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 optic neuropathy, which generally is considered uncommon. 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 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 color 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 decreased amplitude can be detected at a stage when there is little disturbance in neuro-ophthalmologic examination. 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 Helsinki (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. O1-Fz or O2-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 P100 latency was recorded and P100-N70 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 therapy and 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 P100 latency. Although less emphasis was placed on changes in amplitude, we noted a correlation between reduction in the P100-N70 amplitude and increase in the P100 latency.

Patient 4 though looking normal on the basis of latency range was considered abnormal because of P100 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>
<thead>
<tr>
<th>Patient/Age,yr/ Sex</th>
<th>P100 Latency (ms)</th>
<th>Lat.Diff (ms)</th>
<th>Amp.Diff (µV)</th>
<th>Visual Acuity (both eye)</th>
<th>Color Vision (both eye)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
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<td>146</td>
<td>4</td>
<td>1.4</td>
<td>6/12</td>
</tr>
<tr>
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<td>130</td>
<td>127.4</td>
<td>2.6</td>
<td>1.2</td>
<td>6/12</td>
</tr>
<tr>
<td>3/34/ F</td>
<td>116</td>
<td>117</td>
<td>1</td>
<td>2</td>
<td>6/6</td>
</tr>
<tr>
<td>4/29/ M</td>
<td>105</td>
<td>114</td>
<td>9</td>
<td>2.3</td>
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</tr>
<tr>
<td>5/24/ M</td>
<td>109</td>
<td>108.1</td>
<td>1.1</td>
<td>7</td>
<td>6/6</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Case</th>
<th>Right Eye</th>
<th>Left Eye</th>
<th>Right Eye</th>
<th>Left Eye</th>
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<tbody>
<tr>
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<td>111</td>
<td>108</td>
<td>142</td>
<td>146</td>
</tr>
<tr>
<td>2</td>
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</table>

* 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 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, depletion of copper and zinc from retina, effect similar to ethanol or idiosyncrasy.

Leibold 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%. 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 psychophysical 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%. In our study only two patients had decrease in best corrected visual acuity. We observed that P100 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.

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. The use of more sensitive tests like the Farnsworth-Munsell 100 result in better identification of toxicity. 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. 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. 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. Kumar 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 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 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 observed ocular ethambutol toxicity at a dose as low as 12.3mg/kg. The severity of the neuritis of the optic nerve is not related to the total intake of ethambutol. As showed by Nasemann et al permanently pronged latency of the P100 component was found in VEPs even in cases with good recovery from ethambutol-induced damage. Diem et al 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 electrophysiologic evidence of a mild involvement of the anterior visual pathway in our study 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 unaffacted. This finding is consistent with those of Yiannikas, Van Lith and Melamud, 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


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