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Molecular Case Studies

RAPID COMMUNICATION

Episodic ataxia type 2 (EA2) with interictal myokymia and focal dystonia

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Abstract Episodic ataxia type 1 and 2 (EA1 and EA2) are the most well-described of the episodic ataxias. They are autosomal dominantly inherited early-onset diseases characterized by attacks of cerebellar dysfunction. EA1 is clinically characterized by short episodes of ataxia with interictal myokymia, whereas EA2 is characterized by longer-lasting recurrent ataxia, slurred speech, and interictal nystagmus. We report on a patient with EA2 with interictal focal dystonia and also interictal myokymia, which is hitherto not reported as an interictal feature associated to EA2. The patient carries a previously described heterozygous pathogenic de novo frameshift variant in the *CACNA1A* gene, establishing the diagnosis of EA2. She had symptom onset at age 13 and from age 48 she developed interictal myokymia and focal dystonia as illustrated in Supplemental Movie S1. We conclude that interictal myokymia and focal dystonia may be interictal features associated to EA2 caused by the cerebellar pathophysiology of EA2. Episodes of ataxia were successfully treated with acetazolamide in low dose, whereas the interictal features were unresponsive to acetazolamide.

[Supplemental material is available for this article.]

BACKGROUND

Episodic ataxia (EA) is a clinically heterogeneous group of rare disorders characterized by recurrent episodes of short-lasting vertigo, ataxia, and incoordination often associated with nystagmus or dysarthria, typically with onset in the first two decades of life. There are several subtypes of EA defined according to clinical features and genetics; however, clinical and genetic heterogeneity is common (Giunti et al. 2020). EA1 and EA2 have been reported in multiple families worldwide with autosomal dominant inheritance and they are caused by pathogenic variants involving the potassium and calcium channel genes *KCNA1* and *CACNA1A regulating* potassium ion outflow or calcium ion inflow across cell membranes, respectively. Both channel types are highly expressed in neurons in the cerebellum. EA1 is clinically characterized by short episodes of ataxia with interictal myokymia (Jen et al. 2007), whereas EA2 is the most common subtype of EA, characterized by hour-lasting recurrent ataxia, slurred speech, and interictal nystagmus (Indelicato and Boesch 2021). Between the attacks, patients may be free of symptoms but may also develop mildly progressive ataxia. We present an isolated case with EA2 caused by a de novo heterozygous pathogenic c.2847_2856delCACGGGCGCG, p.(Ala952Serfs*115) variant in *CACNA1A* with interictal focal dystonia and interictal myokymia, which is hitherto not reported as an interictal feature associated to EA2.

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Table 1. Variant table

Gene	Chromosome	HGVS DNA reference	HGVS protein reference	Variant type	Predicted effect	dbSNP/ dbVar ID	Genotype
CACNA1A	19: 13409594	NM_001127221.2:c.2847 _2856delCACGGGCGCG	NP_001120693.1: p.Ala952Serfs*115	CGCGCCCGTG/-	Loss of function	424375	Heterozygous

CLINICAL PRESENTATION

This 50-yr-old woman was admitted for a second opinion by her general practitioner. She had no family history of ataxia or other neurological disorders, and no history of migraine or seizures. She was diagnosed with hypothyroidism at age 45 and since then substituted with levothyroxine sodium (Eltroxin) 100 µg daily with no complications. Otherwise, her previous medical history was unremarkable except for a fall from a horse at age 13. She did not have any sequelae from this fall; however, the first time she was riding a horse after the fall, she experienced a short-lasting attack of dizziness. From that time, she experienced episodes of dizziness lasting hours one to two times a month.

The episodes are initiated by a feeling of distress followed by a feeling of alcohol intoxication, imbalance, slurred speech, and double vision. At a younger age, she also experienced nausea but presently she has more a tinnitus-like feeling of airplane noise from a long distance. The episodes may last from 1 to 5 h. During the last 2 years she has noticed almost daily interictal involuntary muscle movements in her thighs and toes, especially the left-sided lateral toes, waxing and waning, lasting minutes to 2 hours, but not necessarily at the same location or simultaneously (see Supplemental Movie S1). She had no excessive use of caffeine or alcohol.

Interictal neurological examination was normal with no nystagmus, dysarthria, or ataxia. There were no fasciculations, myokymia, or dystonia. The patient scored 0/40 on the Scale for the Assessment and Rating of Ataxia (SARA) (Schmitz-Hübsch et al. 2006).

During the years she had been examined by different neurologists and otologists with normal findings and no diagnosis had been established. Blood biochemistry including thyroid function as well as magnetic resonance imaging (MRI) of the brain were normal.

Fragment analyses of genes associated to repeat expansion-caused ataxias were normal, whereas next-generation sequencing of 81 genes (see Supplemental Table S1) related to ataxia identified a heterozygous pathogenic variant (c.2847_2856delCACGGGCGCG, p.(Ala952Serfs*115) [NM_001127221.1]) in *CACNA1A* (see Table 1). This sequence variant changes the reading frame and leads to a premature stop of translation and was previously reported as pathogenic (see ClinVar; https://www.ncbi.nlm.nih.gov/clinvar). DNA from her healthy parents was Sanger-sequenced and none of them carried the pathogenic variant (see Supplemental Fig. S1).

Acetazolamide 125 mg × 2 daily was initiated, which dramatically lessened duration and severity of the episodes.

DISCUSSION

The episodic ataxias are autosomal dominantly inherited disorders usually with clinical onset in the first two decades of life. EA1 is characterized by brief episodes of ataxia and interictal myokymia, whereas EA2 is manifested by longer episodes of ataxia with interictal nystagmus.

Here we describe a 50-yr-old female patient with episodic ataxia since age 13 and a previously described heterozygous pathogenic c.2847_2856delCACGGGCGCG,

p.(Ala952Serfs*115) apparently de novo frameshift variant in *CACNA1A*, establishing the diagnosis of EA2. A different deletion leading to the same effect on the resulting protein sequence, c.2852_2861delCGCGGACGGG, p. (Ala952Serfs*115) has previously been reported; however, no interictal features associated to this variant are reported in the family consisting of nine affected family members (Mantuano et al. 2010).

In accordance with the diagnosis, she had a very beneficial, lasting response to acetazolamide on the episodes. From age 48, she noticed interictal myokymia in her thighs and focal dystonia in her toes. Torticollis and segmental dystonia as well as blepharospasms have previously been reported as interictal features in two families with truncating pathogenic variants in *CACNA1A* (Spacey et al. 2005); however, interictal myokymia is not previously associated with EA2. Most likely these features are part of her EA2 clinical picture as her hypothyroidism was continuously well-treated from 3 years before myokymia and focal dystonia evolved, and also myokymia and dystonia has been previously described as being associated to the episodes of EA2 (Hu et al. 2013; Indelicato and Boesch 2021). We do not have electromyographical evidence of the myokymia and it could be argued that it might as well be fasciculations; however, the clinical appearance as well as the previous association of myokymia to the episodes of EA2 make the muscle contractions more likely in fact to be interictal myokymia. Like the interictal ataxia and nystagmus associated to EA2, the interictal focal dystonia and myokymia seen in this patient developed later in the disease course and is unresponsive to acetazolamide.

Pathogenic *KCNA1* mutations in EA1 are typically missense, whereas most EA2-associated *CACNA1A* variants disrupt the reading frame; however, no consistent pattern for genotype–phenotype correlation has emerged in either EA1 or EA2 (Silveira-Moriyama et al. 2018; Giunti et al. 2020). Genetic modifiers as well as environmental factors are likely to influence the clinical picture, but both have been poorly characterized so far.

Dystonia is also seen in other cerebellar disorders (e.g., Wilson disease and spinocerebellar ataxia type 3), and several studies have reported that dystonia is associated with changes in the activity, structure, and connections of the cerebellum. Recently, using the tottering (tg/tg) mouse, an animal model of EA2, to dissect the mechanisms underlying stress-induced ataxia and dystonia, it was shown that in response to acute stress, activation of α1-adrenergic receptors by norepinephrine induced erratic firing of Purkinje cells by disrupting their spontaneous intrinsic pacemaking via a casein kinase 2–dependent signaling pathway. It was concluded that norepinephrine and casein kinase 2 are required for the initiation of stress-induced attacks in EA2 and therefore may be new targets for therapeutic intervention (Snell et al. 2022). Whether such intervention will also be beneficial to the interictal features remains to be elucidated.

SUMMARY

We conclude that myokymia and focal dystonia may be acetazolamide unresponsive interictal features associated to EA2, which in our patient emerged as a late phenomenon 35 years after clinical age at onset.

ADDITIONAL INFORMATION

Database Deposition and Access

The sequencing data was generated as part of clinical testing, so the underlying raw data is not consented for deposition to a public database. The variant has been deposited in ClinVar

(https://www.ncbi.nlm.nih.gov/clinvar/) and can be found under accession number SCV002574696.

Ethics Statement

Ethical approval was not required for this study in accordance with national guidelines. Written informed consent for publication including video material was obtained from the patient.

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Authors Contributions

E.N.N., B.Á., J.E.N., and S.G.L. were responsible for conception and design. E.N.N., B.Á., L.B.M., J.E.N., and S.G.L. analyzed and interpreted the data and drafted and revised the manuscript. All authors have read and approved the manuscript.

Competing Interest Statement

The authors have declared no competing interest.

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