·Clinical Research·

Ethambutol induced toxic optic neuropathy in HIV positive patients

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Abstract

• AIM: To determine whether HIV and the use of antiretroviral therapy is a risk factor for the development of ethambutol toxic optic neuropathy. To describe the clinical course of ethambutol toxic optic neuropathy in patients with HIV and to identify prognostic factors.

• METHODS: The case notes of 14 consecutive patients referred to the neuro-ophthalmology clinic were reviewed. Data regarding HIV status, antiretroviral therapy, visual function, ethambutol therapy dosage, and ethambutol therapy duration were collected and analysed.

• RESULTS: Eleven of the 14 patients were HIV positive. Ten of the HIV positive patients were receiving antiretroviral therapy. The mean dose of ethambutol was 17.25mg/kg/day. No statistically significant difference in mean dose, duration of therapy, age or CD4 count was found between those who showed visual improvement and those who did not. Delay in presentation of more than one month post symptom onset was correlated with poor visual outcome (P=0.001).

• CONCLUSION: HIV and, perhaps more importantly, the potential mitochondrial toxic effects of Nucleoside analogue reverse transcriptase inhibitors (NRTIs) may be a risk factor for the development of toxic optic neuropathy from ethambutol therapy *via* a multiple hit effect. Delay in presentation results in poor visual outcome. Regular monitoring is recommended for HIV positive patients receiving antiretrovirals and requiring ethambutol therapy in order to avoid permanent visual loss.

• KEYWORDS: ethambutol; HIV; toxic; optic neuropathy

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INTRODUCTION

Ethambutol is an effective first line agent used in the treatment of tuberculosis, which remains a prevalent infectious disease in middle and low income countries [1]. Optic nerve toxicity resulting from the administration of ethambutol is a well-recognised complication of therapy [1, 2]. Carr and Henkind [3], in 1962, initially reported on the dose dependant effect of ethambutol toxicity. Current guidelines recommend doses of 15-20mg/kg/day with a toxicity incidence of 1%[1,4]. Wang and Sadun [5] estimate approximately 100 000 new cases of toxic optic neuropathy from ethambutol each year. A systematic review by Ezer *et al* [6] estimates visual impairment in 22.5/1 000 people on ethambutol therapy, with permanent visual loss occurring in 2.3/1 000. The mechanism of toxicity is not well understood. The postulated mechanism is related to the chelating effects of ethambutol on various mitochondrial metal-containing enzymes[4, 5].

Ethambutol toxicity most commonly presents between three and five months post initiation of therapy as bilateral, progressive, painless visual loss and/or decreased colour vision [1,4,7]. With prompt cessation of therapy, visual acuity may recover over several months. However, there may be significant deficits in recovery of visual fields, colour vision, and contrast sensitivity [4,7-11]. The reported range in visual acuity improvement is between 20% and 80% [1]. No risk factors for poor visual recovery have been identified.

Age, hypertension, renal dysfunction and daily dose of ethambutol therapy have all been positively correlated with an increased risk of toxicity [8-10]. Duration of therapy as a risk factor remains controversial. Talbert Estlin and Sadun [10] found a positive correlation between duration of therapy and toxicity, whereas Lee *et al*'s [9] review of 13 cases found no correlation between duration of therapy and toxicity. HIV and the use of anti-retrovirals as a risk factor for the development of ethambutol toxic neuropathy have not been reported.

The Western Cape of South Africa has one of the highest tuberculosis incidence rates in the world, with a figure of 1 037/100 000 reported in 2002 [12]. An estimated 28.2% of these patients have HIV co-infection [12]. Several studies have looked at the pharmokinetics of ethambutol in HIV affected individuals and found a low maximum concentration of drug

Table 1 Comparison between HIV positive and negative patients

Parameters	HIV positive	HIV negative	*P*
Number	11 (78.57%)	3 (21.43%)	
Mean age (a)	49±9	56.67±2.67	0.184
Number receiving antiretroviral therapy	10 (90.91%)	N/A	
Mean dose of ethambutol (mg/kg/ day)	17.25±1.23	17.12±1.01	0.873
Duration of therapy (month)	5.64± 2.9	6.67±1.15	0.568
Number presenting less than one month after onset of symptoms	5 (45.45%)	2 (66.67%)	0.347
Number with renal impairment	1	0	0.588
Mean visual acuity at presentation			
Right	1.89±0.58	1.66±0.577	0.56
Left	1.91±0.3	1.66±0.577	
Ishihara score at presentation	Test plate only (all)	Test plate only (all)	0.32
Number showing visual recovery	5 (45.45%)	2 (66.67%)	0.347
Mean visual acuity improvement			
Right	1.07±0.43	0.6±0.85	0.561
Left	0.88±0.59	1.2±0	0.325
Ishihara score improvement			
Right	9.75±2.87	3.5±3.53	0.0759
Left	6.75±4.11	5±1.41	0.558

Table 2 Comparison between HIV positive patients with and without visual improvement

Parameters	Visual improvement	No visual improvement	*P*
Mean ethambutol dose (mg/kg/day)	16.66±1.48	17.59±1.03	0.249
Mean duration of therapy (month)	8±2.82	4.29±6.57	0.032
Mean age (a)	44.5±11.9	51.57±6.57	0.228
Number of patients presenting less than one month after onset of symptoms	4	7	0.001
Number of patients with renal Impairment	1	10	0.43
Mean CD4 count	360	260	0.61

in these patients [13,14]. Decreased absorption of oral drug seemed to be the reason for the low serum levels [13, 14]. It would thus be reasonable to assume that HIV positive patients would be at lower risk of development of toxic optic neuropathy.

We report a series of cases referred to the neuro-ophthalmology clinic at Groote Schuur Hospital in Cape Town between 2010 and 2012.

SUBJECTS AND METHODS

Subjects A retrospective review of 14 consecutive patients on ethambutol therapy referred to the Groote Schuur Hospital neuro-ophthalmology clinic between March 2010 and March 2012 was performed. Ethical approval for the study was obtained from the Human Research Ethics Committee of the University of Cape Town.

Methods Diagnosis of ethambutol toxicity was based on bilateral, symmetrical visual loss, presence of a paracentral scotoma, sluggish pupils with no relative afferent defect, and decreased colour appreciation as measured by Ishihara test plates. Information regarding HIV status, CD4 count, antiretroviral therapy, renal function, dose of ethambutol, duration of therapy and visual function was obtained. Visual acuity was measured in Logmar, and Ishihara test plates were used as a measure of colour appreciation.

Statistical Analysis Statistical analysis was performed using STATA version 9.0. Wilcoxon/Man-Whitney Rank sum and Fischer exact tests were used to test statistical significance.

RESULTS

Eleven of the 14 patients seen were HIV positive. Table 1 shows the comparisons between the HIV positive and negative patients. There were no differences. Table 2 shows the comparisons in the HIV positive patients with and without visual improvement. Whilst there is a difference in mean duration of therapy, with the group showing no visual improvement having a shorter mean duration of therapy (P= 0.032), duration of therapy is not a significant predictor of visual improvement on logistic regression analysis(P=0.109). Patients with a delay in presentation of more than a month had a poorer outcome (P=0.001).

DISCUSSION

Given that an estimated 28% of people with tuberculosis in the Western Cape have HIV co-infection, and that 10 of 14 consecutive patients seen in our clinic with ethambutol toxicity were HIV positive on antiretroviral therapy, it would seem that HIV therapy with antiretrovirals may be a risk factor for the development of ethambutol toxicity.

Sadun *et al* [15] have noted secondary inflammatory changes and degenerations in the optic nerve with monocyte infiltration in HIV positive patients. This suggests that HIV

affects the optic nerve *via* immune mediated mechanisms, most notably by action of cytokines and tumour necrosis factor [15, 16]. HIV positive patients may thus have vulnerable optic nerves and may be more predisposed to the development of acquired optic nerve toxicity.

Ethambutol is a metal chelator and its antimycobacterial properties are related to the inhibition of arabinosyltransferase (an important enzyme for mycobacterial cell wall synthesis)[5]. Ethambutol also disrupts oxidative phosphorylation and mitochondrial function by interfering with iron containing complex I & copper containing complex IV. The resultant effect is the generation of reactive oxygen species and a cascade of events resulting in cellular apoptosis [5,6]. The feature of temporal pallor seen commonly in toxic optic neuropathy is due to the high mitochondrial content of the papillomacular bundle, and hence ganglion cells in this area are most affected by mitochondrial disturbance[5].

Nucleoside analogue reverse transcriptase inhibitors (NRTIs) used in antiretroviral therapy target the viral reverse transcriptase enzyme. The drugs have also been noted to cause mitochondrial toxicity affecting several tissue systems by interference of mitochondrial DNA (mtDNA) polymerase gamma [5,17,18]. The effect is acquired defects of mtDNA mutations. Cortopassi *et al* [19] attribute the activation of transcripts of the unfolded protein response in genetic mitochondrial diseases, such as Lebers hereditary optic neuropathy. Acquired mtDNA mutations may cause similar activation of these transcripts. The unfolded protein response results in inhibition of protein synthesis, vesicular secretion and oligodendrogenesis resulting in neurological disease[19].

Ten of the 14 patients in our study were HIV positive and receiving antiretroviral therapy. All of these were on a national guideline based first line therapy consisting of two NRTIs (stavudine and lamivudine) and one non-nucleoside reverse transcriptase inhibitor (Efavirenz)[20]. These patients are thus exposed to a double hit effect on mitochondrial function which may attribute for their majority number in our study.

Despite original drug testing reporting visual recovery after prompt cessation of ethambutol, our study supports the findings of Lee *et al* [9] and Kumar *et al* [11] suggesting that visual function recovers only in a minority of patients. Furthermore, the patients showing recovery in visual acuity still have residual deficits in colour vision. Our series also suggests that poor visual recovery is associated with delayed presentation and therefore delayed cessation of therapy.

Ethambutol dosages were within the recommended "safe" dosage range of 15 and 20 mg/kg/day. The HIV positive patients follow the same clinical course described for otherwise healthy individuals, with delayed onset of symptoms, marked symmetrical visual loss and colour vision deficits, and typical visual field defects. Visual loss on presentation was profound in all our patients, and all patients at presentation were only able to read the test plate of the Ishihara charts.

Guidelines for the early detection and prevention of toxicity have been published. The British Thoracic Society and the American Thoracic Society both recommend visual screening prior to commencement of therapy but do not recommend regular monitoring of visual function during therapy [1]. Several studies have shown colour vision testing with Ishihara test plates to be a sensitive sign of early toxicity[1]. Monitoring of visual function during therapy is not routine in South Africa.

This study has a number of limitations. It is a retrospective case series. The study sample is small and therefore, valuable interpretation of statistical significance is limited. However, ethambutol toxicity is a rare event with only small series of cases reported. Our study demonstrates an increasing trend of patients who are HIV positive and receiving antiretroviral therapy who present with ethambutol toxicity. A case control study might further elucidate and quantify the risk of HIV and antiretroviral therapy for ethambutol toxicity.

This study raises some important issues. Ethambutol toxic optic neuropathy is a rare complication of therapy, but it has potentially devastating effects on vision. HIV positive patients on antiretroviral therapy may be especially vulnerable to the toxic effects of ethambutol *via* a multiple hit effect. Consideration could be given to regular monitoring of visual function in HIV positive patients on antiretroviral therapy receiving ethambutol, or motivation made to exclude ethambutol from their anti-tuberculosis regimen.

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