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LINEZOLID INDUCED OPTIC NEURITIS AND ITS MANAGEMENT: A CASE SERIES OF FOUR PATIENTS

Pulmonary Medicine

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ABSTRACT

Optic neuropathy has been reported as a side effect of long-term use of linezolid. This is particularly seen in cases of multi or extensively drug resistant tuberculosis where treatment with linezolid may continue for about 18-20 months. Here we reported four cases of MDR-PTB treated patients with a regimen containing linezolid who developed progressive painless loss of vision during the course of treatment. In all the four cases, the visual symptoms resolved completely on withdrawing linezolid. In our cases we treated optic neuropathy with steroids. Early recognition of this rare side effect and timely withdrawal may salvage the eyesight of such patients.

KEYWORDS

Optic neuropathy; Linezolid; Tuberculosis; MDR-PTB; Steroids

INTRODUCTION

Worldwide, tuberculosis (TB) affects 10 million people every year. Among them, multidrug-resistant TB (MDR TB) is diagnosed for 484,000 [1]. Overall, an 80% cure rate can be achieved for patients with MDR TB treated with a drug regimen that includes linezolid [2-4]. Linezolid is the first member of a new synthetic class of anti-microbials known as oxazolidinones with activity against many important pathogens including multidrug resistant tubercle bacillus, methicillin resistant staphylococcus and streptococcus [5]. Although linezolid is highly effective, its long-term use in patients with MDR TB is impaired by its adverse effects. Myelosuppression occurs in ≈30% of patients, particularly those receiving high doses (>600 mg/d) [2,3], and neurotoxicity with peripheral neuropathy is experienced by 30% of patients after 2 to 4 months of receiving low doses (<600 mg/d) [3]. Furthermore, linezolid-associated optic neuropathy appears after 5 to 10 months of treatment for 30% of patients [4,6]. Here we describe four cases of progressive loss of vision associated with linezolid therapy and its management.

Case Presentations

Case 1

A 16-year-old girl reported to OPD with painless diminished vision since 3 months. Her medical history included MDR TB calcaneal osteomyelitis and on treatment with tab Delamanid (200 mg/day), tab Linezolid (600 mg/day), tab cycloserine (750 mg/day), tab clofazimine (100 mg/day). The patient presented with visual acuity was 3 fingers. Linezolid induced optic neuritis was suspected. Opthalmology review and visual evoke potential (VEP) test was done. Impression given was – left side increased latency and reduced amplitude on the right side was suggestive of optic neuropathy. The patient was diagnosed with linezolid induced optic neuritis; hence Linezolid was replaced with tab ethionamide. Patient was given inj MPS 500 mg iv od started and planned for 3 days. Sugars and blood pressures were monitored. No complications seen. After 3 days visual acuity increased up to reading the text, so it was extended up to 5 days. Visual acuity increased to 6/24 in both eyes after 7 days. Patient was discharged and advised to follow up. Vision after 3 months of follow up was 6/9.

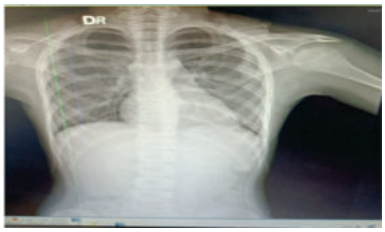

Figure 1: Chest X-ray Pa View

Case 2

A 36-year-old gold craft worker male presented to OPD with painless gradual loss of vision. His medical history suggestive of MDR PTB on Bedaquiline based regimen since ten months. (Tab Bedaquiline 200 mg/alternate day, tab linezolid 600 mg/day, tab moxifloxacin 800 mg/day, tab clofazimine 100 mg/day, tab cycloserine 500 mg/day). Patient experienced decreased vision since 5 months associated with redness of eyes. He was evaluated by an ophthalmologist and was treated with topical steroids, suspecting moxifloxacin induced anterior uveitis. Patient had no relief; he was referred to us. When the patient visited us, his visual acuity was 6/36 in right eye and 6/60 in left eye. Linezolid induced optic neuritis was suspected more than moxifloxacin induced anterior uveitis hence VEP (visual evoke potential) was done. VEP impression was bilaterally increased latency and normal amplitude is suggestive of axonopathy (toxic optic neuritis). Diagnosis of Linezolid induced optic neuritis was established and linezolid was replaced with tab Ethionamide. Patient was started on tab prednisolone 1mg/kg i.e., 70 mg /day for one week followed by tapering of 5 mg every third day to complete in 6 weeks. Visual acuity improved to 6/9 in right eye and 6/12 in left eye.

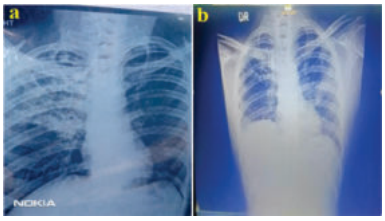

Figure 2: A) Chest X-ray At Initiation Of Treatment; B) Chest X-ray At 3 Months Follow Up

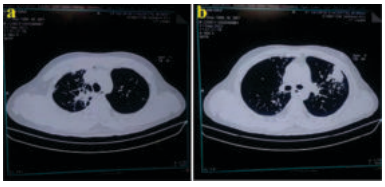

Figure 3: A) April And B)September

Case 3

A 43-year-old man presented to OPD with painless progressive diminution of vision both eyes for the past 10 days. Medical history included MDR-PTB on treatment with linezolid (600 mg/day),

ethambutol (800 mg/day), moxifloxacin (400 mg/day), cycloserine (500 mg/day), and kanamycin (750 mg/day) for the past 6 months. He was evaluated by an ophthalmologist. On examination, his visual acuity was 6/60 meter (OU), not improving with pin hole. Color vision was defective in both eyes. Visual evoke potential (VEP) test was done which showed peripheral constriction and quadrantanopia in the right eye and low reliable fields in the left eye. The possibility of toxic optic neuropathy due to linezolid was considered and linezolid was discontinued. Linezolid was replaced with tab Ethionamide. Rapid improvement in visual acuity was seen four days after discontinuation of linezolid. The patient was given a short course of steroid therapy, which led to initial improvement of his visual acuity to 6/12 bilaterally. Color vision was restored to normal, and the patient's vision was restored to 6/6 meter after one month.

Case 4

A 29-year-old female presented with painless, progressive diminution of vision in both eyes for the previous two months. This was associated with insidious onset reduced sensation of both feet and ankle. Medical history included long standing MDR-PTB under multiple drugs. Linezolid (600 mg/day), tab cycloserine (750 mg/day), tab Delamanid (200 mg/day), tab clofazimine (100 mg/day). She had been on 600 mg of oral linezolid once a day for the previous 14 months. On presentation, the best corrected visual acuity in both eyes was 6/60. Color vision recorded with Farnsworth Munsell D15 test showed protanopia. A clinical diagnosis of linezolid induced optic neuropathy was established hence VEP (visual evokes potential) was done. Linezolid treatment was discontinued and dose of ethionamide was optimized after discussing with the treating physician. She was given a short course of steroid therapy, which led to initial improvement of visual acuity to 6/18 in both eyes after 7 days. Five weeks after discontinuation of treatment, visual acuity improved to 6/6 in both eyes.

DISCUSSION

Multidrug-resistant tuberculosis (MDR-TB) is defined as disease due to Mycobacterium tuberculosis that is resistant to isoniazid (H) and rifampicin (R) with or without resistance to other drugs [7].

Linezolid is recommended by the World Health Organization (WHO) to treat drug-resistant tuberculosis as a medicine with "unclear efficacy" [8]. Linezolid (Zyvox, Pfizer, New York, New York, USA) was introduced in 2000 as the first member of the new oxazolidine synthetic group of antibiotics to help treat patients with drug□resistant pathogens. There is limited data available regarding the efficacy and safety of linezolid in multidrug-resistant TB since it is always administered as part of combination therapy [5]. However, it acts through inhibiting bacterial protein synthesis by binding to bacterial rRNA, specifically to the 23S rRNA of the 50S ribosomal subunit, and thereby inhibiting the formation of the protein synthesis initiation complex. Long-term linezolid interferes with bacterial ribosomes and also with mammalian ribosomes, thereby disrupting mitochondrial oxidative phosphorylation and protein synthesis [9].

Linezolid is usually well tolerated, with few adverse effects and relatively safe drug with a recommended duration of therapy for no more than 28 days [10]. Prolonged use outside the recommended safe period is often undertaken but has previously been associated with optic and peripheral neuropathies [11, 12]. Moreover, a systematic review and meta-analysis of cases of MDR-TB revealed toxic optic neuropathy as an ADR in 13.2% of patients using linezolid exceeding 600mg per day for a mean duration of 9 months [13]. Investigators have postulated mitochondrial dysfunction as a possible etiology, but the exact mechanism leading to linezolid□induced mitochondrial optic neuropathy is still unknown. In our case 1, optic neuropathy occurred after linezolid had been used for three months at a dose of 600 mg per day for infection with Mycobacterium tuberculosis. In case 2, optic neuropathy occurred after linezolid had been used for ten months at dose linezolid 600 mg/day. In our case 3, optic neuropathy occurred after linezolid had been used for six months at a dose of 600 mg per day for infection with mycobacterium tuberculosis. Whereas in case 4 the patient had already been on linezolid 600 mg once daily for fourteen months before she developed symptoms due to its toxicity. We attribute toxic optic neuropathy to linezolid in our patients because after withdrawal of linezolid visual improvement started.

Our cases were presented with progressive loss of vision in both eyes. They had been on multiple second line anti-tubercular drugs along with linezolid. Tests including color vision, contrast sensitivity, visual field and visual evoke potential test supported the diagnosis of optic neuropathy. Toxic optic neuropathies are characterized by gradual, progressive, painless, bilaterally symmetric visual loss affecting central vision, and causing central or centrocecal scotoma [5]. Linezolid may improve the chance of bacteriological cure only in the most complicated MDR-TB cases. Its safety profile precludes its use in cases for which there are other alternatives [14].

In our cases we treated optic neuropathy with steroids. Similarly Lee E et al describe 2 cases of toxic optic neuropathy. The first case of toxic optic neuropathy occurred in a 71-year-old woman and the second case occurred in a 45-year-old man, he was given a short course of steroid therapy, which led to initial improvement of his visual acuity to 6/12 bilaterally [15]. Agashe P and Doshi A. report a case of linezolid induced optic neuropathy in a child treated for extensively drug resistant tuberculosis. Child was given a course of intravenous methylprednisolone and oral steroids with no improvement in vision [16]. Saijo et al. have suggested that oral corticosteroid treatment might be deleterious in these patients [17] but Mehta S. et al noted a marked improvement in all treated patients [18]. However, a larger dataset would be needed to allow any definite conclusions on the benefit of steroids in this condition.

In a developing country like India where infectious diseases such as tuberculosis are still a major problem, awareness among ophthalmologists and physicians regarding visual monitoring in patients receiving long-term linezolid therapy is important. This is because early identification of toxicity of this drug and its discontinuation can result in complete visual recovery. Further studies are needed to evaluate the risk factors associated with linezolid toxicity and to evaluate the best treatment duration to decrease the rate of neurologic adverse effects without affecting MDR TB outcomes. However, systematic clinical examination should be implemented for all patients before treatment and monthly thereafter so that linezolid withdrawal can be discussed if neuropathy develops.

CONCLUSION

There are very scattered case reports of optic neuropathy secondary to the use of linezolid. In our cases we treated optic neuropathy with steroids. So, steroids have a definitive role in management of linezolid induced optic neuropathy. Ophthalmologists and physicians should be aware of the ocular complications associated with prolonged linezolid therapy. This is a potentially reversible adverse effect if picked up early and discontinuation of drug results in complete visual recovery.

REFERENCES

1. World Health Organization. Global tuberculosis report 2018. [cited 2020 Jun 10]. https://apps.who.int/iris/handle/10665/274453 [Ref list]
2. Zhang X, Falagas ME, Vardakas KZ, Wang R, Qin R, Wang J, et al. Systematic review and meta-analysis of the efficacy and safety of therapy with linezolid containing regimens in the treatment of multidrug-resistant and extensively drug-resistant tuberculosis. J Thorac Dis. 2015;7:603–15.
3. Agyeman AA, Ofori-Asenso R. Efficacy and safety profile of linezolid in the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis: a systematic review and meta-analysis. Ann Clin Microbiol Antimicrob. 2016;15:41.
4. Tang S, Yao L, Hao X, Zhang X, Liu G, Liu X, et al. Efficacy, safety and tolerability of linezolid for the treatment of XDR-TB: a study in China. Eur Respir J. 2015;45:161–70.
5. Karuppannasamy, Divya; Raghuram, Andavar; Sundar, Devisundaram. Linezolid-induced optic neuropathy. Indian Journal of Ophthalmology 62(4):p 497-500,
6. Mehta S, Das M, Laxmeshwar C, Jonckheere S, Thi SS, Isaakidis P. Linezolid-associated optic neuropathy in drug-resistant tuberculosis patients in Mumbai, India. PLoS One. 2016;11:e0162138.
7. Prasad R, Gupta N, Banka A. Multidrug-resistant tuberculosis/rifampicin-resistant tuberculosis: Principles of management. Lung India. 2018;35(1):78-81.
8. World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis. Available from: http:// www.who.int/entity/tb/ publications/ 2006/ who_htm_tb_2008_402. pdf.[last accessed on 2012 June 12].
9. De Vriese AS, Coster RV, Smet J, Seneca S, Lovering A, Van Haute LL, et al. Linezolid-induced inhibition of mitochondrial protein synthesis. Clin Infect Dis 2006;42:1111-7.
10. Birmingham MC, Rayner CR, Meagher AK, Flavin SM, Batts DH, Schentag JJ. Linezolid for the treatment of multidrug-resistant, Gram-positive infections: experience from a compassionate use program. Clin Infect Dis. 2003; 36(2):159–68.
11. Linam WM, Wesselkamper K, Gerber MA. Peripheral neuropathy in an adolescent treated with linezolid. Pediatr Infect Dis J. 2009; 28(2):149-51.
12. Ferry T, Ponceau B, Simon M, Issartel B, Petiot P, et al. Possibly linezolid-induced peripheral and central neurotoxicity: report of four cases. Infection.2005;33(3):151-4.
13. Sotgiu G, Centis R, D'Ambrosio L, Alffenaar J, Anger H, Caminero J, et al. Efficacy, safety and tolerability of linezolid containing regimens in treating MD-TB and XDR TB: systemic review and meta-analysis. Eur Respir J. 2012; 40(6):1430-42.
14. Migliori GB, Eker B, Richardson MD, Sotgiu G, Zellweger JP, Skrahina A, et al. A retrospective TBNET assessment of linezolid safety, tolerability and efficacy in multidrug-resistant tuberculosis. Eur Respir J 2009;34:387-93.
15. Lee E, Burger S, Shah J, Melton C, Mullen M, Warren F, and Press R. Linezolid-associated toxic optic neuropathy: a report of 2 cases. Clinical Infectious Diseases 2003; 37:1389–91.
16. Agashe P and Doshi. Linezolid induced optic neuropathy in a child treated for extensively drug resistant tuberculosis: A case report and review of literature. Saudi Journal of Ophthalmology.2019;33(2):188-191.

17. Saijo T, Hayashi K, Yamada H, Wakakura M. Linezolid-induced optic neuropathy. Am J Ophthalmol.2005; 139(6):1114–1116.
18. Mehta S, Das M, Laxmeshwar C, Jonckheere S, Thi SS, Isaakidis P. Linezolid Associated Optic Neuropathy in Drug-Resistant Tuberculosis Patients in Mumbai, India. PLoS ONE 2016;11(9): e0162138.