ROLE OF CONTRAST SENSITIVITY AND OPTICAL COHERENCE TOMOGRAPHY (OCT) IN EARLY DETECTION OF ETHAMBUTOL INDUCED TOXIC OPTIC NEUROPATHY A HOSPITAL BASED PROSPECTIVE STUDY
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ABSTRACT

BACKGROUND
Tuberculosis is one of the major diseases of public health importance in the world. Ethambutol hydrochloride is one of the first line drugs employed in the treatment of tuberculosis. The incidence of ethambutol induced toxic optic neuropathy is directly proportional to the dose and duration of ethambutol therapy. The aim of this study was to evaluate retinal nerve fibre layer thickness (RNFL) on optical coherence tomography (OCT) in patients on ethambutol therapy.

MATERIALS AND METHODS
This was a prospective study of 198 eyes of 100 patients being treated with ethambutol for tuberculosis at DOTS centre of Government Medical College, Srinagar. Visual acuity, contrast sensitivity and RNFL thickness on OCT were assessed. Examination was done before the start of therapy, after two months of treatment and two months after stopping ethambutol.

RESULTS
A total of 9/198 (4.54%) eyes demonstrated RNFL thinning on OCT after two months of ethambutol therapy. After two months of cessation of therapy, OCT changes were seen in 6/198 (3%) eyes.

CONCLUSION
The course of ethambutol induced ocular toxicity is unpredictable. Contrast sensitivity and RNFL thickness measurement are the early indicators of ethambutol induced optic neuropathy.

KEYWORDS
Ethambutol Toxicity, Retinal Nerve Fibre Thickness (RNFL), Optical Coherence Tomography (OCT).

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BACKGROUND
Tuberculosis is a worldwide health problem. The antitubercular drugs which affect the visual function are ethambutol and isoniazid. The ethambutol induced toxicity is quite common while that induced by isoniazid is rare.1

Ethambutol hydrochloride (2, 2-(ethylenedi-imino)-di-1-butanol dihydrochloride), a bacteriostatic drug was introduced as a chemotherapeutic agent in tuberculosis in 1961. Since then, mild to severe toxic amblyopia due to ethambutol has been reported by many authors.2,3

The dose of ethambutol is 15-30 mg/kg in adults. The toxic effects of ethambutol may be related to its chelating activity and the drug has been shown to deplete the eye of zinc. Retinal ganglion cells are predominantly affected in the retina of patients with ethambutol induced optic neuropathy.4 The feature of temporal pallor seen commonly in toxic optic neuropathy is due to the high mitochondrial content of the papillomacular bundle, and hence, the ganglion cells in this area are most affected by mitochondrial disturbance.5

Studies have reported incidence of ethambutol related retrobulbar neuritis of 1-18% depending on the dose administered varying from 15-30 mg/kg in patients receiving ethambutol for more than two months.6

Contrast sensitivity is used to assess the visual function in a number of ocular diseases particularly optic neuritis. Ethambutol therapy in tubercular patients has been found to cause an abnormal contrast sensitivity. Some patients on ethambutol therapy with normal visual acuity and colour perception may complain of visual disturbances due to an isolated loss of contrast sensitivity. The most widely used test for measuring contrast sensitivity is Pelli-Robson chart.

Patients of optic neuritis with lower visual function and low contrast sensitivity are associated with a reduction of
RNFL thickness, therefore, RNFL thickness serves as a structural biomarker supporting the validity of visual function tests in optic neuropathy. Ocular imaging techniques such as OCT have a role in neuro protection and the disease modifying therapies by measuring the RNFL.7

**AIM**
To evaluate contrast sensitivity and RNFL thickness on OCT in patients on etambutol therapy.

**MATERIALS AND METHODS**
The study was conducted on 198 eyes of 100 patients (two patients were one-eyed) suffering from tuberculosis attending the DOTS centre of Government Medical College, Srinagar. The study was approved by the Hospital Ethical and Research board. The patients were studied on the basis of any changes in contrast sensitivity and RNFL thickness after consumption of ethambutol therapy over a period of time.

It was a prospective analytical hospital based clinical study and duration was one and a half year.

All new tubercular patients on etambutol therapy were included. Exclusion criteria were history of tubercular meningitis, renal diseases, past history of use of anti-tubercular therapy, history of vasculitis, demyelinating diseases, other causes of optic neuritis (syphilis, measles) and optic disc oedema.

Detailed ocular history and relevant medical/surgical history was recorded in all cases. General physical and systemic examination was conducted on all the cases. Ocular examination included: best corrected visual acuity, colour vision, contrast sensitivity, intraocular pressure record, slit lamp biomicroscopy, fundus examination and RNFL thickness on OCT.

The patients were evaluated before starting the therapy, at the end of two months of therapy and then after two months of cessation of therapy.

**RESULTS**

**Table 1. Age Distribution of Patients**

<table>
<thead>
<tr>
<th>Age Years</th>
<th>No.</th>
<th>Percentage</th>
<th>Mean±SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 30</td>
<td>35</td>
<td>35%</td>
<td>39.1±15.54</td>
<td>10-65</td>
</tr>
<tr>
<td>31-40</td>
<td>16</td>
<td>16%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>41-50</td>
<td>17</td>
<td>17%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 51</td>
<td>32</td>
<td>32%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>100%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Mean age of the patients was 39.1±15.54 years.

**Table 2. Gender Distribution of Patients**

<table>
<thead>
<tr>
<th>Gender</th>
<th>No. of Patients</th>
<th>No. of Eyes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>62</td>
<td>122</td>
</tr>
<tr>
<td>Female</td>
<td>38</td>
<td>76</td>
</tr>
<tr>
<td>Total</td>
<td>100</td>
<td>198</td>
</tr>
</tbody>
</table>

Out of 100 selected patients 62 (62%) were males and 38 (38%) were females.

**Table 3. Visual acuity in Studied eyes**

<table>
<thead>
<tr>
<th>Visual Acuity</th>
<th>Baseline</th>
<th>Two Months from BL</th>
<th>Two Months after Cessation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percentage</td>
<td>No.</td>
</tr>
<tr>
<td>6/6</td>
<td>198</td>
<td>100</td>
<td>179</td>
</tr>
<tr>
<td>6/9-6/12</td>
<td>0</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>6/18-6/24</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>6/36-6/60</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Total No. of affected eyes</td>
<td>19</td>
<td>9.6</td>
<td>17</td>
</tr>
</tbody>
</table>

On using McNemar Chi-Square Test these differences of visual acuity between baseline and at two months from baseline (P < 0.000004), and between baseline and after two months of cessation of therapy (P < 0.000002) was statistically significant.

**Table 4. Contrast Sensitivity Changes in Studied Eyes**

<table>
<thead>
<tr>
<th>Contrast Sensitivity</th>
<th>Baseline</th>
<th>Two Months from BL</th>
<th>Two Months after Cessation Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percentage</td>
<td>No.</td>
</tr>
<tr>
<td>Normal</td>
<td>198</td>
<td>100</td>
<td>152</td>
</tr>
<tr>
<td>decreased</td>
<td>0</td>
<td>0</td>
<td>46</td>
</tr>
<tr>
<td>Total eyes affected</td>
<td>0</td>
<td>0</td>
<td>46</td>
</tr>
</tbody>
</table>

These differences in contrast sensitivity between baseline and at two months from baseline (P <0.000001), and between baseline and after two months of cessation of therapy (P <0.000001) is statistically highly significant.
In our study of 100 patients with 198 eyes, a total of 9/198 (4.54%) eyes demonstrated OCT changes (retinal nerve fiber layer thinning) at two months of follow up. Of these maximum changes were seen in yellow 6/9 (66.66%) eyes, 2/9 (22.22%) eyes were in red and 1/9 (11.11%) eyes were in both red and yellow. Of these affected 9 eyes all the eyes showed RNFL thinning in temporal quadrants besides other quadrants in some eyes, both at two months of follow up and after two months after cessation of therapy. After two months of cessation of therapy OCT changes were seen in 6/198 (3%) eyes.

It was seen that after two months of cessation of therapy 3/9 (33.33%) eyes had improved, while remaining of the eyes 6/9 (66.66%) eyes showed no improvement. These differences in OCT findings between baseline and at two months of follow up (P<0.0039) and after two months of cessation of therapy (P<0.031) are statistically significant.

In our study, 46/198 (23.23%) eyes demonstrated no changes. These differences in contrast sensitivity at two months of follow up. After two months of cessation of therapy 32/198 (16.2%) eyes had decreased contrast sensitivity. These differences in contrast sensitivity between baseline and at two months from baseline (P <0.000001), and between baseline and after two months of cessation of therapy (P<0.000001) was statistically highly significant. It was observed that after two months of cessation of therapy 14/46 (30.43%) eyes showed an improvement in contrast sensitivity status, while 32/46 (69.56%) eyes demonstrated no changes.

The maximum changes were seen in yellow 6/9 (66.66%) eyes. These differences in OCT findings between baseline and at two months of follow up (P<0.0039) and after two months of cessation of therapy (P<0.031) are statistically significant.

DISCUSSION
Out of 100 patients with 198 eyes, at baseline visual acuity ranged from 6/6 (198 eyes)-6/60 (2 eyes; these 2 eyes were excluded from the study as all the tests conducted on the affected eyes were not applicable to these 2 eyes because of very low baseline vision). At the end of two months i.e; first follow up, a decreased visual acuity was seen in 21/198 eyes (10.6%). After two months of cessation of therapy the decreased visual acuity was seen in 19/198 eyes (9.6%). On using McNemar Chi-Square Test these differences of visual acuity between baseline and at two months from baseline (P < 0.000004), and between baseline and after two months of cessation of therapy (P<0.000002) was statistically significant. It was observed that after 2 months of cessation of therapy 10/19 (52.6%) eyes had an improved status of visual acuity, while 2/19 (10.5%) showed a complete recovery to baseline. It was also seen that 5/19 (26.3%) eyes had a same status, while 2/19 (10.5%) eyes showed a worsening of visual acuity status after 2 months of therapy cessation. Garg P et al (2015). In their prospective study of ocular toxicity of ethambutol evaluated 64 patients. Their baseline visual acuity ranged from 6/6–6/60. Visual acuity loss was seen in 6/126 eyes and this difference in visual acuity between the baseline and second month after start of therapy was statistically significant (P<0.001). It was seen that all the affected 6 eyes improved on stoppage of the drug after a follow up of 1-2 months.

In our study, 46/198 (23.23%) eyes depicted a decrease in contrast sensitivity at two months of follow up. After two months of cessation of therapy 32/198 (16.2%) eyes had decreased contrast sensitivity. These differences in contrast sensitivity between baseline and at two months from baseline (P <0.000001), and between baseline and after two months of cessation of therapy (P<0.000001) was statistically highly significant. It was observed that after two months of cessation of therapy 14/46 (30.43%) eyes showed an improvement in contrast sensitivity status, while 32/46 (69.56%) eyes demonstrated no changes. Kandel H et al (2012). Prospectively evaluated 88 eyes of 44 patients on ethambutol therapy and concluded that there was a significant statistical difference between contrast sensitivity before and after the therapy (P<0.005). Salmon JF et al (1987). conducted a study on use of contrast sensitivity measurement in the detection of sub-clinical ethambutol toxic optic neuropathy, where they evaluated 100 patients of tuberculosis and found that contrast sensitivity measurement was abnormal in 38.2% of patients whose therapy included ethambutol for 3 months and 36.7% of patients on similar treatment for 6 months. This score of patients with abnormal findings was statistically significant.

In our study, 9/198 (4.54%) eyes demonstrated OCT changes (retinal nerve fiber layer thinning) at two months of follow up. Of these maximum changes were seen in yellow 6/9 (66.66%) eyes, 2/9 (22.22%) eyes were in red and 1/9 (11.11%) eyes were in both red and yellow layers. Of these affected 9 eyes all the eyes showed RNFL thinning in temporal quadrants besides other quadrants in some eyes, both at two months of follow up and after two months after cessation of therapy. After two months of cessation of therapy OCT changes were seen in 6/198 (3%) eyes. These differences in OCT findings between baseline and at two months of follow up (P<0.0039) and after two months of cessation of therapy (P<0.031) are statistically significant.
for detection of ethambutol toxicity on 104 eyes of 52 patients found a significant loss of mean temporal RNFL thickness in 3/104 (2.88%) eyes individually. Zoumalan CI et al (2005).12 in their study of three subjects (6 eyes) with a history of ethambutol induced optic neuropathy concluded that there was a combined mean loss of 46% fibres from superior, inferior and nasal quadrants in all the 6 eyes of 3 subjects. Kim U et al (2009).13 conducted a study on 20 eyes of 10 patients who developed optic neuropathy after taking ethambutol and revealed that there was no significant difference between RNFL thickness of the patients with early stage of ethambutol optic neuropathy and those of healthy age matched controls.

CONCLUSION
In present study we conclude that ethambutol therapy in tuberculosis, when taken according to the recommended dose and duration, can cause ocular toxicity. It was also observed that a significant number of patients show an improvement after cessation of therapy.

As early changes are not clinically apparent, OCT can clearly quantify the loss of retinal nerve fibres from the optic nerves of these patients as a sign of early toxicity from the drug, which would not be apparent on fundoscopy. Therefore, in conjunction with visual field testing, it is an additional objective test available to monitor patients on ethambutol.14

REFERENCES