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Case Report

Two Japanese cases of epileptic encephalopathy associated with an *FGF12* mutation

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Abstract

A heterozygous mutation in the fibroblast growth factor 12 (*FGF12*) gene, which elevates the voltage dependence of neuronal sodium channel fast inactivation, was recently identified in some patients with epileptic encephalopathy. Here we report 1 Japanese patient diagnosed with early infantile epileptic encephalopathy (EIEE) and another diagnosed with epilepsy of infancy with migrating focal seizures (EIMFS). These 2 patients had an identical heterozygous missense mutation [c.341G>A:p.(Arg114His)] in *FGF12* , which was identified with whole-exome sequencing. This mutation is identical to previously reported mutations in cases with early onset epileptic encephalopathy. One of our cases exhibited EIMFS, and this case responded to phenytoin and high-dose phenobarbital (PB). *FGF12*-related epileptic encephalopathy may exhibit diverse phenotypes and may respond to sodium channel blockers or high-dose PB.

Keywords: Early onset epileptic encephalopathy (EIEE); Epilepsy of infancy with migrating focal seizures (EIMFS); FGF12; Parental mosaicism; High-dose phenobarbital

1. Introduction

The causative genes of epileptic encephalopathies have rapidly been identified through the adoption of next-generation sequencing approaches [1–3]. The fibroblast growth factor 12 (*FGF12*) gene encodes a member of the fibroblast growth factor homologous factor (FHF) family [4]. Recently, a heterozygous mutation in *FGF12* was identified in some patients with epileptic

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encephalopathy and early onset epilepsy [4–7]. Here, we report 2 Japanese patients with epileptic encephalopathy having an identical heterozygous missense mutation in *FGF12,* which was identified through whole-exome sequencing.

2. Case report

2.1. Patient 1

The patient was a 32-year-old man, who was born after 40 weeks of uneventful pregnancy without asphyxia. He started experiencing frequent seizures, which included spasms and brief tonic seizures, at 7 days after birth. Electroencephalography (EEG) showed a suppression-burst pattern, leading to a diagnosis of early infantile epileptic encephalopathy (EIEE). Although EEG performed at 11 months of age showed hypsarrhythmia, his seizures were successfully controlled with simultaneous administration of phenobarbital (PB), phenytoin (PHT), clonazepam (CZP), acetazolamide (AZA), and vitamin B6. However, he did not achieve the developmental milestone. His seizures were well controlled until 12 years of age. Brain MRI at 13 years of age (Fig. 1A and B) showed mildly enlarged lateral ventricles. Sporadic tonic seizures were noted since 13 years of age. At present, he has spastic-dystonic quadriplegia without rolling or sitting, as well as multiple contractures of the extremities in flexion and dystonic hypertonia of the neck and upper extremities. He has microcephaly (his head circumference was 50.6 cm) and severe intellectual disabilities without any words, as well as reduced visual pursuit and persistent knitting movements. He has sporadic tonic seizures few times a year, and he is taking CZP, carbamazepine (CBZ), and valproate (VPA).

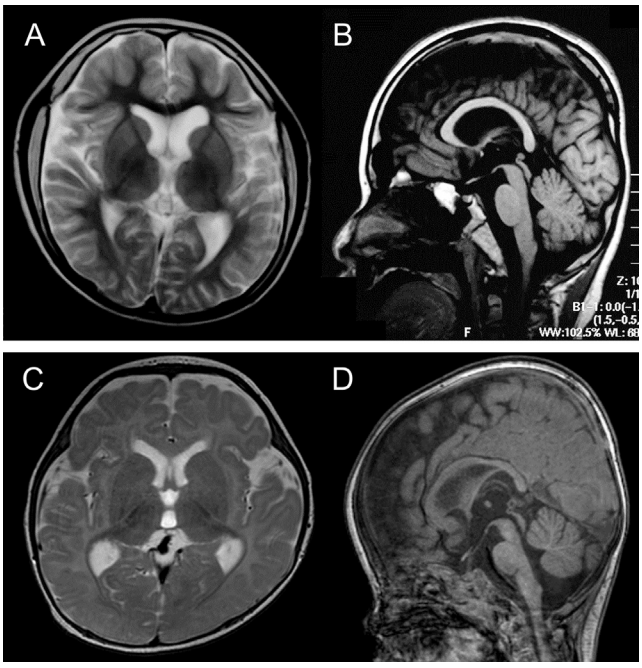

Fig. 1. Brain MRI (axial T2-weighted images: A, C; sagittal T1-weighted images: B, D) of the patients (patient 1: A, B; patient 2: C, D). Brain MRI shows mildly enlarged lateral ventricles in patient 1 at 14 years of age and shows mild cerebral atrophy in patient 2 at 6 months of age.

2.2. Patient 2

The patient was a 1-year-old boy, who was born after 39 weeks of uneventful pregnancy without asphyxia. He suffered from apnea attacks from the day of birth, and tonic seizures began to cluster within a few days after birth. EEG at 5 days after birth showed sharp waves over the left fronto-centro-parietal areas. After treatment with PB and CBZ, the frequency of seizures decreased to once in a few days. Developmental regression was observed as the seizures worsened from around 5 months of age. On referral to our hospital at 6 months of age, he had frequent tonic seizures and focal seizures, and he was bedridden with nasogastric tube feeding. Brain MRI at 6 months of age (Fig. 1C and D) showed mild cerebral atrophy. Notably, ictal EEG in an episode of autonomic seizure with apnea and cyanosis accompanied by mild limb rigidity showed that the seizure activity migrated from one region to another during an episode (Fig. 2), leading to a diagnosis of epilepsy of

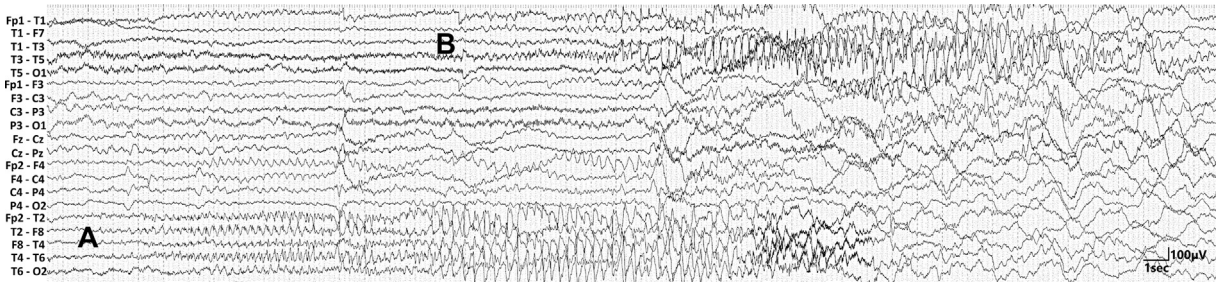

Fig. 2. Ictal EEG of patient 2. Representative ictal EEG of patient 2 at the 6 months of age. Epileptic activity shows attenuation of background EEG activity at seizure onset from the right to the left frontotemporal area, followed by rhythmic spikes in the right frontotemporal area (A). After 15 s, seizure activity migrated to the left frontotemporal area (B).

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Table 1
Clinical features of early onset epilepsy patients with identical *FGF12*(*FHF1*) mutation [NM_021032.4:c.341G>A:p.(Arg114His)].

Reference	Siekierska et al. (2016)		Al-mehmadi et al. (2016)			Guella et al. (2016)		Villeneuve et al. (2017)	present cases	
Patient No.	1	2	3	4	5	6	7	8	9 (patient 1)	10 (patient 2)
Current age	Died age 7y	Died age 3.5y	3y	16y	18y	11m	15y	5y	32y	1y5m
Sex	F	M	M	F	F	F	F	M	M	M
Age at seizure onset	14d	28d	2d	6w	2d	3d	2d	<15d	7d	0d
Seizure types	Tonic seizure	Tonic seizure	Focal motor seizure, GTC	Focal motor seizure, GTC, Myoclonic seizure	Focal motor seizure, Focal to bilateral tonic-clonic seizure	Focal motor seizure	Focal seizure with impaired awareness, Focal to bilateral tonic-clonic seizure	Apnea attack, Focal motor seizure	Spasm, tonic seizure	Apnea attack, GTC, focal seizure with pallor
Interictal EEG	Slow background with multifocal epileptiform discharges, and later hypsarrythmia	Slow background with multifocal epileptiform discharges, and later hypsarrythmia	Slow background with multifocal epileptiform discharges	Slow background with multifocal epileptiform discharges	Slow background with multifocal epileptiform discharges	Multifocal epileptiform discharges, and later normal	Suppression of background and multifocal epileptiform discharges, and later slow background with focal epileptiform discharges	Normal at onset, and later focal epileptiform discharges	Suppression-burst pattern	Slow background with multifocal epileptiform discharges
Ictal EEG	Generalized low voltage fast activity, followed by suppression of background	Generalized low voltage fast activity, followed by suppression of background	Focal rhythmic activity, followed by secondary generalization	NA	NA	Generalized low voltage fast activity, followed by focal rhythmic activity	Generalized spike wave followed by suppression of background	Generalized low voltage fast activity, followed by rhythmic activity	NA	Generalized low voltage fast activity, followed by rhythmic spikes. Seizure activity migrated from one region to another during an episode
Response to treatment	Resistant to AEDs (including phenytoin)	Resistant to AEDs (including phenytoin)	Resistant to AEDs	Partially responded to phenytoin and VNS	Resistant to AEDs (including phenytoin)	Responded to phenytoin and carbamazepine, achieved seizure free	Responded to rufinamide and lamotrigine, achieved seizure free	Partially responded to carbamazepine, ketotic diet and fluoxetine	Resistant to AEDs (including phenytoin)	Responded to phenytoin and high-dose phenobarbital therapy, achieved seizure free
Current therapies			Levetiracetam, phenobarbital	Phenytoin, perampanel, VNS	Phenytoin, pregabalin, perampanel, VNS	NA	NA	NA	carbamazepine, clonazepam, valproic acid	phenytoin, phenobarbital

(*continued on next page*)

Table 1 (*continued*)

Reference	Siekierska et al. (2016)		Al-mehmadi et al. (2016)			Guella et al. (2016)		Villeneuve et al. (2017)	present cases	
MRI findings	Normal (5m), Cerebellar atrophy (6y)	Normal (2m), Cerebellar atrophy (3y)	Normal (at onset), Cerebral atrophy (2y)	Unremarkable (1y), Cerebellar atrophy (8y)	Normal (early childhood), bilateral mesial temporal sclerosis (R > L), mild prominence of cerebellar folia (12y)	Normal (4d)	Normal (2w), Chiari 1 malformation (2y)	Hyperintensity of the parietal areas, cerebellum and brainstem on T2 weighted image (15d), Normal (3y)	Normal (7y), Mildly enlarged lateral ventricles (14y)	Mild cerebral atrophy (7m)
Cerebellar atrophy	+	+	–	+	+	–	–	–	–	–
Intellectual disability	Severe	Severe	Severe	Severe	Moderate	Normal	Moderate	Moderate	Severe	Severe

Abbreviations: AEDs = antiepileptic drugs; GTC = generalized tonic-clonic seizure; NA = not available; VNS = vagal nerve stimulation.

infancy with migrating focal seizures (EIMFS). High-dose PB (blood concentration up to 59.2 μg/ml) and PHT were effective in this patient. The main seizure type at the time of admission was a tonic seizure, but this type of seizures markedly decreased and disappeared within 10 days after the start of high-dose PB and PHT. Then, the seizure type altered to an autonomic seizure with apnea and cyanosis accompanied by mild limb rigidity, and clinical seizures almost disappeared in a few weeks later. It was difficult to determine which drug was more effective because both drugs started almost simultaneously. Since then, seizures have not recurred. Currently, at 1 year 5 months of age, he has developmental delay without any meaningful words or sitting alone, but he has shown gradual development and can take food orally and roll over imperfectly.

To clarify the etiology in these 2 independent patients, we performed whole-exome sequencing as previously described [8]. All parents provided written informed consent. Experimental protocols were approved by the institutional review board of Yokohama City University School of Medicine. We identified an identical mutation in *FGF12* [NM_021032.4:c.341G >A:p.(Arg114His)], which has been reported [4]. In patient 1, the mutation was inherited from the mosaic mother with no apparent phenotype. We could not analyze a sample from the father, as he had died. Sanger sequencing showed a slight peak in the Sanger sequencing electropherogram at the mutation. Sequencing of a TA-cloned PCR product spanning the mutation in the DNA from the mother's peripheral blood leukocytes clearly indicated a mutant allele fraction of 11.7% (11/94 clones). In patient 2, the mutation was *de novo*, as no mutant allele peaks were identified in parental DNA.

3. Discussion

To date, 8 cases of early onset epilepsy with the same *FGF12* mutation have been reported (Table 1) [4–7]. These cases showed the same mutation in FGF12, but another reference sequence NM_004113.5 was used in some cases [5–7]. Among the 8 cases, 4 developed epilepsy within 7 days of birth and 7 developed within 1 month. With regard to seizure type, focal seizures were noted in 6 cases, generalized tonic-clonic seizures and tonic seizures were each noted in 2 cases. Among the 8 cases, EEG showed multifocal epileptiform discharges in 7 cases, slow background in 6 cases, transformation to hypsarrhythmia in 2 cases, and normalization after treatment in 1 case. Brain MRI showed no obvious abnormalities in 7 of the 8 cases at the time of onset, and 4 of them showed cerebellar atrophy later. Among the 8 cases, 2 (Nos. 6 and 7 in Table 1) were free of seizures, and 2 (Nos. 4 and 8 in Table 1) showed partial seizure reduction with antiepileptic drug treatment. The

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clinical prognosis was poor. Among the 8 cases, 2 died and 4 had severe developmental delay. Only 1 patient who was free of seizures (No. 6 in Table 1) showed no developmental delay at 11 months of age.

There were some differences between our cases and previous cases with regard to hereditary form, phenotype, and response to antiepileptic drugs. First, the mother of patient 1 had mosaicism for the mutation described above. This is the first case involving parental mosaicism, although germline mosaicism was suspected in previous sibling cases (Nos. 1 and 2 in Table 1). Second, our case presented with an additional phenotype of the *FGF12* mutation, which was EIMFS. Third, patient 2, who presented with EIMFS, was free of seizures after treatment with PHT and high-dose PB. Siekierska et al. demonstrated that the mutation in *FGF12* [c.341G>A:p.(Arg114His)] acts in a gain-of-function manner on sodium channel gating, with increased neuronal excitability [4]. In terms of treatment, 4 previous cases (Nos. 4, 6, 7, and 8 in Table 1) were free of seizures or showed a partial decrease in seizure activity after treatment with PHT, CBZ, rufinamide (RFN), and lamotrigine (LTG), which have effects on the sodium channel. In another case report of *FGF12*-related epileptic encephalopathy, gene duplication involving *FGF 12* was noted, and the patient responded to PHT [9]. In this context, sodium channel inhibitors may have an effect on *FGF12*-related epileptic encephalopathy, although the effect has not been clearly explained, as PHT was ineffective in one of our cases and in some previous cases. The present report is the first to mention the effectiveness of high-dose PB, may become a treatment option in the future.

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