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Leber Hereditary Optic Neuropathy (LHON): Genetics and Ophthalmology Case Report

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ABSTRACT

It is important to recognize that this clinical case demonstrates that carriers can remain asymptomatic, there may be changes recognizable in the ophthalmological examination. The clinical onset of Leber hereditary optic neuropathy (LHON) usually occurs in young adulthood (ages 18-30) and is divided into subacute (<6 months from onset) and dynamic (6-12 months) stages. It is caused by a mitochondrial mutation that is transmitted from mothers to children. It is the most common inherited mitochondrial disorder, but it is considered a rare disease. It usually causes severe vision loss in both eyes. The classic presentation of LHON is that of a young adult male who develops a severe, painless, acute or subacute unilateral vision loss, followed by a similar vision loss in the fellow eye two to three months later (although rarely the delay can be much longer). In most cases, it starts affecting only one eye and, within a few weeks or months, affects the second eye. It can all be seen with the loss of the pupil's ability to react to light. Complete blindness is rare among patients suffering from this disease.

KEYWORDS: Leber hereditary optic neuropathy, Mutationgenetic advice,Vision loss, Optic nerve,central scotoma

ARTICLE DETAILS

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LEARNING POINTS

• Loss of optic nerve function with gliosis, capillary loss, and axonal tissue loss.

• Sudden (acute) and painless central vision loss that affects both eyes simultaneously or with an interval of weeks or months between one eye and the other. That is, it is bilateral and symmetrical.

• Patients begin by seeing a central scotoma that appears abruptly and usually develops subacutely (over a period of several weeks) until stabilizing.

• Due to damage inside the eye (optic neuritis, papilledema, glaucoma, retinal-choroidal lesions), to the optic nerve or brain (trauma, tumors, demyelinating disorders, hydrocephalus) or congenital (Leber's optic atrophy)

• Gross description on the fundus: Pale white disc.

• Microscopic (histological) description: Loss of optic nerve substance due to degeneration of myelin sheaths and axons. Gliosis inside the nerve

• In some cases, this is accompanied by additional extraocular, typically neurological, symptoms.

• The basis of vision loss is the specific degeneration of the retinal ganglion cells that make up the optic nerve.

• Blindness affects both eyes (bilateral), is sudden, and there may be headache.

METHODOLOGY

A documentary review has been carried out based on data and bibliographies references with reproducible research. Referencing a total of 12 high quality references. The search strategy was based on the key words designated in the clinical case summary. The relationship between optic atrophy and genetics is detailed. We list the databases and search engines that we used when preparing this document: Pubmed, Springer, ScienceDirect, EBSCO, (databases offered by the Pontificia Universidad Javeriana de Cali). The free access program Mendeley was used to manage and organize the information.

INTRODUCTION

Leber hereditary optic neuropathy (LHON) arises from a mutation in the mitochondrial DNA (mtDNA). The latter encodes protein components of the electron transport chain involved in the generation of adenosine triphosphate (1,2).

Mutations in mitochondrial DNA (mtDNA) can cause inability to generate ATP (3,4). This defect particularly affects tissues that require intensive use of ATP, such as skeletal muscle and the central nervous system. It is not known and is not understood why the Leber hereditary optic neuropathy (LHON) defect is limited to the optic nerve and retina (2,3). Other mitochondrial disorders impact skeletal muscle; Mitochondrial encephalopathy with ragged red fibers stands out (3,4).

CASE PRESENTATION

Patient, a 16-year-old man, is admitted with a clinical picture of blurred vision and a gradual exacerbation over the course of 40 days, but does not decide to consult immediately. He is evaluated at the first-level health center in a municipality far from the caucasian After 6 more days, he decided to attend a private consultation at a specialized care center in the city of Cali, Colombia. Where the Ophthalmologist decides to refer to a more complex care center, a fourth level of medical care to evaluate the infectious status and rule out other associated pathologies. In the ophthalmology consultation, he first described that the patient sees a dark spot in the center of the visual field. The dark spot grew over time after 46 days of evolution. He has loss of central vision in the left eye, with a visual acuity test of 20/200 in the left eye and 20/70 in the right eye. The curious thing is the value that is placed in this clinical history. Two of his maternal uncles had vision loss, but his mother did not. The rest of the family had no major visual commitments. No member of the paternal family was affected. Confrontational visual field testing showed a deficit in the left upper quadrant of the left eye, with red dyschromatopsia and an increased cup-to-disc ratio that was double that of the right eye.

Physical examination revealed microangiopathy and retinal vascular tortuosity. An examination was performed in which he found a right eye (OD) IOP of 16 mmHg in tonometry; left eye (LE): 18 mmHg; In the fundus he found almost total optic atrophy in both eyes, but the left predominated with some pigmentation, without further data on the retina. Bilateral optic atrophy was diagnosed, probably Leber's.

He is sent to the emergency room to be evaluated at a genetics care center and to rule out infectious or demyelinating processes. Optokinetic indicator testing was normal bilaterally. Pirrla (equal pupils, round, reactive to light and accommodation). But when he was admitted to a higher level, pediatrics decided to rule out other pathologies, while genetics defined the case.

At the medical board meeting, he developed after being hospitalized for 5 days and seeing how a patient progresses to visual loss. They defined that they had to rule out the possibility of being diagnosed with Leber hereditary optic neuropathy, everything was achieved by considering seeing bilateral optic atrophy, and being a patient under 30 years of age. Another important piece of information is the family history of cases of males with sudden visual loss and when the signs were present, and an uncle had the same report of microangiopathy and vascular tortuosity of the retina, with total blindness.

When having an evaluation by pediatric neurology, who decided to take a computed tomography (CT) of the head, and which was not notable. Then, in consensus with ophthalmology, both specialties decide on a repeated magnetic resonance imaging (MRI) of the brain, seeing no findings of demyelinating lesions in the orbits and spine, ruling out Neuromyelitis Optica Spectrum Disorder.

A lumbar puncture was performed with cerebrospinal fluid (CSF) analysis which showed no oligoclonal bands with a dilution factor of 46, negative immunoglobulin G (IgG) index (indicating no intracerebral IgG production), and negative cytology for etiology. viral or bacterial, HIV and syphilis were ruled out in other tests.

He was initially treated with methyl prednisolone boluses, without a favorable response. He was referred to rheumatology and hematology, where the pertinent examinations and studies were performed, all of which came back normal.

Subsequently, with a delay of 10 days, you have a genetic result; They corroborated the mitochondrial disease through DNA testing, confirming Leber's diagnosis of hereditary optic neuropathy. He did not receive any further treatment, because there was no way to improve his prognosis.

RESULTS

Leber hereditary optic neuropathy (LHON) is inherited via mtDNA mutations; all mtDNA in the body comes exclusively from the egg cell (5,6,8). The sperm does not contribute to the mtDNA. Therefore, Leber hereditary optic neuropathy (LHON) is inherited from his mother (5,6).

Additionally, a typical cell carries 10 to 100 separate mtDNA molecules, only a fraction of which carry the mutation (6,7). This is called heteroplasmy. Heteroplasmy is the presence of different types of mitochondrial DNA in the same cell or

different mitochondrial populations in the same organism (7,8).

Within any affected woman, the concentration of mutant DNA in different ovules can vary from 10 to 90% (7-9). Thus, some offspring may be severely affected, while others may show no signs. Furthermore, even within any given progeny, the numbers of mutant mtDNA vary from tissue to tissue and cell to cell (6,7).

DISCUSSION

Leber's hereditary optic neuropathy (LHON) affects men four to five times more often than women (8,9). This difference is thought to be due to a factor on the Although mtDNA encodes essential components of the electron transport chain, there are copies for nearly all mitochondrial components also encoded in the nuclear genome (7,8).

Differential diagnosis includes optic neuritis, autosomal dominant optic atrophy, Wolfram syndrome, metabolic optic neuropathies (toxic, nutritional and combined), chiasmatic tumors and anterior ischemic optic neuropathy (7-9).

CONCLUSION

It is a rare hereditary optic neuropathy characterized by sudden onset, painless central vision loss, retinal ganglion cell loss, and optic atrophy. LHON is caused by mutations in mitochondrial DNA (mtDNA) (5,6).

More than 90% have been identified to occur at nucleotide positions 3460, 11778 or 14484, corresponding respectively to the mtDNA respiratory chain complex subunit I genes MT-ND1 (6,7), MT-ND4 and MT-ND6 (7.8). Other genetic or epigenetic factors can influence the development of this disease; Furthermore, the NDUFS2 gene (1q23.3) may be associated with a LHON-like phenotype (5-8).

The age of onset is in adolescents and adults. The prevalence of the disease is estimated at 1/27,000 - 1/54,000 in Europe. A lower prevalence is reported in Australia (1 in 113,300) and in Serbia (1/526,000) (9-11). The disease predominantly affects men, who are 4 to 5 times more likely to be affected and lose vision (7-10).

It is important for patients to avoid toxic exposures such as alcohol, smoke (tobacco and environmental), and certain antibiotics that interfere with mitochondrial oxidative phosphorylation. Several compounds have shown positive results in moderating visual loss (8,10).

ETHICAL STATEMENTS:

According to Colombian law, case reports do not need to be approved by the Ethics Committee; However, the work complies with the ethical guidelines of the Helsinki declaration and the Oviedo convention, as well as with the ethical standards of the University (Department of Medical Clinics- Pontificia Universidad Javeriana, Cali - Colombia, Hospital San Juan de DIOS and Imbanaco Clinic of Cali).

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AUTHOR CONTRIBUTIONS

All authors reviewed and approved the final manuscript.

CONSENT

The authors confirm that written consent has been obtained from the patient for the submission and publication of the text associated with this case report in accordance with the COPE guideline.

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