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Case Report

Leigh syndrome with spinal cord involvement due to a hemizygous *NDUFA1* mutation

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Abstract

Leigh syndrome, which is a common phenotype of pediatric mitochondrial disease, is a progressive neurodegenerative disease. The typical neuroimaging findings of Leigh syndrome include bilateral symmetric lesions in the basal ganglia and/or the brainstem. However, there are a few reports on spinal cord involvement in patients with Leigh syndrome. In the present case, magnetic resonance imaging (MRI) obtained during infancy revealed symmetric lesions in the substantia nigra of a patient with Leigh syndrome with an *NDUFA1* mutation; lesions of the bilateral putamen and brainstem were subsequently observed. Additionally, our patient presented large and extended spinal cord lesions. Therefore, this case is suggesting that we should consider the occurrence of spinal cord lesions as an atypical finding in Leigh syndrome.
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Keywords: *NDUFA1*; Leigh syndrome; Spinal cord involvement; Complex I deficiency

1. Introduction

Leigh syndrome (LS) is the most common phenotype of pediatric mitochondrial disease, which is a progressive neurodegenerative disease [1]. The incidence of LS is estimated 1:32,000–40,000 births [2,3]. The onset of clinical symptoms, including hypotonia and psychomotor retardation, typically occurs by 2 years of age, and LS patients often showed rapid deterioration due to metabolic challenges such as infection and prolonged fasting [1,2]. The typical neuroimaging findings of LS include necrotic bilateral symmetric lesions in the basal ganglia and/or the brainstem [1,4,5]. There are a few reports on spinal cord involvement in patients with LS [6,7]. We herein present a case of LS with spinal cord involvement in MRI due to an *NDUFA1* mutation. The c.55C > T, p(P19S) mutation of this patient has already been described and the pathogenicity at the cellular level has already been proven [8].

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2. Case report

The patient was an 11-year-old boy who was born at 36 weeks of gestational age to non-consanguineous parents. The patient had a dichorionic diamniotic twin sister who was not affected and had no significant family history of neurological disorders. His birth weight was 2154 g. At 5 months of age, he exhibited axial hypotonia and horizontal nystagmus. Although his developmental milestones were normal until 4 months of age, he presented a developmental delay after 5 months of age; he was able to sit without support at 18 months of age and was able to walk alone at 3 years and 2 months of age. At 10 months of age, afebrile generalized seizure was observed. At 17 months of age, brain magnetic resonance imaging (MRI) showed bilateral lesions affecting the substantia nigra (Fig. 1A). A neurological examination revealed nystagmus, hypotonia, slurred speech, and diminished deep tendon reflexes in the lower limbs. A cranial nerve examination revealed normal results. From 3 years and 10 months of age, the oral administration of vitamins B1 (100 mg/day), B6 (100 mg/day), B12 (1 mg/day), and CoQ10 (30 mg/day) was started.

The laboratory data showed an increase in the patient's serum lactate and pyruvate levels (55.8 mg/dl and 3.03 mg/dl, respectively). A complete blood count was normal and the levels of liver and renal function markers were within the ranges. The patient's nerve conduction velocity was normal and a cardiological examination showed normal findings. Audiometry revealed no auditory brainstem response at 25–90 dB; I-III waves were detected at 105 dB. Electromyography showed myopathic changes. A muscle biopsy revealed mild type 2B fiber atrophy and no ragged red fibers. An analysis of cultured fibroblast enzymes to investigate respiratory chain activities revealed decreased Complex Ⅰ activity (to 28% of control; Table S1). A mitochondrial genome analysis revealed no mutations. Whole exome sequencing revealed a hemizygous novel missense mutation in the X-linked *NDUFA1* gene; c.55C > T, p(P19S) [8].

After starting treatment, the patient's serum lactate and pyruvate levels decreased to 15.7 mg/dl and 1.18 mg/dl respectively, and nystagmus was not observed. Brain MRI showed the improvement of the lesions of the substantia nigra (Fig. 1B). At 7 years of age, his ataxia became aggravated and he had difficulty in standing and walking after acute viral infection. He could not hold things or eat using a spoon due to his muscle weakness. Brain MRI showed new lesions in the bilateral putamen and medulla (Fig. 1C). From 9 years of age, his ataxia and muscle weakness gradually improved and he was able to stand with support. However, at 10 years of age, he presented central apnea, intention tremor and dysphagia. Brain and cervical MRI revealed cerebellar atrophy and symmetric regions of T2 hyperintensity in the anterior column of the cervical spinal cord without symptoms of myelopathy such as spasticity and sensory deficits (Fig. 1D, E). After 1 year, a mild improvement in his weakness was observed.

3. Discussion

The brain lesions of LS are typically located in the basal ganglia and/or brainstem, where they show hyperintensity on T_2-weighted imaging. These CNS lesions most commonly affect the putamen, thalamus, substantia nigra, nucleus ruber, medulla oblongata, and cerebellar dentate nucleus [4,5]. Spinal involvement is a hallmark of a specific subtype of mitochondrial disease: leukoencephalopathy with brainstem and spinal cord involvement and lactate elevation (MIM 610956), which is associated with mutations of the mitochondrial aspartyl-tRNA synthetase gene. In this disease, spinal involvement is typically found in the dorsum columns of brain stem. On the contrary, the anterior column of gray matter in the cervical spinal cord was affected in our patient. There are few published case reports on spinal cord involvement in LS patients. We could only find three reports of genetically-confirmed cases in which spinal cord involvement was described (Table S2) [6,7]. One patient was a 4-month-old boy, who was diagnosed with LS with a homoplasmic mutation of m.3275C > G (tRNALeu(UUR)). Brain and cervical spinal cord MRI showed abnormal signal intensities in the bilateral thalami, globus pallidus, dentate nuclei, brainstem, and dorsum columns of the upper cervical spinal cord [6]. The other case reports involved two sisters with Leigh syndrome who had mutation of m.3197 T > C in the 16S rRNA mtDNA gene, and who showed presented spinal cord involvement. MRI of the 11-year-old patient showed abnormal signal intensities in the brainstem, cerebral peduncles, thalami, basal ganglia, cerebral white matter, and cervical spinal cord. In the 15-year-old patient, MRI showed signal changes in the bilateral cerebral peduncles, basal ganglia, and cervical and thoracic cord [7]. In our LS patient with an *NDUFA1* mutation, MRI revealed symmetric lesions in the substantia nigra during infancy. This was followed by the development of small lesions of the bilateral putamen and brainstem at 7 years of age, which are typical findings of Leigh syndrome. Additionally, at 10 years of age, the patient presented large and extended lesions in the anterior column of the gray matter of the spinal cord. As there is no clear association between NDUFA1, tRNALeu(UUR), and 16S rRNA, the mechanism for spinal cord lesions by NDUFA1 mutation remains unknown.

Complex Ⅰ deficiency is assumed to be the most common cause of Leigh syndrome [2,9,10]. Complex Ⅰ is composed of 45 subunits, including 7 subunits that are encoded by mtDNA and 38 that are encoded by nuclear genes [9]. *NDUFA1* is one of the nuclear

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