Leber Hereditary Optic Neuropathy – Idebenone, Hope of Treatment

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Leber hereditary optical neuropathy (LHON) is part of the class of optic neuropathies in which the mitochondrial function is impaired and is characterized by a painless, subacute, bilateral decrease of the central vision. We shall present the case of two brothers AM aged 31 and AT aged 40 who were diagnosed with LHON and whom we initiated treatment with idebenone 900 mg / day with monitoring at one month and 6 months. The mitochondrial DNA analysis demonstrated the existence of mutations 11778G>A for the mtND4 gene in both patients. Idebenone is a synthetic benzoquinone, analogue of ubiquinone. We found a slight but significant improvement in the visual field in patient AM at one month of treatment. We have not found another case in the literature with an improvement in vision so fast after this treatment, and this has led us to write this article.

Keywords: Leber hereditary optical neuropathy (LHON), idebenone, mutations 11778G>A, mtND4 gene

Leber hereditary optic neuropathy is one of the most common inherited optic neuropathies causing bilateral central vision loss with genetically demonstrated mechanism and treatment hopes. It was the first mitochondrial disease to be recognized by Dr. Albrecht von Graefe in 1858, but it was named after Dr. Theodore Leber who described 15 patients with the disease among four families [1]. LHON was the first disorder recognized to be maternally inherited and the first to be attributed to a point mutation in the mitochondrial DNA (deoxyribonucleic acid) (mtDNA) [2,3]. The primary cell type that is lost in LHON is the retinal ganglion cell, which is highly susceptible to the disrupted adenosine triphosphate (ATP) production and oxidative stress. Inheritance of LHON follows that of mitochondrial genetics, and it has a highly variable clinical phenotype, as other genetic and environmental factors also play a role [4].

LHON is a rare condition with a prevalence of one in 31,000 in the northern UK [5]. Other epidemiological studies report a prevalence of one in 39,000 and one in 50,000 in the Netherlands and Finland, respectively [6,7]. LHON affects predominantly males (in 80%–90% of cases). Male LHON mutation carriers are more affected than female ones and a small proportion can experience spontaneous partial recovery, often within the first year of symptom onset [8,9].

Symptoms onset typically occurs in the second and third decades of life. LHON carriers rarely lose vision after the age of 50 years, but there have been reports of LHON onset from 2 to 87 years of age [10,11].

The main function of mitochondria is the production of energy in the form of ATP and the secondary functions of mitochondria include detoxification of the reactive oxygen species (ROS), production of heat through non-shivering thermogenesis, facilitation of cell apoptosis through the release of cytochrome C, calcium homeostasis through transient calcium storage. High energy electrons from the citric acid cycle are donated to complex I and II inside the mitochondrion, then shuttled along the respiratory chain. The energy that is released during this process is used to actively pump protons from the matrix to the intermembrane space. The resulting proton gradient across the inner mitochondrial membrane is then used by ATP synthase (complex V) to produce ATP from ADP and inorganic phosphate.

Primary DNA mutations in LHON affect complex I of the mitochondrial respiratory chain leading to deficient function of oxidative phosphorylation, decreased ATP production, thus less energy and increased generation of ROS [12-16].

This initially results in a dramatic loss of retinal ganglion cells (RGC) function, and later, RGC death and permanent vision loss.

Idebenone is a synthetic short chain benzoquinone structurally similar to CoQ10 but with a shorter, less lipophilic alkane tail. This structural difference allows Idebenone to cross the membrane into the mitochondria in its reduced form, where it is re-oxidized by complex III of the mitochondrial respiratory chain [12]. The ability to access cellular compartments and to shuttle electrons is the key to Idebenone's action mechanism [12].

Idebenone addresses impaired mitochondrial function in two ways. It bypasses the dysfunctional complex I of the mitochondrial respiratory chain, thus restoring cellular ATP generation and because raxone is a potent antioxidant it

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reduces the levels of ROS [12]. Therefore, Idebenone may reactivate viable, but inactive RGCs, thereby promoting recovery of vision in patients who experience vision loss. Idebenone has been shown to bypass complex I and maintain ATP production, and inhibits lipid peroxidation to protect mitochondria from oxidative damage [13-22].

Experimental part

Material and method

We shall present the case of two brothers AM aged 31 (female) and AT aged 40 (male) who were diagnosed with LHON and who underwent treatment with idebenone 900 mg / day with ophthalmologic monitoring at one month and 6 months of treatment.

AM presented for consultation accusing a decrease in the visual acuity dating 2 years in the right eye followed at 6 months by a decrease in the visual acuity in the left eye. The diagnosis was optic neuritis and the patient underwent corticosteroid treatment that did not improve the visual acuity. A year before a diagnosis of normal tension glaucoma was made and the patient received local treatment with a prostaglandin analogue but after a few months the patient stopped the treatment on her own initiative. At the time of presentation, she has no clear treatment or diagnosis. We conducted the following clinical and paraclinical investigations: visual acuity, intraocular pressure, anterior pole examination, posterior pole examination, Humphrey computerized visual field (VF), optical coherence tomography (OCT), neurological brain examination with cerebral Magnetic Resonance Imaging (MRI), anti-aquaporin-4 antibodies and infectious disease exam. Following these investigations, we offered the LHON suspicion and conducted specific genetic tests to detect mitochondrial mutations m.11778G> A, m.3460G> A and m.14484T> C. The mitochondrial DNA analysis demonstrated the existence of mutations 11778G> A for the mtND4 gene. The anamnesis shows that patient AM has a 40-year-old brother with very poor eyesight and several relatives on the maternal side with decreased vision (the brother of the maternal grandmother blind from a young age and a sister of the maternal grandmother with decreased vision and with a blind boy). We performed the same tests with brother AT and obtained the same genetic mutation present. The differential diagnosis we made was of glaucomatous optic neuropathy, patients having normal intraocular pressure and central visual field changes, optic neuritis from multiple sclerosis, but the neurological examination has negated this suspicion, optic atrophy secondary to compression, the cerebral MRI has invalidated a compression with secondary ocular atrophy, the biochemical, immunological and bacteriological tests have disproved an infectious neuritis, syphilis, tuberculosis, Lyme, sarcoidosis, lupus and paraneoplastic syndrome.

Based on the medical history, the optic fundus, the visual fields and the OCTs aș well as the genetic test results, the positive diagnosis of LHON was established in both patients and we initiated the idebenone 900 mg / day treatment with monitoring at a month and 3 months.

Clinical examination of AM patient at initiation of the treatment.

Best corected visual acuity right eye (BCVARE) = 0.3

Best corected visual acuity left eye (BCVALE) = 0.9

Intraocular pressure right eye (IOP RE) = 18 mmHg without treatment

Intraocular pressure LEFT eye (IOP LE) = 18 mmHg without treatment

Pachimetry RE = 560, OS = 550

Anterior pole RE: clinically normal

Anterior pole LE: clinically normal

Posterior pole RE : optical atrophy, discolored papilla in the temporal sector

Posterior pole LE : slight papillary discoloration in the temporal

Direct and indirect pupillary reflex present in both eyes.

The visual field was performed using the same Humphrey perimeter. After one month of treatment, the patient AM remarked some vision improvement and is called for a reassessment even though the therapeutic protocol recommends re-evaluation at 3 months of treatment. The ophthalmologic examination at one month of treatment reveals

BCVARE = 0.6

BCVALE = 1

The examination of the computerized visual field shows that an improvement in the central visual field is obtained in the left eye.

At presentation, the patient AT

BCVARE = 0.02

BCVALE = 0.01

IOP RE = 17 mmHg

IOP LE = 15 mmHg

Anterior pole RE: clinically normal

Anterior pole LE: clinically normal

Ophtaloscopy = optic atrophy, lack of macular reflex

The Goldmann visual field exam has been performed due to the severe decrease în the visual acuity.

There was no clinical or paraclinical change after one month and six months of treatment, respectively.

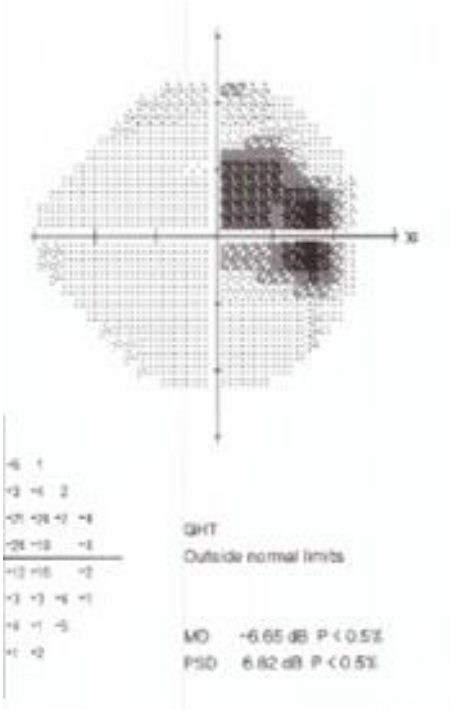
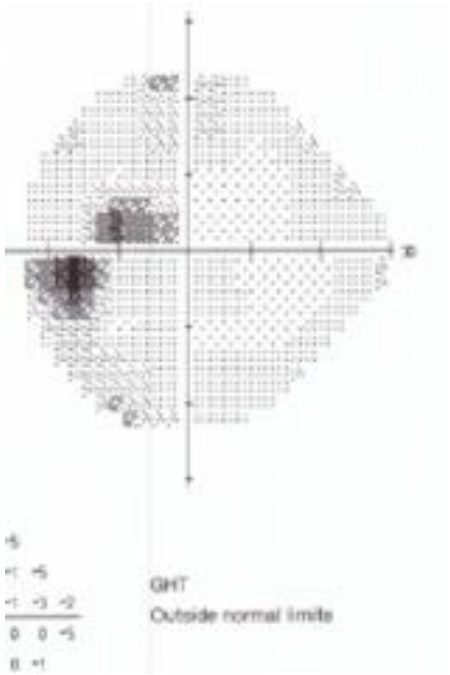


Fig 1. VF RE at presentation



FIig 2. VF LE at presentation

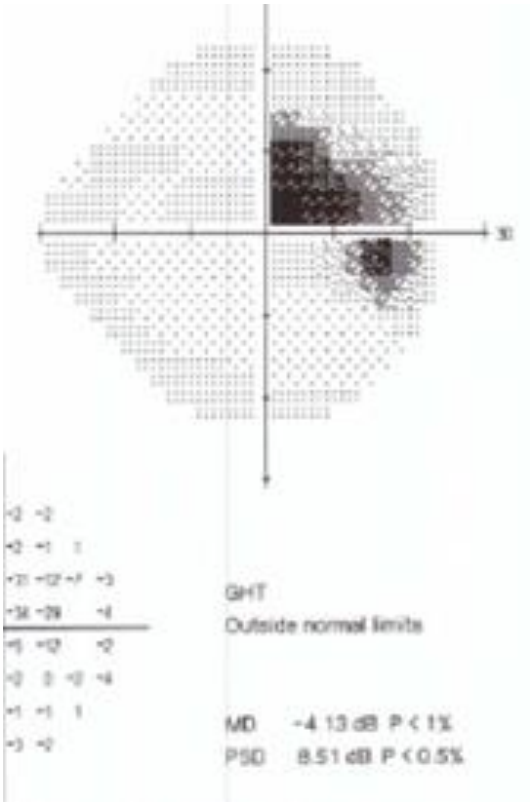
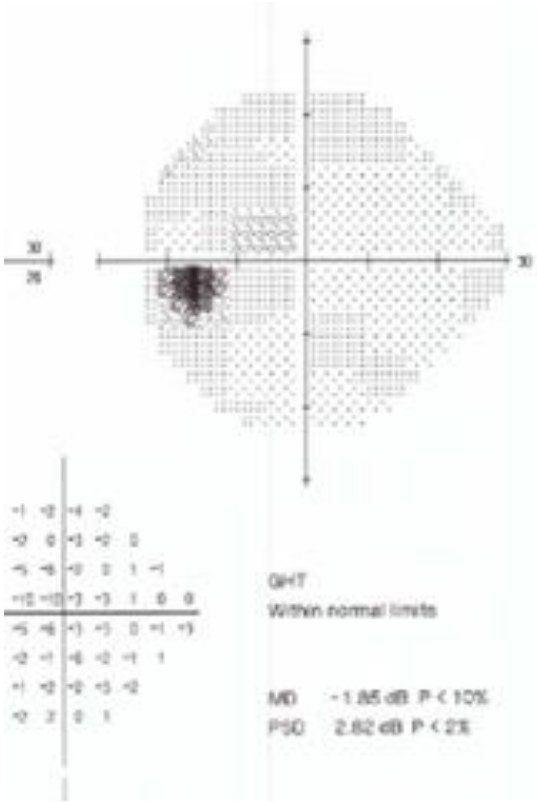


Fig 3. VF RE after 1 month of treatment



FIig 4. VF LE after 1 month of treatment

Results and discussions

Leber hereditary optic neuropathy is a rare disease; in Romania, 10 patients are treated with idebenone, the only drug approved for the LHON treatment. The condition in our patients was detected in the chronic phase of the disease when there was already partial optic nerve atrophy. Better knowledge of the paraclinical and clinical signs and the rapid outcome of the genetic tests will make it possible to diagnose this condition in the acute or subacute phase. The differential diagnosis with normal tension glaucoma is difficult; both entities produce partial nerve atrophy and visual field changes that may be confused in the incipient phases. The genetic changes and the family component are essential in establishing the positive diagnosis of LHON.

The recommended dose is 900 mg / day. Other authors describe the lack of response to low-dose treatment of idebenone [22-28]. The peculiarity of our case is that the patient AM was diagnosed with glaucoma and we had to refute

this diagnosis. The rapid response to treatment with clinical progress and a slight improvement of the central field of vision is another feature that needs to be emphasized. The follow-on protocol for the patient receiving idebenone treatment requires that the patient be re-evaluated at 3 and 6 months. We reevaluated at one month because the patient AM stated an improvement in vision. We have not found another case in the literature with such a fast clinical and paraclinical improvement, perhaps due to the three-month follow-up protocol, it has not been detected. This improvement was also preserved at the 3-month follow-up for the patient AM. For the patient AT, we did not get a positive response to this treatment, but we will continue to use idebenone for one year.

Conclusions

Idebenone is a hope for the patients diagnosed with Leber hereditary optic neuropathy, patients who have a significant decrease in the central visual field and who, without treatment, become blind. The accessibility of genetic testing is important because the genetic test is the key factor in determining the correct diagnosis of LHON.

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Manuscript received: 9.09.2019