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Short communication

Successful treatment of intractable life-threatening seizures with perampanel in the first case of early myoclonic encephalopathy with a novel *de novo SCN1A* mutation

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ABSTRACT

Purpose: Early myoclonic encephalopathy (EME) is a form of developmental and epileptic encephalopathy with myoclonic seizures and a suppression burst on electroencephalogram, which occurs during the neonatal or early infantile period and is characterized by highly intractable seizures and severe development impairment. Although multiple genetic aetiologies of EME have been identified, no *SCN1A* mutation has been reported.
Methods: We described a female patient with EME due to an *SCN1A* mutation.
Results: She developed frequent myoclonic and apnoeic seizures during the neonatal period. As her seizures were refractory to many antiepileptic drugs, she underwent a tracheotomy and has since been treated with continuous mechanical ventilation. Eventually, perampanel was added, which resulted in the cessation of the apnoeic seizures. Genetic analysis revealed a heterozygous *de novo* missense mutation in the *SCN1A* gene (c.2588 T > C:p.Leu863Ser).
Conclusion: This is the first patient with EME due to an*SCN1A* mutation to be successfully treated with perampanel. Recently, perampanel was reported to be effective in treating Dravet syndrome, including cases with an *SCN1A* mutation. Perampanel may contribute to seizure reduction in patients with intractable epilepsy carrying the *SCN1A* mutation.

1. Introduction

Developmental and epileptic encephalopathy with suppression burst (DEE-SB) is a severe disorder in which cognitive, sensory, and motor development are impaired by recurrent clinical seizures or prominent interictal epileptiform discharges during the neonatal or early infantile period. The key electroencephalogram (EEG) finding is the suppression-burst pattern. Seizures are highly intractable, and in previous reports, antiepileptic medications have demonstrated only limited effectiveness in seizure control [1,2]. DEE-SB includes Ohtahara syndrome (OS) and early myoclonic encephalopathy (EME), which are classically distinguished from each other according to their clinical features, particularly seizure types. The initial presentation of EME typically involves the onset of focal myoclonus. Focal seizures are also common, occurring in more than 80% of cases [3]. These seizures sometimes present with only autonomic signs such as facial flushing or apnoea. Aetiologies of EME include brain malformation, inborn errors of metabolism, and gene mutations. Recently, reports of genetic aetiologies have increased [4–7], but no *SCN1A* gene mutation has been reported.

Perampanel is a novel non-competitive a-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate (AMPA) receptor antagonist. Although its efficacy for diverse epileptic conditions has been reported [8,9], there has been no report demonstrating its efficacy for EOEE-SB to date.

We report the first EME case with a novel *de novo SCN1A* mutation who was successfully treated with perampanel.

2. Case report

A young girl, non-Caucasian Japanese, was born to unrelated healthy parents at 38 weeks of gestation *via* caesarean section in the absence of asphyxia. Her birth weight was 2,160 g, her height 43.0 cm,

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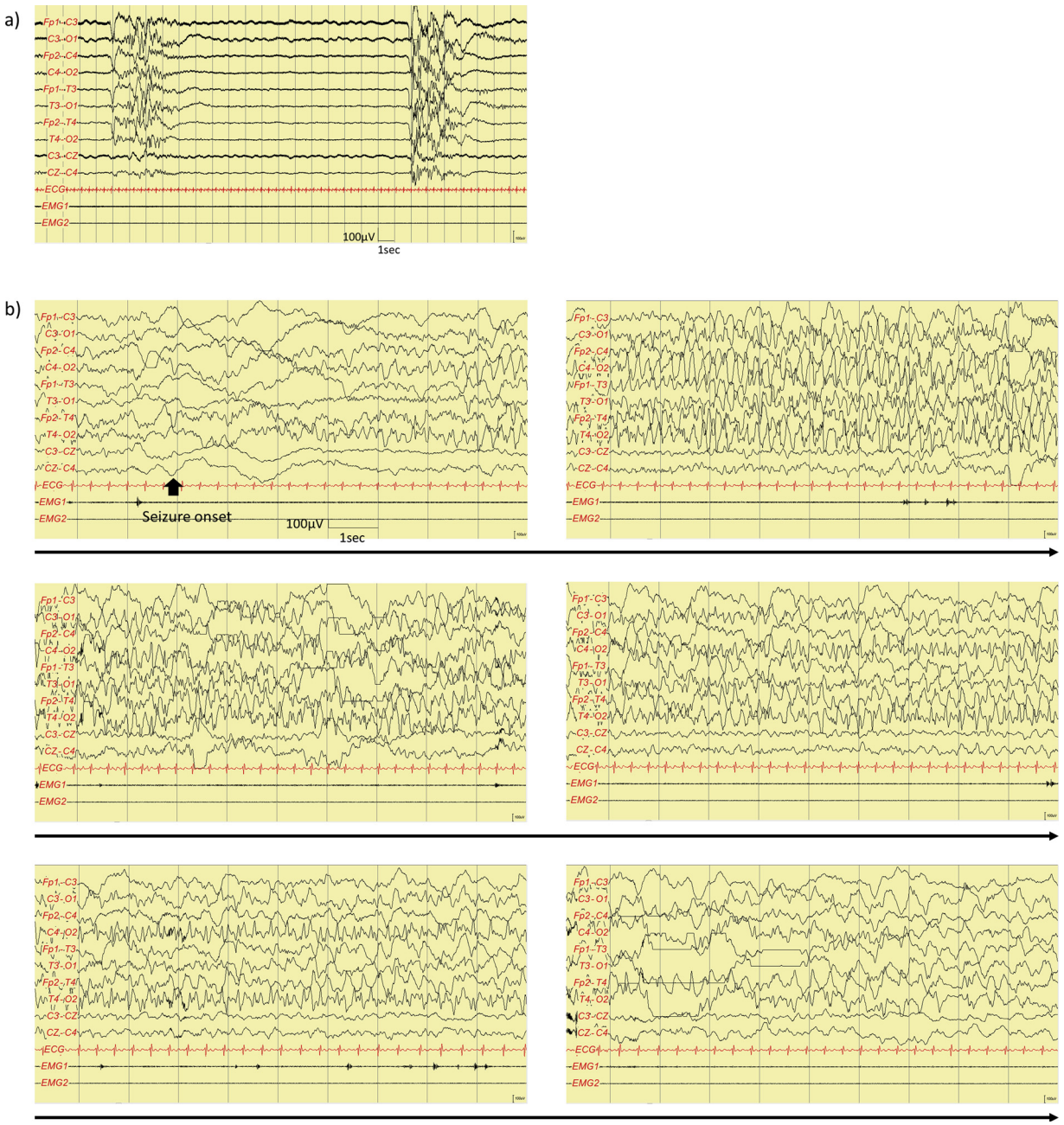

Fig. 1. a) Interictal EEG during sleep at 4 months of age showed a suppression burst pattern. b) Ictal EEG demonstrated that rhythmic activity started from the right temporal region and then evolved into diffuse activity, which corresponded to an apnoeic episode.

and her head circumference 32.5 cm. She was admitted to the neonatal intensive care unit (NICU) soon after birth due to respiratory impairment, which did not require mechanical ventilation. She was discharged from NICU at an age of 23 after improvement. At an age of 26 days, she exhibited frequent cyanosis, followed by frequent erratic myoclonus and brief tonic seizures. Hiccups, nystagmus, tachycardia, and hyper-salivation were also observed. Her initial EEG revealed focal sharp waves; epilepsy was diagnosed and she was commenced on zonisamide, levetiracetam, and valproate, but to no effect. Zonisamide (maximum dose, 10 mg/kg/day) at first, then levetiracetam (maximum dose, 40 mg/kg/day), and followed by valproate (maximum dose, 30 mg/kg/day) were prescribed. Continuous midazolam infusion and mechanical ventilation were started, and she was transferred to our hospital at 3 months of age. Head MRI offered no significant findings. However, after she was weaned from the midazolam infusion and mechanical ventilation, the EEG revealed a marked suppression-burst pattern (Fig. 1a). Blood, urine, and cerebrospinal fluid examinations (including searches for congenital metabolic errors) revealed no underlying disease. Phenytoin (maximum serum concentration, 12.6 μg/ml), followed by phenobarbital (maximum serum concentration, 56.8 μg/ml) provided transient effects (seizures were controlled for 2 weeks by each drug), whereas topiramate (maximum dose, 12 mg/kg/day), clonazepam (1.2 mg/kg/day), potassium bromide (30 mg/kg/day), and clobazam (maximum dose, 0.9 mg/kg/day) were serially administered, all of which had no significant effects. Apnoeic seizures, which corresponded to focal-onset discharges spreading to a diffuse area on EEG (Fig. 1b), occurred frequently. Therefore, she was strictly managed in the intensive care unit. Her seizures markedly worsened during the febrile episodes. Because these frequent apnoeic seizures impaired respiration, tracheostomy featuring laryngotracheal separation was performed. As the severe intractable seizures persisted despite the use of many antiepileptic drugs, perampanel (0.4 mg) was added to

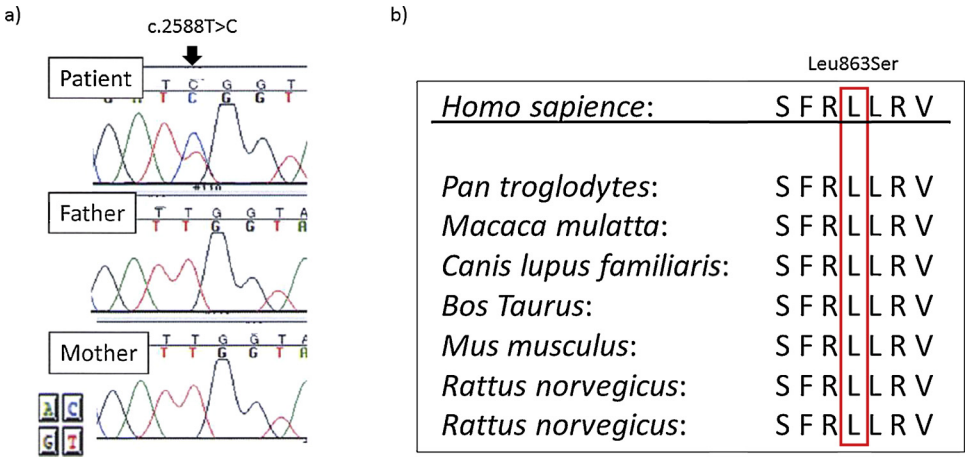

Fig. 2. a) Gene analysis revealed a *de novo* missense mutation in the *SCN1A* gene (c.2588 T > C:p.Leu863Ser). b) The altered amino acid residue has been conserved throughout vertebrate evolution.

potassium bromide (120 mg), phenobarbital (48 mg), and clobazam (3.5 mg) at the age of 7 months; the frequency of apnoeic seizures then fell markedly, although some erratic myoclonus remained. When perampanel was increased to 1.2 mg daily, the apnoeic seizures disappeared for more than 1 year. The EEG was also improved, with a reduction in the suppression-burst pattern. As her life-threatening seizures were controlled, she was discharged to home. At 18 months of age, she presented with severe motor and intellectual disabilities; she remains bedridden on constant mechanical ventilation.

We performed a gene analysis of the patient and her parents. Following whole-exome sequencing as described previously [7], Sanger sequencing revealed a heterozygous *de novo* missense mutation in the *SCN1A* gene (c.2588 T > C:p.Leu863Ser) (Fig. 2a). This mutation is located in the transmembrane segment, the S4 segment of repeat domain 2 of SCN1A, which is expected to severely impair the channel function. This is not found on ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/) or HGMD Professional 2018.1 (https://portal.biobase-international.com/hgmd/pro/start.php); thus, we confirmed that this mutation is novel. Also, the mutation was predicted to be detrimental using SIFT (http://sift.jcvi.org/) and Mutation Taster (http://www.mutationtaster.org/); the altered amino acid residue has been conserved throughout vertebrate evolution (Fig. 2b). Based on these findings, we diagnosed EME due to an *SCN1A* mutation.

This study was approved by the Institutional Review Boards of Hiroshima University Hospital and Showa University School of Medicine, and consent was obtained from the parents regarding publication of this case report.

3. Discussion

EME cases often have inborn errors of metabolism, including non-ketotic hyperglycinaemia, d-glyceric acidaemia, propionic acidaemia, molybdenum cofactor deficiency, methylmalonic acidaemia, and a mitochondrial glutamate transporter defect [10]. In addition, other gene aetiologies have been identified [4]. Although various disease-causing gene mutations, including *ARX, SLC25A22, KCNQ2*, *STXBP1*, *SNC2A*, *PNPO*, *SEPSECS*, *PIGA, UBA5,* and *PLPBP*, have been reported [4–7], to the best of our knowledge, there has been no report of an *SCN1A* mutation.

The *SCN1A* gene encodes the alpha-subunit of neuronal voltage-gated sodium ion channel, type1 (NaV 1.1), and is primarily expressed in the soma of neuronal cells in the central nervous system [11]. Mutations in the *SCN1A* gene have been reported in multiple types of epilepsy, most of which are associated with Dravet syndrome (DS) or its variants, severe myoclonic epilepsy, borderline, and intractable childhood epilepsy with generalised tonic-clonic seizures [12]. The mutation in our case, c.2588 T > C:p.Leu863Ser, is a novel mutation. A different change in the same base, c.2588 T > G:p.Leu863Trp, in a DS case has been registered in HGMD (http://www.hgmd.cf.ac.uk/ac/all.php). The detailed mechanism of the difference in development between these two cases could not be determined, although a sodium channel disturbance may contribute to EME development.

EME is usually highly intractable. Although a few cases have been reported showing the efficacy of the ketogenic diet and carbamazepine combined with lidocaine [13,14], most cases are refractory to any antiepileptic treatment. Recently, perampanel has been demonstrated to have efficacy for various types of paediatric epilepsy. According to a previous report evaluating the tolerability and efficacy of perampanel in 24 children with refractory epilepsy, 42% of patients had a seizure reduction of 50% or greater, 8% had a 33% seizure reduction, and seizures were less severe in 4% [8]. Another report analysing children and adolescents treated with perampanel demonstrated that the rates of seizure reduction > 50% were 30.3%, 37.5%, and 34.7% for all seizure types at 3, 6, and 12 months, respectively; 7.6%, 8.9%, and 14.3% of patients, respectively, became seizure-free at these time points [9]. Additionally, perampanel exhibited efficacy for DS, including in patients with an *SCN1A* mutation [15]. Our case also had an *SCN1A* mutation, and perampanel showed sufficient efficacy, suggesting that it may contribute to seizure reduction in patients with intractable epilepsy who carry an *SCN1A* mutation, although there is no significant evidence about efficacy of perampanel for SCN1A-related epilepsy at present.

The glutamate excess in the synaptic cleft in EME may account for the clinical difference from OS [3]. The AMPA receptor is the main excitatory postsynaptic glutamate receptor. Perampanel, which is a non-competitive AMPA receptor antagonist, may also be effective against EME with other gene mutations. To confirm the efficacy of perampanel against EME, a large number of cases and further study are needed.

Author contributions

NI, YT, HT, YK, and MK, contributed to the conception and design of the study and the acquisition, analysis and interpretation of data. TI, SM, and NM performed NGS data analysis. TI, SM, NM, and MK contributed to the acquisition, analysis and interpretation of data. All authors contributed to the critical revision of the final version of the manuscript for important intellectual content.

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Conflict of interest

None of the authors has any conflict of interest to disclose.

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