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A Novel CACNA1A Mutation Associated With Adult-Onset, Paroxysmal Head Tremor



CACNA1A mutations cause a range of disorders with diverse, sometimes overlapping clinical features. Point mutations, including missense mutations, nonsense mutations, splicing mutations and small deletions/insertions, result in a variety of phenotypes including episodic ataxia type 2 (EA2) and familial hemiplegic migraine type 1 (FHM1).¹ These 2 conditions show clinical overlap with spinocerebellar ataxia type 6 (SCA6), generally caused by CAG repeat expansions in the coding region of *CACNA1A*.² We report a novel missense mutation in *CACNA1A* presenting with adult-onset, paroxysmal head tremor responsive to acetazolamide.

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Case Report

A 26-year-old man was referred with a 5-year history of paroxysmal head tremor provoked at times of heightened stress and when steady head posture was required (for example, when in the barber's chair and when using an electric toothbrush). Paroxysms lasted between 5 and 60 minutes and recurred several times weekly. He was not aware of any sustained directional pull of the head or neck. There was a remote history of episodes of childhood hemiplegic migraine; the last occurred at age 12. He had been mildly unsteady and dysarthric since his midteens. Family history was unremarkable apart from a report of dysarthria in 1 paternal uncle (not examined). Treatment with acetazolamide 250 mg twice daily reduced the frequency of episodes of head tremor by approximately two thirds.

Examination

On examination (see Video) there were persistent mild cerebellar signs: dysarthria, limb ataxia, and impaired tandem gait. Eye movements were normal without nystagmus. Pronounced intermittent, rapid, jerky, horizontal head tremor was consistently provoked when examining pursuit eye movements. Between attacks of head tremor there was mild cervical dystonia with intermittent, sustained head turns to the left. The remainder of the examination was normal.

Investigations

Cranial MRI showed cerebellar atrophy (Fig. 1). A heterozygous novel missense mutation in exon 14 of the CAC-NA1A gene was detected (c.1849C>G, GenBank accession number NM_001127221.1), predicted to result in a p.Leu617Val protein change. This mutation affects a highly conserved amino acid located in a transmembrane region of the CACNA1A protein and in silico analysis supports its likely pathogenicity.

Discussion

We report a case of adult-onset, paroxysmal head tremor as a result of a novel CACNA1A missense mutation and



FIG. 1. Cranial MRI-sagittal FLAIR image showing cerebellar atrophy. The MRI appearance was otherwise normal.

occurring against a background of remote sporadic hemiplegic migraine, cerebellar atrophy, and mild cerebellar signs. Our patient has mild cervical dystonia, and the head tremor may best be classified as dystonic.³

It is well recognized that cerebellar disorders, including stroke and atrophy, can be associated with dystonia, supporting the importance of the cerebellum in the genesis of dystonia.⁴ Links between *CACNA1A* mutations and dystonia or head tremor have rarely been reported: mutations in *CACNA1A* are associated with benign paroxysmal torticollis of infancy, a disorder characterized by episodic dystonic head tilt⁵; interictal, adult-onset, focal, and segmental dystonia was reported in 2 carriers of truncating *CACNA1A* mutations from EA2 pedigrees⁶; and head tremor was a presenting feature in 2 patients with FHM1.⁷

The clinical features in our patient expand the phenotype associated with missense mutations in *CACNA1A* to include adult-onset, paroxysmal head tremor and cervical dystonia.

Legend to the Video

Segment: The patient's head is still before onset of a jerky, horizontal, head tremor when eye movements are examined. Horizontal pursuit eye movements are normal. Throughout the examination there is mild cervical dystonia with intermittent head turn to the left and tilt to the right; this is most evident during examination for dysdiadochokinesis. There is little upper limb ataxia but heel-shin ataxia is evident and there is impaired tandem gait.

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