

## Vigabatrin Therapy for Infantile Spasms in a Case of Cardiofaciocutaneous Syndrome with Cardiac Hypertrophy Developing during Adrenocorticotrophic Hormone Treatment

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In a patient with cardiofaciocutaneous syndrome complicated by intractable infantile spasms (West syndrome), cardiac hypertrophy developed during adrenocorticotrophic hormone treatment. Various types of antiepileptic drugs, intravenous immunoglobulin, thyrotropin releasing hormone, and a ketogenic diet were ineffective in this case. However, vigabatrin both decreased clinical seizures and improved electroencephalogram findings. Although vigabatrin has not been approved for use in Japan, the results in the present case suggest that this drug should be considered as an alternative therapy for cases of infantile spasms associated with syndromes involving cardiomyopathy or its potential risk factors, such as cardiofaciocutaneous syndrome. (*J Nippon Med Sch* 2016; 83: 167–171)

**Key words:** cardiofaciocutaneous syndrome, infantile spasms, hypertrophic cardiomyopathy, vigabatrin

### Introduction

Cardiofaciocutaneous (CFC) syndrome—a disorder with multiple congenital anomalies and characterized by congenital heart disease, craniofacial dysmorphism, and ectodermal abnormalities—belongs to a group of syndromes caused by mutations of genes of the RAS/mitogen-activated protein kinase pathway designated as RASopathies<sup>1,2</sup>. Unlike other RASopathies, CFC syndrome is complicated, in 40% to 50% of cases, by various types of seizures, with infantile spasms (West syndrome) accounting for about 10% of such cases<sup>3,4</sup>.

Vigabatrin is the drug of first choice for treating infantile spasms secondary to tuberous sclerosis complex or other symptomatic or cryptogenic infantile spasms in the European Union<sup>5</sup>.

Here, we report on a patient with CFC syndrome, intractable infantile spasms, and hypertrophic cardiomyopathy during adrenocorticotrophic hormone (ACTH) treatment in whom administration of vigabatrin decreased seizures and improved electroencephalographic (EEG) findings. We obtained consent from the patient's parents to report the clinical course.

### Case Report

A girl was born to nonconsanguineous Japanese parents via cesarean section at 35 weeks' gestation because of the mother's previous history of hysteromyomectomy. There was no family history of epilepsy or neuromuscular disease, and the girl's 4-year-old sister was healthy. At birth, the patient had a body weight of 2,854 g (+0.9 SD), a height of 44.5 cm (−0.5 SD), and a head circumference of 35.6 cm (+1.6 SD). The 1- and 5-minute Apgar scores were 4 and 6, respectively. Thus, the patient required oxygenation and was manually resuscitated with a bag valve mask. She remained in the hospital until 22 days after birth because of poor oral intake of fluids.

At the age of 4 months, infantile spasms (West syndrome) were diagnosed because of their involvement of brief symmetrical contractions of the musculature of the neck and extremities, lasting 1 to 10 minutes and occurring in clusters everyday, and hypsarrhythmia on interictal EEG (**Fig. 1A**). The patient was hospitalized at 5 months of age because epileptic seizures occurred despite treatment with vitamin B6 and valproic acid.

The results of physical examination of the patient on admission were as follows: height, 58.4 cm (−2.7 SD);

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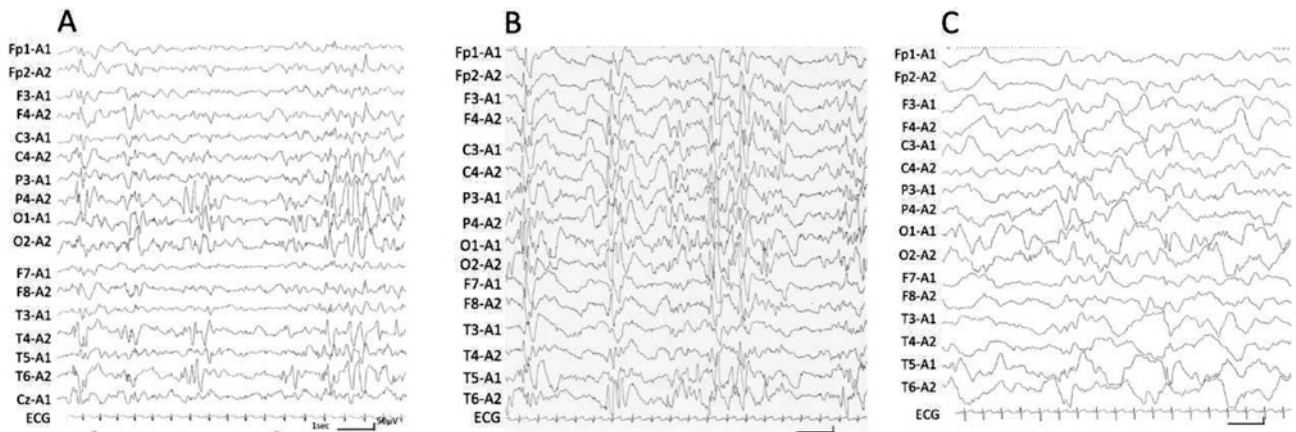


Fig. 1 Electroencephalograms of the patient. Interictal sleep electroencephalograms at the age of 4 months (A) and 1 year 4 months with 120 mg/kg vigabatrin (B) and 140 mg/kg vigabatrin (C).

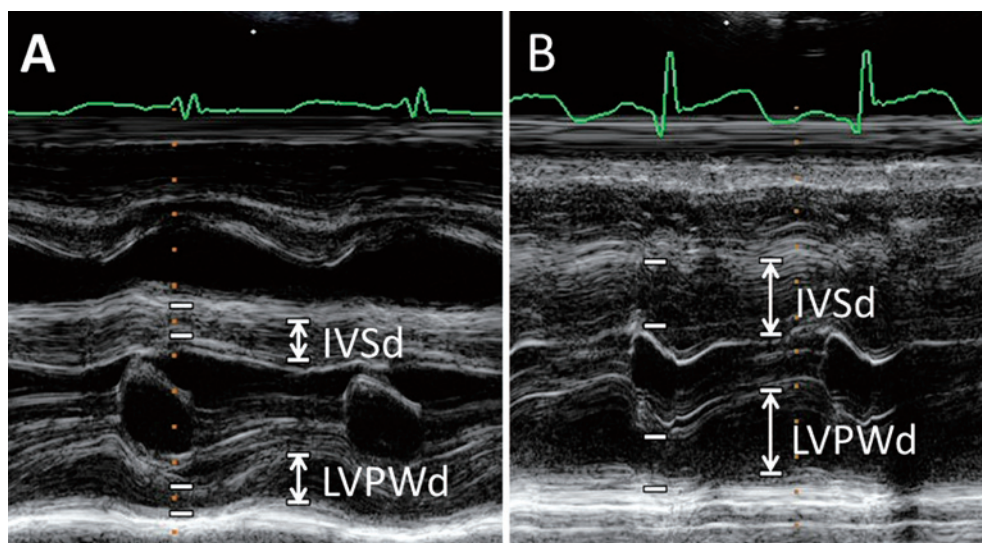


Fig. 2 The M-mode echocardiograms, recorded before and on day 17 of ACTH treatment. A: Before ACTH treatment the interventricular septum at the end-diastolic phase (IVSd) was 4.2 mm, and the left ventricle posterior wall at the end-diastolic phase (LVPWd) was 3.8 mm. B: On day 17 of ACTH treatment the IVSd was 9.1 mm, and the LVPWd was 7.5 mm.

body weight, 4,410 g ( $-3.1$  SD); and head circumference, 41.4 cm ( $+0.0$  SD). She had curly hair, sparse eyebrows, prominent forehead, and a small chin. Eczema was found on the face. She did not smile, fixate, or control her head and showed generalized hypotonia, hyperpassivity, and hyperextensivity.

Magnetic resonance imaging of the brain revealed no significant abnormalities. Cardiac ultrasonography indicated pulmonary valve stenosis and an atrial septal defect but showed no evidence of hypertrophic cardiomyopathy. The blood cell count and the results of biochemical examination were normal, and G-band chromosome analysis showed a karyotype of 46, XX. A diagnosis

of CFC syndrome was made because of mutations of the B-Raf proto-oncogene, serine/threonine kinase gene (*BRAF*) (c. 1785T>G; p. Phe 595Leu).

To control infantile spasms, ACTH therapy was started at a dosage of 0.0125 mg/kg/day, which was ineffective and therefore increased after 2 weeks to 0.025 mg/kg/day. However, ACTH therapy was withdrawn because cardiac ultrasonography on day 17 indicated the development of hypertrophic cardiomyopathy and a decrease of left ventricular stroke volume from 10.5 to 5.90 mL (Fig. 2). The hypertrophic cardiomyopathy had decreased by 7 days after ACTH treatment was discontinued.

Subsequently, the patient was treated with antiepileptic

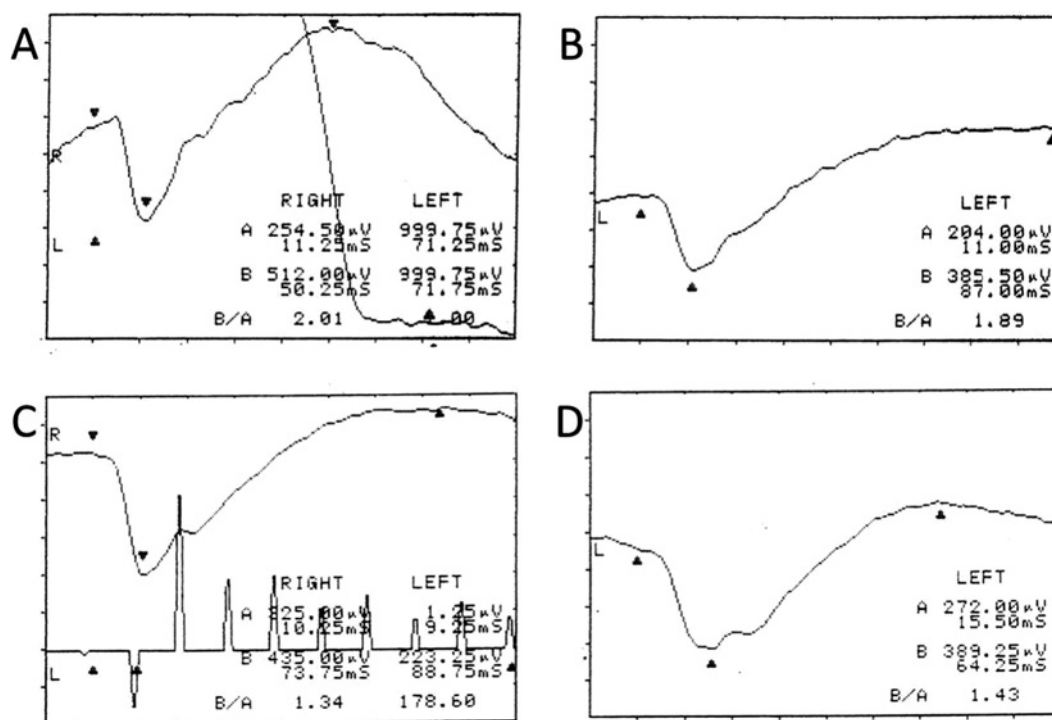


Fig. 3 The latency and amplitude of a and b waves in flash electroretinograms of the right and left eyes before and after the start of vigabatrin treatment. **A**, right eye before treatment: a wave=11.25 ms (latency) and 254.50  $\mu$ V (amplitude), b wave=50.25 ms and 512.00  $\mu$ V. **B**, left eye before treatment: a wave=11.00 ms and 204.00  $\mu$ V, b wave=87.00 ms and 385.50  $\mu$ V. **C**, right eye 3 months after treatment started: a wave=10.25 ms and 325.00  $\mu$ V, b wave=73.75 ms and 435.00  $\mu$ V. **D**, left eye 3 months after treatment started: a wave=15.50 ms and 272.00  $\mu$ V, b wave=64.25 ms and 389.25  $\mu$ V. Oscillatory potential was not evident on each recording.

drugs (levetiracetam, zonisamide, clonazepam, topiramate, phenobarbital, and lamotrigine), intravenous immunoglobulin, thyrotropin-releasing hormone, and a ketogenic diet but showed no decrease in clinical seizures or improvement in EEG findings. Finally, we decided to administer vigabatrin with the consent of our hospital's ethics committee and written informed consent from the parents, because vigabatrin has not been approved for use in Japan. In accordance with the consensus of the Infantile Spasms Working Group<sup>5</sup>, we started vigabatrin at a dosage of 50 mg/kg/day and assessed its efficacy every 2 weeks during dose titration. After the dosage had been increased to 140 mg/kg/day, seizures became nonclustered spasms and the EEG findings improved (Fig. 1C). Although the patient continued to have severe psychomotor retardation and was unable to smile or control her head, she did not require mechanical ventilation or tube feeding. After 3 months of treatment with vigabatrin, electroretinography (ERG) showed no deterioration of retinocytes compared with before treatment (Fig. 3).

## Discussion

The disorder CFC syndrome is caused by mutations of *BRAF*, *MEK1* (mitogen-activated protein kinase kinase 1 [MAP2K1]), *MEK2* (MAP2K2), or *KRAS* (Kirsten rat sarcoma viral oncogene homolog), all of which participate in the RAS/mitogen-activated protein kinase pathway that regulates cell differentiation, proliferation, and apoptosis<sup>1,2</sup>. The prevalence of CFC syndrome in Japan is currently estimated to be 1 in 810,000 persons<sup>6</sup>, and the number of patients with a definitive diagnosis of CFC syndrome will likely increase with advances in genetic diagnosis. Although few cases of CFC syndrome complicated by infantile spasms have been reported in detail, in all reported cases the seizures were resistant to treatment<sup>7,8</sup>. The present case report is, to our knowledge, the first in Japan describing vigabatrin therapy for infantile spasms with CFC syndrome.

Vigabatrin has been used to treat infantile spasms since the late 1980s in Europe and more recently in North America. Vigabatrin is considered the treatment of first choice in these regions, especially for cases of infantile



spasms with tuberous sclerosis<sup>5</sup>. Vigabatrin inhibits GABA transaminase, resulting in increased availability of GABA within the synaptic cleft, thus increasing the effects of inhibitory interneurons<sup>9</sup>. Another mechanism of action may occur through the rapamycin pathway, a key signaling pathway whose dysregulation in tuberous sclerosis complex may account for vigabatrin being effective in cases of tuberous sclerosis complex<sup>10</sup>. Although ACTH is a widely used and effective treatment for infantile spasms, it may have severe adverse effects, including hypertension, infection, electrolyte derangement, hypertrophic cardiomyopathy, adrenocortical dysfunction, sleep disturbance, brain shrinkage, and subdural hematoma or effusion<sup>11</sup>.

In the present case, hypertrophic cardiomyopathy occurred during ACTH therapy. Because hypertrophic cardiomyopathy is a cardiac finding identified in patients with CFC syndrome, whether it was a side effect of ACTH or a complication of CFC syndrome in this case was difficult to determine. However, vigabatrin should be considered as a possible treatment in cases of infantile spasms associated with syndromes involving cardiomyopathy or its potential risk factors, such as CFC syndrome and Noonan syndrome.

The vigabatrin-specific side effects involve bilateral peripheral visual field defects, which are estimated to occur in 30% to 50% of adults and approximately 20% in children, depending on the dosage and duration of treatment<sup>12,13</sup>. Thus, it is recommended that all patient receiving vigabatrin should undergo vision testing before the start of treatment, after every 3 months of treatment, and 3 to 6 months after the end of treatment; ERG or optical coherence tomography should be considered in patients who are unable to undergo perimetry<sup>14</sup>. If the testing indicates peripheral visual field defects, additional confirmatory testing should be performed, and the benefits and risks of further treatment should be evaluated<sup>14</sup>. Although ERG is not the optimal method of vision testing, we performed ERG before and 3 months after starting vigabatrin treatment and confirmed no aggravation.

In the present case, vigabatrin was first administered 6 months after the onset of infantile spasms because it has not yet been approved for use in Japan. For patients with profound mental or motor disability, as in the present case, gazing at their parents and smiling are important aspects of their lives. We suspect that if vigabatrin had been administered earlier, the seizures would have been controlled earlier and the patient would have developed more normally. We believe that vigabatrin should be ad-

ministered early to patients with infantile spasms involving profound mental retardation, and we hope that vigabatrin will be approved for use in Japan.

**Acknowledgments:** We thank Dr. Hirofumi Ohashi of the Division of Medical Genetics, the Saitama Children's Medical Center, for performing genetic screening and Dr. Mitsugu Uematsu and Dr. Tomoko Kobayashi of the Department of Pediatrics, Tohoku University School of Medicine, for providing advice regarding treatment.

**Conflict of Interest:** The authors have no conflicts of interest to disclose.

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(Received, January 7, 2016)

(Accepted, February 4, 2016)