Validity of Visual Evoked Response in measuring Ethambutol induced Optic neuritis in Tuberculosis Patients: Evaluation using Receiver Operating Characteristic (ROC) curves.

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Background: Significant vision loss can occur during treatment with Ethambutol in tuberculosis (TB) patients. Visual Evoked Response (VER) is often used to detect this subclinical visual impairment even before the appearance of symptoms. We assessed the usefulness of three V.E.R parameters- P_{100} latency, amplitude and interocular difference for the early diagnosis of ethambutol-induced optic neuritis (ON). **Methods:** This study was carried out on 60 newly diagnosed adult cases of tuberculosis aged between 20-50 years who were randomly assigned into two groups of 30 each. Nonparametric Receiver Operating Characteristic (ROC) analysis was used to evaluate the validity of VER indexes. **Results:** At a cutoff pint of 116 ms sensitivity for the diagnosis of ON was 77.8% and specificity was 81.1%.Results of the application of Bayes's theorem showed that 87% of the patients scoring 116 ms or higher would actually have ethambutol-induced ON and 99% of those scoring less than 116 ms would not have ON. The best area under curve (AUC) for ROCs, an index of diagnosing accuracy, was 0.91 for P_{100} latency, suggesting very good accuracy. **Conclusions:** The results suggest that P_{100} latency gives the best results for ON screening in ethambutol treated patients. Amplitude and interocular difference were reasonable alternatives. Measurement of P_{100} latency of V.E.R is a valuable tool which can be used more easily than clinical examination in detecting subclinical ethambutol-induced ON.

Key words: Ethambutol, Optic neuritis, Receiver Operating Characteristic curves, Tuberculosis, Visual Evoked Response

INTRODUCTION

Tuberculosis is a worldwide public health problem. With the alarming increase in incidence of tuberculosis over the past several years a review of the potential side effects of anti-tuberculosis medications is warranted. The anti-tubercular drug which affects the optic nerve is ethambutol [1-4] which is used in the initial intensive phase of categories I and II of Tuberculosis. The incidence of ethambutol toxicity has been reported to be from 0.62% to 63% in different studies. [5-8]

Paramount to the modern study and treatment of Tuberculosis is the need for valid and reliable measures to detect and quantify EB induced optic neuritis in research and clinical study group. Accurate detection is especially crucial for the diagnosis as some workers have reported sudden and irreversible loss of vision in ethambutol treated patients. [9-11]

Many studies have reported the usefulness of Visual Evoked Response (VER) for the early diagnosis of ethambutol-induced optic neuritis [12-20]. The VER is very useful in detecting an anterior visual conduction disturbance when there is little disturbance in neuro-ophthalmological examination. Thus, the purpose of this study was to assess the validity of VER in such patients by ROC analysis.

MATERIALS AND METHODS

This study included 60 newly diagnosed adult cases of tuberculosis aged between 20-50 years. They were randomly assigned into two groups. The Group I included 30 patients (60 eyes) who received ethambutol along with isoniazid as a part of their anti-tubercular treatment. The Group II included 30 patients (60 eyes) who received isoniazid and did not receive ethambutol as a part of their anti-tubercular treatment. 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 P_{100} latency of V.E.R.

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 as well as electrophysiological assessment at the time of diagnosis and three months after medication.

V.E.R measurement

For the study of VER a RMS EMG EP MARK-II device was used. The details of equipment calibration as given in ISCEV Calibration Guidelines were

adhered to.[21,22] All subjects were seated comfortably in a dark room 100 cm away from the monitor giving out visual stimuli for VER recordings. The active electrode was positioned at the Oz, and the reference electrode at the C_z point. Electrode impedance was adjusted below 5 kOhms. Right eye monocular recordings of all cases were obtained while the left eye was closed. A "chessboard pattern reversal" method was applied with a speed of 1.5 Hz. The subjects were instructed to gaze at the square-shaped white target in the middle of the screen; the filters were tuned at 0.5–1000 Hz, sweep velocity at 30/ms and 100 responses from each eye were averaged by automatic analysis and artifact rejection. N_{70}, P_{100}, and N_{155} latencies and amplitudes were measured as milliseconds (ms) and microvolts (μV), respectively.[23]

ROC analysis is a way of evaluating the accuracy of a diagnostic test by summarizing the potential of the test to discriminate between the absence and presence of a health condition.[24] In the context of the present study this diagnostic accuracy refers to the ability of the electrophysiological variables to discriminate optic neuritis sub clinically. Signal detection theory terms are commonly used to describe the results of such an analysis. One category constitutes a condition to be detected (e.g., patients who have the diagnosis of optic neuritis) and the other category constitutes a lack of the condition (e.g., patients who do not have the diagnosis of optic neuritis).In these terms, sensitivity is defined as the proportion of TB patients with optic neuritis who are correctly classified (true positives).Specificity is defined as the proportion of TB patients without optic neuritis who are correctly classified (true negatives). Similarly, the false positive rate is defined as the proportion of TB patients without optic neuritis incorrectly classified and the false negative rate is defined as the proportion of TB patients with optic neuritis incorrectly classified.

Bayes' theorem allows one to calculate the positive predictive value and the negative predictive value of a screening test.[25] These values are calculated by taking into account the base rates (prevalence) for the disordered and non disordered conditions in the population of interest as follows:

$$PPV = \frac{sensitivity \times prevalence}{sensitivity \times prevalence + (1 - specificity) \times (1 - prevalence)}$$

$$NPV = \frac{specificity \times (1 - prevalence)}{(1 - sensitivity) \times prevalence + specificity \times (1 - prevalence)}$$

The positive predictive value allows one to calculate how many of all the patients who score over the cutoff will actually have optic neuritis. The negative predictive value indicates what proportion of those who score negative for optic neuritis will actually be true negatives.

A receiver operating characteristic analysis was then performed with a range of cutoff scores so that the validity of V.E.R could be compared [25, 26].In the ROC analysis, the true positive rate (Sensitivity) is plotted against the false positive rate (1-Specificity) across a range of values from the diagnostic test. This provides an estimate of the cutoff that corresponds to the best tradeoff between sensitivity and 1-specificity, suggesting the best accuracy of the V.E.R values to discriminate between TB patients with and without optic neuritis.

One index reflecting the overall accuracy of the diagnostic test derived from an ROC analysis is the area under the curve (AUC) [26, 27].

This is a useful quantitative and descriptive expression of how close the AUC is to the ideal area of 1. When there is a perfect separation of the values of the two groups, i.e. there no overlapping of the distributions, the area under the ROC curve equals 1 (the ROC curve will reach the upper left corner of the plot).In the present study, the AUCs and 95% CIs and the statistical comparisons between the diagnostic usefulness of V.E.R parameters were performed by using a nonparametric approach. [26]

The level of significance for all analysis was set at $P < 0.05$. Statistical analysis were performed with SPSS for WINDOWS (version 10.0; SPSS Inc. Chicago).

RESULTS

The 30 patients in each Group ranged in age from 20-50 years with a mean age of 37.7 years in Group I and 32.1 years in Group II. There was no significant difference between the mean ages of the two groups ($P>0.1$). The findings in patients of ethambutol induced optic neuritis are summarized in Table 1.Of the 30 patients in the group I treated with ethambutol, one showed bilateral optic atrophy with a visual acuity of 6/60.One had temporal pallor of the optic disc with reduced visual acuity. 3 of the 5 asymptomatic patients mentioned in Table 1 were considered to have abnormal V.E.Rs on the basis of findings shown in Table 2 and Figure 1. One of these had mildly increased interocular latency difference of 8 ms (normal upper limit is 6 ms).Another had reduced amplitude.

In Group II patients, the retina appeared normal and the peripheral visual fields were full in all cases. All V.E.R measurements were normal in these patients.

The mean P_{100} latency for Group I was 118 ± 9.6 ms. Patients in Group II had 94.6 ± 6 ms

latency. Comparison showed a statistically significant difference between these two groups.

The best results for sensitivity and specificity were obtained at the cutoff point of 116 ms. The receiver operating characteristic curve for Group I is shown in Figure 2.Sensitivity at 116 ms was 77.8%(95% confidence interval 68.8% to 85.2%).Specificity at this value was 81.1%.Applying the same cutoff point to Group II gave a specificity of 85.9% (69.0% to 94.6%).

Bayes's theorem was applied to the cutoff value to obtain a Positive Predictive Value (PPV) and Negative Predictive Value (PPV). Using the equation already given, the PPV was equal to 0.17.The NPV was equal to 0.99.A ROC analysis was performed on the groups as described by Hsiao et al [25].To further evaluate the accuracy, shown in Table 3 are the total area under the curve (AUC) estimates for the P_{100} latency, amplitude and interocular difference in Group I.

DISCUSSION

The recognition of ocular toxicity as a side effect of ethambutol dates back to 1962 when Carr and Henkind first reported it.[3] Since then 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, papillary reactions, pupil cycle time, visual field charting, critical flicker frequency and visual evoked response.[9,20,28,29]

A detailed analysis of visual function in a five year study showed that visual impairment due to ethambutol lasted several months, and that usually recovery was not complete. [11]

Kahana found that ethambutol appears to contribute little to modern short-course antituberculous regimens that include more potent agents such as isoniazid and rifampin.[30] In view of this and the potential for serious visual impairment, alternative antituberculous agents have also been considered. [31]

There is documentation of ocular toxicity with ethambutol even when administered at dosages generally pronounced as being safe.[1,2,18,30] Use of routine visual acuity and other ocular tests often fail to detect optic nerve toxicity before appearance of symptoms. [13,15] Studies indicate that Visual evoked potential are sensitive enough in indicating even subclinical visual impairment.[9, 11,12,13,15]

Table 1: Characteristics of Patients With Ethambutol-induced Optic neuritis(Group 1)

Patient/ Sex/ Age, yr	Impaired Eye	Visual Acuity		Visual Fields		Color Vision		Optic Disc Appearance		V.E.R	
		OD	OS	OD	OS	OD	OS	OD	OS	OD	OS
1/M/33	OS	6/6	CF*	N	-	N	A	N	OA	A	Flat
2/M/41	Both	6/60	6/60	-	-	-	-	OA	OA	A	A
3/F/25	OD	6/9	6/5	N	N	N	N	TP	N	A	N
4/M/29	OS	6/6	6/9	N	N	N	N	N	N	N	A
5/M/38	-	6/6	6/6	N	N	N	N	N	N	N	A

*CF indicates ability only to count fingers; N indicates normal; A, abnormal; OA, optic atrophy; TP, temporal disc pallor.

Table 2: V.E.R In Patients with Ethambutol-induced Optic neuritis(Group 1)

Patient/ Sex/ Age, yr	P_{100} Latency (ms)		Amplitude (μV)		Inter-ocular Latency Difference
	OD	OS	OD	OS	
1/M/33	137	138	5.1	4.6	1
2/M/41	141	140	5.2	4.5	2
3/F/25	110	108	5.6	5.1	2
4/M/29	108	116	6.7	5.7	8
5/M/38	94	97	2.4	1.3	3
Control Range	89-108 ms		4.5-7.21 μV		0-6 ms

Table 3: Areas under the receiver operating characteristic curves for V.E.R Parameters in the two groups[1]

	Group 1	Group 2	Differences
P_{100} Latency (ms)	0.91± 0.03 (0.85,0.97)	0.62 ± 0.11 (0.47,0.72)	P<0.001
Amplitude (μV)	0.85 ± 0.06 (0.72,0.93)	0.42 ± 0.14 (0.31,0.41)	P<0.001
Inter-ocular Latency Difference (ms)	0.61 ± 0.11 (0.48,0.74)	0.24 ± 0.15 (-6.0,0.54)	P<0.001

[1]mean ± SE; 95% CI in parentheses

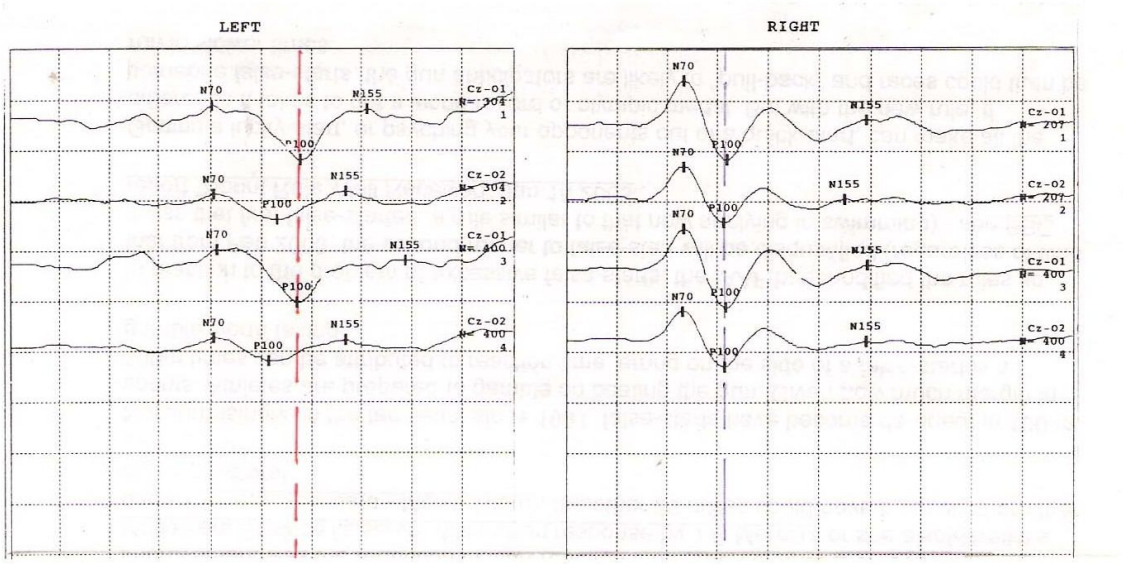

Fig 1. Patient on ethambutol showing abnormal V.E.R in left eye (Normal waveform in right eye).

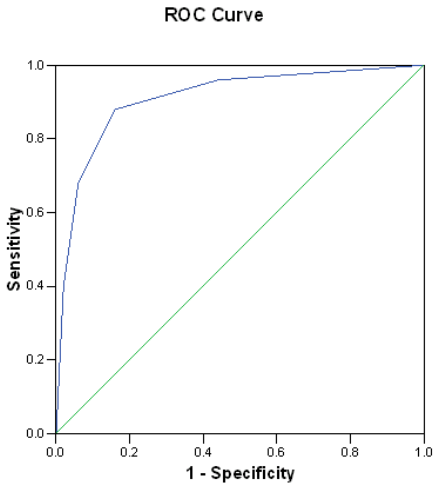

Fig 2. ROC Curve analysis of group 1

Our findings indicate that the visual pathway is commonly affected in tuberculoses patient on ethambutol and rare in those who are not using it.

The findings of V.E.R abnormalities in 5 out of 30 ethambutol treated patients including 3 asymptomatic cases supports the belief of regular monitoring with V.E.R.

We carried out evaluation using ROC curves to see the validity of V.E.R as a screening test. An ROC curve demonstrates, closer it follows the left-hand border and then the top border of the ROC space, the more accurate the test. Fig 2 shows the same pattern in Group I patients. The curve was 45-degree diagonal for Group II patients indicating, the less accuracy in Group II patients. However this group didn't show any V.E.R abnormality, thereby acting as a control group. The area under the curve is a measure of diagnostic accuracy.

We used the AUC as an indication of the overall performance of the V.E.R indexes.

An area of 0.91 for P_{100} latency means that a randomly selected patient from the positive Group I have a test value larger than that for a randomly chosen patient from the negative Group II in 91% of the time. Ethambutol was excluded in Group II patients so there was no incidence of optic neuritis. The AUC in this group was 0.5 (the ROC curve coinciding with the diagonal) meaning that the V.E.R variables under study can not distinguish between the two groups, i.e. where there is no difference between the two distributions.

In Group I, the overall performances of all the three V.E.R indexes were good indicating that serial measurement of V.E.R while using ethambutol will enhance the diagnostic accuracy of detecting subclinical optic neuritis

The AUC for P_{100} latency in our study, the most consistent waveform, was higher than the AUCs for amplitude and interocular difference. Amplitude is reasonable second choice and Interocular latency difference can be excluded as 95% CI for it included an AUC of 0.6.

In summary, our results suggest that measurement of P_{100} latency give the best results for screening ethambutol-induced optic neuritis in tuberculosis patients aged 20-50 years.

V.E.R should be considered a definitive tool for diagnosing ethambutol induced ON in TB patients. The results of application of Bayes's theorem make this point even more clear. Even with low base rate of optic neuritis in TB patients, 87% of those having116 ms or higher P_{100} latency actually had optic neuritis. This means that only about 13% of those with 116 ms or higher latency will not have optic neuritis. Also there is very low probability of incorrectly diagnosing patients who do not have optic neuritis as having the one because 99% of those with latency fewer than 116 ms will, in fact not have optic neuritis.

Measuring delay in P_{100} latency may aid early sub clinical diagnosis of ethambutol induced optic neuritis. Specificity was acceptable when the cutoff point of 116 ms was applied to the control group of patients without ethambutol.

The receiver operating characteristic analysis indicates that V.E.R performs well as a screening device and that a cutoff of 116 ms will produce the best balance of sensitivity and specificity. Our ROC findings confirm the usefulness of V.E.Rs in the detection of subclinical optic nerve disease and suggest their use in routine monitoring of ocular function in patients treated with ethambutol.

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