ORIGINAL ARTICLE

CHANGES IN PATTERN AND MULTIFOCAL ELECTRORETINOGRAM IN TUBERCULOSIS PATIENT WITH ETHAMBUTOL THERAPY

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ABSTRACT

Introduction: Tuberculosis (TB) is a world health problem, especially in Indonesia as the third biggest country for new emerging TB patients. Ethambutol is one of the standard therapies to treat TB patients in Indonesia. Ethambutol has a side effect called ethambutol optic neuropathy which is hard to diagnose due to normal fundus appearance in most cases and therefore often detected late. Early detection is necessary so that permanent damage can be prevented. Examination pattern electroretinography (pERG) and multifocal electroretinography (mfERG) have the advantage to detect and confirm ocular toxicity by ethambutol after the clinical problem had emerged. It is not yet known neither pERG nor mfERG could detect any changes to detect ethambutol ocular toxicity before the clinical problem emerged.
Methods: This study was a prospective clinical trial with 40 eyes samples and analyzed with paired t and Wilcoxon tests. The ocular examination was conducted using the Snellen chart, HRR Richmond Plates, Pelli Robson, pERG, and mfERG in tuberculosis category 1 patient with 2 months follow-up.
Result: Visual acuity, color, and contrast sensitivity were normal in all patients for 2 months follow-up period. In pERG examination, the mean implicit time wave P50 was shortened by -1.27± 4.71 mS (p=0.049), and the mean amplitude wave N95 was reduced by -0.93± 4.49 µV (p=0.038). Both were statistically significant. In the mfERG examination, we did not find any statistically significant changes in both wave N1 and P1.
Conclusion: Changes in pattern ERG presented earlier compared to mfERG after ethambutol therapy for 2 months.

Keywords: electroretinography, ethambutol, multifocal ERG, neuropathy, pattern ERG

INTRODUCTION

Tuberculosis (TB) is a worldwide health problem, especially in Indonesia as 3rd biggest country with new TB patients. Ethambutol is included as one of the standard therapies that are still used to treat TB patients in Indonesia. Ethambutol may cause visual disturbance due to ethambutol optic neuropathy.[1–3]

Ethambutol optic neuropathy incidences vary from 1-18% and it is a dose-dependent condition. The first clinical manifestation of ethambutol neuropathy usually presents as color and contrast sensitivity disturbance after 1.5-2 months of therapy. Ethambutol optic neuropathy

is difficult to diagnose since most cases have normal fundus appearance, therefore delaying detection, and permanent damage could happen in this situation. As permanent damage could happen from ethambutol toxicity, it is necessary to detect this disease as soon as possible.[3–5]

Examination pattern electroretinography (pERG) and multifocal electroretinography (mfERG) have been reported to have the advantage to detect and confirm ocular toxicity by ethambutol after the clinical problem had emerged. It is not yet known neither pERG nor mfERG could detect any changes to detect ethambutol ocular toxicity before the clinical problem emerge. The purpose of this study is to evaluate changes in pERG and mfERG examination in tuberculosis patients with ethambutol therapy.[6–8]

METHODS

This study was a prospective, single-center, clinical trial with pre and post-test groups, conducted at the Department of Ophthalmology at Kirana Cipto Mangunkusumo Hospital, teaching hospital. This study had received ethical clearance from the Institution Ethics Committee.

Data of all consecutive new tuberculosis patients from Persahabatan Hospital, Joharbaru Hospital, Matraman Hospital, and Clinic JRC PPT were collected. The inclusion criteria were; age between 18-60 years old, with visual acuity 6/6 for both eyes, ethambutol doses 15-20mg/kg weight, no history of systemic disease, no ocular congenital disease, no history of ocular surgery, no history ethambutol or TB therapy before, willing not to take alcohol nor vitamin zinc and copper and agree to sign the informed consent. Exclusion criteria were patients with disturbance in the visual field, color and contrast sensitivity, IOP more than 21mmHg, retina disease was found, any defect found in ocular anatomical either congenital or acquired. The sample size was 40 eyes with 20 patients. A drop-out patient was defined as a patient who didn't come to follow up evaluation for more than 7 days or didn't take therapy ethambutol daily.

Participants underwent ophthalmic evaluation consisting of detailed history, best-corrected visual acuity using the Snellen chart, anterior segment slit-lamp biomicroscopy, full-dilated pupil direct funduscopy examination, intraocular pressure using NCT. Color sensitivity was evaluated using Richmond HRR pseudoisochromatic plates, and contrast sensitivity by Pelli-Robson chart. The visual field test was performed using Humphrey Visual Field examination. pERG examination was performed using DTL electrodes to measure P50 and N95 wave time implicit dan amplitude, while mfERG used JET electrodes to measure N1 and P1 wave time implicit and amplitude. Both tests complied with the International Society of Electrophysiology and Vision (ISCEV) standard procedure.

All the enrolled patients were examined before the anti-tubercular treatment was given and after the first and second months of treatment. All patients were evaluated by a single physician. The pERG and mfERG examinations were evaluated by two neuro-ophthalmologist consultants (MS and SN). The data was collected in a Microsoft Excel table and analyzed using software SPSS 21.0 with paired T-test or Wilcoxon test.

RESULTS

This study included 40 eyes from 20 patients, consisting of 9 males and 11 females with a mean age of 34.5 years old, with 19 years old as the youngest and 59 years old as the oldest. Mean intraocular pressure was 14.3mmHg with 7mmHg as the lowest and 20.3mHg as the highest. No visual field defect was found. There were no visual acuity, color, or contrast sensitivity disturbances found in 2 months follow-up evaluation.

Pattern ERGs in all 40 eyes were studied. P50 waves implicit time was found statistically shortened after 2 months from 51.38± 5.09mS to 49.43± 4.60mS (p= 0.049). N95 waves amplitude was found statistically reduced after 2 months follow-up from 12.36±4.36 to 11.43±4.95 (p= 0.038).

Table 1. Characteristic study subjects

Variable	Mean
Total eye sample	40 eyes
Sex	
Male	9 (45%)
Female	11 (55%)
Mean ages	34.5 (19-59) years old
Mean intraocular pressure (IOP)	14.3 (7.0-20.3)
Visual field	Within normal limits

Table 2. Ophthalmological clinical examination

Clinical examination	Mean base	Mean month 1	Mean month 2
Visual acuity test	1.0	1.0	1.0
Pelli-Robson contrast test	1.65	1.65	1.65
HRR Richmond color test	10	10	10

Table 3. Changes in P50 waves pERG examination before and after 2 months follow-up

	Base	Month 1	Month 2	p1	p2
Imp time (mS)	51.38±5.09	50.11±2.99	49.43±4.60	0.096[b]	0.049[a]
Amp (µV)	8.60±3.53	7.74±3.11	8.18±3.17	0.094[a]	0.508[b]

Notes: a=Wilcoxon, b=T pair

Table 4. Changes in N95 waves pERG examination before and after 2 months follow-up

	Base	Month 1	Month 2	p1	p2
Imp time (mS)	101.10±8.24	103.76±7.59	99.14±7.21	0.218[a]	0.282[b]
Amp (µV)	12.36±4.36	11.44±4.04	11.43±4.95	0.243[b]	0.038[a]

Notes: a=Wilcoxon, b=T pair

In mfERG examination we did not find any statistically significant changes in both wave N1 and P1. Pattern ERG had earlier changes compare to mfERG.

Table 5. Changes in N1 waves mfERG examination before and after 2 months follow-up

	Base	Month 1	Month 2	p1	p2
Imp time (mS)	27.79±3.16	28.68±2.53	28.07±2.66	0.102[b]	0.577[a]
Amp (µV)	769.88±384.87	684.63±317.07	693.82±411.47	0.217[b]	0.331[b]

Notes: a=Wilcoxon, b=T pair

Table 6. Changes in P1 waves mfERG examination before and after 2 months follow-up

	Base	Month 1	Month 2	p1	p2
Imp time (mS)	49.78±2.46	49.17±2.83	48.93±3.30	0.418[a]	0.262[a]
Amp (µV)	1416.98±514.23	1324.80±541.97	1257.80±646.43	0.225[b]	0.418[b]

Notes: a=Wilcoxon, b=T pair

DISCUSSION

The pathophysiology of ethambutol optic neuropathy is believed from the zinc-chelating mechanism and its metabolites. There is no safe dosage in ethambutol therapy until today. The dosage of ethambutol in this study is based on Tuberculosis National Guideline Therapy. This disease could make permanent damage if there was a delay in detection and might have irreversible damage. Cease of ethambutol use as soon as possible is still the best therapy until today. Clinical manifestation only appears after 1.5-2 months of ethambutol consumption. A previous study also mentioned that ethambutol consumption may lead to permanent visual loss by inducing dose and duration-dependent optic neuropathy[9]. It is also known that ethambutol consumption can cause peripheral neuropathy, hepatotoxicity, numbness and tingling of extremities due to peripheral neuritis, mental confusion, disorientation, possible hallucinations, and psychosis.[10,11] Pattern ERG is used to check ganglion cells' function and mfERG examination is mostly used to check photoreceptor cells function in the retina. Both pERG dan mfERG shows changes in ethambutol neuropathy with visual disturbance.[3,12–16]

This study found that the changes of implicit time P50 and amplitude N95 in pERG examination were statistically significant. However, the implicit time of P50 does not have clinical significance. Mean changes amplitude N95 in this study was 0,93±4,49 µV, different

from Kakisu et al where the changes of amplitude N95 was 1,90 μV. The difference in N95 amplitude changes could happen because Kakisu et al study had a longer follow-up (7.7 months) and clinical manifestation of the ethambutol optic neuropathy had emerged.[17]
In mfERG examination, we did not find any statistically significant changes in both wave N1 and P1. Lai et al study found longer N1 implicit time in mfERG changes, possibly due to longer follow-up evaluation (3.6 months).[18]

This study found that N95 waves amplitudes in pERG were reduced significantly compared to mfERG examination. This data shows ganglion retinal cells are the most vulnerable variable in ocular toxicity by ethambutol. This hypothetically represents mitochondrial disturbance mechanism from the zinc-chelating effect that causes reduction of ATP production. Ganglion retinal cells are most dependent on ATP production because these cells contain a lot of mitochondria dan have many dendrites branch to photoreceptor cells. These ganglion cells need higher ATP to compare to retinal cone cells, therefore the damage from reduced ATP should initially damage ganglion cells. The N95 amplitude reduction in pERG examination showed specific damage to the ganglion retinal cells. Pattern ERG had earlier changes compared to mfERG.[4,19–30]

CONCLUSION

Pattern ERG examination showed significant changes for the implicit time of p50 waves and amplitude of N95 waves after 2 months follow-up, while mfERG examination found no statistically significant changes in both wave N1 and P1 after the same follow-up time. Pattern ERG had earlier changes compared to mfERG after 2 months of ethambutol therapy.

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