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LETTER TO THE EDITOR

Recurrent optic neuropathy: a case of Harding's disease?

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Dear Editor-in-Chief,

Leber's optic neuropathy (LHON) is a maternally inherited mitochondrial disease. It typically affects young men and is characterized by painless progressive and irreversible vision loss that does not respond to corticosteroids. Patients with LHON who display clinical and/or radiological findings suggestive of multiple sclerosis exhibit a rare phenotype of the disease known as Harding's disease. We present the case of a patient with LHON displaying recurrent painful and partially steroid-responsive episodes of vision loss initially misdiagnosed as an idiopathic optic neuritis.

A 49-year-old woman presented in 2019 to the emergency department with a 4-day history of left vision loss with painful eye movements. She had no relevant past medical history and denied a family history of any neurological, ophthalmological, or immunological diseases. On ophthalmological examination, she had a left visual acuity(VA) of 2/10 without relative afferent pupillary defect and an altitudinal scotoma on the left inferior nasal quadrant (Fig. 1A), without other focal neurological deficits.

Admitted to the neurology ward, an MRI was conducted revealing a gadolinium-enhanced lesion in the anterior third of the left optic nerve (Fig. 2A) and few hyperintense and non-contrast-enhanced punctiform corticosubcortical foci on T2 and T2 FLAIR sequences bilaterally (Fig. 2B–C). No lesions were identified on the spinal cord MRI.

Cerebrospinal fluid (CSF) was unremarkable with a white blood cell count of 4.0 cells/μL, glucose of 87 mg/dl, and total protein of 42 mg/dl with negative gram stain, bacterial and mycobacterial CSF cultures. No oligoclonal bands were detected. Both serum and CSF myelin oligodendrocyte glycoprotein (MOG) and aquaporin-4 (NMO-IgG) antibodies were negative. CSF and blood antineuronal and onconeural antibodies were undetectable (including anti-CV2). A full workup excluded metabolic and infectious causes of optic neuropathy.

The patient received a 5-day IV course of 1000 mg methylprednisolone, with complete resolution of periocular pain and partial recovery of visual acuity (from 2/10 to 8/10). An idiopathic inflammatory neuritis was admitted, and the patient was discharged and referred to the neurology outpatient clinic for follow-up.

Four months later, she was readmitted to the neurology ward due to acute left-eye vision loss without periocular pain. After treatment with a 5-day IV course of methylprednisolone followed by 6 cycles of plasmapheresis, no major improvement in visual acuity was noted, with a VA of 2/10 at medical discharge. This time, a brain MRI did not display optic nerve lesions or new parenchymal hyperintensities on T2 FLAIR sequences. Flash visual evoked potentials showed a prolonged and electric voltage decreased P-wave on the left eye. No CSF oligoclonal bands were identified and both serum and CSF MOG and NMO-IgG antibodies remained undetectable.

One year later (March 2021), the patient returned to the hospital with acute right vision loss with pain on eye movements. A fundoscopic examination showed right macular edema and atrophy of the left optic nerve, congruent to the decreased left eye peripapillary retinal nerve fiber layer thickness detected on the OCT and to the low left optic disc fluorescence on angiography. On perimetrical revaluation, a global loss of visual acuity on the left and a right nasal superior quadrantanopsia (Fig. 1B) were identified. Laboratory and neuroimaging studies did not reveal new findings.

A 5-day IV course of 1000 mg plus an additional 4-day course of 2000 mg of methylprednisolone solved the ocular pain but did not result in recovery of right eye VA (2/10 left and 8/10 right VA). The patient received one cycle of rituximab 1 g and was discharged to the outpatient clinic. Since no clinical improvement was noted, a genetic test was ordered, confirming the diagnosis of LHON after identification of the mitochondrial mutation 11778G > A. Rituximab treatment was interrupted, and the patient was started on idebenone.

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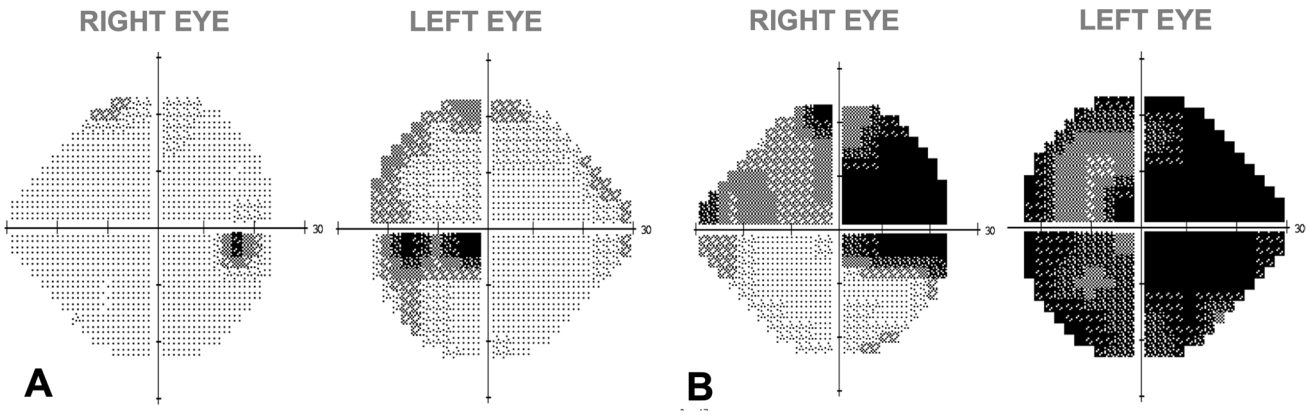

Fig. 1 Visual field test. **A** Exam conducted in 2019 (first episode of acute loss of visual acuity). **B** Exam conducted in August 2021 (third episode of acute loss of visual acuity)

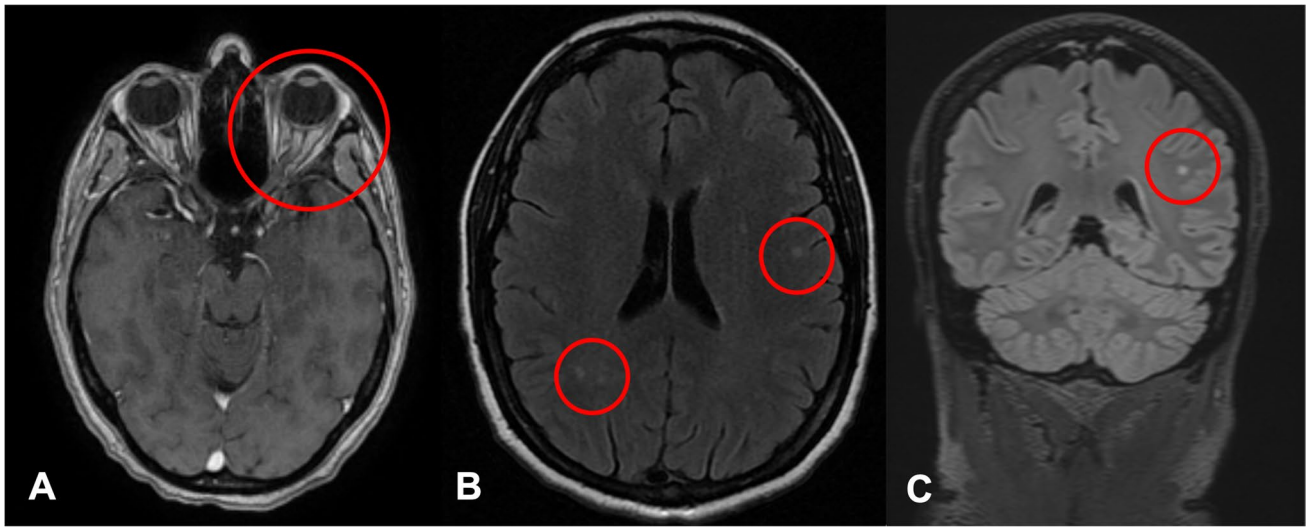

Fig. 2 First brain MRI (acquired in 2019). **A**. T1 post-gadolinium, axial view: gadolinium-enhanced lesion in the anterior third of the left optic nerve (red circle). **B** T2 FLAIR, axial view. **C** T2 FLAIR, coronal view. Corticosubcortical punctiform lesions, hyperintense in T2-FLAIR, affecting the corona radiata, centrum semiovale, and periventricular white matter bilaterally (red circles)

On follow-up, the patient revealed she had 2 maternal cousins and a young nephew with progressive vision loss she failed to remember when previously admitted to the hospital.

Leber hereditary optic neuropathy is a maternally inherited cause of acute or sub-acute bilateral optic neuropathy characterized by the preferential loss of the retinal ganglion cells and subsequent optic nerve degeneration [1]. Affecting 1 in 30–50,000 patients in England and other northern European populations [2], LHON is caused, in 90% of cases, by three mtDNA missense mutations: 3460G > A in the gene ND1, 11778G > A in the gene ND4, and 14484 T > C in the gene ND6 [3]. These genes encode complex 1 of the respiratory chain, causing profound impairment of ATP synthesis when mutated [4].

The majority of LHON patients are male (4:1), with initial symptoms appearing with an average age of onset of 30 years old (despite reports of LHON diagnosis from 8 to 60 years old). The visual disturbance typically begins with a painless blurring of vision and progresses to severe visual loss with a central scotoma on perimetry testing [5]. Bilateral vision involvement is almost universal, with a time interval of less than 6 months before the contralateral eye becomes affected. Unlike multiple sclerosis-related optic neuritis (ON), unilateral optic nerve involvement is rare in LHON and the visual prognosis is poor with the majority of patients becoming legally blind [2]. The mtDNA mutation 11778G > A is the most prevalent and is associated with the worst visual outcome [4].

The coexistence of LHON with multiple sclerosis (LHON-MS) was first suggested in 1964, but the first 11 consistent cases of this overlap phenotype were only described in the

1990s by Professor Anita Harding, with this disease becoming known as Harding's disease [4]. In 2013, Pfeffer et al. performed a cohort study and a meta-analysis of published cases, identifying 12 patients with dual LHON and MS diagnosis in the UK and 44 additional cases from the published literature [2]. According to this study, LHON-MS patients share a common phenotype: they are mostly women (2.1:1), with relapsing–remitting forms of MS (70%) and with the mtDNA 11778G >A mutation. Despite also presenting a poor visual prognosis (contrasting to the 85–95% recovery of visual acuity in MS-related optic neuritis), most patients have atypical features for LHON, such as ocular pain at presentation (48%), an average time interval between bilateral eye involvement of 1.66 years, more than 2 episodes of acute/subacute vision loss (25%) [2] and some patients seem to initially improve with corticosteroid therapy [4].

Regarding imaging findings in MS-LHON patients, patients may present typical MS lesions but some reports have also suggested the presence of atypical lesions, differing in size and shape, with indistinct margins, reduced brightness on T2 sequences, and invisible on post-contrast T1 sequences [4]. MRI of the optic pathways in LHON may also present longitudinally extensive involvement of the affected optic nerves [6].

As LHON is a rare cause of ON in women and since our patient denied relevant family history at first, we initially interpreted her symptoms has an inflammatory optic neuritis, possibly a first presentation of multiple sclerosis. However, as episodes of vision loss became recurrent, affecting both eyes sequentially, with poor long-term response to immunosuppressive therapy and culminating in poor visual outcomes, multiple sclerosis was considered less likely. Supported by the absence of CSF oligoclonal bands and inexistent periventricular white matter lesions, alternative diagnoses were considered, ordering LHON's genetic test. Despite not fulfilling MS diagnostic criteria, a diagnosis of Harding's disease was assumed since the patient presented a mtDNA 11778G > A mutation with two episodes of vision loss suggestive of inflammatory neuropathies (with painful eye movements, partial response to steroids and gadolinium-enhanced lesion of the optic nerve in the first episode).

As far as treatment, we opted to introduce Idebenone 900 mg/daily as it has demonstrated benefits in the patient's visual acuity and PEV outcomes [7]. As our patient failed to fulfill McDonalds' diagnostic criteria for multiple sclerosis, we opted not to start a MS disease-modifying drug. We have also stressed the importance of avoiding alcohol and smoking as these toxic substances are known to represent independent risk factors for visual loss in LHON [5].

As pathological studies have identified active and inactive white matter and optic nerve demyelinating plaques in LHON, some authors have argued that mtDNA mutations and mitochondrial dysfunction might play a role in emerging immunologic mechanisms in MS, opening doors for future discussion regarding medicating LHON-MS patients with MS disease-modifying drugs [4]. In anecdotical evidence, Mitoxantrone has been associated with visual recovery in one patient with LHON and confirmed MS, but its use is hardly justifiable due to its adverse event profile [4]. Therefore, treatment options for LHON-MS patients should still be decided on a case-by-case premise.

Author contribution Miguel Miranda: conceived and designed the analysis; collected the data; and wrote the paper. Maria Margarida Andrade, Maria Inês Sanches, Sandra Castro Sousa, and Cátia Carmona: reviewed the paper. All authors discussed the results and contributed to the final manuscript.

Data availability Not applicable.

Declarations

Ethical approval This article presents a clinical case. Informed consent was obtained directly from the patient. This article is in accordance with the ethical standards of the institutional research committee and with the Helsinki declaration and its 2013 amendments.

Competing interests The authors declare no competing interests.

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