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Research Article

Ethambutol Optic Neuropathy Visual Function and Visual Evoked Potentials

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Abstract

Ethambutol can cause a well-described, dose-related optic neuropathy. We performed a retrospective analysis of patients with ethambutol optic neuropathy to evaluate visual function and Visual Evoked Potentials (VEP). We found that vision decline was more severe if ethambutol cessation took longer than 4 weeks from initial visual decline, but that patients on ethambutol for greater than 8 months actually presented with better vision than patients on it for less than 8 months. VEP amplitudes were reduced in all patients, but latencies were normal. These findings suggest that it is important to monitor vision in the first 8 months of treatment. Although it is important to stop ethambutol as soon as toxicity is detected, most patients will recover some vision upon cessation.

Keywords: Ethambutol; Optic neuropathy; Tuberculosis; Visual evoked potentials

Abbreviations

OCT: Optical Coherence Tomography
ATT: Anti-Tuberculous Treatment
VEP: Visual Evoke Potentials

Introduction

Ethambutol has been used as part of the treatment protocol for tuberculosis since the 1960's. It was more effective and better tolerated than the para-aminosalicilic acid that it replaced [1]. Not long thereafter, however, a dose-related optic neuropathy was recognized affecting 1.5% of patients in one series of 800 patients [2]. Ethambutol chelates zinc, which is an important factor in nerve function in general, and in the optic nerve function in particular [3]. In India, new guidelines were introduced in the 2017 National Strategic Plan for Tuberculosis. This plan increased the duration of treatment for newly diagnosed tuberculosis from 2 months to 6 months [4]. Given these changes and the knowledge that visual loss after ethambutol-induced optic neuropathy can be devastating, a better understanding of the timing and degree of vision loss may be helpful in predicting visual recovery. The purpose of this study was to evaluate visual function and prognosis in patients with Ethambutol optic neuropathy and to measure VEP amplitude and latency in these patients.

Background

Visual loss in ethambutol optic neuropathy can present as central or peripheral field loss with or without dyschromatopsia [5]. Typically, at a dose of under 15 mg/kg/day, optic neuropathy is unlikely to develop, but at doses of 15-25 mg/kg/day, visual symptoms may develop over a period of months [5,6]. Fortunately, some visual improvement may occur with discontinuation of the drug, though some visual field and contrast sensitivity abnormalities may persist [7]. Optical Coherence Tomography (OCT) measurements of the retinal nerve fiber layer have been proposed to monitor visual loss, and better recovery may be predicted from normal OCT measurements at the time of vision loss [8,9].

Methods

A retrospective, observational, single centre study of consecutive patients was performed in the outpatient department of Aravind Eye Hospital, Coimbatore, India between July 2019 to October 2019 to evaluate visual decline in patients with Ethambutol optic neuropathy and visual recovery after cessation of that medication. Appropriate IRB approval was received from the Institutional Ethics committee of Aravind Eye Hospital (Registration № ECR/182/Inst/TN/2013/RR-19) for the Protocol code: RET202000273. Diagnosis of Ethambutol optic neuropathy was made clinically based on bilateral painless vision loss, decreased color vision and contrast sensitivity. Inclusion criteria were (a) age 18≥ years, (b) a diagnosis of tuberculosis requiring combination of Anti-Tuberculous Treatment (ATT) including Ethambutol at dose of 15-25 mg/kg daily. Patients with any known pathology of optic nerve or retina were excluded from the study. Informed consent form was obtained from all individual participants included into the study. All procedures performed in study were in accordance with the ethical standards of the institutional and/or national research committee with the 1964 Helsinki declaration and its later amendments or compatible ethical standards.

Visual acuity was recorded in logMAR for each eye. Ethambutol optic neuropathy was assumed to be symmetric in each patient, so each eye in a patient was included and counted separately. Visual evoked potentials were also recorded at time of presentation to measure changes in amplitude and latency with visual loss and recovery.

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Results

There were 18 men and 12 women enrolled with a mean age of 54±13 years. All patients were on some combination of anti-tuberculous treatment, including ethambutol, and they were on this treatment for an average of 7±4 months before the treatment was stopped for suspected ethambutol optic neuropathy. The dose of ethambutol was 15-25 mg/kg daily. The average interval from onset of vision loss to stopping ethambutol was 4.4±3.8 months. Once Ethambutol was stopped, treatment was continued with Isoniazid and Rifampicin. Ethambutol was replaced with Levofloxacin.

Mean visual acuity of all patients at presentation was 0.25±0.25 (0.57 logMAR, 6/23 or 20/75). At follow up after 3 months mean visual acuity had improved to 0.45±0.36 (0.35logMAR, 6/11 or 20/35).

When we evaluated patients who had been on ethambutol for greater than 8 months (the mean of treatment in our study population), the average presenting vision was 0.4±0.28 (0.40logMAR, 6/15 or 20/50) and at follow up 0.69±0.33 (0.16 logMAR, 6/9 or 20/30). For patients on ethambutol for less than 8 months, average presenting vision was 0.18±0.16 (0.75logMAR, 6/25 or 20/115) and at follow up 0.27±0.24 (0.57logMAR, 6/21±6/25 or 20/70). The presenting and follow up visual acuities were all statistically significantly better in the patients who were on ethambutol greater 8 months than the patients who were on it less than 8 months (Table 1).

	Average Visual acuity at presentation±SD (logMAR; Snellen), n 38	Average Visual acuity at follow up±SD (logMAR; Snellen), n 28
≥ ± 8 months treatment	0.4±0.28 (0.4;6/15 or 20/50)	0.69±0.33 (0.16;6/9 or 20/30)
< 8 months treatment	0.18±0.16 (0.75;6/25 or 20/115)	0.27±0.24 (0.57; 6/21 or 20/70)
p-value	0.0003	0.000005

Table 1: Vision relative to duration of ethambutol treatment.

If we evaluate the duration to stopping ethambutol, patients who stopped 4 or more weeks (the mean of duration from vision change to stopping medication) after initial vision loss presented with average vision of 0.17±0.15 (0.77 logMAR, 6/36 or 20/120) and at follow up had vision of 0.37±0.28 (0.44 logMAR, 6/15 or 20/50). Patients who stopped less than 4 weeks after initial vision loss presented with average vision of 0.36±0.3 (0.44logMAR, 6/18 or 20/60) and at follow up had vision of 0.57±0.4 (0.24 logMAR, 6/9 or 20/30). The presenting vision for patients stopped greater than 4 weeks was statistically significantly worse than for patients stopped before 4 weeks. However, at follow up, although the visual acuity was still worse in the >4 week group compared to the <4 week group, this did not reach statistical significance (Table 2).

Patient on ethambutol for ≥8 months had mean Visual Evoke Potentials (VEP) amplitude was 2.0±1.8 μV compared with patients who were on it for less than 8 months whose mean VEP amplitude was 1.8±1.37 μV, which was not statistically significantly different (p-value 0.6, Table 3). The latencies were also normal and without statistically significant difference between these groups (Table 3).

The mean VEP amplitude was 1.4±0.93 μV for patients who stopped ethambutol greater than or equal to 4 weeks after vision decline, while it was 2.4±2.02 for patients who stopped it less than 4 weeks after visual decline, which was statistically significant (p= 0.046, Table 4), and consistent with the visual acuity differences between these two groups. The latencies were again normal and without statistically significant difference between these groups (Table 4). The normal VEP amplitude in this population is 5 μV [10], so in all cases, it was reduced compared to normal.

	A Average Visual acuity at presentation±SD (logMAR; Snellen), n 38	Average Visual acuity at follow up ±SD (logMAR, Snellen), n 28
≥ 4 weeks to stop	0.17±0.15 (0.77;6/36 or 20/120)	0.37±0.28 (0.44; 6/15 or 20/50)
< 4 weeks to stop	0.36±0.3 (0.44; 6/18 or 20/60)	0.57+0.4 (0.24; 6/9 or 20/30)
p-value	0.005	0.06

Table 2: Vision relative to duration from visual decline to stopping ethambutol.

	Mean VEP amplitude±SD (μV)	Mean VEP latency±SD (μs)
≥ 8 months treatment	2.0±1.80	98.86±13.94
< 8 months treatment	1.8±1.37	103.03±10.62
p-value	0.60	0.23

Table 3: Visual evoked potential at presentation relative to duration of ethambutol treatment, n 38.

	Mean VEP amplitude±SD (μV)	Mean VEP latency±SD (μs)
≥ 4 weeks to stop	1.4±0.93	98.0±13.06
< 4 weeks to stop	2.4±2.02	104.58±11.79
p-value	0.046	0.09

Table 4: Visual evoked potential at presentation relative to duration from visual decline to stopping ethambutol, n 38.

Discussion

The toxicity from ethambutol is dose-related, and the current regimens recommend a dose of 15-25 mg/kg per day [11]. This toxicity is widely felt to be reversible with prompt cessation of the medication. While this toxicity is well known, to our knowledge, there has not been a study to evaluate the time course of vision loss related to treatment and its relationship to visual evoked potentials.

In this study, we demonstrated that the duration of treatment and the interval from visual loss to stopping ethambutol are important markers for presenting visual acuity. Interestingly, patients with ethambutol optic neuropathy who were on medication longer (≥ 8 months) presented with better vision those patients who were on it for less than 8 months. This finding may suggest the presence of some protective property or trait in some patients that prevents a more serious optic neuropathy from developing. More importantly, it suggests that patients who are going to have more severe visual decline, are likely to get that earlier on in treatment (less than 8 months), and so patients should be monitored closely in the first 8 months of treatment with ethambutol. These findings are consistent with other reports of

onset of visual decline from ethambutol toxicity [12,13]; however, both of these studies found poor improvement of vision after withdrawal of ethambutol, calling into question the reversibility of vision loss after ethambutol optic neuropathy. In our study, both groups of patients (≥ 8 months and < 8 months) recovered some vision after cessation of ethambutol, though the patients on treatment longer with better presenting vision ended up with better vision. Kumar found poor presenting vision of between 20/120 and counting fingers, with a mean interval between onset of therapy and toxic effects of 3.4 months. However, an important finding of our study was that the worse the vision was at presentation, the worse was the final vision. These other studies did not evaluate the duration of treatment, making this is an important finding in our study.

Next, we evaluated presenting vision and improvement relative to the time from visual decline to cessation of ethambutol. Not surprisingly, patients who took longer to stop ethambutol (≥ 4 weeks) presented with worse vision than patients who stopped it sooner (< 4 weeks). However, both groups recovered similar vision after cessation. These findings support prompt cessation of ethambutol after presumed optic neuropathy to prevent visual decline, but it seems the total duration of treatment is more important for final visual prognosis than is the duration of time to cessation.

Although all patients had reduced VEP amplitudes, there was no statistical difference between groups to differentiate them or predict visual recovery. Unfortunately, we do not have VEP results after visual improvement to demonstrate if and to what degree amplitudes improved after cessation of ethambutol. There were no significant changes in latency from the normal population in any group, which is consistent with a non-demyelinating optic neuropathy.

Conclusion

Ethambutol can cause a dose-related optic neuropathy. Our study demonstrated that the duration of treatment and the interval from visual loss to stopping ethambutol are important markers for presenting visual acuity. Paradoxically, patients on ethambutol for greater than 8 months actually presented with better vision than patients on it for less than 8 months. Possibly some underlying physical trait may protect some patients from severe optic neuropathy. Since more severe vision loss is most likely in the first 8 months of treatment, it would be important to closely monitor the vision of these patients especially in that time frame. Patients whose treatment was stopped greater than 4 months from onset of vision loss presented with worse vision that those whose treatment was stopped less than 4 months from onset of vision loss. However, final vision was similar in both groups. This finding implies that for patients who develop ethambutol optic neuropathy, stopping ethambutol earlier can prevent severe visual decline, but regardless of the time to cessation, visual recovery is generally good. Finally, VEP amplitudes were consistently reduced in our series of patients, but there was no change in latency. Limitations of our study include the small sample size, and lack of VEP results after visual improvement. Future studies could include formal correlation with visual acuity, OCT and visual field analysis.

Conflicts of Interest

The authors report no conflicts of interest.

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