Optic and Peripheral Neuropathy due to Ethambutol

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ABSTRACT

We present a case of a 77 year-old woman, diagnosed with an atypical mycobacterial pulmonary infection, started on treatment with ethambutol (EMB), rifamycine and ciprofloxacin. Eight months later she presented with symptoms of peripheral sensory neuropathy, detected on electromyography 2 months later. One month after, she developed bilateral optic neuropathy, leading to treatment suspension. Two and a half years of follow-up showed almost complete recovery of visual function, which is not always the case. Peripheral neuropathy should alert clinicians to the risk of optic neuropathy due to EMB. With increased incidence of tuberculosis worldwide, more cases of optic neuropathy associated with EMB may be reported.

Key-words: ethambutol; optic neuropathy; peripheral neuropathy; tuberculosis; drug toxicity

RESUMO

Apresentamos o caso de uma mulher de 77 anos, com o diagnóstico de infecção pulmonar por uma micobactéria atípica, cujo tratamento consistiu em etambutol, rifamicina e ciprofloxacina. Oito meses após o início do tratamento, apresentou quadro de neuropatia periférica sensitiva, confirmada em eletromiografia 2 meses mais tarde. Um mês depois desenvolveu neuropatia óptica bilateral, o que levou à suspensão do tratamento, tendo-se verificado melhoria quase completa da situação clínica. A presença de neuropatia periférica, em doentes a fazer terapêutica com etambutol, deve alertar para a possibilidade de lesão do nervo óptico. Com o aumento da incidência de casos de tuberculose, novos casos de neuropatia óptica por etambutol poderão surgir.

Palavras-chave: etambutol; neuropatia óptica; neuropatia periférica; tuberculose; toxicidade por fármacos

INTRODUCTION

Ethambutol (EMB) is an antimycobacterial agent introduced in 1961 for treatment of patients with tuberculosis. It acts by inhibiting arabinosyltransferase, an enzyme crucial for mycobacterial cell wall synthesis, by its metal-chelating properties, thus impairing prokaryotic ribosomes normal function[1]. The similarity between human mitochondrial DNA and bacterial ribossomes leads to disruption of oxidative phosphorylation chain and mitochondrial function, by interference with iron-containing complex I and copper-containing complex IV. This leads to energy depletion by reduced ATP synthesis, with consequent accumulation of reactive oxygen species, eventually resulting in apoptosis and optic nerve degeneration[2]. Other studies suggest that zinc also might play a role in ethambutol toxicity, and individuals with reduced serum zinc levels may be more susceptible to ethambutol toxicity; this may be related to inhibition of lysosomal activation, resulting in accumulation of zinc in lysosomes with increased lysosomal membrane permeability and death[3].

Optic nerve dysfunction caused by EMB is well known, with the papillomacular bundle being mostly affected, due to its high energy demands with a low energy production. Optic chiasm involvement (primarily[4] or following optic nerve disease[5]) and retinopathy[6] have also been described with the use of EMB.

The importance of mitochondria impairment in this process is supported by several reports of patients with mitochondrial disease who developed optic neuropathy while on treatment with EMB, namely Leber Hereditary Optic Neuropathy[7], Dominant Optic Atrophy[8] and Charcot-Marie-Tooth disease[9], suggesting a synergistic deleterious effect of this anti-mycobacterial drug on the background of a pre-existing pathogenic mtDNA mutation.

Daily dose, treatment duration, renal disease and age (probably related to decreasing renal function) are considered risk factors[10]; one study could not find a correlation between duration of treatment and the development of EMB optic neuropathy[11]. Estimated incidence is 1% of patients taking less than 15 mg/kg/day, increasing to 5-6 % when the daily dose exceeds 25mg/kg/day.

Patients present with painless, bilateral acute or sub-acute cecocentral scotoma, visual color deficiency or bitemporal hemianopia; optic discs may look normal or pale at presentation. Symptoms develop from 15 days to 2 years after treatment initiation.

Peripheral neuropathy (PN) is a serious condition affecting the nerves that is commonly seen in patients with tuberculosis (TB). Causes of PN in patients with TB are multiple, and can include TB itself; other co-morbid conditions, such as Human Immune-deficiency virus (HIV) disease, malnutrition, or diabetes mellitus (DM); and several anti-tuberculous medications[12].

Peripheral nerve disease (mostly sensory but also motor) has long been reported with EMB treatment, although rare, and its incidence has not been estimated in the literature. Association of peripheral and optic nerve damage is uncommon.

In the present case report, we aimed to report one ethambutol-induced optic neuropathy preceded by peripheral nerve disease. Also, we provided a brief review of the literature on the subject.

CASE REPORT

A 77-year-old female was started on rifamycine (600 mg daily), ethambutol (EMB) (1200 mg daily, corresponding to 18 mg/kg/day) and ciprofloxacin (750 mg twice a day), due to pulmonary infection caused by an atypical mycobacteria; she denied taking other antibiotics, namely isoniazid. Three weeks later, the patient developed gastro-intestinal toxicity and ciprofloxacin was suspended.

Eight months after treatment onset, she developed numbness in her feet; neurological exam showed decreased distal pin prick in both feet, with no other changes. An electromyography (EMG) was performed at that time, with no signs of peripheral neuropathy.

The symptoms worsened during the following months and an EMG was repeated two months later, showing a sensory peripheral axonal neuropathy. A decision was made not to suspend the treatment and the patient was prescribed vitamin B12 tablets.

About a month later, she reported bilateral, painless, progressive visual loss over 5 days, at which point she attended our hospital. Best corrected visual acuity (BCVA) was 0.2 OD, 0.4 OS. The patient could only identify the test plate on Ishihara test with each eye; no RAPD was present. Biomicroscopy showed bilateral mild nuclear cataracts; there was no optic disc edema or atrophy on fundoscopy

(figure 1A). Humphrey perimetry revealed bilateral central scotomas (figure 2A); on optical coherence tomography (OCT), there were no changes in the peripapillary retinal nerve fibre layer thickness (RNFL) and a mild reduction of the retinal ganglion cell layer (RGCL) thickness (figure 3A). Visual evoked potentials (VEP) showed normal latency and reduced bilateral and symmetrical amplitude, suggesting bilateral optic neuropathy. At this point, all anti-tuberculous medications were suspended and the patient re-evaluated by her treating physician, who decided the treatment could be stopped at this time, totalling 11 instead of 12 months' treatment.

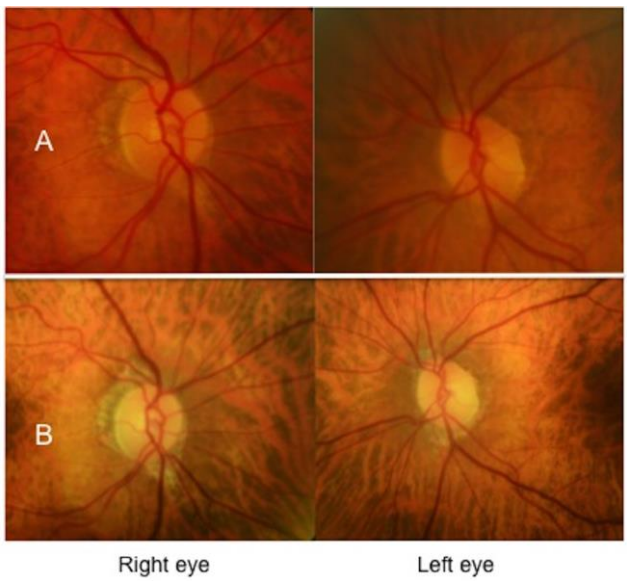

Figure 1

OUTCOME AND FOLLOW-UP

One month later, visual acuity and color vision remained the same but three months after suspending treatment BCVA was 0.3 OD and 0.5 OS. Over the following months there was a progressive improvement, with BCVA 0.8 OD, 0.7 OS and 14/17 plates for both eyes on Ishihara test, 7 months after the initial visual symptoms. VEP performed 8 months after treatment discontinuation were normal.

Follow-up at two and a half years showed complete recovery of BCVA, with 1.0 OU, as well as normal color vision (17/17 Ishihara plates OU); on fundoscopy, there was optic nerve pallor, mostly temporal. Visual field testing, although with a low test reliability, showed a tendency to improvement (figures 2B and 2C). OCT revealed a mild reduction of RNFL, especially regarding the temporal quadrants, and a diffuse loss of macular RGCL on both eyes (3B and 3C).

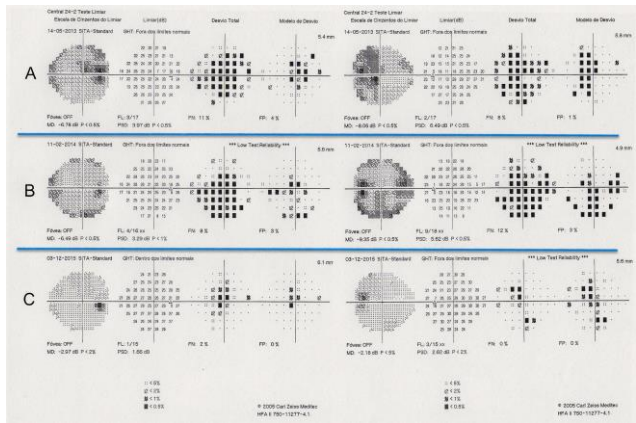

Figure 2

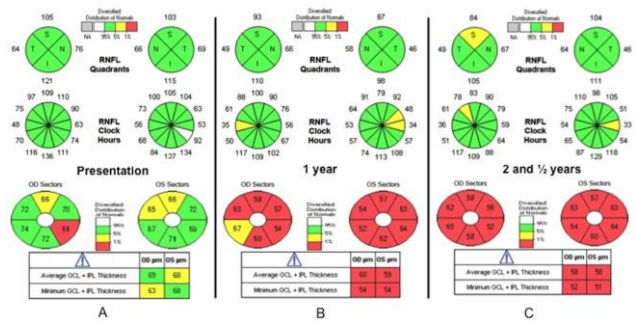

Figure 3

As for sensory symptoms, the patient also reported mild improvement but the EMGs repeated so far haven't shown any changes.

DISCUSSION

EMB is usually associated with the development of optic neuropathy but can be a rare cause of reversible**,** distal sensory neuropathy. Patients presenting with both optic and peripheral nerve dysfunction are uncommon in the literature, with one case recently described[13]. Our patient developed peripheral neuropathy several months before optic nerve dysfunction, as previously reported[14-15].

Visual prognosis is variable, ranging from complete recovery to no improvement upon drug withdrawal. Our

patient had a favourable outcome regarding visual symptoms, with an improvement in visual acuity, color vision, visual fields and VEP. Interestingly, the patient demonstrated a structural-functional dissociation, as described by Masvidal et al[16]: while there was a clinical gain, OCT showed loss of RNFL, as with other optic neuropathies; the authors suggest that some of the axons of the papillomacular bundle may not reach a threshold for apoptosis and are able to survive, emphasising the need for early cessation of ethambutol. Moreover, this patient had thinning of macular RGCL thickness on presentation, which may be an early sign of EMB toxicity, as recently published by Han et al[17]; in their patient, follow-up at three months after drug discontinuation showed a partial recovery of RGCL thickness, which had been severely depressed after three months of EMB therapy.

Although there is clearly a dose-dependent mechanism, some patients have developed optic neuropathy with a "safe dose" and these have been classified as idiosyncratic. During recent years, our knowledge regarding mitochondria functioning, namely in EMB induced neuropathy, has changed and some of these cases may actually be related to pre-existing mitochondrial dysfunction, thus excluding idiosyncrasy; such cases would be explained by a lower threshold to oxidative stress caused by some drugs, namely EMB, ultimately leading to cell death.

It is arguable if EMG-documented peripheral neuropathy could have led to treatment suspension but this was not the case. Fortunately, the optic neuropathy that followed resolved completely after drug cessation. One question that should be raised is whether peripheral nerve involvement predicts optic neuropathy; if this is true, sensory or motor symptomatology, documented by EMG, should lead to suspension of ethambutol.

With increased incidence of tuberculosis worldwide, more cases of ethambutol associated optic neuropathy may be reported. Physicians, namely ophthalmologists, should be alert to this possibility and some authors suggest a baseline evaluation for these patients, with visual acuity, color vision and visual field testing, with repeated tests every 1-3 months, although this follow-up scheme may not be consensual.

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