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# Leber's hereditary optic neuropathy

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## Abstract

Leber's hereditary optic neuropathy (LHON) is a maternally inherited mitochondrial disease caused by several point mutations in mitochondrial DNA. We present the case of a healthy 12-year-old Chinese boy who presented with bilateral, painless, subacute loss of central vision (more severe in the left eye than right eye) for one week. No abnormalities were detected on magnetic resonance imaging of the brain and orbit. Serial Humphrey visual field tests initially showed a centrocaecal scotoma that worsened progressively. Cerebrospinal fluid samples and blood investigations showed normal results. A trial of steroid therapy was commenced with not much improvement in the patient's vision. A blood sample was then sent for LHON genetic testing and a mitochondrial DNA (mtDNA) G11778A pathogenic mutation was detected. The same mutation was also present in the patient's mother.

**Keywords:** genetic testing, Leber's hereditary optic neuropathy, mitochondrial disease

# Neuropati optik keturunan Leber

## Abstrak

Neuropati optik warisan Leber (LHON) adalah penyakit mitokondrial yang diwarisi secara maternal yang disebabkan beberapa titik mutasi pada DNA mitokondria. Di sini kami melaporkan satu kes yang melibatkan seorang kanak-kanak lelaki berbangsa Cina yang mengalami kehilangan penglihatan pusat pada kedua-dua mata secara subakut (mata kiri lebih teruk berbanding dengan mata kanan) tetapi tidak menyakitkan selama seminggu. Penyiasatan lanjut mendapati tiada sebarang perubahan pada bahagian otak dan orbit melalui imej resonan magnetik (MRI). Sementara itu pemeriksaan medan penglihatan bersiri menggunakan mesin Humphrey menunjukkan scotoma centrocecal pada awalnya dan kemudian menjadi semakin teruk secara progresif. Manakala pemeriksaan darah dan cecair cerebrospinal tiada menunjukkan sebarang perubahan. Percubaan rawatan steroid gagal membantu dalam pemulihan penglihatan pesakit ini. Sampel darah juga diambil bagi ujian genetik LHON dan menunjukkan mutasi patogenik pada DNA mitokondria (mtDNA) G11778A. Mutasi yang sama juga dikesan pada ibu pesakit ini.

*Kata kunci:* neuropati optik keturunan Leber (LHON), penyakit mitokondrial, ujian genetik

## Introduction

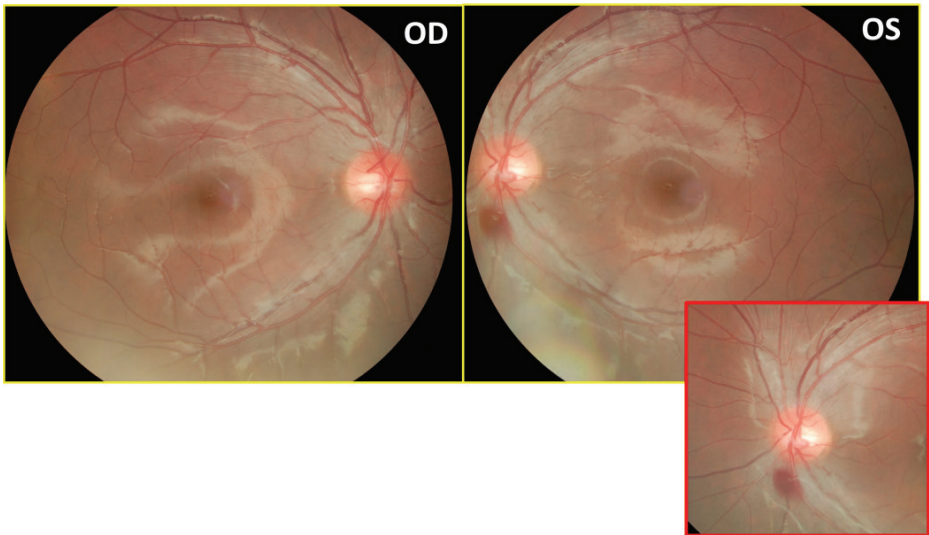
Leber's hereditary optic neuropathy (LHON) was first described in 1871 by German ophthalmologist Theodore Leber, and was subsequently named after him.<sup>1</sup> LHON is a maternally inherited mitochondrial disease caused by three primary mutations (*i.e.* m.3460G>A in *MT-ND1*, m.11778G>A in *MT-ND4*, and m.14484 T>C *MT-ND6*) in the mitochondrial DNA (mtDNA) genes.<sup>2</sup> For unknown reasons, males are more commonly affected than females. Patients are usually young adults who present with bilateral, painless, subacute visual loss. Blurring of vision may begin unilaterally or bilaterally; if vision loss starts in one eye, the fellow eye is usually affected within several weeks or months. Visual acuity and colour vision in both eyes progressively worsens over time. This condition mainly affects central vision, which is vital for tasks such as facial recognition, writing, reading and driving. Optic atrophy usually results by 6 months after onset with stabilization of visual loss.<sup>3</sup>

## Case report

A healthy 12-year-old Chinese boy presented with bilateral, painless, subacute loss of central vision (more severe in the left eye than right eye) for one week. Initially, right eye vision was refracted at 6/24 and left eye at 6/36. Bilateral pupillary reflexes were brisk with no relative afferent pupillary defect. Anterior segments were unremarkable with normal intraocular pressure. Bilateral fundi were initially unremarkable. A week later, the patient's vision deteriorated, with fundi showing hyperaemic discs with blurred margins and a single peripapillary blot haemorrhage in the left eye (Fig. 1). Figure 2 shows fundi photographs at 3 months after presentation. The patient also exhibited impaired colour perception. No abnormalities were detected on magnetic resonance imaging of the brain and orbit. Serial Humphrey visual field tests initially showed a centrocaecal scotoma that worsened progressively (Figs. 3 and 4). Figure 5 shows results from the Esterman Binocular Visual Field test done 3 months after presentation.

A lumbar puncture was performed and cerebrospinal fluid (CSF) samples were sent for routine stains and cultures, in addition to a polymerase chain reaction test to rule out herpes and cytomegalovirus infections. All CSF samples and blood investigations showed normal results.

The patient underwent a visual evoked potential (VEP) test that showed no consistent P100 in the left eye (Fig. 6). There was reduced amplitude and more prolonged implicit time for P100 in the left eye compared to the right eye. This was



*Fig. 1.* Fundus photographs taken 1 week after presentation showing hyperaemic discs with blurred margins and a single peripapillary blot haemorrhage in the left eye.

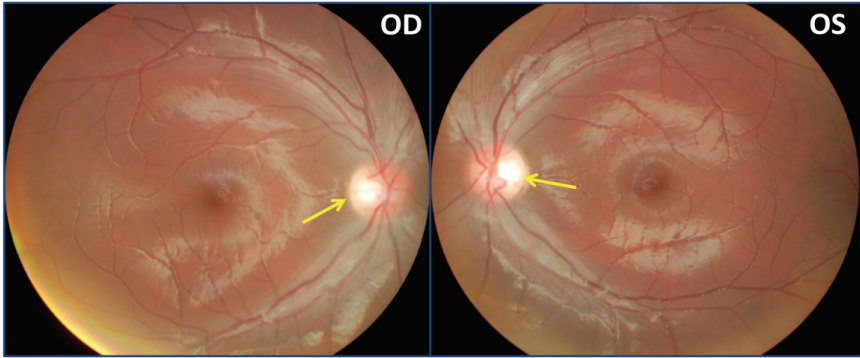


Fig. 2. Fundus photographs taken 3 months after presentation showing bilateral temporal disc pallor (yellow arrows).

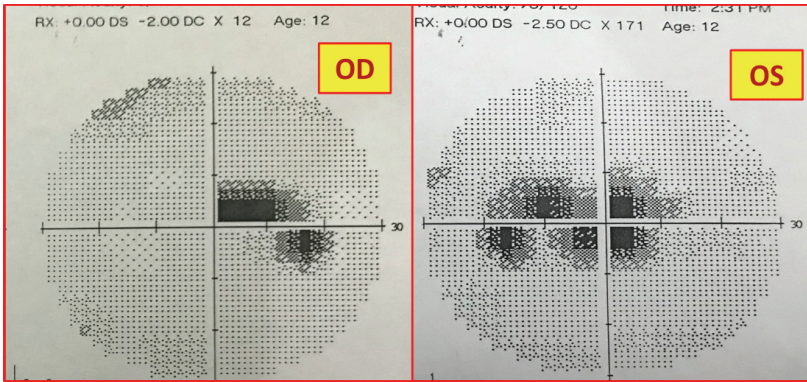


Fig. 3. Humphrey Visual Field test done at initial presentation showing a centrocaecal scotoma.

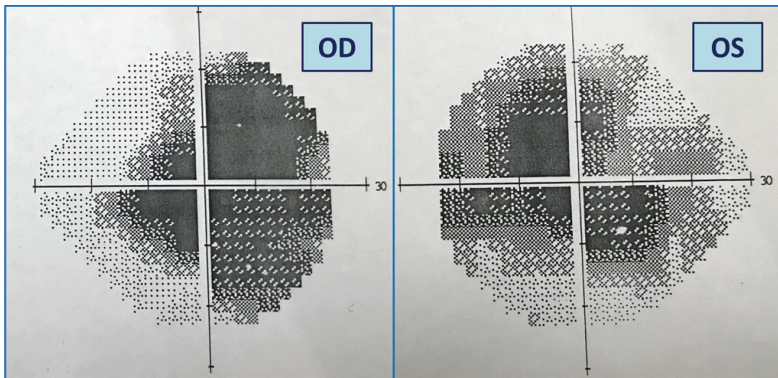


Fig. 4. Humphrey Visual Field test at 3 months after presentation showing significant deterioration.

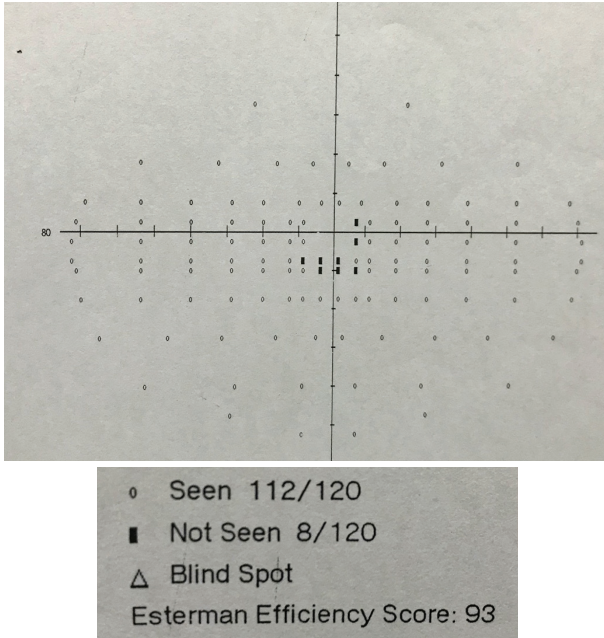


Fig. 5. Esterman Binocular Visual Field test at 3 months after presentation.

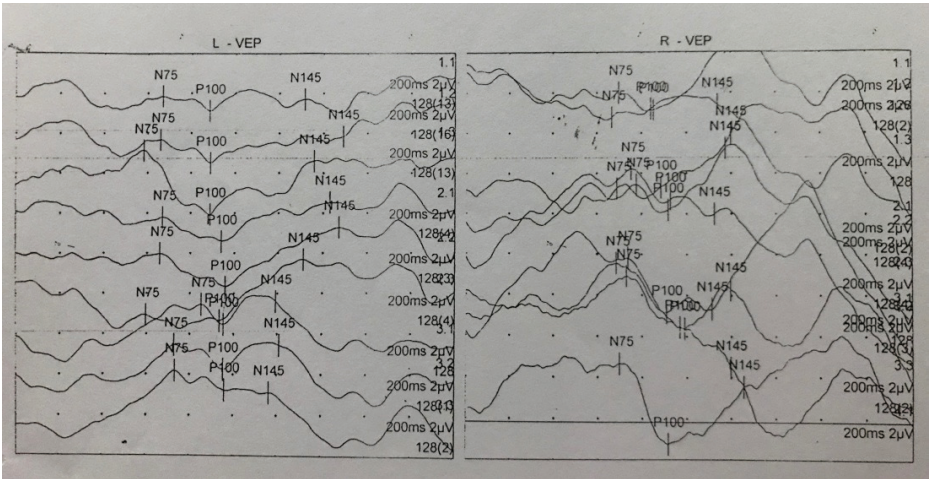


Fig. 6. VEP showed inconsistent P100 for the left eye (L-VEP), suggestive of very poor vision. The right eye (R-VEP) exhibited a small VEP amplitude with P100 still within normal range.

suggestive of very poor vision. The right eye exhibited a small VEP amplitude with P100 still within normal range; this was reported by the neurologist to be suggestive of axonal degeneration of the anterior visual pathway.

A trial of steroid therapy was commenced without much improvement in the patient's vision. A blood sample was then sent for LHON genetic testing and a mitochondrial DNA (mtDNA) G11778A pathogenic mutation was detected. The same mutation was also present in the patient's mother. The child is currently legally blind with best-corrected visual acuity of 3/60 in the right eye and 1/60 in the left eye. At the time of writing, he is registered in special education school.

## Discussion

LHON has a mean age of onset between 18 and 35 years old.<sup>4</sup> This case had a rare presentation of symptoms in childhood with rapid progression. This is consistent with the study done by Barboni *et al.* in Italy, which reported that childhood onset (< 10 years) of LHON accounted for only 11.5% of cases among paediatric patients with hereditary optic neuropathy.<sup>5</sup>

Among the Asian population, a study done in Chinese children aged  $\leq 14$  years with suspected hereditary optic neuropathy showed that 29.3% patients carried one of the three primary mtDNA mutations (LHON group). Mutations at m.11778, m.14484, and m.3460 were observed in 85.4%, 10.1%, and 4.5% of the cases, respectively.<sup>6</sup>

Patients with the m.14484 T>C mutation have been observed to have a better visual prognosis than those carrying either the m.11778 G>A or the m.3460 G>A mutation. The latter two mutations manifest a more severe clinical presentation and the chance of spontaneous recovery from vision loss is lower.<sup>7</sup> Interestingly, a person may carry a mitochondrial DNA (mtDNA) mutation that causes LHON without experiencing any signs or symptoms of vision loss.

The classic clinical signs of optic neuropathy are visual field defect, dyschromatopsia, and abnormal pupillary response. Eyecare providers should suspect hereditary optic neuropathy in children who exhibit discrepancies between pupillary reflex and other optic nerve functions.<sup>1</sup> All it takes is a simple mtDNA blood test to determine if an individual has one of the primary mutations if LHON is suspected.

Sadly, there is currently no established medical treatment for LHON. Gene therapy using an adeno-associated viral vector carrying ND4 genetic material injected intravitreally is still under investigation.<sup>8</sup> In the absence of any clinically effective treatment, supportive services such as low vision aids remain the mainstay of management and should be provided early.

## Conclusion

Due to its rarity, a diagnosis of LHON may be missed if the ophthalmologist does not have a high index of suspicion. This case was initially treated as bilateral optic neuritis with commencement of steroid therapy to no avail. A string of blood and CSF investigations initially yielded negative results. Neuroimaging results were also unremarkable. After ruling out infectious, inflammatory, space-occupying lesion, trauma, and autoimmune causes, we subsequently suspected LHON as a possible aetiology. Hereditary optic neuropathies must always be in an ophthalmologist's differential diagnosis list. A detailed family history is also imperative in diagnosing hereditary optic neuropathies.

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