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

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ABSTRACT

Generalized epilepsy with febrile seizures plus (GEFS$^+$) is characterized by childhood-onset epilepsy syndrome. It involves febrile seizures and a variety of afebrile epileptic seizure types within the same pedigree with autosomal-dominant inheritance. Approximately 10% of individuals with GEFS$^+$ harbor SCN1A, a gene mutation in one of the voltage-gated sodium channel subunits. Considerably less common are focal epilepsies including focal seizures with impaired consciousness. We report vagus nerve stimulation (VNS) in a 6-year-old girl with GEFS$^+$ who exhibited drug-resistant generalized tonic-clonic seizures and focal seizures with impaired consciousness.

1. Introduction

Generalized 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 seizure (GTCS) and focal seizures with impaired consciousness (FSIC) by vagus nerve stimulation (VNS).

2. Case report

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

She suffered numerous GTCSs and FSICs each month. Her developmental age was somewhat delayed. Interictal electroencephalography (EEG) showed frequent bilateral synchronous or independent slow spike waves. Long-term video-EEG detected 4 FSICs in the off-drug state. During 3 FSICs we observed conjugate deviation to the 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 an FSIC observed in the later part of the monitoring period, spike waves began at O1 and T5 with oral automatism, conjugate deviation to the right, and right body-axis rotation. Magnetoencephalography showed a broad dipole cluster in the right posterior temporal-, parietal-, and occipital lobe (Fig. 2). No abnormalities were

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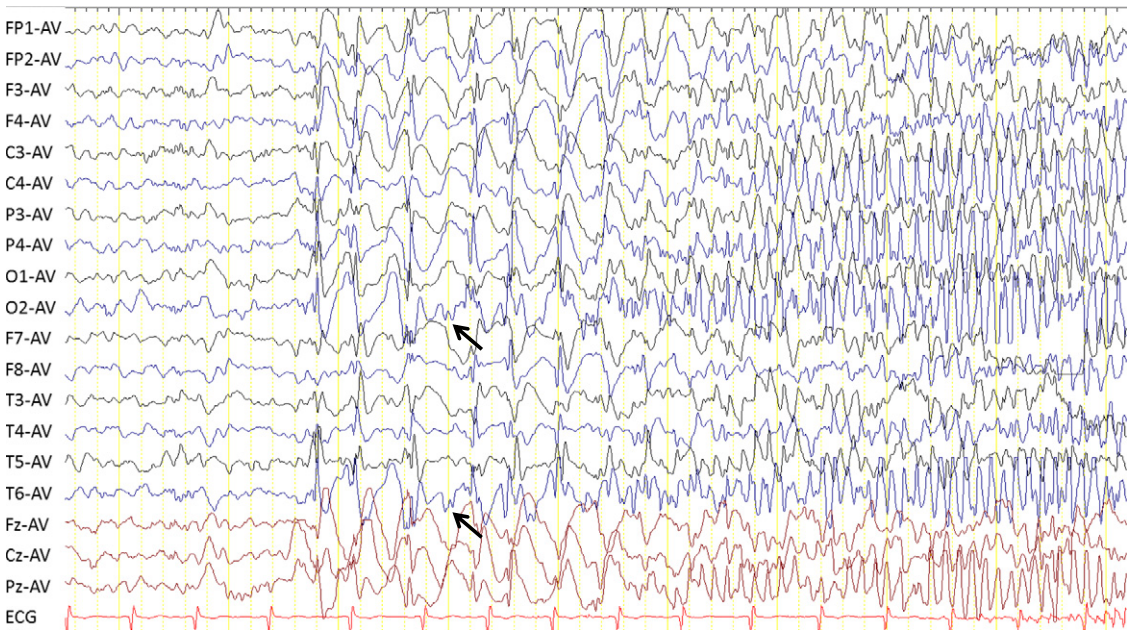

Fig. 1. Ictal scalp electroencephalograph recorded during a complex partial seizure. Note diffuse polyspikes and waves followed by high-voltage 12 Hz waves starting at T6 and O2 (arrow). The 12 Hz waves lasted about 3 min and were dominant in the right hemisphere. The highest amplitude was recorded at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

detected on MRI-, iomazenil- and IMP-SPECT-, and FDG-PET studies. Preoperative evaluation without intracranial recording failed to localize the epileptogenic area although her symptoms indicated that hers would be a focal seizure. While there were no GTCSs in the afebrile state during the monitoring period, their description by her parents suggested that her GTCSs in the afebrile state were primary GTCSs rather than seizures of secondary generalization. We chose VNS instead of resective surgery.

A VNS system was implanted when she was 6 years old. Her father and brother had a history of febrile seizures and her sister suffered afebrile seizures. Gene analysis after VNS implantation detected the mutation; SCN1A encoded the α-subunit of a sodium-gated channel. This examination confirmed that her younger sister had the same mutation.

Stimulation started with the standard setting [4] obtained a seizure reduction of an average of 60% and 72% for GTCSs and FSICs, respectively, in the course of 13–24 months after VNS. In the third year after VNS, the average seizure reduction was 80% and 100% for GTCSs and FSICs, respectively (Fig. 3). While sodium channel blockers exacerbated SCN1A-related seizure disorders, the number of both types of seizure was decreased after the start of VNS. We then replaced carbamazepine with lamotrigine because it had an effect on both GTCSs and FSICs. Her seizures increased again but were reduced by increasing the level of VNS at the fourth year. The stimulation parameters 4 years after the start of VNS were: output current 1.50 mA, frequency 30 Hz, pulse width 500 ms, on-time 7 s, and off-time 0.5 min (duty cycle 30%). In the last 12-month period (43–54 months after the start of VNS), her GTCSs and FSICs were reduced by an average of 90% and 88%, respectively. 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 febrile seizures with focal epilepsies including FSICs are a phenotype they have in common [1].

The SCN1A mutation was found in about 10% of GEFS$^+$ patients. Barba et al. [5] suggested that SCN1A gene mutations and malformations during cortical development may reciprocally affect each other in determining the mechanisms that underlie seizure generation. While sodium channel blockers tend to induce or increase seizures in SCN1A-related seizure disorders [6], in our patient they were effective and the coordination of anti-seizure drugs resulted in a decrease in her seizures during the follow-up period.

Skjei et al. [3] performed neocortical resection in 6 SCN1A mutation-positive children with drug-resistant epilepsy. Surgical histopathology

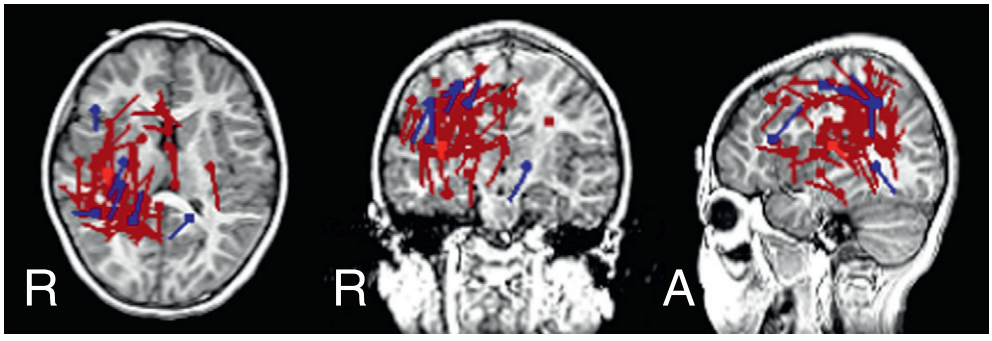

Fig. 2. Magnetencephalographic findings. A cluster of equivalent dipole was observed in the posterior temporal-, parietal-, and occipital lobe. R, right; A, anterior.

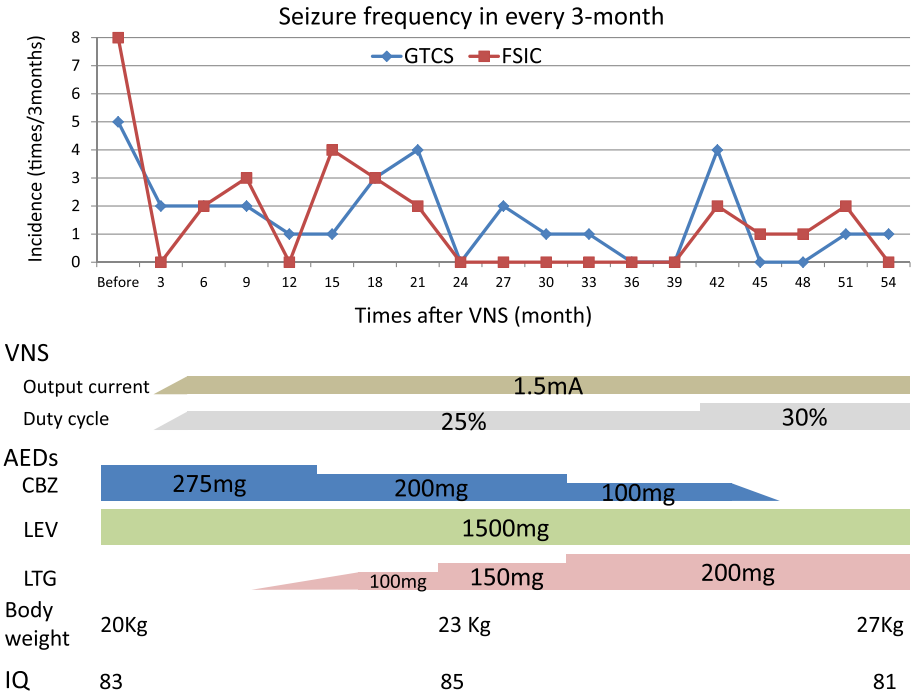

Fig. 3. Frequency of seizures, shown at 3-month intervals, and the treatment status before and after the implantation of vagus nerve stimulation (VNS). The number of generalized tonic-clonic- and focal seizures with impaired consciousness (GTCSs, FSICs) decreased after VNS. CBZ, carbamazepine; LEV, levetiracetam; LTG, lamotrigine; IQ, intelligence quotient measured on the Tanaka-Binet Intelligence Scale.

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 febrile seizures and TLE with hippocampal sclerosis [7]. A meta-analysis revealed a genome-wide significant association at the sodium-channel gene cluster on chromosome 2q24.3 of SCN1A between mesial TLE with hippocampal sclerosis and febrile seizures [8]. While no patients who had undergone resective surgery for TLE with an SCN1A mutation have been reported, 2 patients with GEFS$^+$ with an SCN1B mutation were successfully treated by temporal lobectomy [9]. 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 seizure types. It 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. Morris et al. [10] 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 year 3 after VNS. VNS is also an effective and well-tolerated treatment for patients with Lennox-Gastaut syndrome (LGS), Dravet syndrome, and epilepsy with myoclonic-astatic seizures, and other kind of epileptic encephalopathy (Table 1) [11–18]. The initial parameters were set at an output current of 0.25 mA, a signal frequency of 30 Hz, a pulse width of 250–500 ms, stimulation "on"-time 30 s, and stimulation "off"-time 300 s, with the output current generally increased to 2–3 mA as tolerated [4]. A comparison of standard- and rapid stimulation (7 s "on," 30 s "off") showed no definitive difference in efficacy. According to the guidelines of the American Academy of Neurology, rapid cycling increases the duty cycle and hastens the need for battery replacement; therefore, the efficacy of rapid cycling must be assessed carefully [4]. McHugh et al. [19] proposed a classification of the outcome after VNS insertion that takes into account both seizure frequency and severity. The status of our patient was comparable to their class 1A 4.5 years after VNS as her seizure reduction exceeded 80% and the ictal or postictal severity was reduced.

Cerebrospinal fluid studies showed a significant increase in GABA 3–4 months after the start of VNS, but no significant decrease in glutamate, aspartate, or 5-HIAA after 3–9 months of VNS [10]. 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 [20]. This pathogenesis suggests that VNS is a suitable treatment for drug-resistant GEFS$^+$

Table 1
Effect of VNS on epilepetic encephalopathy.

Epilepetic 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	24	Orosz et al. [16]
	37% (3/8)	12	Dressler et al. [14]
Doose syndrome (epilepsy with myoclonic-astatic seizures)	67% (2/3)	Mean 34 (28-40)	Cersosimo et al. [13]
Lennox–Gastaut syndrome	65% (30/46)	Mean 30 (12-108)	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]

with the SCN1A mutation as it exerted favorable effects on Dravet syndrome with the SCN1A mutation [18].

4. Conclusion

Focal epilepsies with/without impaired consciousness are considerably less common in the GEFS$^+$ spectrum. VNS reduced both GTCSs and FSICs in our GEFS$^+$ patient. The seizure reduction was over 75% and 80% in GTCSs and FSICs, respectively, 4 years after the start of VNS. VNS may be a good treatment option in patients with drug-resistant GEFS$^+$ with both refractory generalized tonic-clonic- and focal seizures.

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References

[1] Scheffer IE, Zhang YH, Jansen FE, Dibbens L. Dravet syndrome or genetic (generalized) epilepsy with febrile seizures plus? Brain Dev 2009;31:394–400.
[2] Thomas RH, Johnston JA, Hammond CL, Bagguley S, White C, Smith PE, et al. Genetic epilepsy with febrile seizures plus: definite and borderline phenotypes. J Neurol Neurosurg Psychiatry 2012;83:336–8.
[3] Skjei KL, Church EW, Harding BN, Santi M, Holland-Bouley KD, Clancy RR, et al. Clinical and histopathological outcomes in patients with SCN1A mutations undergoing surgery for epilepsy. J Neurosurg Pediatr 2015;16:668–74.
[4] Morris III GL, Gloss D, Buchhalter J, Mack KJ, Nickels K, Harden C. Evidence-based guideline update: vagus nerve stimulation for the treatment of epilepsy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2013;81:1453–9.
[5] Barba C, Parrini E, Coras R, Galuppi A, Craiu D, Kluger G, et al. Co-occurring malformations of cortical development and SCN1A gene mutations. Epilepsia 2014;55:1009–19.
[6] Ceulemans B, Boel M, Claes L, Dom L, Willekens H, Thiry P, et al. Severe myoclonic epilepsy in infancy: toward an optimal treatment. Child Neurol 2004;19:516–21.
[7] Varoglu AO, Saygi S, Acemoglu H, Ciger A. Prognosis of patients with mesial temporal lobe epilepsy due to hippocampal sclerosis. Epilepsy Res 2009;85:206–11.
[8] Kasperaviciute D, Catarino CB, Matarin M, Leu C, Novy J, Tostevin A, et al. Epilepsy, hippocampal sclerosis and febrile seizures linked by common genetic variation around SCN1A. Brain 2013;136:3140–50.
[9] Scheffer IE, Harkin LA, Grinton BE, Dibbens LM, Turner SJ, Zielinski MA, et al. Temporal lobe epilepsy and GEFS$^+$ phenotypes associated with SCN1B mutations. Brain 2007;130:100–9.
[10] Morris III GL, Mueller WM, for Vagus Nerve Stimulation Study Group E01-E05. Long-term treatment with vagus nerve stimulation in patients with refractory epilepsy. Neurology 1999;53:1731–5.
[11] Aldenkamp AP, Majoie HJ, Berfelo MW, et al. Long-term effects of 24-month treatment with vagus nerve stimulation on behaviour in children with Lennox-Gastaut syndrome. Epilepsy Behav 2002;3:475–9.
[12] Carosella CM, Greiner HM, Byars AW, Arthur TM, Leach JL, Turner M, et al. Vagus nerve stimulation for electrographic status epilepticus in slow-wave sleep. Pediatr Neurol 2016;60:66–70.
[13] Cersosimo RO, Bartuluchi M, Fortini S, et al. Vagus nerve stimulation: effectiveness and tolerability in 64 paediatric patients with refractory epilepsies. Epileptic Disord 2011;13:382–8.
[14] Dressler A, Trimmel-Schwahofer P, Reithofer E, Muhlebner A, Groppel G, Reiter-Fink E, et al. Efficacy and tolerability of the ketogenic diet in Dravet Syndrome - Comparison with various standard antiepileptic drug regimens. Epilepsy Res 2015;109:81–9.
[15] Kostov K, Kostov H, Taubøll E. Long-term vagus nerve stimulation in the treatment of Lennox-Gastaut syndrome. Epilepsy Behav 2009;16:321–4.
[16] Orosz I, McCormick D, Zamponi N, Varadkar S, Feucht M, Parain D, et al. Vagus nerve stimulation for drug-resistant epilepsy: a European long-term study up to 24 months in 347 children. Epilepsia 2014;55:1576–84.
[17] Park YD. The effects of vagus nerve stimulation therapy on patients with intractable seizures and either Landau-Kleffner syndrome or autism. Epilepsy Behav 2003;4:286–90.
[18] Zamponi N, Passamonti C, Cappanera S, Petrelli C. Clinical course of young patients with Dravet syndrome after vagal nerve stimulation. Eur J Paediatr Neurol 2011;15:8–14.
[19] McHugh J, Singh H, Philips J, Murphy K, Doherty C, Delenty N. Outcome measurement after vagal nerve stimulation therapy: proposal of a new classification. Epilepsia 2007;48:375–8.
[20] Martin MS, Dutt K, Papale LA, Dubé CM, Dutton SB, de Haan G, et al. Altered function of the SCN1A voltage-gated sodium channel leads to gamma-aminobutyric acidergic (GABAergic) interneuron abnormalities. J Biol Chem 2010;285:9823–34.