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A novel mutation of CACNA1A gene in episodic ataxia type 2 family in Korea

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Abstract

Episodic ataxia type 2 (EA-2) is a rare disorder presenting with paroxysmal vertigo and cerebellar dysfunction. EA-2 is known to be caused by mutations of the CACNA1A gene on chromosome 19q13. We examined a family of EA-2 with a novel mutation of the CACNA1A gene showing characteristic ocular symptoms. A-36-year woman visited our hospital with paroxysmal vertigo. When she experienced vertigo attack, she also suffered from gait disturbance, dysarthria, and ataxia. She complained that she could not ride in a car or a train that moved fast, because she could not visually follow the moving objects. Her mother, grandmother, and uncle also complained of similar symptoms. Video nystagmographic findings showed loss of optokinetic nystagmus. We found a novel missense mutation, R279C (c.835C>T), on exon 6 in the CACNAIA gene. This is the first report of a family with new mutation of EA-2 in Korea.

INTRODUCTION

Episodic ataxia type 2 (EA-2) is a rare autosomal dominant disorder characterized by recurrent vertigo and ataxia. Clinically, EA-2 usually presents early in life and is associated with headache and nystagmus during and between the attacks. Interictal nystagmus and abnormal ocular movements are the typical features of EA-2. EA-2 is known to be caused by mutations of the *CACNA1A* gene on chromosome 19q13 which encodes the neuronal P/Q-type calcium channel. Here, we report a case of EA-2 family with a novel mutation in the *CACNAIA* gene, showing characteristic ocular findings.

CASE REPORT

A 36 year-old woman visited our clinic for repetitive vertigo. She began to suffer from vertigo since 15 years of age. During the attack, she experienced vertigo, nausea, vomiting, dysarthria, and loss of coordination. She also complained of generalized weakness at the time of the attack. When she drove a car above 70 miles per hour, she was not able maintain the visual focus. The duration of vertigo usually lasted for 2 hours, and the frequency was approximately 1 attack per month. Her symptoms were aggravated by exercise and physical activity. Neurologic examination revealed normal cerebellar function and gait, but gaze evoked nystagmus. Video nystagmography (VNG) was performed which showed impaired saccade and loss of optokinetic nystagmus (OKN) (Fig.1). Her mother, maternal grandmother, and uncle also suffered from similar symptoms. Her mother showed horizontal and vertical gaze evoked nystagmus. Her ten-year-old daughter had not experienced ataxia, but she showed gaze-evoked nystagmus. MRI revealed normal findings in all patients. The mother and daughter of the proband showed normal OKN in VNG. The clinical manifestations were compatible with EA-2. To confirm the diagnosis, genomic DNA was extracted using standard protocols. Peripheral

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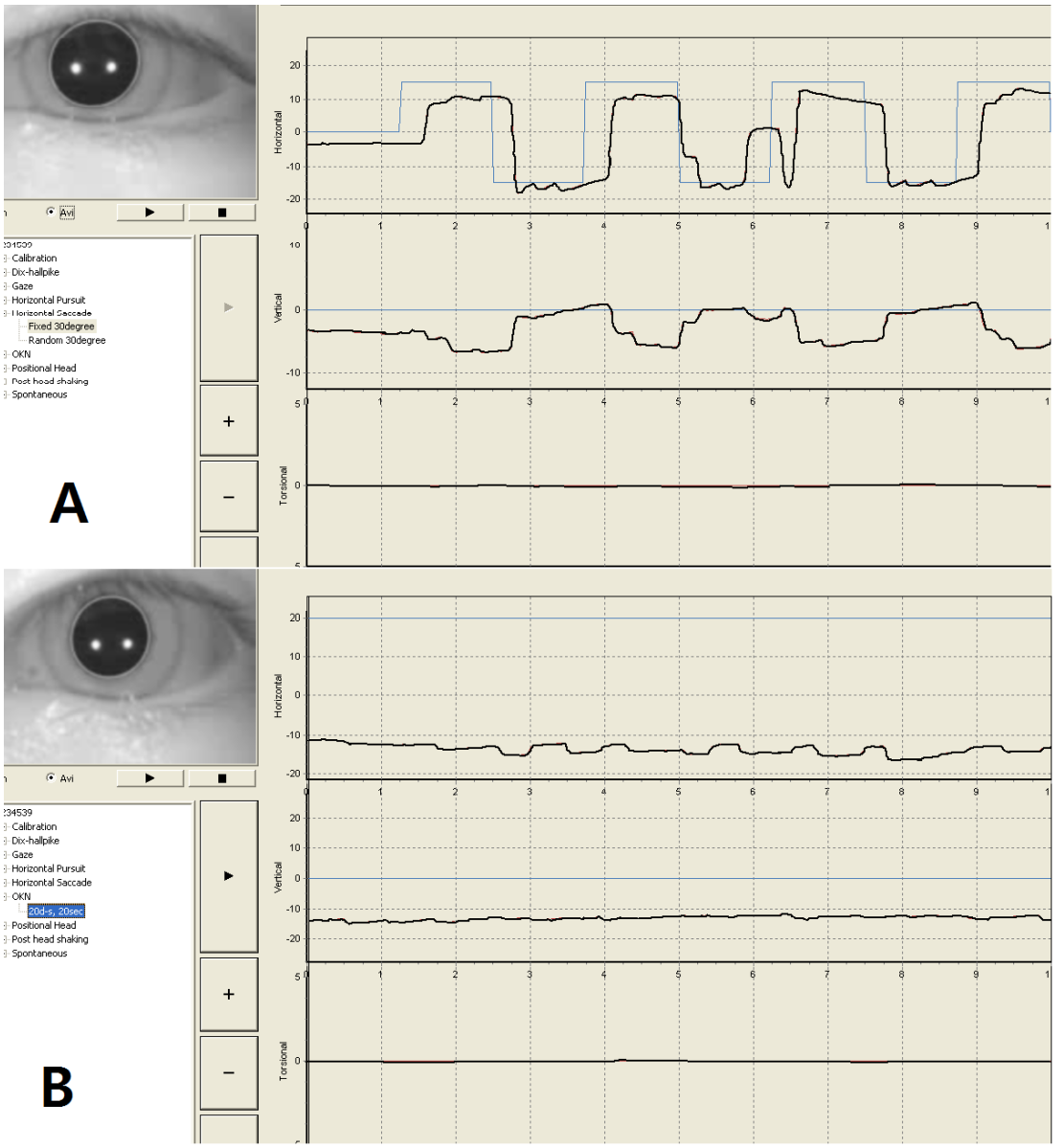

Figure 1. (A). Video nystagmography (VNG) revealed the impaired saccadic movement. The latency of saccade was delayed and the velocity of saccade was reduced. (B). VNG also showed loss of optokinetic nystagmus (OKN).

blood samples were obtained from the proband and her mother, spouse, and two children, with informed consent. Genetic analysis by direct sequencing of all 43 exons of the *CACNA1A* gene and their flanking regions was performed, using the patient's extracted DNA according to the published method.[1] Direct sequencing of the *CACNA1A* gene in this proband revealed a heterozygous missense mutation R279C (c.835C>T) on exon 6. Along with this novel mutation, two non-synonymous heterozygous SNPs (E918D and E993V) were also identified. To confirm this novel sequence variation, exon 6 of *CACNA1A* was amplified repeatedly and sequenced from genomic DNA (Fig 2). The sequences from her husband and unaffected son revealed wild-type (cytosine at cDNA position 835) alleles, whereas, the sequences from the proband and her mother and affected daughter showed heterozygous missense mutation R279C (c.835C>T). We confirmed the diagnosis of EA-2. For treatment, acetazolamide was administrated to all patients. The proband and her mother showed reduced frequency and severity of episodic attacks.

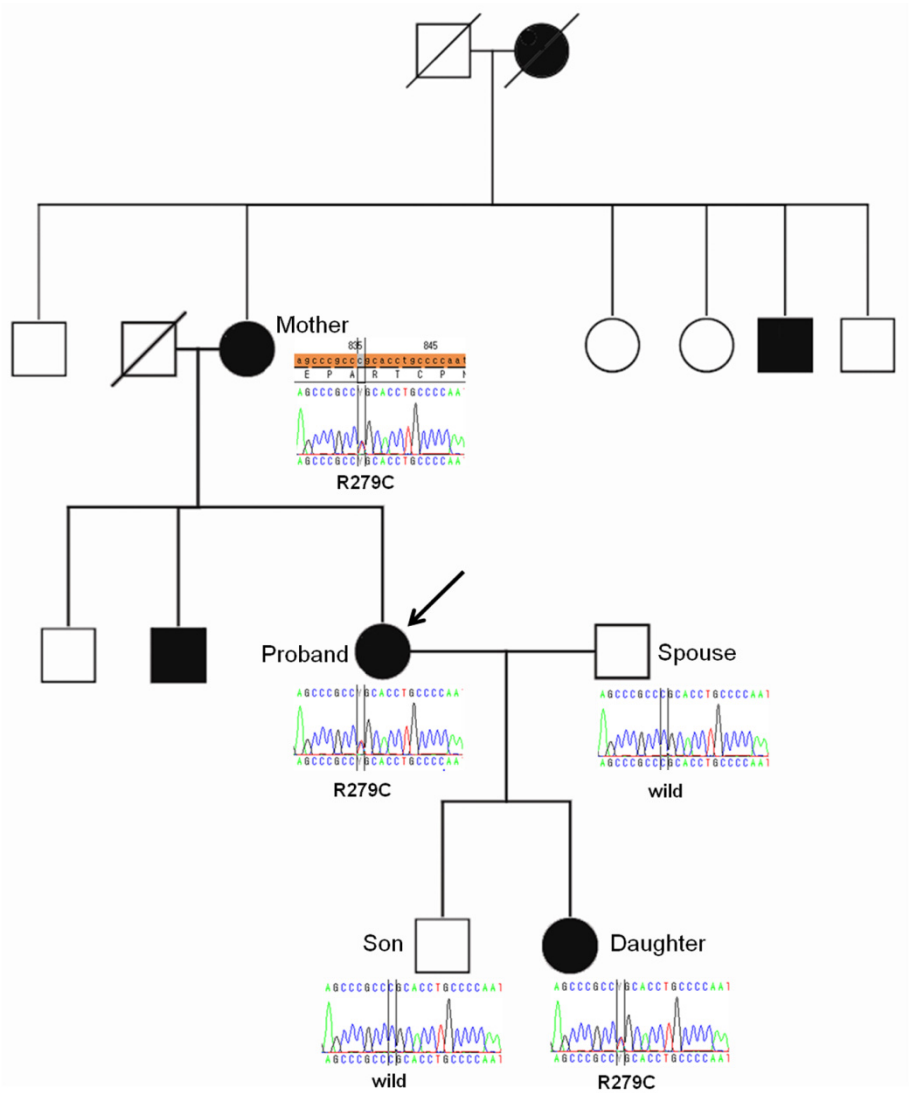

Figure 2. A novel mutation of the CACNA1A gene was identified in the pedigree.

DISCUSSION

Our case is the first novel mutation of EA-2 in Korea. EA-2 is caused by mutations in the *CACNA1A* gene on chromosome 19q13. More than 50 mutations have been found in families with EA-2, and two-thirds have been identified as missense mutations.[2] Such mutations cause disruption in the translational reading frame of the α1a subunit to produce truncated proteins.[3] These proteins impair the function of Cav2.1 subunit of the P/Q-type calcium channel (2262 amino acid). These channels are abundantly distributed in the cerebellum and at neuromuscular junctions. Functional changes of the P/Q calcium channel may cause disinhibition of Purkinje cells leading to ataxia, vertigo, and nystagmus.[4]

Clinical symptoms of our case are in accordance with typical features of EA-2. Similar to previous reports, our case presented various clinical phenotypes within the same family.[5] The proband showed all typical manifestations of EA-2. Her mother and uncle showed milder symptoms and her brother had weaker episodes of ataxia. Besides, the proband complained of myasthenic symptoms which are thought to be caused by impaired neuromuscular transmission.[6] Treatment with acetazolamide was very effective.

However, our cases had several unique features compared to the previous reports. First, the mutation in our cases is a novel mutation in the *CACNA1A* gene which has not yet been reported in the literature. Genetic studies of previous

reports in Korea revealed known mutations of CAG repeat expansion, translocation, and deletion in the *CACNA1A* gene.[7-9] Second, we described abnormal ocular movements in the preclinical stage of EA-2. There were few reports that described the signs in the preclinical stage of episodic ataxia. The daughter of the proband, who has not experienced episodic symptoms yet, showed gaze-evoked nystagmus and saccadic dysmetria. Her genetic study showed a mutation in the same location with the proband. However, her son with normal ocular movements showed negative findings in the gene study. Finally, we described a loss of optokinetic nystagmus by VNG. Although Impaired optokinetic nystagmus in EA-2 was often observed in previous reports, there were no electrophysiologic record of OKN loss.[10] Complete absence of OKN was recorded by VNG in our case. In particular, our patient complained that she could not follow a moving object while driving. This symptom was proven to be related to the loss of OKN, and it always presented without episodic attacks. The symptom functioned as an important clue to distinguish EA-2 from peripheral vertigo.

Our patients had been misdiagnosed with peripheral vertigo for several years because of their brief paroxysmal symptoms. We postulated that the incidence of EA-2 might be underestimated due to the episodic symptoms. Our case highlighted that neuro-ophthalmological findings are important signs for diagnosis of EA-2 and biomarker for early diagnosis in preclinical stage.

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DISCLOSURE

Conflicts of interest: None

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