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Case Report

Two cases of early-onset myoclonic seizures with continuous parietal delta activity caused by *EEF1A2* mutations

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Abstract

Background: Mutations in the elongation factor 1 alpha 2 (*EEF1A2*) gene have recently been shown to cause severe intellectual disability with early-onset epilepsy. The specific manifestations of mutations in this gene remain unknown.

Case report: We report two cases of severe intellectual disability accompanied by early-onset epilepsy with continuous delta activity evident on electroencephalography. Both cases presented with developmental delay and repetitive myoclonic seizures in early infancy. Both cases showed continuous high-voltage delta activity over both parietal areas when awake, as revealed by interictal electroencephalograms. After the emergence of continuous delta activity, development stagnated. One case showed some development after relief of the seizures and epileptic activity, but drug resistant seizures recurred, and the development again became stagnant. In both cases, a *de novo* recurrent heterozygous mutation in *EEF1A2* [c.364G > A (p.E122K)] was identified by whole-exome sequencing.

Conclusion: This report provides clinical data on epileptic encephalopathy in patients with *EEF1A2* mutation. Continuous high-voltage delta activity seen over both parietal areas may be a unique manifestation of *EEF1A2* mutation. Epileptic activity may aggravate the effect of the mutation on brain development.

Keywords: Pediatrics; Epilepsy; Genetics; *EEF1A2*; High voltage delta activity; Intellectual disability; Myoclonic seizure

1. Introduction

Whole-exome sequencing has led to the identification of genes responsible for many epilepsy syndromes. This technique has also identified other phenotypes caused by mutation in known epilepsy-causing genes, and has thus expanded the phenotypic spectrum of known epileptic genes [1].

Abbreviations: *EEF1A2*, elongation factor 1 alpha 2; EEG, electroencephalogram; MRI, magnetic resonance imaging; ESID, Enjoji Scale of Infant Analytical Development; CNS, central nervous system

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Mutations in the elongation factor 1 alpha 2 (*EEF1A2*) gene have been shown to cause severe intellectual disability with early-onset epilepsy, infantile spasms, and autistic spectrum disorder [2–4]. Because the manifestations of reported cases were not specific, the condition cannot be diagnosed until global gene testing is performed.

We report two cases with *EEF1A2* mutations accompanied by characteristic findings on electroencephalograms (EEGs) and EEG changes during development.

We believe that this report may assist in the early diagnosis of mutations in this gene and help us to understand the mechanism by which mutation causes severe intellectual disability.

2. Case studies

2.1. Case 1

A female aged 2 years, 2 months was referred to our clinic for treatment of anticonvulsant-resistant seizures. She had been born normally at 41 weeks of gestation with birth weight, body height and head circumference of 3150 g (+0.4 SD), 50 cm (+0.8 SD) and 33.5 cm (+0.4 SD), respectively. Her family history was unremarkable. She had syndactyly of the left fourth and fifth toes, and internal strabismus was apparent at 1 month. She showed facial features including a tented upper lip, everted lower lip, and downward corners of the mouth.

At 10 months, she presented with repetitive myoclonic seizures. At that time, she had no head control, social smile or visual pursuit. Magnetic resonance imaging (MRI) was normal (Fig. 1A). Her waking EEG showed continuous synchronous high-amplitude delta activity over the both parietal areas, some of which was preceded by sharp waves (Fig. 1B). Frequent diffuse polyspikes and multifocal spikes were seen during sleep. Valproate and pyridoxine had no effect.

At 1 year 3 months although diffuse spike and waves remained, both the seizures and the continuous delta activity were relieved upon treatment with clobazam (Fig. 1C), followed by development of head control, visual pursuit, social smile, vocalization, and reach to toys.

At 1 year 6 months, the continuous delta activity recurred. She presented repetitive atypical absence seizures, which were resistant to acetazolamide and pulse steroid therapy (Fig. 1D), and her development stagnated. At 2 years 2 months, she could not roll over or speak meaningful words. Her developmental quotient was 21 as measured by the Enjoji Scale of Infant Analytical Development (ESID).

2.2. Case 2

A male aged 2 years 2 months was referred to our hospital for treatment of developmental delay. He had been born normally at 41 weeks of gestation with a birth weight of 3280 g (+0.7 SD). His family history was unremarkable. He exhibited unusual facial features, including a depressed nasal bridge, tented upper lip, everted lower lip, and downward corners of the mouth.

At 8 months, he presented with repetitive myoclonic seizures and myoclonic–atonic seizures. At 1 year and 3 months, he was able to sit unaided for only a few seconds. His MRI was normal (Fig. 1E). His EEG showed frequent diffuse spike and waves or multifocal spikes during sleep. Valproate, clonazepam, nitrazepam, levetiracetam, ethosuximide, topiramate, and lamotrgine had no effect.

At 1 year 6 months, his waking EEG showed continuous synchronous high-amplitude delta activity over both parietal areas, some of which was preceded by sharp waves (Fig. 1F). His development stagnated after the continuous delta activity developed. MRI at 1 year 9 months revealed cerebral atrophy (Fig. 1E). At 2 years 2 months, he could not stand unaided or speak meaningful words. His developmental quotient was 18, as measured by the ESID.

3. Genetic analysis

Whole-exome sequencing of the two patients identified a heterozygous *EEF1A2* mutation [c.364G > A (p.E122K)], which was validated *de novo* by Sanger sequencing. In fact, the *de novo* c.364G > A mutation in *EEF1A2* has been reported in a patient with nodding spasms [4]. The mutation was not found in the 6500 exomes sequenced by the National Heart, Lung, and Blood Institute exome project or among our 575 in-house control exomes.

4. Discussion

We report on two patients with the same *EEF1A2* mutation, who exhibited repetitive seizures, continuous delta activity, and severe intellectual disability.

In case 1, development stagnated during the period in which she suffered repetitive seizures and continuous delta activity, and resumed after the delta activity disappeared. In case 2, development stagnated after continuous delta activity developed. The clinical courses of these cases were more severe than that of a previously reported case with the same mutation [4]. This indicates that epileptic activity may aggravate the effect of the mutation on brain development, which can be considered as a form of epileptic encephalopathy.

Synchronous delta activity is also noted in patients with epilepsy with myoclonic–atonic seizures, Angelman syndrome, Rett syndrome, and ring chromosome 20 syndrome [5–8]. The delta activity in our cases was characterized by (1) near-continuous presence while awake