFLE. There are, however, limited data regarding the long-term safety and efficacy of this treatment.

AUTHOR CONTRIBUTIONS

Dr. Pavlakis was involved in the care of the patient and drafted this manuscript. Dr. Douglass was involved in the care of the patient and revised this manuscript. The final version was read and approved by all the authors.

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Pearls & Oy-sters: Niemann-Pick disease type C in a 65-year-old patient

Niraj Kumar, MD, DM
Philippe Rizek, MSc, MD, FRCPC
Yahia Mohammad, MBBCh, PhD
Mandar Jog, MD, FPCPC

Correspondence to Dr. Jog: mandar.jog@lhsc.on.ca

PEARLS

- Niemann-Pick disease type C (NPC) has heterogeneous clinical presentations.
- Although NPC usually affects infants or young adolescents, it should be considered in the differential diagnosis of vertical supranuclear gaze palsy, regardless of age at presentation.
- Adult-onset NPC may rarely present with myoclonus.
- Disease-specific therapy with miglustat has been shown to stabilize the neurologic progression in patients with NPC.

OY-STERS

- NPC can present as late as the 6th–7th decade.
- Although more common disorders like progressive supranuclear palsy (PSP) should be suspected, NPC should also be considered in the differential diagnosis of late-onset vertical gaze palsy, thereby minimizing the diagnostic delay.
- Rare symptoms of myoclonus and sensorineural hearing loss can mislead the clinician away from the diagnosis of NPC.

CASE REPORT A 65-year-old, right-handed man of Polish ancestry developed insidious onset, gradually progressive gait ataxia at the age of 55. Three years later, he started dropping things due to myoclonic jerks involving the trunk and upper extremities (video on the *Neurology*® Web site at Neurology.org). Worsening ataxia and frequent falls resulted in the use of a wheelchair by age 64. His medical history was positive for bilateral hearing loss since his early 50s. There was no history of seizures, dysphagia, mood disorders, psychosis, or any other significant medical illness in the past, besides being a 40-pack-year smoker. He was born of nonconsanguineous parents, and his sister died of an unknown illness at the age of 13. On neurologic examination, cognition was normal and speech was dysarthric. Although visual acuity was normal, there was reduced vertical gaze (more pronounced on downgaze), which responded to oculocephalic maneuver, consistent with a vertical supranuclear gaze palsy (VSGP). Horizontal eye movements were intact, and there was no nystagmus. Bilateral sensorineural hearing loss was detected, right more than left. Generalized myoclonic jerks were present, predominantly involving the upper extremities on posture maintenance. There were no features suggestive of parkinsonism. He had marked gait ataxia with milder appendicular ataxia and dysdiadochokinesia. The remainder of his neurologic examination was normal. Abdominal examination did not reveal any visceromegaly. The NPC suspicion index score[1] was 61. Laboratory workup showed normal complete blood count, serum electrolytes, creatinine, glucose, liver function test, serum lactate, and EEG. Spinocerebellar ataxia gene panel was negative for *SCA1*, *SCA2*, *SCA3*, *SCA6*, *SCA7*, *SCA8*, and *SCA17*. Genetic testing for NPC was positive for 2 pathogenic variants (p.P1007A and p.1077Q) of *NPC1* gene. MRI brain showed cortical and midbrain atrophy with subcortical nonspecific white matter changes (figure). His myoclonic jerks responded to valproate 500 mg oral twice daily. He was started on miglustat 100 mg oral twice daily titrated to 200 mg oral 3 times a day.

DISCUSSION NPC is a rare lysosomal lipid storage disorder characterized by heterogeneity in the age at onset, clinical presentations, and disease course.[2] It has an incidence of 1 per 120,000 live births.[1] While mutation in the *NPC1* gene (located on chromosome 18) results in >95% of cases, mutation in the *NPC2* gene (located on chromosome 14) occurs in approximately 4% of cases.[1] The mutations cause abnormal intracellular transport and accumulation of cholesterol and glycosphingolipids in the brain and other tissues.[1,3] Based on the age at onset, patients with NPC are categorized into 5 subgroups: prenatal/perinatal (age between 0 and 3 months), early-infantile (<2 years), late-infantile (2 to <6 years), juvenile (6 to <15 years), and adolescent/adult (≥15 years).[1,3] Although previously considered a childhood-onset disorder, growing awareness along with advancements in biochemical and genetic diagnostic methods have increased detection of late-onset cases.[4] Adolescent/adult NPC cases comprised 17%–27% of the 309

Supplemental data at Neurology.org

From the Department of Clinical Neurological Sciences, Western University, London, Canada.

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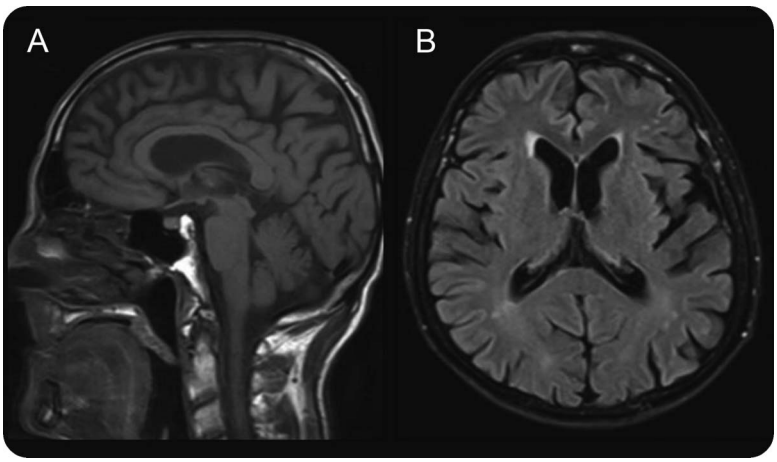
patients reported in 2 separate studies.[2,4] Of the 4 reported patients with NPC with an age >50 years at diagnosis,[5,6] 3 presented with neurologic or psychiatric manifestations.[5] Our patient had onset of neurologic symptoms at age 55 years, second only to a case reported with onset of symptoms at 59 years of age.[7]

The heterogeneous clinical manifestations of NPC include systemic, neurologic, and psychiatric features.[1] Systemic features like neonatal jaundice, hepatosplenomegaly, or isolated splenomegaly are common in early-onset disease, and always precede neurologic manifestations.[1,3] Almost 15% of all patients with NPC, and half of those with adult-onset disease, have minimal or no hepatosplenomegaly.[3] The presence of isolated splenomegaly without any hepatic derangement in patients with a neurodegenerative or psychiatric illness favors NPC.[1] The most common neurologic manifestations include cognitive or motor developmental delay in childhood-onset cases, VSGP, ataxia, dysarthria, dysphagia, dystonia, seizures, and gelastic cataplexy.[1,3] Although VSGP may be seen in other neurologic disorders (table),[8] it is one of the earliest features in NPC, and is present in 70%–80% of patients across all age at onset categories.[1,2,4] With disease progression, horizontal saccadic eye movements are also affected, leading to complete ophthalmoplegia, reflecting progressive brainstem degeneration.[1] Myoclonus is rare in adult-onset NPC,[1] but it was a major neurologic manifestation in our patient, along with VSGP, ataxia, and bilateral sensorineural hearing loss. Sensorineural hearing loss is commonly seen in clinical practice but remains underreported in patients with NPC.[1] Frontal-subcortical cognitive deficits and schizophrenia-like psychosis are usually seen in patients with adolescent/adult-onset NPC.[1,2] The combination of phenotypic and genetic heterogeneity precludes formation of genotype–phenotype correlations in patients with NPC.[4]

In order to facilitate diagnosis of NPC in suspected patients, the NPC suspicion index was developed, which incorporates visceral, neurologic, and psychiatric features, along with the family history.[1] A score ≥70 suggests immediate testing for NPC, and scores from 40 to 69 indicate a need for further follow-up.[1] The probability of NPC is very low with scores below 40.[1] Because of the NPC suspicion index score falling in the gray zone (40–69), along with the heterogeneity in clinical presentation, long diagnostic delays occur in patients with adult-onset NPC,[1–3] as seen in our patient. In the 3 reported patients with NPC with neurologic illness and age at diagnosis >50 years, the mean delay in diagnosis was 13.5 years for the 2 cases where data was available.[5] In our patient, there was a delay of almost 10 years in reaching the diagnosis of NPC. Thus, in adult patients with progressive VSGP, ataxia, dysarthria, dysphagia, cognitive decline, and psychiatric symptoms, one should suspect NPC. An accompanying family history suggestive of NPC is helpful but not necessary. The clinical diagnosis may be supported by brain imaging findings, which alone are nondiagnostic.[1,3] MRI brain may show cerebral or cerebellar atrophy, white matter hyperintensities, and midbrain atrophy,[1] as was seen in our patient. There is a lesser degree of increase in pontine-to-midbrain ratio in adult patients with NPC than that seen in PSP.[9]

Patients with NPC with onset of neurologic disease in early childhood develop rapid disease progression, and die at a younger age, as compared to those with late-onset neurologic involvement.[1,4] Progressive dysphagia leading to repeated aspirations and bronchopneumonia causes the majority of deaths in patients with NPC.[1] Symptomatic treatment for various neurologic and psychiatric manifestations improves quality of life in patients with NPC.[1] The myoclonic jerks in our patient improved on valproate. Miglustat is the only disease-specific therapy approved to treat progressive neurologic manifestations in pediatric and adult patients with NPC.[10] It competitively inhibits glucosylceramide synthase, and reduces glycosphingolipid accumulation in the brain, thereby stabilizing the neurologic features like ambulation, manipulation, swallowing, and language.[1,10] It is advocated for all patients with neurologic, psychiatric, and cognitive manifestations at the time of diagnosis of NPC.[1] The usual recommended dose for adolescent/adult patients is 200 mg oral 3 times a day and should be adjusted according to body surface area in children.[1,10] The clinical improvement is noticeable

Figure MRI brain



MRI brain shows cortical and midbrain atrophy on T1-weighted sequence (A), and cortical atrophy along with subcortical nonspecific white matter changes on fluid-attenuated inversion recovery sequence (B).

Table Neurologic disorders associated with vertical supranuclear gaze palsy (modified from Salsano et al.[8])

Etiology by group	Disorders
Genetic	
Autosomal dominant	Autosomal dominant spinocerebellar ataxia (*SCA1, SCA2, SCA3, SCA6, SCA7, SCA17*)
	Dentatorubral pallidoluysian atrophy
	Autosomal dominant with hereditary spastic ataxia
Autosomal recessive	Kufor-Rakeb disease
	Pantothenate kinase–associated neurodegeneration
	PLA2G6-related dystonia parkinsonism
	Autosomal recessive cerebellar ataxia syndrome with upward gaze palsy, neuropathy, and seizures
	Ataxia telangiectasia
	Nonketotic hyperglycinemia
	Tay-Sachs disease
	Joubert syndrome
Sporadic	Progressive supranuclear palsy
Mitochondrial (autosomal recessive, autosomal dominant, and X-linked)	Leigh syndrome
Structural	Focal midbrain lesion (e.g., from hydrocephalus, stoke, or tumors)
	Following thalamic deep brain stimulation
Metabolic	Kernicterus
	Manganese intoxication
Paraneoplastic	Paraneoplastic brainstem encephalitis (anti-Ma)

by 6 months to 1 year of drug use. The commonly observed side effects are diarrhea, flatulence, abdominal discomfort, weight loss, and tremor.[1,10] While its use in hepatic impairment has not been evaluated, it should be avoided in patients with severe renal impairment (creatinine clearance rate of <30 mL/min/1.73 m^2).[10] Our patient was started on miglustat once genetic diagnosis was made to stabilize his neurologic disease.

We report the second oldest patient at diagnosis with NPC. Myoclonus is not commonly seen in adult-onset NPC, but our patient had myoclonus as one of the major disabling features, along with more commonly reported ataxia and VSGP. Thus, NPC should be suspected in the presence of myoclonus and VSGP. Although increased awareness and improved diagnostic tools have raised the detection rate of NPC, diagnostic delays are still a major concern, especially when substrate reduction therapy using miglustat may stabilize the progression of neurologic disease.

AUTHOR CONTRIBUTIONS

Dr. Kumar: conception, design, and writing the first manuscript. Dr. Rizek: conception, design, review, and critique. Dr. Mohammad: conception, review, and critique. Dr. Jog: review and critique.

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DISCLOSURE

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RESIDENT & FELLOW SECTION

Section Editor
John J. Millichap, MD

Pearls & Oy-sters: The chapeau de gendarme sign and other localizing gems in frontal lobe epilepsy

Yee-Leng Tan, MRCP*
Wolfgang Muhlhofer, MD*
Robert Knowlton, MD, MSPH

Correspondence to Y.-L. Tan: yee-leng_tan@nni.com.sg

PEARLS

- Unlike temporal lobe epilepsy (TLE), the many semiologic features of frontal lobe epilepsy (FLE) are protean, and often epileptiform discharges or ictal patterns on EEG are not localized.
- We highlight 2 lesser-known signs associated with FLE:
  1. Ictal pouting, also known as the chapeau de gendarme sign, is an easily recognizable facial expression with its origins in the frontal lobe, seen early on in frontal lobe seizures.
  2. Interictal rhythmic midline theta (RMT) on scalp EEG occurs with a greater preponderance in FLE compared to TLE, and may be a useful localization clue if not seen during drowsiness or mental activation.

OY-STERS

- Interictal FDG-PET imaging is often used in the identification of epileptogenic cortex. Subtle areas of hypometabolism on FDG-PET may be missed; FDG-PET/MRI coregistration can improve its sensitivity.

CASE REPORT A 28-year-old right-handed woman with a history of medically intractable localization-related epilepsy was admitted to the epilepsy monitoring unit (EMU) for continuous video-EEG, with the aim of characterizing her seizures and evaluating her surgical eligibility. Her seizures began when she was 18 months of age. There were no perinatal complications, and she attained normal cognitive and motor developmental milestones. Her history was negative for febrile seizures, significant head trauma, or CNS infections. No family history of a seizure disorder was present. She had failed several antiepileptic medications that achieved therapeutic dosing levels, including but not limited to carbamazepine, clonazepam, levetiracetam, and eslicarbazepine.

Her epilepsy was characterized by partial-onset seizures arising predominantly during sleep, and only rarely secondarily generalizing into tonic-clonic seizures. Her family described a downward turning of the mouth ("as if she was really sad and about to cry"), followed by tonic posturing of the right arm. When awake at the onset, she recounted an antecedent aura of a pressure-like sensation in her chest and inability to speak. The duration of her habitual seizures was less than a minute; they were usually followed by a short period of postictal agitation and tearfulness. They also had the tendency to cluster, and on average she had at least 3 seizures per night. Her neurology examination yielded normal findings.

She was monitored in the EMU for 11 days. During this period, more than 50 brief focal seizures were captured, averaging 10–30 seconds in duration. Both the semiology and EEG findings were stereotyped. She would rouse, open her eyes, and develop a sustained ictal pout (figure 1). Longer seizures were followed by right gaze deviation, and a tonic extension of first the right, then left arm. The seizures occurred predominantly out of stage 2 sleep, and had the propensity to occur in the early morning between 4:30 and 6:00 AM. One secondarily generalized tonic-clonic seizure was also recorded. She was not able to activate the push button or alert anyone during the seizures, despite remaining conscious. A video-EEG recording of one of her habitual seizures is shown in the video at Neurology.org.

The EEG background in wakefulness consisted of a low-voltage diffuse beta activity, with a poorly sustained 8 Hz posterior dominant rhythm. No interictal epileptiform abnormalities were seen, but there were intermittent rhythmic runs of 3.5–4 Hz central theta slow waves seen maximally at Cz, without accompanying clinical signs (figure e-1). The ictal onset was neither lateralizing nor localizing, and was characterized by widespread paroxysmal fast frequencies seen maximally over the parasagittal electrodes, sometimes preceded by a diffuse attenuation/desynchronization.

Supplemental data at Neurology.org

*These authors contributed equally to this work.

From the Department of Neurology (Y.-L.T., W.M., R.K.), University of California, San Francisco; and the Department of Neurology (Y.-L.T.), National Neuroscience Institute, Singapore.

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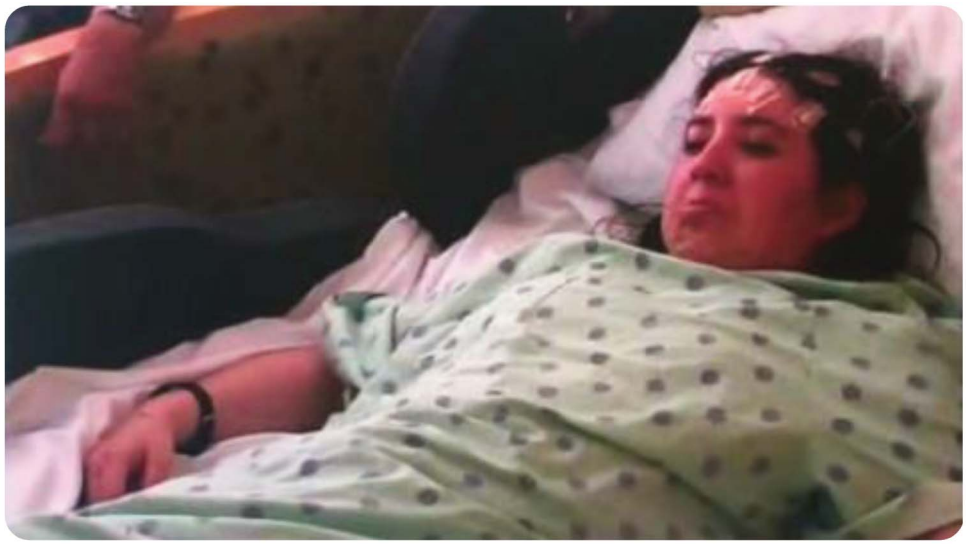
Figure 1 Seizure semiology



The chapeau de gendarme or ictal pout sign is shown here during one of the patient's habitual seizures, characterized by a turned-down mouth.

During the same admission, the patient underwent 3T MRI of the brain, which revealed an area of cortical thickening deep in the left frontal operculum extending into the insula more posteriorly. This thickening was associated with blurring of the gray-white junction and T2 prolongation in subadjacent white matter that formed a transmantle sign (figure e-2). An interictal FDG-PET scan was acquired subsequently a few months later during presurgical planning. Initially read as negative, a further step in image analysis using FDG-PET/MRI coregistration later revealed a focal area of hypometabolism concordant with the lesional site on MRI (figure e-3).

The patient was eager to pursue surgery, and was willing to accept the risk of language deficits posed by the lesion's close proximity to the Broca area (from the anatomical standpoint). Her case was discussed at a multidisciplinary presurgical conference, and a surgical strategy was planned to include intracranial EEG (ICEEG) with both subdural and depth electrodes. ICEEG recorded several of her habitual seizures, confirming an intralesional and perilesional ictal onset (figure e-4). Near-total en bloc resection of the lesion was performed (part of the lesion deep in the insula was left behind due to accessibility limits), and tissue histopathology confirmed FCD type IIB. Due to seizure recurrence, she had further extension of the lesional resection along the inferior aspect of the remaining insula. Postresection MRI did not reveal any residual dysplasia. No neurologic deficits were seen following either of the surgeries. At her last (6 months) postoperative follow-up, she was free of her habitual seizures. Eslicarbazepine and clonazepam were discontinued, and she was maintained on a stable dose of carbamazepine.

DISCUSSION FCDs are intrinsically epileptogenic, and stereo-EEG studies have demonstrated both ictal discharges and intralesional rhythmic spike discharges to originate from dysplastic cortex.[1] Type II FCDs are more common in extratemporal regions, especially in the frontal lobe.[2] This case vignette highlights 2 uncommon but useful features seen in frontal lobe epilepsy, with corroborative anatomical localization from MRI and ICEEG.

The chapeau de gendarme or ictal pout sign is characterized by a turned-down mouth produced by bilateral lip and chin contraction. This term gives reference to the shape of the gendarme's hat seen during Napoléon I's time. If seen early, it confers a high localization value to the frontal lobe. In an analysis of ICEEG recordings belonging to 11 patients with this sign,[3] the epileptogenic zone was localized to the anterior cingulate (n = 4), orbito-frontal region (n = 2), mesial prefrontal/premotor cortex (n = 3), supplementary motor area (n = 1), and inferior frontal gyrus (n = 1). The presence of the ictal pout sign in our patient, together with the stereotyped, brief, and nocturnal nature of her seizures with preserved consciousness, were all highly suggestive of FLE. Although zones of frontal lobe networks underlying semiologic production exist,[4] it remains difficult to pinpoint sublobar anatomical origins of frontal lobe seizures based on semiology alone, due to extensive interregional connectivity within the frontal lobe and rapid seizure propagation.

The RMT on EEG, another feature present in our patient, was first described by Cigánek[5] in 1961 as an abnormal finding associated with epilepsy. Subsequently, RMT was also observed in normal participants

who were drowsy or engaged in cognitive tasks. More recently, a study conducted on 162 patients who underwent at least 3 days of continuous video-EEG monitoring demonstrated that interictal RMT in wakefulness was found significantly more frequently in FLE (26/54; 48.1%) compared to TLE (2/54; 3.7%) patients, and was not observed in healthy controls.[6] Therefore, when care is taken to exclude a drowsy state or mental activation, RMT serves as a useful EEG correlate of dysfunction, seen more commonly in FLE compared to TLE. It may be the only interictal abnormality seen in FLE patients, since many FLE patients lack any form of interictal epileptiform discharges.

MRI is the primary imaging modality used in epilepsy evaluation; however, there is an additional role performed by interictal FDG-PET. FDG-PET is particularly useful for detecting FCDs that are MRI-negative. MRI also often underestimates the extent of the FCD, and FDG-PET can help to identify the perilesional epileptogenic region, or it may reveal a seizure focus at some distance away from the lesion. This is especially pertinent if the scalp EEG findings are nonlateralizing or nonlocalizing, and these additional areas of hypometabolism should be investigated further with ICEEG to delineate the epileptogenic zone. FDG-PET/MRI coregistration has been shown to increase the sensitivity of FCD detection compared to visual analysis of FDG-PET alone.[7] It also gives more precise anatomical information due to better spatial resolution of the MRI. In an observational study,[8] the use of FDG-PET/MRI coregistration aided lesion localization in 48% of patients with type I FCD and 11% of patients with type II FCD with nonconcordant MRI and EEG findings. False-positives were rare (2%). Care should be taken to ensure that FDG-PET scans are performed in the interictal state, as seizures occurring during the FDG uptake period may result in false normalization of an interictal hypometabolic region.

This case is a reminder that complete resection of the FCD lesion remains the most important predictor overall of seizure freedom.[9] In type IIB FCDs, complete cortical resection of the lesion may lead to seizure freedom in as many as 92% of patients.[10]

AUTHOR CONTRIBUTIONS

Dr. Tan: study concept, acquisition of data, data analysis and interpretation, drafting of manuscript. Dr. Muhlhofer: study concept, acquisition of data, data analysis and interpretation, drafting of manuscript. Dr. Knowlton: study supervision, revision of manuscript for intellectual content.

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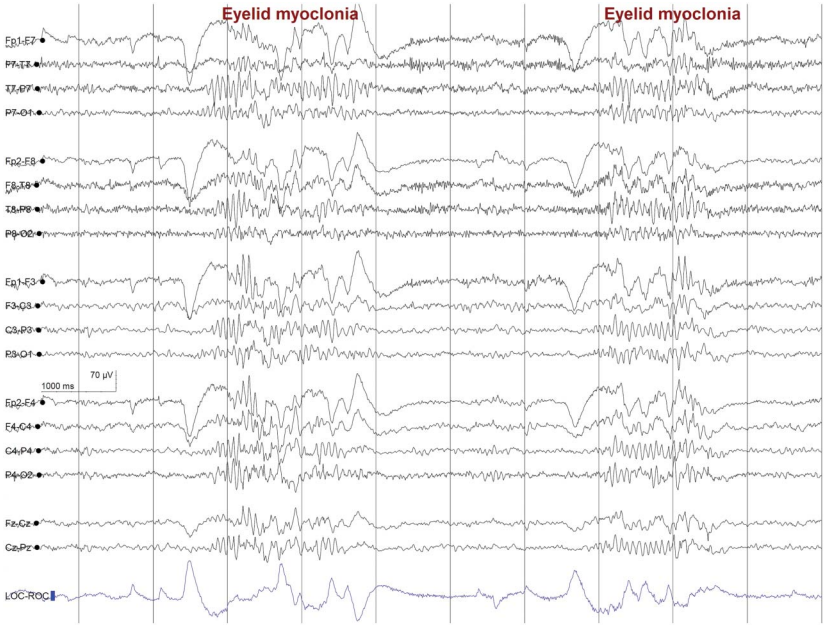
Mystery Case: Eyelid myoclonia with absences in an adult patient

Yousef Hannawi, MD
Shirish S. Satpute, DO
Atul Maheshwari, MD

Correspondence to Dr. Hannawi: yousefhannawi@yahoo.com

Figure 1 Eyelid myoclonia without absence



With levetiracetam: posterior-predominant spiky alpha frequency activity that rapidly spreads to the frontal regions coinciding with eyelid myoclonia.

A 28-year-old man presented to the epilepsy monitoring unit (EMU) with frequent "eye fluttering" episodes since he was 3 years old (video on the *Neurology*® Web site at www.neurology.org). He was diagnosed with epilepsy as a teenager after he developed generalized convulsions at age 12. His convulsions were well-controlled with antiepileptic drug therapy. His neurologic examination was normal.

His EMU study revealed brief episodes of eyelid myoclonia (video) coinciding with a paroxysmal "spiky" posterior alpha activity, which rapidly spread to the frontal regions while he was on levetiracetam (figure 1). These episodes were more prominent in light compared to dark and were often triggered by eye closure. Interictally, the posterior dominant rhythm appeared sharply contoured. Discontinuation of levetiracetam for 3 days resulted in 2 to 3 Hz generalized polyspike and wave activity associated with some of the episodes of eyelid myoclonia, within seconds of eyelid closure (figure 2). Additionally, in sleep there were fragmentary bursts of anteriorly predominant 3 Hz abortive spike and wave discharges. Prior records indicated a photoparoxysmal EEG response.

The patient's clinical and electrographic picture is consistent with eyelid myoclonia with absences (EMA), also known as Jeavons syndrome.

EMA is an underrecognized syndrome of unknown etiology defined by the triad of childhood onset, photosensitivity, and eyelid myoclonia with or without absence seizures.[1,2] Patients often develop generalized tonic-clonic seizures in adolescence.[1,3] The photosensitivity component may decrease as the patients get older.[1,4] Classic EEG features include a sharply contoured or spiky alpha frequency activity that rapidly spreads to the frontal regions with sustained eye closure. Eyelid myoclonia often coincides as well with occipital epileptic discharges or occipital polyspike and wave discharges, with or without generalized polyspike and wave discharges.[3] The overall prognosis of this syndrome is often good as the generalized tonic-clonic and absence

Supplemental data at www.neurology.org

From the Department of Neurology, Baylor College of Medicine, Houston, TX.

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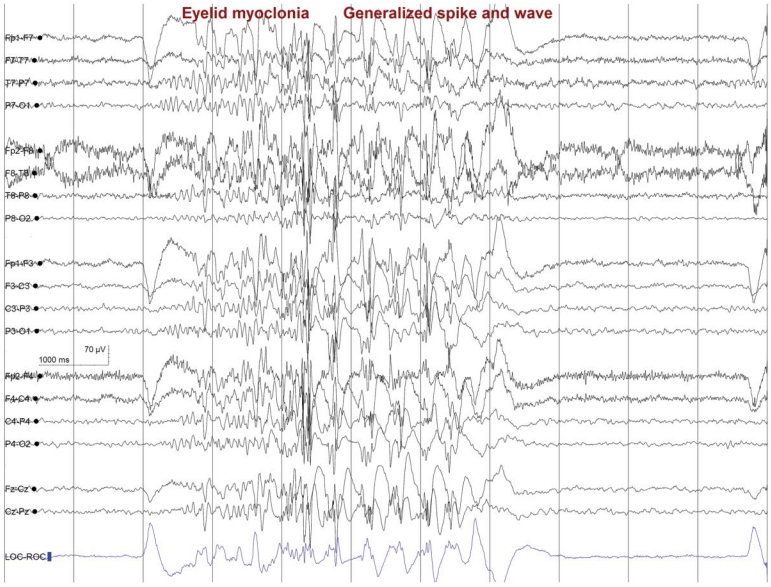
Figure 2 Eyelid myoclonia with absence



After discontinuation of levetiracetam: generalized polyspike and wave discharges within seconds of eyelid myoclonia onset.

seizures become controlled with antiepileptic drug therapy. Despite the sensitivity of the absences to antiepileptic drugs, the eyelid myoclonia often persists, as seen in our patient.[4] A small proportion of patients may continue to have uncontrolled generalized convulsions.[4] Valproic acid, lamotrigine, and levetiracetam are good treatment options,[1,5] whereas sodium channel agents such as carbamazepine may exacerbate the seizures.[6] Our patient initially responded to valproic acid, but he developed a reaction concerning for Stevens-Johnson syndrome. With levetiracetam treatment, his generalized tonic-clonic and absence seizures resolved.

Most adult patients with EMA are diagnosed in childhood, but making the diagnosis in adults for the first time may be challenging. Neurology residents and fellows should be aware of the characteristic clinical and electrographic features of this underrecognized syndrome.

AUTHOR CONTRIBUTIONS

Dr. Hannawi analyzed and interpreted the data, drafted and revised the manuscript. Dr. Satpute analyzed and interpreted the data. Dr. Maheshwari analyzed and interpreted the data, reviewed and revised the manuscript.

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DISCLOSURE

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MYSTERY CASE RESPONSES

The Mystery Case series was initiated by the *Neurology*® Resident & Fellow Section to develop the clinical reasoning skills of trainees. Residency programs, medical student preceptors, and individuals were invited to use this Mystery Case as an educational tool. Responses were solicited through a group e-mail sent to the American Academy of Neurology Consortium of Neurology Residents and Fellows and through social media. All the answers that we received came through social media, from individuals rather than groups.

Most of the respondents (66%) correctly indicated Jeavons syndrome as the most likely diagnosis. The other preferred response was absence epilepsy. The most complete answer came from Dr. Felippe Borlot (Clinical Fellow, Toronto Western Hospital and University of Toronto, Canada). In his response, he pointed out that the key element for this Mystery Case is the fact that these reflex seizures are induced by eye closure and that the epileptiform abnormalities disappear with eye opening. The eyelid myoclonia in this patient is characteristic. Jeavons syndrome can be misdiagnosed as childhood or juvenile absence epilepsy, other forms of genetic or idiopathic generalized epilepsies, or even facial tics.

This Mystery Case illustrates a classic epilepsy syndrome, usually refractory to treatment, which persists throughout life.

Dragos A. Nita, MD, PhD, FRCPC
Division of Neurology, The Hospital for Sick Children, University of Toronto, Canada

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