

Case Report of Metronidazole-Induced Encephalopathy

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ABSTRACT

This report describes the case of an 83-year-old woman who was admitted to a hospitalist service with weakness and falls. She was transferred from an outside facility where she was treated with 3 courses of metronidazole for diagnosed *Clostridium difficile* colitis and presumed recurrences. Magnetic resonance imaging (MRI) demonstrated T2 enhancement of the dorsal pons and dentate nuclei consistent with metronidazole-induced encephalopathy. Her metronidazole was stopped and her symptoms resolved. This condition is rare, poorly understood, and causes reversible changes in the brain that are detectable through T2-weighted MRI. It will need ongoing study with current widespread use of metronidazole.

BACKGROUND

Metronidazole is an antibiotic available for oral or intravenous (IV) use typically used to treat protozoan or anaerobic bacterial infections. One of its important and common uses is as the first-line treatment for *Clostridium difficile*. Metronidazole crosses the blood brain barrier and, since animal experiments in the 1960s, it has been known to potentially cause neurotoxicity in animal models.^{1,2} In 1995 metronidazole was first described as a cause of neurotoxicity in the brain of a human patient.³ Lesions occur in similar areas in nearly all patients and are seen as bright areas on T2-weighted magnetic resonance imaging (MRI). They are most commonly seen in the dentate nucleus of the cerebellum and in the pons. Most published cases describe resolution of symptoms and MRI changes after metronidazole

is stopped. Poor neurologic outcomes and death attributable to metronidazole-induced encephalopathy (MIE) have been reported. One case report from 2015 described a patient whose MRI revealed expected changes after a 3-week course of metronidazole for cholecystitis; however, despite appropriately stopping metronidazole and providing supportive care, her neurological impairment progressed. She was placed on hospice care and died 12 days later. Near the time of her hospice enrollment the T2 MRI enhancement

had spread throughout brainstem, corpus callosum, subcortical white matter, and spinal cord.⁴

CASE REPORT

An 83-year-old woman was transferred to our institution after 7 days of progressive weakness, ataxia, and falls. Her symptoms were exclusively of her truncal muscles and on exam, her limbs had normal strength and coordination. Her muscles were normal in appearance, but she was unable to maintain an upright posture when sitting. When she was assisted to a sitting position she fell backwards or to the side if unsupported. No mental status changes or other neurological symptoms were reported by nursing or on the review of symptoms, and no other focal neurological or muscular symptoms were found by the hospitalist or the neurologist.

The patient had a relevant past medical history of spinal stenosis in her lumbar spine, protein calorie malnutrition, rheumatoid arthritis, chronic prednisone use, and *Clostridium difficile*. She had undergone lumbar spine laminectomy and fusion approximately 3 months prior to admission and had been doing well post-operatively. She lived independently, performed all her activities of daily living, and walked unassisted.

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Figure 1. Axial Magnetic Resonance Imaging Demonstrating Enhancement of the Dentate Nucleus Bilaterally

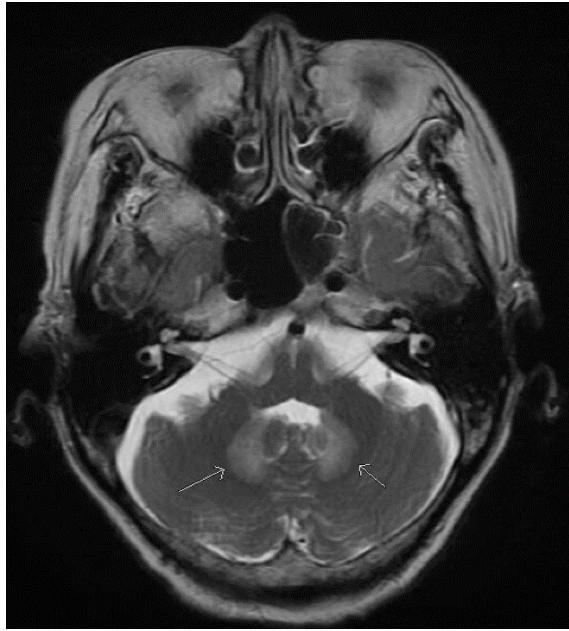


Figure 2. Axial T2 Magnetic Resonance Imaging Demonstrating Enhancement in the Bilateral Posterior Pons



One month after surgery she developed diarrhea. Stool testing was positive for toxigenic *Clostridium difficile* and she was treated with metronidazole 500mg 4 times daily orally for 10 days. She had complete resolution of her diarrhea and reportedly had returned to her normal state of health. Two weeks after

treatment was completed she developed a recurrence of diarrhea and was started on 500mg 4 times daily orally for 21 days. A second stool test was not performed to verify relapse. On day 17 of treatment she was taken to her local hospital after a fall with a prolonged downtime. On admission, she was started on 500mg IV metronidazole 3 times daily instead of her oral dose. She received 11 doses of IV at the referring hospital prior to discontinuation. The total amount of metronidazole she received was 56 grams by mouth and 5.5 grams IV with a treatment duration of 31 days. Approximately 44 grams orally were taken over 22 days before the onset of weakness and ataxia.

On admission, an MRI of the brain was obtained without IV contrast. It demonstrated bilateral T2 bright signal symmetrically in the dentate nuclei and dorsal pons. The most likely differential included MIE, Wernicke encephalopathy, methyl bromide intoxication, and enteroviral encephalomyelitis.

She was treated with IV vitamin supplementation for potential Wernicke encephalopathy and the metronidazole was discontinued. Neurology was consulted and an electromyogram found no evidence of peripheral neuropathy or myopathy. One day after discontinuation of metronidazole she was feeling stronger and her ataxia was improved enough that she sat up in bed unassisted. On day 2, she could stand with a walker and the assistance of a physical therapist. Three days after discontinuation she was able to walk in the hallways with a wheeled walker and without help from a therapist. She was discharged on day 6 to a skilled nursing facility for ongoing rehabilitation.

Fifteen months after her initial episode of *Clostridium difficile*, the patient was contacted via phone for follow up. She had recovered fully from her truncal weakness and ataxia after a short stay in a rehabilitation facility. At the time of our call, she was living in her own home and independent in all her activities of daily living.

DISCUSSION

Imaging Findings

This patient had symmetrical T2 bright lesions located in the dentate nucleus of her cerebellum and posterior pons (Figures 1 and 2). In 2007, Kim et al described a case series of 7 patients who had reversible symmetrical lesions on MRI after prolonged treatment with metronidazole. Lesions varied from patient to patient but all had involvement of the dentate nucleus and pons.⁵ These findings are consistent with other smaller case reports of MIE. Lesion locations vary and have included the dorsal pons, the splenium of the corpus callosum, the inferior olivary nuclei bilaterally or unilaterally, the cerebral white matter, and the anterior commissure.⁶

Symptoms and Resolution

Our patient had symptoms of truncal weakness and ataxia. Reported symptoms in previous cases include dysarthria, ataxia,

vertigo, nausea, vomiting, weakness, confusion, and tingling of the extremities. Case reports describe resolution of symptoms about 1 to 2 weeks after stopping the metronidazole,⁵ although there are isolated case reports of symptoms persisting past 2 weeks. The earliest case reported was in 1995, which describes peripheral nerve pain that persisted longer than 6 weeks.³ Peripheral neuropathy is a known side effect of metronidazole, so it is likely that the reported pain is unrelated to the central nervous system changes seen on MRI. A majority of patients, including the patient described in this report, experience the onset of symptoms during their treatment with metronidazole. A 2012 report describes a patient who had the onset of symptoms 12 days after stopping therapy. The patient had MRI changes and symptoms consistent with MIE, confirming the diagnosis despite having stopped metronidazole treatment.⁷

Metronidazole Dosage

The dosage received and duration of metronidazole treatment varied among case reports. Most authors discuss larger dosages or longer duration as key risk factors for development of MIE. The Table identifies several typical case reports and the duration of metronidazole. Although the amount and duration of metronidazole treatment was different in each case, the total exposure for each patient is higher than the current recommendation for initial treatment of *Clostridium difficile*, which suggests 1.5 grams daily for 10 to 14 days, for a total dose of 15 to 21 grams. The patient in this report was treated with 2 grams daily for 10 days—a total of 20 grams. Relapses after initial therapy are common, in which case a second course of metronidazole is often tried. This gives the patient a total of 30 to 42 grams of metronidazole and 28 days of treatment, which could put the total dose and duration in the range known to have caused MIE.

CONCLUSIONS

Metronidazole-induced encephalopathy is a rare but potentially serious neurologic syndrome presenting with typical symptoms and imaging findings in patients with a history of metronidazole exposure. The diagnosis can be made based on the history, exam, and constellation of MRI findings. With increasing prevalence of *Clostridium difficile* infection and metronidazole as a first-line agent, primary care and hospital clinicians should be aware of MIE and how to treat it.

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Table. Metronidazole Dosing, Duration, and Time to Neurologic Recovery in Reviewed Case Reports

Paper	Daily Dose (Grams)	Total Dose (Grams)	Duration of Treatment (Days)	N	Time to Recovery or Discharge (Days)
Ahmed A, et al, 1995 ³	.75-2.25	35	30	1	7
Hobbs K, et al, 2015 ⁴			21	1	N/A
Kim E, et al, 2007 ⁵	1.5	58.1 (average)	38.7 (average)	7	6.7 (average)
Kalia V, et al, 2010 ⁶	1.2	67.2		1	
Huang YT, et al, 2012 ⁷	1.5	32.6 (average)	25-28	2	
Kim H, et al, 2011 ⁸	1.5	45.5	31	1	
Moriya M, 2013 ⁹	2			1	14
Shah H, 2014 ¹⁰	2.4	75	27	1	10
Our patient	2	44	22	1	6

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