Three Different Phenotypic Presentations Of Leigh's Syndrome

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INTRODUCTION

Leigh syndrome (LS) is a life-threatening neurodegenerative disease caused by mitochondrial dysfunction due to gene mutations in either the nuclear or mitochondrial genome. Isolated complex I deficiency is the most common mitochondrial disorder, which accounts for approximately 30% of cases with Leigh syndrome.

CASE 1

Six-month-old girl was admitted with dystonia and feeding difficulties. At the age of 4 months, she had a regression in neuromotor developmental stages, loss of head control, feeding difficulties, weakness, sleepiness, and the severity of these complaints increased. She was born 2950 g by section at the 39th gestational week. Her mother has had gait disturbance since the age of 30. Her father and 4-year-old brother were both healthy. She was hypotonic. Her deep tendon reflexes (DTR) were increased. Generalized dystonic movements were observed. Glucose, electrolyte values, creatinine value, infection markers, thyroid function tests, plasma amino acids, and tandem test were within normal limits. Laboratory examination showed increased AST (86 U/L), ALT (77 U/L), lactate (3 mmol/L; normal value 0.4-1.4), 3 hydroxybutyric acid (48; normal value 0-11), fumaric acid (34; normal value 1.4-9.9). Electroencephalography showed cerebral dysfunction without epileptic activity. On T2 weighted brain magnetic resonance images (MRI), hyperintensities were seen bilaterally in the caudate nucleus, putamen, globus pallidus, medial thalamus, substantia nigra and aquaductal gray matter (Figure I).

Ophthalmological and cardiological examinations were normal. With suspicion of Leigh Syndrome, mitochondrial genome analysis was performed, and mt.10197G>A variant (100%) was found in the ND3 gene. Mitocondial coctail was started. At one year, she was unable to hold up her head and made no eye contact. She was fed with nasogastric feeding and received respiratory support with a tracheostomy, home type mechanical ventilator. She died at the age of 15 months due to cardiac arrest.

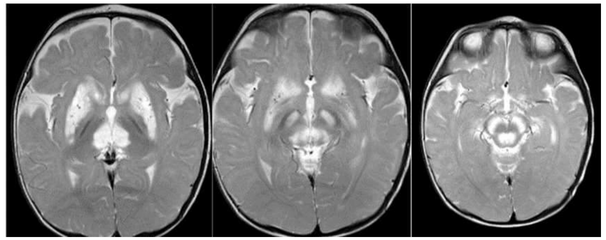

Figure I. Hyperintensities in the caudate nucleus, putamen, globus pallidus, medial thalamus, substantia nigra, aquaductal gray matter on axial T2 weighted brain magnetic resonance images

CASE 2

The mother of the first case, a 30-year-old woman, presented with complaints of gait disturbance and tremors. She had tremors in the hands since the age of seven, gait disturbance since the age of 14, and slowness in movements. She was born 3000 g at term from unrelated parents from the same village. She had episodes of dystonic contractions that repeated 2-3 times a year. She had hypophonic speech, semiptosis, limited vertical gaze and hemifasial spasm on the left. DTR could not be taken at the upper extremities but also was hyperactive at the lower limbs.

She had dysmetria on the left side, positive postural and intentional tremor bilaterally, clonus, and ataxic gait. Lactate level and nerve conduction studies were normal. On MRI, symmetrically located T2 hyperintense signal changes were observed (Figure II). Magnetic resonance spectroscopy revealed a prominent lactate peak in bilateral putamen and periaqueductal lesions. We suspected with Leigh Syndrome, mitochondrial genome analysis was performed, mt.10197G>A variant (42%) was found in the ND3 gene.

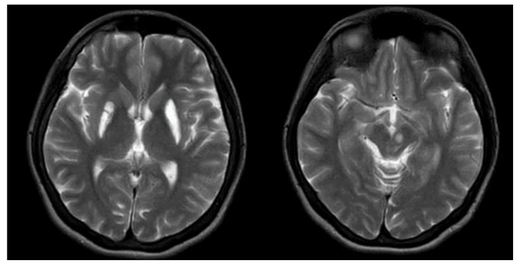

Figure II. Hyperintensities in the periaquaductal area, putamen, and mesencephalon on axial T2 weighted brain magnetic resonance images

CASE 3

A 14-year-old boy presented with gait and speech disturbances. Gait disturbance developed after the age of 5, and his speech was impaired at the age of 12. He was born with term section from healthy parents and had no postnatal problems. He started to walk at the age of one and speak after the age of two. His two sisters were healthy. Deep tendon reflexes were hyperactive in the lower extremities and the plantar reflexes flexor. His left leg was shorter.

He had pes equinovarus deformity in the left foot (Figure III). Ammonia, lactate, tandem, plasma amino acids, and urine organic acid screening were normal. Ophthalmological examination, Wechsler Intelligence Scale for Children-Revised, EMG, and spinal MRI was normal. Brain MRI showed T2 hyperintensities in the bilateral putamen (Figure IIIb). With suspicion of Leigh Syndrome, mitochondrial genome analysis revealed mt.10197G>A variant (100%) in the ND3 gene.

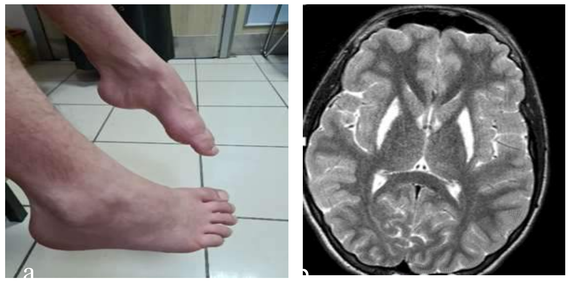

Figure III. a: Pes equinovarus deformity on the left side, b: Hyperintensities in the putamen on axial T2 weighted brain magnetic resonance images

CONCLUSION

Leigh syndrome is a neurodegenerative disorder with both phenotypic and genetic heterogeneity. The symptoms may develop slowly or with rapid progression, usually associated with the age of onset. Due to the diverse phenotype of mitochondrial diseases even in the same family, it is challenging for clinicians to diagnose.

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