Ethambutol toxic optic neuropathy

Irimpan Lazar FRANCIS 1, Ramalingam MOHAN 1, Nayan JOSHI 1, Nadir Ali MOHAMAD ALI 1, Allimuthu NITHYANANDAM 2

1 Department of Ophthalmology, RIPAS Hospital, and 2 Division of Neurology, Department of Medicine, RIPAS Hospital, Bandar Seri Begawan, Brunei Darussalam

ABSTRACT

Ethambutol is a commonly used anti-tuberculous medications. Ocular toxicity of ethambutol is well established. It needs to be detected early and medication stopped promptly to avoid irreversible damage. A 64-year-old lady was referred for gradual deterioration of her vision of both eyes. Examination and investigations confirmed bilateral toxic optic neuropathy secondary to ethambutol. The drug was stopped with immediate effect. Three months later, her distance vision and colour vision improved significantly. The course and outcome of ethambutol induced toxic optic neuropathy is unpredictable. Optic nerve head remains normal on Fundoscopy until late in the disease. Improvement of vision after discontinuation of ethambutol occurs only in a minority of patients. This case highlights the importance of ocular screening to detect toxic neuropathies early to possibly prevent permanent visual disability.

Keywords: Ethambutol, dyschromatopsia, scotoma, optic neuropathy

INTRODUCTION

The proximal human visual pathway is prone to toxic and nutritional insults, leading to defective vision from to optic neuropathy. Toxic and nutritional optic neuropathies form a group of diseases characterised by gradual deterioration of the central and colour vision superadded with visual field defects. There has been an ever increasing list of drugs (Table: Refer Supplementary Text) that have the potential to evoke toxic optic neuropathy (TON). This diverse group is bound by shared symptoms and signs. All ages and both genders are affected without any national or racial boundaries. These neuropathies tend to be bilateral, mostly symmetric, painless and progressive. 1

Tuberculosis, a specific infective granulomatous disease has existed since Neolithic times. Anti-tuberculous drugs are usually prescribed for at least six months, and in some cases for a period of 12 months. Tuberculosis has been treated with combination therapy for over half a century. In 1961, Ethambutol was introduced as an anti-tuberculous drug. Carr and Henkind in 1962 reported TON caused by ethambutol. 2 Combination anti-tuberculous drug therapy remained the mainstay in treating tuberculosis. Combination drug therapy is advocated to

Correspondence author: Irimpan Lazar FRANCIS
Department of Ophthalmology, RIPAS Hospital, Bandar Seri Begawan, BA1710, Brunei Darussalam.
Tel: +673 8772253
E mail: fril50@hotmail.com
make use of their differential properties namely bacteriostatic or cidal, and thereby reducing drug resistance. Though known for their efficacy, these drugs are known to cause TON. Eradication of tuberculosis has not been completely successful yet, and hence anti-tuberculous drugs would still have an active role in future.

CASE REPORT
A 49-year-old moderately built and nourished lady was referred to the eye clinic with gradual progressive painless deterioration of vision in both eyes for distance and near sight since late June 2012. Two months previously, she had been diagnosed with pulmonary tuberculosis and was started on anti-tuberculous medications. Her therapeutic regimen included ethambutol.

On her visit, her best corrected visual acuity was recorded as 6/12 in the right eye and 2/21 in the left eye with dyschromatopsia. The intraocular pressures were normal in both eyes. The ocular anterior segments were normal. Pupils were brisk and equal with no Relative Afferent Pupillary Defect (RAPD). She had early cataractous lens changes in her left eye. Fundii examinations were unremarkable. Her central visual fields revealed bilateral Centro-caecal defects (Figure 1). Optical Coherence Tomography (OCT) showed rarefaction of the Retinal Nerve Fibre Layer (RNFL) and her Visual Evoked Potentials (VEP) showed delayed P100 on both sides (Table 1). She was diagnosed to have TON secondary to ethambutol. Treatment with ethambutol was stopped in consultation with the pulmonologist with immediate effect. She was followed-up regularly. Three months later, her best corrected visual acuity had improved to 6/7.5 in the right eye and 6/12 in the left eye.

DISCUSSION
Ethambutol and isoniazid are two commonly used anti-tuberculous first-line drugs worldwide. Ocular toxicity due to these drugs is
Table 1: Visual Evoked Potential Readings of the patient.

<table>
<thead>
<tr>
<th>Test</th>
<th>P1 Latency (ms)</th>
<th>Latency Difference (ms)</th>
<th>Amplitude (µv)</th>
<th>Amplitude Difference (µv)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OD</td>
<td>OS</td>
<td>OD</td>
<td>OS</td>
</tr>
<tr>
<td>1</td>
<td>115.80</td>
<td>124.50</td>
<td>8.7</td>
<td>2.9</td>
</tr>
<tr>
<td>2</td>
<td>115.50</td>
<td>124.80</td>
<td>9.3</td>
<td>9.2</td>
</tr>
<tr>
<td>3</td>
<td>114.60</td>
<td>151.80</td>
<td>37.2</td>
<td>4.9</td>
</tr>
<tr>
<td>4</td>
<td>115.80</td>
<td>120.30</td>
<td>4.5</td>
<td>7.4</td>
</tr>
</tbody>
</table>

well established. The exact mechanism of toxic effects of ethambutol on the optic pathway is unclear. 1, 3, 4 It remains largely unestablished as to why some drugs are toxic to the optic nerve while others are not. It is hypothesised that these drugs possibly cause TON through impairment the vascular supply or affects the tissue metabolism of the anterior visual pathway. It is thought that ethambutol causes mitochondrial insufficiency in the optic nerve fibres resulting in impairment of axonal transport along the optic nerve leading to neuropathy. 1, 5

Dyschromatopsia or alteration of colour perception, is often the first symptom and the earliest indicator of TON. 1, 3 Ethambutol causes blue-yellow colour defect early in the disease. Ishihara colour vision test used for congenital and acquired red-green defect may be of limited use in detecting early cases of ethambutol toxicity. 3 Fransworth Munsell 100 (FM 100) Hue test may be used for early detection. 3

The anterior segments are usually intact and the pupillary responses normal in the early stages. Fundoscopy typically shows no abnormal changes in early cases, but optic atrophy may ensue finally. 3, 6 A decrease in the RNFL thickness may be noted early in the disease process. 8 Even before the onset of ocular symptoms, electro-physiological tests such as VEP can detect the involvement of anterior visual pathway. Contrast sensitivity is affected even in the subclinical stages. Contrast sensitivity, OCT and VEP may therefore be considered essential tools for early detection of TON and for monitoring the progress after stopping ethambutol therapy. 2

TON caused by ethambutol primarily affects the central vision, characterised by a central field defect and not infrequently a centro-caecal scotoma. The peripheral vision invariably remains intact. It is still unclear why the papillo-macular bundle of the retina is specifically affected. Rarely ethambutol can present with bitemporal scotoma. It is hypothesised that damage of the nerve initially spreads to the anterior chiasm and later to whole chiasm producing “ethambutol chiasmopathy” causing bitemporal field defect. 1, 7

Ethambutol induced TON is related to the dose and duration of treatment. 1, 3, 8 The onset and course of the disease are highly variable. 9 Onset of the disease symptoms may occur between two and 12 months after
initiation of treatment. No "safe dose" has been suggested. 4 Ocular toxicity in susceptible patient is observed at a rate of 18% in those who receive a dose of 35 mg/kg/day, 6% in 25 mg/kg/day, and less than 1% in those receiving 15mg/kg/day of ethambutol. 3 The United States’ Food and Drug Administration (FDA) approved a dose of 15–25 mg/kg/day as comparatively safe.

Symptoms of TON are traditionally thought to be reversible. 6, 10, 11 There is no specific treatment for ocular toxicity caused by ethambutol. 12 Once toxicity is established, ethambutol should be stopped with immediate effect. Most patients are expected to recover in weeks or months. But there are patients whose vision may fail to recover or even further deteriorate in spite of discontinuation of the drug due to irrevocable damage to the visual pathway. 3, 4, 7, 8 Older patients and those who have impaired renal function are at the highest risk. 3 It is suggested that ethambutol should only be given to selected patients. The dose and duration of treatment should be optimised. Patients should be counselled on possible side effects and should also be screened before initiation and regularly thereafter for detection of TON during the treatment period. The routine visual screening tests may not be effective. 2

In conclusion, toxic and nutritional optic neuropathies resemble each other in their clinical presentation. TON is not only underdiagnosed but is often diagnosed late when visual recovery is not possible. The importance of proper counselling about the visual side effects of drugs with potential visual hazard cannot be over-emphasised. The course of the ethambutol induced ocular toxicity is unpredictable. Ophthalmologists should be aware of the potential ocular hazards of non-ophthalmic medications. Despite the widespread use of Ethambutol for the treatment of tuberculosis, there are no definite guidelines for monitoring its ocular toxicity. It is therefore desired that physicians are aware of medications that can cause TON. TON must also be considered in a patient who presents with bilateral symmetric and gradual painless visual disability while on medications. Early detection before symptoms occur is important and prompt management at this stage may ameliorate or possibly prevent permanent visual disability.

REFERENCES

