Pearls & Oy-sters:

Episodic ataxia type 2

Case report and review of the literature

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PEARLS

- Episodic ataxia type 2 (EA2) is an autosomal dominant calcium channelopathy caused by a mutation in *CACNA1A*.
- Spells are characterized by ataxia, which may be accompanied by vertigo, diplopia, dysarthria, and generalized weakness.
- Between spells, patients often demonstrate persistent nystagmus.
- Acetazolamide and 4-aminopyridine are reported to decrease severity and frequency of spells.

OY-STERS

- Patients may not report a family history of episodic ataxia or familial hemiplegic migraine.
- Patients who initially have episodic symptoms may develop a progressive ataxia syndrome.
- Coexisting functional disorder may make evaluation more difficult.

CASE REPORT A 38-year-old man presented to our clinic for evaluation of increasingly frequent spells of gait instability, diplopia, vertigo, and dysarthria. These spells began at 12 years of age. Initially, he experienced isolated periods of vertigo without accompanying symptoms. He told no family or friends of his problem at the time. Two years later, the symptoms progressed, manifesting as semistereotyped episodes characterized by a shock-like sensation radiating from his neck down his back followed by binocular diplopia, vertigo, gait instability, mental clouding, and nausea lasting 2–8 hours. Later, he experienced dysarthria during spells. Interictally, he returned to his baseline except for a persistent mild diplopia.

The patient concealed his symptoms for many years. His mother first witnessed a spell when he was 27 years old. She found him disoriented and imbalanced. He was carried to the emergency department, where he received diazepam for anxiety, and his symptoms as usual resolved within 1–2 hours. He

continued to use diazepam for future spells, which physicians variably diagnosed as seizures, anxiety attacks, TIA, a functional disorder, or malingering (table 1). He was empirically treated with phenytoin without improvement. He underwent closure of a patent foramen ovale for possible recurrent TIA. Ultimately, he was diagnosed with a functional disorder, and no further workup was conducted for 10 years. The frequency of these spells varied throughout his life, occurring daily, monthly, or even yearly. Then, following the unexpected death of a family member 2 months before our initial evaluation, his symptoms became nearly continuous. He had no family history of episodic neurologic symptoms, gait impairment, migraines, or epilepsy. He had a history of remote methamphetamine use and ongoing tobacco and marijuana use. He had normal motor and social development, but language and cognitive development were delayed. His speech was incomprehensible as a child, prompting childhood speech therapy and special education through 8th grade, when he dropped out of school.

During physical examination, he did not experience a typical spell. Much of his neurologic examination was elaborated, requiring several attempts with coaching to accurately perform routine tests of function unrelated to his symptoms. For the majority of his neurologic testing, he ultimately performed the maneuvers without deficit over a short time interval. Notable findings on his examination included bilateral esophorias, hypometric saccades with catch-up bilaterally, bilateral gaze-evoked nystagmus, mild dysarthria, and overshoot with finger follow bilaterally. While seated he had truncal titubation, and on gait testing he had a wide-based stance and significant difficulty with tandem walking. Gait and posture were markedly irregular and variable, presumed to represent a functional overlay on what was likely a mildly abnormal gait. Finally, his cognitive evaluation showed mild to moderate impairment in frontal-executive, episodic memory, visuospatial, and language tasks. His Montreal Cognitive Assessment score was 23 out of 30.

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Table 1 Differential diagnosis for episodic ataxia

Central causes	Peripheral causes
TIA	Benign paroxysmal positional vertigo
Migraine	Labyrinthitis
Presyncope	Meniere disease
Multiple sclerosis	Acoustic neuroma
Toxic (alcohol, antiepileptics)	Perilymphatic fistula
Seizures	Immune-mediated inner ear disease
Chiari type 1 malformation	
Atlantoaxial abnormalities	
Paroxysmal dyskinesias	
Functional disorders	

Laboratory evaluation had previously excluded metabolic, endocrine, nutritional, infectious, autoimmune, and paraneoplastic etiologies of ataxia. His CSF revealed a normal protein level, leukocyte count, immunoglobulin G index, and no unique oligoclonal bands. Brain MRI the year before our evaluation was reported as normal although in retrospect, mild midline cerebellar atrophy was likely present. Cervical and thoracic MRI showed no spinal cord abnormalities. He did not undergo EMG. Genetic testing for episodic ataxia type 2 (*CACNA1A*) demonstrated a heterozygous, single base pair deletion in *CACNA1A* causing a pathologic frameshift mutation. He was started on acetazolamide for symptomatic therapy.

DISCUSSION The first published clinical description of EA2 dates back to 1946 while the molecular basis of the disorder was identified in 1996 with the discovery of mutations in the P/Q type voltage-gated calcium channel *CACNA1A*. It is an autosomal dominant disorder and the most

common inherited episodic ataxia, though the prevalence is estimated at less than 1 in 100,000 with high though incomplete penetrance.^{1,2}

Clinically, the disorder is characterized by ataxic spells lasting hours to days, often with interictal nystagmus; however, there is considerable variation in disease presentation.³ The spells may be characterized by isolated ataxia or, as seen in our patient, a broader range of symptoms, often localizing to the brainstem. Associated features include generalized and hemiplegic weakness, migraine, intellectual disability, dystonia, and seizures. Indeed, there is a broad range of neurocognitive deficits associated with *CACNA1A* mutations, although until recently this has been largely unexplored.³ While initially an episodic disorder, some patients will develop a secondarily progressive ataxia, as in our patient. Notable triggers include physical and emotional stress. Disease onset is typically between 5 and 20 years of age.³ It is clinically differentiated from other episodic ataxias through a variety of features including age at onset, spell duration, interictal nystagmus, and genetic locus (table 2).^{2,4,5}

Genetically, the disorder has been linked to *CACNA1A*, which encodes the pore-forming subunit of the P/Q-type voltage-gated calcium channel.¹ The P/Q channel is expressed throughout the CNS, but is most densely expressed in cerebellar Purkinje cells and granule layer neurons. It is found principally on presynaptic terminals and plays a key role in synaptic transmission.⁶ Over 80 different pathologic mutations have been identified to date, and they typically result in premature truncation of the protein via nonsense or frameshift mutations though a number of missense mutations have also been found to be pathologic. Based on these observations, EA2 is believed to be characterized by loss of P/Q channel function in the cerebellum. This hypothesis is supported by electrophysiologic studies that demonstrate that EA2-associated mutations result in loss of or diminished channel function when expressed in vitro.⁷ Research

Table 2 Clinical features of the episodic ataxias (EA)

	EA1	EA2	EA3	EA4	EA5	EA6
Gene/chromosomal location	KCNA1	CACNA1A	Chromosome 1q42	Unknown	CACNB4	SLC1A3
Age at onset	Adolescence	Adolescence	Variable	Early adulthood	Early adulthood	Childhood
Attack duration	Seconds to minutes	Hours	Minutes	Seconds to hours	Hours	Hours to days
Nystagmus	No	Downbeating gaze-evoked	Rare congenital nystagmus	Gaze-evoked	Downbeating	No
Myokymia	Yes	No	Yes	No	No	No
Acetazolamide response	Variable	Yes	Yes	No	Yes	No
Associated features	Epilepsy	Epilepsy	Epilepsy	Epilepsy	Epilepsy	Epilepsy
	Neuromyotonia	Headache	Tinnitus	Tinnitus		Headache
		Hemiplegia	Headache			Hemiplegia

also suggests that the mutation may exert a dominant negative effect on the wild-type channel by interfering with proper channel folding and trafficking rather than simple haploinsufficiency.⁶ None of these explanations, however, clearly accounts for the unmistakably episodic nature of the disease.⁸

Interestingly, mutations in *CACNA1A* have also been identified in familial hemiplegic migraine type 1 and spinocerebellar ataxia type 6 (SCA6).^{1,3} Thus, EA2 is allelic with these disorders and there is recognized clinical overlap. Familial hemiplegic migraine is reliably associated with a wide range of missense mutations.⁹ In SCA6, a CAG repeat expansion in the C-terminus of the gene is believed to cause cerebellar degeneration. These and other mechanisms of disease in P/Q-type channel dysfunction have been well reviewed previously.⁸

Our patient was found to have a novel single base pair deletion (3,535C) leading to a frameshift mutation in exon 20 of *CACNA1A* resulting in a premature stop codon and aberrant mRNA likely destined for nonsense mediated decay. He has no family history of the disease, though nonpaternity was not explored. He has 3 children, all of whom are under age 20 and are currently healthy with no neurologic symptoms, including migraine and intellectual disability.

Therapeutically, acetazolamide responsiveness is a hallmark of the disease. Though there are patients who do not have symptomatic benefit, an estimated 50%–75% of patients report improvement in episode severity and frequency with acetazolamide doses ranging from 250 to 1,000 mg daily.² Therapeutic benefit was seen in our patient. He developed nephrolithiasis while on acetazolamide 1,000 mg/d and discontinued the medication; however, after his genetic diagnosis, the medication was restarted at a lower dose with close clinical monitoring. For those who cannot tolerate acetazolamide, the potassium channel blocker 4-aminopyridine at doses of 5 mg 3 times daily has also been shown to decrease episode frequency and improve quality of life in a randomized controlled trial of 10 patients.¹⁰

Finally, there are no earlier reports of functional disorders among patients with EA2. Comorbid functional disorders create a diagnostic challenge. In patients with psychogenic nonepileptic seizures, time to correct diagnosis is estimated to be 7 years from spell onset.¹¹ Our patient's experience would suggest that equally lengthy diagnostic delays are possible in EA2 when comorbid functional disorder is present. Importantly, this case also highlights the fact that functional overlay can lead to premature diagnostic closure after the symptoms are

labeled as such. Improved recognition and understanding of episodic ataxias is necessary. EA2 must be considered for any patient with episodes of ataxia lasting hours, although shorter and longer attacks do occur, and more rarely in patients who present with a progressive ataxia syndrome.

AUTHOR CONTRIBUTIONS

Dr. Guterman: drafting of manuscript. Dr. Yurgionas: drafting of manuscript. Dr. Nelson: critical revision of the manuscript for important intellectual content.

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