CASE REPORT

Spectrum and Clinical Course of Visual Field Abnormalities in Ethambutol Toxicity

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ABSTRACT

Visual toxicities from ethambutol are rare but represent one of the few causes of non-glaucomatous and non-compressive bitemporal hemianopsia. The authors present a six-patient case series illustrating variable clinical presentation and reversibility of visual loss in patients treated with ethambutol for *Mycobacterium avium* complex, including four patients who presented with visual field defects suggestive of bitemporal hemianopsia. Two additional patients were being followed for glaucoma, developed visual field defects with ethambutol treatment, and subsequently recovered with cessation of drug. In patients being treated with ethambutol, reversible bitemporal hemianopsia was the most commonly noted presentation of ethambutol toxicity.

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Introduction

Since its introduction in the 1960s,¹ ethambutol has been used to treat various mycobacterial infections, including *Mycobacterium tuberculosis* (MTB) and *Mycobacterium avium* complex (MAC). Concomitantly, numerous reports have linked ethambutol usage to visual system toxicity,^{2,3} including optic neuropathy⁴ and retinopathy,^{5,6} with variable reversibility of visual loss.^{7–10} Reversible and permanent visual loss induced by ethambutol has primarily been reported only in patients treated for MTB. However, MAC also represents a significant pathogen in certain populations, including the immune-compromised and particularly the elderly where non-tuberculous mycobacterial infection prevalence has risen to 30 of every 100,000 people older than 70 years of age,¹¹ or approximately 8350 persons based on 2010 Census data. Because many patients with MAC are also treated with ethambutol, and the medication's potential for visual toxicity,¹² we report a series of six patients who developed vision loss due to this treatment. These patients presented with bitemporal hemianopsias that mimic the clinical features for compressive optic neuropathy.

Long-term follow-up data are available for most of these patients, some of whom had significant improvement of their acuity and fields.

Materials and methods

Presented is a retrospective case report of six patients being treated with ethambutol for MAC who demonstrated visual field changes. Presenting patient data are summarised in Table 1. Institutional review boards at the University of North Carolina and Duke University health care systems approved the de-identified retrospective study.

Results

Patient 1

An 80-year-old Caucasian female presented with blurred vision for 4 weeks. Her medical history was remarkable for MAC, for which she had been on ethambutol for 4 months. When seen by her ophthalmologist 8 weeks prior, she had had no complaints and her examination was normal. One week later, she began to develop blurred vision and was seen again by her ophthalmologist. The patient was

Table 1. Acuity and colour testing data on presentation.

Patient	Glaucoma Dx	Presenting VA OD	Presenting VA OS	Colour plates correct OD	Colour plates correct OS
1	No	20/70	20/400	1 of 10	0 of 10
2	No	20/50	20/60	5 of 10	8 of 10
3	No	20/80	20/400	8 of 10	8 of 10
4	No	20/100	20/40	8 of 10	9 of 10
5	Yes	20/20	n/a	1 of 15	n/a
6	Yes	20/120	20/160	0 of 8	0 of 8

referred to a retina specialist, who felt that visual complaints might be due to ethambutol toxicity.

On examination, uncorrected visual acuities were 20/70 OD and 20/400 OS. The patient identified 1/10 Hardy-Rand-Rittler (HRR) colour plates, right eye (OD), and 0/10 plates, left eye (OS). Visual field testing was suggestive of bitemporal hemianopsia (Figure 1A). Dilated fundus examination revealed normal nerves and fundus.

An magnetic resonance imaging (MRI) of the brain, orbits, and chiasm was normal.

Patient 2

A 68-year-old Caucasian female who had been taking ethambutol for atypical *Mycobacterium* for 16 months was referred for evaluation of ethambutol-related optic neuropathy. The patient

Figure 1. Visual fields of the first four patients demonstrating respect for the vertical midline for the first four patients (A–D, respectively).

noticed coloured, flashing lights from both eyes. She also reported blurring in both eyes and loss of the temporal field in the left eye. The patient's pulmonologist suspected ethambutol toxicity, and the medication was discontinued 2 weeks prior to the patient's neuro-ophthalmology evaluation.

On examination, corrected visual acuities were 20/50 OD and 20/60 OS. The patient correctly identified 5/10 colour plates OD and 8/10 plates OS. Visual fields were suggestive of a bitemporal hemianopsia that did not respect the vertical meridian (**Figure 1B**). Dilated fundus examination revealed normal optic discs.

An MRI of the brain, chiasm, and orbits revealed no compressive or vascular lesions. Six months after presentation, best-corrected acuities were 20/30 OD and 20/25 OS. Her colour vision improved to 9/10 HRR plates OD and 9/10 OS. The patient was seen 5 months later with subjectively normal vision, with acuities improving to 20/25 OD and 20/25 OS with restoration of visual fields and normal discs.

Patient 3

A 71-year-old Caucasian male who was being treated for 17 months with ethambutol and rifampin for atypical mycobacterial lung infection presented with blurring vision OU over 1 month. The ethambutol dose was lowered, but the patient noted continuing deterioration of vision.

On examination, best-corrected visual acuity was 20/80 OD and 20/80 OS. The patient correctly identified 8/10 Ishihara isochromatic colour plates in OU. Visual fields demonstrated bitemporal depression (**Figure 1C**). The optic nerves were normal. The remainder of the ophthalmic examination was unremarkable. MRI of the brain and chiasm was normal.

Two months after discontinuing ethambutol, best-corrected visual acuity was 20/80 OD and 20/400 OS. Colour vision testing demonstrated 4/10 HRR colour plates OU. Three months later, acuities improved to 20/30 OD and 20/60 OS with correct identification of 5–6/10 HRR plates in both eyes. Ten months after stopping ethambutol, the acuities were 20/25 OU with 9/10 HRR colour plates. The patient remained stable when seen again 6 months later.

Patient 4

A 59-year-old Caucasian female treated with ethambutol, rifampin, and azithromycin for MAC was referred to our clinic for suspected ethambutol toxicity. The patient developed subacute blurring, reported as “foggy,” in both eyes with onset 3 weeks prior to presentation. Past medical history, other than MAC infection, was non-contributory.

Uncorrected visual acuities were 20/40 OD and 20/30 OS. The patient identified 8/10 HRR colour plates OD, and 7/10 OS. Visual fields suggested mild bitemporal depression (**Figure 1D**). Dilated examination showed normal discs OU. There was no disc pallor or swelling in either eye. Dilated fundus examination and MRI of the brain were normal.

The patient was seen 3 weeks later with acuities of 20/100 OD and 20/40 OS, with 8/10 colour plates correct OD and 9/10 correct OS. Visual field testing revealed bitemporal loss in both eyes, strictly respecting the vertical midline. Retinal consultation suggested possible toxicity related to ethambutol treatment. Ethambutol and rifampin were discontinued. The patient had gradual recovery of visual acuity. Three months later, examination revealed acuities of 20/60 OD and 20/25 OS. Five months later, vision improved to 20/25 OU. The patient remained stable with normal visual function, including visual field recovery, during 3 years of follow-up.

Patient 5

An 81-year-old monocular, Caucasian female who was being treated for exfoliation glaucoma developed marked constriction of peripheral and central visual fields (**Figure 2A**). Her visual acuity was 20/20 OD and long-standing light perception OS from glaucoma and chronic hypotony post filtration surgery. No dyschromatopsia was noted in the right eye. The patient had been followed closely due to her monocular status and with a stable superior and an inferior nasal step, which had progressed little over years of follow-up.

At follow-up appointment 6 weeks later, marked visual field demonstrated continued progressive loss, despite intraocular pressures measured at 6 mm Hg on maximum medical treatment (**Figure 2B**). Colour vision had

Figure 2. Significant progression of visual field loss out of proportion to intraocular pressure trends and history of the patient's glaucomatous optic neuropathy. Note that the patient had been followed for years with stable visual fields before the regression plot below (A), even before the baseline field in (B). Ethambutol use commenced at age 76, and it was stopped at the arrow in (A). The progression velocity stabilised at this point, but she did not experience an improvement in field testing (C).

worsened to 1 out of 15 plates OD. An MRI verified normal brain, nerves, or optic chiasm. Because of otherwise well-controlled intraocular pressures, the patient's progressive visual loss and dyschromatopsia were attributed to a non-glaucomatous aetiology. After re-evaluating her history, it was noted that the patient had been treated with ethambutol for the past 5 years for MAC. Suspecting that the visual field deterioration may be due to ethambutol, the medication was stopped. Subsequent visual fields remained stable without improvement, her visual acuity remained stable, but colour vision did not improve during 4 years of follow-up.

Patient 6

A 79 year-old Caucasian female, with mild asymmetric optic nerve cupping, was being followed as a glaucoma suspect for several years. The patient had consistently normal visual fields (Figure 3A) and untreated intraocular pressures (IOPs) in mid-teens OU. The patient began complaining of worsening vision, which she suspected was due to a recent diagnosis of MAC bronchitis. Visual acuities were 20/30 OD and 20/25 OS.

Her follow-up appointments did not reveal any changes until 1 year later, when best-corrected visual acuity was noted to be 20/60 OD and 20/40 OS and colour vision measured by Ishihara colour plates was 6 of 8 OD and 8 of 8 OS.

Subsequent visual field testing revealed generalised reduction of sensitivity in both eyes, with non-specific bitemporal changes in both eyes. Three months later (Figure 3B), significant visual field worsening and development of a bitemporal hemianopsia that did not respect the vertical meridian was noted. Interestingly, confrontation visual fields were normal in both eyes, and Amsler grid testing was normal in the right eye. Visual acuity had deteriorated to 20/126 and 20/160, right and left eyes, respectively. Ishihara colour vision had worsened to 0 out of 8, in both eyes. The patient was evaluated by retina, glaucoma, and neuro-ophthalmology specialists. An MRI of the brain, chiasm, and optic nerves was normal. An extensive laboratory work-up for other types of optic neuropathy was performed and was unremarkable. Ethambutol toxicity was suspected, and the medication was discontinued.

Two months after stopping ethambutol treatment, visual acuity remained poor at 20/200, but colour vision had improved to 4 out of 8 plates in both eyes. Visual acuity improved to 20/80 OD and 20/60

Figure 3. Visual fields demonstrating presentation (A), progression (B), and resolution (C) of patient 6's visual field defects.

OS 3 months later, and 20/50 in both eyes after 6 months with complete restoration of colour vision. Visual fields also had improved (Figure 3C), but continued to exhibit some generalised and non-localising depressions.

Discussion

This case series underscores the importance of following all patients taking ethambutol for MAC or other related conditions. Epidemiologic studies of non-HIV (human immunodeficiency virus) patients in Europe and New York City report incidences of MAC respiratory infection in 0.2–2.0 in 100,000 people, and 2.7–3.1 in 100,000 for infection in any part of the body. In patients with acquired immunodeficiency syndrome and a CD4 count of less than <50 cells per cubic millimetre, 30–50% will eventually develop a severe, disseminated MAC infection.^{13–15} Therefore, familiarity of the visual consequences of ethambutol is necessary by prescribers and ophthalmologists alike.

We have observed several interesting features of ethambutol-related optic neuropathy. These include patient-reported changes in visual acuity and the

visual field, superotemporal field involvement, and frequent field loss temporal to the blind spot. Although there were some variations in the visual fields of the six reported patients, our case series suggests that bitemporal hemianopsia, reduction of visual acuity, and loss of colour vision are the most common presentations of visual toxicity due to ethambutol used to treat MAC. Subjective changes in visual functioning developed in all patients and were noted in glaucoma patients, who often fail to note visual field loss. These subjective changes of both visual acuity and visual fields prompted the patients to seek medical attention for their symptoms. Most of the patients demonstrated either improvement of visual function, or at least stabilization following cessation. Ethambutol-associated vision loss was largely reversible and occurred a few months after discontinuing the medication (Figure 4). The temporal field was most commonly affected, and the superotemporal quadrant was involved in all eyes in all patients in our series. The inferonasal quadrant was the least likely to be involved with visual field testing. A temporal wedge, or defect temporal to the blind spot, was appreciated in 72.7% of the eyes in the series.

Figure 4. Visual acuity over time for each patient from presentation and follow-up, if available.

Two patients in this series were being treated for glaucoma or followed as a glaucoma suspect. The data from our case series illustrate a critical need to be vigilant for non-glaucomatous visual field and visual acuity changes. In the setting of serial visual field testing for glaucoma, these changes can be easily misinterpreted for glaucoma progression. This could expose glaucoma patients to increased risks and complications of escalated glaucoma medical and surgical therapy while not recognising the need to discontinue ethambutol treatment. Non-glaucomatous aetiology should always be suspected in the setting of normal-tension glaucoma or well-controlled intraocular pressure, as illustrated by Patients 5 and 6. Colour vision testing is often useful in these cases. Clinicians should also determine whether the visual field changes are sufficient to explain significant and rapid decreases in visual acuity. It is interesting to note that Patient 5, who had been stable for several years, developed worsening of her fields at the same time as initiation of ethambutol use. There was a significant reduction in progression velocity upon its cessation. However, her visual acuity and field performance did not return. One may suspect that the glaucomatous nerve may be particularly vulnerable to any insult, and further studies are warranted to investigate whether ethambutol use may be particularly toxic in this patient group.

The pathophysiological mechanism of ethambutol-associated optic nerve toxicity is unclear. It has been suggested that increased concentration of

mitochondria within the papillomacular bundle predispose these fibres to damage from ethambutol and other agents that block oxidative phosphorylation.¹⁶ However, our findings suggest that retinal ganglion cells and their axons located in an inferior and nasal distribution are most at risk for ethambutol-related toxicity, thus causing superior and temporal depression. However, optical coherence tomography (OCT) imaging suggests that damage to retinal nerve fibre layer (RNFL) fibres is largely located on the temporal side of the macula within the papillomacular bundle.¹⁷ Reduction in visual acuity is consistent with injury in this area. Our clinical data suggest that ethambutol toxicity causes axonal dysfunction throughout the retina, affecting both the papillomacular bundle and the nasal retina.

In summary, we present six patients who presented with ethambutol toxicity that was reversible in most cases. These data underscore the need to perform regular ophthalmic follow-up for patients being treated with ethambutol. Periodic screening examinations appear warranted, although patients who develop toxicity frequently present with acute onset of subjective symptoms. Ordinarily, bitemporal hemianopsia manifests as a result of compression of the optic chiasm. Once a tuberculous infection of the central nervous system is known, one study found that 17.8% of patients manifested with optochiasmal involvement.¹⁸ However, central nervous system (CNS) involvement is only observed in 1–3% of tuberculous infections.¹⁹

Further, if properly treated with ethambutol, there are no known cases of development of tuberculoma in the CNS while already on therapy. To the best of our knowledge, there is only one reported case in a patient who was non-compliant with ethambutol treatment.²⁰ Additionally, although our patients were not systematically evaluated with OCT, our data more convincingly suggest that the site of pathology is the retina. Thus, although presentation of a patient with bitemporal hemianopsia may merit MRI evaluation, we do not recommend such radiologic surveillance for every patient in the absence of visual symptoms while taking ethambutol. Prescribers of ethambutol should be aware of its visual effects remain vigilant of patient's reported visual symptoms, and should have a low threshold to consult an ophthalmologist.

Declaration of interest

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

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