Non-Paroxysmal Progressive Ataxia in an Adult Due to a Novel Mutation of the CACNA1A Gene

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Abstract

Mutations of voltage gated calcium channels are commonly associated with episodic ataxia. There has been no case reports in the literature that describe a non-episodic presentation of ataxia in patients affected with this mutation. This current case report describes a 61-year-old female patient with progressive ataxia and mutations that commonly cause an episodic ataxia.

ABBREVIATIONS

EA2: Episodic Ataxia Type 2; CACNA1A: Voltage Gated Calcium Channel Subunit Alpha 1

INTRODUCTION

Abnormalities of the voltage gated calcium channel subunit alpha 1 (CACNA1A) gene have been implicated primarily in paroxysmal disorders with childhood onset, episodic ataxia type 2 (EA2) and familial hemiplegic migraine. It has rarely been associated with non-paroxysmal ataxia and these cases have had other major neurological disorders. We report a case of progressive, non-episodic ataxia in an adult, without signs of other brain involvement, which we believe is due to a previously unreported abnormality of this gene.

CASE PRESENTATION

This 61-year-old woman with a history of bipolar disease, developed problems with her gait and balance when she was 51 years old. Two years after her gait problems began she reported reduced dexterity and slurred speech. Family history revealed a brother who died of Down syndrome in infancy. Her mother died in her 40’s and had no history of neurological problems but her father was using a walker, when he was in his 70’s, for unknown reasons and died at age 84. The patient denied tremor, autonomic problems, or any episodic worsening. She was taking lamotrigine 100 mg bid, clonazepam 0.5 mg tid, paroxetine 40 mg qd, for bipolar disorder, omeprazole, naproxen, and baclofen 10 mg qid.

Mental status was normal aside from slurred, slow speech. She had saccadic pursuit, upbeat nystagmus in primary position and gaze evoked nystagmus, which was more prominent horizontally. There was no pronator drift. She had prominent, symmetric ataxia in her arms and legs. Tone was normal and she did not have spasticity. Deep tendon reflexes were absent in the arms, 2+ at the knees and 1+ at ankles. The Babinski reflex was negative. She displayed titubation. The sensory examination was normal. She could barely stand from the sitting position without using her arms. She walked with a very wide base and was severely ataxic.

Routine blood tests have been normal. The patient’s folic acid and vitamin B 12 level were within normal limits. A brain MRI revealed cerebellar atrophy. Genetic testing revealed a CACNA1A heterozygous frame shift mutation, c.1475-1490 (Isoform 1) with 16 bp deletion; codon: 492-497 and a POLG heterozygous missense mutation. The CACNA1A mutation was predicted (by Athena Laboratory) to be highly likely pathogenic. It was a unique mutation in the Athena Laboratory experience and not recorded in the Human Gene Mutation Database. A four week trial of acetazolamide 250 mg tid resulted in no clear improvement.

DISCUSSION

POLG mutations have been associated with several neurological disorders but none with cerebellar ataxia [1], whereas the CACNA1A gene has been associated with ataxic disorders and antibodies to the calcium channel receptor has also been associated with cerebellar ataxia and atrophy [2]. We therefore believe the calcium channel abnormality is the likely explanation for her neurological syndrome. Aside from EA2, genetic abnormalities of CACNA1A have been associated with progressive cerebellar ataxia starting at age of 30 [3]; a child with interictal ocular movement disorder and mild ataxia with paroxysmal migraine-like symptoms [4]; ataxia with episodic tremor [5]; progressive cerebellar ataxia [6]. These non-EA cases had paroxysmal or non-paroxysmal neurological problems in...
addition to their progressive ataxia. This case demonstrates the variability of clinical presentation associated with different abnormalities of this calcium channel gene, and suggests that testing of the CACNA1A gene may be useful in the evaluation of patients with non-paroxysmal, adult onset ataxic syndromes.

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CONFLICT OF INTEREST

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REFERENCES