Leber´s hereditary optic neuropathy: vision recovery due to spontaneous remission or Idebenone treatment outcome? - a case report

Neuropatia óptica hereditária da Leber: recuperação da visão devido a remissão espontânea ou resultado do tratamento com Idebenone? - um relato de caso

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ABSTRACT
Leber’s Hereditary Optic Neuropathy (LHON) is a neurodegenerative disease that commonly affects young male leading to acute central visual loss – bilaterally in most cases. The patients carry DNA mutations that sometimes can express Leber’s disease symptoms. Diagnosis is based on complementary exams but mostly expensive genetic studies. Treatment is still an ongoing process. The case of the young male patient reported here has the objective to highlight that in most countries, such as Brazil, public policies are needed to enable genetic medical diagnosis and treatment.

Keywords: optic neuropathy, Leber’s neuropathy, acute visual loss, genetic visual loss, idebenone.

RESUMO
A Neuropatia Óptica Hereditária da Leber (LHON) é uma doença neurodegenerativa que comumente afeta jovens do sexo masculino levando a uma perda visual central aguda - bilateralmente na maioria dos casos. Os pacientes carregam mutações de DNA que às vezes podem expressar os sintomas da doença de Leber. O diagnóstico é baseado em exames complementares, mas, na maioria das vezes, caros estudos genéticos. O tratamento ainda é um processo em andamento. O caso do jovem paciente masculino aqui relatado tem o objetivo de destacar que na maioria dos países, como o Brasil, são necessárias políticas públicas para possibilitar o diagnóstico e tratamento médico genético.

Palavras-chave: neuropatia óptica, neuropatia de Leber, perda visual aguda, perda visual genética, idebenone.
1 INTRODUCTION

Leber’s Hereditary Optic Neuropathy (LHON) is a silent neurodegenerative disease that leads to irreversible acute and subacute central vision loss¹. It is a maternally inherited disorder that culminates with optic nerve atrophy².

The genetic disorder was first described by the german ophtalmologist Theodor Leber.² Later, genetical trials have shown that the mitochondrial DNA abnormalities can affect diferent sites, most commonly m.3460G>A MT-ND1, m.11778G>A MTND4, and m.14484T>C MT-ND6.³

LHON is one of the most common mitochondrial DNA mutation diseases.² It mainly affects young male, specially from de ages 15 to 35.³ Its simptoms usually affects both eyes simultaneously or sequentialy in a few months period and the prognosis is very poor.²

2 CASE REPORT

HSM, 16 years old, had his first appointment at Maria Pedrossian University Hospital Ophtalmology Department on March, 2020. He explained he had had low visual acuity on the right eye for over one year. It had been an acute episode of vision loss, and did not get better or worse for over one year. The left eye had poor eyesight due to ambliopia.

At the examination, best corrected visual acuity on de right eye was 20/200 and 20/400 on the left eye (ambliopic eye). Biomicroscopy had no alterations at all. Intraocular pressure showed 12mmHg at aplanation Goldman tonometric in both eyes. Fundoscopy showed papilary palor and no other alterations.

Optic Coherence Tomography (OCT) showed structural alterations on retinal nerve fiber layer on both eyes (figure 1). Retinography showed papilary palor on both eyes – retinal alterations were not found (figure 2). Computerized Visual Field showed paracentral visual alterations on both eyes, although the examination on the left eye was considered not trustable due to ambliopia (figure 3).
Due to the epidemiological characteristics and the examination results, the strongest diagnostic hypothesis was Leber’s Disease. Financial difficulties disabled the conduction of
genetic studies. Idebenone treatment was initiated on the dosage of 750mg a day. After one year treatment, the patient returned with eyesight improvement on the right eye. The ophthalmologic evaluation showed best corrected visual acuity of 20/50p on the right eye and 20/400 on the left eye.

3 DISCUSSION

Leber’s Disease is an hereditary neuropathy that affects the optic nerve, leading to painless acute central vision loss.¹ Young man are the most affected by this disease that leads to incurable simultaneously or sequential eyesight commorbity.²

It’s a maternally inherited disorder due to mutations on mitochondrial DNA.² The three most common mtDNA point mutations are: m.3460G>A MT-ND1 (5–10%), m.11778G>A MTND4 (50–70%), and m.14484T>C MT-ND6 (15–30%). Although these three mutations are responsible for most cases of LHON, there are far more possibilities of point mutations that culminate with phenotypes compatible with Leber’s disease. It is now known that the symptoms severity are related to those mtDNA point mutations.⁴,⁵

Besides the undeniable link to the mtDNA alterations, Leber’s Hereditary Optic Neuropathy has proven to be far more complex as a disease – environmental triggers such as excessive smoking and alcohol consumption may start the disease on mutation carriers.³

Other factors concerns the gender of patients – some studies present data on relation of hormonal differences between male and female. The higher level of estrogen, for example, may be related to less cases of LHON affecting women, though they may be carriers of gene mutations. Estrogen is also related to exert neuroprotective effect on retinal ganglion cells during heightened cellular stress, which may explain more severe symptoms on men compared to women.³

There are few studies on Leber’s Hereditary Optic Neuropathy. Most of them are conducted on different countries. It’s well known that different population present different types of mutation points. It is also known that not only the disease expression as symptoms and prognosis vary regarding on different sites of mtDNA point mutations. Some of them may be related to spontaneous recovery of vision loss.⁵

Nevertheless retinal Ganglion Cells (RGCs), as any neurons, are known for the amount of mitochondria due to the high need of energy. Oxidative phosphorylation happens in the mitochondria and produces Adenosine Triphosphate (ATP). LHON’s mutations affect NADH dehydrogenase (complex I), an enzyme involved in oxidative phosphorylation. Therefore, the electron transport chain is deeply affected, causing decrease of ATP production and excessive
reactive oxidative species production – it ultimately causes energy production failure and cell death. It initiates the symptoms cascade.\textsuperscript{6,7}

Idebenone (Raxone\textsuperscript{®}) is an orphan drug so called synthetic analog of coenzyme Q10. It is an organic antioxidant substance of the quinone family – it is allegedly able to transfer electrons to complex III of the eléctron transport chain creating a deviation path around complex I. It causes the restoration of energy (ATP) production on mithochondria leading to the reactivation of some viable but inactivated ganglionar retinal cells. Vision loss, though, can only be recovered in some patients due to time lapse between the symptoms begginig and treatment.\textsuperscript{8,9}

RHODOS study evaluated 85 LHON patients, ages 14 to 66, with DNA point mutations on the main 3 sites and disease duration of 5 years maximun. The patients initiated treatment with Raxone\textsuperscript{®} 900mg/day or placebo for 6 months. Although p value was not ideal, patients developed some vision improvement. Raxone\textsuperscript{®} was then considered effective, safe and well tolerated.\textsuperscript{8,9}

Following observation RHODOS study showed visual acuity improvement sustained after 131 weeks post drug discontinuation. RHODOS post hoc patient analysis evaluated best corrected vision acuity of patients that improved vision loss on the study.\textsuperscript{8}

Lenadogene nolparvovec intravitreal injection (IVI) is another drug alternative to LHON’s treatment. The REVEAL study was able to determine that the drug is safe and well tolerated. Although the 5 years follow-up study evidenced durable treatment effect, recover of LHON’s related visual loss remain unclear.\textsuperscript{10}

Both Idebenone and Lenadogene nolparvovec are drug agents prescribed to reduce the symptoms of ganglionar cells death due to Leber’s disease. On the other hand, although the challenges of in situ mitochondrial gene therapy, there is progress involving a pathologically responsive mitochondrial gene delivery vector named [triphenylphosphine-terminated poly(sulfur-containing thioketal undecafluorohexylamine histamine) and Ide-terminated poly(sulfur-containing thioketal undecafluorohexylamine histamine)] (TISUH). Allegedly by targeting disabled mitochondria TISUH could release functional genes and allow genetic correction abnormalities such as LHON’s mutations. Mouse models show satisfactory effect of gene therapy but it is still an ongoing work.\textsuperscript{10,11}

Leber Hereditary Optic Neuropathy is an inherited gene disorder that leads to central vision loss. Diagnose relies on symptoms and ophtalmological examinations but most importantly expensive genetic studies. Treatment efficacy depend on time lapse between symptoms begginning and treatment prescription – among other factors. Public policies are
necessary to enable the genetic diagnosis as fast as possible. More studies are necessary to establish which one is the best treatment alternative to each DNA mutation or disease expression. For now, visual improvement related to each treatment remain unknown. In the future, Science advance may establish the exact relation between spontaneous or treatment related vision recovery on Leber’s disease.
REFERENCE


