Brain & Development 36 (2014) 730–733

BRAIN & DEVELOPMENT
Official Journal of the Japanese Society of Child Neurology

www.elsevier.com/locate/braindev

Case report

Leigh syndrome with Fukuyama congenital muscular dystrophy: A case report

Hidehito Kondo [a,b,*], Koichi Tanda [a], Chihiro Tabata [a], Kohei Hayashi [a], Minako Kihara [a], Zenro Kizaki [a], Mariko Taniguchi-Ikeda [c], Masato Mori [d], Kei Murayama [e], Akira Ohtake [f]

[a] *Department of Pediatrics and Neonatology, Japanese Red Cross Kyoto Daiichi Hospital, Japan*
[b] *Department of Pediatrics, Osaka University Graduate School of Medicine, Japan*
[c] *Division of Pediatrics, Kobe University Graduate School of Medicine, Japan*
[d] *Department of Pediatrics, Jichi Medical University, Japan*
[e] *Department of Metabolism, Chiba Children's Hospital, Japan*
[f] *Department of Pediatrics, Saitama Medical University Hospital, Japan*

Received 20 January 2013; received in revised form 2 September 2013; accepted 13 September 2013

Abstract

We report the first case of Leigh syndrome (LS) with Fukuyama congenital muscular dystrophy (FCMD). A neonate suffered from lactic acidosis and subsequently presented with poor feeding, muscle weakness, hypotonia, cardiopulmonary dysfunction, and hydrocephalus. He died at 17 months. The findings of brain magnetic resonance imaging indicated some specific features of both LS and FCMD, and FCMD gene mutation was detected. Decreased mitochondrial respiratory complex I and II activity was noted. Mitochondrial DNA sequencing showed no pathogenic mutation. A case with complex I + II deficiency has rarely been reported, suggesting a nuclear gene mutation.

Keywords: Leigh syndrome; FCMD; Mitochondria; Complex I + II deficiency

1. Introduction

Fukuyama congenital muscular dystrophy (FCMD), one of the most common autosomal recessive disorders in the Japanese population, is characterized by congenital muscular dystrophy with cortical dysgenesis. The gene responsible for FCMD is located on 9q31. Most FCMD-bearing chromosomes (87%) have a 3-kb retrotransposal insertion in the 3′-untranslated region of the gene [1].

Leigh syndrome (LS) is a progressive neurodegenerative disorder with psychomotor retardation, signs and symptoms of brain stem and/or basal ganglia involvement, and raised lactate levels in blood and/or cerebrospinal fluid (CSF). In majority of the cases, dysfunction of the mitochondrial respiratory chain is responsible for the disease. LS is caused by either mitochondrial or nuclear gene mutations with large genetic heterogeneity [2]. Here, we report the first case of LS with FCMD.

2. Case report

2.1. Index case

A Japanese boy was born at term as the third child to non-consanguineous healthy parents. His serum creatine

* Corresponding author at: Department of Pediatrics, Osaka University Graduate School of Medicine, 2-2 Yamadaoka, Suita City, Osaka 565-0871, Japan. Tel.: +81 6 6879 3932; fax: +81 6 6879 3939.
E-mail address: hkondo@ped.med.osaka-u.ac.jp (H. Kondo).

0387-7604/$ - see front matter © 2013 The Japanese Society of Child Neurology. Published by Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.braindev.2013.09.005

kinase concentration was extremely high (45149 IU/L) on the day of birth without any anomaly. Serum lactate level, plasma amino acid profiles, and carnitine profiles were normal. Urinary organic acid profiles showed no specific abnormalities. The patient suddenly suffered from severe lactic acidosis, hyperglycemia, and acute heart failure at day 17. Levels of lactate and pyruvate in the CSF were 4.9 mM and 0.21 mM. A mitochondrial disorder was suspected and treatment was started with carnitine, ubiquinone, and other vitamins in addition to cardiotonics and insulin. The infant's condition improved, but he subsequently presented with poor feeding, muscle weakness, and hypotonia at 1 month. Hypertrophic cardiomyopathy occurred at 3 months and cardiopulmonary function worsened after repeated lactic acidosis, and he required mechanical ventilation from the age of 6 months. He presented with an enlarged head circumference and a tense anterior fontanelle at 12 months, and died of pneumonia at 17 months.

Magnetic resonance imaging (MRI)at 2 months revealed cerebellar cysts, pachygyria, and T2-hyperintense lesions in white matter and the brainstem, but basal ganglia were normal (Fig. 1A). A follow-up investigation at 4 months indicated extended T2-hyperintense lesions (Fig. 1B). A brain computed tomography (CT) scan at 14 months showed severe hydrocephalus and extensive cerebral atrophy (Fig. 1C).

Cerebellar cysts and pachygyria are characteristic of FCMD, genetic testing for *FCMD* was performed. We examined retrotransposal insertion into the 3′-untranslated region (UTR) of the *FCMD* gene using a polymerase chain reaction (PCR)-based diagnostic method involving peripheral blood leukocytes of this case and his parents [1]. A homozygous mutation of this case and heterozygous mutation of his parents were detected. Repeated lactic acidosis and brain stem lesions led us to suspect LS. A skin biopsy was performed for mitochondrial analysis at 1 month. Activities of mitochondrial respiratory chain complex (Co) I, II, III, and IV were assayed from skin fibroblasts, as described previously [3]. The activities were also calculated as the percent relative to citrate synthetase (CS), a mitochondrial enzyme marker and to Co II activity, and evaluated according to the diagnostic criteria [4]. Respiratory chain complex I and II activities were very low, but CS, Co III, and Co IV activities were normal (Table 1). Expression of the mitochondrial respiratory chain CoI, II, III, and IV proteins was concurrently examined by Western blotting

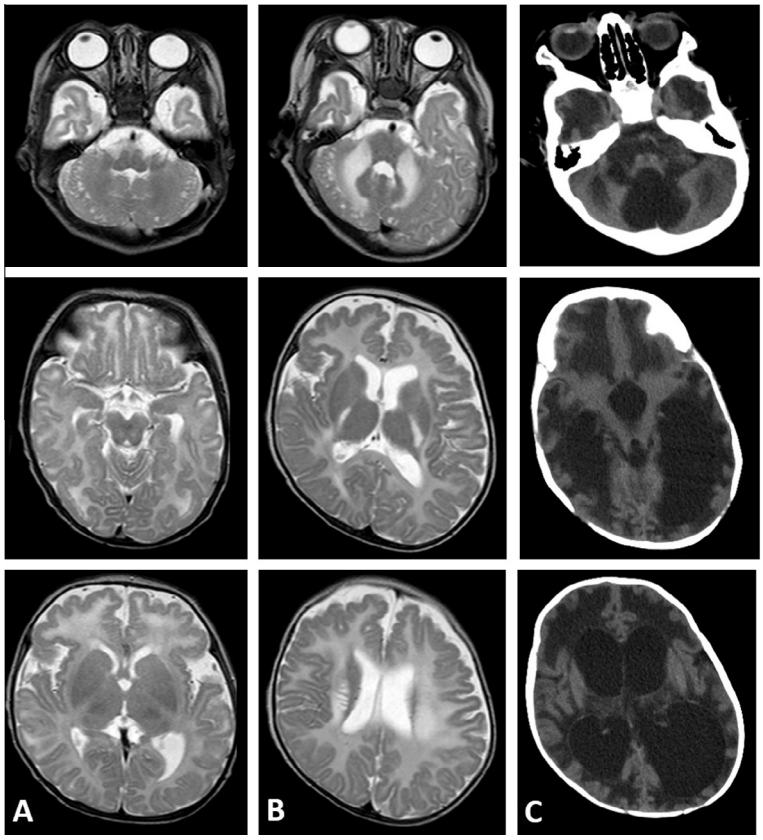

Fig. 1. Magnetic resonance image (MRI) at the age of 2 months (A) shows cerebellar cysts (A, top), bilateral symmetrical lesions in the brainstem (A, middle), pachygyria, and T2-hyperintensity in white matter, predominantly in the frontal lobes (A, bottom). An MRI at 4 months of age indicated T2-hyperintensity extending into the middle cerebellar peduncles, posterior limb of the internal capsule, and the corona radiata (B). A brain computed tomography scan at 14 months of age showed severe hydrocephalus, widespread hypodensity of white matter, and extensive cerebral atrophy (C).