Macular Vessel Density as Early Biomarker of Subclinical Ethambutol-Induced Optic Neuropathy: An OCTA based Cohort Study

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Abstract: *Ethambutol is an essential component of Anti-Tubercular Therapy (ATT) but is associated with dose-dependent optic neuropathy.* <u>*Aim*</u>*: To detect subclinical ethambutol-induced optic neuropathy (EON) by evaluating macular vessel density (mVD) and structural retinal changes.* <u>*Methods*</u>*: A cohort study of 30 patients receiving ATT was conducted. Ophthalmic examinations and OCT/OCTA imaging (mVD, mGCIPL, and pRNFL) were performed at baseline and after six months.* <u>*Results*</u>*: 56.7% of patients experienced decreased visual acuity. OCTA analysis revealed a statistically significant decrease in mVD in the affected group (p = 0.021). However, structural changes in macular Ganglion Cell–Inner Plexiform Layer (mGCIPL) and peripapillary Retinal Nerve Fiber Layer (pRNFL) did not reach statistical significance (p > 0.05).* <u>*Conclusion*</u>*: Macular vessel density (mVD) serves as a more sensitive biomarker than traditional structural thickness for the early detection of subclinical Ethambutol toxicity. These findings facilitate timely clinical intervention and dosage adjustment to prevent irreversible vision loss in tuberculosis patients.*

Keywords: Ethambutol, Optic Neuropathy, OCT Angiography, Macular Vessel Density, Subclinical Toxicity.

1. Introduction

Approximately 26% of the Indian population is infected with Tuberculosis [1]. Anti-tubercular therapy (ATT) commonly utilizes Ethambutol, a bacteriostatic agent. However, ethambutol-induced optic neuropathy (EON) is a significant adverse effect, with the risk exceeding 18% at daily doses above 35mg/kg [2].

EON is hypothesized to result from metal chelation of zinc and copper, causing mitochondrial dysfunction, destruction of myelin, and impaired axonal transport [3]. Advanced imaging modalities like Optical Coherence Tomography Angiography (OCTA) can detect subclinical microvascular changes before traditional clinical signs, such as reduced visual acuity or color vision changes, become apparent [4].

2. Methodology

A prospective observational cohort study was conducted on 30 patients diagnosed with Tuberculosis starting Ethambutol therapy. Inclusion criteria required patients to be asymptomatic with no objective visual impairment at baseline. Patients with pre-existing optic neuropathy, retinal disease, or intake of other neurotoxic drugs were excluded.

This study was approved by the Institutional ethics committee. Written informed consent was obtained from all participants. The study adhered to the declaration of Helsinki.

Examination and Imaging Protocol: Patients underwent visual acuity, color vision, and fundus examinations. At 6 months, OCT and OCTA scans (AngioPlex SD-OCT) were used to measure:
- mGCIPL: Macular Ganglion Cell–Inner Plexiform Layer thickness.
- pRNFL: Average peripapillary Retinal Nerve Fiber Layer thickness.
- mVD: Macular Vessel Density.

The data was analysed using SPSS version 25.0

Independent t-test was used to compare continuous variables between the two groups. A p-value <0.05 was considered statistically significant.

3. Results

At the 6-month follow-up, 17/30 patients (56.7%) showed decreased visual acuity whereas color vision was affected in 47.1% of those with decreased acuity.
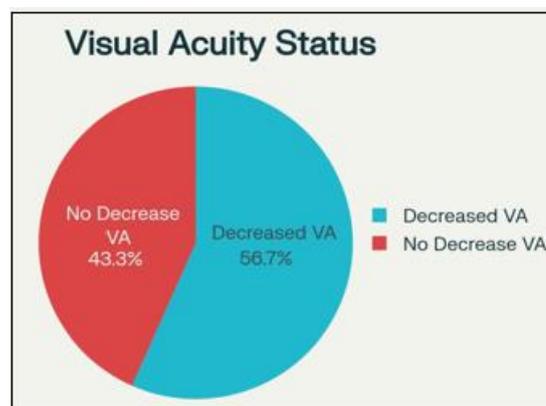

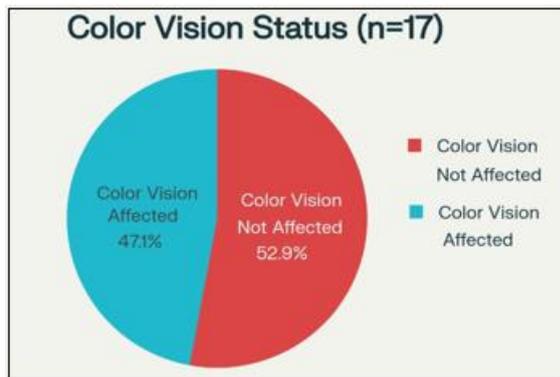**Figure 1:** Pie chart denoting comparison of Visual Acuity

Figure 2: Pie chart denoting comparison of Color Visual

Table 1: Data of patients with no change in visual acuity

No	Age	Sex	mVD	mGCIPL	pRNFL
1.	65	M	11.05	89.7	111.1
2.	37	F	10.8	89.5	93.4
3.	63	F	10.99	79.8	110.7
4.	54	M	6.4	88.9	111.3
5.	25	M	11	79.6	94.5
6.	40	M	6.2	89.3	101.6
7.	60	M	11.3	79.7	101.9
8.	31	F	8.3	89.43	106.7
9.	55	M	7.3	85.9	99.4
10.	24	M	11.13	82.6	101.6
11.	35	F	7.1	83.7	108.2
12.	47	F	11.2	82.8	98.9
13.	79	M	9.8	83.1	100.8
Mean±SD	47.3		9.42±2.03	84.92±4.04	103.06±6.04

Table 2: Data set in patients with decreased visual acuity

No	Age	Sex	mVD	mGCIPL	pRNFL
1.	67	M	8.29	91.29	113.4
2.	26	F	5.19	89.4	103.6
3.	58	F	8	85.5	98.7
4.	30	F	5.22	84.9	109.3
5.	32	F	4.93	88.7	97.8
6.	51	F	6.31	99.1	102.2
7.	34	F	8.12	85.9	111.8
8.	49	F	9.6	84.6	104.2
9.	19	M	5.8	87.3	100.3
10.	62	M	5.27	89.1	109.8
11.	68	M	5.1	86.7	111.1
12.	24	F	7.9	84.03	103.5
13.	32	M	6.5	87.9	99.5
14.	70	M	5.7	90.2	102.3
15.	41	M	6.09	84.23	106.8
16.	70	M	6.74	88.56	110.6
17.	50	F	4.6	86.35	104.6
Mean±SD	46.05		7.54±2.10	87.39±2.36	105.26±4.95

Table 3: Comparative Analysis of Parameters

	Patients without decrease in VA (n=13)	Patients with decrease in VA (n=17)	P – value
mVD	9.42±2.03	7.54±2.10	0.021
mGCIPL thickness	84.92±4.04	87.39±2.36	0.057
pRNFL thickness	103.06±6.04	105.26±4.95	0.091

OCTA measurements of mVD showed a significant decrease in the group with reduced vision (p=0.021). Structural markers (mGCIPL and pRNFL) did not show statistically significant changes.

4. Discussion

The significant reduction in mVD among symptomatic patients, despite the absence of significant structural thinning in pRNFL or mGCIPL, suggests that microvascular changes precede mechanical tissue loss. Ethambutol's toxic effect on mitochondria likely leads to a reduction in metabolic demand or direct microvascular insult [4, 5]. Because mVD serves as a sensitive indicator while structural layers remain stable, it represents a superior biomarker for detecting toxic insult at a subclinical stage, allowing for earlier dosage adjustments.

5. Conclusion

To prevent irreversible visual impairment, mVD should be monitored as a highly sensitive indicator for preclinical Ethambutol toxicity. Utilizing OCTA in clinical practice allows for informed decisions regarding the cessation or adjustment of ATT in tuberculosis patients.

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