CASE REPORT

Cerebellar ataxia following prolonged use of metronidazole: case report and literature review

Kalpeshkumar Patel, Israel Green-Hopkins, Stanley Lu, Allan R. Tunkel

Introduction

Metronidazole, a 5-nitroimidazole with bactericidal activity against most anaerobic and facultative anaerobic bacteria and protozoa, is widely used for the treatment of anaerobic bacterial and protozoal infections. The drug has few adverse reactions, most commonly nausea, dry mouth, vomiting, and diarrhea. Neurologic toxicity is rare and has included peripheral neuropathy, headache, dizziness, syncope, vertigo, and confusion. Cerebellar toxicity is a reported, although very unusual, manifestation of metronidazole therapy. Here, we report a case of ataxia and cerebellar lesions following therapy with metronidazole, which resolved rapidly after discontinuation of drug therapy, and review the literature on this unusual adverse event.

Case report

A 63-year-old male with a past medical history of schizophrenia presented to an outpatient clinic with purulent drainage from the mandible. The patient was diagnosed with a submental abscess and mandibular osteomyelitis. He underwent surgical drainage of the abscess and mandibular debridement; cultures grew *Streptococcus mitis*, *Enterococcus faecalis*, and *Staphylococcus epidermidis*. He was discharged on a regimen of metronidazole (500 mg orally every 6 hours) and intravenous vancomycin.

The patient did well, but presented approximately 6 weeks into the course of therapy complaining of progressive unsteadiness of gait and subsequent inability to walk that began three days earlier. On the day of admission, the patient reported that he fell while trying to stand after getting out of bed and was unable to regain his stance. On neurologic examination, he was alert and oriented to

Key Words

Metronidazole; Cerebellar toxicity; Ataxia

Summary

Cerebellar toxicity is a rare adverse event in patients treated with metronidazole. Here, we present a patient who developed cerebellar toxicity accompanied by objective abnormalities on magnetic resonance imaging, and review the literature on this unusual reaction. Discontinuation of metronidazole almost always results in resolution of symptoms and structural lesions.

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person, place, and time. His speech was not dysarthric. Cranial nerve examination revealed minimal horizontal nystagmus of 2—3 beats on lateral gaze; there was no vertical nystagmus. The left pupil was sluggishly reactive to light. Cerebellar testing revealed that heel-to-shin maneuvers, finger-to-nose testing, and lateral alternating movements were all normal. The patient’s muscle strength and bulk tone were normal, and reflexes were physiologically active and equal except in the ankles where they were absent bilaterally. His stance was wide-based; although he could stand with his feet together, he felt very unsteady and was unable to walk without support. His sensory exam revealed normal position and thermal senses, but absent vibration sensation in the toes bilaterally. The Romberg sign was negative. A non-contrast computed tomography (CT) scan of the head showed no evidence of acute hemorrhage, mass effect, or midline shift.

Upon admission, antimicrobial therapy was discontinued. Magnetic resonance imaging (MRI) of the head revealed abnormal T2-hyperintense symmetric signal and nodularity within the cerebellar parenchyma along the posterior margin of the fourth ventricle (Figure 1a); no masses, hemorrhage, or herniation were seen. After discontinuation of metronidazole therapy, the patient began to regain ambulatory function. He was able to walk with the support of a walker in two days and was ambulating without support in four days. The patient was seen in follow-up six weeks later and he noted no recurrence of symptoms, although there was persistence of absent vibration sense in the toes bilaterally. Repeat MRI of the head revealed complete resolution of the hyperintense signals in the posterior cerebellum (Figure 1b).

Discussion

Cerebellar toxicity is a rare adverse event in patients treated with metronidazole, with ten cases previously reported in the literature; we have summarized these along with our case in Table 1.2-10 The age range was 17—74 years, with most patients presenting with symptoms of ataxia and dysarthria; our patient presented with isolated ataxia and no speech impairment. Cerebellar toxicity was related to high cumulative doses of metronidazole (range of 25 to 1080 grams). Nine patients had objective findings on MRI. Despite some variability in clinical and diagnostic features in these reports, all patients had ataxia. Cerebellar lesions were described on neuroimaging studies in all cases except for one patient who had a normal CT; however, MRI was not performed in this. Following discontinuation of metronidazole therapy, clinical improvement was noted in all patients in whom it was reported (generally within 3—7 days), and MRI revealed resolution of the cerebellar abnormalities in eight patients who had follow-up studies.

The mechanism by which metronidazole causes cerebellar ataxia and reversible MRI findings is unclear. Axonal swelling has been suggested as one possible mechanism,3 likely a result of localized vasogenic edema, as opposed to ischemia or demyelination. High doses of metronidazole in rats have also been shown to induce lesions in the cerebellum;11 these alterations were qualitatively and topographically comparable to central nervous system lesions induced by thiamine deficiency in rats and in Wernicke’s encephalopathy in humans. Studies in dogs have found Purkinje cell lesions after prolonged metronidazole administration,12 and other studies in mice have revealed carbon-labeled metronidazole detected in the cerebellum.13

In summary, cerebellar toxicity should be considered in any patient who presents with ataxia and/or dysarthria and is receiving prolonged therapy with metronidazole. MRI should be performed for definitive diagnosis and metronidazole should be immediately discontinued. Further stu-
<table>
<thead>
<tr>
<th>Patient number</th>
<th>Patient age, sex, and symptoms</th>
<th>Total metronidazole dose</th>
<th>Neuroimaging findings</th>
<th>Clinical course after discontinuation of therapy</th>
<th>Follow-up neuroimaging</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 [2]</td>
<td>45-year-old female with ataxia, dysarthria, and paresthesias</td>
<td>84 g</td>
<td>CT — normal</td>
<td>Ataxia improved on day 6; paresthesias resolved at 4 months</td>
<td>Not done</td>
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<td>2 [3]</td>
<td>45-year-old female with ataxia, confusion, dysarthria, and painful peripheral neuropathy</td>
<td>35 g</td>
<td>CT — negative MRI — symmetric T2-weighted increased signal in cerebellar nuclei, genu and splenium of the corpus callosum and frontal and parietal cortical white matter</td>
<td>Ambulation on day 3; discharge on day 7; paresthesias persisted at &gt;6 weeks</td>
<td>MRI at 6 weeks showed complete resolution</td>
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<tr>
<td>3 [4]</td>
<td>34-year-old male with paresthesias, ataxia, dysarthria, and disorientation</td>
<td>66 g</td>
<td>MRI — increased signal intensity in inferior basal ganglia lateral to hypothalamus and below, and lateral to 4th ventricle</td>
<td>Cerebellar and speech symptoms improved on day 2; residual paresthesias at 2 weeks</td>
<td>Not done</td>
</tr>
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<td>4 and 5 [5]</td>
<td>62-year-old male with ataxia and dysarthria</td>
<td>60 g</td>
<td>MRI — symmetric increased T2-weighted signal in the dentate, obtained via FLAIR images</td>
<td>Ataxia and dysarthria resolved within 5 weeks</td>
<td>MRI at 5 weeks showed complete resolution</td>
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<tr>
<td></td>
<td>74-year-old male with ataxia and dysarthria</td>
<td>42 g</td>
<td>MRI — symmetric increased T2-weighted signal in the dentate; obtained via FLAIR images</td>
<td>Improvement in ataxia and dysarthria over 2 weeks</td>
<td>MRI at 2 weeks showed complete resolution</td>
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<td>6 [6]</td>
<td>17-year-old male with ataxia, visual disturbance, tremor, gait imbalance, and peripheral neuropathy</td>
<td>500 mg 3 times daily (total dose and duration not specified)</td>
<td>MRI — symmetric foci of hyperintense signal on T2-weighted and FLAIR images in the red nuclei, substantia nigra, and splenium of the corpus callosum</td>
<td>Gait imbalance and peripheral neuropathy resolved, visual acuity improved at 3 months</td>
<td>MRI at 1 year revealed complete resolution</td>
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<td>7 [7]</td>
<td>50-year-old male with ataxia, distal sensory neuropathy, proximal motor neuropathy, dizziness, diplopia, disorientation, and dysarthria</td>
<td>200 g</td>
<td>CT — bilateral hypodense areas in the cerebellum</td>
<td>Ataxia and speech abnormality resolved at 4 days; neuropathic symptoms did not improve</td>
<td>Not done</td>
</tr>
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<td>8 [8]</td>
<td>74-year-old female with ataxia, dysarthria, dysphagia, and sensory neuropathy</td>
<td>180 g</td>
<td>MRI — increased signal intensity in subcortical white matter, anterior commissure, splenium, midbrain, basal ganglia, and cerebellar white matter; increased signal intensity in the inferior olivary nuclei</td>
<td>Complete resolution of symptoms at 4 months</td>
<td>MRI at 4 months showed near-complete resolution; inferior olivary lesions became hypertrophied</td>
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dies are needed to define the pathogenesis of this unusual event.

Conflict of interest: No conflict of interest to declare.

References


