



Case Report

An infant case of diffuse cerebrospinal lesions and cardiomyopathy caused by a *BOLA3* mutation

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Abstract

Introduction: Mitochondrial dysfunction results in a wide range of organ disorders through diverse genetic abnormalities. We herein present the detailed clinical course of an infant admitted for extensive, rapidly progressing white matter lesions and hypertrophic cardiomyopathy due to a *BOLA3* gene mutation.

Case: A 6-month-old girl with no remarkable family or past medical history until 1 month prior presented with developmental regression and feeding impairment. Ultrasound cardiography and brain magnetic resonance imaging (MRI) respectively disclosed the presence of hypertrophic cardiomyopathy and symmetrical deep white matter lesions. She was transferred to our hospital at age 6 months. High lactate levels in her cerebrospinal fluid suggested mitochondrial dysfunction. Despite vitamin supplementation therapy followed by a ketogenic diet, the patient began exhibiting clusters of myoclonic seizures and respiratory failure. Brain and spinal cord MRI revealed rapid progression of the white matter lesions. She died at 10 months of age. Fibroblasts obtained pre-mortem displayed low mitochondrial respiratory chain complex I and II activity. A homozygous H96R (c. 287 A > G) mutation was identified in the *BOLA3* gene.

Discussion: No reported case of a homozygous *BOLA3* gene mutation has survived past 1 year of life. *BOLA3* appears to play a critical role in the electron transport system and production of iron-sulfur clusters that are related to lipid metabolism and enzyme biosynthesis.

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Keywords: *BOLA3* gene; Cardiomyopathy; Encephalopathy; Magnetic resonance imaging; Mitochondrial respiratory chain complexes

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1. Introduction

Mitochondrial disorders are characterized by biochemical respiratory chain complex deficiencies and reportedly occur in 1 out of every 5000 births [1]. Mutation in any of 1500 identified nuclear-encoded mitochondrial proteins may cause dysfunction of mitochondrial energy production [2,3]. Specifically, the genetic mutation of *BOLA3* among more than 250 reported gene aberrations is known to cause severe mitochondrial disorders [3]. This mutation involves the biosynthesis of the iron-sulfur (Fe-S) cluster and results in multi-enzyme deficiency, reduced respiratory chain complex function, and ultimately multi-organ failure. Only 10 cases of a *BOLA3* mutation have been reported, for which the clinical course and complete radiological, electrophysiological, and pathological findings were not described in detail. In the present case report, a very rapidly progressing clinical course including diffuse and severe magnetic resonance imaging (MRI) findings and profound depression on electroencephalography (EEG) was found in an infant with a homozygous mutation in *BOLA3*.

1.1. Case report

A 6-month-old girl was admitted to a local hospital due to developmental regression and feeding impairment following a brief history of fever (Fig. 1). She was the fourth child of non-consanguineous healthy Japanese parents. There was no other remarkable family history apart from 2 spontaneous abortions for the mother. The patient's birth weight was 3076 g after 40 weeks and 5 days of gestation. She exhibited no anomalies and her development had been normal until 6 months old. Ultrasound cardiography and brain MRI

respectively disclosed the presence of hypertrophic cardiomyopathy and symmetrical deep white matter lesions without spinal involvement (Fig. 2a, b). Increased lactate levels (31.4 mg/dl) in the cerebrospinal fluid suggested a mitochondrial disease. Tandem mass spectrometry at birth and 6 month-old, and urinary organic acid analysis at the onset did not detected any abnormality, denying organic acid metabolic disorders. Tube feeding and vitamin supplementation therapy along with diuretics and beta-blocking agents were administered to prevent exacerbation of cardiac dysfunction. She was transferred to our institution at the age of 6 months.

On admission to our hospital, she exhibited low physical activity and reduced level of consciousness. Plasma glycine level (584.8 $\mu\text{mol/L}$) was higher than normal range (<343 $\mu\text{mol/L}$). The deep white matter lesions on brain MRI were progressed and mild slow waves were recorded on EEG (Fig. 2i). Ketogenic dietary treatment was added at 7 months of age, but she developed respiratory failure and required mechanical ventilation, corticosteroids, intravenous immunoglobulin, and antibiotics. Her spontaneous breathing and movement gradually deteriorated and an unexplained fever appeared. Cerebrospinal fluid findings revealed high lactate levels without pleocytosis (total protein: 19 mg/ml, myelin basic protein: <31.2 pg/ml, neuron-specific enolase: 110 ng/ml, lactate: 35.6 mg/dl, pyruvate: 1.6 mg/dl). Brain and spinal cord MRI showed reduced signal intensity of diffusion weighted imaging in the entire white matter involving the subcortical region and cerebellum that had spread to the brainstem and level of the 12th thoracic vertebra (Fig. 2c, d). EEG displayed asynchronous high-voltage slow waves and a partly suppression-burst pattern (Fig. 2j).

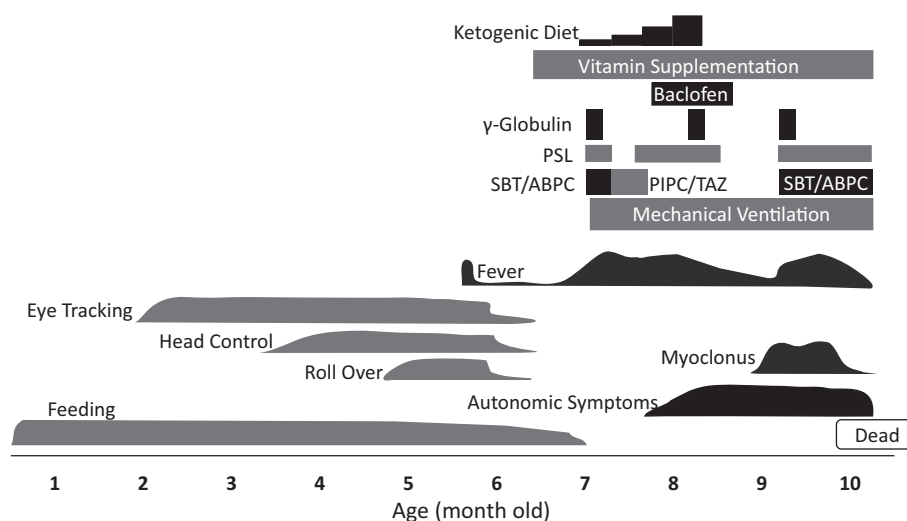


Fig. 1. Clinical course. The patient exhibited rapid developmental regression and severe symptoms. Autonomic symptoms included bladder and rectal disturbance, hypertension, and tachycardia. PIPC/TAZ, piperacillin/tazobactam; PSL, prednisolone; SBT/ABPC, ampicillin/sulbactam.

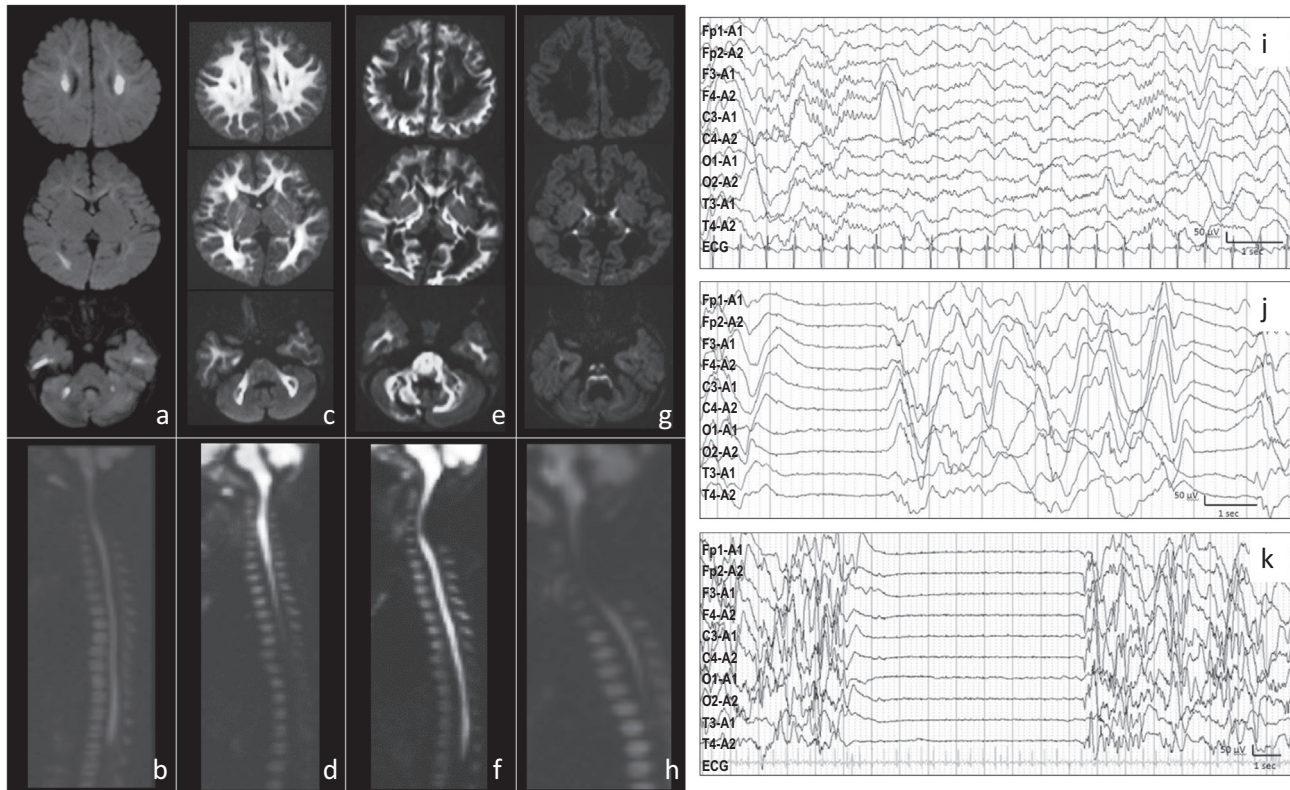


Fig. 2. Diffusion-weighted MRI and EEG findings. Symmetrical deep white matter lesions without spinal involvement were observed at 6 months of age (a, b). The lesions had spread rapidly to the bilateral trigone of the lateral ventricles, corona radiata, brainstem, cerebellar hemisphere, and spinal cord at the level of the 12th thoracic vertebra at 7 months old (c, d). Afterwards, the high signals in the deep white matter disappeared and were found in the cerebral cortex, cerebellum, and lower spinal cord at age 8 months (e, f). Finally, high signals in diffusion-weighted MRI of the brain and spinal cord were reduced at 10 months of age (g, h). Serial EEG showed slow waves with spindles at 6 months of age (i), high-voltage, slow-wave bursts with a suppression pattern at 7 months (j), and prolonged suppression at 8 months (k).

The patient also exhibited dysuria, constipation, and recurrent desaturation. She underwent tracheostomy and her ketogenic diet was discontinued at the age of 8 months. The high signals in diffusion-weighted MRI had disappeared and spread to the cerebral cortex, cerebellum, and lower spinal cord (Fig. 2e, f). Hypertrophic cardiomyopathy also gradually progressed to impair cardiac dilatation. The auditory brainstem response was absent and the suppression region in EEG became prolonged (Fig. 2k). She developed clusters of myoclonic seizures and eyelid movements that were unsynchronized with epileptic-form abnormalities on EEG. High-intensity findings on diffusion-weighted MRI of the brain and spinal cord were reduced at 10 months (Fig. 2g, h). Ultimately, her pneumonia and atelectasis became resistant to therapy, her hypercapnia progressed, and multi-organ failure soon followed. She died at 10 months of age.

Autopsy revealed thin, atrophied muscle fibers. Mitochondrial swelling was observed by electron microscopy (Fig. 3a, b, d). In the spinal cord section, severe neuronal loss and vascular hyperplasia were observed in the gray matter (Fig. 3c). The analysis of mitochondrial

respiratory chain complex activities revealed a marked reduction of complexes I and II in skeletal muscle (6.7 and 7.9% of the control, respectively), myocardium (5.4 and 5.0%, respectively) at autopsy, and fibroblasts (6.8 and 9.4%, respectively) obtained from biopsy on admission, and decrease of complex IV only in myocardium (12.5%). A homozygous H96R (c. 287 A > G) mutation was identified in the *BOLA3* gene.

2. Discussion

In the present case of a *BOLA3* mutation, MRI showed high-signal lesions in the deep white matter at 6 months of age that were consistent with previous reports [4,5]. In addition, serial diffusion-weighted MRI findings demonstrated that the early stage cytotoxic edema in the deep white matter of the cerebrum spread rapidly to the entire white matter, cortex, cerebellum, and spinal cord, and finally diffuse neuronal loss was observed in the brain and spine. EEG findings also changed drastically such that suppression-burst patterns were observed and suppression intervals gradually became prolonged during radiological progression.

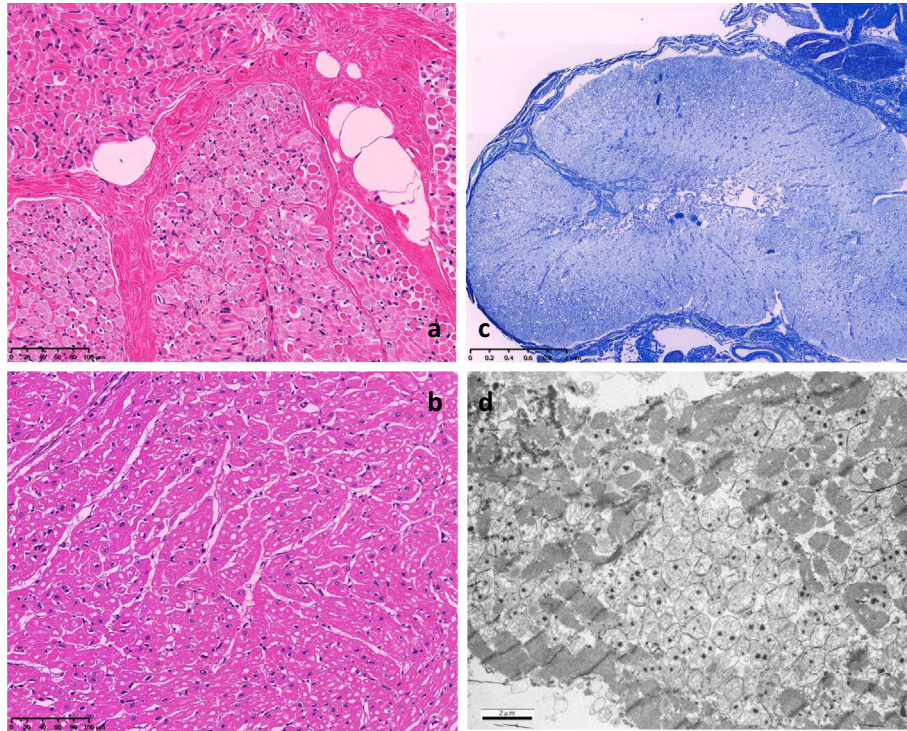


Fig. 3. Histopathological findings. Optical microscopic findings of the quadriceps muscle (a) obtained from autopsy revealed diffusely distributed atrophic muscle fibers without inflammatory cell infiltration (Hematoxylin-Eosin staining). The findings of myocardium (b) also indicated thin, atrophied muscle fibers with vacuolar degeneration. Severe neuronal loss and vascular hyperplasia were dominant in the gray matter and demyelination was observed in the white matter in a section obtained from the lower spinal cord (c, Klüver-Barrera staining). Mitochondrial proliferation and swelling were observed in electron microscopic findings of the myocardium (d).

The suppression-burst pattern on EEG is present in cases of severe brain dysfunction, such as metabolic disorders including nonketotic hyperglycemia, infectious disease, and hypoxic encephalopathy.

Gene mutation of 4 mitochondrial proteins, *BOLA3*, *IBA57*, *ISCA2*, and *NFU1*, have been reported to cause severe syndromes of multiple mitochondrial enzyme deficiency [6]. Most patients with these genetic abnormalities die within the first year of life by lactic acidosis, nonketotic hyperglycinemia, or infantile encephalopathy. These proteins are considered to play roles in Fe-S cluster assembly in the mitochondria. Fe-S clusters convert [2Fe-2S] to [4Fe-4S] in lipoic acid synthase and respiratory chain complexes I and II [6,7,8]. *BOLA3* factors prominently in the late step of [4Fe-4S] cluster biogenesis [6,9]. Dysfunction of lipoic acid synthase causes nonketotic hyperglycinemia, which has both inhibitory effects in the brainstem and obligatory coagonistic function of excitatory glutaminergic receptors in the cerebral cortex and cerebellum, and leads to respiratory insufficiency, lethargy, seizure, and severe neuropathy [10]. The clinical features and severities in patients with the other three genes mutations were not apparently different from *BOLA3* mutation according to the case reports, though there were only a few reports.

This patient is the fifth reported Japanese case of a genetic abnormality in *BOLA3*. Four cases including this one had a homozygous H96R (c. 287 A > G) mutation in the *BOLA3* gene, with the remaining case harboring a heterozygous H96R mutation [3]. The other 6 cases found in the literature [4,5,7] were not Japanese and had no H96R alterations, suggesting that the H96R mutation might be specific to the Japanese population.

3. Conclusion

This is the first report of *BOLA3* mutation with a detailed description of a very rapid clinical course, severe and diffuse radiological findings, profound depression on EEG, and other pathological findings. *BOLA3* appears to play a critical role in lipid metabolism and enzyme biosynthesis and requires further study.

Written informed consent was obtained from her parents for this report.

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