Novel Adeno-Associated Virus-Based Genetic Therapy for Leber Hereditary Optic Neuropathy: A Case-Report

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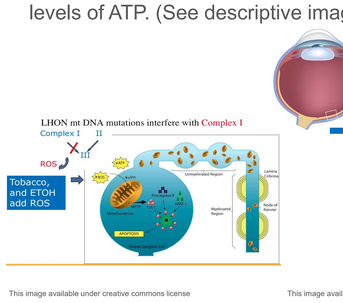
Introduction

Leber Hereditary Optic Neuropathy (LHON) is of the most common maternally inherited mitochondrial optic neuropathy with a prevalence of 1:30,000. It is a rare but devastating disease that leads to central vision loss, optic nerve atrophy and blindness. It predominantly affects males with a ratio of 3:1, most commonly in the second and third decades of their lives. The 11778G>A/ND4 (NADH dehydrogenase protein subunit 4) mutation of complex I in mitochondrial electron transport chain is the most common and severe one accounting for 70%-90% of mutations in patients with LHON. Since retinal ganglion cells have high mitochondrial load, they are particularly vulnerable to these mutations leading to apoptosis due to increased number of reactive oxygen species and depleted levels of ATP. (See descriptive images 1, 2, 3 below)



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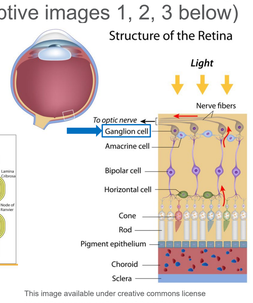

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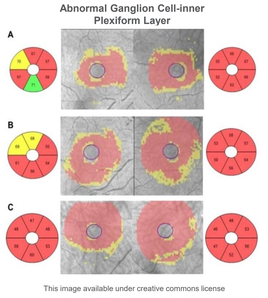

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Currently there is one FDA approved therapy for LHON: human-made short-chain Coenzyme Q10 (CoQ) analog. We present a case-report of a 14 y/o male who was diagnosed with LHON (mutation 11778G>A/ND4) and was subsequently treated with a CoQ analog and intravitreal gene therapy, an adeno-associated virus, serotype 2, that contains cDNA coding for ND4.

Objective

To explore the potential of gene therapy by presenting a case report about a patient afflicted by Leber Hereditary Optic Neuropathy who received treatment with an intravitreal injection of experimental intravitreal gene therapy.

Case Presentation

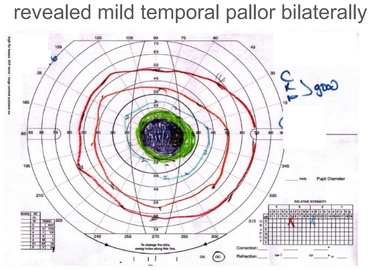
14 y/o male with no significant medical history presented to the office with a chief complaint of decreased vision. ROS was negative. Visual acuity exam was significant for scDva 20/800 in the right eye (OD) and scDva 20/400 in the left eye (OS). Intraocular pressure (IOP), slit-lamp and fundus examinations were unremarkable. Optical Coherence Tomography (OCT) of retina and optic nerve of both eyes were normal. MRI of the brain w/wo contrast was done and did not reveal any abnormalities.

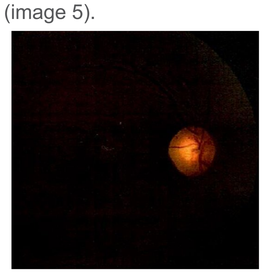
One month later, patient's vision worsened affecting his daily life and school work. The patient needed to look eccentrically to the left in order to clear the image and mentioned having a blur in the center of each eye. On exam, visual acuity was scDva CF (counts fingers) at 10' OD and scDva 20/400 OS. Visual field test revealed general decreased vision OD and large central scotoma with left quadrantanopsia OS. Assessment and plan included an outpatient consultation with neurologist, retinal specialist, CT chest, lumbar puncture with cerebrospinal fluid analysis, bone marrow biopsy and genetic testing for LHON.

Case Presentation

The differential diagnosis included neuromyelitis optica, paraneoplastic autoimmune encephalopathy, MOG antibody disease (MOGAD), idiopathic intracranial hypertension and LHON. LP aided to rule out the diagnoses of idiopathic intracranial hypertension and neuromyelitis optica.

Two months later, the patient was referred to a vitreoretinal specialist who suspected LHON from the clinical exam and genetic testing was ordered at this visit. Testing revealed a mutation 11778, ND4, confirming a diagnosis of LHON. Physical examination was notable for worsening visual acuity: scDva CF at 4' OD and scDva 20/800 OS. Goldman Visual Field (GVF) test showed large central scotoma in both eyes (Image 4). Disk photos were taken and revealed mild temporal pallor bilaterally (OU) (image 5).





Once diagnosis of LHON was confirmed, the patient was offered and started on CoQ analog therapy (300mg PO TID). In addition, an option of compassionate care dispensation of LHON gene therapy was discussed.

Patient was referred to a center of academic excellence that had been involved in LHON clinical trials and received intravitreal gene therapy treatment in both eyes. Patient also kept receiving CoQ analog 300mg PO TID. The patient had 2+ vitreous cells, so he was treated with prednisone 20mg for 2 weeks then tapered down to 10mg for another 2 weeks.

On follow up, patient had recorded VA of 20/640 OD and 20/400 OS and 1+ vitreous cells, so treatment with prednisone 10mg was continued.

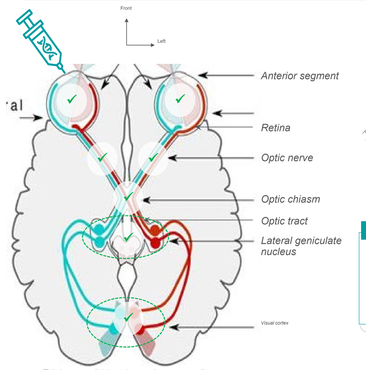
Discussion

LHON is a rare and devastating mitochondrial optic neuropathy that causes a bilateral progressive and painless central blindness. In addition to human-made short-chain CoQ analog, the latest medical advance includes an intravitreal adeno-associated virus gene therapy.

Gene therapy involves an intravitreal injection with AAV-based vector that transports cDNA encoding for wild type ND4 thus restoring function of retinal ganglion cells. Clinical data was gathered during two Phase 3 randomized, double blinded, clinical trials RESCUE and REVERSE that showed improved visual scores in patients after a right eye unilateral injection in experimental group and a left eye unilateral injection in control group. A follow-up study RESTORE is being conducted to monitor the visual scores of the patients from RESCUE and REVERSE studies. The results did not show a statistically significant difference between the groups, however, visual acuity had improved over the three years when compared to a natural course of LHON leading researchers to explore a plausible mechanism of this finding.

The study was repeated on primates leading to an observation that after the unilateral injection into the right eye, adeno-associated virus ND4 DNA was observed in the contralateral eye. The main explanation of the bilateral visual acuity improvement after unilateral injection with gene therapy was attributed to the adeno-associated virus ND4 DNA transfer to the contralateral eye and was confirmed by finding DNA in the following tissues: anterior segment of the eye, retina, optic nerve, optic tract, lateral geniculate nucleus and the optic chiasm. (Images 6 and 7 right, above, table 1 right, above).

Discussion



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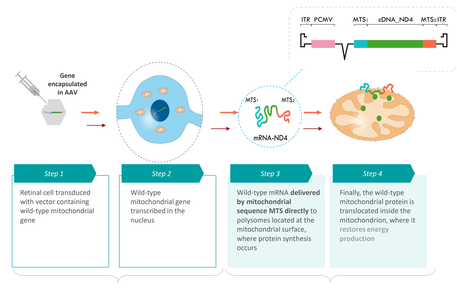

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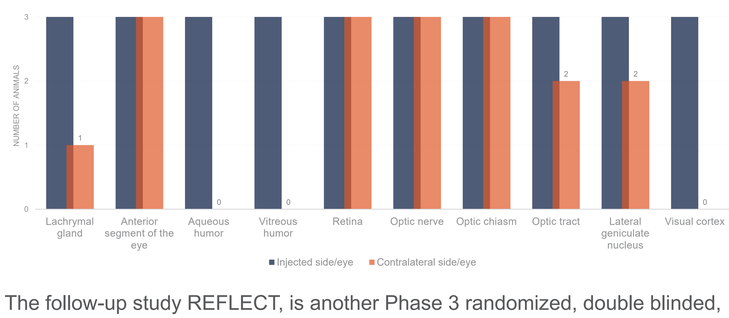

The follow-up study REFLECT, is another Phase 3 randomized, double blinded, clinical trials where patient in the experimental group received a bilateral intravitreal injections with an intravitreal gene therapy vs control group where patients received only unilateral injection. The study has not finished yet but the preliminary results show statistically significant results in terms of visual acuity improvement between the experimental and control groups.

Since the primary pathophysiological mechanism of LHON involves apoptosis of retinal ganglion cells due to inadequate supply of ATP and increased concentrations of reactive oxygen species (ROS) secondary to mitochondrial dysfunction, a short-chain CoQ analog works as a potent antioxidant and helps to restore ATP synthesis, thus aiding retinal ganglion cells to function properly. The randomized clinical trial failed to prove statistically significant results, however, post-hoc analysis showed that some patients with discordant vision loss were able to benefit from the drug. The latter finding was supported by a retrospective cohort study of 103 patients.

Conclusion

LHON has detrimental effects on those affected by it by causing a bilateral, progressive and painless blindness. The pathophysiological mechanism of the disease has a high degree of complexity thus impeding the development of successful treatment modalities. The latest and most promising advance in treatment of patients afflicted by LHON involves genetic therapy. Specifically, adeno-associated virus based intravitreal gene therapy with promising clinical data from multiple phase 3 trials where the majority of patients achieved improved visual acuity scores.

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