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Clinical profile and incidence of toxic optic neuropathy (TON) in patients receiving anti tuberculous therapy: A prospective study

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Abstract
Introduction: Ethambutol is a first line drug against tuberculosis. It can cause side effects like optic neuropathy, hyperuricemia and allergic reactions. Optic neuritis due to ethambutol is said to be dose dependent and with varying reversibility on discontinuation of the treatment in different studies. Several studies showed incidence of TON close to 1%.
Aim: To study the incidence and clinical profile of patients developing toxic optic neuropathy after receiving standard Anti tuberculous treatment (ATT).
Methods: We evaluated the enrolled patients who met the inclusion criteria between December 2021 and December 2023 by assessing their BMI, comorbidities and conducted an ophthalmic evaluation at the start of treatment and periodically thereafter at 3 monthly interval and 4 weeks after stoppage of treatment. After the development of defective vision, visual evoked response was done, ethambutol was stopped and patients were reassessed periodically. The data was processed with SPSS software version 20.0.Descriptive data were explained in frequency. Pearson's Chi - square test was used to compare the categorical variables and Fischer exact test when expected values were less than 5 with a p value <0.05 significance.
Results: Among 86 patients studied there was equal distribution of males and females. 7 (8.1%) presented with Toxic Optic Neuritis (TON). All TON patients were given ethambutol in the dose more than 15 mg /kg. 71.4% TON occurred after 8 weeks of ATT. Colour vision was normal in 43% of patients even when they presented with blurred vision. However Visual evoked potential (VEP) showed increased latency in all patients. Only 57.1% showed vision improvement to pre - optic neuropathy levels.
Conclusion: TON is commonly seen with higher doses of ethambutol and after 4 months of therapy. Apart from visual acuity, visual field, colour vision and fundus examination, visual evoked response and OCT may be done to detect early optic nerve involvement.

Keywords: Anti TB drugs, adverse events, TON

Introduction
India accounts for ¼ the of Global TB burden [1]. Ethambutol is used as first line treatment against tuberculosis. It can cause side effects like optic neuropathy, hyperuricemia and allergic reactions [2]. Optic neuritis due to ethambutol is said to be dose dependent and reversible on discontinuation of the treatment in certain studies [3]. However, there are certain other studies showing the irreversible nature of this optic neuropathy due to ethambutol [4, 5]. EON presents with painless loss of central vision and cecocentral scotomas in the visual field. There have been several studies showing incidence of EON in different countries, which is close to 1% [6, 7].
Daily anti tubercular treatment has been introduced in RNTCP (now NTEP) since 2016.Earlier ethambutol was given in the intensive phase and now drug has been extended into continuation phase of ATT. Few small studies and case reports started appearing in the literature regarding ATT induced optic neuropathy after this modification in the anti tuberculous regimen.
Toxic optic neuropathy (TON) is not only underdiagnosed but also diagnosed at a stage when a recovery is not possible [1]. Ethambutol is said to cause TON in 1 -5% of patients using ATT [17].

Its toxicity is classically described as dose and duration dependent and reversible on discontinuation of treatment. But this reversibility is controversial.

Rationale of the study: Lack of similar large studies in our area shows the importance of this study. High degree of awareness should be there among physicians regarding the possible adverse effects of anti-tubercular treatment.

Aim and objectives

- To study the incidence of toxic optic neuropathy in patients receiving standard Anti-tuberculous treatment
- To study the clinical profile of patients developing toxic optic neuropathy after receiving standard Anti tuberculous treatment.

Materials and methods

After considering the inclusion and exclusion criteria the patients between 15 to 70 years were enrolled into the study. We evaluated them by calculating their BMI, their comorbidities and conducted an ophthalmic evaluation at the start of treatment and periodically thereafter at 3 and 6 months interval and 4 weeks after stoppage of treatment. Ophthalmic evaluation included visual acuity, confrontation field, colour vision and fundus examination. Standard anti tuberculous therapy were given to these patients, ethambutol dosage was calculated and recorded for each patient in mg per kg. On development of defective vision, patients were evaluated with visual evoked response (VER) also to confirm the diagnosis, ethambutol was stopped and patients were reassessed periodically.

Inclusion criteria: All patients between 15 to 70 years who are diagnosed to have Tuberculosis (pulmonary and extra pulmonary; clinically diagnosed or microbiologically confirmed), notified under Nikschay and started on standard anti tuberculous treatment were enrolled into the study.

Exclusion criteria

- Optic neuropathy due to other causes.
- Diabetic retinopathy.
- Glaucoma.
- History of intraocular or refractive surgery other than cataract.
- Ocular tuberculosis.
- Congenital optic disc abnormalities.
- Cataract causing visual drop beyond 6/12 at initial visit
- Patients receiving modified ATT.
- History of intake of drugs causing TON other than ATT.
- PLHIV.

Study design

A Prospective study conducted in Malabar Medical College, Modakkallur, Kozhikode.

Study period: December 2021 to December 2023 following Institutional ethics committee approval.

Statistical analysis

The data obtained was coded and entered in Microsoft Excel and analysed using the SPSS software version 20.0. Baseline characteristics of study subjects were explained in terms of frequency, percentage mean and SD. Pearson's Chi - square test was used to compare the categorical variables and the Fischer exact test when expected values were less than 5. A p value < 0-05 was considered significant.

Results

101 patients were enrolled into the study.15 patients expired before completion of the study. Among 86 patients studied there was equal distribution of males and females Figure 1. Majority belonged to age group of 51 to 66 yrs. group Figure 2 and most of them belong to a normal BMI group Figure 3.

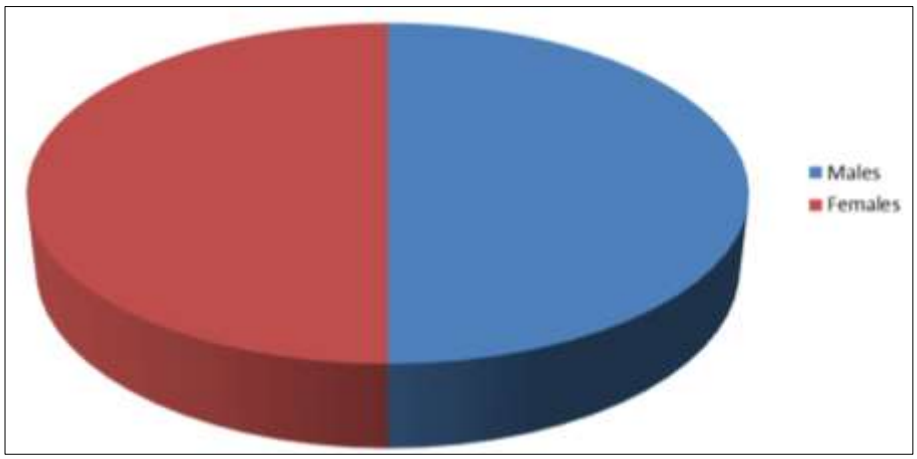

Fig 1: Gender

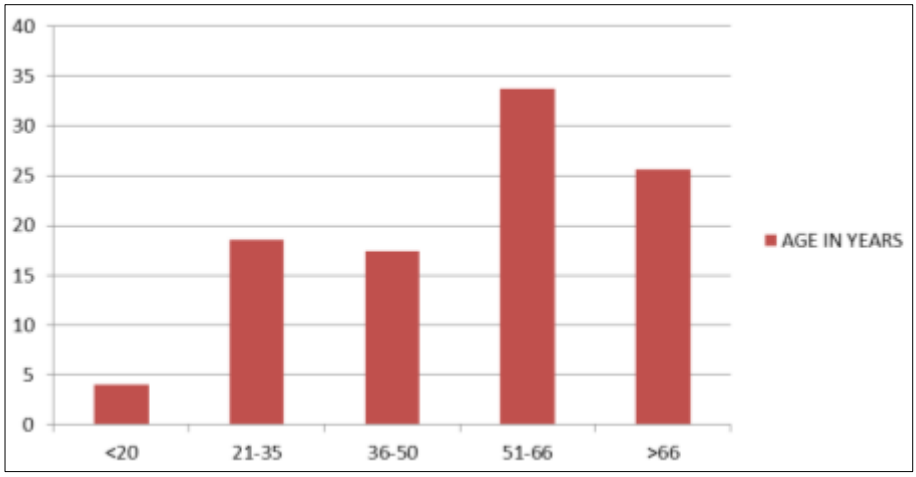

Fig 2: Age in years

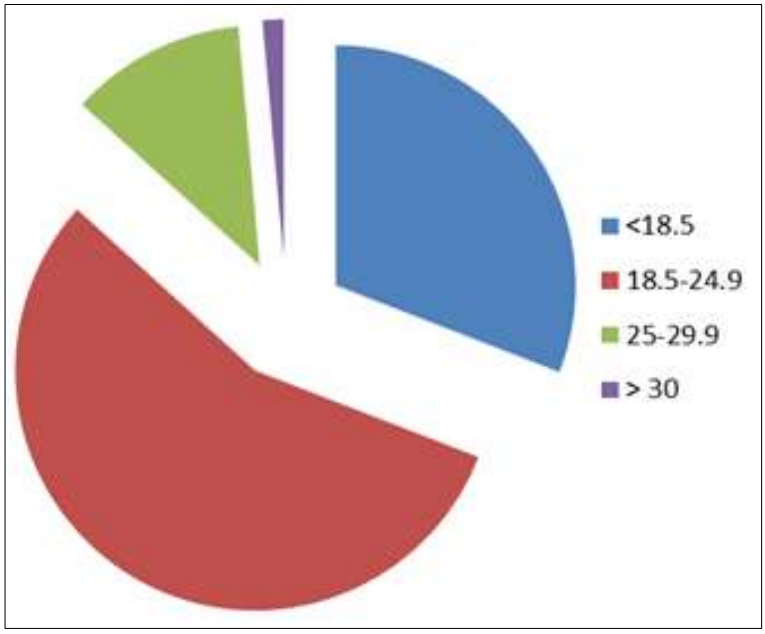

Fig 3: BMI

Out of the 86 study participants, 7(8.1%) presented with Toxic Optic Neuritis. (TON). Figure 4.

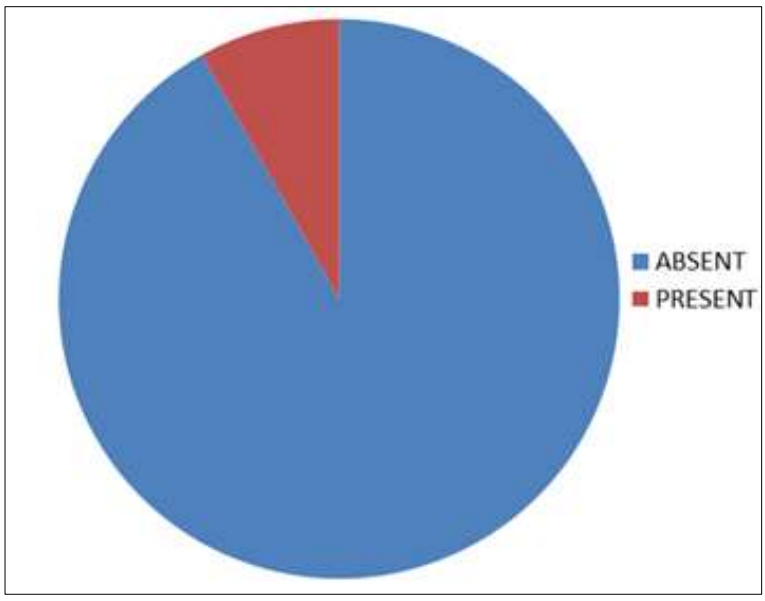

Fig 4: TON

Table 1: Patient Data

Serial Number	Age	Sex	DM	Smoker	Alchohol	HIV	BMI	Ethambutol dose mg/kg	TON START in weeks	Reversibility of vision
1.	51	Male	No	Yes	No	No	19.9	21.6	24	Yes
2.	34	Female	No	No	No	No	21.8	20.1	32	Yes
3.	68	Female	No	No	No	No	24	18.87	20	No
4.	60	Male	Yes	No	No	No	24.9	17.64	20	No
5.	59	Female	No	No	No	No	17.48	19.64	2	Yes
6.	70	Female	Yes	No	No	No	20	18.3	16	No
7.	58	Female	No	No	No	No	25	17.18	4	Yes

Clinical profile of ton patients

In our study of the 7 patients with TON 71.5% were females, 2 patients were diabetic and majority were in the normal BMI group. Of these 7 cases 2 were pulmonary and 5 were extra pulmonary tuberculosis cases.

Out of 86 patients who were started on ≥15 mg/kg ethambutol, 7(8.4%) presented with TON. All TON patients were given ethambutol in the dose more than 15 mg per kg. Table 1.

Table 2: Clinical Characteristics and Ethambutol-Induced Optic Neuropathy Associations in Tuberculosis Patients

Ethambutol dose	TON n (%)		Total	p value*
	Absent	Present		
<15	3(100)	0	3	0.47
≥15	76(91.6)	7(8.4)	83	
Total	79	7	86	

*Fisher exact test

None of the study subjects who were started on dose lower than 15 mg/kg presented with TON. But the difference was not found to be significant. Table 2.

All patients with optic neuropathy presented with vision impairment which was more or less symmetrical but vision was better than 6/60 in 71.4% (5 patients).Only 2 patients had less than 6/60. Colour vision was normal in 43% (3 patients) even when they presented with blurred vision. However Visual evoked potential (VEP) showed increased latency in all patients (100%).

Majority i.e.; 6 cases (85.7%), of the patients developed vision involvement before 24 weeks (6 months) of starting ATT which is within the standard total duration of therapy. 5 out of 7 cases (71.4%) occurred after 8 weeks of ATT which was in the continuation phase of treatment whereas only 2 patients (28.6%) developed optic neuropathy in less than 8 weeks which was in the intensive phase and one patient around 32 weeks. Fundus examination was normal at the onset of optic nerve involvement for all. Figure 5.

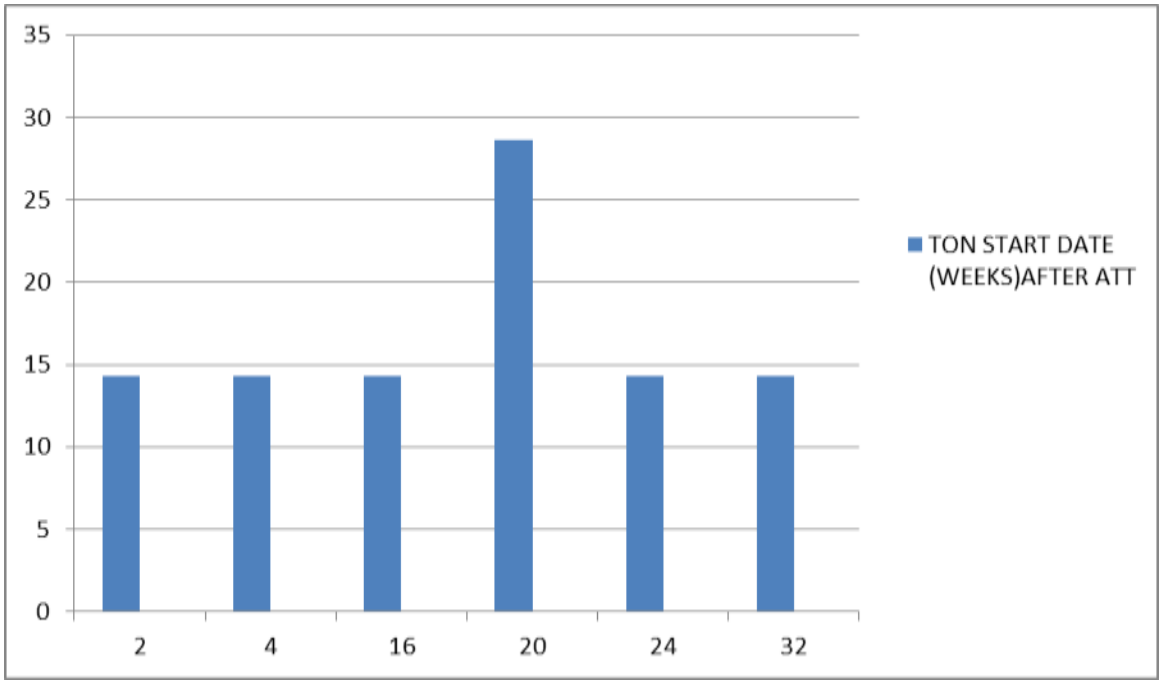

Fig 5: Clinical Characteristics and Progression of Optic Neuropathy in Tuberculosis Patients

No significant association was observed between age, gender, BMI, smoking, alcohol addiction and TON.

After the development of defective vision ethambutol was stopped and patients were reassessed periodically.

Even though 4 patients (57.1%) showed vision improvement to pre - optic neuropathy levels, there was permanent vision impairment in 3 patients (43%) even after stoppage of the drug and 1 patient had a permanent vision less than 6/60 (14.2%). Of the 3 patients with permanent vision impairment 2 cases were diabetic with abnormal serum creatinine values.

Discussion

In the present study incidence of TON was 8.1%.Smaller sample size may contribute to this much magnitude of TON. A similar larger review study in Kerala, India showed that only around 1.1% had ocular adverse events after anti tuberculous treatment [23]. The incidence of ethambutol related ocular toxicity in other previous studies varies from 1%-2.5% for dosage of 15 mg/kg per day, upto to 5%-6% for dosage of 25 mg/kg/day and 18% for dosage of 35 mg/kg/day [7]. That is the occurrence of this side effect was dose dependent. During this previous study the treatment

under the national programme was quoted as intermittent [7]. But in our study there was no statistically significant dose relation for this side effect compared to the previous studies. Many previous studies showed occurrence of TON due to ethambutol between 3-5 months of usage, though it may present as early as within 1 month and as late as 12 months of use [8-14]. In our study 85.7% of cases occurred within 6 months of anti tuberculous therapy and 71.4% occurred at more than or equal to 4 months of ATT which was comparable to previous studies. But cases occurred even at 2 weeks of starting Anti tuberculous therapy.

Recent Indian literature also points towards the importance of early detection and management of ethambutol associated optic neuropathy since there is evidence that the reversal on stoppage is variable and may be partial [18]. These are the inferences from our study as well. Even though we examined for colour vision defects at every visit, only 43% of patients who developed ethambutol toxicity had colour vision defects which is in concordance with the studies which emphasise that colour vision may not be an early sign [5, 19, 20]. There is also evidence that pattern visual evoked response (VER), visual field and OCT are sensitive tests to detect subclinical involvement [8, 15, 19, 20, 21, 22].

Conclusion

Toxic optic neuropathy can be a serious side effect after starting Anti tuberculous therapy. It is more commonly seen with higher doses of ethambutol and by more than or equal to 4 months of therapy even though a statistical significance was not observed in our study.

A recent consensus statement from India suggested that patients started on ethambutol need to be screened at least at 2 monthly intervals after the initial assessment and wherever possible. Apart from visual acuity, visual field, colour vision and fundus examination, visual evoked responses and OCT may be done to detect early optic nerve involvement[18]. This can be included in the guidelines for Anti tuberculous therapy as well.

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