of probable IA based on the European Organization for Research and Treatment of Cancer (EORTC) criteria could not be established. Nevertheless, intravenous voriconazole was added to the antifungal regimen at 3 mg/kg/12 h. As would be expected, both Aspergillus species isolated in our patient were susceptible to the 2 antifungal agents used.

The main side effects of voriconazole are elevated transaminases, visual disturbances, retinopathy in preterm infants, skin reactions because of photosensitization and renal dysfunction resulting from accumulation of a solubilizing excipient, sulfobutylthetacyclodextrin, which is only present in the intravenous formulation.2 Our patient developed severe renal impairment that did not improve even after stopping the nephrotoxic drugs and hepatotoxicity that reappeared after discontinuing the drug and the parenteral nutrition. No other hepatotoxic drugs had been used. There were no drug interactions that could raise voriconazole plasma levels.

Our patient’s skin lesions healed without surgical resection. Other authors have reported successful nonsurgical treatment of PCA in neonates.3,4 Preterm infants may not tolerate surgical intervention because of photosensitization and renal dysfunction resulting from accumulation of a solubilizing excipient, sulfobutylthetacyclodextrin, which is only present in the intravenous formulation.2

Our patient’s death was presumably multifactorial (extreme prematurity, bacterial sepsis, severe renal dysfunction, cerebral aspergillosis and intestinal perforation). Interpretation of galactomannan antigen findings in the neonatal population can be confusing because false-positive results occur frequently because of Bifidobacterium spp. gut colonization, formula-milk feeding and use of beta-lactam antibiotics. In one study, galactomannan antigen monitoring was reported to be useful in a term newborn affected by bilateral renal aspergillosis, showing decreases as the patient improved and ultimate normalization.5 Serum polymerase chain reaction assays for Aspergillus spp. may be more specific for IA detection in neonates than galactomannan antigen testing.

PCA usually occurs in isolated cases, although clusters caused by contamination of incubator humidity chambers, nonsterile disposable latex gloves or adhesive tapes have been reported.6 Prompt source recognition and implementation of isolation precautions prevent its spread throughout the NICU. No contaminated specimens were detected in the NICU and no other cases occurred in our case. In conclusion, PCA can occur in preterm infants, and it is important to rule out IA to decide the optimal antifungal regimen. Further studies are needed to establish the appropriate dosage and duration of voriconazole therapy and to determine the safety profile of the drug in neonates and, particularly, in preterm infants. In situations where voriconazole is needed its serum concentrations should be closely monitored to avoid toxicity.

REFERENCES

PROBABLE LEVOFLOXACIN-ASSOCIATED SECONDARY INTRACRANIAL HYPERTENSION IN A CHILD WITH MULTIDRUG-RESISTANT TUBERCULOSIS

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Abstract: Fluoroquinolones are a key component of multidrug-resistant tuberculosis treatment. We describe the first reported case of probable levofloxacin-associated intracranial hypertension in a 6-year-old girl with pulmonary multidrug-resistant tuberculosis. The case highlights the potential risk of secondary intracranial hypertension in multidrug-resistant tuberculosis patients who require prolonged fluoroquinolone therapy and the need for ophthalmologic screening in children with suggestive signs and symptoms.

Key Words: levofloxacin, secondary intracranial hypertension, serious adverse events, children, multidrug-resistant tuberculosis treatment

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Multidrug-resistant tuberculosis (MDR-TB; ie, resistance to both rifampicin and isoniazid) is a growing global health problem, with as many as 33,000 pediatric MDR-TB cases in 2010 based on modeling estimates. Fluoroquinolones are highly bactericidal against Mycobacterium tuberculosis and are a key component of the treatment of MDR-TB. They are
also increasingly used as preventive therapy for MDR-TB. The fluoroquinolones are generally well tolerated; however, a variety of central nervous system adverse effects have been reported.\(^3\)\(^2\) We describe a case of probable levofloxacin-associated secondary intracranial hypertension in a child treated for drug-resistant tuberculosis.

**CASE**

A 6-year-old female was evaluated as a household contact of her mother who was recently diagnosed with a mixed infection with rifampicin-monoresent and MDR-TB. The child had no reported symptoms, but a significant cough was noted by the clinical staff. Her medical history was unremarkable; she was uninfected with human immunodeficiency virus and had been vaccinated with Bacille Calmette-Guérin at birth. At presentation, her anthropometric measurements (weight 20.6 kg, height 110 cm and body mass index 17 kg/m\(^2\)) were all normal. Respiratory examination revealed dullness to percussion and decreased air entry in the right middle zone, but the remainder of the examination, including the neurologic system, was normal. The chest radiograph showed dense right middle lobe opacification and right hilar lymphadenopathy. Sputum was smear negative but culture positive for *M. tuberculosis*, and drug susceptibility testing showed rifampicin monoresistance. She was started on routine treatment with high-dosage isoniazid 15–20 mg/kg, ethambutol 20–25 mg/kg, ethionamide 15–20 mg/kg, levofloxacin 15–20 mg/kg, terizidone 15–20 mg/kg, pyrazinamide 30–40 mg/kg, amikacin 15 mg/kg and pyridoxine 50 mg, all administered once daily. The isoniazid was adjusted to a lower dose range (10–15 mg/kg/d) after susceptibility to isoniazid was confirmed. The patient’s clinical condition improved, and MDR-TB medication was well tolerated, with no clinically significant abnormalities detected during routine monitoring (creatinine, potassium, alanine aminotransferase, full blood count and thyroid function tests).

After 12 weeks of MDR-TB treatment, she underwent ophthalmologic assessment as part of routine screening for participation in a research study. This assessment noted bilateral papilledema, with the rest of the ocular examination reported as normal, including visual acuity. She had no symptoms of raised intracranial pressure such as headache, vomiting or altered vision and had a normal neurologic examination. She was immediately referred to a pediatric neurologist who also noted papilledema in isolation. A computed tomography scan of the brain was normal.

Subsequently, a second ophthalmologist confirmed the findings of bilateral papilledema in the presence of normal visual fields. A lumbar puncture showed an elevated opening cerebrospinal fluid (CSF) pressure of >50 cm H\(_2\)O (normal <18 cm H\(_2\)O).\(^1\) CSF chemistry and cell count were normal: glucose, 3.2 mmol/L (normal = 2.2–3.9); chloride, 132 mmol/L (120–130); protein, 0.10 g/L (0.15–0.45); polymorphonuclear cells, 0/mm\(^3\); lymphocytes, 0/mm\(^3\); erythrocytes, 0/mm\(^3\); cryptococcus India Ink Test, negative. Routine bacterial culture showed no growth. A smear for acid-fast bacilli was negative; *M. tuberculosis* complex was not detected by Xpert MTB/RIF, and the mycobacterial culture was negative. The normal CSF and normal computed tomography scan were inconsistent with intracranial infection and suggestive of secondary intracranial hypertension. As there were no other obvious causes, and secondary intracranial hypertension has been described in association with fluoroquinolones, levofloxacin was considered to be the most likely cause. The levofloxacin was stopped and para-aminosalisylic acid was added to her other routine TB medications. Acetazolamide (30 mg/kg 8 hourly) was started for treatment of the elevated intracranial pressure. The lumbar puncture was repeated 4 days after starting treatment, which still revealed an opening pressure of >50 cm H\(_2\)O, and furosemide (1 mg/kg 8 hourly) was therefore added. The following day, the patient started vomiting and had malaise, which prompted concern for increased intracranial pressure; however, a repeat lumbar puncture on the same day revealed normalization of the previously raised lumbar CSF pressure (13 cm H\(_2\)O). The symptoms were ascribed to acetazolamide-induced metabolic acidosis, which resolved shortly after discontinuation of acetazolamide. Furosemide was continued, and repeat CSF opening lumbar pressure 10 days later revealed resolution of the intracranial hypertension (7 cm H\(_2\)O). Magnetic resonance imaging and magnetic resonance venography of the brain performed after normalization of the CSF pressure proved normal.

She was continued on furosemide for 4 weeks, after which it was discontinued. She remained asymptomatic throughout this period with normal neurologic examination. A final ophthalmology assessment, 2 weeks after stopping furosemide, revealed a normal examination without any papilledema. The final diagnosis was secondary intracranial hypertension, probably related to levofloxacin. She remained on MDR-TB treatment (excluding levofloxacin) and has continued to be clinically well.

**DISCUSSION**

This is the first report describing the finding of levofloxacin-associated secondary intracranial hypertension in a young child being treated for MDR-TB.

Intracranial hypertension is defined as raised intracranial pressure (papilledema, elevated CSF pressure and, if symptoms present, reflecting generalized intracranial hypertension with normal mental status) in the presence of normal neuroimaging and CSF composition and is referred to as idiopathic or primary if the cause is unknown or secondary if the cause is known.\(^3\)\(^4\) Permanent visual loss can occur in children with intracranial hypertension, which emphasizes the potential morbidity of this condition.\(^3\)\(^4\)

Several case studies have described the association of secondary intracranial hypertension with fluoroquinolone use including ciprofloxacin, nalidixic acid, ofloxacin and pefloxacin.\(^5\)\(^–\)\(^8\) Two case studies reported the occurrence of secondary intracranial hypertension specifically with levofloxacin treatment for routine bacterial infections: one in a 13-year-old boy after 2 weeks of levofloxacin therapy\(^7\) and another in an obese 18-year-old male after 5 days of levofloxacin therapy.\(^9\) Both patients presented with diplopia, headache, tinnitus and vomiting. They both had papilledema with a normal magnetic resonance imaging scan. Symptoms of intracranial hypertension resolved after 1–2 weeks of stopping the levofloxacin treatment. No other treatment for the raised intracranial pressure was used. The pathogenesis of secondary intracranial hypertension is postulated to be because of increased venous sinus pressure and decreased CSF absorption; however, this is not completely understood.\(^9\) The fluoroquinolones are known to interact with the neurotransmitter gamma-aminobutyric acid, opioid, dopamine and glutamate receptors, but these mechanisms are mostly ascribed to epileptogenic and depressive adverse effects; the mechanism for causing intracranial hypertension is not well described.\(^1\)

Efforts were made to exclude other etiologic factors known to be associated with intracranial hypertension in children.\(^3\)\(^4\) Our patient was a well-nourished, nonobese child with no associated endocrine disorders. She never received any thyroid hormone (thyroxine), growth hormone replacement therapy or any other medication associated with secondary intracranial hypertension. She had normal cortisol, adrenocorticotropic hormone, hemoglobin, white
cell count and coagulation panel. She did not have any signs or symptoms of concurrent acute viral or bacterial infections. There was no history of recent head trauma, and the normal neurologic examination excluded Miller Fisher syndrome. There was no evidence of vitamin A intoxication.

The diagnosis of levofloxacin-induced intracranial hypertension in this report is supported by the rapid normalization of intracranial pressure after withdrawing the agent. In cases of idiopathic intracranial hypertension, the intracranial pressure usually takes weeks to normalize, even on diuretic treatment.

Clinicians should be aware of the possibility of secondary intracranial hypertension when using fluoroquinolones, even if rare, and this should be considered in the differential diagnosis when fluoroquinolone-treated patients present with signs and symptoms consistent with intracranial hypertension. In patients treated for MDR-TB, visual changes, headaches or vomiting may be ascribed to ethambutol and central nervous system manifestations of TB including meningitis or abscess formation or to adverse effects of other antituberculosis medications; fluoroquinolone-associated secondary intracranial hypertension may therefore need to be an additional consideration.

Levofloxacin remains a key component in the treatment for MDR-TB and is used more frequently as a result of increasing MDR-TB case burden globally. This apparently rare adverse effect should not limit the use of this important medication in children with MDR-TB, for whom the risk-benefit ratio remains greatly in favor of fluoroquinolone use. We would not recommend any change in clinical practice as a result of this case report, other than increased awareness, and lack of ophthalmologic screening should not preclude fluoroquinolone use when indicated. However, additional studies may be warranted to assess whether this phenomenon is more common than previously realized.

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REFERENCES


SOFOSBUVIR AND SIMEPREVIR TREATMENT OF A STEM CELL TRANSPLANTED TEENAGER WITH CHRONIC HEPATITIS C INFECTION

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Abstract: There have been no previous reports on the use of interferon-free combinations in pediatric patients with chronic hepatitis C infection. An infected adolescent with severe sickle cell disease underwent stem cell transplantation and subsequent treatment with sofosbuvir and simprevir during ongoing immunosuppression. Despite the emergence of peripheral edema as a side effect, treatment was continued with sustained antiviral response.

Key Words: hepatitis C, sickle cell disease, stem cell transplantation, direct-acting antivirals

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Disease progression in chronic hepatitis C virus (HCV) infection is known to be accelerated in patients with underlying disorders. In particular, individuals with chronic hepatitis C infection needing immunosuppressive treatment are at increased risk of developing progressive liver disease. Some very effective combinations of direct-acting antivirals (DAAs) against HCV have been licensed in the last 1–2 years for adults older than 18 years of age.1 The rates for sustained viral response have, thereby, been increased to 90% or above.2 However, none of these new drugs are licensed for children or adolescents. We here describe a teenager with severe sickle cell disease and chronic hepatitis C infection who was successfully treated with a DAA combination while still on immunosuppressive treatment after allogeneic hematopoietic stem cell transplantation (SCT).

CASE REPORT

A 13-year-old boy, from central Africa, presented to us shortly after moving to Sweden. He had a known history of severe sickle cell disease, including frequent pain crises, cerebral manifestations and disability caused by osteonecrosis, and was, therefore, considered for SCT. He was found to be hepatitis C (genotype 4c) infected, presumably via blood transfusions, and had moderate elevations of transaminases, but normal hepatic synthetic function. Liver biopsy was not performed because of a known increase in risk of severe complications in patients with sickle cell disease. To obtain a surrogate marker for liver fibrosis, we performed elastography, yielding a value of 6 kPa (normal value <5 kPa), suggesting mild fibrosis.

At that time, the only available treatment for hepatitis C infection was the combination of pegylated interferon and ribavirin. Given the high risk of severe adverse events to such treatment in this specific patient with presumably mild fibrosis, it was decided to proceed with the SCT and to aim for antiviral treatment afterward.

For a couple of months before the SCT, the patient received treatment with hydroxyurea and hypertransfusions. Thereafter,