Ethambutol-induced conversion in Leber's hereditary optic neuropathy: 6 years follow-up

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Key words: Ethambutol-induced optic neuropathy, idebenone, Leber's hereditary optic neuropathy

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Quick Response Code:	**Website:** www.ijo.in
	DOI: 10.4103/ijo.IJO_1758_21

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Received: 06-Jul-2021 Revision: 22-Aug-2021
Accepted: 22-Sep-2021 Published: 30-Jun-2022

Leber's hereditary optic neuropathy (LHON) is a maternally inherited disease which is blinding with variable penetrance. Three primary mitochondrial deoxyribonucleic acid (DNA) mutations which affect the respiratory complex I are known to cause blindness. Reduction of adenosine triphosphate (ATP) synthesis and increased oxidative stress in LHON sensitize the retinal ganglion cells to apoptosis.[1]

A 17-year-old gentleman presented to us with a history of bilateral sequential painless loss of vision 8 weeks back. On inquiry, the patient gave a history of sudden painless loss of vision 8 weeks back in the left eye of 6 days duration. He had then been on an anti-tuberculous treatment for pulmonary tuberculosis for 8 months of which four drugs (isoniazid, rifampicin, pyrazinamide, and ethambutol) were used for the initial 4 months after which pyrazinamide had been stopped and the remaining three drugs had been continued for the remaining 4 months. With a diagnosis of a possible drug-induced optic neuropathy; all three drugs were stopped. Four days later, the patient complained of a similar painless

Cite this article as: Moreker MR, Sharma TR, Khadilkar SV. Ethambutol-induced conversion in Leber's hereditary optic neuropathy: 6 years follow-up. Indian J Ophthalmol 2022;70:2760-2.

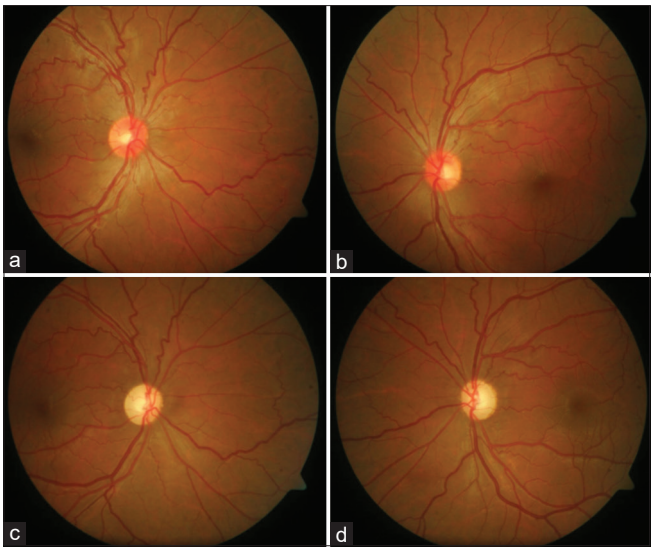

Figure 1: (a) Shows disc hyperemia with circumpapillary telangiectatic microangiopathy in the right eye. (b) Shows disc hyperemia with circumpapillary telangiectatic microangiopathy in the left eye. (c) Shows resolution of disc hyperemia with the pallor of the optic nerve in the right eye after 15 months of the treatment. (d) Shows resolution of disc hyperemia with the pallor of the optic nerve in the left eye after 15 months of treatment

loss of vision in the right eye. Prior to presentation to us, visual evoked potentials were done which were reported as normal in the right eye and had a prolonged P100 latency in the left eye. The contrast magnetic resonance imaging (MRI) of the brain with orbit was normal. The patient had received elsewhere, before presentation to us, five doses of 1 gm pulsed intravenous methyl prednisolone and eight injections of vitamin B12 but had no improvement in the vision. On presentation to us, he had best-corrected visual acuity of finger counting 2 ft in the right eye and finger counting close to the face in the left eye. His anterior segment and intraocular pressures were normal in both eyes. The pupils were normal-sized but showed a mild sluggish reaction to light. His lenses were clear. The fundus examination showed bilateral disc hyperemia with a nerve fiber layer edema and mildly tortuous vessels around the optic nerve (circumpapillary telangiectatic microangiopathy) in both eyes [Fig. 1a and b]. The rest of the fundus examination was within normal limits. Because of the bilateral sequential loss of vision with a clinical picture of disc hyperemia with a nerve fiber layer edema and mildly tortuous vessels in both eyes in a young gentleman not responding to steroids, Leber's hereditary optic neuropathy was suspected and he was advised a genetic test for the same. Serum vitamin B12 was checked which was 535 pg/mL despite eight injections of vitamin B12 that he had previously received. Neuromyelitis optica (NMO) antibodies, serum angiotensin converting enzyme (ACE), antinuclear antibody (ANA) blot, and cerebrospinal fluid (CSF) studies were done and were normal. The genetic test for LHON showed mitochondrial point mutation 11778 G > A in the gene coding subunit ND4 of the NADH-CoQ oxidoreductase. He was then started on idebenone 450 mg/day. CO Q 10 200 mg/day was added to the treatment regimen as suggested by our neurologist. The patient showed a gradual stabilization of vision within the first year of treatment with resolution of disc hyperemia, nerve fiber layer edema, and also the tortuosity of the vessels [Fig. 1c and d] and attained a best-corrected visual acuity of finger counting at 2 m in the right eye and finger counting 1 m in the left eye. Binocularly, he could count fingers at 3 m and had a near vision of N12 in both eyes with a + 14 Dsph which allowed him to pursue his engineering degree, although with difficulty but with determination. At 6 years of follow-up being 2 years off treatment (i.e., total 4 years of treatment with idebenone and CO Q 10), he continues to maintain his vision and has stable optic nerves.

Discussion

Certain agents can prompt conversion in LHON.[1] These include antibiotics like ethambutol, aminoglycosides, chloramphenicol, zidovudine, and linezolid.[1] Toxins such as smoke, pesticides, cyanide, methanol, and ethanol can cause a similar effect.[1] Antituberculosis medication may be an "epigenetic factor" of LHON in individuals with a primary LHON mutation with very few previous reports of these agents including ethambutol causing vision loss in LHON.[2-4] As in our patient, the mutation G11778A in the mitochondrial gene MTND4 was identified in all these patients reported in the literature. This risk should be recognized by physicians and LHON carriers while using ethambutol or the other agents.[4] Our Revised National Tuberculosis Control Program (RNTCP) in India has increased the duration of the use of ethambutol to 6 months for the new cases (2HRZE + 4HRE) and for 24–27 months in multi-drug-resistant tuberculosis with physicians using doses of ethambutol (up to 1200 mg/day), especially in drug-resistant tuberculosis which is likely to significantly increase the risk of ocular complications.[5] Ethambutol administration to patients with a family history of LHON should be avoided, especially in extended regimens.

A knowledge of ethambutol-induced conversion in LHON as in our patient can help prompt suspicion of LHON. The clinical picture of LHON is classical, and in our patient, we did not request for an fundus fluorescein angiography (FFA) or an ocular coherence tomography (OCT). However, when done, the FFA showed disc edema without any disc leakage in the acute phase of LHON and the OCT showed retinal nerve fibre layer (RNFL) edema which can be diagnostic of the disease and prompt genetic testing. Further management of this condition with novel drug idebenone (and CO Q 10) can be undertaken, especially in adult patients with the m.11778G>A ND4 mutation, as in our patient as these patients would otherwise have the worst visual outcomes in their natural course.

Physicians and ophthalmologists should be aware of ethambutol-induced conversion in LHON. Careful clinical examination and interpretation of the fundus pictures, especially disc hyperemia with nerve fiber layer edema and mildly tortuous vessels around the optic nerve (circumpapillary telangiectatic microangiopathy) can help prompt diagnosis and further management of this condition with novel drug idebenone.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Acknowledgments

The Authors wish to acknowledge Dr. Bhim S. Singhal and Dr. Nandkishore Shingne for their technical help in the management of this patient. The authors also acknowledge the extraordinary grit and determination showed by the 17 year old gentleman; who despite all odds pursued his engineering studies; with his residual vision; using various low vision aids and continues to live a fruitful life; at 6 years follow-up.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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