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Case report

Peripheral neuropathy from use of linezolid and metronidazole in a pediatric patient

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An 11-year old boy presented with a 7–10 day history of paresthesia when he attended follow-up with Pediatric Neurosurgery, Pediatric Infectious Diseases and Plastic Surgery after 49 days of antibiotics for a hardware associated infection.

The boy had a congenital craniofacial deformity and had undergone craniotomy with calvarial bone reconstruction of the orbit and placement of titanium mesh three months previously. He developed erythema of the right upper nasal bridge and purulent nasal discharge on post-operative day 24, but was afebrile and hemodynamically stable. Interval reconstructive facial surgery, including right frontal craniotomy with mesh overlying a large portion of the right frontoparietal region and several extracranial peripherally enhancing fluid collections suspicious for abscess were demonstrated over the right aspect of the nasal bridge, overlying the left frontal region and posterior to the right zygoma on computed tomography (CT) scan. There was gas superficial and deep to the mesh overlying the right frontoparietal area and the mesh was presumed to be infected. Although removal of the mesh was discussed, prolonged antibiotic treatment was ultimately preferred. He underwent irrigation and debridement of the nasal and frontoparietal areas three times over the subsequent 2 weeks, and cultures of the operative tissue grew *Streptococcus constellatus*, *Prevotella buccae*, *Prevotella denticola*, *Eikenella corrodens*, and *Staphylococcus epidermidis*. Empiric treatment included vancomycin, ceftriaxone, and metronidazole. Vancomycin was changed to linezolid to accommodate home intravenous antibiotics. The patient was discharged home on ceftriaxone, metronidazole (500 mg q8h, 30.5 mg/kg/day) and linezolid (600 mg BID and 300 mg OD, 30.5 mg/kg/day).

At the time of follow-up, the patient described a persistent sensation in both of his feet akin to “walking on glass” for the past week. This was most prominent over his toes, was rated as three out of ten in severity at rest and increased to nine out of ten when walking, using a 11-point numerical rating scale. This sensation was constant but did not wake the patient from sleep. There was no associated weakness of the extremities, difficulties swallowing or constipation. There was no history of similar symptoms previously. The patient and caregiver reported no focal or systemic signs of infection from the incision for several weeks and the sole medications at time of symptom onset were ceftriaxone (53 days), metronidazole (43 days, (64.5 g cumulative dose) and linezolid (30 days, 45 g cumulative dose). There remained a non-fluctuant and non-tender scabbed lesion (2 mm × 2 mm) at the right nasal bridge. The right parieto-temporal incision overlying the mesh was non-tender, dry and intact. There were no obvious abnormalities involving the feet. Gait, tone and gross motor strength were normal. A clinical diagnosis of peripheral neuropathy was given. Considering the extent of the infection and presence of hardware, continued antibiotic treatment was recommended. The patient was prescribed gabapentin for symptomatic relief. The following day, the caregiver reported that the patient developed a “pins and needles” sensation in his hands and was refusing to

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weight bear, given the discomfort in his feet. In consultation with the clinical pharmacist, amitriptyline was prescribed as bridging medication, in addition to the gabapentin, for neuropathic pain.

Two weeks later, the patient presented with dehiscence of the parieto-temporal incision and a 0.5 cm area of the mesh could easily be seen. He was diagnosed with a persistent hardware associated infection and failure of the antibiotics. He underwent surgical removal of the titanium mesh and all hardware of the right parietotemporal area. Operative cultures grew *Candida dubliniensis* (sensitive to fluconazole) and *Achromobacter xylosoxidans*. As a result of anemia and the culture results, the antibiotics were changed to ertapenem and fluconazole. All antimicrobials were stopped 32 days following removal of the right parieto-temporal hardware and he had no symptoms of persistent infection following antibiotic discontinuation. In total, the patient received 77 days of metronidazole (115.5 g cumulative) and 58 days of linezolid (87 g cumulative). The symptoms in the patient's hands and feet persisted seven to eight weeks following discontinuation of metronidazole and linezolid.

Discussion

Neuropathic pain may result from a lesion or disease of the central or the peripheral somatosensory system. Neuropathic pain may be of peripheral or central origin and may be spontaneous or evoked. Common signs and symptoms include allodynia, paresthesia, dysaesthesia, and hyperalgesia [1]. Depending on the underlying lesion or disease, other neurological deficits, such as numbness and weakness, may be present [2].

Painful polyneuropathies present with neuropathic pain affecting the distal extremities. In childhood, the most common cause of painful polyneuropathy is chemotherapy. However, polyneuropathy may be caused by exposure to other neurotoxic drugs, infectious diseases (e.g. Human immunodeficiency virus), exposure to environmental or occupational toxins, autoimmune, familial (e.g. Fabry disease) or metabolic causes (e.g. B12 deficiency, chronic uremia due to renal failure) [2–6].

A case series describes 13 patients (12–22 years of age) with Crohn's disease that developed metronidazole induced peripheral neuropathy after 4–11 months of treatment. At the time of diagnosis, the mean cumulative dose received was 166 g (range 92–257 g), although the authors were unable to report at what doses symptom onset began. More than half had resolution of symptoms within 5–13 months, three had improved but continued symptoms, and one did not improve. Two patients continued therapy for 10–12 months at a lower dose (<10 mg/kg) with mixed results [7]. One case of polyneuropathy has been reported in a 17 year old with pancreatitis treated with metronidazole and total parenteral nutrition [8]. Furthermore, autonomic neuropathy has been reported in a previously healthy 15-year old after a short course of treatment with metronidazole [9]. Among adults, the risk of neurotoxicity associated with metronidazole use may be dose related. The overall incidence is unknown. The incidence is as high as 18 % among adults receiving more than 42 g over treatment periods extending beyond 4 weeks [10]. The pathogenesis of metronidazole-induced peripheral neuropathy is related to axonal degeneration secondary to binding of neuronal RNA [11].

Peripheral neuropathy has been reported in 11 pediatric patients treated with linezolid after durations ranging from four weeks to 24 months, with the majority reporting sensory disturbance after four to eight months of linezolid use [12–16]. The daily dose associated with peripheral neuropathy varied from 600 to 1200 mg daily. While dose reduction led to some improvement in symptoms, symptoms eventually led to discontinuation of linezolid. Of seven patients where outcome and time to outcome was reported, one patient had full recovery at two months post-discontinuation of linezolid, [14] and five patients had improved sensation two to ten months later [12,13,15]. One patient was noted to have persistence of symptoms more than 24 months after linezolid had been stopped [16]. Full recovery does not appear to be related to the duration of treatment given that our patient received eight weeks while the only other case of complete cessation of symptoms occurred in a young girl who received two years [14]. The cause of linezolid induced peripheral neuropathy remains unknown.

The approach to treatment of painful polyneuropathy includes removal of the offending agent or treatment of the underlying cause, management of pain and associated symptoms, and prevention of disability. Consultation with pediatric neurology may help guide further investigation and management. The current evidence available to inform pharmacotherapy is limited and often extrapolated from adult studies. Consensus guidelines suggest gabapentinoids and tricyclic antidepressants for children with chronic neuropathic pain [3,17]. If amitriptyline is effective, but too sedating, nortriptyline may be considered [17]. A multimodal approach combining rehabilitation, psychology interventions and medical management is advised [18].

The cause of the peripheral neuropathy in our patient could not be definitively linked to either of the two antibiotics, neither of which could be stopped. While uncommon in children, drug-induced peripheral neuropathy can occur and therefore the length of treatment should be balanced against the risk of adverse effects. In children requiring prolonged treatment with drugs that can lead to peripheral neuropathy, use of the lowest dose and duration is prudent. Vigilance must be maintained to screen for early signs and symptoms, and pain management should be addressed to support functional recovery. Complete recovery from peripheral neuropathy may be possible, but the factors that contribute to this outcome are not yet known.

Ethics

Reviewed by University of Saskatchewan Research Ethics Board, Exempt.

Ethical approval

This was reviewed by the University of Saskatchewan Research Ethics Board and declared exempt.

Consent

Written informed consent was obtained from the legal guardian for case report publication. A copy of the written consent is available for review by the Editor-in-Chief of this journal on request.

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Author contribution

Dr. McConnell reviewed the patient chart, conducted part of the literature review, and wrote the initial draft. Dr. Baerg conducted part of the literature review, wrote the section on management of peripheral neuropathy and critically reviewed the initial draft.

Declaration of Competing Interest

The authors report no declarations of interest.

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