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Ataxia and Diplopia

A New *SCN8A*-Related Phenotype

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Abstract

Objectives

The objective of this study was to describe the first patient with recurrent ataxia and diplopia in association with a pathogenic variant in *SCN8A*.

Methods

We identified a girl with a heterozygous *SCN8A* pathogenic variant and performed thorough phenotyping.

Results

A 10-year-old girl was previously well with normal intelligence. She had recurrent diplopia, dysmetria, and unsteady gait, which occurred only in the context of febrile illnesses. EEG during her initial acute episode showed multifocal epileptiform discharges, with similar findings seen on a follow-up study 3 months later when she was well. Brain MRI finding was normal. A gene panel identified a de novo *SCN8A* variant, p.Arg847Gln, classified as likely pathogenic. One year after her initial presentation, the girl is well and developmentally normal and has never had an event concerning for seizure.

Discussion

This case presentation demonstrates that *SCN8A* pathogenic variants should be considered in children with transient ataxia, dysmetria, and diplopia in the context of viral febrile illnesses, even if there is no history of seizures. While there are clinical and molecular data suggesting that SCN8A dysfunction can cause temperature-sensitive phenotypes, further research is necessary to determine how the functional changes caused by our patient's *SCN8A* variant result in her unique phenotype.

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Go to Neurology.org/NG for full disclosures. Funding information is provided at the end of the article.

SCN8A (OMIM 600702) encodes the sodium channel voltage-gated alpha-8 subunit ($Na_v1.6$) and is widely expressed in the brain.[1] Pathogenic variants in *SCN8A* are a recognized cause of moderate-to-severe infantile-onset developmental and epileptic encephalopathy, often associated with other neurologic signs, including movement disorders, hypotonia, and ataxia.[2] Other phenotypes have also been reported in association with *SCN8A*, including self-limited infantile seizures, as well as intellectual disability with movement disorders or ataxia, but no history of seizures.[3,4] In this study, we describe a girl with a de novo heterozygous *SCN8A* pathogenic variant, who presented with recurrent ataxia and diplopia in the context of viral febrile illnesses. This report further expands the phenotypic spectrum that may be associated with *SCN8A* pathogenic variants.

Patient Description

A 10-year-old girl initially presented with a 3-day history of fever, sore throat, fatigue, diplopia, dysmetria, and unsteady gait and was found to be influenza A positive. The severity of symptoms fluctuated, directly correlating with fever. Her medical history was unremarkable. She had a history of mild language delay, but was in a normal class at school and considered an average student. Her mother was originally from Cambodia and father was of Vietnamese descent; there was no known consanguinity and no known family history of seizures, ataxia, or other neurologic disorders.

On examination, she had normal growth parameters and was nondysmorphic. On extraocular muscle testing, she had limited abduction of the right eye. Her gait was wide-based and unsteady, and she had bilateral dysmetria. Head CT and MRI findings were both normal. EEG showed frequent-to-abundant focal epileptiform discharges, mostly from the left frontal region in addition to the right frontal and left occipital regions (Figure). The patient's ataxia and diplopia resolved spontaneously over several days, and she was discharged home.

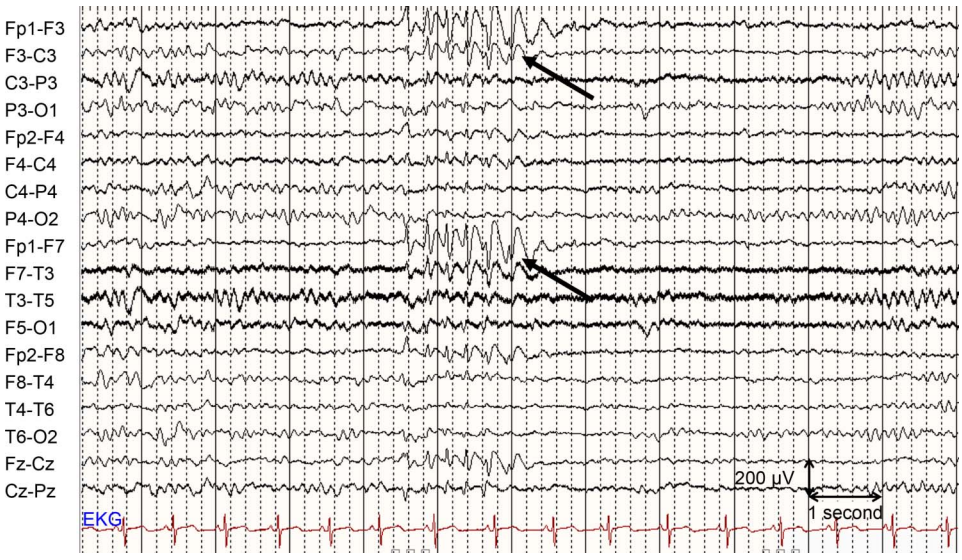
Two months later, she had fever in association with COVID-19 infection and again developed ataxia, fatigue, and diplopia. These symptoms again worsened with higher fever and improved after antipyretic medication, resolving after 2–3 days, in concert with the illness. EEG was repeated 3 months after her initial presentation, while asymptomatic, and showed occasional-to-abundant focal spikes, most commonly over the left occipital region but also over the right occipital region. Her development remained as per baseline, and the ataxia and other symptoms again resolved after the viral illness.

Comparative genomic hybridization microarray was normal, as were plasma amino acids, acylcarnitine profile, and urine organic acids. An autism/intellectual disability gene panel including more than 2,300 genes (GeneDx, Gaithersburg, MD) identified a de novo heterozygous variant in *SCN8A* (NM014191.3, c.2540G>A, p.Arg847Gln), classified as likely pathogenic by American College of Medical Genetics & Genomics criteria.[5] *In silico* testing predicts deleterious effects on protein structure and function, and the variant is not present in the Genome Aggregation Database.[6] The patient's family provided written consent for this publication.

Discussion

This case presentation expands the phenotypic spectrum that may be associated with *SCN8A* pathogenic variants to include transient ataxia, dysmetria, and diplopia in the context of viral

Figure EEG at Initial Presentation



On longitudinal bipolar montage in drowsiness, a burst of spike-wave discharges at approximately 3.5 Hz is seen, maximal over the left anterior region, but having broad bilateral field (arrows). Background activity is normal.

Table Previously Published Patients With Ataxia and *SCN8A* Pathogenic Variants

Ref	Sex	Age	*SCN8A* variant	Presentation
Blanchard et al.[7]	F	7 y	c.2952C>G, p.Asn984Lys	Severe developmental impairment from birth. Nonverbal. Cerebellar atrophy, dysmorphic features, and ataxia
	M	33 y	c.4351G>A, p.Gly1451Ser	From age 18 mo, generalized seizures. Moderate-to-severe developmental impairment, nystagmus, cerebellar atrophy, and ataxia. At age 29 y, decline in motor function
Trudeau et al.[8]	M	9 y	p.Pro1719ArgfsX6	Marked cognitive and motor impairment, cerebellar atrophy, and ataxia
Wagnon et al.[3]	M	10 y	c. 3652G>A, p.Glu1218Lys	Marked speech and motor impairment, ID, ataxic gait (resolved)
Veeramah et al.[1]	F	15 y	c.5302A>G p.Asn1768Asp	From 6 mo, generalized seizures. At age 4 y, epileptic spasms with regression. Hypotonia, ataxia, developmental delay, and ID. SUDEP at age 15 y

Abbreviations: ID = intellectual disability; SUDEP = sudden unexpected death in epilepsy.

febrile illnesses. Notably, the girl has normal intelligence and developmental history. She has no history of seizures, though her EEG showed multifocal interictal epileptiform discharges, and we cannot rule out the possibility that her symptoms reflected postictal phenomena after subtle, unrecognized focal seizures.

Ataxia has been previously described in at least 5 patients with *SCN8A* pathogenic variants, 4 with de novo heterozygous missense variants,[1,3,7] and 1 with a maternally inherited deletion (Table)[8]; however, this case presentation is markedly different. All the previously described patients had significant intellectual disability and developmental impairment, and ataxia was usually stable or progressive, when compared with intermittent with febrile illness in our patient. Three of the previously described patients had cerebellar atrophy on brain MRI.

The pattern of presentation in this patient also suggests that sodium channel dysfunction due to *SCN8A* pathogenic variants can be temperature sensitive, exacerbated by hyperthermia. This is interesting because, while febrile seizures have been reported in association with *SCN8A*, such presentations are rare.[9] Studies using mouse models have shown that the $Na_V1.6$ subtype is relatively less susceptible to hyperthermia than $Na_V1.2$.[10] Functional evaluation of our patient's *SCN8A* variant would be helpful in determining how and why it results in a temperature-sensitive, apparently fully reversible, phenotype.

Of interest, the variant in our patient has a known pathogenic paralog in another sodium channel subunit gene. The *SCN2A* variant, p.Arg853Gln, is one of the most frequent recurrent pathogenic variants identified in SCN2A-related disease. This variant results in decreased neuronal excitability, with clinical phenotype of a later-onset developmental and epileptic encephalopathy with epileptic spasms and moderate-to-severe developmental impairment.[11] Choreoathetosis and/or dystonia are also frequently reported.[11] The clinical significance of the patient is unclear, but the observation supports the pathogenicity of the *SCN8A* variant identified in our patient.

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Disclosure

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Alexandra Laliberté, MSc, RD	Faculty of Medicine and Health Sciences, McGill University, Montreal, Quebec, Canada	Including medical writing for content; major role in the acquisition of data; analysis or interpretation of data
Kenneth A. Myers, MD, PhD, FRCPC	Research Institute of the McGill University Medical Centre, Montreal, Quebec, Canada	Including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data

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