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LETTER TO THE EDITOR

Efficacy of levetiracetam in patients with episodic ataxia type 2 caused by CACNA1A mutation: three case reports

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Introduction

Episodic ataxia type 2 (EA-2) is an autosomal dominant disease caused by the *CACNA1A* gene mutation [1]. Patients with EA-2 usually manifest episodes of dizziness, disequilibrium, dysarthria, ataxia, and headaches. During the interictal period, patients can reveal central ocular motor signs, slowly progressive limb ataxia, or truncal imbalance. Acetazolamide is the treatment of choice for EA-2, but its clinical effect is known to be partial with a response rate of approximately 50–70% and it is transient in many cases [1]. In a small population study consisting of ten patients with EA, a potassium channel blocker named dalfampridine (4-aminopyridine) was shown to be beneficial and effective at reducing attack frequency [2].

Electroencephalogram (EEG) abnormalities were noted in patients with EA [3, 4]. It is not uncommon for EA-2 to be accompanied by epilepsy; therefore, epileptiform EEG readings can be observed in EA-2 patients with epilepsy [4]. In contrast, the association between abnormal EEG findings and the clinical aspects of EA-2 patients without epilepsy are unclear.

Herein, we report three patients with EA-2 caused by *CACNA1A* gene mutations. All three patients revealed intermittent rhythmic delta activities (IRDA) during interictal phases. Concomitant polytherapy or monotherapy with levetiracetam significantly reduced the frequency and severity of episodic attacks, and the frequency of IRDA was reduced on the EEG as well. Clinical data are summarized in Table 1.

Case report

Patient 1

A 26-year-old woman presented with recurrent vertigo, imbalance, nausea, and vomiting. She denied any family history related to episodic vertigo, epilepsy, or migraine. She revealed perverted downbeat head-shaking nystagmus in the interictal period, and showed prominent downbeat nystagmus during the ictal period. The MRI was within normal limits and EEG showed generalized IRDA. The patient was analyzed by genetic testing using a targeted gene sequencing with MiSeq platform (Illumina, San Diego, CA). We found a point mutation of the *CACNA1A* gene as c.5035C > T/p.Arg1679Cys. This variation has been reported previously [5], and classified as pathogenic [6, 7]. Initially, the patient was prescribed acetazolamide but the dose could only be increased up to 125 mg/day because of her condition with hypersomnolence. Concomitant administration of levetiracetam of 250 mg/day was prescribed, and subsequently the frequency of attacks significantly decreased from three times per week to once per 3 months. Accordingly, the frequency of IRDA was substantially decreased on follow-up EEG.

Patient 2

A 27-year-old man presented with intermittent vertigo, imbalance, and dysarthria since he was 5 years old. He reported that his mother and maternal grandmother had also similar symptoms without any determined diagnosis. He showed spontaneous downbeat nystagmus, gaze-evoked nystagmus, and saccadic pursuit in the interictal period. The brain MRI was unremarkable and EEG revealed generalized IRDA. The genetic testing showed a heterozygous nonsense variation in the *CACNA1A* gene, in exon 23 (c.3855C > G/p.Tyr2319*), which was a novel variation, and it was confirmed by conventional Sanger sequencing. After administration of acetazolamide up to

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Table 1 Clinical data of three patients with EA-2

	Case 1	Case 2	Case 3
Age/sex	26/F	27/M	62/F
Onset age	5	6	17
CACNA1A gene mutation	c.5035C > T/p.Arg1679Cys	c.3855C > G/p.Tyr2319*	c.3855C > G/p.Tyr2319*
Triggers	None	After wake-up	Stress, exhaustion
Interictal finding	Perverted head-shaking nystagmus	Spontaneous downbeat nystagmus, gaze-evoked nystagmus, saccadic pursuit	Gaze-evoked nystagmus
Ictal symptoms	Dizziness with downbeat nystagmus, nausea, blurry vision, dysarthria, and headaches	Dizziness, dysarthria, nausea, vomiting, and disequilibrium	Dizziness, dysarthria, nausea, vomiting, and disequilibrium
Ictal frequency	3–4 times/week	3–4 times/week	1–2 times/month
Ictal duration	Several hours to 1 day	For 2 h to 1 day	20 min
EEG	IRDA, generalized	IRDA, generalized	IRDA, generalized
After ATZ			
ATZ dose	125 mg/day	750 mg/day	
ATZ S/E	Hypersomnolence	None	
Ictal frequency	1 time/week	3 times/week	
After LEV			
LEV dose	250 mg/day	1500 mg/day	750 mg/day
LEV maintenance duration	1 year	5 years	3 years
Ictal frequency	1 time/3 months	1 time/week, with lesser severity	1 time/3–4 months
EEG	IRDA almost disappeared	IRDA almost disappeared	IRDA almost disappeared

ATZ acetazolamide; *LEV* levetiracetam; *EEG* electroencephalogram; *IRDA* intermittent rhythmic delta activities

750 mg/day, the frequency of vertigo attacks was transiently decreased to half of the baseline attack frequency and eventually returned to the previous baseline state. Thus, levetiracetam of 750 mg/day was added concomitantly. Subsequently, the patient's symptoms were relieved from three times per week to less than once per week, with less severity. The follow-up study of EEG revealed a decreased frequency of IRDA than the previous baseline EEG.

Patient 3

A 62-year-old woman, who is the mother of the case 2 patient, presented with episodic dizziness with disequilibrium that started in her 30 s. She denied any medical history. Gaze-evoked nystagmus was observed during the attack-free period. During the attack, she complained of dizziness, dysarthria, nausea/vomiting, and disequilibrium. She reported the dizziness attacks occurred approximately once or twice per month, which was less frequent than when her symptoms first started in her 30 s. The brain MRI was normal and the EEG showed generalized IRDA. She started levetiracetam monotherapy up to 750 mg/day without acetazolamide, resulting in symptoms occurring from once or twice per month to once per 3 months. The frequency of IRDA pattern was also decreased on the follow-up EEG.

Discussion

All three patients with EA-2 in this study showed episodic dizziness/ataxia and generalized IRDA on EEG, both of which were clearly responsive to levetiracetam.

Episodic ataxia type 2 is well-known as acetazolamide-responsive ataxia [8]. For long-term use of acetazolamide, adverse effects including potential formation of renal stone should be monitored. Although acetazolamide is largely effective in EA-2, its partial and transient effect and intolerance of the adverse effects necessitate a further look into effective and adherable additional or alternative therapeutic options. Dalfampridine (4-aminopyridine) is another treatment option for EA-2 [2, 9]. Dalfampridine is a potent proconvulsant agent; therefore, it is contraindicated in patients with epilepsy. This is a major disadvantage in treatment of EA-2 given that this condition is often accompanied by epilepsy and abnormal epileptiform EEG [4]. Epilepsy may develop in patients with mutations of CACNA1A gene, which encodes the alpha 1A subunit of the P/Q-type calcium channel, playing a role in the control of membrane excitability. Levetiracetam is a widely used anti-epileptic drug that involves synaptic vesicle glycoprotein 2A inhibiting calcium release from intraneuronal calcium stores and N-type calcium channels, and it also affects voltage-gated potassium channels [10].

We previously reported the effectiveness of levetiracetam in a single EA-2 patient case study [11].

The incidence of having epilepsy or abnormal EEG findings in EA-2 are higher than those in the general population [4]. Epilepsy accompanies patients with CACNA1A gene mutation because it is a gene that plays a role in channelopathy. EA-2 patients without epilepsy can also show various abnormal EEG findings. Photoparoxysmal response, spike and wave complexes, slow background activity, or IRDA were observed in EA-2 [3, 4, 12]. Thus, abnormal EEG in the setting of recurrent episodic dizziness spells could provide a diagnostic clue for EA. However, the relationships between abnormal EEG and the frequency or severity of attacks and treatment response have not been studied and remain unclear in EA-2 patients without epilepsy. In our cases, the frequency of IRDA was attenuated accordingly along with the improvement of episodic attacks. However, because IRDA is most often due to metabolic encephalopathy or structural brain lesions and it can also be encountered in patients with generalized epilepsy or neurodegenerative disorders [13, 14], these conditions need to be excluded before the association between EA-2 and IRDA is established.

We suggest that levetiracetam could be an additional or alternative therapeutic option in EA-2, and there could be a possibility that the frequency of abnormal EEG correlates with clinical attacks and treatment response in EA-2 patients without epilepsy. However, with the limitation of a small open-label study, larger and sophisticated studies are needed to confirm this correlation.

Author contribution SN wrote the manuscript. TK supervised the project.

Declarations

Ethical approval The authors declare that these case reports has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Informed consent was obtained from the patients and The Institutional Review Board at Incheon St. Mary's Hospital approved this case report.

Conflict of interest The authors declare no competing interests.

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