Clinical Case Report

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Linezolid-associated optic neuropathy in a pediatric patient with *Mycobacterium nonchromogenicum*

A case report

Napoleón González Saldaña, MD[a], Diego Mauricio Galvis Trujillo, MD[a], Ana Maria Borbolla Pertierra, MD[b], Ana Ivette Mondragón Pineda, MD[a], Hugo Juárez Olguín, PhD[c,*]

Abstract

Background: Toxic optic neuropathies are alterations of the optic nerve and can be caused by environmental, pharmacological, or nutritional agents.

Case: It is about a 7-year-old male patient, a native of the State of Mexico, Mexico who was diagnosed with cervical mycobacterial lymphadenitis that required management with linezolid.

Observations: After 7 months of treatment, visual acuity of the left eye decreased and was accompanied by headache. Neuroinfection and other central nervous system affections were discarded. An adverse effect related to treatment with linezolid was suspected, and linezolid was suspended. The symptoms subsided after discontinuation; however, the patient continued to show decreased visual acuity of the left eye, assessed by his ability to count 2 fingers. The right eye remained unaffected.

Conclusions: Neurotoxicity can be decreased by reducing the total dose of linezolid or by administrating it in an intermittent form. To avoid progression and loss of vision, we suggest frequent periodic ophthalmological evaluation in patients treated with linezolid.

Abbreviations: AFB = acid–fast bacilli, CF = counting finger, CNS = central nervous system, FNAB = fine needle aspiration biopsy, MDR/XDR = multidrug-resistant/extensively drug-resistant, PCR = polymerase chain reaction, PPD = purified protein derivate, RE = right eye, TB = tuberculosis.

Keywords: children, linezolid, optic neuropathy, tuberculosis

1. Introduction

Linezolid was approved in the year 2000 as a treatment for multidrug-resistant/extensively drug-resistant (MDR/XDR) tuberculosis (TB). Linezolid is an oxazolidinone, which is a class of antibiotics that inhibit the synthesis of proteins by binding with the 23s subunit of bacterial ribosomal RNA.

Toxic optic neuropathies are alterations of the optic nerve caused by environmental, pharmacological, or nutritional agents. Usually this condition is bilateral, and it has been associated with agents such as ethylene glycol, methanol, isoniazid, ethambutol, and fluoroquinolones, as well as deficiency of vitamin B12, folates, or thiamin.[1] The clinical manifestations are decreased visual acuity in both eyes (visions <20/100 have been reported in the majority of cases), alterations of chromatic vision and visual field, afferent pupillary defect, and variable changes in the papilla that progress from normal aspect to blurring of the edges, hyperemia, peripapillary bleeding, and atrophy.[2] It has been reported that the use of linezolid at standard doses for a prolonged time can lead to optic neuritis, especially when treating *Staphylococcus aureus* infections. Based on this finding, periodic ophthalmological evaluations are recommended while this antibiotic is being used in order to detect adverse events and to suspend its use accordingly. In certain patients, neuropathies by linezolid can be accompanied by papilla of normal aspect. It is therefore recommended that diagnosis be based on visual functions (visual acuity, color, and field) and history of exposure to the drug.

In a meta-analysis by Sotgiu et al,[3] approximately 13% of patients treated with linezolid developed optic neuritis. Cases of onset of optic neuritis after 16 days of treatment have been reported, but on average optic neuritis usually appear at approximately 7 months of use. So far, the majority of the reported cases have been in adults, and very few have been in children.[4]

2. Case report

This case report was approved by the Ethical Committee of the National Institute of Pediatrics in Mexico prior to its submission.

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[a] Department of Infectology, National Institute of Pediatrics, [b] Department of Ophtalmology, National Institute of Pediatrics, [c] Laboratory of Pharmacology, National Institute of Pediatrics, and Faculty of Medicine, National Autonomous University of Mexico, Mexico City, Mexico.

[*] Correspondence: Hugo Juárez Olguín, Laboratorio de Farmacología, Instituto Nacional de Pediatría, Avenida Imán N 1, 3rd piso Colonia Cuicuilco, CP 04530 Mexico City, Mexico (e-mail: juarezol@yahoo.com)

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In addition, informed consent was obtained from the guardians of the case patient.

The patient is a 7-year-old male without any perinatal or postnatal pathologic background that could be associated with his illness. His vaccination scheme was complete for his age.

The heredofamilial background revealed that his maternal grandmother suffered untreated chronic cough for 15 years prior to the onset of the patient's symptoms. The grandmother tested negative for acid–fast bacilli (AFB) in sputum and purified protein derivate (PPD) test. In additional, the patient's paternal grandfather also suffered from chronic cough for 7 years before the disease symptoms of the patient began. In the case of the grandfather, test was not performed nor was any treatment administered.

The patient's illness began in June 2010, with increase in volume of the anterior face of the sternocleidomastoid muscle. This growth was gradual, painless, and without change in color or local temperature. At the beginning, the swelling had no secretion outlet. Four months later, he presented with pain, erythema with a rise in local temperature and limitation to twiddle the head to the right. He was taken to a medical doctor, who requested biopsy of the ganglion in November 2010. The patient was diagnosed with acute and chronic lymphadenitis with calcification but was not given any treatment.

In January 2011, the patient presented more increase in volume but this time in the area of the biopsy with exit of yellowish-white nonfetid thick liquid secretion whose drainage was not constant. PPD test carried out in March 2011, reported a size of 15×15 mm and yet the patient was not given any treatment. A fine needle aspiration biopsy (FNAB) of the ganglion was performed in April 2011. The results of this FNAB showed abundant polymorphonuclear leukocytes intermixed with macrophages, remnants of cell damage materials, and fibrin. The cytological images suggested an abscessed lymph node without signs of malignancy. Drainage of the same secretion continued as before.

In August 2011, he was evaluated by an infectious disease specialist who recommended excision of the ganglionic chain in October 2011, after a pathological report of chronic granulomatous lymphadenitis with cheesy necrosis and multinucleated giant cells that suggested infection by TB. A lymph node polymerase chain reaction (PCR) test was performed at Technical Institute of Epidemiological Diagnosis and Reference in October 2011, but the results were negative. In November 2011, antimycobacterial treatment based on isoniazid, rifampicin, and pyrazinamide was initiated and maintained for 3 months. Ziehl–Neelsen staining showed scarce AFB. *Mycobacterium tuberculosis*/resistance to rifampicin PCR was negative, while culture and DNA analysis of the colony was positive for *Mycobacterium nonchromogenicum*. In December 2011, the patient presented with a ganglionic growth in the posterior region of sternocleidomastoid muscle without any outlet for secretion. He was referred to the National Institute of Pediatrics and was evaluated by the Department of Infectology in April 2012. Medication was changed to clarithromycin, ethambutol, and ciprofloxacin due to the persistence of symptoms. Consultation from the Immunology Department was requested to evaluate immunodeficiency. After 6 months of treatment with the same regimen, in November 2012, the patient began to show enlarged cervical lymph nodes, and thus the medications were changed to clarithromycin, rifampicin, amikacin, and linezolid. These medications were orally administered every 12 h at 10 mg/kg per day for approximately 5 months.

In April 2013, the patient was hospitalized for fatigue, weakness, headache, and pale skin. Complete blood count was as follows: hemoglobin 8.1 g/dL, hematocrit 24.9%, mean corpuscular volume 93.6 μm^3, mean corpuscular hemoglobin 32.7 pg, leukocytes $2700 \times 10^3/\mu L$, neutrophils $900 \times 10^3/\mu L$, lymphocytes $1600 \times 10^3/\mu L$, monocytes $100 \times 10^3/\mu L$, eosinophils $100 \times 10^3/\mu L$, and platelets $212 \times 10^3/\mu L$. The laboratory parameters showed anemia and neutropenia.

In May 2013, the patient began to experience a frontal headache of moderate intensity that occurred predominantly in the morning and which could not subside with common analgesics. The headache usually intensified on effort and provoked occasional vomiting. In addition, he began to have photopsias and decreased visual acuity, and he was brought to the National Institute of Pediatrics 3 weeks after the onset of these symptoms. He was evaluated by the Ophthalmology Department with the observation of papilledema in the left fundus. This was treated with an ophthalmic steroid without improvement. Based on that, it was decided to hospitalize the patient again.

Simple brain computerized axial tomography and magnetic resonance were performed, but there were no results that suggested meningeal TB or vasculitis. A lumbar puncture revealed 20 mg/dL microproteins, 96 mg/dL glucose, and 2 cells. AFB-ZN and mycobacterial culture were each negative. PCR for *M tuberculosis* complex was negative. After discarding all the suspected etiologies already mentioned, it was decided to suspend treatment with linezolid and treat the patient with streptomycin instead. This occurred in June 2013, after 7 months of treatment with linezolid. The patient was discharged but continued to be monitored. Ophthalmological reports at the time of discharge were right eye (RE) counting finger (CF) distance 50 cm and left eye CF distance 1 m. A hyperemic optic nerve and circumferential edema were also noted in the RE. A month later, in August 2013, RE CF distance had improved to 2 m, and left eye CF distance was 1 m. Following this improvement, an annual follow-up of the patient was decided. Figure 1 shows a magnetic resonance image with no suggestions of meningeal TB, vasculitis, or intracranial mass.

In August 2014, RE visual acuity was 20/25, while the CF distance remained unchanged. Visual potentials performed in September 2014 showed a bilateral affectation of the visual pathway due to decreased cortical potential amplitude. In May 2015, the visual acuity of the RE was 20/20, the macula showed no alterations as well as the visual acuity. The left eye CF distance was 3 m, and pale papilla were noted. In September 2014, motor and sensory nerve conduction studies showed a sensorial neuropathy in the pelvic limbs, while the superior limbs were normal. However, the patient was clinically asymptomatic.

The patient remained asymptomatic for signs of infection as of September 2017. He fulfilled the treatment scheme of ciprofloxacin for 20 months, clarithromycin for 18 months, and streptomycin for 3 months. Two ganglionic biopsies were performed in January and March 2014, respectively, and the results were negative for mycobacterium infection. Immunodeficiency was discarded, and the patient remained under monitoring as of September 2017.

3. Discussion

Anti-TB agents are recommended when a child presents with granulomatous disease, with or without FNAB, or when PPD test results are positive (<15 mm). The initial therapy for the

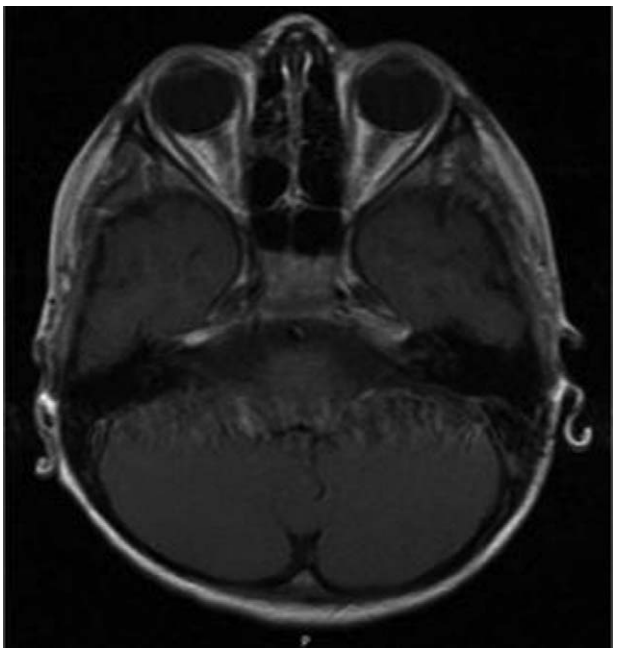

Figure 1. Magnetic resonance findings did not suggest meningeal tuberculosis, vasculitis, or intracranial mass.

disseminated form is clarithromycin, ethambutol, and rifampicin; however, there is no established scheme, and linezolid is recommended in drug-resistant cases.[3,5]

Atypical mycobacteria are classified into 4 groups. In the case of our patient, the type involved was nonchromogenic mycobacterium, which is a group of bacteria that form unpigmented colonies and show slow growth. This group includes *Mycobacterium avium*, *Mycobacterium gastri*, *Mycobacterium terrae*, and *Mycobacterium intracelular*. *Mycobacterium avium* is the most important pathogen in disseminated diseases, while *M intracellular* is the most important pathogen in respiratory diseases.[3,5] Excisional surgery without antimicrobial treatment is the recommended management for children with cervical lymphadenopathy due to atypical mycobacteria.

There have been reports of decreased visual acuity occurring within the range of 16 days to 17 months,[6–8] and our patient presented this symptom after 7 months of treatment. We performed a sensory evoked potentials tests and found abnormalities in the lower extremities, despite the fact that the patient did not have any associated symptoms. In our case, we concluded that linezolid was the trigger agent of optic neuritis because of the relationship between the duration of its administration and the appearance of decreased visual acuity and because other causes of optic neuritis were discarded, including papilledema or endocranial hypertension due to central nervous system (CNS) TB.

Neurotoxicity can be decreased by reducing the total dose of linezolid or by administrating it in an intermittent form. Unfortunately, the minimum adequate dose for the treatment of MDR/XDR TB is still uncertain.[9] It has been reported that a dose of 600 mg/d may decrease the occurrence of adverse effects.[10] Because neuroinfection was discarded in the present case, it was decided to suspend treatment with linezolid and to reevaluate the ophthalmological condition of the patient. Two months after, the patient showed improvement in visual acuity, despite the CF distance. There have been reports of cases where, after 8 months of linezolid suspension, patients fully recovered their visual acuity. There have also been cases of peripheral neuropathy,[8] and irreversible loss of visual acuity. Our patient presented unilateral CF vision 2 years after linezolid suspension.

The onset of optic neuritis can be related to the duration of treatment, especially when it is used for more than 28 days in multidrug-resistant TB.[11,12] However, the incidence of optic neuritis is unknown. Rucker et al[12] reported optic neuritis in 2 patients with methicillin-resistant *S aureus* who were treated for 11 and 16 months with linezolid.

It is possible that linezolid, like chloramphenicol, has adverse effects on protein synthesis within the mitochondria. This, along with its high concentration in the CNS and eyes, could enhance its neuropathic effects.[13] To avoid progression and loss of vision, patients who are being treated with linezolid should regularly undergo ophthalmological evaluation.

The paramount objective of this publication is to inform healthcare professionals who are in contact with TB patients receiving second- or third-line management, such as linezolid, of the need to check for blurred vision in their patients, identify changes in their reading patterns, and pay attention to the complaints of the patients. This is a challenge for pediatric healthcare personnel because, in many cases, the caretakers of the patients are not aware of these changes in visual patterns for the inability of a young child to provide such information. Nevertheless, adverse effects and secondary reactions of drugs should be considered at every follow-up visit.

4. Conclusions

Neurotoxicity can be decreased by reducing the total dose of linezolid or by administrating it in an intermittent form. To avoid progression and loss of vision in patients treated with linezolid, we suggest frequent ophthalmological evaluation.

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