

Leber's Hereditary Optic Neuropathy and Ocular Hypertension - a case report

Rita Couceiro¹, André Diogo Barata¹, Inês Leal¹, Helena Proença¹, Ana Fonseca¹,
Fátima Campos¹, Manuel Monteiro-Grillo¹

¹Departamento de Oftalmologia, Hospital de Santa Maria, Lisboa, Portugal

RESUMO

Objetivos: Descrição de um caso raro de Neuropatia Ótica Hereditária de Leber (NOHL) e hipertensão ocular concomitante.

Métodos: caso clínico de um doente de 40 anos, com diminuição recente da acuidade visual do olho direito (OD).

Resultados: O OD apresentava hipertensão ocular com atrofia ótica e escavação total, induzindo a suspeita de atrofia ótica glaucomatosa. Duas semanas mais tarde, foram referidas queixas de diminuição progressiva, mas pronunciada, da acuidade visual do olho esquerdo (OE), sem alterações fundoscópicas associadas. O doente apresentou-se progressivamente mais ansioso e pouco colaborante, levantando-se a hipótese de perda visual não orgânica no OE. Foi necessária a realização de vários potenciais evocados visuais até ser registada redução na amplitude e aumento da latência da onda P100. Testes genéticos foram positivos para a mutação 11778 G>A da NOHL.

Conclusões: Este caso realça a importância de considerar o diagnóstico de NOHL em todos os casos de neuropatia ótica de etiologia indeterminada, incluindo casos sem alterações fundoscópicas, enfatizando ainda que, na perda visual inexplicada, a causa não orgânica deverá ser sempre um diagnóstico de exclusão. São muito raros os casos de NOHL com glaucoma concomitante, sendo incerto se as mutações do DNA mitocondrial associadas a NOHL constituem um fator de risco para glaucoma. Pensa-se, contudo, que estas duas patologias possam contribuir cumulativamente para o dano sofrido pelas células ganglionares, com rápido desenvolvimento de perda visual.

Palavras-chave

Neuropatia ótica hereditária de Leber, glaucoma, hipertensão ocular, perda visual não-orgânica, potenciais visuais evocados.

ABSTRACT

Purpose: to report an unusual case of Leber's Hereditary Optic Neuropathy (LHON) and simultaneous ocular hypertension.

Methods: case report of a 40 year-old patient, who complained of recently noticed vision loss in the right eye (OD).

Results: OD presented with simultaneous ocular hypertension, optic atrophy and total cupping, leading to the suspicion of glaucomatous optic atrophy. Progressive vision loss was later noticed in the left eye (OS), but no fundoscopic findings were detected in sequential examinations. The patient became increasingly anxious and uncooperative, raising the hypothesis of non-organic visual loss in OS. Several visual evoked potentials were needed to prove reduction in

amplitude and increased latency of P100 wave. Genetic results for LHON were positive for the 11778 G>A mutation.

Conclusions: This case highlights the importance of considering the diagnosis of LHON in all cases of unexplained optic neuropathy, including cases with normal fundoscopic appearance. It also emphasizes that nonorganic vision loss should always be a diagnosis of exclusion in the context of unexplained vision loss. Concomitant LHON and glaucoma have been rarely described before and it is uncertain whether LHON-associated mitochondrial DNA mutations are risk factors for glaucoma. However it is hypothesized that the two diseases may have a cumulative effect on retinal ganglion cell damage with the consequent rapid progression of visual impairment.

Keywords

Leber's hereditary optic neuropathy, glaucoma, ocular hypertension non-organic visual loss, visual evoked potentials.

INTRODUCTION

Leber's hereditary optic neuropathy (LHON) is a rare mitochondrial genetic disease that predominantly affects young adult males.¹ Over 90% of cases have mitochondrial DNA mutations located at nucleotide positions 3460, 11778 or 1448.^{42,3,4} Retinal ganglion cells decrease by apoptosis, and finally the retinal nerve fiber thins in LHON.³

LHON usually causes subacute, painless, central visual loss, sequentially affecting both eyes and resulting in severe visual loss. In the acute/subacute stages some patients may show circumpapillary telangiectatic microangiopathy and optic disc pseudoedema.^{4,5,6} However some patients never exhibit this typical fundoscopic appearance, which has occasionally led to the misdiagnosis of nonorganic visual loss.⁶

Case Report:

A 40 year-old man attended the emergency room after noticing severe vision loss in his right eye (OD) when his left eye (OS) was occluded during a routine examination with his optometrist. He had never noticed a decrease in visual acuity before and presented no other associated symptoms. Besides being a heavy smoker, he did not have any prior relevant medical history. There was a family history of glaucoma related to his father, who had recently been diagnosed with the disease.

On examination, best corrected visual acuity (BCVA) in OD was counting fingers and BCVA in OS was 20/20. A relative afferent pupillary defect was present in OD. Intraocular pressure (IOP), measured with Goldmann tonometry, was 36 mmHg in OD and 32 mmHg in OS. Biomicroscopy was unremarkable in both eyes (OU).

Funduscopy revealed slight pallor and total cupping of the optic disc; a normal coloured disc was seen in OS with a physiological cup. No macular changes were evident in OU (Figure 1).

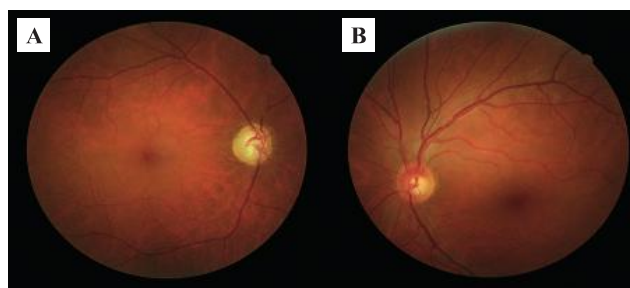


Fig. 1 | Fundus photographs - A) OD showing slight pallor and total cupping of the optic disc; no macular changes. B) Normal coloured disc with a physiological cup; no macular changes.

Brain and orbital magnetic resonance imaging showed a reduction in the volume of the right optic nerve, which was consistent with right optic atrophy, but no other changes were detected on neuroimaging. At this point the patient was assumed to suffer from terminal glaucoma in OD and ocular hypertension in OS and was medicated accordingly with topical anti-glaucomatous drugs.

On reevaluation a few days later, IOP was 14 mmHg in OD and 16 mmHg in OS. Spectral-domain optical coherence tomography (SD-OCT) revealed generalized loss of peripapillary nerve fiber layer in OD, with no changes of nerve fiber layer in OS (Figure 2). Macular SD-OCT and fundus autofluorescence were unremarkable bilaterally.

The patient underwent computed static perimetry evaluation, which revealed a complete visual field loss in OD

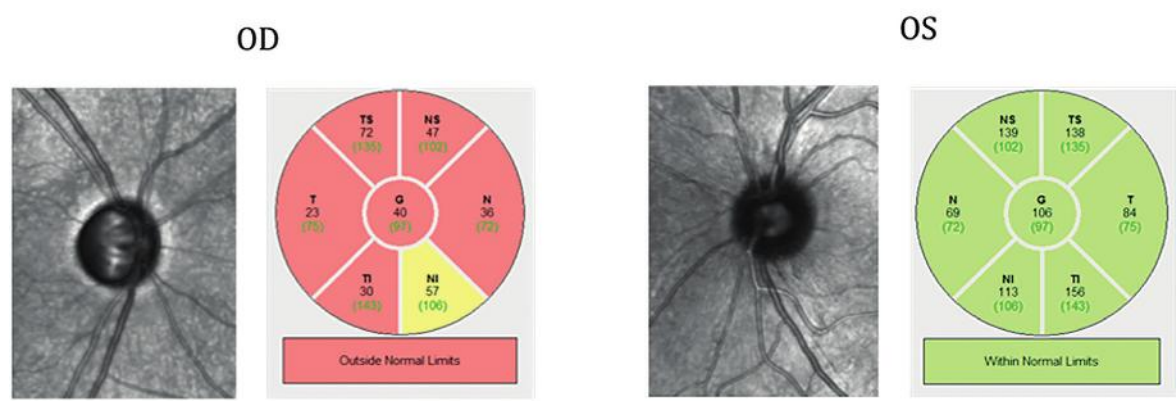


Fig. 2 | Spectral-domain optic coherence tomography (SD-OCT) of the peri-papillary nerve fiber layer reveals generalized loss in OD and no changes in OS. The optic nerves infrared images show total cupping in OD and physiological cupping in OS.

but results were unreliable in OS due to a significant number of false positive and negative answers.

During the following two weeks the patient noticed progressive vision blurring in OS, with visual acuity decreasing to 20/40. On ophthalmic examination and in SD-OCT, no changes from baseline were detected. Colour vision testing (Farnsworth-15) showed red-green dyschromatopsia in OS and computed static perimetry revealed a superior altitudinal field defect in OS, involving the paracentral area (Figure 3).

Carotid artery and ophthalmic circulation ultrasonounds were normal. Blood tests showed high levels of triglycerides and infectious serologies were negative. Normal full field electroretinogram (ERG) and multifocal ERG were

recorded in both eyes. Visual evoked potentials (VEP) revealed a significant reduction in amplitude and increased latency of P100 wave in OD and a distortion of its shape in OS, compromising the reliability of these test results.

During this period of investigation, the patient revealed high levels of anxiety, insistently inquiring about early retirement and social benefits arising from low vision. He was often unable to comply with electrophysiological testing due to anxiety. We suggested an observation by our hospital's psychiatry department in order to control anxiety but the patient refused. A non-organic cause was then suspected, however we carried on with our investigation, requesting genetic testing for LHON.

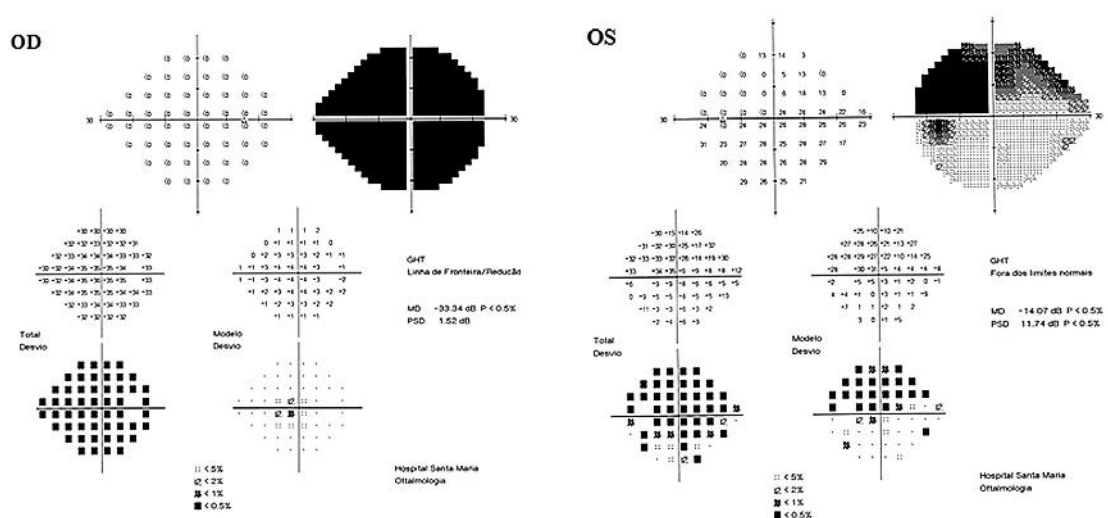


Fig. 3 | Computed Static Perimetry (Humphrey®), macular program, revealed a complete visual field loss in OD and a superior arcuate scotoma in OS.



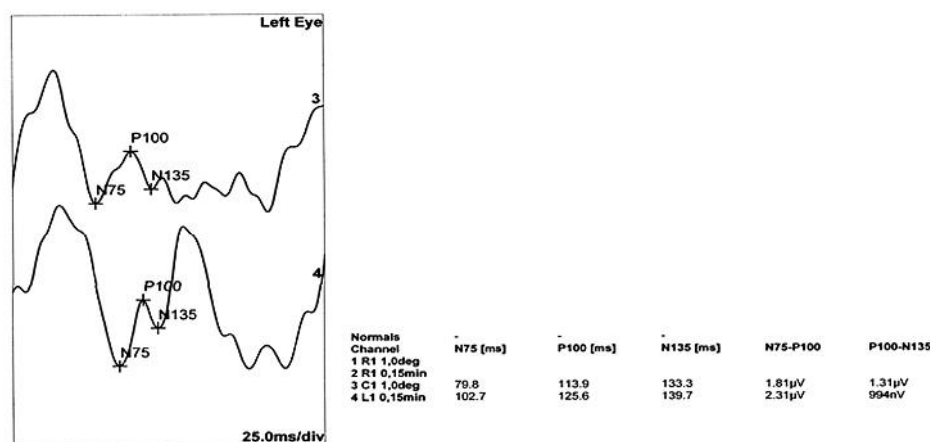


Fig. 4 | Pattern visual evoked potentials revealed a reduction in amplitude and increased latency of the P100 wave in OS.

Three months after the initial episode, the patient's BCVA in OS continued to decrease to counting fingers and a second computed static perimetry of OS was extremely consistent with the previous one, confirming a superior altitudinal defect. A new VEP testing was successfully performed, revealing a reduction in amplitude and increased latency of the P100 wave in OS (Figure 4). Fluorescein angiography showed bilateral optic disc hypofluorescence. Genetic results for Leber's optic neuropathy were positive for the 11778 G>A mutation. The patient was immediately started on idebenone and a smoking cessation program. After several months, nerve fiber layer OCT changes in OS were finally detected.

DISCUSSION

The reported LHON case represented a diagnostic challenge - the patient presented with simultaneous ocular hypertension and optic atrophy with total cupping in OD, which led to the suspicion of glaucomatous optic atrophy. The fact that the patient had never noticed vision loss until OS was occluded suggested chronic evolution and glaucoma seemed consistent with a chronic vision loss course, although the patient was at a very young age for such an outcome. In LHON, optic atrophy universally develops within 6 months and non glaucomatous cupping may also occur,^{5,6} which can mislead to the assumption of glaucomatous optic atrophy.

In the acute/subacute stages some LHON patients may show circumpapillary telangiectatic microangiopathy and optic disc pseudoedema.^{4,5,6} However, 20% of LHON cases never exhibit this characteristic optic disc appearance,⁴ even if examined at the time of acute visual loss⁶, which was the case with this patient. Detectable changes on OCT may

progress over a period of months, with optic nerve atrophy eventually settling.⁶ In the presented case, when vision loss was reported in OS, colour vision testing was consistent with dyschromatopsia but electrophysiological results were repeatedly compromised and no structural changes in the optic nerve were detected on fundoscopy or SD-OCT. This fact, along with evidence of disruptive behaviour by an extremely anxious patient, raised the suspicion of non-organic visual loss. Interestingly the visual field defect seen in OS (a superior altitudinal defect) was not the most typical of LHON, since centrocecal scotomas are more common.⁴ However, the altitudinal defect involved the paracentral area which we believe, in an uncooperative patient, can result in a very poor visual acuity determination.

Cases of LHON, misdiagnosed as non-organic visual loss, have been previously described, highlighting the fact that LHON should be considered in all cases of unexplained optic neuropathy, including cases with normal funduscopy appearance.⁷ In the context of unexplained vision loss, one must keep in mind that non organic vision loss should always be a diagnosis of exclusion and all efforts must be undertaken in order to investigate visual loss, even if repeating tests is necessary. Unfortunately SD-OCT analysis of retinal ganglion cells was not available at that time. Given the fact that LHON selectively affects retinal ganglion cells, this exam could have been extremely helpful in the early detection of the disease, when nerve fiber layer does not reveal a decrease yet.³

Concomitant LHON and glaucoma have been rarely described before, namely in cases of open-angle glaucoma and normal tension glaucoma.^{8,9} It has been hypothesized that the two diseases may have a cumulative effect on oxidative stress and retinal ganglion cell death with the consequent rapid progression of visual impairment.⁸ However, larger



epidemiologic studies have found rare or absent LHON-associated mitochondrial DNA mutations in patients with open-angle glaucoma and normal tension glaucoma, concluding that whether mitochondrial DNA mutations are risk factors for glaucoma is still open to question.^{9,10}

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CONTACTO

Rita Couceiro MD

Avenida Professor Egas Moniz, Hospital Santa Maria -
Secretariado do Serviço de Oftalmologia

1649-035 Lisboa, Portugal

Tel: +351 913988901

Fax: +351 217 805 653

Email: anaritacouceiro@gmail.com

