· Original article ·

Evaluation of anatomical and visual function for early detection of ethambutol toxicity among tuberculosis patients

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在结核病患者中通过评估解剖结构和视功能变化早期发现乙胺丁醇毒性

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摘要

目的:通过评估比较治疗前后解剖结构和视功能的变化,包括视网膜神经纤维厚度、图形视觉诱发电位、传统视神经功能检查,早期检测乙胺丁醇毒性。

方法:前瞻性研究,包括参加马来西亚理科大学医院的短期治疗观察项目的36例72眼结核病患者。视力和视神经功能检查由同一位研究者进行。同样,Humphrey自动视野检查、光学相干断层扫描(OCT)检查视网膜神经纤维厚度(RNFL)和图形视觉诱发电位(PVEP)均由同一位技术人员进行。在开始乙胺丁醇治疗前和治疗3mo后各进行检查一次。

结果:乙胺丁醇治疗前后视力、彩色视觉、光亮度、红光反射和眼底检查无明显改变。然而,平均视野缺损在治疗后较前变差($P=0.010$)。OCT和PVEP有显著变化,P100潜伏期延长、幅度降低,RNFL在各个象限均增厚($P<0.05$)。

结论:通过OCT检测RNFL厚度以及使用PVEP检测P100波峰潜伏期和幅度,可以在传统视神经功能检查异常之前,发现乙胺丁醇治疗后早期解剖结构和视功能的亚临床改变。

关键词:乙胺丁醇毒性;视神经功能;视网膜神经纤维厚度;光学相干断层扫描;视觉诱发电位

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Abstract

• AIM: To evaluate if early ethambutol toxicity can be detected by comparing pre- and post-treatment anatomical and visual function using retinal nerve fiber thickness, pattern visual evoked potentials and conventional optic nerve function tests.

• METHODS: This was a prospective study involving 72 eyes of 36 patients treated with ethambutol according to directly observed treatment short-course(DOTS) strategy in Hospital Universiti Sains Malaysia, Kelantan, Malaysia. The visual acuity and optic nerve function tests were performed by a single investigator. Likewise, Humphrey automated perimetry, optical coherence tomography (OCT) measurement of the retinal nerve fibre layer (RNFL) and pattern visual evoked potential (PVEP) were performed by a single technician. The examinations were performed before initiating ethambutol treatment and 3mo after that.

• RESULTS: There was no change in visual acuity, colour vision, light brightness, red saturation and fundus findings pre and post ethambutol. However, there was a statistically significant deterioration in the mean deviation of the visual field post treatment ($P=0.010$). There were also significant changes on OCT and PVEP, with increased RNFL thickness in all quadrants ($P<0.05$) and PVEP delayed P100 peak latency and amplitude ($P<0.001$).

• CONCLUSION: Ethambutol toxicity is a known complication of tuberculosis treatment. Early detection of this toxicity may prevent severe irreversible visual loss. The use of OCT to detect RNFL thickness and PVEP to assess P100 latency and amplitude can assist in the detection of subclinical anatomical and visual function changes prior to development of abnormalities on conventional optic nerve function tests.

• KEYWORDS: ethambutol toxicity; optic nerve function; retinal nerve fiber layer; optical coherence tomography;

visual evoked potential

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INTRODUCTION

Tuberculosis is an endemic disease in most developing countries, including Malaysia. It is caused by mycobacterium tuberculosis, which can infect any part of the body, but mainly affects the lungs.

Ethambutol hydrochloride is used as a first-line drug in the treatment of tuberculosis, as part of the directly observed treatment short-course (DOTS) strategy recommended by the World Health Organization (WHO).

Ethambutol has the potential to cause toxic optic neuropathy[1]. The incidence of ethambutol toxicity has been reported to range from 1% to 18% in various studies[2-3]. Despite the recommended dose of 15-20mg/kg perday, ethambutol toxicity has been found to occur in doses that are lower than the normal recommended dose[4-5]. There is no reported safe dose of ethambutol[6]. Although this toxicity has been considered reversible on discontinuation of the treatment, there have also been reports of irreversible severe visual loss despite immediate cessation of ethambutol[1,6-9].

Early detection of ocular toxic effects before occurrence of symptoms may prevent permanent optic nerve damage and allow complete recovery of normal function[10-11]. However, it remains to be determined whether early ocular toxicity can be accurately detected by regular clinical tests like visual acuity, visual field, colour vision test, light brightness and red saturation (optic nerve function tests). Optical coherence tomography (OCT) of the retinal nerve fiber layer (RNFL) and electrophysiological tests like pattern visual evoked potential (PVEP) have the potential to document subtle anatomical and functional changes[11-15]. However, studies regarding the use of these investigations in detecting ethambutol toxicity are limited, and their results sometimes conflicting[11,14-17]. Our study thus aims to evaluate the role of optic function tests, OCT and PVEP in the early detection of ocular ethambutol toxicity.

SUBJECTS AND METHODS

This study was conducted inthe Ophthalmology Clinic of Hospital Universiti Sains Malaysia, Kelantan, Malaysia, after obtaining approval from the Human Research Ethics Committee of Universiti Sains Malaysia.

The inclusion criteria was all patients aged 18y and above who were referred to the eye clinic for assessment prior to starting anti tuberculosis medication, which included treatment with ethambutol at a dose of 15mg/kg preday. All patients were also on isoniazid, rifampicin and pyrazinamide treatment as part of the DOTS strategy. Patients with ocular or neurological problems which could have affected PVEP findings were excluded. We also excluded patients with impaired drug metabolism, such as those with renal or hepatic disease. Informed consent was obtained from all patients.

A complete history taking and eye examination was performed in all patients by a single investigator. The ocular examination included visual acuity, refraction, color vision using Ishihara plates, assessment of light brightness and red saturation (by comparing them between eyes), slit lamp examination, pupillary examination and funduscopy. The visual field was assessed using Humphrey visual field 24-2 (Carl Zeiss, Germany).

The OCT and electrophysiological tests were performed by a single, trained operator. OCT, which uses low-coherence interferometry to measure the thickness of the retinal nerve fibre layer, was done using a Spectral-Domain Heidelberg Spectralis OCT. PVEP, which is based on detection of an electrical potential in response to a stimulus in the visual field, was performed based on the ISCEV PVEP protocol 2009, using a Granzfield PVEP Roland-Consult, RETI-port 32, Germany. Standard silver-silver chloride skin electrodes were placed based on the "10-20 International System". The stimuli used was a checkerboard with large 1°(i.e. 60min of arc) and small 0.25° (15min of arc) checks. PVEP was tested monocularly in each eye of a single patient, with appropriate refractive correction. All examinations were performed immediately prior to commencement of anti-tuberculosis treatment and repeated 3mo later.

Data was analyzed using Statistical Package for the Social Sciences IBM Version 22.0 (SPSS Inc. Chicago, IL, USA). Paired *t*-test was used to compare the differences in the optic nerve function, OCT and PVEP parameters pre and post ethambutol treatment.

RESULTS

A total number of 72 eyes of 36 patients were examined. The patients from this study were all Malays from Kelantan, ranging from 18 to 72y of age, with the median age of 40y. There were 22 males (61.1%) and 14 females (38.9%). Among these patients, 19 (52.8%) had no medical comorbidities; of the remainder, 7 (19.4%) had hypertension, while 5 (13.9%) had diabetes mellitus. The majority (94.4%) were non smokers.

During the course of this study, none of these 36 patients had ocular complaints. Clinically, there were also no anterior or posterior segment changes in all these patients. Pre and post treatment, there were no changes in visual acuity among these patients. There was also no relative afferent pupillary defect. Red saturation, light brightness and colour vision pre and post 3mo of ethambutol treatment remained unaffected.

Table 1 shows the comparison of the visual field mean deviation before initiation of ethambutol treatment and 3mo after it. There was a statistically significant deterioration from pre-treatment values ($P=0.010$).

Table 1 Comparison of visual field mean deviation of a paired sample $n=72$

Parameters	Mean (SD)	Mean difference (95% *CI*)	*t*-statistics[a] (dt)	*P*
Pre-treatment	-0.88 (1.73)	-0.19(-0.34, -0.05)	-2.66 (71)	0.010
Post-treatment	-1.07 (1.78)			

[a]Paired *t*-test was applied.

Table 2 Comparison of retinal nerve fiber layer thickness of a paired sample $n=72$

Parameters	Mean (SD)	Mean difference (95% *CI*)	*t*-statistics[a] (dt)	*P*
Superior RNFL				
Pre- treatment	132.85(9.17)	1.57 (0.59, 2.55)	3.18 (71)	0.002
Post- treatment	134.42(8.16)			
Inferior RNFL				
Pre- treatment	126.58(14.87)	2.25 (1.22, 3.28)	4.37 (71)	<0.001
Post- treatment	128.83(14.88)			
Nasal RNFL				
Pre- treatment	79.36(9.03)	1.82 (1.10, 2.54)	5.01 (71)	<0.001
Post- treatment	81.18(8.07)			
Temporal RNFL				
Pre- treatment	74.96(8.92)	5.53 (4.20,6.86)	8.30 (71)	<0.001
Post- treatment	80.49(10.41)			

[a]Paired *t*-test was applied; RNFL: Retinal never fiber layer.

Table 3 Comparison PVEP latency and amplitude of a paired sample n=72

Parameters	Mean (SD)	Mean difference (95% *CI*)	*t*-statisticsa[a] (dt)	*P*
P100 latency (1°)				
Pre- treatment	102.40 (2.81)	16.94(13.64, 20.25)	10.23 (71)	<0.001
Post- treatment	119.35 (13.93)			
P100 latency (0.25°)				
Pre- treatment	114.32 (3.04)	13.75(11.04, 16.46)	10.11 (71)	<0.001
Post- treatment	128.07 (10.81)			
P100 amplitude (1°)				
Pre- treatment	11.75 (3.00)	-0.83(-1.12, -0.55)	-5.92 (71)	<0.001
Post- treatment	10.91 (3.12)			
P100 amplitude (0.25°)				
Pre- treatment	13.30 (3.50)	-1.24(-1.75, -0.74)	-4.90 (71)	<0.001
Post- treatment	12.06 (3.59)			

[a]Paired *t*-test was applied.

OCT showed an overall statistically significant increase in the RNFL after 3mo of ethambutol treatment ($P<0.05$). The changes were strongly significant in the inferior, nasal and temporal quadrants ($P<0.001$) (Table 2).

The PVEP showed significant differences pre and post ethambutol treatment. Prior to treatment, all PVEP values were normal, while post-treatment, there were abnormalities in P100 peak latency and amplitude.

The P100 peak latency showed significant delay ($P<0.001$) with both the large (1°) and small (0.25°) checkered box stimuli post-treatment. Likewise, the P100 amplitude was reduced compared to prior to treatment (Table 3).

DISCUSSION

Tuberculosis is a disease that poses a global problem[18-19]. With the emergence of drug-resistant tuberculosis strains, tuberculosis has become increasingly difficult to treat. In 2014, 9.6 million people worldwide contracted tuberculosis, and 1.5 million of them died[20]. The morbidity and mortality caused by this disease necessitates effective treatment strategies. WHO has recommended a regime of medications, which, in combination, have proven useful in the management of this disease[3]. Unfortunately, as with all drugs, patients and clinicians have to be aware of potential medication side effects.

Ethambutol hydrochloride, a butanol derivative, is a main player in the treatment of tuberculosis[21-22]. It has been postulated to cause toxic optic neuropathy by the production of its metabolite, ethylene diaminobutyric acid[21]. The latter causes transformation of metal ions into chelating agents, thus leading to decreased levels of copper, iron, and other metals associated with the mitochondrial cytochromes[23]. Paramount among its effects is chelation of the copper irons of cytochrome C oxidase within optic nerve axons, causing depletion of copper levels[21,24]. Without sufficient copper, cytochrome C

oxidase is unable to transport the electrons needed for ATP production. The decreased ATP levels cause a decrease in axonal transport of mitochondria, leading to a vicious cycle of energy depletion and subsequent axonal swelling[25]. Other mechanisms by which ethambutol is hypothesized to cause toxicity are demyelination of the visual pathway[7] and neutralization of lysosomes, resulting in impaired autophagy[26].

Since the 1960's, when ethambutol was still an experimental drug in tuberculosis treatment, monitoring for drug toxicity has been *via* visual function tests. Reduced red saturation has been cited as the earliest clinically detectable parameter of optic nerve dysfunction in ethambutol toxicity[27]. In our study, although none of the participants had clinically significant abnormalities in optic nerve function, the visual field showed deterioration of the mean deviation, suggesting progression of optic nerve damage. This is in line with the changes we observed in the RNFL and PVEP.

Previous studies have documented both increased and decreased RNFL thickness in the OCT of patients on ethambutol[11-12,15,28-29]. As discussed earlier, ethambutol toxicity results in copper chelation, resulting in disruption of axonal transport to the mitochondria. This process causes energy depletion and later development of axonal swelling, which explains the increase in RNFL thickness in the early stages. However, as the disease progresses, the initial swelling reduces and is followed by thinning and necrosis of the papilomacular bundle due to apoptosis, manifesting as RNFL thinning[30].

Electrophysiological tests have been used in various studies to diagnose ethambutol toxicity[11-12]. PVEP is an electrophysiological test used to detect electrical potentials that occur in the cortex after visual stimulation with checkered box stimulus of specific sizes. It is particularly specific for assessing optic nerve function in the anterior pre-chiasmal region. As reported in several other studies, the early stages of toxic optic neuropathy are characterized by delay in PVEP P100 latency and reduction in its amplitude, prior to detection of optic nerve dysfunction[11-12]. Latency represents a prolonged time in milliseconds for the stimulus observed by the patient's eye to reach and be processed by the brain, and is usually abnormal in demyelinating conditions. Amplitude in turns reflects the integrity of the visual pathway, and is affected by axonal damage. The changes detected on PVEP are related to the pathophysiology explained earlier.

In view of the statistically significant changes in OCT, which concur with the results of previous research[14,31-32], we postulate that the changes in OCT and PVEP are subclinical early signs of ethambutol toxicity. However, one limitation of our study is that our tuberculosis patients were all on a multi-drug regimen, which included isoniazid. This medication has also been implicated in toxic optic neuropathy, and may thus act as a confounder[33]. Regardless, our study demonstrates that toxic optic neuropathy manifests with changes in RNFL thickness and prolonged P100 peak latency and decreased amplitude, prior to development of clinical optic nerve dysfunction.

Ethambutol toxicity is a known complication of tuberculosis treatment. Optic nerve function tests have traditionally been used to monitor for signs of toxicity; however, by the time visual impairment occurs, optic nerve damage may be irreversible. The use of OCT to detect RNFL thickness and PVEP to assess P100 latency and amplitude may allow detection of subclinical anatomical and visual function changes secondary to ethambutol toxicity, prior to development of abnormalities on conventional optic nerve function tests.

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