Consensus Statement

Ethambutol toxicity: Expert panel consensus for the primary prevention, diagnosis and management of ethambutol-induced optic neuropathy

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Ethambutol use may lead to permanent vision loss by inducing a dose- and duration-dependent optic neuropathy. This has been of concern to ophthalmologists and physicians both; however, ethambutol continues to be used because of its anti-mycobacterial action with relative systemic safety. Recently, the guidelines of the Revised National Tuberculosis Control Programme of India have been revised to allow for fixed dose and longer duration of ethambutol use; this is likely to result in an increase in vision-threatening adverse effects. Taking cognizance of this, neuro-ophthalmologists, infectious disease specialists, and scientists met under the aegis of the Indian Neuro-Ophthalmology Society to deliberate on prevention, early diagnosis, and management of ethambutol-related toxic optic neuropathy. The recommendations made by the expert group focus on early suspicion of ethambutol toxicity through screening at the physician's office and opportunistic screening by the ophthalmologist. Further, they focus on an early diagnosis through identification of specific clinical biomarkers and on management in way of early stoppage of the drug and supportive therapy. This statement also describes the mechanism of reporting a case of toxic optic neuropathy through the Pharmacovigilance Programme of India and emphasizes the need for spreading awareness regarding vision-threatening adverse effects among patients and healthcare workers.

Key words: Antitubercular therapy, ethambutol, optic neuropathy, prevention, toxic optic neuropathy

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Ethambutol forms one of the first-line drugs for the treatment of tuberculosis. Despite being considered very safe and one of the least systemically toxic first-line drugs, it was shown to result in optic neuropathy within two years of its invention in 1961.[1,2] Since then, numerous studies have shown its definitive role in causing a partially reversible optic neuropathy with variable loss of visual functions.[3-15]

The reported incidence of ethambutol-related ocular toxicity varies widely in different studies, ranging from 1%–2.5% for dosage of 15 mg/kg per day and increasing to 5%–6% for dosage of 25 mg/kg/day and reaches as high as 18% for dosage of 35 mg/kg/day. The toxicity typically occurs between 3–5 months of usage, though it may present as early as within 1 month and as late as 12 months of use.[8,16-21]

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Earlier, Ethambutol ocular toxicity was considered to be largely reversible, but over time, this concept has changed to one of variable or partial recovery with increased emphasis on early detection and management.[1-7]

In India, under the erstwhile Revised National Tuberculosis Control Programme's Direct Observed Treatment Strategy (DOTS) protocol, ethambutol was given in the first 2 months of therapy with ocular toxicity of ethambutol reported in 0.3%–12.6% of patients.[6,7,12] The *Revised National Tuberculosis Control Programme (RNTCP) 2016* guidelines have increased the duration of the ethambutol intake from 2 months to 6 months, and the thrice-a-week regimen has now been changed to a daily-dose regimen. [Tables 1–3]. This has led to apprehension about a possible increase in the incidence of ocular toxicity, which unless monitored, can result in significant visual morbidity in patients undergoing treatment.

Fixed dug combinations wherein a single tablet contains a fixed strength of isoniazid, rifampicin, pyrazinamide, and ethambutol are being used under the RNTCP 2016 guidelines. The number of tablets prescribed is based on the weight

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band of the patient [Tables 2 and 3], and this may offer some safety against ocular toxicity. Nonetheless, the fixed dosage combinations do take away the flexibility of modifying or eliminating the dosage of a single drug like ethambutol while keeping the others as required as the strengths are fixed within each tablet. This is particularly important in patients with risk factors for ethambutol ocular toxicity such as low body weight, kidney disease, older age, chronic hypertension, and chronic smoking.

With the aim of recognizing and highlighting this concern, the Indian Neuro-Ophthalmology Society (INOS) organized a meeting of leading experts from India to create a consensus on the level of risk, possible advisory, and examination schedule to pick up early toxicity.

Methods

An online web-based meeting of experts in the field of neuro-ophthalmology, pulmonary medicine, and pediatrics was conducted under the aegis of the INOS on July 5, 2020. The expert committee comprised 31 neuro-ophthalmologists from 25 super specialty ophthalmology centers, 3 internists, 1 pulmonologist, 1 pediatrician, 1 scientist, and 2 representatives of the health ministry. The professional experience of experts ranged between 5 and 35 years in their respective fields with a median of 18 years. A lead faculty comprising three expert panelists (RS, SP, and DS) performed a literature review of the topic prior to the online meeting and presented the findings to the rest of the panel. The expert panel shared their knowledge, experience, and clinical protocols in light of the published literature to recommend guidelines for diagnosis and management of ethambutol optic neuropathy. A point-by-point discussion for each aspect of ethambutol optic neuropathy was done to achieve a consensus on clinical presentation and diagnosis, screening and primary prevention, treatment, and reporting. After the meeting, a draft statement was generated by the lead faculty and circulated among selected expert panelists, who then vetted or modified the document. Based on all inputs, the resultant final document was created. This final document was then ratified by all the experts prior to submission for publication.

Table 1: Table comparing the new and old guidelines of DOTS therapy as per the RNTCP in India in light of ethambutol usage

New guidelines	Previous guidelines
1. Daily regimen	1. Intermittent regimen
2. Ethambutol part of treatment even in Continuation Phase	2. Ethambutol not part of treatment in Continuation Phase
3. Fixed dose combination as per weight band	3. No fixed dose, limited weight band

Table 2: Dose of Ethambutol in adult patients based on weight category

Weight category	Number of tablets	
	Intensive phase HRZE 75/150/400/275 (mg)	Continuation phase HRE 75/150/275 (mg)
25-39 kg	2	2
40-54 kg	3	3
55-69 kg	4	4
>=70 kg	5	5

Consensus statement

The experts concurred that there is a need to highlight the potential risk of optic neuropathy secondary from the use of ethambutol, particularly in view of the longer periods for which it would be used as per the latest RNTCP guidelines.

The consensus statement is divided into three parts. The first part covers the clinical presentation of ethambutol toxicity, including ophthalmic investigations; the second part covers the protocol for screening and follow-up of patients on ethambutol treatment; and the final part covers potential treatment options for toxic optic neuropathy.

Clinical presentation

Background

Toxic optic neuropathy may occur at any time interval after use of ethambutol, but most often, it is seen after 3–5 months of use. While ethambutol toxicity generally occurs with doses higher than 15 mg/kg, it has also been reported in lower doses; therefore, all patients on ethambutol treatment need to be monitored for ocular toxicity.

Typically, patients present with subacute, bilateral, and painless symmetric loss of central vision, though visual involvement may be asymmetrical or sequential.[5-12,15] They may describe cloudy or blurry vision and difficulty in reading or in distinguishing colors. In the early stages of ethambutol toxicity, the pupillary responses are preserved and normal,

Table 3: Dose of Ethambutol in pediatric patients based on weight category

Weight Category	Number of Tablets			
	Intensive Phase		Continuation Phase	
	P [HRZ pediatric (50/75/150 mg)] A [HRZE adult (75/150/400/275 mg)]	Ethambutol 100 mg	P [HR pediatric (50/75 mg)] A [HRE adult (75/150/275 mg)]	Ethambutol 100 mg
1-7 kg	1P	1	1P	1
8-11 kg	2P	2	2P	2
12-15 kg	3P	3	3P	3
16-24 kg	4P	4	4P	4
25-29 kg	3P + 1A	3	3P + 1A	3
30-39 Kg	2p + 2A	2	2p + 2A	2

but in asymmetric cases or advanced cases, relative afferent pupillary defects or sluggish reactions may be observed. The fundus exam is often normal in the initial stages, or a small peripapillary hemorrhage and hyperemic discs may be observed. If not managed early, ethambutol toxicity would eventually lead to optic disc pallor.

Color vision loss may be seen and typically there is difficulty in distinguishing red and green colors, though blue-yellow defects may also occur.[22,23] Reduction in contrast sensitivity has also been reported as a marker of ethambutol toxicity. However, several studies have shown no changes in color vision or contrast sensitivity, and some experts feel it may not be an early marker of ocular toxicity.[5,12,24]

Visual field testing most often reveals central or ceco-central scotoma, though bitemporal breakout of the visual field defect with optic chiasma involvement has also been reported.[5-12]

The optical coherence tomography (OCT) has proven to be a useful tool for the detection of toxic optic neuropathy and changes may be seen in the retinal nerve fiber and ganglion cell layers. While changes on the OCT are not specific to toxic optic neuropathy, they may help in the prognosis and follow-up.

Early changes in OCT can be seen in form of an increase or no discernible change in retinal nerve fiber layer (RNFL) thickness and thinning of ganglion cell complex layer (GCC).[24-26] Generally, RNFL thinning on follow-up is a sign of progressive damage due to toxicity.

Visually evoked potentials (VEP) may reveal abnormalities in the amplitude or latency of the p100 wave.[5,7,12,15,20] Delay in VEP latency is shown to be an early biomarker for ethambutol toxicity.[24]

Electroretinogram and electrooculogram changes have also been documented in ethambutol toxicity, though these are nonspecific.[27,28] Recently, the multifocal electroretinogram has also been used to document ethambutol-related neuroretinopathy.[5,29]

Consensus

The experts took cognizance of the available literature and their own experience and concurred that the treating physician or ophthalmologist has to have a high index of suspicion for ethambutol toxicity in any patient on ethambutol and ask for early symptoms, including a reduction in vision, change in the quality of vision (altered color perception and reduced brightness), or difficulty with current pair of glasses. The ophthalmologist should then examine the eye, including the fundus, for any abnormal pupillary reactions, disc hyperemia, peripapillary hemorrhages, or disc pallor, but being wary that no such changes may be present despite ocular toxicity.

To further confirm the presence of ocular toxicity, the experts recommend a few ocular investigations, particularly the visual fields (automated 24- or 30-degree fields) and visual evoked potential (VEP) (pattern VEP preferred over flash). Additionally, other investigations such as color vision, contrast sensitivity, and optical coherence tomography (OCT) should be done, where possible. The ophthalmologist should specifically look out for the presence of central or centrocecal scotoma in the visual fields, prolonged latency and reduced amplitudes on VEP, and relative symmetry in both eyes. Color vision changes may be absent in the early phase of toxicity and only subtle changes may be noted in contrast sensitivity, and hence, the absence of color deficiency and normal contrast sensitivity does not rule out ethambutol toxicity. Changes such as thinning in the RNFL and GCC may be looked for on the OCT, and even if the OCT appears normal, it can be used as a baseline to look for changes on subsequent follow-up. As there is no one pathognomic ocular change of ethambutol toxicity, the whole clinical picture needs to be kept in perspective while making the diagnosis.

Screening and Primary Prevention

Background

Ethambutol-related toxic optic neuropathy has been reported in 1%–18% of patients on antitubercular treatment dependent on dose and duration, both in the adult and pediatric age groups.[16-21,30] Several risk factors for ethambutol toxicity have been described, but the most common ones include old age, renal disease, and low weight.[31,32] Literature has shown that ethambutol toxicity is only partially reversible and even after recovery, there is a long-term impact on visual functions.[1-7,20,33] This impact may include a permanent reduction of vision, altered color perception, reduced contrast sensitivity, visual field defect, and depressed visual evoked potentials. To minimize this impact, it has been emphasized that there is a need for early detection of ethambutol toxicity, even in a subclinical stage, and for remedial measures, including reducing the dose or more often stoppage of the drug.[6,24,29,34]

The biomarkers that may help detect ethambutol toxicity at the subclinical stage include a change in average RNFL thickness, most pronounced in the temporal quadrant (initial increase followed by decrease) and GCC thinning on OCT, reduction in visual field index, presence of visual field defect on the pattern standard deviation plot, and prolonged VEP latency.[12,15,16,24,25,30]

Consensus

The expert panel recognized the need to detect ethambutol toxicity early and recommended the need to spread awareness about the issue. There is a need to increase awareness in physicians who are prescribing ethambutol and in patients who are taking the treatment about the potential ocular toxicity of the drug. The panel recommended that while prescribing ethambutol, all physicians should inform their patients about the need to notice any changes in their vision. The specific recommendations for physicians include the need to document the history of any pre-existing visual or ophthalmic complaints at the initiation of treatment, and if present, the patient should be referred for ophthalmic evaluation before initiation of the treatment. Moreover, any patients with high risk for developing ethambutol toxicity (old age, low weight, malnourishment, renal disease, co-existing diabetes mellitus, tobacco or alcohol abuse, and preverbal children) or those receiving combined therapy with linezolid higher than 15 mg/kg dose and prolonged ethambutol therapy need to be referred for a baseline ophthalmic examination at the start of treatment. For all patients on ethambutol, the treating physician should ask for complaints of a decrease in vision or a change in the quality of vision and difficulty in reading on their routine

follow-up visits. Ideally, a physician who is routinely treating patients with tuberculosis should have a visual acuity chart in the office and perform a quick vision assessment on each follow-up visit.[35]

For the ophthalmologist, the panel recommended that an opportunistic screening of every patient on ethambutol treatment should be done, even if they visit the ophthalmology outpatient department for an unrelated cause. The baseline evaluation should include visual acuity, color vision, contrast sensitivity, and visual field test. Additionally, if the facility is available, baseline OCT RNFL and VEP should be documented. The patient's awareness of potential ethambutol toxicity should be reinforced, and the patient may be taught to check visual acuity, color vision, and central field at home with a smartphone-based app or given a visual acuity chart printout and an Amsler's grid chart. The ophthalmologist should screen for possible risk factors for ethambutol toxicity and warn the patient and physician accordingly and ensure a close follow-up. After establishing baseline visual functions, the patient may be followed up at 2-monthly intervals thereon and explained to review urgently if a drop in vision or change in the quality of vision is noted.

Children younger than 5 years need to be followed up carefully. Though the risk in children is not as high as in adults, it may be challenging to diagnose the toxicity, particularly in preverbal children and children who fall toward the lower segment of the weight band [Table 2]. They may not be able to express any visual symptoms nor be able to perform the required investigations. In these cases, a high index of suspicion is necessary and parents should be encouraged to monitor and report if there is any change in the child's ability to perform his daily visual task.

Treatment of Ethambutol-Induced Toxic Optic Neuropathy

Background

At present, there is no effective treatment for ethambutol-induced toxic optic neuropathy (other than stoppage of drug) and no known prognostic factors other than young age.[21,36] Early detection of the disease and stopping of ethambutol may help in preventing further deterioration of visual functions, though visual functions may continue to deteriorate for a few weeks even after stopping the drug. Recovery of visual functions is most often partial and incomplete, though complete recovery has been shown in several cases over 1 to 6 months when ethambutol was stopped early.[7,12,15,20,21,24,37,11]

There has been some promising research into the treatment of ethambutol ocular toxicity though no acceptable treatment options have been approved at present.[38-40]

Consensus

The expert panel emphasized the need for primary prevention of ethambutol toxicity keeping in view the absence of a definitive treatment. The panel recommended keeping a high index of suspicion and that ethambutol be stopped at the first sign of ocular toxicity in consultation with the treating physician. The patient may be started on a cocktail of vitamins (particularly hydroxocobalamin or methylcobalamin along with thiamine and pyridoxine). Additionally, based on anecdotal and experiential evidence, the patient may be started on ubiquitin, vitamin C, zinc, or copper supplementation. If there is no improvement in 4–6 weeks, stoppage of isoniazid or linezolid should be considered after consultation with the treating physician.

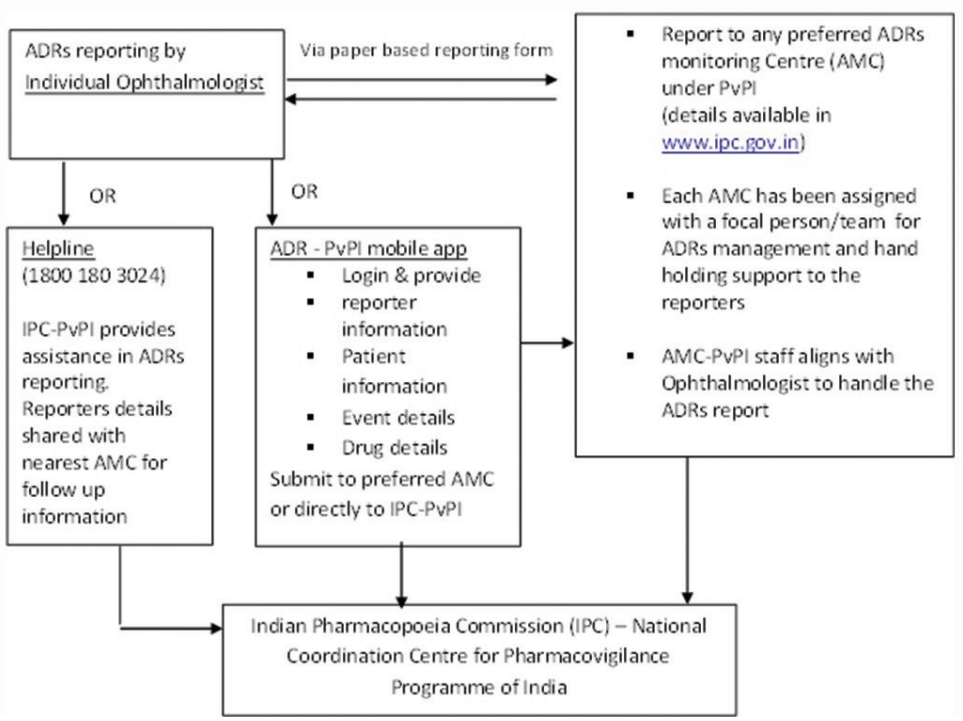

Figure 1: The procedure for reporting ADR

Table 4: Table describing the tenets of the Consensus Statements

Statement Category	Tenets
Clinical presentations and diagnosis	High index of suspicion needed for ethambutol optic neuropathy Symptoms under focus include decrease in vision, altered quality of vision, and frequent change of glasses. Ocular examination to focus on visual acuity, pupillary reactions (sluggish or rarely a relative afferent pupillary defect), fundus evaluation (disc hyperemia or pallor, peripapillary hemorrhages; or may be normal), color vision (normal or impaired), and contrast sensitivity (normal or reduced). Supportive investigations include visual fields (central or centrocecal scotoma, most often bilateral); visual evoked potentials (prolonged latency and reduced amplitudes); optical coherence tomography (RNFL or GCC thinning, or normal)
Screening and primary prevention	Need to spread awareness of ethambutol optic neuropathy among physicians and patients Physicians should inform their patients about the need to notice any changes in their vision. Physicians need to document the history of any pre-existing visual or ophthalmic complaints at the initiation of treatment, and if present, refer for ophthalmic evaluation. Patients with a high risk for developing ethambutol toxicity need to be referred for a baseline ophthalmic examination at the start of treatment. For all patients on ethambutol, the treating physician to inquire about a decrease in vision or change in the quality of vision and difficulty in reading on their routine follow-up visits and if possible document visual acuity in their clinics on every visit. The ophthalmologist should perform opportunistic screening of every patient on ethambutol treatment. The baseline evaluation should include visual acuity, color vision, contrast sensitivity, and visual field test. Additionally, if the facility is available, baseline OCT RNFL and VEP should be documented. Plan 2-monthly follow-up visits. Ophthalmologists to encourage patients for self-assessment of visual acuity color vision and visual fields by use of smartphone-based applications or Amsler's grid. Patients to be advised to consult the ophthalmologist immediately if any visual disturbance is noticed. Children under five years need careful follow-up. Parents to be sensitized to ethambutol toxicity and to bring the child immediately if there is any change in the child's ability to perform his daily visual task.
Treatment	Ethambutol to be stopped at the first sign of ocular toxicity in consultation with the treating physician. The patient may be started on a cocktail of vitamins, (hydroxocobalamin or methylcobalamin in particular) and optionally ubiquitin, vitamin C, zinc, or copper supplementation. If there is no improvement in 4-6 weeks, stoppage of isoniazid or linezolid should be considered.

Reporting Ethambutol Toxicity

It is the responsibility of ophthalmologists and physicians to report ethambutol toxicity to understand the magnitude of the problem and take remedial measures at a policy level. This should be done through the Pharmacovigilance Programme of India (PvPI), which was launched by the Ministry of Health and Family Welfare (MoHFW), Government of India, in 2010 to monitor adverse events caused by medication used in Indian patients. The Indian Pharmacopoeia Commission (IPC) under MoHFW functions as National Coordination Centre for PvPI to collect, collate, analyze, and communicate the adverse drug reactions (ADRs) to the stakeholders and are also responsible for recommending to the Central Drugs Standard Control Organization for taking appropriate regulatory decisions upon safety of medicines.

To collect ADRs, the IPC recognizes teaching hospitals (both from public and private), corporate hospitals, TB treatment centers, etc., as ADRs monitoring centers in a dynamic process. The following reporting tools are available to ensure and promote seamless reporting for the stakeholders:

1. Customized "PvPI suspected ADRs reporting form" – a paper-based conventional reporting form for the healthcare providers
2. XML E2B format – electronic submission of Individual Case Safety reports by the marketing authorization holders
3. Android-based mobile app – features have been made for the healthcare providers and patients to report ADRs and prompt acknowledgment to the reporters.
4. Helpline (toll-free) – 1800 180 3024.

Use of these tools is demonstrated in Fig. 1.

Conclusion

Ethambutol toxicity is a cause for potentially permanent vision loss and needs to be addressed in the current scenario of longer duration of its use under the new tuberculosis treatment guidelines in India. While the impact of ethambutol on the optic nerves and retina has been long known, no definitive treatment has been found; thus, prevention of ocular toxicity and management with early discontinuation of ethambutol are the only effective strategies to address this condition. A panel of experts has recommended the need for patient and physician awareness about the issue along with the guidelines for ophthalmologists to enable early detection and management of toxicity. [Table 4]

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Conflicts of interest

There are no conflicts of interest.

References

1. Carr RE, Henkind P. Ocular manifestations of ethambutol. Arch Ophthalmol 1962;67:566-71.
2. Harada I. Two cases of neuritis retrobulbaris due to orally administered ethambutol. Nihon Ganka Kiyo 1963;14:278-84.
3. Grzybowski A, Zulsdorff M, Wilhelm H, Tonagel F. Toxic optic neuropathies: An updated review. Acta Ophthalmol 2015;93:402-10.
4. Wasinska-Borowiec W, Aghdam KA, Saari JM, Grzybowski A. An updated review on the most common agents causing toxic optic neuropathies. Curr Pharm Des 2017;23:586-95.
5. Kandel H, Adhikari P, Shrestha GS, Ruokonen EL, Shah DN. Visual function in patients on ethambutol therapy for tuberculosis. J Ocul Pharmacol Ther 2012;28:174-8.
6. Koul PA. Ocular toxicity with ethambutol therapy: Timely recaution. Lung India 2015;32:1-3.
7. Garg P, Garg R, Prasad R, Mishra AK. A prospective study of ocular toxicity in patients receiving ethambutol as a part of directly observed treatment strategy therapy. Lung India 2015;32:16-9.
8. Chan RY, Kwok AK. Ocular toxicity of ethambutol. Hong Kong Med J 2006;12:56-60.
9. Melamud A, Kosmorsky GS, Lee MS. Ocular ethambutol toxicity. Mayo Clin Proc 2003;78:1409-11.
10. Vistamehr S, Walsh TJ, Adelman RA. Ethambutol neuroretinopathy. Semin Ophthalmol 2007;22:141-6.
11. Sivakumaran P, Harrison AC, Marschner J, Martin P. Ocular toxicity from ethambutol: A review of four cases and recommended precautions. N Z Med J 1998;111:428-30.
12. Menon V, Jain D, Saxena R, Sood R. Prospective evaluation of visual function for early detection of ethambutol toxicity. Br J Ophthalmol 2009;93:1251-4.
13. Libershteyn Y. Ethambutol/Linezolid toxic optic neuropathy. Optom Vis Sci 2016;93:211-7.
14. Geyer HL, Herskovitz S, Slamovits TL, Schaumburg HH. Optochiasmatic and peripheral neuropathy due to ethambutol overtreatment. J Neuroophthalmol 2014;34:257-8.
15. Goyal JL, De Sarmi, Singh NP, Bhatia A. Evaluation of visual functions in patients on ethambutol therapy for tuberculosis: A prospective study. J Commun Dis 2003;35:230-43.
16. Kim U, Hwang JM. Early stage ethambutol optic neuropathy: Retinal nerve fiber layer and optical coherence tomography. Eur J Ophthalmol 2009;19:466-9.
17. Chai SJ, Foroozan R. Decreased retinal nerve fibre layer thickness detected by optical coherence tomography in patients with ethambutol-induced optic neuropathy. Br J Ophthalmol 2007;91:895–7.
18. Zoumalan CI, Agarwal M, Sadun AA. Optical coherence tomography can measure axonal loss in patients with ethambutol induced optic neuropathy. Graefes Arch Clin Exp Ophthalmol 2005;243:410-6.
19. Fraunfelder FW, Sadun AA, Wood T. Update on ethambutol optic neuropathy. Expert Opin Drug Saf 2006;5:615-8.
20. Lee EJ, Kim S-J, Choung HK, Kim JH, Yu YS. Incidence and clinical features of ethambutol-induced optic neuropathy in Korea. J Neuroophthalmol 2008;28:269-77.
21. Tsai RK, Lee YH. Reversibility of ethambutol optic neuropathy. J Ocul Pharmacol Ther 1997;13:473-7.
22. Trusiewicz D. Farnsworth 100-hue test in diagnosis of ethambutol induced damage to optic nerve. Ophthalmologica 1975;171:425-31.
23. Polak BC, Leys M, van Lith GH. Blue-yellow color vision changes as early symptoms of ethambutol oculotoxicity. Ophthalmologica 1985;191:223-6.
24. Kim KL, Park SP. Visual function test for early detection of ethambutol induced ocular toxicity at the subclinical level. Cutan Ocul Toxicol 2016;35:228-32.
25. Taffner BMP, Mattos FB, da Cunha MC, Saraiva FP. The use of optical coherence tomography for the detection of ocular toxicity by ethambutol. PLoS One 2018;13:e0204655.
26. Mandal S, Saxena R, Dhiman R, Mohan A, Padhy SK, Phuljhele S, *et al*. Prospective study to evaluate incidence and indicators for early detection of ethambutol toxicity. Br J Ophthalmol 2021;105:1024-8.
27. Kakisu Y, Adachi-Usami E, Mizota A. Pattern electroretinogram and visual evoked cortical potential in ethambutol optic neuropathy. Doc Ophthalmol 1987;67:327-34.
28. Hennekes R. Clinical ERG findings in ethambutol intoxication. Graefes Arch Clin Exp Ophthalmol 1982;218:319-21.
29. Behbehani RS, Affel EL, Sergott RC, Savino PJ. Multifocal ERG in ethambutol associated visual loss. Br J Ophthalmol 2005;89:976-82.
30. Jin KW, Lee JY, Rhiu S, Choi DG. Longitudinal evaluation of visual function and structure for detection of subclinical Ethambutol induced optic neuropathy. PLoS One 2019;14:e0215297.
31. Talbert Estlin KA, Sadun AA. Risk factors for ethambutol optic toxicity. Int Ophthalmol 2010;30:63-72.
32. Kanaujia V, Jain VK, Sharma K, Agarwal R, Mishra P, Sharma RK. Ethambutol-induced optic neuropathy in renal disorder: A clinico-electrophysiological study. Can J Ophthalmol 2019;54:301-5.
33. Woung LC, Jou JR, Liaw SL. Visual function in recovered ethambutol optic neuropathy. J Ocul Pharmacol Ther 1995;11:411-9.
34. Preventive Measures Against Drug-Induced Ocular Toxicity During Anti-Tuberculous Treatment (General Recommendations). Annual Report. Hong Kong: Department of Health; 2002.
35. Saxena R, Phuljhele S, Prakash A, Lodha R, Singh D, Karna S, *et al*. The INOSrG. Ethambutol optic neuropathy: Vigilance and screening, the keys to prevent blindness with the revised anti-tuberculous therapy regimen. J Assoc Physicians India 2021;69:54-7.
36. Chen S-C, Lin M-C, Sheu S-J. Incidence and prognostic factor of ethambutol-related optic neuropathy: 10-year experience in Southern Taiwan. Kaohsiung J Med Sci 2015;31:358-62.
37. Mendel T, Fleischman D, Allingham RR, Tseng H, Chesnutt DA. Spectrum and clinical course of visual field abnormalities in ethambutol toxicity. Neuroophthalmology 2016;40:139-45.
38. Cinici E, Cetin N, Ahiskali I, Suleyman B, Altuner D, Alp HH, *et al*. The effect of thiamine pyrophosphate on ethambutol-induced ocular toxicity. Cutan Ocul Toxicol 2016;35:222-7.
39. Vijayakumar AR, Anuradha H, Biswas NR, Menon V, Saxena R, Halder N, *et al*. Evaluation of the protective effect of NMDA/Non-NMDA receptor antagonists against ethambutol induced retinal toxicity using ERG in wistar rats. Indian J Physiol Pharmacol 2016;60:268-81.
40. Xu J, Dai Q, Wu S, Sheng W, Zhao S, Zhong L. Treatment of ethambutol-induced optic neuropathy by buqihuoxue formula combined with methycobal. Int J Clin Exp Med 2017;10:7011-5.