Case Report

Rapidly developing Optic Neuritis secondary to Ethambutol: possible mechanism of injury

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Abstract

Optic neuritis has been described among the toxic effects of Ethambutol. This side effect is dose related. The mean duration of Ethambutol induced optic neuritis (EON) is three months. We report a case of EON after few days of exposure to Ethambutol and the symptoms resolved after discontinuation of Ethambutol. This most likely represents an idiosyncratic reaction which is different as compared to dose related optic neuritis.

Introduction

Ethambutol gained acceptance in tuberculosis therapy because of improved patient tolerance and convenience of administration and has been used in the treatment of tuberculosis for more than 25 years.[1] It acts only on proliferating cells, apparently by interfering with the synthesis of RNA by inhibiting the incorporation of mycolic acid into the mycobacterial cell wall.[2] The most important side effect of this drug is optic neuritis, resulting in decreased visual acuity and colour blindness. This reaction is proportional to the dose of ethambutol and is observed in 15% of patients receiving 50 mg per kg per day, in 5% of patients receiving 25 mg per kg per day and in less then 1% of patients receiving daily doses of 15 mg per kg.[3] These symptoms usually develop after few weeks of treatment. We report a patient who developed bilateral optic neuritis on day three of ethambutol therapy. Possible mechanism of optic nerve injury is discussed.

Case Report

A 35-year-old female presented to the emergency room with the history of intermittent fever for one month, altered mental status and left eyelid drooping for a day. Her neurological examination showed anisocoric pupils, left partial ptosis and left abducent nerve palsy. Visual acuity in both eyes was normal. Neck stiffness and Kerning's sign were positive. MRI brain revealed multiple ring enhancing lesions involving the supra and infratentorial brain compartment and diffuse meningeal enhancement. CSF analysis showed glucose=10 mg/dL; protein=161 mg/dL; pleocytosis=618 cells with lymphocytic predominance (80%). A diagnosis of tuberculous meningitis was suggested. A CSF culture was later reported positive for AFB. She was started on rifampicin 10 mg/kg, isoniazid 5 mg/kg, ethambutol 25 mg/kg and pyrizinamide 30 mg/kg of body weight per day, along with pyridoxine 50 mg daily. She was also started on adjuvant therapy with Prednisolone 30 mg twice daily. She returned after three days with complaints of progressive visual loss. Neurological examination revealed visual acuity of 20/400 on the right and 20/200 on the left. Visual Evoked Potentials, using checkerboard pattern stimulation showed bilateral optic pathway dysfunction (P100 latencies of 140 and 146 on the right and left side respectively). Ethambutol was discontinued and streptomycin was started. Her visual acuity improved to 20/40 on the right and 20/20 on the left after one month of follow up.

Discussion

Ethambutol induced optic neuritis (EON) is well documented. A survey of 37 ethambutol toxicity cases reported in the Danish Board of Adverse Reactions showed preponderance in the elderly and females, counting to 1% of patients receiving ATT.[4] In one study, 13 patients developed optic neuritis between 1 to 6 (mean = 2.9) months after receiving ethambutol at a dose ranging from 13 to 20 mg/kg/day (mean=17 mg/kg/day) for pulmonary tuberculosis or of the lymph nodes.[5] Choi et al reported ethambutol toxicity at a dose as low as 12.3 mg/kg[6], while others have reported over 20 mg/kg/day after 3 weeks to 15 months.[2] As in this case reported, changes in visual acuity, visual field, fundal appearance and colour sensation have been reported with EON in other studies.[2,5] The occasionally observed reddish optic disc, retinal hemorrhages, a very fine granular pigment alteration of the macular region and loss of vision for more than a year without optic disc pallor suggests a toxic retinitis or retinoneuritis rather than neuritis.[3] However in our patient, slit lamp examination revealed normal anterior chamber and optic disc hyperemia with mild disc edema bilaterally.

EON has been reported to be reversible after withdrawal of the drug; however severe damage can lead to irreversible visual loss. Out of 13 patients at Siriraj Hospital, 54% experienced visual recovery after stopping the drug.[5] In a series of seven consecutive patients[7] with severe visual deficit due to ethambutol toxicity, only 42.2% achieved a visual recovery of 20/200 on a follow-up of 8.3 $\pm$ 2.1 months after stopping the drug. On fluorescein angiography, three cases (42.2%) progressed to optic atrophy during the follow-up with permanent visual damage. There was no predisposing or risk factors contributing toward the visual loss.[7] However the association of old age with irreversible visual loss has been considered.

The pathogenic mechanism underlying EON is controversial. Data from animal models showed that in doses of 105 to 2500 mg/kg per day for 18 to 102 days, 16% albino rats developed bilateral lesions consisting of focal axonal swelling without demyelination, in optic chiasma and the intracranial portions of optic nerves.[9] Retinal toxicity has also been implicated as a mechanism of Ethambutol damage. The toxicity of ethambutol and related agents was evaluated in rodent retinal dissociated cell preparations and whole eyes. Calcium fluxes and mitochondrial function were evaluated by fluorescent and staining techniques. For in vivo assays, adult rats were administered oral ethambutol over a 3-month period. Cell survival was assessed by stereology. Ethambutol is specifically toxic to retinal ganglion cells in vitro and vivo both. Endogenous glutamate is necessary for the full expression of ethambutol toxicity, and glutamate antagonists prevent ethambutol-mediated cell loss. Ethambutol causes a decrease in cytosolic calcium, an increase in mitochondrial calcium, and an increase in the mitochondrial membrane potential. The visual loss associated with ethambutol may be mediated through an excitotoxic pathway, so that ganglion cells are rendered sensitive to normally tolerated levels of extracellular glutamate. Ethambutol perturbs mitochondrial function. Its toxicity may depend on decreased ATPase activity and mitochondrial energy homeostasis. Glutamate antagonists may be useful in limiting the side effects seen with ethambutol.[10]

As ethambutol toxicity is dose related, rapid development of optic neuritis in our patients is most likely related to an idiosyncratic reaction to drug. Karnik et al reported rapidly progressive deterioration of vision after only three days of treatment with ethambutol.[11] In conclusion, ethambutol could cause an optic neuritis after a few doses. Mechanism of injury is probably different from the common optic neuritis secondary to ethambutol. Early detection of these cases and withdrawal of ethambutol may be associated with good recovery.

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