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Multiple sclerosis associated with leber's hereditary optic neuropathy: a case report

Leber'in herediter optik nöropatisi ve multipl skleroz birlikteliği: olgu sunumu

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Abstract

Leber's hereditary optic neuropathy (LHON) is a mitochondrial inherited disease characterized by acute/subacute painless central visual loss. Except for optic atrophy, LHON patients are usually otherwise healthy. Occasionally, LHON is associated with neurological, cardiac, and skeletal changes. The same MRI pattern of abnormalities can be found in patients with LHON. It is sometimes associated with clinical signs of multiple sclerosis (Harding Syndrome). In this report, we present the case of a male patient with complaints of bilateral visual loss, who was diagnosed with Leber's hereditary optic neuropathy that was confirmed by the presence of a mutation at 3460G>A position. He was also diagnosed with comorbid multiple sclerosis which was confirmed by clinical findings and MR imaging.

Keywords: Optic Neuropathy; Leber; Multiple Sclerosis; Hereditary.

Öz

Leber'in kalıtsal optik nöropatisi (LHON) akut/subakut, ağrısız, santral görme kaybı ile karakterize, mitokondriyal genetik bir hastalıktır. Olguların çoğunda sadece göz tutulumu olur, bazen kardiyak bozukluklar, nörolojik semptomlar, iskelet anormallikleri tabloya eklenir. LHON'lu hastaların beyin ve omurilik MRG'lerinde nadir olmayarak demyelinizan lezyonlar görülebilir, bazen multipl skleroz benzeri klinik tablo ortaya çıkabilir (Harding Sendromu). Bu yazıda, eşzamanlı bilateral görme kaybı yakınması ile başvuran ve mt. DNA gen mutasyonu (mt.DNA 3460G>A) saptanıp LHON tanısı alan, eşlik eden nörolojik belirtileri ve beyin MRG bulguları multipl sklerozu telkin eden erkek olgu sunulmaktadır. Bu olgularda tanı süreçleri ve özellikle MS tedavisi gözden geçirilmektedir.

Anahtar Kelimeler: Optik Nöropati; Leber; Multipl Skleroz; Kalıtsal.

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INTRODUCTION

Characterised by acute or subacute onset of central vision loss, Leber's hereditary optic neuropathy (LHON) is a rare maternally inherited mitochondrial disease (1). It was first described in 1871 by German ophthalmologist Theodor Leber. LHON arises from mitochondrial mutations. The disease originates from the main 3-point mutation in the mitochondrial respiratory complex 1 gene (2). LHON mostly occurs in males in the 2nd and 3rd decades of life (3). Loss of vision is painless and effects both eyes. Though rarely, LHON patients may also present with neurological symptoms, cardiac symptoms, and skeletal deformities (4).

Some LHON patients have clinical symptoms similar to that of MS (LHON-MS). LHON patients are reported to be 50 times more risky to develop MS compared to the normal population (5). The way MS develops in LHON patients is not clear. While LHON is more common in males, female ratio is higher in LHON-MS patients. On this gender difference, pathogenetic causes are said to be responsible (6). Antioxidant compounds and free radical scavengers are used in the treatment of LHON (7).

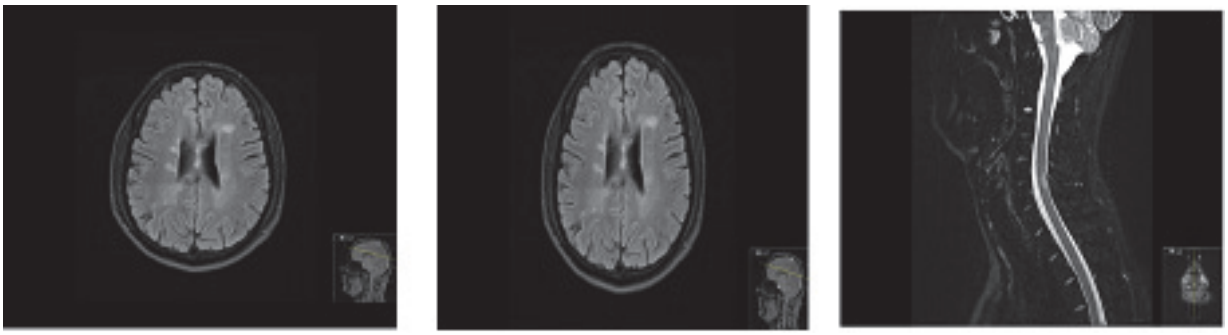
The kind of treatment to be applied for LHON-MS is not clear. There are reports of the use of immunosuppressive and immunomodulatory drugs in these cases (3, 8, 9). In this article, we present the case of a male patient who presented with symptoms of simultaneous bilateral vision loss and was diagnosed with LHON due to mt. DNA (3460G> A) gene mutation though further accompanying neurological symptoms and brain MRI findings suggested the presence of comorbid multiple sclerosis. In such cases, we recommend that diagnosis processes and particularly the MS treatment modalities should be revised.

CASE REPORT

A 24-year-old male patient was admitted to Neurology clinic in 2011 with acute onset of pain in both eyes (more severe on the right) and blurred vision accompanied by pain. It was noted that, two months before his admission, the patient had had numbness in his his left arm and leg that resolved within weeks.

The neurological examination showed bilateral optic atrophy with a visual acuity of 20/200 in the left while the right eye was able to notice light from 1 meter. The DTR revealed bilaterally hyperactive eyes on the top and bottom, reduction in the duration of the vibration in the left upper and lower extremities, and hypoesthesia in the upper left eye. The visual evoked potential (VEP) examination showed prolonged P100 latency on both sides (right: 179 msn and left: 177 msn) and decrease in the amplitude, more pronounced on the left, (right: 2.4μv; left: 1.4μv).

The MR imaging of the brain (T2 and flair signal increases in the right corona radiate, in the neighbouring areas of the left lateral ventricle occipital horn, and in the genu of the corpus callosum as well as minimal contrast in the corona radiate and lesions neighbouring right lateral ventricle) and the examination of the cervical spine (T2 signal increase in the central spinal cord at C5-6 level) revealed evidences consistent with demyelinating plaques (Figures 1-3). The orbital MRI was normal.



Figures 1-3. Brain and cervical MRI images.

Anti-Aquaporin4 antibodies requested for the differential diagnosis of neuromyelitis optica and markers studied for vasculitis were negative. The patient was applied 1 g/day IV methylprednisolone pulse therapy for 7 days.

In the follow-up after two months, the blurred vision complaint continued yet there were improvements in the neurologic examination findings except for the eyes. The visual acuity was 20/400 on the right and 20/200 on the left. Brain and cervical MR imaging showed no decline in the previously detected lesions and the patient was referred to a neuro-ophthalmology centre as it was decided that the vision problem was not related to multiple sclerosis. After the examinations in the neuro-ophthalmology centre, the patient was informed that he had mt.DNA gene mutation (mt.DNA 3460G>A) and was offered Idebenone treatment with a diagnosis of Leber's hereditary optic neuropathy.

The patient was re-admitted to the neurology department with weakness in the legs in March 2015. The neurological examination revealed bilateral optic atrophy, a visual acuity of 20/50 on the right and 20/30

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on the left, and horizontal gaze nystagmus on the left. Muscle strength in both lower limbs were 4/5; DTRs were hyperactive; and ether was an extensor on the TCR right.

The brain MR imaging displayed multiple (in the mesencephalon, bulb, corona radiate, centrum semiovale, and corpus callosum) demyelinating lesions. There were contrast enhancements after the IVCM application in many lesions (right temporal, bilateral occipital, left frontal, left frontoparietal, mesencephalon, and left posterior). The cervical MR imaging displayed chronic demyelinating plaques in C2 and C5-6 while the thoracic MR imaging revealed chronic demyelinating plaques in T9-10. The patient was administered methylprednisolone pulse IV 1 g/day for 10 days. However, there was no change in the visual complaints in the follow-up. There was partial improvement in terms of his weakness. The patient was scheduled for dimethyl fumarate (tecfidera) therapy in addition to the ongoing idebenone treatment.

DISCUSSION

Vision loss in LHON is twofold and starts at the same time in both eyes in 1/5 of the cases though the involvement of the other eye usually occurs within weeks to months. Characteristically, pain does not accompany loss of vision. In addition to central or czecho-central scotoma extending to the periphery, patients may have dyschromatopsia. Visual complaints progress very fast while spontaneous recovery is rare (10). Neuro-ophthalmic examination usually reveals peripheral retinal phlebitis, peripapillary telangiectasia, microangiopathy, pseudo-edema on the discs, and vascular tortuosity. The advanced stage of the disease entails a spectrum of symptoms ranging from a visual acuity level of 20/50 to the absence of light perception. Clinical findings in LHON often start between the ages of 18 and 30.

In most cases, only the eyes are involved. The symptoms in the eyes may rarely be accompanied by neurological symptoms (4) (postural tremor, tic disorders, dystonia, peripheral neuropathy, pyramidal signs, cerebellar ataxia, headache, seizures), cardiac disorders (11) (arrhythmia and conduction defects like Wolff-Parkinson-White and Lown-Ganong-Levine), or skeletal deformities. Depending on the mitochondrial disorders, LHON may also cause retinal ganglion cells, degeneration in the axonal extensions, and optic nerve atrophy (2).

LHON arises from the mitochondrial DNA mutations. In 95% of the cases, there are three localised mutations in 1 complex gene. These are 3460G>A, 11778G>A, and 14484T>C point mutations and their nucleotide locations are in the 1, 4 and 6 subunit genes of the respiratory complex I, respectively. Cases with 11778G>A or 3460G>A mutations are often clinically more severe than patients with 14484T>C mutation.

The diagnosis of LHON is set with medical history of patients as well as neurological and molecular examinations. In this context, hereditary optic neuropathies should be kept in mind in patients presenting with vision loss symptoms in I-IV decades. Congenital optic atrophy, retrobulbar neuritis, nutritional and toxic optic neuropathies should be considered in the differential diagnosis. The painless nature of LHON is an important sign in the differential diagnosis of optic neuritis, which is seen in the same age group.

Brain and spinal cord MRIs of LHON patients may occasionally show demyelinating lesions. In particular, practitioners may encounter lesions in the putamen, necrosis in the striatal, and cerebral oedema.

After a comprehensive report in 1992 by Harding et al., LHON-MS cases are called Harding syndrome patients (12). The possibility of finding MS in LHON patients is 50 times more than the non-LHON population (6). The reason for this relationship is not clear. Due to mutations in the subunits of mitochondrial respiratory chain complex 1, mitochondrial mechanism deteriorates in LHON and this results in increased oxidative stress, which in turn leads to aggravated inflammatory processes and tissue damage. LHON often occurs in men (%77) while the LHON and MS union is only found in 34% of male patients (5, 6). Palace et al. interpret this gender difference by linking it to pathogenesis. According to this, mitochondrial mutation severity threshold required for the emergence of LHON is high in women and this damage caused by the severity of mutations brings about a MS-like pathology (6).

Studying MS patients with bilateral visual loss for Leber's mutation, it is found that 2% of these patients share 3 common mutations. When they are examined for MS, 5% of LHON patients were positive for MS.

While immunosuppressive therapy can be successful in stopping the immunological process in LHON-MS combination, it cannot prevent optic nerve degeneration. Idebenone (coenzyme Q10 analog formation stimulating ATP formation) treatment can improve visual recovery. For our patient, too, we are planning to administer dimethyl fumarate, which is a molecule with immunomodulatory influence as well as anti-oxidative stress effects (13).

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