Efficacy of methylprednisolone therapy in atypical Rolandic epilepsy with heterozygous RELN mutation

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Case report

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Abstract

Background: Atypical Rolandic epilepsy, also known as benign childhood epilepsy with centrotemporal spikes (BECTS) variant is defined by the appearance of severe neuropsychological impairments and refractory epilepsy. The etiology of the disease remains unclear, and recent studies indicated that it is related to several gene mutations. The suitable treatment is also need to be further explored. Here, we present the case of a 9-year-old boy with BECTS variant found to have heterozygous RELN mutation, responded well to the corticosteroid therapy. Case presentation: A 9-year-old male patient with atypical benign Rolandic epilepsy was successfully treated with high-dose intravenous methylprednisolone pulse therapy (15 mg/kg daily for 3 consecutive days, and the infusion was repeated three times with a 4-day interval between each course). The treatment improved his electroencephalogram (EEG) and cognitive performance, reduced seizure frequency, and the effect maintained for one year of follow-up. Whole-exome sequencing (WES) revealed a meaningful heterozygous missense mutation in the RELN gene. Conclusion: We conclude that corticosteroid therapy should be considered as a therapeutic option in patients with BECTS variant who are also found to harbour RELN mutations.

Background

Recently RELN mutations have been reported to be associated with various forms of epilepsy, including autosomal dominant lateral temporal lobe epilepsy, Landau-Kleffner syndrome (LKS)[1-3].BECTS variant, together with continuous spike-and-waves during sleep syndrome (CSWS) and LKS, are common types of ESES related syndromes which are generally resistant to conventional anti-epileptic drugs while responding to corticosteroids therapy[4-6]. Patients with BECTS variant usually experience other types of seizures (mainly epileptic negative myoclonic or atonic seizures, atypical absences), linguistic/behavioral disorders and global cognitive regression, atypical EEG changes (such as ESES) and poor seizure control[7-9]. Here, we report a case of BECTS variant with a RELN gene missense mutation in which the patient was responsive to corticosteroids therapy.

Case Presentation

A 9-year-old male was born after an uneventful, full-term pregnancy with normal psychomotor development. Family history was positive for patient's father once experienced facial paresthesia in his childhood. At the age of 6, patient was referred to our outpatient clinic for a short history of epileptic seizures without identified triggers. At that presentation, he was normal on detailed neurological examination, and workup, consisting of biochemistry profile, urine test and magnetic resonance imaging (MRI) were unremarkable. Sleep EEG revealed bilateral centrotemporal spike-and-wave discharges. Thereby, levetiracetam (LEV) was commenced but soon replaced by oxcarbazepine (OXC) due to poor symptom control. The patient had 8-month seizure free while taking OXC before he revisited hospital for a course of 3-times nocturnal generalized seizures in a month, multiple absence seizures and several drop attacks. EEG at the time showed up to 55% spike-wave index during slow-wave sleep(Figure 1). In order to regain control of seizures, OXC was changed to valproate acid sodium (VPA) and followed by an add-

on clonazepam (CZP) after 2 months. Upon turning 8 years of age, patient was free from generalized seizures. However, he developed early morning left upper limb clonus lasting for 10 seconds, 2-3 times per month. From then on, his cognitive function deteriorated with prominence in school performance, which resulted in hospital admission.

As an inpatient, he was started on an overall six-month steroid course initiated with 15mg/kg intravenous methylprednisolone sodium succinate as daily dose for 3 consecutive days and a 4-day steroid-sparing interval between cycles. Three steroid pulse cycles were repeated and followed by oral prednisolone at a dose of 2mg/kg which was gradually tapered toward the end of the course. Meanwhile, he was also maintained on the same prior doses of VPA and CZP. Upon approaching the end of the 6-month course, the patient was free from seizures and his cognitive performance improved significantly. On 1-year follow-up, he remained symptoms free with a corresponding resolution of the EEG discharges (Figure 1) without any adverse events.

The patient underwent whole-exome sequencing (WES) which revealed a heterozygous missense mutation in the RELN gene: c.449(exon3) C>T, p. Ala150 Val (exome sequencing and bioinformatic analysis of sequencing raw data were completed in Joy Orient Translational Medicine Research Center Co., Ltd.). Both of his parents were tested and his father, who once experienced facial paresthesia in his childhood, turned out to have the same RELN missense mutation. This mutation was present in the Exome Aggregation (ExAC) with minor allele frequencies (MAF) of 0.00001. The mutated region was found to be highly conserved among species (Figure 2a.). The in-silico analysis predicts that the change is likely damaging to the protein structure and function. As shown in Table 1, many scores indicate that this variant would be damaging to the encoded protein. WES result was verified by Sanger sequencing (Figure 2b.).

Discussion And Conclusions

Our patient fulfilled the criteria for BECTS variant as aforementioned and had a heterozygous RELN mutation predicted to be disease-causing. Recently, remarkable progress in unraveling genetic ethology of BECTS or Rolandic epilepsy has been achieved with more than ten susceptible genes spotted to be linked with the syndrome, including GRIN2A, ELP4, SRPX2, BDNF, KCNQ2, KCNQ3, DEPDC5, RBFOX, GABRG2, PRRT2 and so on[9-11]. However, these identified genes do not account for all known cases and more research is required for exploring this possible multi-gene disease. We report a case with RELN mutation that may expand the known disease-relating gene group of BECTS. RELN gene encodes a protein called reelin that regulates the correct formation of laminated structures during embryonic development and modulates dendritic growth and synaptic plasticity at postnatal and adult stages [12]. Homozygous RELN mutations[13] were reported to cause lissencephaly and cerebellar hypoplasia while a series of heterozygous mutations(c.2392C>A, c.2531C>T,c.8347G>T, c.2288A>G, c.2168A>G, c.9526G>A, c.2015C>T) were found in Autosomal-Dominant Lateral Temporal Epilepsy[14].With regard to BECTS or Rolandic epilepsy, the RELN gene mutation(c.9976C>T, p.Arg3326Ter) was once reported in the Clinvar database and classified as pathogenic. Additionally, Dr Judith Conroy [3]established a cohort of Landau-

Kleffner syndrome with two discordant monozygotic twin pairs and 11 isolated cases, discovering a number of candidate genes including RELN mutations(c.7438G>A, c.5284G>A). The study of LKS, BECTS and CSWS suggested that the disease spectrum may share the common genetic basis[15].Therefore we speculate that RELN gene may be a candidate gene for this disease, and certainly more study is needed to prove the assumption.

In our case, the patient responded well to the methylprednisolone pulse therapy. Several other studies have also confirmed the efficacy of corticosteroids in treating refractory epilepsy, especially in cases with ESES (including BECTS variant, LKS and CSWS). The responder-rate (seizure frequency reduce >50%) vary between 59% and 85%, while the relapse rate is ranging from 0 to 51% within 6-12 months[6, 16-19]. Luckily, no relapse has occurred in our case over the 1-year follow-up. The mechanism of corticosteroids therapy for epilepsy may be as follows: promotes brain maturation; directly acts on central nervous system receptors to increase cerebrospinal fluid-GABA levels; performs anti-inflammation, immune regulation and immunosuppression [6].

The gene mutation of ELP4 and SRPX2 have been identified in the ESES related diseases[20, 21], and discovered to play an important role in cell proliferation, motility, migration, and adhesion[11, 22, 23]. Coincidentally, the RELN gene is also related to the development of the central nervous system, which includes neuron migration, proper formation of cortical layers, and synaptogenesis [24]. Corticosteroids therapy can help myelin and dendrite formation as well as assisting brain maturation, thereby to compensate the effects caused by the gene mutation[25]. Moreover, another common genetic mutation GRIN2A in this disease spectrum, encoding glutamate receptor, N-methyl-D-aspartate (NMDA), implies that BECTS may have other pathogenic mechanisms like NMDA receptor abnormalities[26, 27]. It has been showed that seizures can be induced by upregulating NMDA receptors on post-synaptic cells via an activation of the GluN2B subunit of the NMDA receptor [28].Once significant mutations occur to the RELN gene, the blocking of reelin protein will increase the concentration of GluN2B –NMDA[29], so as to trigger the seizure. Fainberg [30] once reported a patient with LKS and GRIN2A mutation, who was responsive to immunotherapy, suggesting that autoimmune mechanism could be a component of the underlying disease-causing factors. So this maybe another reason why our patient with RELN mutation was responsive to corticosteroids therapy.

We report a case of BECTS variant with RELN gene mutation successfully treated by methylprednisolone pulse therapy. The underlying causes of the BECTS variant could be the brain immaturity caused by gene mutation and immune factors, both of which are responsive to corticosteroids therapy. Undoubtedly, further studies and more cases are needed for confirmation.

Abbreviations

BECTS: benign childhood epilepsy with centrotemporal spikes

EEG: electroencephalogram

WES: Whole-exome sequencing

ESES: electrical status epilepticus in sleep

LKS: Landau-Kleffner syndrome

CSWS: continuous spike-and-waves during sleep syndrome

LEV: levetiracetam

OXC: oxcarbazepine

VPA: valproate acid sodium

CZP: clonazepam

MRI: magnetic resonance imaging

MAF: minor allele frequencies

ExAC: Exome Aggregation

NMDA: N-methyl-D-aspartate

Declarations

Ethics approval and consent to participate

The study was in accordance with the ethical guidelines of the Helsinki Declaration and was approved by the Human Ethics Committee of Wuxi Children's Hospital. Written informed consent was obtained from the guardian participants.

Consent for publication:

Written informed consent for publication of their clinical details and clinical images was obtained from the parent of the patient.

Availability of data and materials:

The datasets generated during the current study are not publicly available for the sake of protecting patient privacy but are available from the corresponding author on reasonable request.

Competing interests:

The authors declare that they have no competing interests.

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Authors' contributions:

XYH were involved in manuscript preparation and editing. XYH and MJ were directly involved in the clinical work-up, diagnosis and treatment of the patients. YH revised the manuscript critically for important content and were involved in the submission. All authors have read and approved the final manuscript.

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Figures

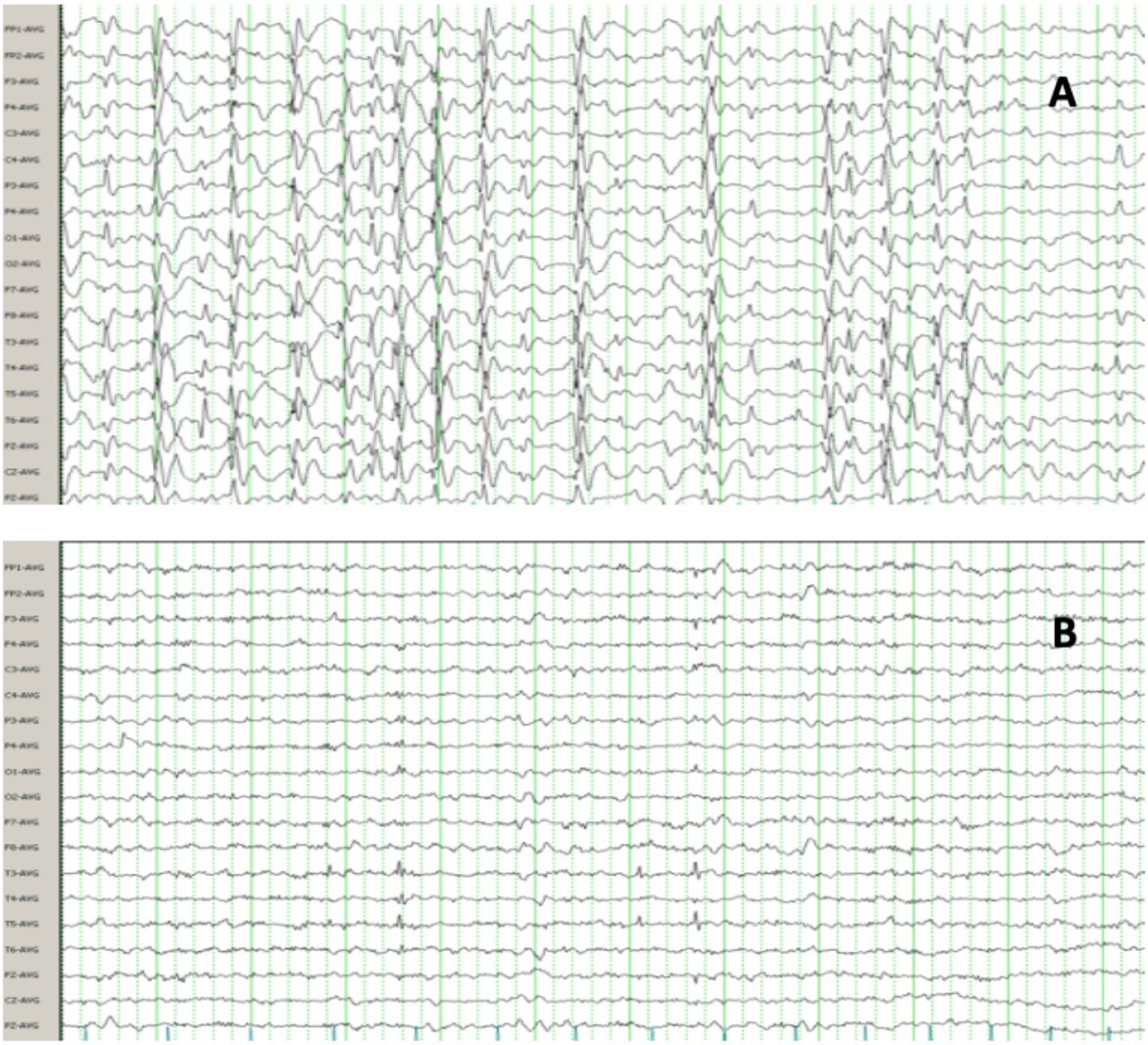

Figure 1

a. Slow sleep electroencephalogram (EEG) of the patient with BECTS variant. Bilateral continuous spike-and-wave activity was present during >55% of this stage of sleep. b. Repeat electroencephalogram after corticosteroid therapy. The epileptic discharges have ameliorated.

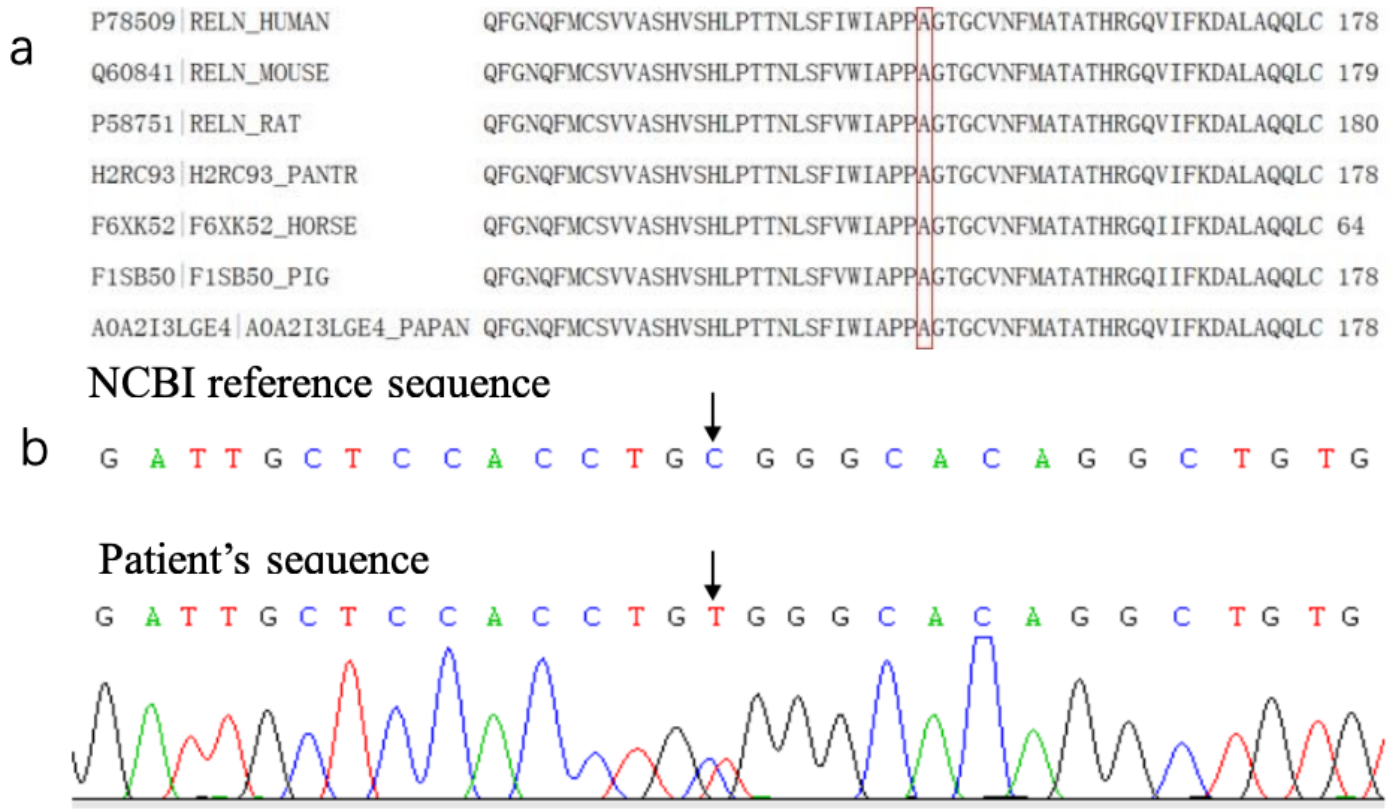

Figure 2

Figure 2a. The mutated region of the RELN locus was found to be highly conserved among species. Figure 2b. The sequencing results of the RELN gene in the patient. Arrows indicated the mutated sites.

Supplementary Files

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