Treatment Options for Infantile Spasms Syndrome with *SCN8A*: A Case Report and Literature Review

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Abstract

"Infantile spasms syndrome (IS)," previously known as "West syndrome (WS)," is characterized by epileptic spasms (ES), abnormal electroencephalography (EEG) patterns such as hypsarrhythmia, and developmental stagnation or regression in infancy. IS has various etiologies, including genetic abnormalities. *SCN8A* variants are associated with developmental and epileptic encephalopathy, characterized by developmental delay, seizures starting from infancy, and refractory epilepsy with multiple seizure types. However, previous studies have not focused on the treatment of IS caused by *SCN8A* variants. We report a case of a previously healthy boy who presented ES and developmental regression at 6 months of age. His EEG revealed hypsarrhythmia, leading to the diagnosis of IS. After admission, the patient was treated with hormonal therapy using intravenous methylprednisolone pulse therapy (MPT). ES and hypsarrhythmia on EEG disappeared in the early stages of MPT administration with no observed treatment complications. Furthermore, we observed no recurrence of EEG abnormalities or seizures at 17 months of age. Genetic testing revealed a novel *de novo* *SCN8A* variant (NM_001177984.2:c.2882T > G:p. M961R). The literature review confirmed that 13 patients, including our described patient, were reported to have ES owing to missense variants of *SCN8A*. While the previous articles do not mention intravenous MPT for ES with *SCN8A*, our case findings suggest that intravenous MPT therapy may be effective for short-term suppression of ES caused by the *SCN8A* variant in IS.

Keywords

- developmental and epileptic encephalopathy
- electroencephalography
- hypsarrhythmia
- methylprednisolone pulse therapy
- West syndrome

Introduction

Infantile spasms syndrome (IS), also known as West syndrome (WS), is characterized by epileptic spasms (ES), distinctive electroencephalography (EEG) abnormalities, such as hypsarrhythmia, and developmental stagnation or regression in infancy.[1] Hormonal therapy, including adrenocorticotropic hormone (ACTH) or steroid treatments, is reportedly most effective for short-term suppression of ES.[2] However, its treatment efficacy and prognosis depend on the etiology.

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Various underlying causes of IS, including cortical dysplasia, hypoxic-ischemic encephalopathy, and metabolic and genetic abnormalities, have been reported.[1] *SCN8A*, which encodes a neuronal sodium channel (Nav 1.6),[3] was first identified as one of the causative genes for epilepsy in 2012.[4] Notably, *SCN8A* mutations are reportedly associated with IS; these variants result in developmental and epileptic encephalopathy (DEE), multiple seizures, and refractory epilepsy, which is resistant to antiepileptic drugs.[5] The severity of neurological deficits associated with *SCN8A* variants is variable, with mild to often severe intellectual developmental deficits present in almost all patients.[6] Consequently, the clinical presentation of patients with *SCN8A* variants is diverse. However, there is a need for comprehensive reports on the treatment options for IS caused by *SCN8A* variants.

Here, we first report the case of a 6-month-old boy harboring a novel variant of *SCN8A* who developed IS, which was successfully treated with intravenous MPT. Furthermore, we also reviewed case reports on ES with *SCN8A* variants to assess potential treatment options. Informed consent was obtained from the patient's parents to publish this case report's data.

Case Description

A 6-month-old boy who presented with ES for 2 weeks was referred to our hospital. The boy was born to a nonconsanguineous couple via vaginal delivery without complications at full-term gestation. He had mild motor developmental delay without rolling over at 5 months of age, with no apparent language developmental delay noted. The family history of the patient was unremarkable. Initially, a 1-minute episode of extension of the extremities and flexion of the head was observed before and after sleep. The frequency gradually increased, and the number of episodes increased to over three series per day 2 weeks after the onset. During this period, he smiled less and expressed decreased interest in toys (developmental regression).

Upon admission, the patient was alert and had normal vital signs. His height, weight, and head circumference were 69.9 cm (+1.6 SD), 8,381 g (+1.1 SD), and 43.6 cm (+1.1 SD), respectively. Neurological examination revealed no abnormalities except for the inability to turn over. No facial dysmorphic features or external deformities were observed. General blood tests, urinalysis, and cerebrospinal fluid analyses were unremarkable. Magnetic resonance imaging revealed no abnormalities in the brain; however, EEG revealed a hypsarrhythmia pattern (►**Fig. 1A**); therefore, the patient was diagnosed with IS. He was first administered valproic acid and vitamin B6; however, the ES and hypsarrhythmia persisted. ACTH was unavailable in Japan during the coronavirus disease-2019 pandemic; therefore, we initiated intravenous MPT. The frequency of seizures decreased on day 2, ceased entirely on day 3, and the patient started smiling again on day 5 after the administration of MPT. After a week of treatment (initial intravenous administration of 30 mg/kg/day MPT for 3 days, followed by 1 mg/kg/day intravenous prednisolone (PSL) for 4 days), EEG confirmed the disappearance of hypsarrhythmia; however, the frequent multifocal spikes persisted. Administering a second dose of intravenous MPT (30 mg/kg/day) for 3 days and tapering off oral PSL (1 mg/kg/day for 7 days, followed by 0.5 mg/kg/day for 7 days and 0.25 mg/kg/day for 7 days) after the MPT resulted in the complete disappearance of the EEG abnormalities and seizures (►**Fig. 1B**).

We observed no further complications after the treatment. Subsequently, the patient achieved milestones in motor development: rolling over at 7 months of age, sitting unassisted, pulling to stand at 11 months, and crawling at 12 months. After discharge, G-banded karyotype analysis revealed a normal male karyotype of 46, XY, and the epilepsy-related 331-gene panel (►**Supplementary Table S1**) helped identify a novel *de novo SCN8A* variant (NM_001177984.2:c.2882T > G:p.M961R). The variant was confirmed using Sanger sequencing and was considered "likely pathogenic," according to the American College of Medical Genetics and Genomics and the Association of Molecular Pathology (ACMG-AMP) guidelines (PS2+ PM2+ PP3) (►**Fig. 2**).

By the age of 17 months, the patient began expressing a few words and demonstrated the ability to walk with assistance but could not walk independently. No recurrence of seizures or EEG abnormalities was observed.

Discussion

In the present case, we demonstrated that intravenous MPT could promptly resolve ES and alleviate EEG abnormalities (hypsarrhythmia) in a patient with a novel missense variant in *SCN8A*, an IS disease-related gene.

As far as we know, basic research articles on the relationship between *SCN8A* and IS have yet to be reported. It is, therefore, unclear how *SCN8A* variants cause IS. DEE resulting from mutation of *SCN8A* is known as EIEE13 [OMIM: # 614558]. Most of the mutations of *SCN8A* have been reported as a gain of function mutations, leading to increased neuronal excitability.[7,8] Sprissler et al reported the region-specific increases in $I_{Na,P}$ density with altered action potential waveforms in *Scn8a*$^{N1768D/+}$ mouse excitatory and inhibitory hippocampal neurons and the critical role of *Scn8a* in neuronal excitability.[9] Since IS has been reported in various genetic variants, it may not be a unique effect of *SCN8A,* and it is presumed that neuronal excitability is involved in the cause of IS.

To evaluate the therapies used for managing ES with *SCN8A* variants, the literature (English) was reviewed for cases reported as IS with *SCN8A* variants. The PubMed database was searched (up to October 8, 2022) using the following search terms: "SCN8A" and "West syndrome" or "SCN8A" and "spasm." We considered "SCN8A" and "West syndrome" as IS was previously referred to as WS; however, some reports used the term "infantile spasms syndrome" instead of WS. Therefore, to search broadly, we used "SCN8A" and "West syndrome" or "SCN8A" and "spasm." We identified 31 articles, including 19 original articles, 3 literature reviews, 2 clinical studies, and 7 case reports. After assessing these

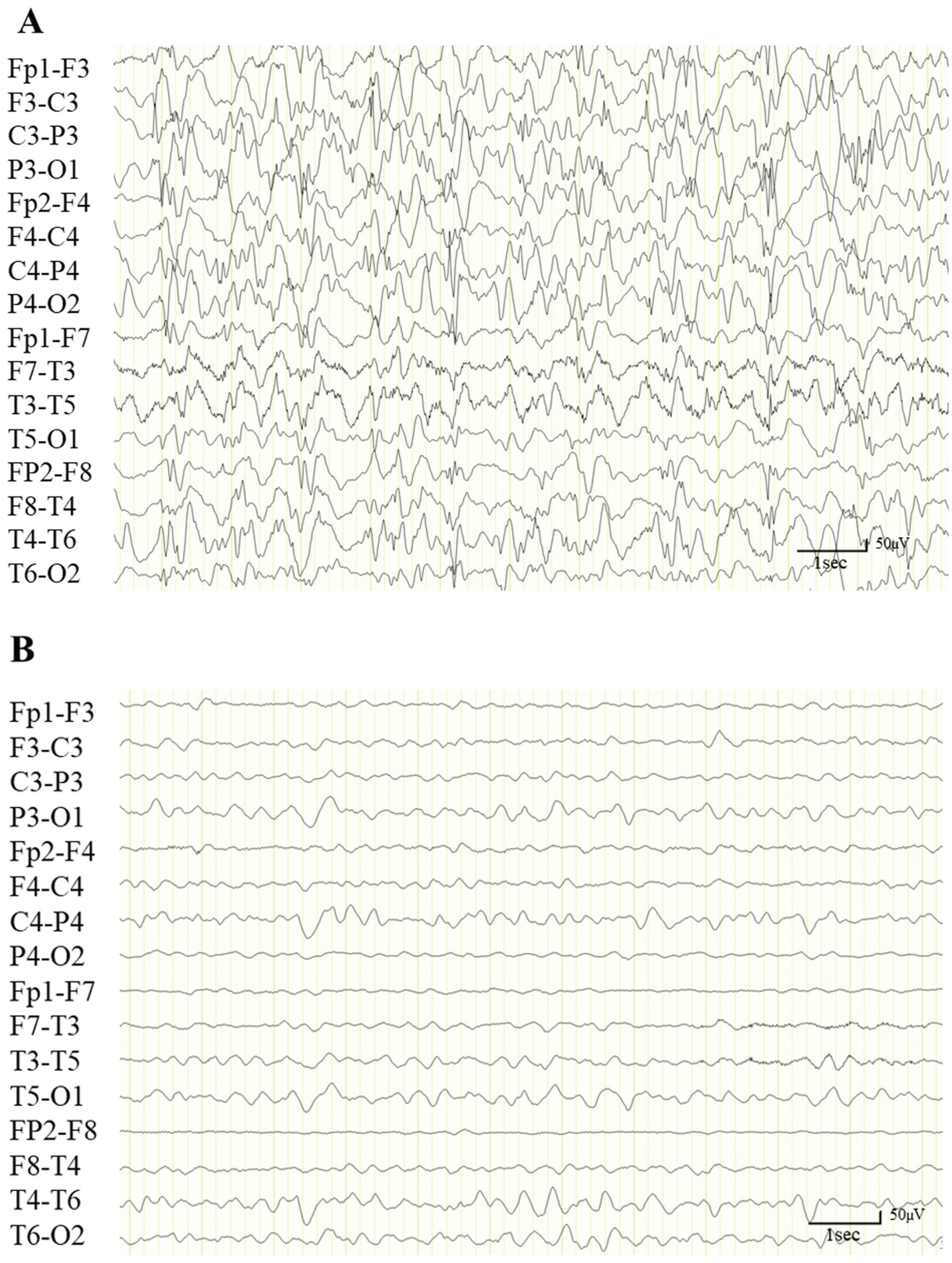

Fig. 1 Interictal electroencephalography (EEG). (**A**) EEG findings at the onset of infantile spasms syndrome. EEG is indicating hypsarrhythmia before treatment. (**B**) EEG findings confirming the complete disappearance of EEG abnormality after the second dose of intravenous methylprednisolone pulse therapy.

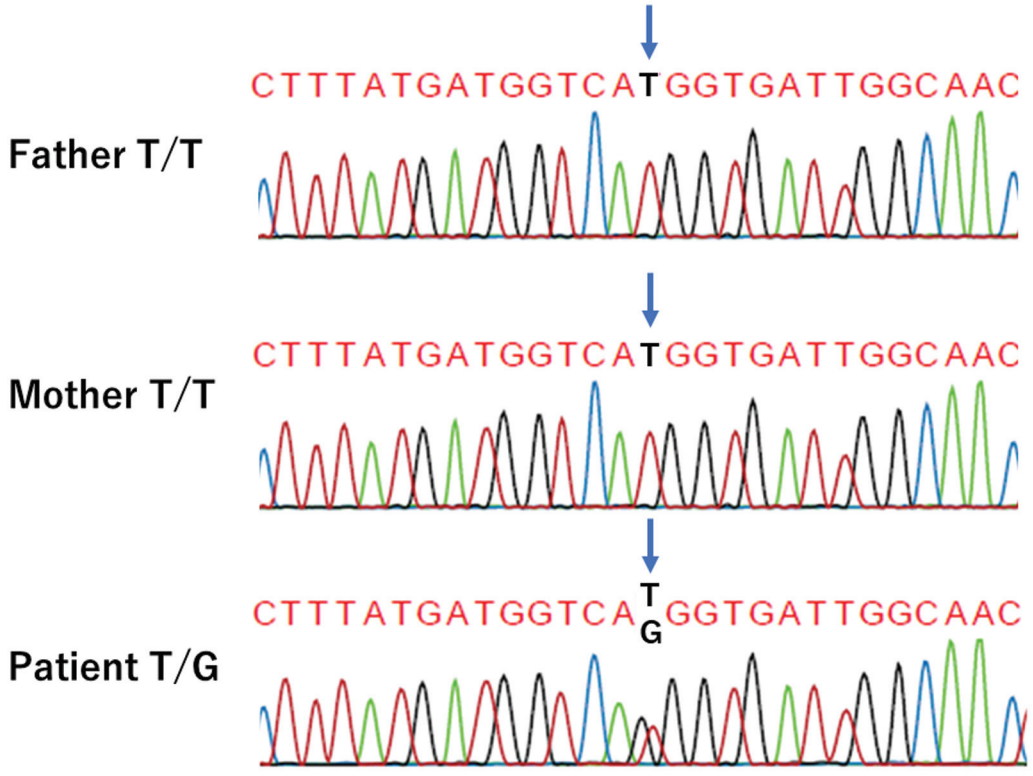

Fig. 2 *De novo SCN8A* variant. Sanger sequencing analysis confirming the presence of the *de novo* missense *SCN8A* variant [c.2882T > G (p.M961R)] in the proband but not in the parents.

articles carefully, we identified two articles describing the clinical presentation and treatment of cases with WS or IS and *SCN8A* variants.[6,10] Collectively, we examined reports on 13 patients, including our patients. The characteristics of patients with the *SCN8A* variant from the literature and our case are presented in ►**Table 1**. The patients were aged between 1 and 22 years old, among whom six were male and seven were female. All patients harbored missense variants, and two had the same nucleotide substitution. The age of seizure onset ranged from 14 days to 6 months, and all presented with some form of seizure within 6 months of age. The diagnosis of IS was established in one patient who experienced neonatal onset focal seizure, while an additional five patients were also diagnosed with IS. ES was observed during the clinical course in remaining seven patients whose epilepsy diagnosis was not specified. Furthermore, one study reports the administration of hormonal therapy for ES with *SCN8A*; patients with ES were treated with high-dose PSL or ACTH, and these treatments were effective in half of the patients.[6] In addition, vigabatrin (VGB) was also reported to be effective in some patients of ES with *SCN8A*. All 12 patients, except our patient, reportedly had refractory epilepsy with multiple seizure types and exhibited resistance to multiple antiepileptic drugs. These patients developed severe intellectual disability with impaired speech-language or eye contact. Sodium channel blockers were often effective for other types of epilepsy; phenytoin was effective in four out of five cases, carbamazepine in three out of three cases, and lamotrigine in three out of three cases. The developmental prognosis revealed moderate-to-severe intellectual disability, with hyper- an hypotonicity in nine cases and dyskinesia in four cases. Nonetheless, none of the reported cases of IS or WS caused by *SCN8A* variants were treated with intravenous MPT, as in our case.

We present the first case report of short-term success in treating IS caused by the *SCN8A* variant using an intravenous MPT. As far as we know, basic research articles on the relationship between MPT and sodium channels have not been reported. Seizures have been reported to be associated with inflammation.[11] Steroids are hypothesized to affect suppressing inflammatory processes in epileptogenesis,[12] prolonging the duration and frequency of the ligand-gated chloride channel opening and suppressing a possible hyperexcitability.[13] Sprissler et al reported an altered gene expression profile in a mouse model of *SCN8A* encephalopathy after seizures.[9] They reported altered gene expression in Scn8aN1768D/+ mice after seizures and reactive astrocytosis in response to seizures. Since cytokines and chemokines are released in such situations, steroids may also have an anti-inflammatory effect and promote neuronal survival. Probably, intravenous MPT may have a strong anti-inflammatory effect. Because this is the first report of intravenous MPT on IS with *SCN8A*, more research will be needed to elucidate the steroid therapy on IS with the *SCN8A* variant.

Numerous studies have reported the optimal treatment for IS or WS with any etiologies.

Furthermore, the effectiveness of hormonal therapy has been widely reported.[1,14,15] There are three main options for hormonal therapy: ACTH, oral PSL, and intravenous MPT; however, the optimal steroid regimen, dosage, and duration

Table 1 Existing reports of infantile spasms syndrome with *SCN8A*

		Mutations						Treatment for any epilepsy				
								Effective		Ineffective		
Reference		Nucleotide change	Mutation type	Sex	Age	Seizure onset age	Seizure types	AEM	Others	AEM	Others	Developmental delay
Present case	1	c.2882T > G	Missense	M	1 y	6 m	ES		Intravenous MPT	VPA		
Kim et al[10]	2	c.4423 G > A	Missense	F	3 y, 9 m	5 m	ES	CBZ, CLB, PHT, VPA		VGB		Delayed
	3	c.2549 G > A	Missense	F	2 y, 11 m	3 m	ES	VPA, ZNS	KD	PB	CTx	Delayed/ Regression
	4	c.782 G > T	Missense	F	9 y	5 m	ES	LCM, LTG, ZNS		CLB, VPA, PB	CC, Rt.T disconnection, KD	Delayed
	5	c.424A > G	Missense	M	4 y	14 d	FS, ES	OXC, PB, PHT, VPA, ZNS		LEV	CTx, KD	Delayed/ Regression
	6	c.5614C > T	Missense	M	5 y, 1 m	3 m	ES	LEV, OXC, PB, VPA			KD	Delayed/ Regression
Gardella et al[6]	7	c.1228G > T	Missense	M	3 y, 10 m	4 m	TS, Sp	CLB, TPM, VGB	PSL		KD	Severe ID, no SP, hypotonus, hypokinesia
	8	c.2549G > T	Missense	F	2 y, 1 m	5 m	FS, Sp, TCS	CLB, OXC, VPA		LEV, PB, TPM		Severe ID, no SP, hypotonus, dyskinesia
	9	c.2879T > A	Missense	F	9 y, 9 m	2 m	FS, Sp, TCS	CLB, OXC, TPM, ZNS		GVG, LEV, PB	PSL	Severe ID, no SP, hypo/ hypertonus, EM, PEG
	10	c.2932A > G	Missense	M	27 m	4 m	TS, Sp, FS, TCS	CBZ, GVG, PB, TPM	ACTH	LEV, PHT, VPA		Severe ID, no SP, hypotonus, dyskinesia
	11	c.4594A > T	Missense	F	3 y, 10 m	3 m	FS, Tv, Sp, TCS	CBZ, CLB, ESM, PB, PHT, STP, TPM, VPA		CLB, CZP	PSL	Severe ID, no SP, EM, hypo/ hypertonus, dyskinesia, PEG
	12	c.4639T > G	Missense	M	22 y	15 d	FS, TS, Sp, TCS	FLB, LTG, NZP, PB, PHT, RFM, TPM, VGB, VPA, ZNS	KD			Severe ID, no SP, EM, hypotonus, dyskinesia
	13	c.5614C > T	Missense	F	5 y	4 m	FS, TS, Tv, Sp, TCS	CLB, DZP, LTG, OXC, PB, TPM, VPA	KD		LEV, RFM	Severe ID, no SP, EM, PEG

Abbreviations: A, adenine; ACTH, adrenocorticotropic hormone; AEM, antiepileptic medicine; C, cytosine; CBZ, carbamazepine; CC, corpus callosotomy; CLB, clobazam; CZP, clonazepam; CTx, mitochondrial cocktail treatment; d, days; DZP, diazepam; EM, epileptic myoclonus; ESM, ethosuximide; F, female; FLB, felbamate; FS, focal seizure; G, guanine; GVG, gamma-vinyl GABA; ID, intellectual disability; KD, ketogenic diet; LEV, levetiracetam; LCM, lacosamide; LGT, lamotrigine; m, month; M, male; MPT, methylprednisolone pulse therapy; NZP, nitrazepam; OXC, oxcarbazepine; PEG, percutaneous endoscopic gastrostomy feeding tube; PB, phenobarbital; PHT, phenytoin; PSL, prednisolone; Pt, patient; RFM, rufinamide; Rt.T, right temporal; Sp, spasm-like episodes; SP, speech language; STP, stiripentol; T, thymine; TPM, topiramate; TS, tonic seizures; TCS, tonic-clonic seizures; Tv, tonic vibratory; VGB, vigabatrin; VPA, valproic acid; y, year; ZNS, zonisamide.

of treatment have yet to be established. ACTH is recommended for short-term seizure control[14] and is currently the standard treatment in Japan; however, treatment choices vary from country to country, depending on regional characteristics and medical background.[14,16] We lack large-scale studies simultaneously comparing the efficacy of ACTH, oral PSL, and intravenous MPT; however, several studies have at least compared two groups and reported similar short-term outcomes.[14,17,18] Each of these treatment protocols has its advantages. Intravenous MPT results in faster resolution of seizures than oral PSL,[18] whereas oral PSL and intravenous MPT are more cost-effective than ACTH.[14,16] Furthermore, MPT can be reliably administered intravenously, whereas administering large doses of oral PSL to infants is often challenging. The mechanism of antiepileptic action of steroids for ES is unclear; however, glucocorticoids are hypothesized to have several effects: 1) they may act indirectly by modulating neurotransmitters and second messenger systems; 2) they may alter neuronal excitability by acting through specific receptors, thereby modulating the expression of several genes in the central nervous system; 3) they exhibit anti-inflammatory action and may suppress neuronal excitability through modifications of neuronal channels owing to ongoing brain inflammation, lowering the seizure threshold; 4) they accelerate myelination and brain maturation; and 5) increase gamma-aminobutyric acid receptor sites.[19,20] However, the mechanisms by which MPT affects sodium channels remain unknown, and further research is warranted to address these gaps in the literature. VGB is especially effective in patients with tuberous sclerosis complex. However, Xu et al recently reported a systematic review and meta-analysis to evaluate the efficacy of VGB in treating IS and they revealed hormonal monotherapy superiority compared to VGB monotherapy for nontuberous sclerosis complex-associated IS.[21]

Our report has some limitations. First, we reported only one case of *SCN8A*-related IS that was successfully treated with MPT. Therefore, the efficacy of MPT in other patients with *SCN8A*-related IS remains to be assessed. Second, in the present case, administration of the intravenous MPT resulted in ES remission on day 3 and the disappearance of hypsarrhythmia, as confirmed using EEG, within a week. However, the long-term effects of MPT remain unclear.

In conclusion, we report the case of a 6-month-old boy with a novel *SCN8A* variant who developed IS. Short-term treatment with intravenous MPT resulted in the early resolution of seizures and helped achieve developmental milestones. Further research will be required to validate the efficacy of MPT for IS with the *SCN8A* variant.

Authors' Contributions

O.S. and H.Y. designed and conceptualized the report and drafted the manuscript. M.J.Y. analyzed and interpreted the sequencing data and revised the manuscript for intellectual content. H.H., S.T., K.T., M.N., and N.M. analyzed and interpreted the data and revised the manuscript for academic content. K.N. and H.N. designed and conceptualized the study and revised the manuscript for academic content. All authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

Conflict of Interest

None declared.

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