

Leber's Disease or Multiple Sclerosis: When Diagnosis is not the Real Challenge

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ABSTRACT

We present the case of a 19-year-old Moroccan patient with bilateral severe optic neuropathy resistant to conventional immunomodulatory and immunosuppressive treatments. Brain MRI revealed typical multiple sclerosis (MS) lesions. Lumbar puncture revealed unmatched Oligoclonal Bands (OCB). Given red flags against a typical MS and the bilateral, sequential, and severe visual loss with no improvement of his optic neuritis, investigation for Leber's Hereditary Optic Neuropathy (LHON) was conducted and confirmed the diagnosis genetically. This case highlights the intriguing association of Leber's disease with demyelinating lesions, raising questions about a potential common pathophysiology, and discussing the added value of a maintaining treatment of MS.

Keywords

LHON (Leber's hereditary optic neuropathy), Cerebral MRI, Optic neuritis, Oligoclonal bands, Multiple sclerosis.

Introduction

LHON is a rare inherited optic neuropathy caused by mitochondrial DNA mutations, characterized by subacute, painless visual loss leading to blindness [1,2]. Traditionally considered solely an ophthalmologic condition, recent observations suggest a 25% association with central nervous system demyelinating disorders [3]. We present a case of a 19-year-old male patient with sequential optic neuritis, poor recovery, and typical MS demyelinating lesions in the cerebral MRI. Extensive optic nerve involvement and inadequate response to intravenous immunoglobulins and anti-CD20 treatment raised the hypothesis of other etiologies especially the Leber's disease, which was later confirmed by genetic testing.

Case Presentation

A 19-year-old male, otherwise healthy, with congenital strabismus and non-consanguineous parents, reported painless progressive visual loss in the left eye a month before hospitalization. Ophthalmological examination revealed bilateral vision impairment (visual acuity at 1/10 left eye, 3/10 right eye). Optical coherence tomography (OCT) confirmed bilateral optic fiber loss, with bilateral optic disc pallor. Brain and spinal MRI showed typical MS demyelinating lesions. The radiological red flags were the absence of lesions in the subtentorial area, and extensive T2 and FLAIR hyperintensities in the left optic nerve. None showed gadolinium enhancement. CSF study revealed unmatched oligoclonal bands. CBA technique was used to rule out anti-AQP4 and anti-MOG antibodies. Other possible etiologies (infectious, auto-immune, toxic and metabolic) were also ruled out. The patient initially experienced improvement in symptoms after receiving high-dose intravenous methylprednisolone. However, three months later,

there was a reported deterioration in vision in both the left and right eyes. The patient received then additional methylprednisolone and intravenous immunoglobulins. Despite the absence of all criteria for MS an anti-CD20 treatment was conducted (3 doses were administered). Poor recovery, progressive vision deterioration, the absence of complete diagnosis criteria for MS prompted LHON investigation, which was confirmed by genetic testing. The patient has a T14484C mutation. Idebenone was prescribed to improve visual prognosis. Given the absence of improvement and no new clinical signs, the lack of new T2 or FLAIR lesions, as well as the absence of contrast-enhancing MRI lesions over a two-year follow-up, the decision was made to cease anti- CD20 therapy and continue symptomatic treatment with Idebenone.

Discussion

LHON represents a mitochondrial disorder characterized by severe bilateral optic neuropathy. The condition arises due to point mutations in mitochondrial DNA, with the most prevalent mutations occurring at nucleotide positions (np) 3460 in the ND1 gene, np 11778 in the ND4 gene, or np 14484 in the ND6 gene. Notably, some LHON patients manifest a clinical and radiological syndrome suggestive of multiple sclerosis (MS) [4]. The hallmark features of LHON include a severe, painless, subacute bilateral

decline in visual acuity [1,4,5], differing from optic neuritis in MS, which is mostly acute or subacute, unilateral, painful, less severe, and typically associated with favorable recovery [5]. From an MRI perspective, both LHON and MS may exhibit T2 hyperintensity of the optic nerve. However, in MS, T1 enhancement after Gadolinium injection is often observed [5]. Distinguishing between these entities on MRI can be challenging, though a study involving two LHON cases demonstrated some differences, such as less hyperintense lesions in T2 FLAIR and the absence of T1 hypointensity [4].

It's important to highlight that other researchers have reported cases of multiple sclerosis (MS) with positive oligoclonal bands associated to Leber's hereditary optic neuropathy (LHON) [6,7]. Our treatment approach aligns with suggested protocols for such situations, involving the administration of intravenous corticosteroids, intravenous immunoglobulins (IV Ig), and the potential initiation of MS immunosuppressive therapy, if deemed appropriate. This approach is particularly relevant in cases associated with "Leber-plus" cases, displaying signs of Leber's disease and MS [2,6] and is complemented by LHON-specific treatment (Idebenone).

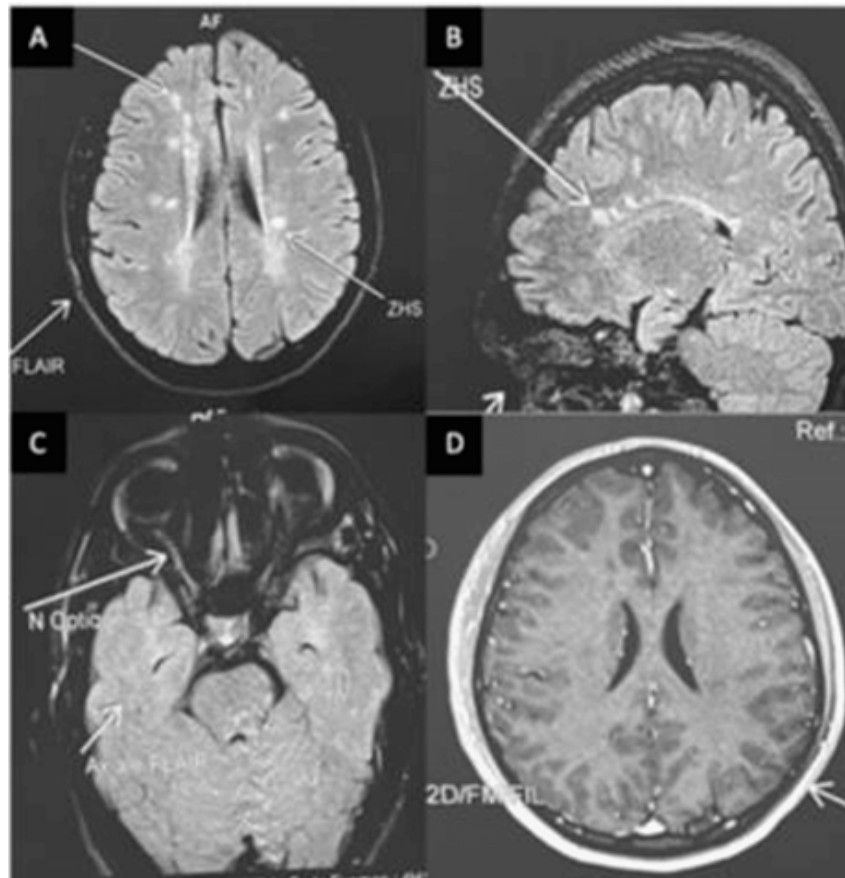


Figure 1: Brain MRI.

A: axial FLAIR weighted Brain MRI image showing multiple hyperintensities perpendicular to the ventricles, some of them are juxtacortical. B) Sagittal T2 FLAIR brain MRI showing hyperintense T2 lesions perpendicular to the ventricular axis. C) Axial T2 FLAIR MRI revealing extensive optic nerve lesion. D: axial T1-Gado brain MRI image displaying no enhancement of the existing lesions.

While there is currently no recommendation supporting routine screening for LHON mutations in all patients presenting with imaging and biomarkers consistent with MS, this case underscores the importance of considering LHON in high-risk individuals and once red flags are noticed. These individuals may include those with severe or bilateral visual loss or a suggestive family history [6]. Optic pathway MRI in LHON may reveal longitudinally extended optic neuritis involving the middle to posterior segments of the nerve (Figure 1).

The actual dilemma in this case revolves around deciding whether to maintain the anti-CD20 treatment. Considering the patient is a young, active, and bright student who is eager to explore any opportunity to enhance his vision, this decision becomes particularly challenging. Despite our patient displaying MS-like periventricular demyelinating lesions, they did not meet the MacDonalds Diagnostic criteria, as the dissemination in space was not evident. Furthermore, the patient's lesions never enhanced with gadolinium. Although, the presence of unmatched oligoclonal bands in the cerebrospinal fluid examination indicates an elevated risk of developing MS in the future. Therefore, vigilant monitoring of clinical and radiological features is crucial to promptly diagnose and potentially treat a confirmed associated MS. This approach aligns with recommendations from various authors who have studied this patient population [1-3,6,7]. And that's what we opted for with our patient: a "wait and see" approach.

Conclusion

LHON may co-occur with multiple sclerosis. It's essential to recognize this possibility in MS patients experiencing unusual,

bilateral, sequential, extensive, painless vision loss with limited recovery. This increased awareness is crucial, especially as new LHON treatments, such as gene therapy, are being tested in clinical trials. Considering disease-modifying therapy for MS is advisable if there are enough criteria, with the goal of mitigating any potential additional disability linked to MS.

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