CASE REPORTS

Compressive Optic Neuropathy with a Concurrent Mutation of Leber's Hereditary Optic Neuropathy: A Case Report

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ABSTRACT

Leber's hereditary optic neuropathy (LHON) is a mitochondrial genetic disease that leads to acute or subacute, painless, bilateral loss of vision, caused by degeneration of retinal ganglion cells that most affects men in their second or third decade of life. We describe a woman with compressive optic neuropathy with a concurrent LHON-associated mitochondrial mutation. Temporal hemifield defect connected to central scotoma and concurrent abduction limitation are diagnostic clues in identifying chiasmal compression with craniopharyngioma. This case emphasizes an awareness of the possible coexistence of compressive and hereditary optic neuropathy.

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Introduction

Optic atrophy, or pallor of the optic nerve head, leads to visual loss due to pathology of the optic nerve or retinal ganglion cells. The causes of optic atrophy include inflammation, ischemia, compression, nutritional deficiencies, effect of toxins or drug, trauma, and hereditary conditions. Leber's hereditary optic neuropathy (LHON) is a maternally-inherited eye disease that generally affects young adults and manifests as acute or subacute, painless, bilateral loss of central vision. LHON is caused by various point mutations in mitochondrial DNA (mtDNA), which lead to dysfunction in the mitochondrial respiratory chain.^{1,2} Here we describe a patient with concurrent compressive optic neuropathy and LHON-associated mtDNA mutation.

Case report

A 35-year-old female patient was referred to our clinic complaining of progressive vision loss in both eyes. The vision in her left eye had decreased over the previous year, and she had also experienced visual acuity decrease in her right eye three months prior to presentation. She denied a history of any ocular, systemic, or hereditary disease. She did not

take any medications and did not smoke nor drink alcohol. Her best-corrected visual acuity (BCVA) was 20/160 in her right eye and 20/1000 in her left eye. Her pupils were isocoric and both reacted normally to light. She also complained of inward deviation of her left eye, which had recently developed. She exhibited a left esotropia of 25 prism dioptres in primary position with limited abduction of the left eye. Fundus examination showed optic disc pallor in both eyes (Figure 1a), and the thickness of peripapillary retinal nerve fibre layer and the ganglion cell-inner plexiform layer were decreased on optical coherence tomography (Figure 1b). Visual field examination showed temporal field defects connected to central scotomas in both eyes (Figure 1c). A Leber's hereditary optic neuropathy (LHON) gene test revealed a homoplasmic m.3394T>C mtDNA mutation (Figure 2c). Subsequent magnetic resonance imaging (MRI) of the brain revealed a 47 × 31 × 36 mm-sized rim-enhancing cystic mass in the sellar and suprasellar area compressing the optic chiasm and completely occupying the suprasellar cistern, with features suggestive of craniopharyngioma (Figure 2a). Also, an irregular enhancing lesion at the level of the left sixth cranial nerve was found (Figure 2b), raising the possibility of inflammatory changes due to the closely located

Figure 1. (a) Clinical fundus photography of both eyes at initial presentation showing temporal pallor of both optic discs and a diffuse temporal retinal nerve fibre layer defect. (b) Optical coherence tomography retinal nerve fibre layer and ganglion cell layer analysis revealing diffusely decreased thickness in both eyes. (c) Visual field examination showing temporal field defects connected to central scotomas in both eyes.

Figure 2. (a) Axial T2-weighted image (left) and sagittal contrast-enhanced T1-weighted image (centre) showing a $47 \times 31 \times 36$ mm-sized rim enhancing cystic mass in the sellar and suprasellar area (yellow arrows). This mass completely occupied the suprasellar cistern, where the pre-chiasmatic optic nerve and optic chiasm are usually located. On thin-section coronal contrast-enhanced T1-weighted images (right), The pre-chiasmatic optic nerves can be seen (blue arrowheads) at the inferior aspect of the cystic mass. However, the optic chiasm could not be visualised, probably due to profound effacement by this mass (last image of right side). (b) Axial contrast-enhanced T1-weighted image showing an irregular enhancing lesion at the level of the left abducens nerve (white arrow), raising the possibility of inflammatory changes due to the closely located mass or cerebrospinal fluid spread from the mass. (c) Genetic evaluation for Leber's hereditary optic neuropathy revealing a homoplasmic m.3394T>C mitochondrial DNA mutation.

craniopharyngioma or cerebrospinal fluid spread from the mass.

Discussion

We have described a patient with concomitant optic chiasmal compression due to a craniopharyngioma and an LHON-associated mtDNA mutation. The patient complained of subacute painless bilateral progressive visual loss starting one year from presentation, and a m.3394T>C mutation was initially detected. However, clinical features that were atypical of LHON: (1) a visual field defect mainly involving the temporal hemifield connected to the central visual field and (2) a recently developed esotropia with abduction limitation of the left eye, prompting us to perform visual pathway imaging that revealed optic chiasmal compression due to a craniopharyngioma.^{1,2}

Ran et al. described different characteristics of visual field defects according to the different stages of LHON.³ Visual field defects in LHON patients within one week after symptom onset were mostly central or paracentral scotomas, which enlarged to incorporate the blind spot and become caeco-central defects after three to six months. Hemianopias or quadrantanopias were found in 4.1% of patients one week after onset and in 10.2% after six months. Optic nerve damage in LHON initially appears in the papillomacular bundle and gradually expands outwards. It should be noted that hemianopias or quadrantanopias are not commonly found visual field defects in LHON, and they require neuroimaging to rule out a compressive lesion.

Since the first report of a mtDNA mutation in LHON at np 11778 by Wallace et al.,¹ many kinds of mtDNA mutations associated with LHON have been reported.^{4–7} The m.3394T>C mutation has been reported to be associated with LHON in previous studies with various ethnic backgrounds.^{7–9} In addition, our previous study revealed six different kinds of LHON-associated mtDNA mutations in 34 unrelated Korean patients with bilateral visual impairment due to optic atrophy, and the m.3394T>C mutation was detected in three genetically unrelated patients (8.8%).⁶ The m.3394T>C mutation, which changes the enzymatic activity of NADH,¹⁰ may be pathogenic, although it can also be found in some naïve patients, so the effect of the mutation on

mitochondrial function is thought to be relatively mild.¹¹ However, the occurrence of the m.3394T>C mutation in several genetically unrelated subjects affected by visual impairment strongly supports its involvement in the pathogenesis of visual impairment.^{6,7} Liang et al. reported a low penetrance of visual impairment in Chinese families carrying the m.3394T>C mutation.⁷ Additional genetic (nuclear or mitochondrial) and epigenetic factors may play a role in the phenotypic expression of the LHON-associated m.3394T>C mutation.

Craniopharyngiomas are embryogenic tissue malformations of the sellar and parasellar area, which can cause persistent sequelae of visual acuity loss and visual field defects due to the proximity of the tumour to the optic nerves and chiasm.¹² There has been a report of an acute manifestation of LHON caused by m.11778G>A in a 24-year-old male with a pituitary adenoma that compressed the optic chiasm.¹³ The authors suggested the compression by the pituitary adenoma as a trigger factor in the penetrance of LHON.¹³

It is hard to determine the contribution of craniopharyngioma and LHON in developing the visual symptoms in our patient. Unfortunately, this is a retrospective case report and we have limited knowledge of how the visual symptoms and signs progressed after onset. Mechanical compression due to the craniopharyngioma could have been a triggering factor for the phenotypic expression of LHON. Alternatively, dysfunctional mitochondria may be more prone to cause additional optic nerve damage after compression. We would like to emphasise the possible coexistence of compressive and hereditary optic neuropathy. An analysis of thin-section serial contrast-enhanced T1-weighted images reveals the tumor does not compress the pre-chiasmatic optic nerves bilaterally (Figure 2b). Subacute bilateral visual loss and central scotomas connected to temporal hemifield defects could be explained by the concurrent onset of LHON as well as the chiasmal compression itself. Our patient might have had an unrecognised bitemporal hemifield defect from chiasmal compression by the craniopharyngioma. Central scotomas from LHON then developed which led to the visual disturbance described by our patient, which first involved the left eye and then the right eye. Recently, increased tumorigenesis via mtDNA mutations has been reported.¹⁴ Different LHON-associated mtDNA variants, including

m.3460G>A, m.11778G>A, m.14484T>C, modulate the tumorigenicity of the osteosarcoma cell line.¹⁴

In conclusion, we describe an uncommon case of LHON coexistent with compressive optic neuropathy. Although there is no specific treatment for optic atrophy itself, the cause of optic atrophy may threaten the patient's life or vision, and it is important to identify the underlying cause. In our patient, temporal hemifield defects connected to central scotomas and concurrent abduction limitation were diagnostic clues in identifying her coexisting craniopharyngioma. A thorough ophthalmological evaluation of the optic discs and other clinical features together with a careful history can provide the necessary clues to find the underlying cause of optic atrophy.

Declaration of interest statement

The authors have no proprietary or commercial interest in any materials discussed in this article.

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