Leigh syndrome associated with mitochondrial complex I deficiency due to novel mutations in NDUFV1

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• Introduction

Mitochondrial diseases have a broad clinical spectrum and can occur at any age (1). While some patients present with a single organ involvement such as myopathy, septal hypertrophy and elevated transaminases, it may lead to acute and fatal conditions with multi-organ involvement in some patients (2). This broad clinical spectrum causes difficulties in the diagnostic process. Therefore, detailed anamnesis and physical examination are very important in the diagnosis and evaluation of mitochondrial disease. Complex I deficiency is one of the most common mitochondrial respiratory chain defect. Complex I, also called NADH-coenzyme Q reductase/ubiquinon oxidoreductase, carries the reduced equivalents from NADH to coenzyme Q (KoQ) by oxidizing NADH. This deficiency of oxidative phosphorylation results from mutation in nuclear and mitochondrial DNA (3). Seven of its subunits are encoded in mitochondrial DNA (mtDNA), while the remainder are encoded in nuclear DNA (nDNA). While mtDNA has maternal or sporadic inheritance, nDNA has mendelian or sporadic inheritance and mitochondrial diseases develop due to mutations here. Mutations in NDUFV1 (Flavin binding subunit of Respiratory complex 1) results in neurological manifestations including Leigh syndrome and leucoencephalopathy (4,5).

• Case Report

A seven-year-old boy presented with complaints of dyspnea on exertion, bruising around the mouth, nausea, vomiting and headache. Our patient occasionally had complaints of a feeling of something stuck in his throat, swallowing and clearing his throat. He was the third child born alive from the third pregnancy of the first-degree cousin parents. There was an uncomplicated pregnancy. His birth history demonstrated 36+5 weeks of gestation, 2000 grams weight, delivery by cesarean section. The patient and his family had no history of seizures. The patient did not have significant facial dysmorphism, had gait disturbance, speech delay and contractures in the fingers.

Biochemical tests of our patient (kidney function tests, liver function tests, CK: 182 U/L (32 – 294), lactate 8.9 mg/dl (4.5-19.8), pyruvate 0.85 mg/dl (0.3-1), ammonia (NHI) 15.5 µmol/L (11.2 – 35.4)) were normal. Metabolic work-up revealed normal urine organic acid and tandem mass spectrometry. The esophagus-stomach-duodenum radiograph was reported as normal. Cranial MRI showed increased intensity in the bilateral putamen, also cystic areas were observed in cranial MRI. Lesions showed increased diffusion. Hypointensity was observed in bilateral globus pallidum and mesencephalon. As a result of these findings, mitochondrial disease (Leigh’s syndrome) was suspected in the patient and thiamine 100 mg/g, biotin 2x5 mg, carnitine 50mg/kg/g, evicap 200u, coenzyme Q10 11 mg/kg/g, riboflavin 100mg/g treatments started.

In the mitochondrial myopathy panel performed on the patient, NDUFV1 c.613G>A (p.Glu205Lys) homozygous mutation was found and the patient was diagnosed with mitochondrial complex I deficiency. Our patient continues the mitochondrial cocktail treatment. The complaints of the patient, who is now 8 years old, have regressed. There was no worsening in his clinic, and his walking and speech partially improved.
• Discussion

Complex I deficiency is the second most common biochemical abnormality after complex IV deficiency in LS. Complete blood count, kidney function tests, liver function tests, creatine kinase, blood sugar, and lactate values are the tests that should be taken in a patient who is thought to have mitochondrial disease (Leigh syndrome vs) as they provide information about many systems (3).

An increase in lactate in both cerebrospinal fluid and blood is an important finding. Acyl carnitines and urinary organic acids may support the diagnosis although not diagnostic. Radiologic imaging findings are very important in mitochondrial diseases. In particular, involvement and atrophy of the white matter, periventricular area, basal ganglia in cranial MR imaging, and lactate peak in cranial MR spectroscopy can be seen.

The definitive diagnosis is made by molecular genetic evaluation. In complex I deficiency, NDUFA11, NDUFS1, NDUFS2, NDUFS3, NDUFS4, NDUFS6, NDUFS7, NDUFS8, NDUFV1, NDUFV2 mutations are seen (6). 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. In the studies and reported cases, the clinic of patients with NDUFV1 mutation starts later and has a better course (7). In our patient, the onset was 7 years old and the prognosis was good. In mitochondrial diseases, involvement in tissues and organs (muscle, brain, heart, liver, etc.) with high energy requirements is more prominent and this helps the differential diagnosis. In other words, if the patient has more than one tissue, organ and system involvement, the probability of mitochondrial disease is higher.

Treatment in mitochondrial diseases is symptomatic and supportive in the acute period. Vitamin and cofactor cocktails are given. Vitamins B1, B2 and C; CoQ10, lipoic acid, vitamin E as antioxidants; Creatine, L-carnitine, L-arginine and folic acid are included in the treatment as metabolic regulators. In complex I deficiency, vitamin B2 (riboflavin), which is involved in the regulation of mitochondrial electron transport, is especially used in treatment. In our patient, clinical improvement and a decrease in complaints were observed after mitochondrial cocktail treatment. This highlights the importance of early and effective treatment in mitochondrial diseases such as complex I deficiency.

References