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LETTER

Ethambutol-induced optic neuropathy: should we mandate ophthalmic examination in TB treatment?

Dear Editor,

India's National Tuberculosis Elimination Programme (NTEP)[1] and the WHO have recommended ethambutol (EMB) for use in the continuation phase of TB treatment due to the higher prevalence of isoniazid resistance in the patient community. This leaves only a single drug in the continuation phase that might adversely affect treatment outcomes.[2] While reporting adverse drug reactions (ADRs), we found that EMB often induced optic neuropathy during anti-TB therapy (ATT) for drug-susceptible TB (DS-TB). In the study presented here, we define these ADRs and recommend adopting safety precautions when treating DS-TB patients.

A review of the literature indicates that ophthalmic toxicities due to EMB is dose-related,[3,4] reported as retro-bulbar neuritis, with a range of less than 1–3%.[3] Although up to 12% occurrence has been reported in India[5] and globally,[6] the pooled cumulative incidence of any visual impairment was 22.5/1,000 persons, with permanent impairment in 4.3/1,000 persons. However, these data need to be further substantiated through analysis. Under the aegis of the Indian Neuro-Ophthalmology Society, a team of neuro-ophthalmologists, infectious disease specialists and scientists met to formulate consensus statements for the prevention and management of EMB-induced toxic optic neuropathy.[7]

The National Institute for Research in Tuberculosis (NIRT) Adverse Drug Reactions Monitoring Centre (AMC) was tasked with reporting ADRs and, in 6 months (September 2022–February 2023), we reported 75 ADRS from 400 cases on TB treatment. Of these, 11 cases (11/75, 14.6%) reported EMB-induced optic neuropathy/neuritis under NTEP and complained of initial diminished vision. These patients were referred to ophthalmologists. The majority were male (9/11), and although most were aged ≥50 years (7/11), four patients were <50 years of age, with one 19-year-old male. The majority had bilateral eye involvement (10/11), and defective vision manifested as decreased visual acuity with of loss of central vision due to involvement of the papillomacular bundle, and defective colour vision, mainly red-green defect identified using the Ishihara pseudo-isochromatic colour vision plates. The symptoms did not correlate with dosage given. Of the 11 patients, seven had a history of diabetes mellitus and were on treatment, with blood sugar levels under control at the time of review. Only 1/11 was HIV-infected (on antiretroviral therapy for a long period of time); 2/11 presented with ocular complaints at Months 2 and 3; 1/11 at Month 4; 4/11 at Month 5; and 1/11 at Months 6 and 7 after initiating ATT. The majority either had completed ATT when the decision was made to discontinue EMB (5/11) or had their EMB discontinued with a few doses remaining for completion (4/11). After 6 months of discontinuing treatment, 7/11 cases said there was no improvement in the vision, while the remainder reported a mild (subjective) improvement. The majority were hesitant to attend for ophthalmic examinations.

In addition to the 11 ADRs reported by the NIRT, there were 500 Individual Case Safety Reports (ICSRs) from other AMCs of the Pharmacovigilance Programme of India (PvPI) associated with ocular disorders resulting from ATT. Results of the causality assessment of these ICSRs is not known. The PvPI have come across similar situations where blindness was due to miltefosine (used in visceral Leishmaniasis treatment). After assessing these cases, it was recommended that patients under miltefosine treatment should have a mandatory periodic eye examination. The 11 ADRs associated with EMB given during DS-TB treatment raises concerns. Although the numbers are small, we are concerned because 1) the majority of the other ADRs reported, including hepatotoxicity, arthralgia, itching, etc., resolved completely; however, none of these cases had recovered completely after a year. 2) The reporting of ADRs due to any drug is gathering pace after recent awareness campaigns (including continuous medical education activities and observance of the National Pharmacovigilance Week); nevertheless, we believe that ophthalmic toxicity due to ATT continue to be underreported. 3) Because of the slow progression of ophthalmic toxicity, many cases are likely to be missed if not followed up carefully.

The risk factors associated with ocular toxicity of EMB include increasing age, duration of EMB use, higher dose, hypertension, renal impairment, diabetes, consumption of tobacco/alcohol and concurrent optic neuritis due to other diseases; onset generally varies between a few days to 2 years after starting ATT.[3,8,9] Most importantly, due to its insidious onset and slow progression, there is a delay in detection, leading to delay in appropriate management. Typical presentation include painless loss of central vision and cecocentral scotomas in the visual field;[3,9] there are also reports of loss in visual acuity, visual field defects, colour vision abnormalities and optic disc abnormalities.[6] In the majority of cases, there is bilateral eye involvement, and although some report that these are reversible on

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discontinuing EMB, there are also reports of permanent damage.[3,6,8] Optical coherence tomography, which could be used to quantify the loss of retinal nerve fibres from the optic nerves, as well as loss of Gangion cell complex; multifocal electro retinogram; and visually evoked potentials (VEPs) are some of the advanced tests that have been recommended,[3,7,8] as some vision abnormalities are sub-clinical;[10] however, the availability of and access to these tests at primary healthcare centres are not guaranteed (Table).

Table. Reported cases of optic neuritis as EMB-induced adverse drug reaction among patients with drug-susceptible TB on TB treatment

Case no	Age (years)	Sex	Ocular complaints	Ophthalmic diagnosis	Diabetic status	HIV status	Time of complaint during TB treatment	Time of ATT when EMB withheld	Ophthalmic status at follow-up (after Month 12 of ATT)	Weight (kg)	Number of FDC* tablets (dose)
Case 1	50	F	Diminished vision both eye, left more than right	Optic neuritis	Yes, controlled	NR	Month 3 of ATT	Month 5	No improvement	52	4
Case 2	54	M	Defective vision right eye	Toxic optic neuropathy	No	NR	Month 4 of ATT	ATT completed before withhold	Mild improvement subjectively	30	2
Case 3	51	M	Defective vision both eyes	Toxic optic neuropathy	Yes, controlled	NR	Month 3 of ATT	Month 5	No improvement	68	5
Case 4	45	M	Diminished vision both eye	Toxic optic neuropathy	Yes, controlled	NR	Month 6 of ATT	Month 5 (CP without EMB)	No improvement	74	5
Case 5	58	M	Defective vision both eyes	Toxic optic neuropathy	No	Reactive	Month 5 of ATT	ATT completed before withhold	No improvement	55	4
Case 6	65	M	Defective vision both eyes	Toxic optic neuropathy	Yes, controlled	NR	Month 5 of ATT	Month 5	No improvement	55	4
Case 7	19	M	Diminished vision both eyes	Optic neuritis	No	NR	Month 7 of ATT (CP extended due to missed doses)	Month 7	No improvement	41	3
Case 8	70	F	Diminished vision both eyes	Optic neuritis	Yes, others (CKD/COPD)	NR	Month 2 on ATT	Month 2	No improvement	45	3
Case 9	34	M	Blurred vision both eyes	Optic neuritis	No	NR	Month 2 of ATT	Month 3	Mild improvement subjectively	80	6
Case 10	50	M	Defective vision both eyes	Toxic optic neuropathy	Yes, controlled	NR	Month 5 of ATT	ATT completed before withhold	No improvement	73	5
Case 11	49	M	Defective vision both eyes	Toxic optic neuropathy	Yes, controlled	NR	Month 5 of ATT	ATT completed before withhold	Mild improvement subjectively	49	3

**Each FDC tablet contains rifampicin 150 mg, isoniazid 75 mg, EMB 275 mg and pyrazinamide 400 mg.*
ATT = anti-TB treatment; EMB = ethambutol; FDC = fixed-dose combination; F = female; NR = not reported; M = male; CP = continuation phase; , CKD = chronic kidney disease; COPD = chronic obstructive pulmonary disease.

Because of the need for EMB during the continuation phase in countries like India with significant isoniazid resistance,[11] we recommend increased vigilance for ophthalmic toxicities. We propose an ophthalmic examination at baseline, and at Months 2, 4 and 6 for all patients started on ATT for DS-TB. If ophthalmic examinations are not feasible at frequent intervals, then the minimum should be at baseline and at Month 2 of treatment (or later). An advisory awareness note about ophthalmic toxicity due to EMB to Medical Officers treating TB patients, stressing the necessity of reporting such ADRs in accordance with clinical standards[12] could improve detection. The healthcare professionals and patients are encouraged to report such adverse effects/ADRs to the nearest ADR Monitoring Centre of PvPI using the relevant ADR Reporting Form. As we did not follow up these patients on ATT prospectively for the development of ophthalmic toxicity, we could not assess the actual proportion of ophthalmic toxicity among DS-TB patients.

To conclude, we suggest ophthalmic screening for all DS-TB patients started on ATT. Early detection of EMB-induced optic neuropathy to prevent further progression will significantly improve quality of life for those undergoing TB treatment.

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S. R. Kumar,[1] S. S. Hissar,[1] P. M. Ramesh,[2,3] M. Shanmugam,[4] V. Kalaiselvan,[5] J. Prakash,[6] C. Padmapriyadarsini[7]

[1]Department of Clinical Research, Indian Council of Medical Research-National Institute for Research in Tuberculosis (ICMR-NIRT), Madurai Unit, Madurai, [2]Department of Respiratory Medicine, Stanley Medical College, Chennai, [3]Government Hospital for Thoracic Medicine, Tambaram, Chennai, [4]Neuro-ophthalmology services, Aravind Eye Hospital, Madurai, [5]Indian Pharmacopoeia Commission, Ministry of Health & Family Welfare, Government of India, Ghaziabad, [6]National Coordination Centre, Pharmacovigilance Programme of India, Indian Pharmacopoeia Commission, Ministry of Health & Family Welfare, Government of India, Ghaziabad, [7]ICMR-NIRT, Chennai, India

Correspondence to: S Ramesh Kumar, ICMR-National Institute for Research in Tuberculosis, ICMR-NIRT Madurai Unit, Ward 62 (upstairs), Government Rajaji Hospital, Madurai 625020, India.
email: santhana.k@icmr.gov.in; drrameshskumar@yahoo.co.in

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