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Case Report

Levetiracetam-induced a new seizure type in a girl with a novel SV2A gene mutation

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ABSTRACT

The target brain binding site of levetiracetam (LEV) is synaptic vesicle glycoprotein 2A (SV2A). Up to now, only a homozygous pathogenic SV2A gene mutation was reported in human. We now report a novel heterozygous pathogenic SV2A gene mutation both in a girl and her mother result in epilepsy and poor response to LEV. Furthermore, the girl developed a new seizure type after using LEV. Our report had a clinical relevance that LEV could potentially produce contradictory efficacy in patients with SV2A gene mutation. If patients' seizures became exacerbated while using LEV, SV2A gene testing is recommended.

1. Introduction

Epilepsy is known as a severe paroxysmal brain disease with complicated and unknown pathogenesis. Over the past few decades, the identifications of gene mutations have provided unprecedented insights into the causes of epilepsy. The majority of findings have revealed ion channel dysfunction caused by gene mutations involved in the process of epilepsy. And most anti-epileptics we have known mainly play their antiepileptic roles through affecting the function of ion channels by binding to the channel protein. The target brain binding site of levetiracetam (LEV) is synaptic vesicle glycoprotein 2A (SV2A) [1]. Up to now, only a homozygous pathogenic SV2A gene mutation was reported in human [2]. We now report a novel heterozygous pathogenic SV2A gene mutation both in a girl and her mother result in epilepsy and poor response to LEV. Furthermore, the girl developed a new seizure type after using LEV.

2. Case report

The proband was a 3.5-years-old girl of non-consanguineous Chinese parents. She was delivered at full term. Early developmental milestones were noted with slight retardation. The proband developed initial episodic symptoms of myoclonic seizures at age two months and was diagnosed until 18 months of age based on video electro-encephalogram (v-EEG) showing a burst of poly-spikes bilaterally that correlated with clinical myoclonic jerks. The MRI otherwise didn't show any specific abnormalities. Then the proband was given LEV to control the seizures. However, myoclonic seizures were unresponsive to LEV and concurrently clustered epileptic spasm occurred almost every day. Given the above conditions, the proband was recommended to reduce the LEV and add another anti-epileptics sodium valproate. Henceforth, the clustered epileptic spasm disappeared, and myoclonic seizures alleviated with the combination of sodium valproate and clonazepam. The mother also developed first episode of confusion at about 9-years-old and was seizure free when receiving a combination treatment of lamotrigine and sodium valproate. However, monthly seizure re-occurred after a gradual sodium valproate replacement with LEV to prevent the potential teratogenicity during pregnancy. Genetic testing reported a heterozygous mutation from C to T in nucleotide position 1708 of the coding region (c.1708C > T) in the SV2A gene (NM_014849), accounting for arginine to cysteine change in amino acid position 570 (p. Arg570Cys). Protein function prediction of SV2A was probably damaging, deleterious, disease-causing by SIFT, Polyphen2 and Mutation Taster analysis software respectively. A same heterozygous mutation was confirmed in her mother with epilepsy while no mutation was discovered in her healthy father (Fig. 1).

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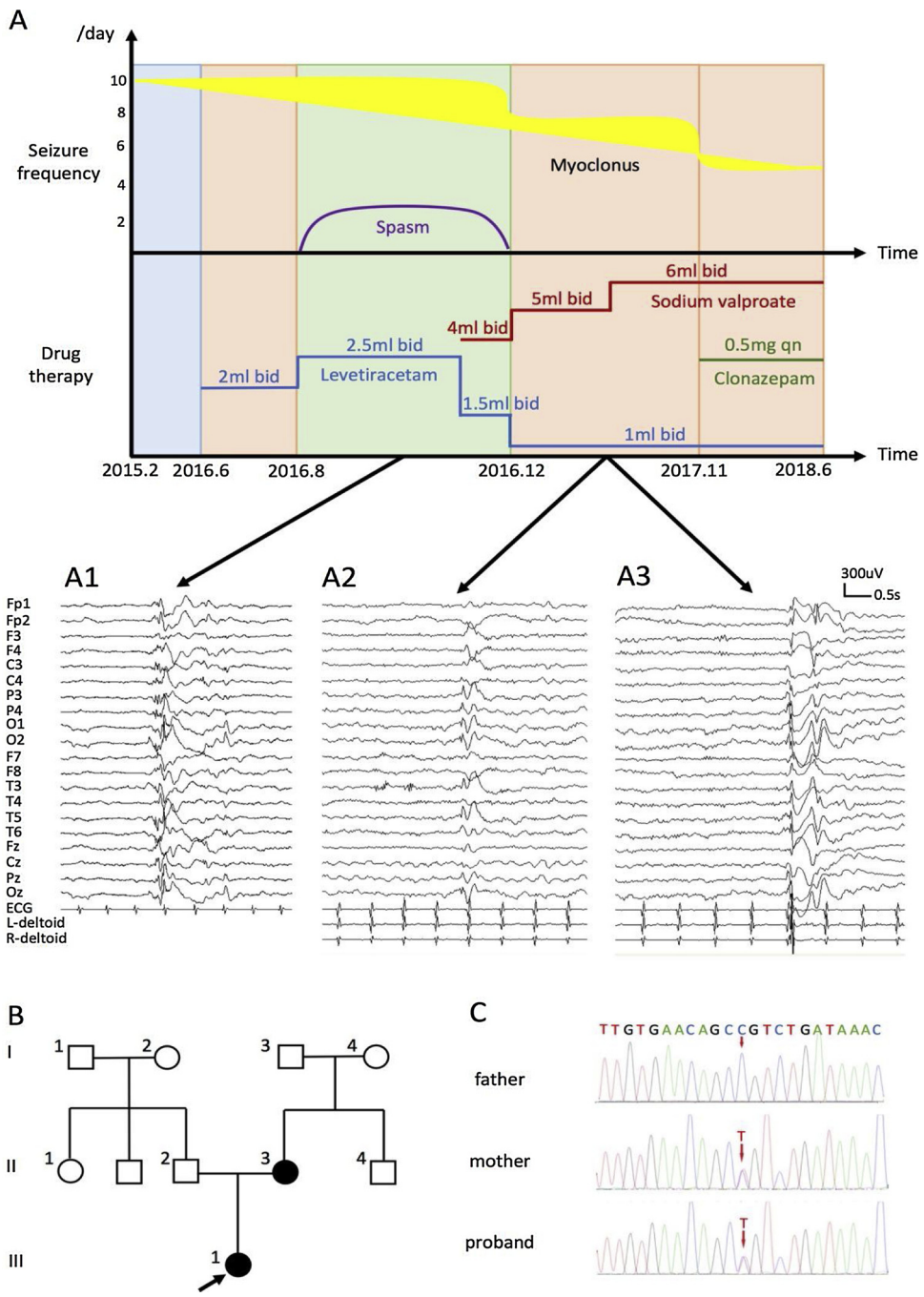

Fig. 1. (A) (Upper) Clinical Course, Therapy, and the seizure frequency of the proband. A new epileptic spasm was induced by levetiracetam. (Bottom) EEG during different clinical course. (A1) EEG showed very frequent interictal bilateral ploy-spikes and wave discharges during the patient manifesting new epileptic spasms. (A2) EEG showed improved background and sparse migrating spike and waves when LEV was replaced gradually. (A3) EEG showed one myoclonic seizure. (B) A three-generation pedigree of the family with the arrow pointed to the proband. (C) Sequencing results of a novel SV2A gene mutation. Sequencing showed c.1708C > T mutation of SV2A gene in the proband and her mother rather than her father.

3. Discussion

SV2A is a ubiquitous synaptic vesicle glycoprotein encoded by SV2A gene in humans and identified as the brain binding-site for the anti-epileptics LEV. SV2A acts a pivotal part in command of normal secretion in neural cells, increasing low-frequency neurotransmission selectively and regulating vesicle fusion by keeping the secretory vesicles' readily releasable pool [3]. LEV may modulate SV2A functions to play its antiepileptic and neuro-protective role. Although a large amount of studies has revealed that SV2A gene mutation could lead to epilepsy in animal models [4], only a homozygous pathogenic SV2A gene mutation was reported before in human [2]. Except for intractable epilepsy, the patient reported before manifested distinct different symptoms including involuntary movements, microcephaly, and developmental and growth retardation compared with the proband in this case. Here we demonstrated a novel genetic and clinical phenotype of SV2A gene mutation in a girl and her mother. We find that not only homozygous but also heterozygous SV2A gene mutation could lead to epilepsy. Besides, patients who have SV2A gene mutations were all Asians and poor responsive to LEV. More controversially, when the proband in our report was given LEV to control the myoclonic seizures, a new type of seizures clustered epileptic spasm appeared. Spasms then disappeared dramatically 2 months later due to the replacement of levetiracetam with valproate. This phenomenon hasn't been reported in the human study. Moreover, the LEV side effect as such spasm in non-mutated patients has not been reported to the best of our knowledge. A recent study has found that in the SV2A (+/−) mice, LEV's antiepileptic effect was prominently reduced in keeping with the reduced binding to SV2A [5]. Conversely, in both SV2A (+/+) and SV2A (+/−) mice, sodium valproate produced the same antiepileptic efficacy. These evidence

indicated that LEV's antiepileptic activity is mediated by SV2A, and even partial deficiency of SV2A may result in enhanced seizure vulnerability and accelerated epileptogenesis [5]. It is similar to the phenotype that seen in our report, but how can LEV cause a new type of seizure remains to study further. The preliminary observations in our study show the association between such spasm and SV2A-mutation seems to be specific. Our report had a clinical relevance that LEV could potentially produce contradictory efficacy in patients with SV2A gene mutation. If patients' seizures became exacerbated while using LEV, SV2A gene testing is recommended.

4. Conclusion

To our best knowledge, this was the first time a heterozygous mutation in the SV2A gene has been identified. Moreover, in this case and other similar cases, we believe that the identification of SV2A gene mutations in patients with epilepsy is suggestive of a deleterious role of the LEV efficacy.

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