Harding's Syndrome – Clinical Case Report and Literature Review

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ABSTRACT

Introduction: Leber's hereditary optic neuropathy (LHON) is a maternally inherited disease that manifests as painless bilateral visual loss, usually in early adulthood. Patients with LHON associated with Multiple Sclerosis were mostly female and the association of both pathologies is termed as "Harding's disease".

Case report: A 21-year-old woman presented with a typical episode of optic neuritis (ON) in the right eye, which led to Multiple Sclerosis (MS) diagnosis after imagiological and analytical investigation. The episodes of ON were repeated, with progressive severe visual impairment and the lack of recovery with the treatment for acute attacks, which warned the possibility of LHON. The diagnose was supported by genetic tests by detecting a mutation of the mtDNA 11778 base pair. The patient started oral Idebenone 900mg/day and remained stable for 12 months, with progressive RE visual recovery. Genetic tests for her mother were also applied and the same mutation was identified, although she always remained without visual symptoms.

Discussion: Due to the presentation and optic disc findings, LHON is frequently misdiagnosed as ON in the context of MS. However, continuous vision loss in patients with MS during the treatment should raise suspicion for an alternative diagnosis.

Conclusions: LHON associated with MS is suggested to be a distinct entity with challenging diagnose and more severe involvement of optic nerve. Our case highlights the importance of genetic tests in individuals who present recurrent ON, with reduced visual recovery during the treatment, even if there is a positive study for MS and no identified family history for LHON.

Keywords: Leber's Hereditary Optic Neuropathy, Multiple Sclerosis, Harding's disease, Neuroinflammation, Neurodegeneration

INTRODUCTION

Leber's Hereditary Optic Neuropathy (LHON) is a maternally inherited rare disease characterized by acute or subacute painless bilateral visual loss, usually in young adults.[1]

The disorder results from point mutations in mitochondrial DNA (mtDNA) and subsequent mitochondrial dysfunction. Because of their susceptibility, retinal ganglion cells are preferentially affected, causing optic nerve degeneration.[2]

Although LHON usually presents with isolated vision loss, some patients suffer from another concomitant associated neurological disease, like Multiple Sclerosis (MS), Movement Disorders, Deformities of the vertebral column or Epilepsy.[1,2,3] The coexistence of LHON with MS disease (LHON-MS) is rare and also known as Harding's syndrome. It was first described in 1964,[4] with only 56 cases reported until now.[5] The observation of both diseases simultaneously suggests a potential role for the interaction between the mitochondrial dysfunction characteristic of LHON and the typical immunologic mechanism of MS.[2-6,7] The majority of LHON patients carry one of three mtDNA point mutations: m.11778 G.A, m.3460 G.A, or m.14484T.C.

Although isolated LHON primarily affects men, patients with the co-occurrence of LHON-MS were more commonly females.[2] It is known that those patients usually present atypical symptoms of LHON, like a longer duration between vision loss in the first and second eye, a persisting unilateral vision loss, or more than two visual events.[1,2] Treatment options of LHON are very limited and visual prognosis is generally poor.[8,9]

This case report describes a MS-like disorder in a female patient with LHON who is being successfully managed with Idebenone. We present the diagnostic challenges and review the literature regarding the treatment options on LHON.

CASE REPORT

A 21-year-old woman presented sudden visual loss in the RE and retro-ocular pain in the emergency department. Her best corrected visual acuity (BCVA) was 20/200 in the RE and 20/20 in the left eye (LE), with 3+ right relative afferent pupillary defect (RAPD). Ishihara plates were 3/17 RE and 14/17 LE. Biomicroscopy and fundoscopy were all normal, as well as the Optical Coherence Tomography (OCT), without asymmetry between the eyes. Before, she was healthy and denied any recent illness or neurologic symptoms. Regarding the familial history, her mother has relapsing-remitting MS without any episodes of ON. She was admitted to the neurology department and was treated with five days of intravenous methylprednisolone pulse (1000 mg/day), with complete recovery of visual acuity to 20/20 in the RE. Cerebrospinal fluid analysis contained five oligoclonal IgG bands without corresponding in serum. Magnetic Resonance Imaging (MRI) of the brain and spinal cord showed a slight hyperintense right optic nerve on T2 and FLAIR, multiple supratentorial T2 lesions and one contrast-enhancing infratentorial lesion. MS was diagnosed, and she was started on glatiramer acetate 40 mg/day subcutaneously three times weekly. Five months later, she had a new episode of painless RE visual loss. BCVA was 20/25 in the RE and 20/20 in LE, with 1+ RAPD in the RE. Color vision, fundoscopy and optic nerve OCT still normal. Goldmann Perimetry (GP) revealed blind spot enlargement in both eyes, with exclusion in the RE. She was hospitalized and brain MRI revealed new supratentorial T2 and T1 hypointense lesions. The virologic study was negative. The neurologist considered switching to Natalizumab 300 mg IV over 1 hour once every 4 weeks with an associated three days pulse of intravenous methylprednisolone (1000 mg/day). Despite the treatment, over the subsequent three months, vision in the RE deteriorated to 20/400 and color vision was worsened (1/17). Fundoscopy revealed temporal pallor of optic nerve and OCT showed temporal thinning of the Retinal Nerve Fiber Layer (RNFL). Due to this atypical evolution, LHON was suspected and a genetic test was performed. We found a mtDNA 11778 base pair mutation and the patient started treatment with oral Idebenone 900mg/day. She remained stable for 12 months, with progressive RE visual recovery to 20/25 on her last visit. Color vision improved to 15/17 on Ishihara plates, and OCT showed continuous thinning of the RNFL. The evolution of OCT and GP are shown both in figure 1 and 2, respectively. At this stage, OCT-A was also performed and revealed a decrease in vessel density in the affected eye when compared with the fellow eye. We opted to investigate genetic LHON mtDNA mutations in her mother, and the same mutation was found, which supports the diagnose of Harding's syndrome also in her mother, although she remained without visual symptoms.

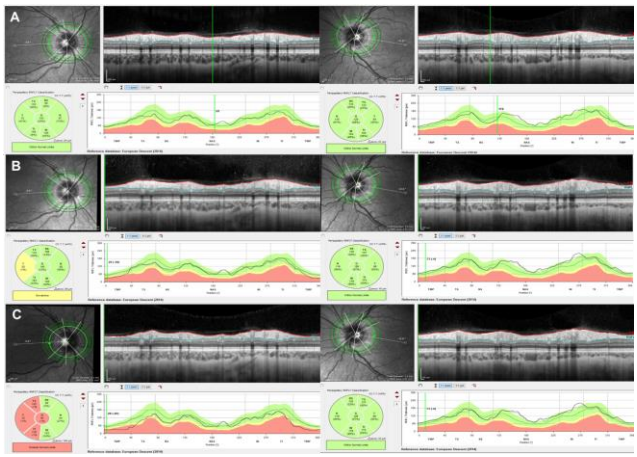

Figure 1 – Evolution of Optic Nerve OCT during the time (A – Initial presentation; B – 6 months later; C – 12 months later). We can see a progressive decrease in RNFL in all temporal sectors in the RE.

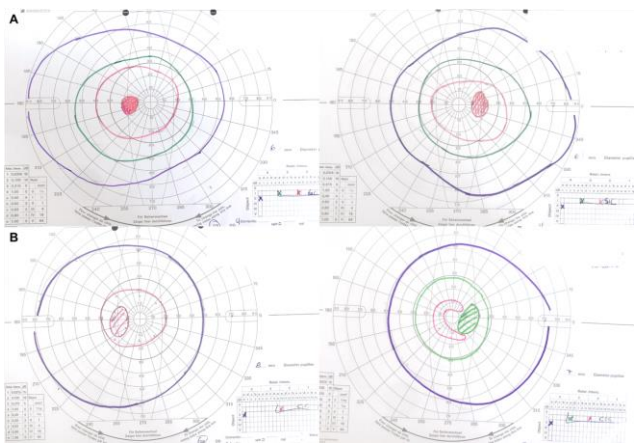

Figure 2 - Evolution of Goldmann perimetry (A – initial presentation; B - 6 months later). At the beginning (A), we can see an enlargement of blind spot in the right eye, and six months later (B), we can see an enlargement and exclusion of blind spot in the RE and enlargement of blind spot in the LE.

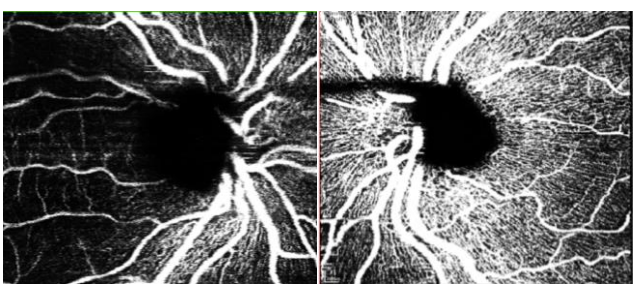

Figure 3 - OCT-A performed 12 months after initial presentation, showing a decreased in vessel density in RE, when compared with the fellow eye.

DISCUSSION

A relationship between ON and MS has been recognized for many years. Due to the time of onset, age at presentation, optic disc findings, MRI lesions and cerebrospinal fluid characteristics, our case-report was initially diagnosed as recurrent ON in the context of MS. As LHON is rarely considered cause of ON in women and ON episodes could occur in 30% of all studied patients within five years,[10,11] we initially interpreted the subsequent relapses in the context of MS, delaying the genetic research and camouflaging the LHON diagnostic. However, it was noted that the recurrences were atypical in its frequency and characteristics and always associated with poor treatment response, which can lead us to suspect another underlying cause. As a result, further investigation was made and the diagnostic of LHON was unmasked.

In LHON, the 11778 mutation is clearly associated with the disease in many families, but its presence does not appear to be the main determinant of the phenotype. In these patients, particularly females, this process may involve other myelinated axons in the central nervous system, producing a disorder indistinguishable from MS, although the underlying mechanism is still unclear. It is known that some individuals with a high proportion of mutant mtDNA remain unaffected, making the genetic test in family members controversial. Despite the diagnostic benefit, there are significant implications for genetic counseling, both because it causes anxiety about the disease and because there is no specific treatment recommended for asymptomatic individuals. Despite the controversies, after explaining the advantages and disadvantages to the patient and her family, we opted to make a genetic test on her mother to understand the family profile.

Although there is no proven therapy for LHON, since 2015, the European Medicine Agency has approved Idebedone in exceptional circumstances.[12] The Idebenone is short-chain ubiquinone analog that can overcomes respiratory chain deficiency in patients with LHON by transferring electrons directly, restoring cellular energy (Adenosine Triphosphate - ATP) production and re-activating inactive, but viable, retinal ganglion cells. In that way, it protects mitochondria from oxidative damage, prevents further vision loss and promotes vision recovery.[13] It was initially successful in 1992 with a 10-year-old boy who had the 11778 mutation.[14] Subsequently,

in a retrospective study of 103 LHON[15] patients and in another randomized, double-blind, placebo-controlled trial of 39 LHON patients, those treated with idebenone were found to recover vision more than the control cohort. The improvement was more prominent with early initiation and longer duration of treatment. Recently, a retrospective case-controlled study about the effects of Idebenone (900 mg/daily) on 30 patients with LHON due to m.3460 G > A, m.11778 G > A and m.14484 T > C mutations, provided evidence that Idebenone may be beneficial and improve visual acuity and the amplitude of the visual evoked potential.[16]

Other treatments have also been tried. Several combinations of vitamins, such as B2, B3, B12, C, E, and folic acid, and other supplements such as alpha-lipoic acid, carnitine, creatine, L-arginine and dichloroacetate have been experimented, despite little proof of efficacy.[17] More recent approaches, including gene therapy have shown therapeutic potential, although this remains technically difficult and further studies are required to evaluate the adverse effects and ideal duration of the treatment.[17,18] Final results of RESCUE and REVERSE, a Phase III, randomized, double-masked, sham-controlled trials in LHON subjects with G11778A mutation, showed clinical improvements of visual functions, with a single unilateral intravitreal injection of rAAV2/2-*ND*, rAAV2/2-*ND4*, a gene therapy enabling allotopic expression and delivery of the wildtype ND4 protein to mitochondria of retinal ganglion cells.[19]

Until gene therapy become available, as over the years, some studies demonstrated the safety and effectiveness of Idebenone in LHON patients, in line with the literature, we opted to introduce the medication 900mg daily, which contributed to the excellent visual improvement.

CONCLUSIONS

Our case highlights the importance of mtDNA analysis in individuals who present recurrent ON, with poor visual recovery during the treatment, even if there is a positive study for MS and no identified family history for LHON. Although discoveries are continuously being made regarding the treatment options for LHON, many questions remain to be answered before a curative treatment becomes first-line therapy. At this point, however, despite promising research, clinical treatment for LHON remains supportive rather than curative. Idebenone appeared effective in improving visual acuity and quality, although further research is needed to determine the optimal dose and treatment duration.

LHON-MS is a distinct entity with a challenging diagnose, because it could be delayed due to a misinterpretation of the findings in the context of MS. We have to be aware of atypical signs, which could be the missing clue for the correct management of the disease.

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