Original Article

Ethambutol Induced Toxic Optic Neuropathy - A Retrospective Study in a Tertiary Eye Care Centre in Southern India

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ABSTRACT

Introduction: Ethambutol is an antibiotic used as a first line drug in the treatment of tuberculosis and a vision threatening side effect of EMB is ethambutol-induced optic neuropathy (EON). The aim of the study is to create awareness about the potentiality of ethambutol to cause ethambutol-induced optic neuropathy, careful monitoring of dose and patient education.

Materials and methods: A retrospective observational study of 14 patients whose complete Anti-tubercular treatment records could be retrieved were included. Epidemiological data including age, sex, systemic illness were recorded. Duration between optic nerve toxicity , usage of ethambutol and the drug dosage were noted. Best corrected visual acuity, anterior segment examination including pupils, extraocular movements, colour vision, central fields and fundus examination were evaluated. The patients were followed up at one and three month intervals.

Results: Associated systemic illness was found to be a confounding factor for the development of ethambutol-induced optic neuropathy. 57% of patients had diabetes mellitus followed by hypertension (14.2%), renal disease (7.1%). The average daily dose of Ethambutol ingested was 1078.5 mg (21 mg/kg) and this high dose could have been the primary cause for development of ethambutol-induced optic neuropathy. Vision ranged from total blindness to mild visual impairment and poor recovery of vision was noted even after discontinuing ethambutol.

Conclusion: Only a minority of patients showed improvement in visual function following discontinuation of ethambutol and the toxicity was found to be dose-dependent. Patients with comorbidities like renal impairment and diabetes mellitus appeared to be at greater risk. Ophthalmological examination before commencing treatment and periodic evaluation thereafter is mandatory.

Key words: Anti-tubercular treatment, Ethambutol, Optic neuropathy, Vision loss.

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INTRODUCTION

Tuberculosis is endemic in many countries in the world and India accounts for 27% of the global incidence(*Global tuberculosis report 2019*). Ethambutol has been in use to treat Tuberculosis (TB) since the 1960s. Ethambutol hydrochloride is a bacteriostatic antimicrobial agent used as a first-line defence against TB (Kahana et al.,1990). The drug has been frequently associated with optic nerve toxicity. Zinc is an important component of multiple enzymes in the retina and optic nerve tissue. The intake of ethambutol can deplete zinc ions, causing metabolic disorder and the occurrence of drug-induced optic neuritis (Wang and Sadun, 2013). Since its first use to treat TB, the drug's ability to cause toxic optic neuropathy has been sufficiently recognized and is found to be a dose-dependent adverse effect (Citron and Thomas, 1986).

The clinical characteristics of ethambutol induced toxic optic neuropathy (EON) include painless loss of vision and a centrocecal or bitemporal defect in the visual field (Melamud et al., 2003; Boulanger et al., 2013). Dyschromatopsia could be the earliest sign of toxicity. Red-green dyschromatopsia can occur but blue-yellow color vision defects are seen early (Polak et al., 1985). Hence all patients commencing treatment with ethambutol should have a baseline ophthalmological examination. Patients who experience ethambutol toxicity can have severe, persistent visual defects and permanent vision loss. This study emphasises the need for awareness about the potentiality of ethambutol to cause optic nerve toxicity, careful monitoring of drug dosage, risk factors in a South-Indian population and patient education.

MATERIALS AND METHODS

A total of 40 patients were diagnosed with EON from June 2019 to Feb 2020 in the neuro-ophthalmology department, Aravind Eye Hospital, Madurai, a tertiary eye care centre in South India. A retrospective observational study of 14 patients whose complete Anti- tubercular treatment (ATT) treatment records could be retrieved were included in the study. Toxic optic neuropathy was defined as a decrease of visual acuity, suppressed colour discrimination ability and visual field damage with or without changes in the fundus (Phillips, 2005). Patients with other causes of optic neuropathy were excluded. Epidemiological data including age, sex, systemic risk factors were recorded. The duration between the optic nerve toxicity, usage of ethambutol and the drug dosage was noted. All patients were advised neuroimaging to rule out optic chiasmatic arachnoiditis and TB optic neuritis as the cause of visual dysfunction. Ophthalmological examination included best-corrected visual acuity, anterior segment examination with significance to pupils, extraocular movements and fundus examination. Colour vision was tested by Ishihara pseudoisochromatic plates 38 plates edition (Kanehara Trading, Tokyo, Japan) at 33 cm and central fields by Humphrey's automated perimetry.

Patients with EON were advised to stop ethambutol immediately after the diagnosis, following the communication to the treating physician and were treated with methylcobalamin injections twice a week, methylcobalamin 1000 mcg tablets, zinc supplements and idebenone. The patients were followed up at intervals of one month and three months. Snellen's visual acuity test, colour vision and central fields were documented during the follow-up visits after one and three months.

Mean ± standard deviation and frequency (percentage) were given for continuous and categorical variables respectively. Visual acuity was converted to Logarithm of Minimum angle resolution value (LogMAR). The Shapiro Wilk test was used to check the normality of the data. To compare between the baseline and follow-up data ANOVA / Friedman test was used. A P-value less than 0.05 was considered statistically significant. All statistical analysis was done by using STATA software version 14.0.

RESULTS

Fourteen patients were diagnosed with EON. The range of the age of the patients was between 29 and 76 years (mean - 51.57 years). Ten (71.4%) were men and four (28.6%) were women. Out of the 14 patients, 57.1% had Diabetes, 14.2% hypertension, 7.1% renal disease and 7.1% had other systemic illnesses as summarised in Table 1. Both eyes were affected in twelve people (85.7%) and only the left eye was affected in two. (14.3%).

In the intensive phase regimen of ATT, the mean dose of rifampicin was 664.3mg (450-1350), isoniazid 326.8mg (225-600) and ethambutol was 1078.5mg (800-1375). The dose of the continuation phase regimen was, rifampcin 578.6mg (300-1350) isoniazid 289.3mg (150-600) and ethambutol 841.8mg (110-1200) (Figure 1)

The mean ± SD time interval between the appearance of visual symptoms and ethambutol ingestion was 146.4 days ± 60.6 days. Likewise, the mean time interval between diagnosis of toxic optic neuropathy and ethambutol stoppage was 36.9 ± 26.9 days as depicted in Table 2.

Table 1: Associated systemic illness in the patients diagnosed with ethambutol induced optic neuropathy.

Systemic illness	Yes (%)	No (%)	Total
Diabetes mellitus	8(57.1)	6(42.9)	14(100)
Hypertension	2(14.2)	12(85.8)	14(100)
Renal disease	1(7.1)	13(92.9)	14(100)
Others	1(7.1)	13(92.9)	14(100)

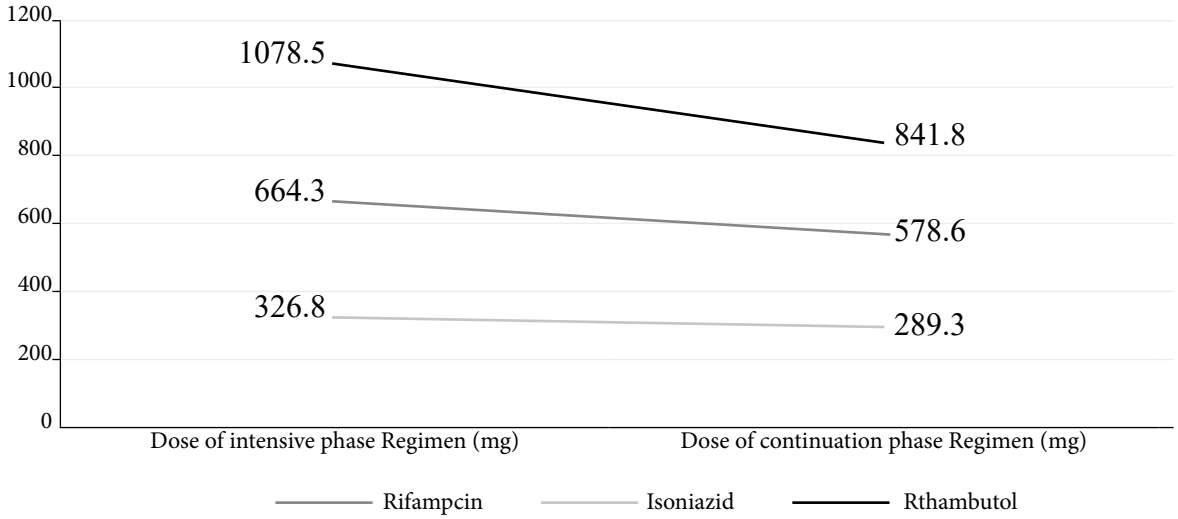

Figure 1: Dose of ethambutol, isoniazid, rifampicin ingested by patients receiving ATT (Anti-tubercular treatment) in intensive and continuation phase.

Table 2: The time interval between ingestion of ethambutol to the appearance of symptoms and diagnosis of EON to discontinuation of ethambutol.

	n	Mean(SD)	Min-Max
The time interval between ingestion of ethambutol and appearance of symptoms(days)	14	146.4(60.6)	20 – 258
The time interval between diagnosis of ETON and discontinuation of Ethambutol (days)	14	36.9(26.9)	0 - 76

Best-corrected visual acuity (BCVA) was calculated in logMAR. BCVA was normal in 4 eyes, 7 eyes had moderate visual impairment, 10 had severe visual impairment and blindness was recorded in 5 eyes. Colour vision was defective in 22 eyes, two eyes had a normal colour vision and in two eyes examination was not possible due to poor vision. Of the 26 eyes, central scotoma was found in 2 (16.7), hemianopia in 2(16.7) and peripheral constriction in 2 (16.7). 14 eyes had normal central fields and were not possible in three eyes due to poor vision.

Fundus examination showed normal disc in 17 eyes and temporal pallor in 6 eyes .12 of 14(85.7%) patients complained of defective vision, 2 (14.2) had a central defective vision.

The mean BCVA of the right eye (RE) was 1.0 at presentation, 1.1 in the first follow-up (1 month) and 1.2 in the second follow-up 2 (3 months) as summarised in Table 3. ANOVA / Friedman test was used to compare the BCVA in baseline and follow-up visits. P-value was 0.265,which was not statistically significant.

Table 3: Comparison of best-corrected visual acuity (BCVA) in the right eye (RE) between baseline and follow up visits.

BCVA RE logMAR	N	Mean(SD)	Median(Snellen's)	Min -Max	p-value
Baseline	14	1.0(0.6)	1.04(5/60)	6/9 – 1/2/60	0.265
Followup1	10	1.1(0.7)	1.15(4/60)	6/9 – 1/2/60	
Followup2	5	1.2(0.8)	1.3(3/60)	6/6 – 1/2/60	

Table 4: Comparison of best-corrected visual acuity (BCVA) in the left eye (LE) between baseline and follow up visits.

BCVA LE logMAR	n	Mean(SD)	Median(Snellen's)	Min-Max	p-value
Baseline	14	1.0(0.4)	1.08(5/60)	6/12 – 2/60	0.349
Followup1	10	0.8(0.4)	0.78(6/36)	6/9 – 2/60	
Followup2	5	0.8(0.6)	1(6/60)	6/6 – 3/60	

The mean BCVA of the left eye (LE) was 1.05 at presentation, 0.8 in the first follow-up and 0.8 in the second follow-up as shown in Table 4. P-value was 0.349 which is also not statistically significant. Improvement in colour vision was documented during both the follow-up visits. The p-value of colour vision of RE and LE was >0.999, which is not statistically significant.

DISCUSSION

In our study, 71% were men and this indicates the male preponderance of this disease similar to the study by Lee et al. (2008) Middle-aged people were more affected than others. Associated systemic illness was found to be a confounding factor for developing toxic optic neuropathy. 57% of the patients had diabetes mellitus followed by hypertension (14.2%), renal disease (7.1%) and others. Similarly, a study by Chen et al. (2012) in 231 patients, found that age greater than 65 years, hypertension and the presence of renal disease were associated with a greater risk of developing EON. Kanaujia et al. (2019) suggested that ethambutol should be avoided in renal disorder patients given the high incidence of toxic optic neuropathy.

Patients with EON present with painless, defective vision and examination reveals dyschromatopsia and visual field defects. Though EON is almost always bilateral, we had two patients with single eye affection. This is a unique feature in our study. Most of our patients (26 eyes) had defective colour vision and defects in central fields including central

scotoma, hemianopic field defect and peripheral constriction.

With reference to previous studies, EON develops from 15 days to 2 years after initiation of ethambutol treatment (Chatterjee et al., 1986). The mean interval between starting the medication and documentation of EON has been 3.4 to 5 months (Chatterjee et al., 1986). The incidence of EON has been found to be in correlation with the daily dose of ethambutol (Leibold, 1966). In our study, in the intensive phase of ATT, the average daily dose of Ethambutol ingested was 1078.5 mg (21 mg/kg). The normal dose recommended in the intensive phase is (15-20 mg/kg). This high dose was the primary cause for the development of EON. On average, visual symptoms developed after 146 days. (range 1-36 months) . Owing to this wide range, a correlation could not be found between duration of treatment and development of EON which was similar to the results of the study by Lee et al. (2008).

Immediately after the diagnosis, a letter was given to the treating physician to stop EMB. From the data recorded, it was found that the average time taken to stop was 37 days. This might be due to accessibility and other personal reasons.

Visual acuity ranged from total blindness to mild visual impairment. This wide range can be attributed to age, associated systemic illness, time of consultation after vision loss and renal impairment (Chen at al.,2012).

Ethambutol toxicity affects the small-calibre papillomacular bundle axons, and optic disc pallor does not develop till weeks to months after the fibres are lost. The clinical signs due to ethambutol toxicity are said to be usually absent on examination of the fundus (Koul, 2015; Makunyane and Mathebula, 2016). This is proven in our patients as normal disc was seen in 17 eyes and temporal pallor in 6 eyes. This again is the reason for central scotoma in a few of our patients. Kumar et al. (1993) described 7 patients treated with 25 mg/kg/day ethambutol, among whom only 3 patients had a documented gain in visual acuity to better than 20/200 after 8.3 ± 2.1 months.Tsai and Lee (1997) reported a series of 10 patients with EON, only 5 of whom had any degree of improvement in visual acuity with a follow-up period of 21.8 ± 8.8 months. In the same study, it was found that in patients over 60 years old the recovery rate was only 20%, whereas it was 80% for patients less than 60 years old, suggesting that older age may predict poorer recovery.

Though EON is reported to be reversible, complete recovery may not always be possible resulting in permanent visual impairment (Mandal et al., 2021). Hence, primary prevention is the most suitable way to prevent ethambutol optic neuropathy and awareness should be created about the side effects of the drug. Patient awareness programs highlighting the risk of ethambutol toxicity and the necessity of reporting to an ophthalmologist at the earliest signs of decrease in vision are needed (Mandal et al., 2021; Saxena et al., 2021).

CONCLUSION

Only a minority of patients showed improvement in visual function after discontinuation of ethambutol and was found to be dose-dependent toxicity. Patients with comorbidities like renal impairment and diabetes mellitus appeared to be at greater risk. All newly diagnosed TB patients must be subjected to an ophthalmological examination before commencing treatment with ethambutol and periodic evaluation thereafter. The prescribing doctor and the patient need to be well aware of the potential toxicity of ethambutol.

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