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Case Report

Linezolid induced optic neuropathy in a child treated for extensively drug resistant tuberculosis: A case report and review of literature

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Abstract

Linezolid induced optic neuropathy occurring after prolonged use of the drug is rarely reported in the paediatric age group. We report a case of Linezolid induced optic neuropathy in a child treated for extensively drug resistant tuberculosis. The optic neuropathy completely reversed with good improvement in vision after stopping the drug, which to the best of our knowledge has not been reported before.

Keywords: Drug induced optic neuropathy, Linezolid induced optic neuropathy, Optic neuropathy in tuberculosis

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Introduction

Toxic optic neuropathy has been reported as a rare complication of prolonged Linezolid therapy, with most of the reports being in adults.[1–5] There have been very few cases reported in the paediatric age group. The following is a report of a six year old child, who was on Linezolid therapy for extensively drug resistant (XDR) Tuberculosis (TB) for a year, who suffered from this complication. To the best of our knowledge, this is the first report of optic neuropathy occurring in a child on therapy for XDR-TB.

Case report

A 6-year-old boy, who was on treatment for XDR Mediastinal TB for the past one year, was referred to our ophthalmology clinic for blurring of vision since 2 months. The patient was continuously receiving oral Linezolid (10 mg/kg TDS) for one year along with Cycloserine (15 mg/kg daily), Pyridoxine (10 mg) and Para Aminosalicylate Sodium (200 mg/kg/day).

On examination, his visual acuity was finger counting at two metres in either eye. His pupils were sluggishly reacting to light. Anterior segment examination was normal in both the eyes. Cycloplegic refraction revealed no significant refractive error. Fundus examination revealed significant bilateral disc edema. (Fig. 1) Extraocular motility was full and free in all directions of gaze. On colour vision testing on Ishihara pseudoisochromatic plates the patient could not identify a single plate.

Based on these findings a provisional diagnosis of bilateral optic neuritis was made. However, the child was investigated

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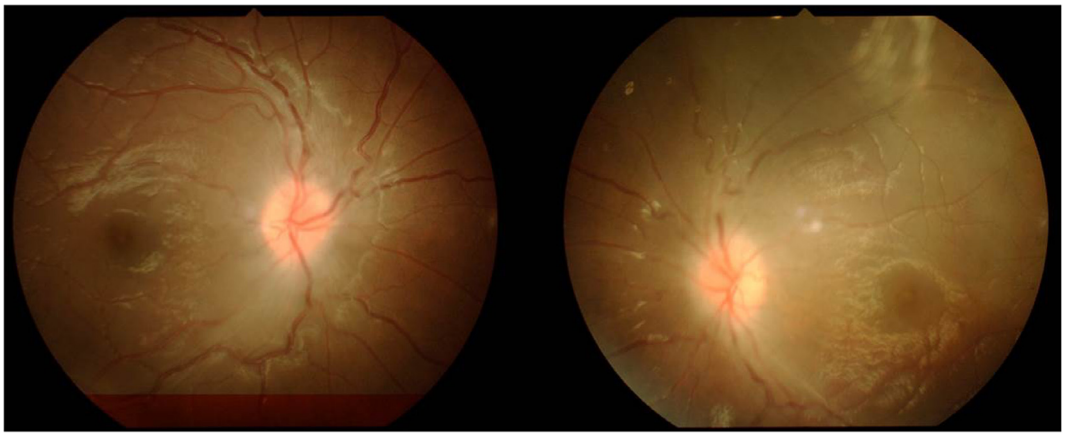

Fig. 1. Fundus photo showing bilateral optic disc edema with hyperemia with blurring of margins and edema of the adjacent nerve fibre layer.

in detail to rule out papilledema due to intracranial pathology as papilledema has been reported to be a predictor for poor visual prognosis in patients with TB meningitis in association with arachnoiditis.[6] MRI Brain with contrast and CSF analysis were done which turned out to be normal. Hematologic work up was normal except for a marginally raised ESR. Analytical, infectious and autoimmune work up was negative. The child's coagulation profile was also normal. A normal blood pressure reading ruled out malignant hypertension to be a likely cause. Idiopathic Intracranial hypertension was thought of; however a normal CSF opening pressure of 20 cm of H_2O ruled that out. The absence of cells in the anterior and posterior chamber ruled out uveitis as the likely cause for the disc edema. The child was given a course of intravenous methylprednisolone and oral steroids with no improvement in vision. Thus, the diagnosis of drug induced toxic optic neuropathy was thought of as a diagnosis of exclusion and a therapeutic trial of withdrawing Linezolid was performed.

On withdrawal of Linezolid, patient started showing almost immediate improvement. At one week follow-up, his vision had improved to 20/200. Cessation of Linezolid without altering the other medications causing vision improvement confirmed the diagnosis.

On subsequent follow ups, the visual acuity and colour vision improved and the child attained 20/20 vision in either eye with normal colour vision at three months after stopping the drug. Disc edema completely resolved with mild disc pallor of the optic discs. (Fig. 2) Visual field testing was attempted; however the reports were unreliable as the child was very young.

Discussion

Linezoild, an antibiotic of the oxidalozidine group has found its application in the treatment of methicillin resistant Staphylococcus aureus infections (MRSA), Penicillin resistant streptococcal infections, Vancomycin resistant enterococcal infections and Mycobacterial infections.[7] Optic neuropathy and peripheral neuropathy are known side effects of Linezolid especially when used for more than 28 days.[8] The other reported side effects include lactic acidosis, myelosuppression and serotonin syndrome. However, certain resistant infections require Linezolid to be given for longer periods.

Linezolid acts by inhibiting the protein synthesis by binding to the ribosomal RNA of the bacterial ribosomal subunit. As the bacterial ribosomes are similar to the mitochondrial ribosomes disruption of protein synthesis occurs. The toxicity induced by Linezolid is postulated to be a drug related mitochondrial optic neuropathy (MON).[9] Linezolid injures the optic nerve by interfering with the mitochondrial oxidative phosphorylation. The fibres of the papillomacular bundle are characteristically involved in MON. The distinctive anatomical features of these nerve fibres are that they are unmyelinated and have a narrow calibre. The high susceptibility of damage to these fibres is due to the high require-

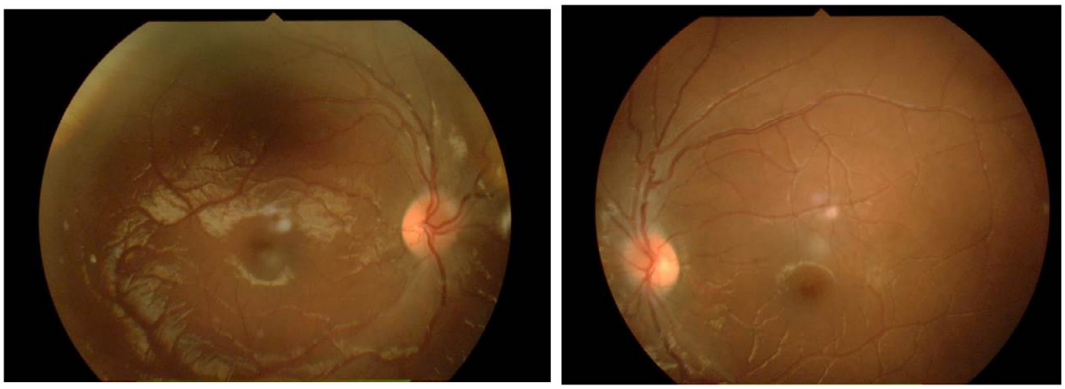

Fig. 2. Fundus photo showing resolution of bilateral disc edema with mild temporal pallor 3 months after stopping Linezolid therapy.

ment of energy levels coupled with low energy production, a high surface area to volume ratio and absence of saltatory conduction due to their unmyelinated nature.

Mitochondria provide majority of the energy during conduction by oxidative phosphorylation which involves transfer of electrons along a chain of complexes. When electron transfer is incomplete reactive oxygen species are generated. The combined effect of energy depletion with oxidative stress results in leakage of cytochrome *c* from the mitochondrial pore leading to apoptosis and nerve damage.

The actual apoptosis is preceded by stages of mitochondrial conglomeration, slowed axonal transport and axon swelling. This provides a window for reversal of the damage when functional impairment occurs without loss of axons.

Majority of the patients with optic nerve damage improve when the drug is stopped which possibly could be because the inciting factor is withdrawn before apoptosis begins and permanent axonal loss ensues.

Numerous reports have reported the occurrence of Linezolid optic neuropathy occurring in adults.

Though most of the reports have reported reversal of optic neuropathy on stopping the drug Azamfieri et al have reported complete blindness only 16 days after institution of Linezolid for MRSA with the patient having muscular dystrophy.[10] Joshi et al have also reported the occurrence of Linezolid optic neuropathy 16 days after starting treatment in a patient with acute lymphocytic leukaemia.[11]

There are few cases in literature that have described Linezolid induced optic neuropathy in children. Jahaveri et al have described Linezolid induced toxic optic neuropathy in a 6 year old child on treatment for MRSA osteomyelitis of the mandible one year after Linezolid intake which was very similar to our patient.[12] They reported improvement in visual acuity to 20/25 two weeks after discontinuation while our patient improved to 20/200 two weeks after discontinuation of Linezolid. However final acuities reached 20/20 in their as well as our patient.

Another report has reported two children, one 9 year old and one 15 year old; the onset of optic neuropathy being after 5 months of treatment in the first patient and after 8 months in the second patient.[13] First child was being treated for Mycobacterium chelonae mastoiditis and the second child was being treated for Mycobacterium bovis infection. However, in both the patients optic neuropathy resolved after stopping Linezolid.

Linezolid associated optic neuropathy has been reported in a seven year old child who was treated for cervical lymphadenitis 7 months after treatment with Linezolid. The offending organism was identified as Mycobacterium nonchromogenicum and the patient had developed bilateral disc edema with decrease in visual acuity. On withdrawal of Linezolid the visual acuity of the patient improved in the right eye but the patient developed disc pallor in the left eye and suffered permanent visual impairment.[14]

Han et al have described optic neuropathy in an adult patient suffering from multidrug resistant tuberculosis; however, that patient did not have clinically significant disc oedema as against our patient who had swollen discs.[15] Visual acuity and colour vision improved completely in that patient after stopping the drug. Karuppanasamy et al have described Linezolid induced optic neuropathy in a 45 year old male patient being treated for extensively drug resistant tuberculosis similar to our patient though that patient was also being given Ethambutol.[16] Stoppage of ethambutol did not lead to any vision improvement in that patient. However, after stopping Linezolid, disc oedema resolved and vision improved completely over a month, while in our patient it took longer, around 3 months for the vision to improve completely.

Ours is the first case report of a child on therapy for extensively drug resistant tuberculosis suffering from this complication. The dose and duration dependent toxic effect of Linezolid on the optic nerve and complete reversal on withdrawing the drug confirmed drug induced optic neuropathy in our patient.

XDR-TB is a very serious condition with high mortality and morbidity and there are very few drugs which are effective in it. A serious adverse effect occurring in one of the main drugs in its therapy, like in our case puts the entire treatment regimen in jeopardy. Hence, a close observation is necessary in children on Linezolid therapy for its side effects, especially in conditions like Multidrug resistant (MDR) and XDR TB which are steadily increasing in the Indian sub-continent. Routine ophthalmologic examination of any patient on Linezolid for more than 3 months is highly recommended.

Conflict of interest

The authors declared that there is no conflict of interest.

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