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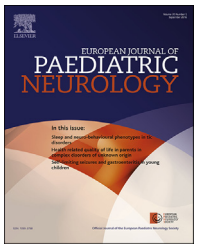

Case Study

Episodic ataxia associated with a *de novo* SCN2A mutation

Emma L. Leach [a], *Clara D.M. van Karnebeek* [b,c,d], *Katelin N. Townsend* [a,c], *Maja Tarailo-Graovac* [d], *Juliette Hukin* [e], *William T. Gibson* [a,c,*]

[a] *Department of Medical Genetics, University of British Columbia, Vancouver, Canada*
[b] *Division of Biochemical Diseases, Department of Pediatrics, British Columbia Children's Hospital, Vancouver, Canada*
[c] *Child and Family Research Institute, British Columbia Children's Hospital, Vancouver, Canada*
[d] *Centre for Molecular Medicine and Therapeutics, University of British Columbia, Vancouver, Canada*
[e] *Division of Neurology, Department of Pediatrics, British Columbia Children's Hospital, Vancouver, Canada*

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ABSTRACT

Introduction: Episodic ataxia (EA) is characterized by paroxysmal attacks of ataxia interspersed by asymptomatic periods. Dominant mutations or copy number variants in *CACNA1A* are a well-known cause of EA.

Clinical presentation: This boy presented with clinical features of episodic ataxia, and also showed cerebellar atrophy, hypotonia, autism and global developmental delay at age 4 years. Acetazolamide prevented further episodes of ataxia, dystonia and encephalopathy. Extensive biochemical and genetic tests were unrevealing; whole exome sequencing found a previously unreported variant in *SCN2A*, proven to be *de novo* and predicted to be protein-damaging.

Conclusion: Considered alongside previous reports of episodic ataxia in *SCN2A* mutation-positive patients, our case further illustrates the genetic heterogeneity of episodic ataxia. In addition, this case suggests that acetazolamide may be an effective treatment for some aspects of the phenotype in a broader range of channelopathy-related conditions.

1. Introduction

The emergence of whole exome sequencing (WES) in research and clinical contexts has proven that many sporadic conditions, including seizure disorders, have a broader range of genetic causes than was previously suspected. Similarly, genes previously thought to cause unique disorders when mutated have been shown to cause disorders in which they had not previously been implicated.

* *Corresponding author*. Child & Family Research Institute, Room A4-182, 950 West 28th Avenue, Vancouver, BC V5Z 4H4, Canada. Fax: +1 604 875 2373.
E-mail address: wtgibson@cfri.ca (W.T. Gibson).
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Episodic ataxia type 2 (EA2) is characterized by paroxysmal attacks of ataxia.[1,2] Attacks typically onset in childhood or early adolescence, and range in frequency from annually to several times per week, with asymptomatic periods of variable duration. Episodes can include other neurological manifestations such as vertigo, nausea, headache, dysarthria, diplopia, tinnitus, dystonia, hemiplegia, and seizures.[1,3] Maintenance treatment with oral acetazolamide (Diamox®) effectively prevents or reduces the frequency and severity of attacks.[1,2]

Heterozygous variants in the voltage-gated calcium channel encoding *CACNA1A* account for over 95% of EA2 cases.[1] However, Hirose et al.[4] described a large family with autosomal dominant acetazolamide-responsive EA2 wherein no *CACNA1A* mutations were identifiable, supporting genetic heterogeneity in the EA2 phenotype and suggesting that other causative genes remain to be identified.[3] Indeed, more recently, additional genes have been associated with the EA2 clinical presentation. A 2 year-old boy with periodic attacks of ataxic gait, repeated vomiting, and abnormal eye movement was diagnosed with EA2 and treated with acetazolamide; he was found to have glucose transporter type 1 deficiency attributed to a *de novo* frameshift insertion in the *SLC2A1* gene.[5] Conroy et al.[6] also proposed *UBR4* may be associated with a form of episodic ataxia characterized by periods of unsteadiness, generalized weakness and slurred speech in early childhood. As genome sequencing technology yields additional genes associated with discrete clinical phenotypes, so does it also identify new phenotypes associated with genes implicated previously in other disorders.

SCN2A (MIM 182390) encodes the alpha subunit of voltage-gated, type II sodium channels, highly expressed in the brain. Pathogenic *SCN2A* mutations are also known to cause benign familial neonatal-infantile epilepsy,[7] and generalised epilepsy with febrile seizures plus (GEFS+).[8] However, recent studies have associated coding variants in *SCN2A* with a broader phenotypic spectrum, including severe infantile-onset epilepsy,[9] intellectual disability without seizures,[10] and autism.[11,12] *SCN2A* mutations have also been identified among patients with episodic ataxia.[13,14] Liao et al.[13] described a patient with neonatal-onset seizures and variable episodes of ataxia, myoclonia, headache, and back pain associated with a *de novo* missense mutation (p.Ala263Val) in *SCN2A*. Three additional patients with a similar phenotype to the patient described by Liao et al.[13] were also found to harbour *SCN2A* mutations.[14] The *de novo* p.Ala263Val mutation previously reported was identified in one of the additional cases, and the two patients were found to have a novel *de novo* p.Arg1882Gly mutation, as well as a paternally inherited p.Gly1522Ala variant in one case.[14] *In vitro* studies showed gain-of-function effects for both *de novo* mutations, and predicted neuronal hyperexcitability.[13,14] Ogiwara et al.[15] identified two *de novo* *SCN2A* mutations in a cohort of *SCN1A*-negative intractable epilepsy cases. Recently, Nakamura et al.[16] identified *SCN2A* mutations in 15 of 328 patients with Ohtahara syndrome, West syndrome or unclassified early-onset epileptic encephalopathies and recommended that *SCN2A* molecular analysis should be considered for children with different epileptic conditions.

Here we describe a novel *SCN2A* variant associated with acetazolamide-responsive episodic ataxia identified through WES, and thus broaden the clinical spectrum of this genetic sodium channelopathy.

2. Case report

Parents provided informed consent for publication of this report. The family was enrolled into both the GARD study (protocol H09-01228) and TIDEX Study (protocol H12-00067), each approved by the Clinical Research Ethics Board of the University of British Columbia, Vancouver Canada.

This 5-year old boy, born after an unremarkable pregnancy and delivery with normal birth weight and normal Apgar scores, presented acutely to our centre at 11 months of age with a history of minor head injury due to a fall forward out of his stroller that was accompanied by decreased level of consciousness, vomiting and possible seizures. Though there had been steady gains in motor skills with no regression prior to his first episode, his developmental profile had not been entirely typical. Specifically, he was not yet standing independently, cruising, nor engaged in canonical babbling, and would not respond to his name being called, despite normal hearing and normal interest in other sounds. While in hospital, he was markedly hypotonic and had encephalopathy. He also experienced episodes of intermittent limb stiffness and dystonic posturing, with arching of his back, rightward deviation of his eyes and head, and concomitant nystagmus. EEG on the day of presentation was normal, thus these episodes were interpreted as dystonic posturing. Head CT and cerebrospinal fluid (CSF) glucose were normal. He was initially treated with phenytoin and diazepam, but developed choreoathetoid movements. These were attributed to phenytoin toxicity, so because of his normal EEG the phenytoin was stopped. MRI shortly after admission demonstrated cerebellar oedema with T2 hyperintensity, and bilateral arachnoid cysts of the middle cranial fossa (Fig. 1).

Biochemical investigations (performed according to the algorithm for treatable inborn errors of metabolism in developmentally and intellectually delayed patients[17]) in blood (plasma amino acids, homocysteine, copper, ceruloplasmin), urine (glycosaminoglycans, oligosaccharides, organic acids, purines, pyrimidines and creatine metabolites) and CSF (protein, glucose, lactate), did not yield significant abnormalities (Supplementary Table 1). His encephalopathy, dystonia and ataxia gradually decreased over the next five days, though he had not completely returned to his baseline level of developmental functioning. He was discharged on day five on no medications, much improved clinically with residual mild clumsiness and central hypotonia. Presumptive diagnosis at that time was post-infectious encephalitis.

The family history is positive for migraines without hemiplegia or any neurologic deficit in his mother; as well as migraine with aura in a second cousin. His father experienced adult-onset seizures secondary to two separate oligodendrogliomas. There was no other reported family history of migraine, ataxia, epilepsy or autism.

At 17 months of age, he again presented after another unprovoked fall with minor head injury, having manifested an