EFFICACY OF PS-VEPS IN THE DETECTION OF SUBCLINICAL OPTIC NEURITIS FOLLOWING ETHAMBUTOL IN THERAPEUTIC DOSAGE

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Background: Ethambutol is an antimicrobial agent used frequently to treat tuberculosis. The most commonly recognized toxic effect of ethambutol is optic neuropathy, which may sometime results in irreversible vision loss. However, early recognition not only prevents this complication, it also increases compliance of the drug. This study was carried out to assess the usefulness of pattern-shift visual evoked potentials (PS-VEPs) in the detection of sub clinical optic neuropathy in patients on ethambutol for the treatment of tuberculosis in the recommended dosage. **Methods:** 30 consecutive patients of tuberculosis were studied before and after two months of ethambutol therapy. Ethambutol was administered in the WHO recommended dosage of 15mg/kg of body weight. All the patients underwent pattern shift visual evoked potential tests, which check the function of the visual pathway from the retina to the occipital cortex. **Result:** PS-VEP abnormalities were seen in 5 patients (16.7%),out of which prolonged latency was documented in 3 patients (10%),increased latency difference was seen in 1 patient (3.3%) and abnormal amplitude difference was reported in 1 patient (3.3%).Associated psychophysical abnormalities of visual acuity in 2 patients(6.7%) and color vision abnormality in 1 patient (3.3%) were also seen. **Conclusion:** Our study confirms that during the treatment with ethambutol, PS-VEPs may reveal a surprisingly high percentage of sub clinical optic neuritis even at dosages considered to be safe. This needs attention in terms of patient care and drug compliance.

Key words: Tuberculosis, Ethambutol, Optic neuritis, Pattern-shift visual evoked potentials

INTRODUCTION

Ethambutol hydrochloride is one of the routinely used drugs as the first line of antitubercular agents. The most commonly recognized toxic effect of ethambutol is opticneuropathy, which generally is considered uncommon.[1,2] Medical literature suggested in the past that the toxic effects of ethambutol are readily reversible, albeit after sometime; however recent ophthalmologic experience does not support this belief. In fact, several recent studies[3-6] show that patients who experience ethambutol toxicity often have severe and persistent visual defects despite the fact that they receive appropriate dosages and are monitored regularly for visual acuity and colour vision and despite prompt discontinuation of ethambutol, when symptoms are discovered. Use of routine visual acuity and other ocular tests often fail to detect optic nerve toxicity before appearance of symptoms. An increased latency and decereased amplitude can be detected at a stage when there is little disturbance in neuro-ophthalmological examination.[7,8] The potential severity of ocular toxicity attributed to ethambutol and often its irreversibility necessitate a screening procedure capable of detecting ocular toxic effects before a deficit occurs. The purpose of our study was to evaluate the efficacy of PS-VEP in detecting early optic nerve involvement following ethambutol therapy.

MATERIAL AND METHODS

Thirty patients (24 male, 6 females) of pulmonary and extra-pulmonary tuberculosis aged between 20 and 40 years taking ethambutol were taken for the study after obtaining their consent. Thirty age and sex matched healthy controls were also studied. Ethambutol hydrochloride dose was 15 mg/kg body weight in all cases, and no other neurotoxic agents were being taken at the time. Patients with tubercular meningitis, cerebral tuberculosis, renal impairment and past history of anti-tubercular therapy were excluded from the study as they affect P100 latency.

The ethical principles of the Declaration of Helsinski (1964) concerning human experimentation were followed. Both patients and controls underwent a detailed neuro-ophthalmological assessment which included corrected visual acuity (Snellen's chart), color vision (Ishihara's test), visual field charting and ophthalmoscopy. Subjects were briefed about the procedure to ensure complete relaxation. Each subject was seated comfortably in a quite and dark room one meter away from the VEP monitor and instructed to fix on a small square at its center with one eye; while the other was covered with a patch. Electrodes were applied to the scalp with impedance kept below 5000 ohms.O_1-Fz or O_2-Fz montages were used with Fz as reference point. A black and white checker board was generated on VEP monitor by an electronic pattern generator housed in RMS EMG EP MARK-II. The field size measured 11°

vertically and 14° horizontally at the subjects eye and check size was 8x8 subtending an angle at 32° of an arc at a distance of one meter. Luminance of dark checks was 6.31 ft-L and of the light checks was 31.6 ft-L giving contrast between black and white checks of 67%.

The checks were made to reverse at a rate of 1 Hz and 256 responses were recorded and averaged by evoked potential recorder with low and high frequency filters of 2-100 Hz and with line filters on. At least two trials were always obtained to ensure replicability of the VEP. The P_{100} latency was recorded and P_{100}-N_{70} amplitude was measured.

Patients were given short breaks in between sets of stimuli to avoid loss of concentration. During the examination patients' state of relaxation was checked on the basis of incoming signals which were less than 50-60% of display dimension. Comparison and analysis of data were done at the end.VEP was done once before the start of therapy and once after completion of therapyand in each sitting at least two trials were always obtained to ensure replicability of VEP.

RESULTS

For the purposes of this study, "abnormality" was defined as that defined by Shahrokhi [9] in his classic paper as:

- a *latency* in excess of 116 ms,
- a *latency difference* between the two eyes of more than 8 ms,
- an *amplitude difference* between the two eyes of more than 6µV, and
- Failure to record a measurable response.

In this study five patients among the thirty studied showed an altered VEP. The clinical evaluation in four of the five cases, no objective change in visual acuity, color vision or fundi were present. Patient 1 had deteriorated visual acuity and color vision after two month. Patient 2 and 3 complained of blurred vision, but no objective abnormality was found. On electrophysiological assessment, left eye of patient 3 and both eye of patient 1 and 2 showed prolongation of P_{100} latency. Although less emphasis was placed on changes in amplitude, we noted a correlation between reduction in the P_{100}-N_{70} amplitude and increase in the P_{100} latency.

Patient 4 though looking normal on the basis of latency range was considered abnormal because of P_{100} latency difference between the two eyes of more than 8ms (9 ms in this case). Also patient 5 with normal latencies of 109 and 108.1 ms was found to be abnormal on the basis of an amplitude difference between the two eyes of 7µV. None of the patient in our study failed to record a measurable response in any of the eye. These results are tabulated in table-1.

None of these patients had any other attributable cause for optic neuritis.

Table 1-Results in Patients with PS-VEP Abnormalities*

Patient/Age,yr/ Sex	P_{100} Latency (ms)		Lat.Diff (ms)	Amp.Diff (µV)	Visual Acuity (both eye)	Color Vision (both eye)
	Right	Left				
1/ 36/ M	142	146	4	1.4	6/12	Abn
2/ 30/ M	130	127.4	2.6	1.2	6/12	N
3/ 34/ F	116	117	1	2	6/6	N
4/ 29/ M	105	114	9	2.3	6/6	N
5/ 24/ M	109	108.1	1.1	7	6/6	N

* PS-VEPs indicates Pattern-shift visual evoked potentials
Abn-Abnormal, N-Normal

Table 2- P_{100} Latencies in PS-VEPs for Five Patients*

	P_{100} Latency (ms)			
	Pretreatment		Post treatment	
Case	Right Eye	Left Eye	Right Eye	Left Eye
1	111	108	142	146
2	108.3	107	130	127.4
3	95	96	116	117
4	99.4	103	105	114
5	94.2	93.1	109	108.1

* PS-VEPs indicates Pattern-shift visual evoked potentials

DISCUSSION

Ethambutol hydrochloride is a bacteriostatic first-line anti-tubercular drug, which was introduced in 1961 by Lederle Laboratories. It is well tolerated by the majority of patients. The only major side effect of ethambutol is its retrobulbar neuritis, which was first reported by Carr and Henkind[10] in 1962.The precise mechanism of ocular toxicity of ethambutol is not known. The various mechanisms hypothesized are demyelination of optic nerve, chiasma and optic tract,[11,12] depletion of copper and zinc from retina,[13-15] effect similar to ethanol[16] or idiosyncrasy.[6,17,18]

Leibold[19] classified ethambutol toxicity into two types. Patients with central or axial toxic effects had reduced visual acuity, impaired color vision, and a central scotoma. Those with periaxial toxic effects had a defect in peripheral isopters of their field with little or no decrease in visual acuity and normal color vision.

The incidence of ethambutol toxicity has been reported to be from 0.62% to 63%.[20-25] The incidence depends upon the sensitivity of the tests used. Several studies have been conducted using various parameters of visual function, to evaluate the ocular toxicity of ethambutol. These parameters include visual acuity, ophthalmoscopy, color vision testing, contrast sensitivity, pupillary reactions, pupil cycle time, visual field charting, critical flicker frequency and visual evoked potentials. The visual evoked potential tests the function of the visual pathway from the retina to the occipital cortex. The PS-VEP abnormalities occur despite the fact that psychophysicial parameters of visual function are often normal at that time. The fall in visual acuity may be the presenting symptom of ethambutol induced optic neuritis. Its incidence has been 0.62% to 44.4%.[10,21,23,24,26] In our study only two patients had decrease in best corrected visual acuity. We observed that P_{100} values of 105,114,142 and 146 ms were associated with diminished visual acuity. Color vision defects (especially red-green) have been reported in patients on ethambutol therapy.[20,27,28] In our study abnormal color perception was seen in only one patient. Ishihara charts used in our study are not very sensitive to pick up milder forms of color vision defects, as has been reported by Griffin et al.[29] The use of more sensitive tests like the Farnsworth-Munsell 100 result in better identification of toxicity.[30] Most of the patients with ethambutol induced optic neuritis have normal ophthalmoscopic findings (retrobulbar neuritis), but disc edema, hyperemia and blurring of disc margins have been reported.[6,31] In our study none of the patients showed abnormal fundus picture.

The increase in PS-VEP latency is usually ascribed to decreased conduction velocity in optic nerve fibres consequent to segmental demyelination. The papillomacular bundle seems to be especially involved in ethambutol eye toxicity[32]. The histopathologic evidences concerning the site of disturbance of the anterior visual system by ethambutol has been studied by Schmidt in monkeys and the areas most vulnerable to the toxic effects were the optic nerves, chiasm, and tracts.[11] Kumar[3] recommend discontinuation of ethambutol from the antituberculous regimen.

As an additional sidelight he emphasized on the value of VEP in the monitoring of patients on ethambutol, especially cases with periaxial neuritis. 50% of patients in Tsai and Lee's[4] study had permanent visual impairment without recovery. They concluded there is no so-called "safe-dosage" and suggested reconsideration regarding the use of ethambutol as one of the first-line antitubercular drugs, especially in older patients. In our study the optic neuritis rate was 8-16%. Kahana[33] found serious visual impairment in three out of four patients even though they were on a maintenance dose of 15mg/kg/day. Choi and Hwang[34] observed ocular ethambutol toxicity at a dose as low as 12.3mg/kg. The severity of the neuritis of the optic nerve is not reated to the total intake of ethambutol.[17] As showed by Nasemann et al[35] permanently pronged latency of the P_{100} component was found in VEPs even in cases with good recovery from ethambutol-induced damage. Diem et al[36] concluded that an underlying pathological process threatening axonal integrity may not be reliably reflected by clinical parameters due to the distinct ability of the visual system to compensate for axonal loss. PS-VEPs may thus serve as an objective tool to diagnose and to monitor axonal pathology in ethambutol toxicity.

At the time when visual acuity was normal there was still electrophysiological evidence of a mild involvement of the anterior visual pathway in our study[32] VEPs are most useful in testing optic nerve function and less useful in postchiasmatic disorder.it detects an anterior visual conduction disturbance even subclinically when psychophysiological parameters like acuity remains unaffected..This finding is consistent with those of Yiannikas[7], Van Lith[37] and Melamud[38], who found that VEP may be considerably disturbed at a stage when there is little neuro-ophthalmologic examination abnormality.

CONCLUSION

The detection of ocular toxic effects before symptoms occur is of great value in preventing extensive optic nerve damage and in allowing complete recovery of function. We found PS-VEPs to

be more sensitive than physical examination in prechiasmatic lesions. It is an objective and reproducible test for optic nerve function. Any patient under going medical treatment for tuberculosis requires proper education concerning potential side effects of ethambutol. Routine PS-VEP monitoring prior to starting ethambutol and on follow up for the early detection of optic neuropathy is thus strongly recommended.

REFERENCES

1. Carr RE. Racemic isomer of ethambutol. Arch Ophthalmol 1962; 68: 718-21.
2. Place VA, Thomas JP. Clinical pharmacology of ethambutol. Am Rev Respir Dis1963; 87: 901-4.
3. Kumar A, Sandramouli S, Verma L, Tewari HK, Khosla PK. Ocular ethambutol toxicity: is it reversible? J Clin Neuroophthalmol 1993; 13(1): 15-7.
4. Tsai RK, Lee YH. Reversibility of ethambutol optic neuropathy. J Ocul Pharmacol Ther. 1997; 13(5): 473-7.
5. DeVita EG, Miao M, Sadun AA. Optic neuropathy in ethambutol-treated renal tuberculosis. J Clin Neuroophthalmol 1987; 7(2):77-86.
6. Sivakumaran P, Harrison AC, Marschner J, Martin P. Ocular toxicity from ethambutol: a review of four case and recommended precautions. N Z Med J 1998; 111: 428-30.
7. Yiannikas C, Walsh JC, McLeod JG. Visual evoked potentials in the detection of subclinical optic toxic effects secondary to Ethambutol. Arch Neurol 1983; 40: 645-8.
8. Halliday AM, McDonald WI, Mushin J. Delayed visual evoked response in optic neuritis. Lancet 1972; 1: 982-5.
9. Shahrokhi F, Chiappa KH, Young RR. Pattern shift visual evoked responses: two hundred patients with optic neuritis and/or multiple sclerosis. Arch Neurol 1978; 35: 65- 71.
10. Carr RE, Henkin d P. Ocular manifestations of ethambutol. Arch Ophthalmol 1962; 67: 566-71.
11. Schmidt IG. Central nervous system effects of ethambutol on monkeys. Ann NY Acad Sci 1966; 135.
12. Dijk BW,Spekreijse H. Ethambutol changes the color coding of retinal ganglion cells reversibly. Invest Ophthal Vis Sci. 1983;24:128-33.
13. Lessell S. Histopathology of experimental intoxication. Invest Ophthal 1976;15(9):765-9
14. Buyske SA, Sterling W, Peets E. Pharmacological and biochemical studies on ethambutol in laboratory animals. Ann NY Acad Sci 1966; 135:711-16
15. Campbell IA, Elmes PC. Ethambutol and the eye: Zinc and copper. Lancet 1975; 2: 711-6.
16. Roberts SM. A review of the papers on the ocular toxicity of ethambutol hydrochloride (Myambutol) an anti-tuberculosis drug. Am J Optom Physiol Opt 1974; 51: 982-7.
17. Chatterji VKK, Buchanan DR, Friedman AI, Green M. Ocular toxicity following ethambutol in standard dosage. Br J Dis Chest 1986; 80: 288-91
18. Karnik AM, Al-Shamali MA, Fewech FF. A case of ocular toxicity due to ethambutol: an idiosyncratic reaction. Postgrad Med J 1985;61: 811-3
19. Liebold JE. The ocular toxicity of ethambutol and its relation to dose. Ann NY Acad Sci 1966; 135: 904-9.
20. Polak BCP,Leys M,VanLith GHM. Blue-yellow color vision changes as early symptoms of ethambutol oculotoxicity. Ophthalmologica Basel 1985;191: 223-6.
21. Narang RK, Varma BMD. Ocular toxicity of ethambutol (a clinical study). Ind J Ophthalml 1979;1: 37-40.
22. Bobrowitz ID, Gokulnathan KS. Ethambutol in the retreatment of pulmonary tuberculosis. Dis Chest 1965; 48(3):239-50
23. Mathur KC, Sankhla JS. Ophthalmic manifestation of the toxicity of ethambutol. Ind J Ophthalmol 1976; 24(3): 6-9.
24. Mathur SS, Mathur GB. Ocular toxicity of ethambutol. Ind J Ophthalmol 1981; 29:19-21.
25. Harcombe A, Kinnear W, Britton J, Macfarlane J. Ocular toxicity of ethambutol. Resp Med 1991; 85:151-3
26. Kass I. Chemotherapy regimens used in the retreatment of pulmonary tuberculosis: 11. Observations on the efficacy of combinations of ethambutol, capreomycin and companion drugs, incuding 4-4 diisoamyloxy-thiosemicarbanilide. Tubercle 1956; 46: 166-79.
27. Belcher S, Greenshields K, Wright WD. A color vision survey. Br J Ophthalmol 1958; 42:355-59
28. Roussos T, Tsalkos A. The toxicity of Myambutol on the human eye. Ann Ophthalmol 1970; 2: 577-80.
29. Griffin JF, Wray SH. Acquired color vision defects in retrobulbar neuritis. Am J Ophthalmol 1978; 86:193-201
30. Trusiewicz D. Farnsworth 100-hue test in diagnosis of ethambutol-induced damage to optic nerve. Ophthalmologica 1975; 171(6):425-31
31. Smith LJ. Should ethambutol be barred? J Clin Neuroophthalmol 1987; 7 : 84-6.
32. Petrera JE, Fledelius HC, Trojaborg W. Serial pattern evoked potential recording in case of toxic optic neuropathy due to ethambutol. Electroencephalogr Clin Neurophysiol 1988; 71(2):146-9
33. Kahana LM. Toxic ocular effects of ethambutol. Can Med Assoc J. 1987;1:137(3): 213-6.
34. Choi SY,Hwang JM. Optic neuropathy associated with ethambutol in Koreans. Korean J Ophthalmol 1997;11(2):106-10.
35. Nasemann J, Zrenner E, Riedel KG. Recovery after severe ethambutol intoxication-psychophysicial and electrophysiological correlations. Doc Ophthalml.1989; 71(3):279-92.
36. Diem R, Tschirne A, Bahr M. Decreased amplitudes in multiple sclerosis patients with normal visual acuity: a VEP study. J Clin Neuro Sci 2003; 10(1):67-70.
37. Van Lith GHM. Electrophthalmology and side-effects of drugs. Doc Ophthalmol 1977; 44: 19-21.
38. Melamud A, Kosmorsky GS, Lee MS. Ocular ethambutol toxicity. Mayo Clin Proc.2003; 78(11):1409-11

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