

Ethambutol-associated Optic Neuropathy⁺

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Abstract

Introduction: Ethambutol is used in the treatment of tuberculosis, which is still prevalent in Southeast Asia, and can be associated with permanent visual loss. We report 3 cases which presented with bitemporal hemianopia. **Clinical Picture:** Three patients with ethambutol-associated toxic optic neuropathy are described. All 3 patients had loss of central visual acuity, colour vision (Ishihara) and visual field. The visual field loss had a bitemporal flavour, suggesting involvement of the optic chiasm. **Treatment:** Despite stopping ethambutol on diagnosis, visual function continued to deteriorate for a few months. Subsequent improvement was mild in 2 cases. In the third case, visual acuity and colour vision normalised but the optic discs were pale. **Outcome:** All 3 patients had some permanent loss of visual function. **Conclusions:** Ethambutol usage is associated with permanent visual loss and should be avoided if possible or used with caution and proper ophthalmological follow-up. The author postulates that in cases of ethambutol associated chiasmopathy, ethambutol may initially affect the optic nerves and subsequently progress to involve the optic chiasm.

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Key words: Bitemporal hemianopia, Complications, Ethambutol, Toxic optic neuropathy, Tuberculosis

Introduction

Tuberculosis (TB) has been present since ancient times. Around 460 BC, Hippocrates identified phthisis, which is the Greek term for consumption (TB seemed to consume people from within with its symptoms of bloody cough, fever, pallor and long relentless wasting) as the most widespread disease of the times, which was almost always fatal. Today, centuries later, TB is still the most common infectious disease, infecting millions of people worldwide.

In 2003, a total of 1997 new cases of TB were reported in Singapore.¹ The incidence of TB in Southeast Asia is similar to or higher than that in Singapore. As such, TB remains a major public health problem in Southeast Asia.

TB was a major cause of mortality until 1946, when streptomycin was developed. Since then, many other drugs have been used to treat TB. Due to the nature of the causative organism, *Mycobacterium tuberculosis*, which is a slow-growing bacterium that divides every 16 to 20 hours, treatment regimes comprise multiple drugs for a minimum period of 6 months, if not longer.

Ethambutol has been used to treat TB since the 1960s. The potential for visual impairment was recognised soon after its introduction.² The original formulation was a racemic mixture. However, when it was discovered that the L-form was predominantly responsible for its toxicity, and the D-form for its therapeutic effects, the L-form was withdrawn. Despite this, cases of irreversible visual loss have been reported in the literature and some authors have even gone on to suggest that ethambutol should not be used routinely to treat TB.^{3,4}

We report 3 cases of ethambutol-associated optic neuropathy, 2 with little or no recovery and recommend that ethambutol be used with caution, proper patient education, and proper ophthalmologic monitoring. This consists of baseline (pre-treatment) best corrected visual acuity, colour vision, and Humphrey visual field (HVF). Subsequent monitoring in asymptomatic patients is also important. We also postulate that in cases of ethambutol associated chiasmopathy, ethambutol initially causes an optic neuropathy, and later progresses to involve the optic chiasm.

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Case Reports

Case 1

A 67-year-old male was referred for neuro-ophthalmology consultation for investigation of persistent poor vision after bilateral cataract surgery. A HVF and computed tomography (CT) of the brain had been done prior to our consultation. The HVF showed bitemporal hemianopia (Fig. 1) and the CT of the brain was normal. Significantly, there was no space-occupying lesion in the para-sellar region.

Examination revealed visual acuity of counting fingers in the right eye and 6/60 in the left eye with no improvement on looking through a pinhole. There was no relative afferent pupillary defect (RAPD). Colour vision (Ishihara) was abnormal bilaterally; only the test plate was seen. Confrontation visual field testing was normal by finger counting, but revealed red desaturation temporally when tested with the red mydracyl cap. There was bilateral optic disc pallor.

He was diabetic and hypertensive. On specific questioning, he revealed that he had been diagnosed with pulmonary tuberculosis, and has been taking rifampicin, isoniazid and ethambutol for the past 13 months.

Blood tests for autoimmune diseases [erythrocyte sedimentation rate (ESR), anti-nuclear antibody titres (ANA), double-stranded deoxyribonucleic acid titres (ds DNA)] and syphilis [venereal disease research laboratory (VDRL)] were performed, all of which were negative.

He was diagnosed with ethambutol-associated optic neuropathy and the medication was stopped immediately. He was followed up for 30 months. There was initial worsening of his visual fields over 2 months despite stopping ethambutol (Fig. 2). On his last visit, visual acuity was 6/30 in the right eye and 6/24 in the left eye, improving on looking through a pinhole to 6/30 and 6/12 respectively.

Case 2

A 64-year-old Chinese female was diagnosed with rheumatoid arthritis, and treated with prednisolone and hydroxychloroquine. She was on regular review with the ophthalmologist, with documented visual acuities of 6/6 in each eye. Colour vision was abnormal (3/15 Ishihara colour plates) due to congenital colour blindness (family history of colour blindness).

She developed tuberculous arthritis of her knee in August 2000, for which she was started on rifampicin, isoniazid, ethambutol and pyrizinamide. Baseline visual acuity was normal although colour vision was abnormal (congenital colour vision deficiency, 3/15 Ishihara plates bilaterally).

She was followed closely. Nine months after the commencement of TB treatment, visual acuity decreased

from 6/6 in both eyes to 6/9 in the right eye and 6/12 in the left eye with no improvement on looking through a pinhole. At this point her optic discs were pink. HVF showed scattered defects (Fig. 3). Her retina was normal and fluorescein angiography did not show any changes suggestive of plaquinil toxicity. This was communicated to her attending physician and ethambutol was stopped.

On review 2 months later, visual acuity had worsened; 6/60 in the right eye and counting fingers in the left eye with no improvement on looking through a pinhole. Her optic discs now showed temporal pallor. HVF showed progression with a suggestion of bitemporal field loss (Fig. 4). A CT of the brain, performed as a result of the visual field progression, was normal. She has now been followed up for 42 months. Visual acuity remains poor at 6/21 in the right eye and 6/45 on the left eye with bilateral pale discs.

Case 3

A 63-year-old Chinese female was started on ethambutol and isoniazid for pulmonary TB. She was referred for eye screening 4 months after starting the medication for complaints of floaters bilaterally.

Examination revealed visual acuities of 6/7.5 bilaterally, normal colour vision by the Ishihara test and bilateral pink optic discs. There was no evidence of toxic optic neuropathy at that time.

She was reviewed 2 months later. She had no visual complaints at this visit. Visual acuity was 6/7.5 in each eye, with full colour vision and bilateral healthy disc.

A month later she complained to her respiratory physician of decreased vision bilaterally over the previous 2 weeks. The respiratory physician recorded decreased visual acuity but normal colour vision by the Ishihara plates. He reduced her dosage of ethambutol (from 800 mg daily to 600 mg daily) and referred her to the ophthalmologist.

Examination revealed best corrected visual acuities of 6/15 bilaterally, normal colour vision (Ishihara) and healthy pink disc bilaterally.

She was referred for neuro-ophthalmological consultation 2 weeks later. At this time, visual acuity was 6/18 bilaterally and colour vision was suboptimal (Ishihara plates: 14/17 in the right eye and 15/17 in the left eye). The HVF showed a junctional scotoma (Fig. 5). Ethambutol was stopped immediately. Magnetic resonance imaging (MRI) of the brain was normal.

She was diagnosed with ethambutol-associated optic chiasmopathy. After cessation of ethambutol however, her visual acuity continued to worsen. Ten days and 3 weeks after cessation, visual acuity was 6/24 in the right eye and 6/18 in the left eye, and counting fingers in the right eye and 6/24 in the left eye respectively. The right disc was pale

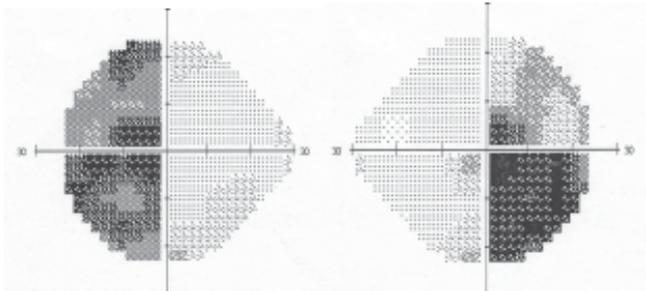


Fig. 1. Humphrey visual field of patient (Case 1) showing bitemporal field loss.

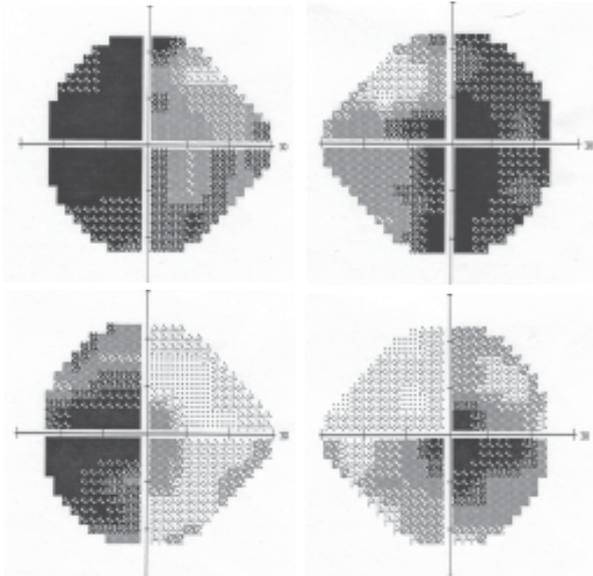


Fig. 2. Sequential Humphrey visual fields of patient (Case 1) showing initial progression of the field defect over 2 months (top) and subsequent mild improvement (bottom).

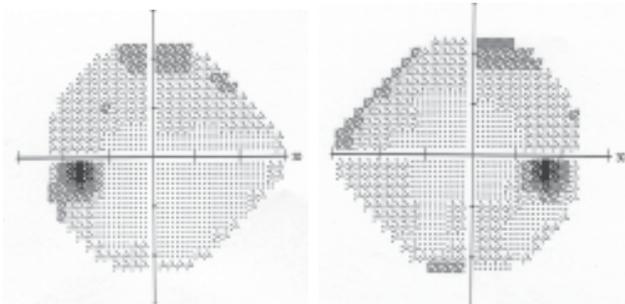


Fig. 3. Initial Humphrey visual field of patient (Case 2).

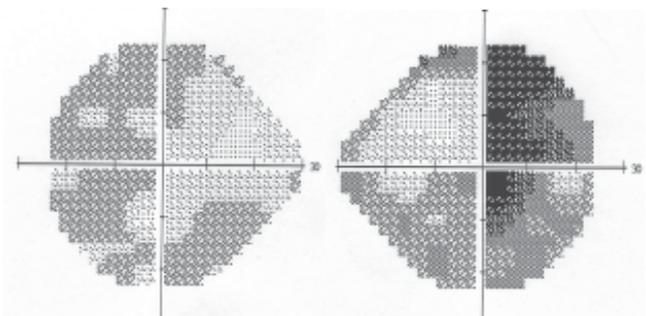


Fig. 4. Humphrey visual field of patient (Case 2) 2 months after cessation of ethambutol showing progression of visual field defects.

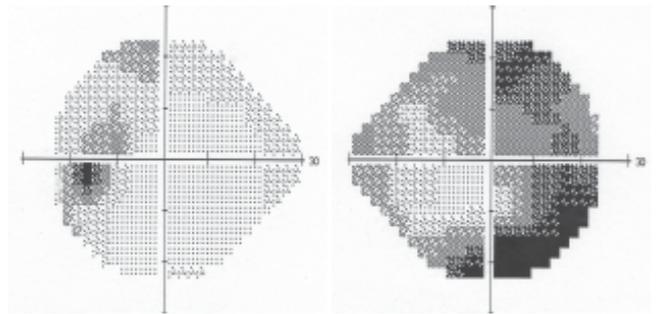


Fig. 5. Humphrey visual field of patient (Case 3) showing bitemporal field loss.

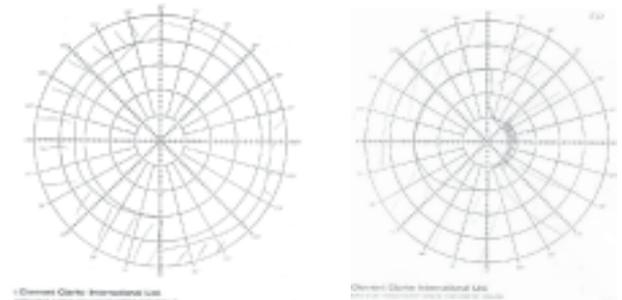


Fig. 6. Bjerrums visual field of patient (Case 3) showing bitemporal visual field defects.

while the left was pink. A Bjerrums visual field done 8 weeks after cessation of ethambutol showed temporal defects respecting the vertical midline (Fig. 6). Her visual acuity and colour vision improved slowly over the next 9 months. On her last visit, visual acuity was 6/7.5 bilaterally. Colour vision and HVF had normalised.

Conclusion

Ethambutol-associated optic neuropathy is an established “ocular” drug complication. These 3 cases remind us that ethambutol usage is associated with a real risk of toxic optic neuropathy and permanent visual loss. The incidence of this is approximately 1%.^{5,6} Although isoniazid may also be responsible, ethambutol-associated optic neuropathy is more widely recognised. In addition, ethambutol toxicity has frequently been reported to present with central or centrocecal scotomas. However, bitemporal field defects have occasionally been reported.⁷

This disorder has been studied in several animal models. Monkey experiments using the racemic mixture demonstrated that ethambutol first affects the optic chiasm.^{8,9} Studies in rats using the D-isomer confirmed the special susceptibility of the optic chiasm.¹⁰ In rabbits, however, the damaged was in the optic nerves.¹¹

In our series, Case 1 had a convincing bitemporal hemianopia (Fig. 1). This case was diagnosed late when

visual acuity had already deteriorated to counting fingers in the right eye and 6/60 in the left eye. Cases 2 and 3 showed defects that had a bitemporal flavour. In addition, the Bjerrum's visual field done for Case 3 showed a temporal defect respecting the vertical midline. Cases 2 and 3 were identified at an earlier stage of the disease process. In Case 2, when visual acuity was initially affected (6/9 in the right eye and 6/12 in the left eye), visual field tests showed scattered defects. These defects, however, progressed to one having a bitemporal flavour (Fig. 2). This is more convincing in the right eye. We could not use colour vision to monitor Case 2 as the patient had congenital red-green colour blindness. In Case 3, visual acuity was 6/15 bilaterally with normal colour vision on presentation. Two weeks later, visual acuity had deteriorated to 6/18 bilaterally with abnormal colour vision. HVF at this point showed changes consistent with a junctional scotoma (central/ temporal defect in the right with a superior temporal defect in the left). Bjerrum's visual field done 8 weeks after onset showed bilateral temporal defects respecting the vertical midline.

The author postulates that in the early stages of ethambutol-associated optic chiasmopathy, the optic nerves are initially affected. If ethambutol is continued, the damage spreads to the anterior chiasm and later, to the whole chiasm resulting in a bitemporal hemianopia. A caveat here is that we did not perform Bjerrum's visual fields on all our patients which would provide more information on the peripheral visual field. Bjerrum's visual field was performed only for Case 3. The patient had a visual field respecting the vertical midline, suggesting a bitemporal hemianopia and, hence, a chiasmopathy. However, centrocaecal scotomas can be confused with bitemporal hemianopias as reported by Rucker et al.¹² In addition, central or centrocaecal scotomas have been more frequently reported with ethambutol optic neuropathy.

Due to the nature of the tuberculous bacilli, it would be difficult to eradicate the disease altogether and the use of ethambutol will most likely continue. How then can we make it safer for our patients? It is important to remember that this requires the patient, the physician and the ophthalmologist to work closely together.

The first step is to identify patients in whom ethambutol is relatively contraindicated. These include patients who are unlikely to notice or describe visual symptoms, such as patients with dementia, mental retardation and children. Others include patients with pre-existing ophthalmological diseases with poor baseline vision. These patients should not be treated with ethambutol.

The second step is to educate all patients treated with ethambutol on its side effects. Ethambutol causes loss of visual acuity, colour vision and visual field. The occurrence

of ocular toxicity is dose related, loss of vision most likely to occur in patients receiving 25 mg/kg/day or more. However, vision loss has been documented in approximately 1% of patients receiving the recommended therapeutic dose of 15 to 25mg/kg/day.¹³⁻¹⁵ This rarely occurs before the patients have been on treatment for 2 months, with 7 months being the average.² Patients with impaired renal function from renal tuberculosis may be more prone to ethambutol-associated optic neuropathy; perhaps because ethambutol depends on the kidneys for excretion.^{16,17} It is also important for the clinician to be aware that there are reports of rapid onset, severe, bilateral visual loss despite treatment with therapeutic doses of ethambutol.^{18,19} Patients taking ethambutol should be instructed to discontinue the drug immediately at the onset of any visual symptoms and seek medical consult.

Thirdly, all patients commencing treatment with ethambutol should have a baseline (pretreatment) ophthalmological examination. This comprises best-corrected visual acuity, colour vision and visual field. These parameters are usually monitored periodically (every 1 to 3 months) during the treatment of asymptomatic patients. However, there is no consensus regarding the specific visual test and testing intervals appropriate for monitoring asymptomatic patients during treatment.¹⁹

In summary, ethambutol is associated with a real risk of permanent visual loss. The author postulates that in cases of ethambutol-associated chiasmopathy, ethambutol initially affects the optic nerve and subsequently, the optic chiasm, and can result in a bitemporal hemianopia. All physicians prescribing the drug should be aware of this and the drug should be used with proper patient education and ophthalmological monitoring.

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