Case Report

Vagus nerve stimulation for genetic epilepsy with febrile seizures plus (GEFS+) accompanying seizures with impaired consciousness

Ryosuke Hanaya,⁎ Fajar H Niantiarno, Yumi Kashida, Hiroshi Hosoyama, Shinsuke Maruyama, Toshiaki Otsubo, Kazumi Tanaka, Atsushi Ishii, Shinichi Hirose, Kazunori Arita

⁎ Department of Neurosurgery, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan
b Department of Neurosurgery, Medical Faculty of Diponegoro University, Semarang, Indonesia
c Department of Pediatrics, Graduate School of Medical and Dental Sciences, Kagoshima University, Kagoshima, Japan
d Fujimoto General Hospital, Miyakonojo, Japan
e Department of Pediatrics, Saiseikai Sendai Hospital, Satsuma-Sendai, Japan
f Department of Pediatrics, Fukuoka University School of Medicine, Fukuoka, Japan

Abstract

Genetic epilepsy with febrile seizures plus (GEFS+) is characterized by childhood-onset epilepsy syndrome with febrile seizures and a variety of afebrile epileptic seizures. Its inheritance is autosomal dominant [1] and its spectrum is comprised of a range of mild to severe phenotypes varying from classical febrile seizures to Dravet syndrome. GEFS+ patients manifest a mutation encoding voltage-gated sodium channel subunits (SCN1A, SCN1B, SCN2A) and GABA receptor subunits (GABRG2, GABD) [1]. Typically, the mutations are missense mutations, and about 80% of affected individuals present with some form of seizure disorder. Approximately 1/3 of GEFS+ patients may experience a variety of generalized epilepsies. Some families include individuals with focal epilepsy, particularly temporal lobe epilepsy (TLE) of varying severity [2]. While surgical resection is one treatment option for the drug-resistant focal symptoms of GEFS+, due to the genetic defect, children are unlikely to benefit from cortical resection [3]. We treated a girl with an SCN1A mutation and generalized tonic-clonic- and complex partial seizures (GTCS, CPS) by vagus nerve stimulation (VNS).

1. Introduction

Genetic epilepsy with febrile seizures plus (GEFS+) is characterized by childhood-onset epilepsy syndrome with febrile seizures (FS) and a variety of afebrile epileptic seizures. Its inheritance is autosomal dominant [1] and its spectrum is comprised of a range of mild to severe phenotypes varying from classical febrile seizures to Dravet syndrome. GEFS+ patients manifest a mutation encoding voltage-gated sodium channel subunits (SCN1A, SCN1B, SCN2A) and GABA receptor subunits (GABRG2, GABD) [1]. Typically, the mutations are missense mutations, and about 80% of affected individuals present with some form of seizure disorder. Approximately 1/3 of GEFS+ patients may experience a variety of generalized epilepsies. Some families include individuals with focal epilepsy, particularly temporal lobe epilepsy (TLE) of varying severity [2]. While surgical resection is one treatment option for the drug-resistant focal symptoms of GEFS+, due to the genetic defect, children are unlikely to benefit from cortical resection [3]. We treated a girl with an SCN1A mutation and generalized tonic-clonic- and complex partial seizures (GTCS, CPS) by vagus nerve stimulation (VNS).

2. Case report

This girl had the first FS at the age of 6 months; in the next 8 months she had 6 more FSs. Her first afebrile seizure occurred when she was 2 years old. Multiple antiepileptics, i.e. clobazam, valproate, phenobarbital, carbamazepine (CBZ), lamotrigine, and levetiracetam failed to inhibit her seizures and she was admitted to our hospital at the age of 5 years.

She suffered numerous GTCSs and CPSs each month. Her developmental age was somewhat delayed. Interictal electroencephalography (EEG) showed frequent bilateral synchronous or independent slow spike waves. Long-term video-EEG could detect 4 CPSs off-drug state. During 3 CPSs, we observed conjugate deviation to left, extension of the left limbs, flexion of the right limbs, and body-axis rotation to left after motion arrest. EEG showed diffuse polyspikes in the right hemisphere followed by high-voltage 12 Hz waves at T6 and O2 (Fig. 1). During a CPS observed in the later part of the monitoring period spike waves began at O1 and T5 with oral automatism, conjugate deviation to right, and right body-axis rotation. No abnormalities were detected on MRI-, iomazenil- and IMP-SPECT-, and FDG-PET studies. MEG showed a broad dipole cluster in the right posterior temporal- and parietal- and occipital lobe (Fig. 2). The epileptogenic region was expected to be broad. There were no GTCSs in the afebrile state during the monitoring period, but explanation by her parents indicated she
had primary GTCS without secondary generalization in afebrile state and often coincided with fever. A VNS system was implanted when she was 6 years old.

Her father and brother had a history of FS; her sister suffered afebrile seizures. Gene examination after VNS implantation detected the mutation; SCN1A encoded the α-subunit of a sodium-gated channel. The same finding was made in her sister. VNS in the first year decreased the frequency and severity of both GTCSs and CPSs (Fig. 3). The seizures were remained, and CBZ was deduced to avoid the possibility of seizure induction by sodium channel blockers in SCN1A-related seizure disorders. But seizures re-increased after reduction of CBZ. Lamotrigine was administered and converted from CBZ. Seizure decreasing was continued for at least 4 years. Her intelligence quotient was in the normal range and she attends a regular elementary school.

3. Discussion

GEFS+ families are grouped into 4 broad subphenotypes, i.e. classical GEFS+, borderline GEFS+, unclassified epilepsy, and an alternative syndromal diagnosis [2]. Borderline and classical GEFS+ share many characteristics; early-onset FSs with focal epilepsies including CPSs is a phenotype they have in common [1].

The SCN1A mutation was found in about 10% of GEFS+ patients. Barba et al. [4] suggested that SCN1A gene mutations and malformations during cortical development may reciprocally affect each other in determining the mechanisms that underlie seizure generation [4]. Skjei et al. [3] performed neocortical resection in 6 SCN1A mutation-positive children with treatment-resistant epilepsy. Surgical histopathology showed subtle cortical dysplasia in 4 of their patients. They concluded that cortical resection was unlikely to be beneficial due to the genetic defect and unexpected mild diffuse cortical malformations.

There is an association between prolonged FS and TLE with hippocampal sclerosis [5]. A meta-analysis revealed a genome-wide significant association between mesial TLE with hippocampal sclerosis and febrile seizures at the sodium-channel gene cluster on chromosome 2q24.3 of SCN1A [6]. No patient who underwent resective surgery for TLE with an SCN1A mutation has been reported. However, 2 patients with GEFS+ with an SCN1B mutation were successfully treated by temporal lobectomy [7]. Both had the C121W mutation, a characteristic of the SCN1B mutation; one patient also presented with hippocampal sclerosis.

VNS is effective in patients with many kinds of seizure. Terra et al. [8] reported a post-VNS implantation seizure reduction of approximately 50% in 36.8% of patients at year 1, in 43.2% at year 2, and in 42.7% at

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**Fig. 1.** Ictal scalp electroencephalograph recorded during a complex partial seizure. Note diffuse polyspikes and waves were followed by high-voltage 12 Hz waves starting at T6 and O2 (arrow). The 12 Hz waves lasted about 3 min and were dominant in the right hemisphere. The highest amplitude was recorded at T6 and O2.

**Fig. 2.** Magnetoencephalographic findings. A cluster of equivalent dipole was observed in the posterior temporal-, parietal-, and occipital lobe. R, right; A, anterior.
year 3. VNS is thought to modulate electrical stimuli to the nucleus tractus solitarius and the brainstem reticular formation, and to interrupt the characteristic synchronous activity of seizures. Also in this patient, GTCS and CPS in the first year after VNS were decreased at the same drug condition before operation. Generally, sodium channel blocker can induce or increase seizures in SCN1A-related seizure disorders [9]. But sodium channel blocker would effective in this patient and coordination of antiepileptics could decrease the seizures during follow up periods (Table 1).

Cerebrospinal fluid studies showed a significant increase in GABA after 3–4 months of VNS, but no significant decrease in glutamate, aspartate, or 5-HIAA after 3 to 9 months of VNS [8]. In a mouse model, the SCN1A mutation predominantly impaired sodium-channel activity in GABAergic interneurons and led to decreased inhibition without affecting excitatory cortical pyramidal neurons [10]. This pathogenesis suggests that VNS is a suitable treatment for pharmaco-resistant GEFS+ with the SCN1A mutation as it exerted favorable effects on Dravet syndrome with the SCN1A mutation [11].

4. Conclusion

Focal epilepsies including complex partial seizures are considerably less common in GEFS+ spectrum. VNS would become good treatment option to pharmaco-resistant GEFS+ with both refractory generalized tonic-clonic seizures and partial seizures.

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Table 1

| Epileptic encephalopathy | Patients with >50% reduction in seizures (%) | Follow-up periods (M) | Study (ref) |
|--------------------------|---------------------------------------------|-----------------------|-------------|
| Dravet syndrome (severe myoclonic epilepsy in infancy) | 50% (4/8) | 12 | Zamponi et al. (18) |
| | 38% (5/13) in predominantly GTCS | | Oroz et al. (16) |
| | 37% (3/8) | 12 | Dresler et al. (14) |
| Doose syndrome (epilepsy with myoclonic-astatic seizures) | 67% (2/3) | 24 | Cersosimo et al. (13) |
| | 65% (30/46) | Mean 30 (28–40) | Cersosimo et al. (13) |
| | 67% (20/30) | Mean 52 (17–123) | Kostov et al. (15) |
| | 21% (4/19) | 24 | Aldenkamp et al. (11) |
| West syndrome | 100% (2/2) | 20 and 24 | Cersosimo et al. (13) |
| Landau-Kleffner syndrome | 50% (3/6) | 6 | Park (17) |
| Epilepsy with continuous spikes-and-waves during slow-wave sleep (other than Landau-Kleffner syndrome) | Seizure-free (a case report) | 12 | Carosella et al. (12) |
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