

## The Clinical Presumption of Leber's Hereditary Optic Neuropathy a Case Report

Redouane Messaoudi MD<sup>1\*</sup>, Mohamed Kriet MD<sup>1</sup>, Karim Reda MD<sup>2</sup>, Abdelbarre Oubaz MD<sup>1</sup>

<sup>1</sup>Department of Ophthalmology, Military Hospital Avicenne, Marrakech, Morocco

<sup>2</sup>Department of Ophthalmology, Military Hospital Mohamed V. Rabat, Morocco

DOI: 10.36347/SJMCR.2019.v07i09.014

Received: 18.09.2019 | Accepted: 26.09.2019 | Published: 30.09.2019

\*Corresponding author: Redouane Messaoudi MD

### Abstract

### Case Report

We report a case of a young moroccan male presenting with sequential, painless, bilateral visual loss. Diagnosis of Leber's hereditary optic neuropathy had been retained based on clinical pattern. The course was rapidly marked by the bilateralisation and worsening of the visual function. The management was a real challenge. To our best knowledge it is the first case report of this devastating disease in morocco.

**Key words:** Leber's hereditary optic neuropathy, mitochondrial neuropathies, papillary edema. Optic atrophy.

**Copyright @ 2019:** This is an open-access article distributed under the terms of the Creative Commons Attribution license which permits unrestricted use, distribution, and reproduction in any medium for non-commercial use (NonCommercial, or CC-BY-NC) provided the original author and source are credited.

### INTRODUCTION

Leber's hereditary optic neuropathy (LHON) (OMIM 535000) is a primary mitochondrial DNA (mt DNA) disorder [1], The majority 95% [2] of patients harbour one of three common mt DNA mutations (m.3460G > A in MTND1, m.11778G > A in MTND4 and m.14484T > C in MTND6) that affect complex I subunits of the mitochondrial respiratory chain. Typically presents in young health adult males, it causes a severe visual impairment; the visual prognosis is invariably poor.

### OBSERVATION

We report a case of 28 year-old mediterranean man who had been referred for a rapid vision loss lasting for three weeks in right eye and regaining the left one.

He was a moderate cigarette smoker, no alcohol consumption. There was no relevant medical history in the family. The exam finds a healthy policeman a healthy policeman, the visual acuity was 3/10 OD and 5/10 OS on Snellen scale. All anterior segment structures were normal. The intra-ocular pressure measured by Goldmann applanation was 17 mmHg OD and 16 mmHg OS. There was a clear corneas, no anterior chamber Tyndall, no relative afferent pupillary defect, a clear lenses, the oculomotility was normal in different gazes without restrictions, after dilation the examination uncovered a papillary edema (crowded papilla) with peripapillary telangiectatic microangiopathy and vessels tortuosity Fig 1 (a). The maculae was normal as well as peripheral retina.

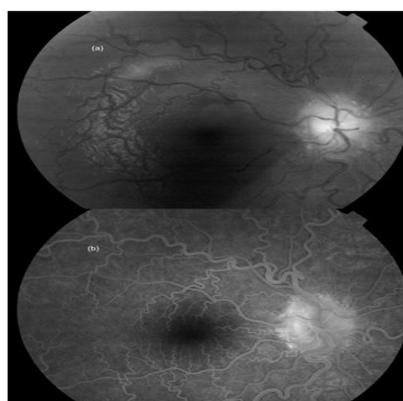
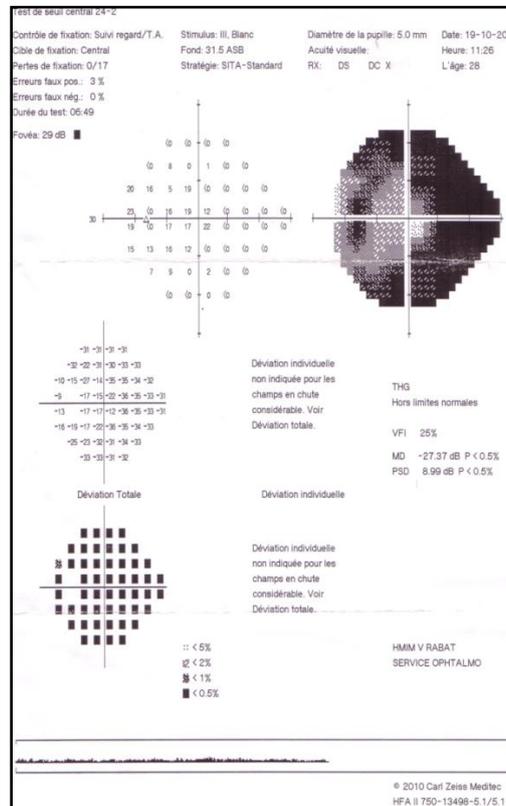


Fig-1: (a) right eye fundus, crowded papillae: optic disc swelling, vascular tortuosity. (b) Right Fundus Fluorescent angiography; shows no optic disc head leakage without haemorrhage nor exudates

The color vision was perturbed on Ishihara plates and on the panel D-15 tests with red-green dyschromatopsy, the visual evoked potentials exam noted a latency delay. Humphry field analysis revealed

a central scotoma Fig 2. Fluorescein angiography findings found dilated capillary vessels at the temporal margin of the optic disc, but no staining or leakage in the late phase Fig 1(b).



**Fig-2: Right visual field shows a central scotoma**

Three weeks after, the visual acuity worsened to hand motion OD and 1/10 OS. Unfortunately the genetics exam wasn't available. The MRI hadn't found any abnormality as well as the electrocardiographic

trace. The patient has been advised to improve his hygiene of life with stop of smoking and avoid toxic ones. Monthly IM vitamine B12 was administered.

**Table-1**

Differential diagnosis	Exemples
Tumors	Meningioma, optic nerve glioma, craniopharyngioma
Infiltrative diseases	Lymphoma, Leukaemia
Traumatic	
Toxins	Chloramphenicol, isoniazid, amiodarone, ergot,...
Nutritional deficiency	Folic acid, vitamins B1, B2, B6, B12
Infections	Toxoplasmosis
Inflammatory	Multiple sclerosis, Neuromyelitis optica
Ischaemic	Thromboembolism,
Genetic	LHON, Wolfram syndrom..

**DISCUSSION**

The prevalence of LHON has been estimated at about 1 in 35.000 of the population with a much higher prevalence in men at about 1 in 14.000. It is, therefore, a relatively rare disorder [3]. The only environmental factor shown to trigger vision loss in LHON is cigarette smoking, which significantly decreases mtDNA copy number [4].

Leber's hereditary optic neuropathy is a maternally inherited genetic disease. More than 30 LHON-associated mtDNA mutations have been identified, the ND1 G3460A, ND4 G11778A and ND6 T14484C mutations account for more than 95% of LHON [2]. The penetrance of LHON is variable, even with the same pathogenic mutation in homoplasmic fashion within the same family [1].

LHON presents with a bilateral, sequential, painless, subacute and severe central vision loss. At onset there is a marked loss of color vision, and central or cæocentral defects are seen on visual field testing, with preservation of the peripheral visual field in most cases. During the acute phase of visual loss, the fundoscopic appearance may be normal, or the triad of: (1) hyperemia and “pseudoedema” of the optic disc; (2) peripapillary telangiectatic engorged microvessels; and (3) absence of leakage on fluorescein angiography may be seen. The presence of retinal hemorrhages or exudates should suggest an alternate diagnosis [6] Table 1, retinal ganglion cells (RGCs) within the papillomacular bundle are particularly severely affected accounting for the characteristic dense central or caecocentral scotoma in this disorder.

Spontaneous improvement in visual acuity may be seen, despite loss of the RNFL measured by optical coherence tomography [5], it is related to G3460A and T14484C mutations while the G11778A is linked to a poor prognosis.

Many studies were interested in different patterns of retinal ganglion cell dysfunction in Leber hereditary optic neuropathy. The OCT shows an initial thickening in retinal nerve fiber layer which lasts for three months followed, soon after the loss of vision, by a thinning and atrophy [7], on the OCT-A a spread of radial peripapillary capillaries (RPC) defect areas could be seen and is correlated with retinal full thickness thinning [8].

The treatment targets to prevent initial visual loss among LHON carriers, to protect the unaffected fellow eye in patients with unilateral optic neuropathy and to preserve visual function in already compromised optic nerves.

Idebenone is a synthetic analog of coenzyme Q10 that has a preventive effect on the oxidative action

## REFERENCE

1. Yen MY, Wang AG, Wei YH. Leber's hereditary optic neuropathy: a multifactorial disease. *Progress in retinal and eye research*. 2006 Jul 1;25(4):381-96.
2. Tong Y, Sun YH, Zhou X, Zhao F, Mao Y, Wei QP, Yang L, Qu J, Guan MX. Very low penetrance of Leber's hereditary optic neuropathy in five Han Chinese families carrying the ND1 G3460A mutation. *Molecular genetics and metabolism*. 2010 Apr 1;99(4):417-24.
3. Patrick Yu-Wai-Man, Patrick F. Chinnery. *Leber Hereditary Optic Neuropathy*. *Mitochondrial Case Studies*. <http://dx.doi.org/10.1016/B978-0-12-800877-5.00007-3>  
Copyright © 2016 Elsevier Inc.
4. Sanchez MIGL, Crowston JG, Mackey DA and Trounce IA. *Emerging Mitochondrial Therapeutic*

of oxygen-reactive species in mitochondria. A major finding of the RHODOS (clinical trials gov identifier: NCT00747487) [9, 10] evaluating visual recovery in LHON patients underwent idebenone high dose 900mg trial is that patients with LHON were more likely to benefit from idebenone if they were treated relatively early in the course of the disease [10], the proportion of clinically relevant recovery (CRR) after 6 months was of 30.2% in the idebenone group against 10.3% in the placebo group (RHODOS) [11]. LHON carriers harbouring the m.11778G>A mutation were the best responders [10], surprisingly contrasting with the severity of visual impairment supposed related to this mutation. But there is still no solid evidence base to guide the optimal dose and duration of treatment [12]. The involvement of the second eye couldn't be avoided with Idebenone [13].

The gene therapy seems to be a promising way. After intravitreal injection of an adeno-associated virus vector (AAV) expressing a normal ND4 complementary DNA,

Visual acuity improved to 1 letter at day 7 and 2 letters at day 30 after injection [5]. In 3-years results of intravitreal injection of rAAV2-ND4 for LHON suggested that is a safe and promising treatment [14]. No serious ocular or systemic adverse effects associated with this approach to gene therapy for LHON during the follow-up period was signaled, Treatment efficacy also suggests treatment feasibility [14, 15].

## CONCLUSION

NOHL is a hereditary, rare but devastating neuropathy occurring in young people. While diagnosis is easily made by genotype and clinically in large part the managing and treatment is still a real challenge with a poor prognosis, the gene therapy is still at the beginning but carrying hope.

Targets in Optic Neuropathies, Pharmacology and Therapeutics. 2016.

5. Feuer WJ, Schiffman JC, Davis JL, Porciatti V, Gonzalez P, Koilkonda RD, Yuan H, Lalwani A, Lam BL, Guy J. Gene therapy for Leber hereditary optic neuropathy: initial results. *Ophthalmology*. 2016 Mar 1;123(3):558-70.
6. Atkins EJ, Biousse V, Newman NJ. Optic neuritis. *In: Seminars in neurology* 2007 Jul (Vol. 27, No. 03, pp. 211-220). Copyright© 2007 by Thieme Medical Publishers, Inc., 333 Seventh Avenue, New York, NY 10001, USA..
7. Barboni P, Carbonelli M, Savini G, do VF Ramos C, Carta A, Berezovsky A, Salomao SR, Carelli V, Sadun AA. Natural history of Leber's hereditary optic neuropathy: longitudinal analysis of the retinal nerve fiber layer by optical coherence tomography. *Ophthalmology*. 2010 Mar 1;117(3):623-7.

8. Matsuzaki M, Hiramami Y, Uyama H, Kurimoto Y. Optical coherence tomography angiography changes in radial peripapillary capillaries in Leber hereditary optic neuropathy. *American journal of ophthalmology case reports*. 2018 Mar 1;9:51-5.
9. Klopstock T, Yu-Wai-Man P, Dimitriadis K, Rouleau J, Heck S, Bailie M, Atawan A, Chattopadhyay S, Schubert M, Garip A, Kernt M. A randomized placebo-controlled trial of idebenone in Leber's hereditary optic neuropathy. *Brain*. 2011 Jul 23;134(9):2677-86.
10. Yu-Wai-Man P, Soiferman D, Moore DG, Burté F, Saada A. Evaluating the therapeutic potential of idebenone and related quinone analogues in Leber hereditary optic neuropathy. *Mitochondrion*. 2017 Sep 1;36:36-42.
11. Castillo L, Arruga J. Leber hereditary optic neuropathy: What are the therapeutic perspectives?.
12. Yu-Wai-Man P, Chinnery PF. Leber hereditary optic neuropathy—Therapeutic challenges and early promise. *Taiwan journal of ophthalmology*. 2011 Dec 1;1(1):12-5.
13. Carelli V, La Morgia C, Valentino ML, Rizzo G, Carbonelli M, De Negri AM, Sadun F, Carta A, Guerriero S, Simonelli F, Sadun AA. Idebenone treatment in Leber's hereditary optic neuropathy. *Brain*. 2011 Aug 2;134(9):e188-.
14. Yang S, Ma SQ, Wan X, He H, Pei H, Zhao MJ, Chen C, Wang DW, Dong XY, Yuan JJ, Li B. Long-term outcomes of gene therapy for the treatment of Leber's hereditary optic neuropathy. *EBio Medicine*. 2016 Aug 1;10:258-68.
15. Feuer WJ, Schiffman JC, Davis JL, Porciatti V, Gonzalez P, Koilkonda RD, Yuan H, Lalwani A, Lam BL, Guy J. Gene therapy for Leber hereditary optic neuropathy: initial results. *Ophthalmology*. 2016 Mar 1;123(3):558-70.