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Case Report

A child with mitochondrial DNA deletion presenting diabetes mellitus as an initial symptom ☆,☆☆

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ABSTRACT

Children with mitochondrial disease may present with diabetes mellitus (DM) without autoimmune antibodies as an initial manifestation, however, it is difficult to make a precise diagnosis in early stages. We present a 2-year-old male patient with mitochondrial disease who showed insulin-dependent DM without autoimmune antibodies as an initial symptom. He later presented with progressive motor deterioration, hearing disability, ptosis, external ophthalmoplegia, and retinitis pigmentosa at 6 years and 6 months. T2- and diffusion-weighted imaging revealed high signal lesions in the subcortical white matter, anterior thalamus, globus pallidus, and brainstem. MR spectroscopy showed elevated lactate and low N-acetylaspartate in the affected white matter. Genetic analysis revealed a single large-scale mitochondrial DNA deletion at 7117-13994, leading to a diagnosis of mitochondrial DNA deletion syndrome associated with insulin-dependent DM. Although the frequency of DM in pediatric mitochondrial disease is low, mitochondrial disease, especially due to mitochondrial DNA deletion, should be considered as a differential diagnosis in those with insulin-dependent DM without autoimmune antibodies, and MRI and MR spectroscopy are recommended for an early diagnosis.

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Introduction

Mitochondrial disease is caused by functional deterioration of mitochondria, which exist in every cell in the body. Diabetes mellitus (DM) affects 24.4% of adult patients with mitochondrial disease, but only 2% of pediatric patients [1]. We herein report a pediatric patient with mitochondrial DNA (mtDNA) deletion syndrome who developed insulin-dependent DM (IDDM) without autoimmune antibodies as an initial symptom.

Case report

A Japanese boy, now 10 years old, was born to healthy non-consanguineous parents at 41 weeks of gestation at 3132 g. There were no abnormalities in the perinatal history. He controlled his head at 4 months, sat alone at 7 months, and walked alone at 1 year and 2 months. He uttered some words at 1 year. His motor and mental development was normal at 2 years and 4 months, but he developed polydipsia, polyuria, weight loss, and poor vitality. His height and weight were 86.5 cm (−0.6 SD) and 11.5 kg (−0.6 SD). Laboratory examination revealed a glycated hemoglobin (HbA1c) level of 13.7%, a fasting plasma glucose level of 529 mg/dL, and a C-peptide level of 0.4 ng/mL with negative pancreatic islet-related autoantibodies (insulin autoantibody [IAA], glutamic acid decarboxylase [GAD] antibody, and islet antigen-2 [IA-2] antibody). Serum lactate and pyruvic acid were 30.4 mg/dL and 1.48 mg/dl, which were considered elevated due to his intense movements. He was given a diagnosis of IDDM without autoimmune antibodies, leading to insulin therapy. His blood glucose was under good control, however, he went to a special support class in elementary school because of mild psychomotor developmental delay. At 6 years and 9 months, he presented with rapidly progressive muscle weakness, wobbling during walking, falling repeatedly, and an inability to maintain a sitting position. At 7 years and 4 months, he was admitted to our hospital for evaluation of his neurological deterioration. He showed binocular ptosis with no oculomotor paralysis, and muscle weakness, which was more prominent in the lower limbs (manual muscle testing [MMT] 2/5) than the upper limbs (MMT 4/5) with normal tendon reflexes. Laboratory examination revealed increased lactate, 43.0 mg/dL, and pyruvic acid, 1.48 mg/d, with an increased lactate-pyruvic acid ratio of 29. There were no abnormalities in the optic fundus, or on electrocardiography or echocardiography. Auditory brainstem response examination showed hearing loss on both sides, the hearing thresholds of the right and left ears being 30 and 50 dB, respectively. Magnetic resonance imaging (MRI) showed symmetric hyperintensity on T2 and diffusion-weighted images (DWI) in the subcortical white matter, anterior thalamus, globus pallidus, cerebral peduncle, and upper pons (Fig. 1). MR spectroscopy of the parietal subcortical white matter (Fig. 2; point resolved spectroscopy, repetition time/echo time/number of excitations = 5,000 msec/30 msec/32; voxel size, 1.5×1.5×2.0 cm) was performed at the same time as MRI. Quantification of brain metabolites was performed using the water scaling method of LCModel [2], which revealed decreased *N*-acetylaspartate (NAA) (5.22 mM/L; age-matched control, 9.3 ± 0.4 mM/L) and increased lactate (2.97 mM/L), which was not observed in controls (Fig. 2). Serum growth dif-

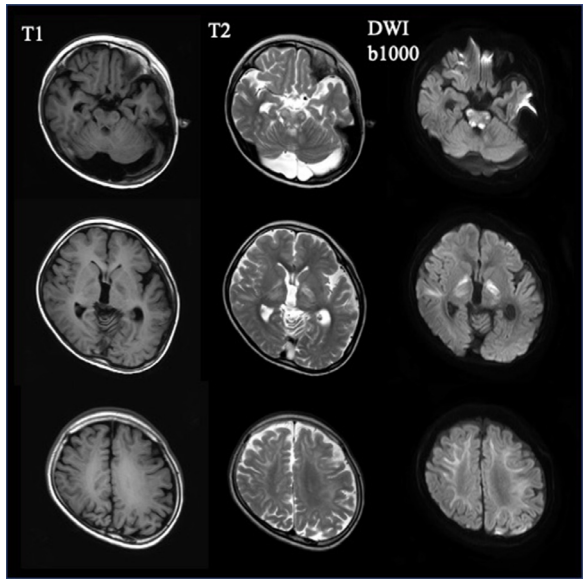

Fig. 1 – MRI at the age of 7 showed symmetric hypointensity on T1- (left column), and hyperintensity on T2- (middle column) and diffusion-weighted (right column) images in the subcortical white matter, anterior thalamus, globus pallidus, cerebral peduncle, and upper pons.

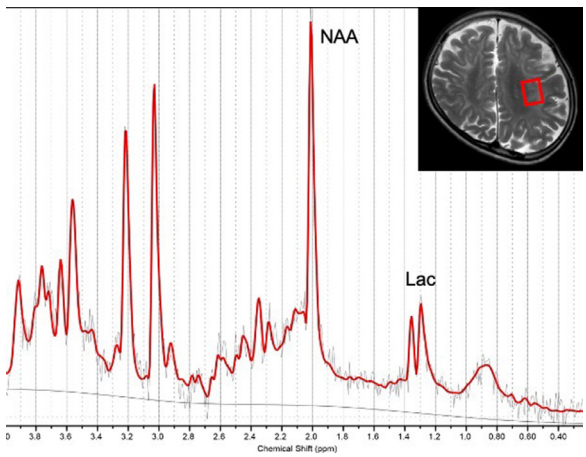

Fig. 2 – MR spectroscopy of the parietal subcortical white matter (point resolved spectroscopy, repetition time/echo time/number of excitations = 5000 msec/30 msec/32; voxel size, 1.5 × 1.5 × 2.0 cm) was performed at the same time as MRI (Fig. 1), which revealed a decrease in *N*-acetylaspartate (5.22 mM/L; age-matched control, 9.3 ± 0.4 mM/L) and elevated lactate (2.97 mM/L). The region of interest of the white matter is shown in the T2-weighted image. NAA; *N*-acetylaspartate, Lac; lactate.

ferentiation factor-15, which is a biomarker for mitochondrial disease, was as high as 2117.9 pg/mL (reference value, <707.4 pg/mL). Genetic analysis revealed a single deletion of mtDNA 7117-13994 (mutation rate in blood, 65%), leading to a final diagnosis of mitochondrial deletion syndrome. He participated in a clinical trial of 5-aminolevulinic acid and sodium ferrous citrate. At 8 years and 7 months, he exhibited acute exacerbation, and was subjected to tracheostomy and placed on a ventilator due to central respiratory failure. Retinitis pigmentosa and ocular motor restriction were detected out at the age of 10 years. He was given a clinical diagnosis of Leigh syndrome combined with chronic progressive external ocular muscle palsy (CPEO) and IDDM, based on his neurological symptoms, and MRI and MR spectroscopy findings. He has now improved to a level where he is able to talk and hold a sitting position for a few seconds. Informed consent was obtained from the parents for the study and publication.

Discussion

The most important findings in this case report are that mitochondrial disease should be considered as a differential diagnosis for patients with infantile-onset IDDM without autoimmune antibodies, and that MRI and MR spectroscopy are keys for a precise diagnosis.

Mitochondrial disease is characterized by various organ disorders, which result from an ATP production disorder due to abnormalities in nuclear DNA or mtDNA. MtDNA abnormalities are classified into depletion, deletion/duplication, and point mutations. The prevalence of mitochondrial disease is 9.2 to 16.3 per 100,000 births, among which 1.2 to 1.5 per 100,000 births have a single mtDNA deletion [3–5]. Typical clinical phenotypes of mtDNA deletion syndrome include CPEO, Kearns-Sayer syndrome (KSS), Pearson syndrome (PS), and rarely Leigh syndrome [6], as observed in the present patient showing both Leigh syndrome and CPEO.

The age of onset of mitochondrial disease caused by mtDNA deletion syndrome varies from birth to 65 years, with a mean age of 19.8 ± 13.9 years, and 65% of patients are younger than 20 years at onset [6]. In addition, according to a report on pediatric patients with mtDNA deletion syndrome, the median age of onset, excluding PS that develops from the neonatal period to infancy, was 6 years (n = 23, 10 with KSS, 3 with CPEO, 7 with CPEO-plus, and 3 with unclassified, 1 month to 15 years old) [7]. It has been reported that the larger the mtDNA deletion, the earlier the onset and the more severe the clinical course. The present patient also had a widespread single major deletion of mtDNA 7117-13994, and the onset was as early as 2 years.

A total of 24.4% of adult-onset mitochondrial disease patients have DM and 80% of them have the 3243 (A>G) mutation [8]. On the other hand, the DM complication rate in pediatric patients is as low as about 2% [1]. The most common initial symptom of single large scale mitochondrial DNA deletions is ptosis, however, it has been reported that DM and a short stature may occur as the initial symptoms under 5 years old [6,7,9]. It is, therefore, reasonable that a precise diagnosis may likely be delayed in pediatric patients presenting DM as an initial clinical symptom, as this patient did [8]. In general, some islet autoantibodies, including IAA, and GAD, IA-2, and zinc transfer 8 antibodies, are positive in about 90% of childhood IDDM patients [10], however, they are basically negative in those associated with mitochondrial disease [4]. Genetic analysis for mitochondrial DNA deletion syndrome should be performed in pediatric IDDM patients without autoimmune antibodies, especially when neurological symptoms and other multiorgan symptoms are presented.

Some kinds of clinical phenotypes of mitochondrial disease present typical MRI findings. The most common finding in Leigh syndrome is bilateral lesions in the basal ganglia, especially in the striatum, and brainstem. On the other hand, the subcortical white matter lesions are thought to be a typical finding in CPEO/KSS [11,12]. In the present patient, MRI revealed symmetric lesions in the basal ganglia and brainstem characteristic of Leigh syndrome, and in the subcortical white matter typical of CPEO, both of which are compatible with the clinical phenotypes of Leigh syndrome and CPEO.

MR spectroscopy findings in mitochondrial disease are characterized by the presence of lactate peaks and decreased NAA (a marker for neuro-axonal function) in the affected areas [12]. In this patient, MR spectroscopy actually showed a prominent lactate peak and a decreased NAA level in the subcortical white matter. MRI in a patient with mitochondrial disease may be normal with decreased NAA on MR spectroscopy [13]. It has also been reported that detection of lactate on MR spectroscopy is more sensitive than in serum or cerebrospinal fluid [14]. MR spectroscopy, in addition to MRI, is recommended in patients with suspected mitochondrial disease.

In conclusion, patients with mitochondrial DNA deletion can present with infantile-onset IDDM without autoimmune antibodies disease as an initial clinical manifestation, for which MRI and MR spectroscopy are recommended for an early diagnosis, especially when neurological symptoms and other multi-organ symptoms are observed.

Patient consent statement

A written consent was obtained from the parents for publication of this report.

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