CASE REPORT

Sibling Ethambutol Optic Chiasmopathy

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ABSTRACT

Ethambutol is utilised in the treatment of *Mycobacterium avium* and *Mycobacterium tuberculosis* infection. The authors report two siblings who developed the adverse effect of ethambutol-induced optic chiasmopathy, with recovery following cessation of ethambutol. Discussion explores potential genetic predisposition to development of this condition and its resolution. Ethambutol optic neuropathy (EON), Leber's hereditary optic neuropathy (LHON), and other optic neuropathies of mitochondrial origin share a common pathophysiology. Consequently, the authors postulate treatments utilised in LHON, including vitamin B supplementation and idebenone, may have benefit in EON. This article presents concepts for further research, suggesting a potential genetic susceptibility to EON and its treatment.

ARTICLE HISTORY

Received 31 January 2017
Accepted 20 April 2017

KEYWORDS

Ethambutol; Leber's hereditary optic neuropathy; mitochondria; optic chiasmopathy; optic neuropathy

Cases

Case 1

A 70-year-old man treated with ethambutol (15 mg/kg/day) for *Mycobacterium avium* lung infection was referred for routine ophthalmic screening. Initial visual acuity (VA) was 6/4; he correctly identified 14/14 Ishihara colour plates bilaterally, with normal automated Humphrey visual fields (HVF).

At 1-year review, despite having developed a subtle bilateral superior field defects (Figure 1a), he still correctly identified 14/14 Ishihara plates at this stage. The patient and his respiratory team were informed, and it was decided to continue ethambutol therapy with closer follow-up. Unfortunately, the patient failed to attend follow-up.

Eighteen months later, he returned with VAs of 6/9 and now had subtle right optic disc pallor (Figure 1b) with a bitemporal hemianopia (Figure 1c). Neuroimaging with both non-contrast and contrast magnetic resonance imaging (MRI) was normal. A diagnosis of ethambutol chiasmopathy was made, and ethambutol was ceased.

Repeated automated perimetry 2 and 5 months (Figure 1d and e, respectively) later showed improvement of visual fields. At this 5-month

follow-up, right eye colour vision had dropped to 11/14 Ishihara plates, whilst his left eye continued to score all correctly. By 14 months VAs improved to 6/6 with ongoing improvement of field defects (Figure 1f).

Case 2

The 69-year-old sister of Case 1 also presented after commencing treatment with ethambutol (17 mg/kg/day) for *Mycobacterium avium* lung infection. Findings at initial review were normal. Five months later, she presented with symptomatic dyschromatopsia and ethambutol was ceased. At our clinic, 2 months later, her vision was 6/60 OD, 6/120 OS, and she identified 10/14 Ishihara plates OU. Fundoscopy was normal, but HVF demonstrated bitemporal hemianopia (Figure 2a).

Fifteen months after ceasing ethambutol, her right VA had improved to 6/45 but optical coherence tomography (OCT) now showed retinal nerve fibre layer thinning (Figure 2b). One year later, vision recovered to 6/9 OD and 6/12 OS, colour vision was normal, and HVF had significantly improved (Figure 2c).

In both cases, non-contrast and contrast magnetic resonance imaging of the chiasm and orbits were

Figure 1. Case 1. **a.** HVF – Early superior defects. **b.** Subtle right optic disc pallor. **c.** HVF – Development of bitemporal hemianopia. **d.** HVF – Improvement of left temporal defect. **e. & f.** Continuing resolution of bitemporal hemianopia.

Figure 2. Case 2. **a.** HVF – Early bitemporal defects. **b.** OCT - Displaying temporal thinning. **c.** HVF – Near complete resolution of prior defects.

unremarkable, with neuroradiologists excluding chiasmal and meningeal tuberculosis, commenting only on scattered nonspecific white matter changes, expected in this age group. This was true for both early scans, and later follow-up imaging. Further, blood tests for reversible causes of optic neuropathy, including syphilis serology, vitamin B levels, folate, copper, zinc, and inflammatory markers (erythrocyte sedimentation rate [ESR], C-reactive protein [CRP],

angiotensin-converting enzyme [ACE]), were normal. Leber's hereditary optic neuropathy (LHON; 11778, 14484, 3460) mutation screening was negative.

Discussion

Ethambutol is first-line treatment for *Mycobacterium tuberculosis* and *Mycobacterium avium* complex lung disease. However, ethambutol has serious ocular

adverse effects, namely, optic neuropathy and optic chiasmopathy.¹ Chiasmopathy is thought to occur due to proximal progression of the optic neuropathy, explaining poor VA in these patients.^{1,2} We describe two siblings with chiasmopathy and severe bilateral vision loss secondary to ethambutol, showing visual recovery 12–18 months after ethambutol cessation. The presentations of these siblings may suggest a genetic role in the pathogenesis and potential recovery of ethambutol optic neuropathy (EON).

Ethambutol-related ocular toxicity bears similarities to other toxic and nutritional optic neuropathies. The common pathophysiological process is an impairment of mitochondrial oxidative phosphorylation, with subsequent activation of apoptosis pathways. This occurs preferentially within the papillomacular bundle due to its high surface area to volume ratio.³ Therefore, exclusion of other reversible causes of optic neuropathy, including checking B₁₂ and folate, is important.

Inherited optic neuropathies also result from impairment of mitochondrial function, either directly in LHON or indirectly via chromosomal mutations in *OPA1*. Indeed, cases of LHON-related vision loss have been reported in patients taking ethambutol, with some authors postulating that ethambutol may be an epigenetic trigger for LHON.⁴ Although this remains controversial, with some authors finding no synergism between the two, LHON should be considered in atypical cases of EON, including those with early disc hyperaemia, severe late optic atrophy, continuing visual decline following ethambutol cessation, and advanced age at onset, as in our cases.^{4–6}

Furthermore, ethambutol has been associated with cases of *OPA1*-related optic atrophy and one case of *CMT2A2*-related optic atrophy with systemic signs of muscle weakness.^{7–9} With differing pathophysiology, LHON impairing oxidative phosphorylation, whilst *OPA1* and *CMT2A2* disturbing mitochondrial fusion, these reports strengthen the suggestion of an epigenetic, or synergistic, effect between mitochondrial genetics and ethambutol in the development of EON or optic atrophy.

Delayed recovery of vision is also a feature in some cases of LHON with the 14484 mutation and may be explained by activation of previously dormant retinal ganglion cells.¹⁰ Similarly, Tsai and Lee reported late visual recovery in EON patients between 12 and 36 months of follow-up, a feature

that may also be accounted for by the aforementioned mechanism.¹¹ Therefore, the genetics of mitochondrial function, whether mitochondrial DNA or chromosomal, may influence the incidence and progress of EON.

Due to a similarity in basic pathophysiology, we believe therapeutic options employed in LHON may have a role in treatment of EON. Treatments employed for LHON include vitamin B supplementation and idebenone therapy, both of which may have efficacy in EON, a subject for further research.^{12,13} Indeed, in Case 2, vitamin B supplementation was employed with this rationale in mind, despite the patient having levels within the lower end of the normal range.

This case series demonstrates the complication of chiasmopathy, and late recovery of vision. Although the similarities in these siblings' visual loss and return may be circumstantial, they may also indicate a genetic component to this condition. Consequently, a potential genetic predisposition to EON poses an interesting topic for continued research. Furthermore, the recovery in vision could arise from activation of specific retinal ganglion cell populations unaffected by ethambutol's effects. Analysis of other mitochondrial disorders may provide insight into the disease process and treatment options available.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the article.

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