Case Report

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Three siblings with self-limited familial infantile epilepsy with *PRRT2* mutation: A case series

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Abstract

We report three sisters with self-limited familial infantile epilepsy, caused by a mutation in proline-rich transmembrane protein2. Self-limited familial infantile epilepsy has been established as a distinct epileptic syndrome characterized by focal seizures in clusters of infantile-onset. The seizure types of our cases were focal with or without secondary generalization. The seizures manifested at 3–5 months of age, and each lasted 1–2 min. All three sisters fulfilled the criteria for self-limited familial infantile epilepsy, except in one case who showed interictal spikes in the right central area. The seizures were controlled with carbamazepine. When carbamazepine treatment was started, one case developed a rash, and her treatment was switched to valproic acid. However, the seizures persisted in this case such that carbamazepine was restarted. The rash did not recur. Electroencephalography showed spikes in only one case on interictal electroencephalography. All three sisters were developmentally normal, and no dyskinesia was observed during follow-up. All three sisters and their father, but not their mother, had the following pathogenic variant in proline-rich transmembrane protein2: NM_001256442.2(PRRT2): c.649dup[p.(Arg217Profs*8)]. This mutation has been identified in the majority of families with self-limited familial infantile epilepsy, paroxysmal kinesigenic dyskinesia, and/or infantile convulsion and choreoathetosis. Their father had no history of either self-limited familial infantile epilepsy or paroxysmal kinesigenic dyskinesia. The lack of a clear genotype–phenotype correlation was demonstrated in our cases with this proline-rich transmembrane protein2 mutation.

Keywords

Self-limited familial infantile epilepsy, paroxysmal kinesigenic dyskinesia, infantile convulsion and choreoathetosis, *PRRT2*, carbamazepine

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Introduction

Self-limited familial infantile epilepsy (SeLFIE), previously termed benign familial infantile epilepsy, is an autosomal dominant disorder characterized by partial seizures with or without secondary generalization, occurring in clusters. It manifests in infancy with the seizure onset being at a mean age of 6 months, while seizure offset usually occurs by 2 years of age with no clear etiological factors. SeLFIE typically has normal interictal electroencephalography (EEG) and neuroimaging findings, and psychomotor development is usually normal.[1–3] Paroxysmal kinesigenic dyskinesia (PKD) is an autosomal dominant disorder characterized by episodic movements, such as dystonia or choreoathetosis, that usually last no more than 1 min, triggered by the initiation of voluntary movements. PKD manifests in late childhood or adolescence.[3–5] Infantile convulsion and choreoathetosis (ICCA) is an epileptic syndrome in which SeLFIE and PKD co-occur in the same patient or within a family.[1,3,5] The genetic basis for SeLFIE was identified as a mutation in the gene encoding proline-rich transmembrane protein 2 (*PRRT2*), identified as a major causative factor in SeLFIE, PKD, and ICCA.[1–7]

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However, no obvious genotype–phenotype correlation has been observed in patients with the *PRRT2* mutation.[1,2,8]

Case report

We experienced three cases, who were sisters born to non-consanguineous parents, developing cluster seizures in infancy. Their perinatal histories were unremarkable and there was no history of febrile seizures in the family.

The eldest sister, who was 10 years old at the time of preparation of this report, had presented with cluster formation of focal seizures and/or secondarily generalized tonic–clonic seizures at the age of 4 months. The focal seizures produced leftward deviation of the eyes, associated with drowsiness. The seizures lasted 1–2 min and 11 seizure episodes were observed. Carbamazepine (CBZ) (KYOWA Pharmaceutical Industry, Gifu City, Japan) (7–10 mg/kg dose) was prescribed and her seizures stopped 10 months after starting this treatment. The second sister, who was 8 years old at the time of report preparation, had presented with cluster formation of focal seizures and/or secondarily generalized tonic–clonic seizures at the age of 3 months. The focal seizures produced leftward deviation of the eyes, associated with drowsiness. The seizures lasted 1–2 min and 6 seizure episodes were observed. CBZ (5–10 mg/kg dose) was prescribed and her seizures stopped 1 month after starting this treatment. The third sister, 5 years old at the time of report preparation and with an allergic tendency, had presented with cluster formation of focal seizures and/or secondarily generalized tonic–clonic seizures at the age of 5 months. The focal seizures initially produced staring or a facial grimace, associated with drowsiness. The seizures lasted 1–2 min and 20 of these episodes were observed. CBZ (5 mg/kg dose) was administered. Ten days later, a skin rash appeared on the face and trunk. Her treatment regimen was thus switched to valproic acid (VPA) (15–20 mg/kg dose). However, her seizures were not adequately controlled, and 2 months later, CBZ (5–10 mg/kg dose) was restarted. Subsequently, no skin rash developed and her seizures were well controlled.

These sisters were treated with CBZ for 12–20 months. All three showed normal psychomotor development. None had neurological abnormalities. Brain magnetic resonance imaging findings were normal. Their interictal EEG results were normal, except for the third sister, who showed interictal spikes in the right central area, though only once, during follow-up after the seizures had been brought under control (Figure 1).

Based on their seizure histories, SeLFIE was strongly suspected, and written informed consent was obtained from the sisters' parents to conduct genetic testing for *PRRT2* on family members. Peripheral blood samples were collected, and after DNA extraction, PCR and subsequent Sanger sequencing were performed as described in detail elsewhere.[1] All three sisters and their father, but not their mother, had the following pathogenic variant in *PRRT2*: NM_001256442.2(PRRT2):c.649dup [p.(Arg217Profs*8)]. (Figure 2). The three sisters are currently free of PKD symptoms. Their father has no history of seizures or PKD.

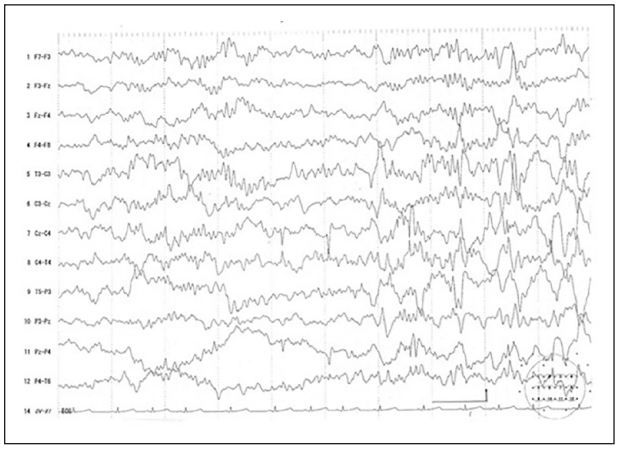

Figure 1. Interictal electroencephalography (EEG) obtained from the youngest sister (third sister) during sleep. The EEG shows interictal spikes in the right central area.

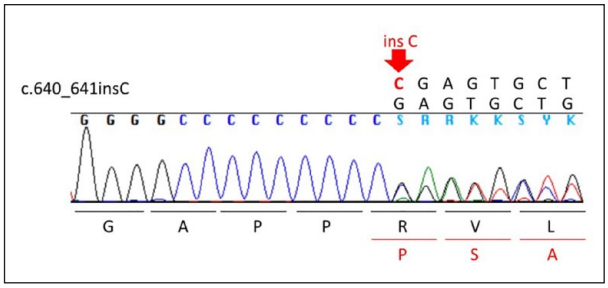

Figure 2. Electropherogram of the direct sequencing. A common insertion mutation, designated c.640_641insC, is shown. The locations of the nucleotide insertion are indicated by an arrow.

Discussion

PRRT2, located on chromosome 16p11.2, is a neuron-specific protein at axonal and pre-synaptic domains present mainly in the cerebral cortex, basal ganglia, and cerebellum.[2,3,5,8] *PRRT2* has been suggested to modulate voltage-gated Na^+ channels and/or to regulate synaptic transmission. Thus, pathogenic mutations involving the *PRRT2* gene may lead to a state of neuronal hyper-excitability, but neither the function of this gene nor the pathogenic mechanisms underlying the effects of mutations have yet been elucidated.[3–6]

Among patients diagnosed with the aforementioned *PRRT2*-associated disorders, the majority had SeLFIE, PKD, and/or ICCA. Other rare associated disorders, such as hemiplegic migraine and episodic ataxia, have also been reported.[2,3,8] Many cohort studies have demonstrated *PRRT2*

mutations such as c.224C>T, c.284C>G, c.439G>C, c.649delC, and c.950G>A, as well as c.649dupC.[2,8,9] Ebrahimi-Fakhari et al. reported 144 published cases with *PRRT2* mutations, including SeLFIE (41.7% of cases), PKD (38.7%), and ICCA (14.3%). In all, 73 different disease-associated *PRRT2* mutations have been described, with the c649dupC frameshift mutation accounting for the majority of cases (78.5%).[10] The presence of both SeLFIE and PKD in one case has been noted, while other individuals, even within the same family, manifest only one of these disorders despite having the same mutation of *PRRT2*. There are also reports of families with a *PRRT2* mutation in which none of the family members have any symptoms of either SeLFIE or PKD.[1,2,4,8–10] In other words, no clear genotype–phenotype correlation has been demonstrated in patients with *PRRT2* mutations.[1–3,11,12] The lack of a clear genotype–phenotype correlation was demonstrated in our cases with this *PRRT2* mutation. However, while the reasons for this lack of a correlation have not been fully elucidated, these observations suggest a high likelihood of incomplete penetrance in cases with *PRRT2* variants,[1–4] and the high incidence of asymptomatic carriers suggests the involvement of additional factors in modulating expressions of *PRRT2*-related disorders.[8]

It is also noteworthy, however, that the pattern of PRRT2 brain expression matches the human phenotype. The observed dissociation in terms of age at onset between the SeLIE and the PKD phenotypes raises the possibility of an expression pattern shift across different brain regions during development.[3] In experiments using mice, *PRRT2* mRNA concentrations were highest on postnatal day 14, which corresponds to an approximate age of 1–2 years in humans. These results are consistent with the clinical onset of infantile seizures.[4,9] By postnatal day 46, the expression of *PRRT2* mRNA was seen throughout the mouse brain, which would equate approximately with adolescence in humans, an observation consistent with its role in the pathogenesis of PKD.[4,9]

In the family described herein, the father and his three daughters had the most common *PRRT2* mutation. All three sisters fulfilled the criteria for SeLFIE,[2] except for the third sister who showed interictal spikes in the right central area, though epileptic patterns have been reported on interictal EEG in patients with SeLFIE.[2] In our cases, clinical manifestations of SeLFIE without PKD symptoms were observed in these three sisters during follow-up. However, all three are as yet pre-adolescent, such that having indications of PKD would not be inconsistent with the SeLFIE diagnosis. They may develop PKD in the future and thus require meticulous follow-up. However, their father has never had symptoms related to *PRRT2*. It is important to understand the characteristics of *PRRT2* variants when conducting long-term follow-ups of patients harboring these mutations.

Complete deletion of the *PRRT2* gene was reported to be associated with status epilepticus and mild developmental delay/intellectual disabilities. Furthermore, patients with homozygous, compound heterozygous, and microdeletions of the *PRRT2* gene reportedly presented with relatively severe phenotypes, including intellectual/developmental disorders, more frequently than those with heterozygous mutations.[2,3] On the other hand, heterozygous *PRRT2* mutations have also been described as possibly causing intellectual disability and/or developmental delay.[3,8,12,13]

Our cases had the most common heterozygous mutation (c.649dup) in *RRPT2* and showed normal psychomotor development. *PRRT2* plays a beneficial role in neurogenesis and brain development, such that the association between intellectual disability and heterozygous *PRRT2* mutations merits additional research.[3]

Levetiracetam, oxcarbazepine (OXC), CBZ, lamotrigine, zonisamide, topiramate, and VPA are used to treat SeLFIE.[2] Furthermore, CBZ was reported to apparently be more effective than the other medications in patients with *PRRT2*-associated PKD.[2,3,14] CBZ and OXC, sodium channel blockers, probably have specific mechanisms for controlling symptoms in *PRRT2*-associated disorders.[2,14] In our cases, CBZ was used to treat SeLFIE, and the seizures were adequately controlled. However, the third sister developed a skin rash due to CBZ, which disappeared within a few days after discontinuation of this therapy and did not recur when it was reinitiated. Approximately 10% of patients treated with CBZ develop a skin rash soon after starting this therapy.[15] CBZ is an effective and safe anticonvulsant drug, but careful management is necessary at the initiation of administration.

Conclusion

The three sisters reported herein had SeLFIE, caused by the most common mutation (c.649dupC) in *PRRT2*. Genetic testing revealed the *PRRT2* mutation in all three sisters and their father but not their mother. All three sisters have been developmentally normal, to date, and have shown no evidence of dyskinesia during follow-up. Their father has no history of seizures or dyskinesia. The lack of a clear genotype–phenotype correlation was demonstrated in our cases with this *PRRT2* mutation. CBZ was prescribed and the seizures were controlled in all three cases, but the youngest sister developed a rash in response to the first course of CBZ and showed interictal spikes epileptic on EEG.

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Author contributions

N.I., S.N., and T.Y. drafted the manuscript. N.I., A.G., D.A., N. I., S.N., and T.M. treated the patients and contributed to the acquisition of clinical data. T.Y. performed the statistical analysis and data interpretation.

Declaration of conflicting interests

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Ethical approval

Our institution does not require ethical approval for reporting individual cases or case series.

Informed consent

Written informed consent was obtained from the parents for their anonymized information to be published in this article.

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