A 10-Month-Old With Intermittent Hypotonia and Paralysis

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A 10-month-old boy presented with a 1-day history of flaccid quadriplegia and dysconjugate gaze. His history was remarkable for stereotyped episodes of flaccid quadriplegia or hemiplegia, oculomotor abnormalities, and limb or neck posturing, beginning in the first days of life and becoming more frequent and more prolonged over time. The patient was healthy and developmentally normal between episodes. Results of extensive laboratory evaluations, including EEG and brain imaging studies, were negative. The patient's history, diagnostic evaluation, and final diagnosis are reviewed. This case illustrates the importance of a fundamental understanding of neurologic localization in pediatric care and a focused diagnostic approach to an infant with paroxysmal neurologic signs.

CASE HISTORY WITH SUBSPECIALTY INPUT

A 10-month-old boy presented to the emergency department with flaccid quadriplegia and dysconjugate gaze of 1 day's duration. One day before, he had become irritable, followed by development of generalized hypotonia and weakness, occurring over minutes; in addition, his gaze was periodically dysconjugate. There were no respiratory symptoms, and he was able to feed, although he had significant drooling. His consciousness was preserved. His symptoms persisted up to the time of presentation.

The child had been born at term after an uneventful pregnancy to a 32-year-old G2P1A1 mother. He was born by cesarean delivery due to failure of labor to progress. No resuscitation was needed. He was observed in the nursery to have an episode of right arm and leg posturing and shaking, lasting several minutes. The patient was transferred to the NICU, where he had several episodes with extension of his right upper limb, mouth movements, and nystagmoid eye movements. An EEG and head computed tomography scan were normal. He was discharged from the hospital.

For the first 5 months of life, the patient was healthy and developmentally normal, although his parents noted episodes of facial grimacing, head turning, and limb posturing, lasting seconds. At 5 months of age, his episodes became more prolonged and consistent in semiology. They consisted of flaccid quadriplegia or, less often, left hemiplegia, with eye deviation to either side (more often the left), nystagmus, and ocular convergence, with arm flexion and torticollis. During these episodes, his consciousness was preserved. There were no clear triggers for these episodes, which lasted from seconds to hours and resolved with sleep. The episodes continued to recur approximately every 2 weeks. There was no history of toxic exposure.

The patient was hospitalized for 1 of his more prolonged episodes, which was terminated with lorazepam. A

abstract

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48-hour EEG captured 2 additional episodes, with no accompanying EEG correlate and no interictal epileptiform activity. An MRI of the brain was normal. He was discharged from the hospital on omeprazole, with a diagnosis of Sandifer syndrome (abnormal posturing secondary to gastroesophageal reflux), but he did not improve.

Over the next 4 months, the patient's episodes increased in frequency and duration. He was asymptomatic between episodes, and his development remained normal. The family history was unremarkable, and all immunizations were current.

In summary, this patient is a 10-month-old boy with paroxysmal episodes of abnormal limb posturing, hypotonia, weakness, and oculomotor abnormalities that worsened over time. Dr Rosman, could this be an infant with a seizure disorder in which the motor activity, or semiology, changes with time?

Dr N. Paul Rosman (Pediatric Neurology):

The combination of paroxysmal movements, eye deviations, hypotonia, and weakness led us initially to think of recurring seizures followed by Todd's paralysis. Todd's paresis or postictal paresis is a period of transient paralysis, usually unilateral, and contralateral to an epileptogenic focus.[1] It can last from minutes to 36 hours, but it usually resolves fully within 12 to 15 hours.

Paroxysmal involuntary movements are common in children. Etiologies in addition to seizures include breath-holding spells, convulsive syncope, benign myoclonus of infancy, shuddering attacks, dystonias (including benign paroxysmal torticollis of infancy), other dyskinesias, tics, and tremors.

Abnormal eye movements can occur during a seizure. An epileptogenic lesion in a frontal eye field, for example, can cause contralateral eye deviation. Other etiologies include spasmus nutans, a self-limited triad of asymmetric (even monocular) nystagmus, head nodding, and a head tilt, unlike what was seen in our patient. Opsoclonus (or rapid, chaotic, conjugate vertical and horizontal eye movements) is often accompanied by myoclonus of the limbs and trunk ("dancing eyes and dancing feet").[2] It is always an important consideration in young children, given its strong association with neuroblastoma. Our patient's eye deviations, however, were much less chaotic than those of opsoclonus. Oculomotor apraxia presents with rapid horizontal head movements, an attempt to compensate for an underlying impairment of saccadic eye movements. Our patient did not exhibit rapid head movements; he did experience intermittent eye deviations, but his volitional eye movements were normal.

Dr Beate C. Beinvogl (Pediatrics, Resident):

The patient was seen in our emergency department at age 10 months after his most profound episode to date. On examination, his weight was in the 90th percentile, height was in the 15th percentile, and head circumference was in the 98th percentile. He had a prominent metopic ridge, and his head shape was mildly dolichocephalic. The anterior fontanelle was almost closed. The pupils were equal and reactive to light. He had full visual fields. He had intermittent esotropia and hypertropia, and pursuit eye movements were smooth. There was no ptosis and no facial weakness, and he had a strong cry with symmetric palate elevation. The patient's muscle bulk was normal; he had decreased axial tone with a head lag on pull to sit, slip through on upright suspension, and draping on ventral suspension. There was less spontaneous movement in the right arm and leg than in the left limbs. He had difficulty moving his limbs against gravity, and there was mildly decreased resistance to passive movement of the extremities. Sensory testing was performed by applying a finger stroke to the soles of the feet and palms of the hands and looking for changes in the child's facial expression, attention, and reactive limb movements; results were normal. There were no sensory deficits. Tendon reflexes were 3+ uniformly. Plantar responses were flexor. He had normal cardiovascular, respiratory, and abdominal examinations. There were no skin rashes, neurocutaneous stigmata, or periods of abnormal flushing or sweating.

Dr Rosman:

Although decreased tone and decreased strength frequently coexist, it is important to distinguish between these 2 factors. Hypotonia is reduced resistance to passive movement. Hypotonic infants, when lying supine, typically have abducted hips, abnormally extended limbs, and reduced spontaneous activity. There is decreased resistance of muscles to passive stretch. Weakness is defined as reduced ability to move muscles actively. There are numerous causes of hypotonia and weakness; a selection is summarized in Table 1 according to the level of the motor pathway that is affected, journeying from the upper motor neuron (UMN; cerebral cortex, corticospinal tracts, brainstem, then spinal cord) to the lower motor neuron (LMN; α-motor neuron [the cell body of the peripheral motor neuron located in the anterior horn of the spinal cord], to the spinal nerve root, peripheral nerve, neuromuscular junction, and skeletal muscle).

Dr Beinvogl:

Examples of more common UMN causes of hypotonia include hypoxic-ischemic encephalopathy, intracranial hemorrhage, and genetic syndromes such as Down syndrome.

Examples of more common disorders of the LMN resulting in hypotonia include Guillain-Barré syndrome, infantile botulism, and Werdnig-Hoffman disease. Figure 1 schematically illustrates the anatomy of the UMNs and LMNs. Dr Rosman, could you briefly review how our physical and neurologic examinations can help to localize pathologies at different levels of the motor pathway, and how this approach can help to narrow our differential?

Dr Rosman:

Although there are many exceptions, with central nervous system disorders, tone is usually reduced more than muscle strength, with the limbs often retaining antigravity power. In neuromuscular disorders, on the other hand, weakness typically predominates, with difficulties moving against gravity.[3] In our patient, there was no clear predominance of either hypotonia or weakness. His preserved deep tendon reflexes with the findings of abnormal eye movements and limb posturing, however, did direct us to an UMN localization and argued against an LMN problem.

Dr Beinvogl:

There was concern that abdominal pain was a potential cause of our patient's irritability, raising concern for intussusception. Sandifer syndrome, unusual posturing of the head and neck (often with arching of the back) secondary to gastroesophageal reflux, could also explain some of the signs in this case but would not explain the limb paralyses or abnormal eye movements.

Our initial laboratory results are summarized in Table 2. An abdominal plain film and an abdominal ultrasound examination were normal. The child was hospitalized for further evaluation, including consultation from Neurology and Genetics/Metabolism.

TABLE 1 Illustrative Causes of Hypotonia and Weakness in Infants

Neuron	Cause of Hypotonia and Weakness
UMN	
Cortex	Hypoxic-ischemic encephalopathy
	Intracranial hemorrhage
	Stroke (thrombotic or embolic)
	Genetic syndromes
	Down syndrome
	Prader-Willi syndrome
	Folate deficiency states
Corticospinal tracts	Cervical spinal cord injury
	Paraspinal infection
	Postinfectious myelitis
LMN	
α-Motor neuron	Spinal muscular atrophy type 1 (Werdnig-Hoffman disease)
	Poliomyelitis
Peripheral nerve root/nerve	Congenital hypomyelinating neuropathy
	Guillain-Barré syndrome
Neuromuscular junction	Congenital myasthenic syndrome
	Transient acquired neonatal myasthenia
	Aminoglycoside toxicity
	Magnesium toxicity
	Infantile botulism
	Organophosphate and carbamate poisoning
Muscle	Congenital myopathies
	Centronuclear myopathy, including myotubular myopathy
	Nemaline myopathy
	Central core disease
	Congenital muscular dystrophies
	Bethlem myopathy
	Ullrich congenital muscular dystrophy
	Hyperkalemic periodic paralysis
UMN and LMN	
Mixed	Congenital muscular dystrophies
	Fukuyama congenital muscular dystrophy
	Muscle-eye-brain disease
	Walker-Warburg syndrome
	Metabolic and genetic diseases
	Acute intermittent porphyria
	Metachromatic leukodystrophy
	Neuroaxonal dystrophy
	Zellweger syndrome

Dr Rosman:

The intriguing aspect of this case was the paroxysmal nature of the signs. Considering potential causes of paroxysmal hypotonia and weakness, the differential diagnosis becomes narrower. At the level of the cerebral cortex, we would consider seizures, migraine, transitory ischemic attacks, paroxysmal dyskinesias, and channelopathies as possible etiologies. Spinal cord or peripheral nerve disorders typically do not present in this paroxysmal manner. Congenital myasthenic syndrome is a disease of the neuromuscular junction that can present episodically but is typically progressive. Hyperkalemic periodic paralysis affects the muscle itself and is heralded by paroxysmal symptoms. Zellweger syndrome, a rare peroxisomal disorder, affects both UMN and LMN and presents with severe hypotonia and seizures but usually also with liver dysfunction, dysmorphisms, and skeletal abnormalities.

Dr Gerard T. Berry (Pediatric Genetics and Metabolism):

This patient's presentation was indeed consistent with seizure activity, which is a presenting

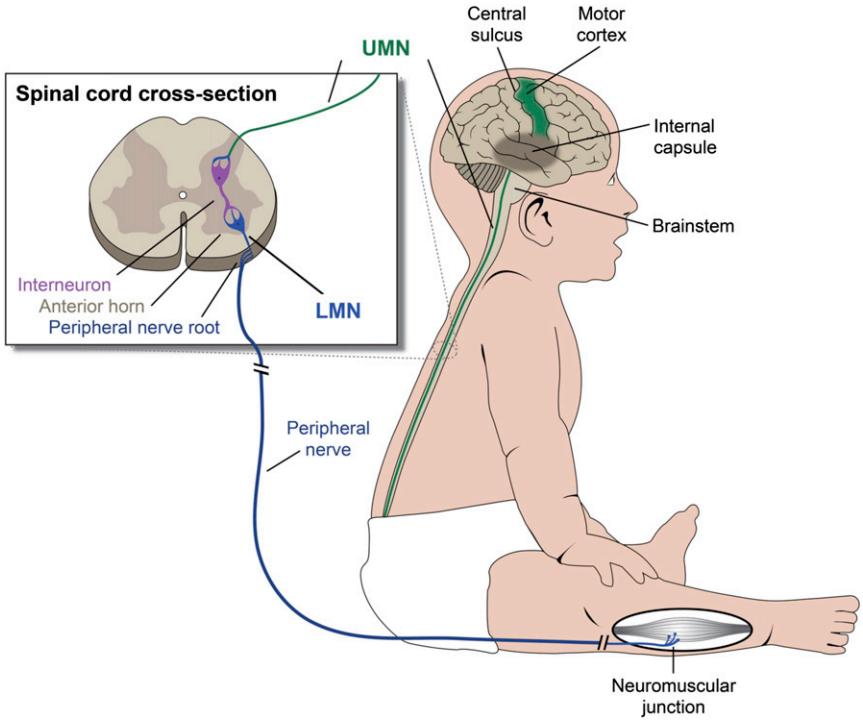

FIGURE 1
The anatomy of the UMNs and LMNs.

symptom in many genetic and metabolic diseases. Hypotonia and weakness are also nonspecific signs of many metabolic diseases and can be episodic. Symptom onset within the first days of life, as in our patient, is consistent with a broad range of inborn errors of metabolism. A number of these were diagnostic considerations in our case, as discussed here.

Organic acidemias can present with seizures but given the absence of a metabolic acidosis and normal urine organic acids, this disorder was unlikely.

Urea cycle defects, the most common being ornithine transcarbamylase deficiency, may present early in life, after a provocative protein load with initiation of feeds. Hyperammonemia, lethargy, vomiting, poor feeding, hypoventilation, and hyperventilation are frequently seen. Hyperammonemia can cause cerebral edema with abnormal posturing and seizures and, frequently, developmental delay. None of the laboratory abnormalities seen in urea cycle disorders, including elevated plasma ammonia and low blood urea nitrogen, were present in our patient.

Fatty acid oxidation defects can also present with lethargy, hypotonia, and seizures, especially in the setting of an acute metabolic crisis, usually triggered by a prolonged period of fasting. The absence of nonketotic hypoglycemia, with normal plasma carnitine and acylcarnitine and normal urine organic acid levels, effectively excluded that etiology.

Carbohydrate-deficient glycoprotein syndromes with onset in infancy present with failure to thrive, developmental delay, internal strabismus, hypotonia, hyperreflexia, occasional seizures, stroke-like episodes, and dysmorphic features; most of these findings, however, were not seen in our patient. Also considered but not clinically supported were cerebral folate deficiency states and glucose transporter defects.

The constellation of signs in the study case were suggestive of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes. Early symptoms include muscle weakness, temporary hemiparesis, altered consciousness, vision abnormalities, seizures, and severe headaches that typically appear after a period of normal development. The child's early presentation, his normal lactic acid level, and normal head MRI made mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes highly unlikely, however. Of note, most patients who present with mitochondrial diseases in early infancy have nuclear encoded autosomal recessive gene defects and not a maternally inherited mitochondrial cytopathy.

Pyruvate dehydrogenase deficiency is another mitochondrial disorder to be considered. It has heterogeneous clinical presentations, including severe metabolic lactic acidosis, lethargy, hypotonia, and seizures but rarely periodic paralysis or abnormal eye movements. Our child did not have lactic acidosis or lactate elevation according to the brain MRI with spectroscopy.

Dr Beinvogl:

What further diagnostic evaluation would you recommend at this point?

Dr Rosman:

I would recommend a repeat EEG telemetry, looking again for epileptiform activity. Given the progressive neurologic picture, particularly in view of the clinical concerns for possible seizures (with postictal Todd's paralysis), an initially normal EEG could have changed, with the appearance of abnormalities not seen on the earlier study.

As with an EEG, in the face of neurologic worsening, an initially normal MRI may become abnormal. An MRI with spectroscopy, as

TABLE 2 Laboratory Data

Test	Result	Reference Range
Initial laboratory studies		
WBC	9.6	7.73–13.12
Neutrophil/band, %	20	23–69
Lymphocyte, %	72	15–67
Monocyte, %	6	4–10
Eosinophil, %	1	1–5
Basophil, %	1	0–1
Atypical lymphocyte, %	1	0–4
Hemoglobin, g/dL	10.4	10.4–12.5
Hematocrit, %	31.1	30.5–36.4
Platelets, cells/μL	433	223–461
Sodium, mEq/L	135	135–148
Potassium, mEq/L	4.5	3.2–4.5
Chloride, mEq/L	99	99–111
Bicarbonate, mmol/L	19	17–29
Anion gap, mmol/L	15	7–14
Urea nitrogen, mg/dL	10	4–19
Creatinine, mg/dL	0.2	0.2–0.4
Glucose, mg/dL	101	60–100
Magnesium, mg/dL	2.3	1.5–2.2
Calcium, mg/dL	10.4	8–10.5
Phosphorus, mg/dL	5.8	3.5–6.6
Lactic acid, whole blood, mmol/L	1.2	0.5–2.2
Ammonia, μg/dL	72	28–80
Lactate dehydrogenase, U/l	525	180–430
Creatine kinase, U/L	97	4–175
pH venous	7.35	7.31–7.41
Pco_2 venous, mm Hg	41.4	35–45
Po_2 venous, mm Hg	42.3	30–50
Bicarbonate venous, mmol/l	22	20–33
TSH, μ unit/mL	0.94	0.7–5.7
Lead level, U	<2	0–5
Serum tricyclic antidepressant, acetaminophen, and salicylate level	Undetectable	Undetectable
Urine toxicology screen	Undetectable	Undetectable
Serum toxicology screen	Undetectable	Undetectable
Additional laboratory studies		
Acylcarnitine profile	Normal	Normal
Carnitine, total, μmol/L	56.5	32–84
Carnitine, free, μmol/L	42.7	26–60
Homocysteine, total, umol/L	7.1	1.0–10.9
Prolactin, ng/dL	7.5	<26
Plasma amino acid profile	Normal	Normal
CSF Total protein, mg/dL	18	15–45
CSF Glucose, mg/dL	60	60–80
CSF Lactic acid, mmol/L	1.3	0.5–2.8
CSF Pyruvic acid, mmol/L	0.11	0.06–0.19
CSF amino acid profile	Normal	Normal
CSF THB and neopterin profile	Normal	Normal
CSF neurotransmitter studies	Normal	Normal
CSF 5-methyltetrahydrofolate	Normal	Normal
Urine ketones	Negative	Negative
Urine organic and amino acids	Normal	Normal
Urine acylglycines	Normal	Normal

CSF, cerebrospinal fluid; TBH, tetrahydrobiopterin; TSH, thyroid-stimulating hormone; WBC, white blood cell count.

mentioned by Dr Berry, can help to detect anatomic and biochemical abnormalities in the brain. Electromyography/nerve conduction velocity studies usually provide evidence of LMN involvement, and repetitive peripheral nerve stimulation can be helpful in indicating the presence of neuromuscular junction disorders. A tensilon test (and more specifically a neostigmine test) would confirm the presence of a congenital myasthenic syndrome.

Dr Beinvogl:

With regard to the neurologic evaluation, a repeat prolonged video EEG, which captured another 2 events, was again normal. Cranial and spinal MRIs, including brain spectroscopy, were also normal, as were results of a tensilon test (pyridostigmine 1 mg/kg intravenously). Electromyography/nerve conduction velocity studies produced normal left ulnar sensory and motor responses, with no significant decrement with prolonged repetitive nerve stimulation. How do these results help you to narrow your differential?

Dr Rosman:

Although seizures were a leading initial concern, they were largely ruled out by the child's normal extended EEG studies. The child's normal brain MRI, in combination with his normal physical and neurologic examinations between episodes, essentially excluded a structural brain disorder. The possibility of a neuromuscular junction disorder, particularly myasthenia, was excluded by the child's negative result on tensilon testing (although there are occasional false-negative and false-positive findings).

Dr Beinvogl:

The most challenging aspect of this case was the episodic nature of the child's signs, with complete recovery between episodes. Most etiologies for such episodes, such as breath-holding spells, convulsive syncope, spasmus nutans, benign paroxysmal torticollis, infantile spasms, and other seizure disorders, are either benign and self-limited or have characteristic EEG abnormalities. Dr Berry, results of the metabolic evaluation for the diseases

you mentioned were negative (Table 2), and no structural correlate was identifiable on MRI; however, unexplained concerning clinical signs remained. What is your next thought?

Dr Berry:

We then have to consider rarer conditions that may reversibly affect physiology, such as the primary neurotransmitter disorders. These disorders affect the synthesis, metabolism, and catabolism of neurotransmitters, mainly dopamine and serotonin. These disorders include sepiapterin reductase deficiency, dihydropteridine reductase deficiency, guanosine triphosphate cyclohydrolase I deficiency, tyrosine hydroxylase deficiency, and dopamine transporter deficiency, also known as infantile parkinsonism-dystonia. The diagnosis of primary neurotransmitter diseases is usually confirmed by the presence of abnormal levels of neurotransmitter metabolites in the cerebrospinal fluid, but these levels were normal in our patient. In addition, his prolactin level, which is often increased in dopamine-deficient states, was normal.

The episodic nature of the child's signs in the setting of a negative metabolic evaluation so far suggests another category of rare disorders, the channelopathies, defects in the proteins that are ion pores or that regulate ion movement. The channels are essential for normal electrical signaling to ensure proper functioning of neurons and muscle cells. Possible channelopathies to consider included familial hemiplegic migraine (affecting a variety of ion channels), hyperkalemic periodic paralysis (sodium channels), myotonia congenita (chloride channels), and alternating hemiplegia of childhood (AHC) (sodium-potassium-ATPase). AHC typically presents in infancy, with its early course characterized by intermittent episodes of hemiplegia or quadriplegia, dystonia, abnormal eye movements, and tremor. Attacks of transient unilateral weakness are seen in AHC and are commonly misinterpreted as seizures followed by Todd's paralysis, although true epileptic seizures can also occur in AHC. Hemiplegic migraine differs from AHC by the absence of dystonias, ocular abnormalities, and episodic quadriplegia.[4] The patient's normal serum potassium level excluded hyperkalemic periodic paralysis, whereas the absence of both overdeveloped skeletal muscles and clinical myotonia ruled out myotonia congenita.

Dr Beinvogl:

Dr Rosman, are there any other neurologic disorders seen in infants that could account for these unusual signs?

Dr Rosman:

Yes, paroxysmal dyskinesias are a group of movement disorders characterized by episodes of abnormal movements, including dystonia, chorea, and hemiballismus. Flaccid paralysis, however, is typically not seen with the paroxysmal dyskinesias.

FINAL DIAGNOSIS AND DISCUSSION

Dr Beinvogl:

What is your final diagnosis, and how did you arrive at it?

Dr Berry:

The final diagnosis was AHC, based on the child's defining clinical findings. Genetic test results were positive for a heterozygous mutation in the gene ATP1A3, a missense mutation (D801N) in exon 17 (c.2401G>A; pAsp801Asn) that has been associated with AHC.

Dr Beinvogl:

Is this a classic presentation of AHC?

Dr Rosman:

Yes. To my knowledge, no disorder, other than AHC, exhibits episodes of abnormal eye movement, dystonia, hemiplegia, and quadriplegia, a combination of findings that is probably pathognomonic for AHC.[4] AHC is an autosomal dominant, sodium-potassium-ATPase channelopathy. The pathophysiology of AHC is incompletely understood. Pathogenic mutations cause consistent reductions in ATPase activity of the cellular sodium-potassium pump, without affecting the level of protein expression.[5,6] Resulting changes in the sodium gradient may perturb neuronal sodium efflux and potassium uptake, resulting in disturbed neurotransmitter release.[7,8] Genetic and/or mitochondrial abnormalities, brainstem dysfunction, and cerebrovascular alterations may also play a causative role.[9–11]

AHC is characterized by recurrent episodes of abnormal neurologic signs followed by ataxia and cognitive impairment later in its course. The leading presenting symptoms are abnormal eye movements (65%), dystonia (60%), and hemiplegia (32%). Abnormal eye movements appear within the first few days to months of life and include nystagmus (eg, horizontal, vertical, rotatory, monocular), horizontal or vertical eye deviations, convergent strabismus, or loss of convergence.[6,12,13] Hemiplegia occurs in one-half of cases by 6 months of age and in nearly all by 18 months. Patients with early-onset hemiplegic spells have the poorest developmental outcome. The hemiplegic attacks can be unilateral, bilateral (quadriplegia), or can switch sides during an attack; they are often accompanied by head and eye deviation toward the hemiplegic side.[14] Involuntary movements, including dystonia, choreoathetosis, and facial dyskinesia, can occur concurrently with the hemiplegia or independent of it. Common

triggers for symptomatic episodes of AHC include emotional upset and sleep deprivation. Irritability often precedes the episodes. The attacks occur with varying frequency, multiple times a day in the most severe cases, and each can last from minutes up to 2 weeks.[15] The attacks typically resolve during sleep.[4,10] Epileptic seizures occur in 18% to 50% of patients with AHC, with onset usually within the first 5 years of life.[10,14]

Nonparoxysmal manifestations occur later in the disease course, and they usually persist. These manifestations include developmental delay (89%–100%), ataxia (68%), and choreoathetosis (50%).[6,10,16]

AHC is a clinical diagnosis. Sweney et al[6] have suggested that the current diagnostic criteria for AHC (Table 3) may be too specific, requiring the manifestations of multiple neurologic signs before clinicians feel comfortable considering the diagnosis. They have suggested more simplified screening criteria for early suspicion of AHC.

Negative results on imaging studies and EEGs are essential to exclude structural central nervous system abnormalities and seizures as an explanation for the paroxysmal events. Laboratory testing with extensive metabolic screening, including cerebrospinal fluid neurotransmitter metabolites, are important in excluding other disorders that can present with paroxysmal neurologic findings (Table 4).[6,19]

TABLE 3 Diagnostic Criteria for AHC

Diagnostic criteria for classic AHC[6]
Onset of signs before 18 mo
Repeated attacks of hemiplegia alternating sides
Other paroxysmal disturbances, including dystonic or tonic spells, oculomotor abnormalities, and autonomic phenomena
Episodes of bilateral hemiplegia or quadriplegia as generalization of a hemiplegic episode or at onset
Disappearance of signs during sleep
Later developmental delay, dystonia, choreoathetosis, and ataxia
Screening criteria for early suspicion of AHC[17,18]
Unilateral paroxysmal dystonia and/or flaccid hemiplegia in the first 6 mo of life
Paroxysmal ocular movements, including binocular and monocular nystagmus and/or eye deviation in the first 3 mo
Absence of epileptiform activity during acute episodes

TABLE 4 Evaluating the Child With Undiagnosed Paroxysmal Events

Evaluation Tool	Diagnostic Considerations
12- to 24-h video EEG monitoring	To exclude seizures as a cause for abnormal movements; repeat EEG indicated for new or evolving episodes or in case of failure to capture episodes
MRI, MRA, MRS	To exclude structural and vascular abnormalities, as well as metabolic disorders such as MELAS or PDH deficiency
Blood/urine studies Serum ammonia, acylcarnitine, carnitine, homocysteine, plasma AA, blood lactate, pyruvate Urine AA and OA, acylglycine, ketones	To exclude treatable disorders of intermediary metabolism (organic acidemias, aminoacidopathies, fatty acid oxidation, carnitine, and urea cycle disorders)
CSF studies Neurotransmitters Pterin metabolites 5-Methyltetrahydrofolate Lactate Pyruvate Glucose	To exclude neurotransmitter (biogenic amine) disorders, cerebral folate deficiency, MELAS (mitochondrial disorders), PDH deficiency, and glucose transporter defects
Genetic screening ATP1A2 ATP1A3 CACNA1A SLC1A3	To look for mutations associated with channelopathies or to differentiate between channelopathies with partially overlapping phenotypes, such as familial hemiplegic migraine type 1 (CACNA1A) and type 2 (ATP1A2) or episodic ataxia type 6 (SLC1A3)

AA, amino acids; CSF, cerebrospinal fluid; MELAS, mitochondrial encephalomyopathy, lactic acidosis, and stroke-like episodes; MRA, magnetic resonance angiography; MRS, MRI with spectroscopy; OA, organic acids; PDH, pyruvate dehydrogenase.

Dr Beinvogl:

Dr. Berry, what is the role of genetic studies in confirming this diagnosis?

Dr Berry:

In 1 large cohort, mutations in the ATP1A3 gene were identified in 78% of patients with clinically diagnosed AHC.[7] The penetrance of pathogenic variants in the ATP1A3 gene associated with AHC is not known. Most cases reported to date have occurred de novo.[20] The recurrence risk for future pregnancies is therefore low, unless 1 of the parents has a germline mosaicism.

In addition, mutations in the ATP1A2 gene (the gene implicated in familial hemiplegic migraine type 2) have been reported in association with an atypical presentation of AHC, not strictly meeting the clinical criteria described earlier.[10] There is a genotype–phenotype correlation with mutations in the ATP1A3 gene. Mutations E815K, D801N, and G947R, which are also associated with AHC, may provide prognostic information.[16,19] To the best of my knowledge, there are no additional genes known to be associated with AHC at this time, although others likely exist. Different heterozygous missense mutations in the gene ATP1A3, however, have been identified as the cause of other rare clinical syndromes, including rapid-onset dystonia-parkinsonism, and cerebellar ataxia, areflexia, pes cavus, optic atrophy, and sensorineural hearing loss syndrome.[7,17,20,21]

If the clinical diagnosis of AHC is uncertain and results of genetic testing of the ATP1A3 gene are negative, consideration can be given to testing for additional channelopathies with partially overlapping phenotypes. These channelopathies include familial hemiplegic migraine type 1 (CACNA1A) and episodic ataxia type 6 (SLC1A3).[17,18,21]

Dr Rosman:

There is no known cure for AHC. Effective treatment strategies include avoiding triggers and aborting episodes by encouraging sleep. In those patients who benefit from pharmacologic treatments, the calcium channel blocker flunarizine, benzodiazepines, and topiramate have been associated with improvement of dystonic and hemiplegic episodes.[22] Flunarizine in particular, which has become the drug of choice, has been shown to reduce the frequency, severity, and duration of hemiplegic attacks in approximately three-quarters of patients, but whether this treatment benefits long-term developmental outcome remains uncertain. Anticonvulsants (eg, carbamazepine, gabapentin, barbiturates), selective serotonin reuptake inhibitors, and acetazolamide have produced insignificant effects or no benefit. The clinical outcome in AHC is variable but frequently poor, with persisting developmental delays and fixed neurologic deficits, including ataxia, choreoathetosis, and dystonia.[6,10,23]

Dr Beinvogl:

After discharge from the hospital, the frequency of our patient's episodes increased to almost daily recurrences. Triggers included hunger, cold, illness, and stress. The episodes typically lasted most of the day. They were improved with meals and after sleep, but relief was short-lived. Given the high suspicion for AHC, the patient was started on acetazolamide (4 mg/kg), which was immediately available, but it did not help. At age 15 months, with the diagnosis genetically confirmed, the patient was started on flunarizine (initially 0.2 mg/kg every other day, increased to 0.6 mg/kg daily). Flunarizine is not available in the United States and was imported from Canada. Due to known cardiac side effects of calcium channel blockers, including hypotension and arrhythmia, clearance by Cardiology was awaited prior to initation of therapy.

The patient's hemiplegic episodes became less frequent, and his development accelerated. In the months after starting flunarizine, in an average month, he had full body strength >80% of the time, with full body weakness or, more often, partial weakness in <20%. By 18 months, although his development was delayed, he was able to cruise, stand unsupported, and say 8 words. He grabbed objects, scribbled, and occasionally fed himself.

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ABBREVIATIONS

AHC: alternating hemiplegia of childhood
LMN: lower motor neuron
UMN: upper motor neuron

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