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Case Report

An acute encephalopathy with reduced diffusion in *BRAF*-associated cardio-facio-cutaneous syndrome

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Abstract

Background: Cardio-facio-cutaneous syndrome (CFCS) is a rare genetic disorder characterized by cardiovascular anomalies, dysmorphic faces, ectodermal abnormalities and developmental delays. Mutations in *BRAF* and other RAS-MAPK pathway-associated genes are commonly identified in patients with CFCS. While this molecular pathway is known to be associated with neuro-inflammatory conditions, only one case with CFCS has been reported thus far to develop acute encephalopathy in childhood.

Case report: A 3-year-old boy with dysmorphic features and mild psychomotor delay developed acute encephalopathy. After a 45-min long, generalized seizure, the magnetic resonance imaging revealed that the restricted diffusion signals spread to the bilateral subcortical white matters on day 1 of illness. Despite the 14 days of intensive care, the acute symptoms of encephalopathy left him intractable epilepsy and severe neurocognitive impairments. The whole-exome sequencing analysis identified a *de novo* heterozygous mutation of *BRAF* (NM_004333:p.Thr241Met) in this case.

Conclusion: The present case suggests that the hyperactive condition of ERK signals might augment the development of acute encephalopathy and post-encephalopathic epilepsy in childhood.

Keywords: Cardio-facio-cutaneous syndrome; Acute encephalopathy; *BRAF*; Magnetic Resonance Imaging (MRI)

1. Introduction

Cardio-facio-cutaneous syndrome (CFCS) belongs to a group of genetic disorders that manifest clinically overlapping phenotypes with those of Noonan syndrome (NS) and Costello syndrome (CS). Germline mutations in RAS-MAPK pathway-associated genes are known to cause these syndromes [1]. Among them, *BRAF* has been characterized as one of commonly mutated genes in these syndromes, and as a regulator

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of the RAS-MAPK signals in various immune reactions [2]. This molecular pathway is also implicated in the synaptic connectivity both in physiological and neuroinflammatory conditions [3]. To date, however, only one case in which acute encephalopathy developed in childhood has been described [4]. We herein report the second case of CFCS complicated with acute encephalopathy.

2. Case presentation

The patient was born to healthy, non-consanguineous parents at 39 weeks' gestational age. His birth weight was 2980 g and the height was 49.5 cm. The Apgar scores were 9 and 9 at 1 and 5 min, respectively. Because a growth delay with height 59 cm (−1.6 standard deviations [SD]) and weight 4.9 kg (−2.5 SD) was noticed at 3 months of age, he started visiting the outpatient clinic for the regular checkups of his growth (Table S1). He began to smile at 3 months and obtained the head control at 5 months, whereas he acquired meaningful words at 18 months, started walking independently at 22 months, and spoke 2-word sentences at 35 months of age. His motor, social and language development were considered to be equivalent to those at 24 months of age before admission.

At 35 months of age, he developed pharyngitis with unidentified pathogens. His body temperature was elevated to 38.7 °C. His consciousness was clear, while his general activity remained stable at the onset of the fever. On the first day of illness (6 h after the onset of a febrile condition), he presented with generalized convulsive seizures. The seizure was terminated by repeated infusions of diazepam after 45 min after the onset. Because his consciousness remained disturbed, he was transferred to our hospital on the first day of illness. On admission, his heart rates and blood pressures were stable. He was 82.3 cm tall (−3.1 SD) and 10.8 kg in weight (−1.5 SD). He had general hypotonia and weakly evoked deep tendon reflexes. A blood gas analysis showed mild acidosis without an elevated anion gap. Hyperammonemia, hypoglycemia and electrolyte imbalances were all excluded. Liver enzymes and creatinine kinase remained within normal ranges. Cerebrospinal fluids did not show pleocytosis. Bacterial cultures, virus isolation tests and polymerase chain reaction provided negative results for influenza, rotavirus and herpes simplex virus in the cerebrospinal fluids.

An electroencephalogram showed irregular high-voltage slow waves (Fig. 1A). Brain magnetic resonance imaging (MRI) on day 1 of illness did not reveal any distinct lesions on fluid-attenuated inversion recovery (FLAIR; Fig. 1B, left), whereas diffusion-weighted images (DWI; b value 1000 s/mm^2) and apparent diffusion coefficient (ADC) mapping detected massive cortical and subcortical white matter lesions with cytotoxic edema (Fig. 1B, DWI and ADC). DWI and ADC mapping further revealed bilateral thalamic lesions with reduced diffusion. Based on his clinical symptoms and these neuroimaging features, he was diagnosed with acute encephalopathy with unclassified category. Therapeutic hypothermia at 35 °C was promptly introduced and conducted for 72 h. Serial computed tomography and MRI studies detected brain atrophy after 4 weeks of illness. Follow-up MRI at six years of age showed that diffuse atrophy of the cerebral cortex and white matters had progressed over the three-year convalescent period, resulting in the marked enlargement of the lateral ventricles (Fig. 1B, 6 years). When he was discharged after 40 days of illness, his motor and cognitive skills had deteriorated to 2–4 months of age. He never reacquired meaningful words or language skills. The developmental quotient scores have been less than 20 during the follow-up period. He has been suffering from intractable seizures consisting of myoclonic jerks, tonic spasms, and generalized tonic-clonic seizures. Multiple anti-epileptic drugs have proven ineffective for controlling his daily seizures.

Considering the characteristic dysmorphisms, delays in postnatal development, and the history of severe acute encephalopathy, we performed the whole-exome sequencing (WES) for this patient and his parents. Subsequent Sanger sequencing confirmed that this patient carried a *de novo* heterozygous mutation in the *BRAF* gene (NM_004333:c.C722T:p.Thr241Met). He is presently 12 years of age, with a height of 114 cm (−4.6 SD) and weight of 24 kg (−1.9 SD). His dysmorphic features include the coarse facial appearance consisting of broad foreheads, hypertelorism, downslanting palpebral fissures, ptotic eyelids, short nose, long philtrum, a small mandible and low-set ears (Fig. 1C). The hair is curly and sparse. Atopic skin with keratosis pilaris are also prominent, and his palms and soles have characteristic deep wrinkles (Fig. 1D). Echocardiography and electrocardiograms excluded the presence of intracardiac defects, pulmonary artery stenosis, cardiomyopathy and arrhythmia.

3. Discussion

Neuronal excitotoxicity explains the degenerative process of encephalopathy in childhood [5]. The excessive release of glutamate allows the calcium influx into the postsynaptic neuron, resulting in necrotic cell death or apoptosis. Similarly, the overproduction of pro-inflammatory cytokines TNF-α and IL-1β from microglia leads to the glutamate-mediated neurotoxicity [6]. MRI studies on acute encephalopathy with biphasic seizures and reduced diffusion (AESD), usually detect the reduced diffusion signals at three to five days of illness [5], whereas our case already presented with reduced diffusion on day 1. Thus, his condition was not considered

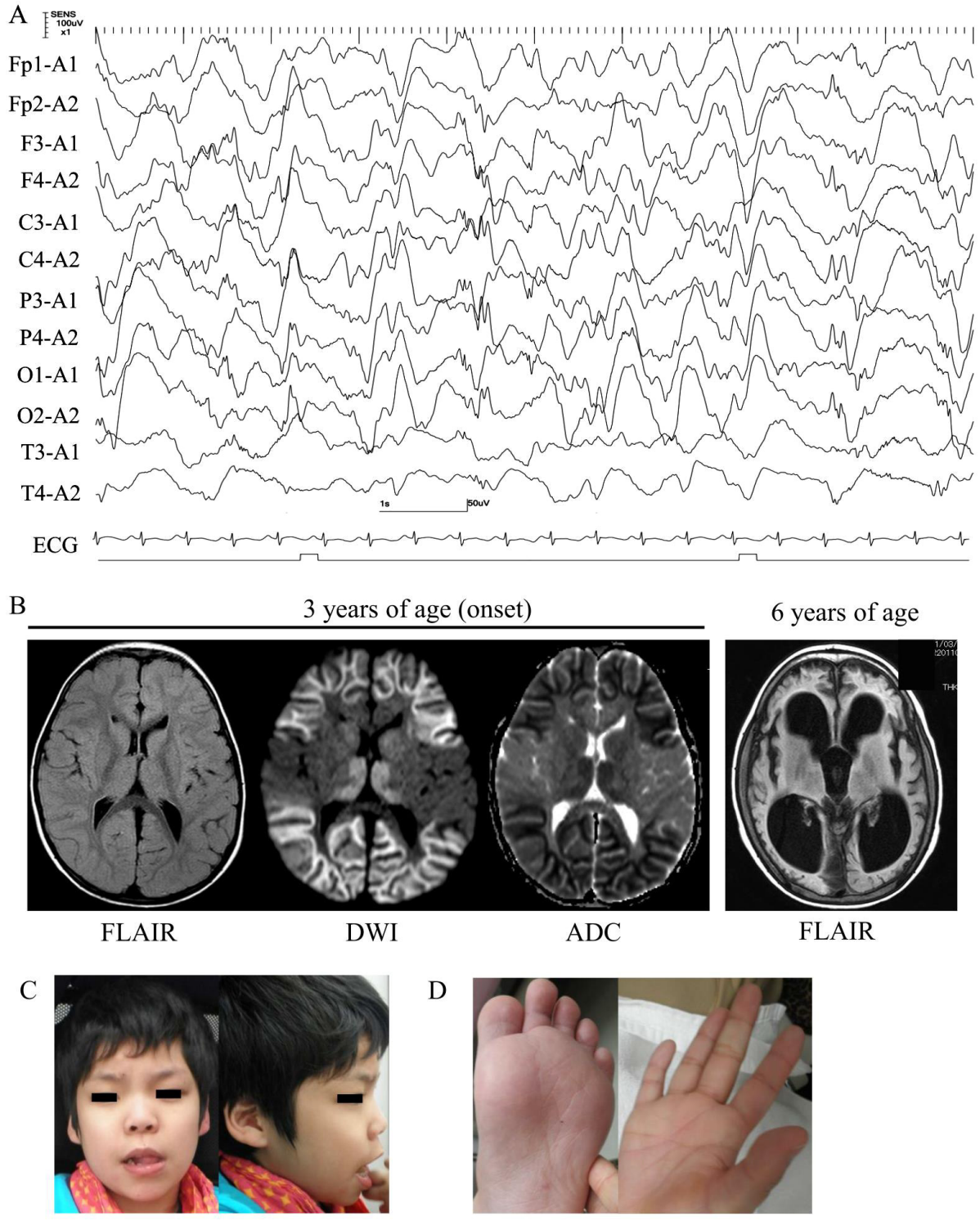

Fig. 1. Clinical features of the present case and the magnetic resonance imaging (A) Electroencephalogram recorded at the time (day 1) of admission to our hospital. (B) Panels show the axial views of magnetic resonance imaging (MRI) taken at indicated time points. Represented slices from fluid attenuated inversion recovery (FLAIR), diffusion-weighted images with b factor of 1000 (DWI), and apparent diffusion coefficient (ADC) map are shown. Note that the DWI and ADC map detected the reduced diffusion signals at the subcortical white matter on admission. FLAIR at six years of age (three years after the onset) showed diffuse atrophy of the cerebrum with remarkable enlargement of lateral ventricles. (C) Frontal and lateral views of the facial appearance. The written consent was obtained from the parents to use these photographs (C, D). (D) Deep creases in the palm and sole.

case of AESD. Taking this chronological difference into account, we hypothesized that the hyperactive ERK signals in our case promoted the development of encephalopathy with reduced diffusion at its super-acute phase.

The *BRAF* gene encodes the B-Raf proto-oncogene, serine/threonine-protein kinase, which phosphorylates MEK1 and thereby activates the downstream signaling, involving ERK1/2 [7]. An identical mutation to that in the present case (p.Thr241Met) has been reported to induce hyperactive ERK signals *in vitro* [8]. ERK signals have been also implicated in the development of epilepsy [9]. Although the epileptogenic contributions of hyperactive ERK signals remain elusive in the present case, we may reasonably speculate that the hyperactive condition of ERK signals augments the process of epileptogenic circuit formation after acute encephalopathy. The functional roles of ERK signals have been also implicated in various neuro-inflammatory conditions [10]. Acute encephalopathy has also been reported as a severe side effect of dabrafenib, an effective BRAF inhibitor for melanoma patients. These previous findings suggest that aberrant ERK signals may lead to the excessive production of cytokines in the central nervous system, with BRAF consequently inducing neurotoxicity as well as encephalopathy.

Taken together, the present findings provides important clues in the search for the genetic backgrounds of acute encephalopathy with reduced diffusion on MRI. A molecular link between ERK signals and neuronal excitotoxicity might be the key to understand the pathophysiology of acute encephalopathy in pediatric cases.

4. Ethics statements

Written informed consent was obtained from the parents for the genetic analysis, presenting clinical data, and using photographs in this manuscript. This study was approved by the Institutional Review Board at Kyushu University (No. 461-04).

Conflict of interests

The authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.braindev.2018.10.012.

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