Leigh syndrome (LS) is a progressive neurodegenerative disease caused by either mitochondrial or nuclear DNA mutations resulting in dysfunctional mitochondrial energy metabolism. The onset of clinical features is typically between 3 and 12 months of age; however, a later onset has been described in a few patients. Complex I deficiency is reported to be the most common cause of mitochondrial disorders. We described a patient with a late-onset LS, who presented with gait ataxia, caused by complex I deficiency (NDUFV1 gene).

Keywords: Complex I deficiency, late-onset Leigh syndrome, NDUFV1 gene

INTRODUCTION

Leigh syndrome (LS), caused by dysfunction in mitochondrial energy metabolism, is an inherited, heterogeneous, and progressive neurodegenerative disorder of infancy and childhood.[1] It is characterized by symmetrical necrotic lesions in the central nervous system (CNS), involving the basal ganglia, brain stem, spinal cord, and cerebellum. The most common symptoms are regression of motor milestones with pyramidal and cerebellar features.

Complex I deficiency, which is notably the most common biochemical defect among mitochondrial disorders in infancy and childhood, is associated with a wide spectrum of clinical phenotypes, including LS.[2] LS most often begins before 12 months of age, but a few patients with late-onset LS have been identified in literature.[3-5]

In this report, we describe a 10-year-old boy with late-onset LS, complex I deficiency resulting in late-onset LS, and a mutation in the NDUFV1 gene who presented with progressive gait difficulties.

CASE REPORT

A 10-year-old boy presented with a history of progressive difficulty in walking, and progressively slurred speech for 1 year. The patient had no history of seizures. His parents were first-degree relatives. There was no family history of neurodegenerative disorders.

Clinical examination revealed normal growth parameters. He had horizontal nystagmus, dysarthria, bilateral dysmetria and intention tremor, dysdiadochokinesia, and gait ataxia. Tendon reflexes were mildly hyperactive and symmetric. Babinski sign was negative. The fundus oculi examination was normal.

In laboratory data, urine organic acids, plasma amino acids, and lactate levels were normal. Magnetic resonance imaging (MRI) showed bilateral, symmetric, hyperintense signal in the putamen and right caudate nucleus on T2-weighted imaging and a high lactate peak in the affected areas on MR spectroscopy [Figures 1 and 2].

Clinical and radiological findings suggested LS, and the mutation analysis of the NDUFV1 gene revealed a homozygous mutation p.Thr423Met (c.1268C > T).

DISCUSSION

LS, as described by Leigh in 1951, is characterized neuropathologically by focal, bilaterally symmetrical lesions, especially in the thalamus and brain stem regions.[1] It is a mitochondrial disease related to various enzymatic defects that affect the oxidative metabolism.

How to cite this article: Incecik F, Herguner OM, Besen S, Bozdoğan ST, Mungan NO. Late-onset Leigh syndrome due to NDUFV1 mutation in a 10-year-old boy initially presenting with ataxia. J Pediatr Neurosci 2018;13:205-7.
Although LS often occurs in early childhood, there are few reports of late-onset presentation in literature. The most common neurological features are developmental delay, seizures, and altered level of consciousness. Other associated neurological features include abnormalities in tone, muscle weakness, movement disorders, ataxia, tremor, peripheral neuropathy, central respiratory disturbance, bulbar symptoms (dysarthria, dysphagia), and abnormalities of thermoregulation. This syndrome can present with a variety of clinical presentations, progression, and prognosis. Thomé et al. reported two cases with late-onset of LS with involuntary movements. In another case, Ashrafi et al. presented a late-onset LS in a 14-year-old girl whose symptoms were initiated following head trauma. Prasun and Del Mar Pena reported a case of a 17-year-old girl with late-onset LS mimicking as CNS vasculitis. In our patient, one of the main clinical features was ataxia.

LS is genetically heterogeneous, with mutations identified in both nuclear DNA and mitochondrial DNA-encoded components of the mitochondrial respiratory chain complexes. Complex I deficiency is the second most common biochemical abnormality after complex IV deficiency in LS. Several patients with mutations in NDUFV1 have been identified in literature. The clinical phenotype of complex I–deficient patients with NDUFV1 mutations is broad and includes pyramidal tract dysfunction, ataxia, signs of brain stem dysfunction, oculomotor abnormalities, seizures, and lethargy. Some of these patients have leukoencephalopathy. Schuelke et al. reported a patient with homozygous mutation of the NDUFV1 gene, who presented with muscular hypotonia, myoclonic epilepsy, as well as a progressive macracyclic leukoencephalopathy with brain atrophy. Bénit et al. identified six NDUFV1 mutations in three unrelated patients. The first patient presented with ataxia and seizures; the second with vomiting.

**Figure 1:** T2-weighted axial magnetic resonance imaging shows hyperintense signal in the right caudate nucleus and bilateral, symmetric, hyperintense signal in the putamen

**Figure 2:** Cerebral magnetic resonance spectroscopy reveals high lactate peak in affected areas
lethargy, and subsequent apnea; and the third with ataxia and oculomotor dysfunction. None of these patients had leukoencephalopathy on MRI. Laugel et al.\(^9\) described early-onset ophthalmoplegia in LS due to NDUFV1 mutations. Zafeiriou et al.\(^9\) reported NDUFV1 mutations in a patient with regression of motor milestones and signs of mild spastic diplegia. Vilain et al.\(^9\) presented two siblings with a very similar course of early-onset, lethal encephalopathy and complex I deficiency, in whom a genome-wide approach identified a novel mutation in NDUFV1. Interestingly, in our patient, clinical features began in the late childhood.

**CONCLUSION**

LS is genetically heterogeneous. Patients with complex I deficiency related to NDUFV1 mutations display a broad spectrum of clinical signs, but genotype-phenotype correlations have remained elusive. Therefore, genotype-phenotype correlations are important and should be necessarily studied in the future.

**Financial support and sponsorship**

Nil.

**Conflicts of interest**

There are no conflicts of interest.

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