Title: Metronidazole Induced Encephalopathy Risk Increased in Cirrhosis: Brain MR Findings

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Abbreviations:
- Fluid-attenuated inversion recovery (FLAIR)
- International normalized ratio (INR)
- Metronidazole induced encephalopathy (MIE)
- Magnetic resonance imaging (MRI)
- Partial thromboplastin time (PTT)
- Prothrombin time (PT)

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Purpose: The purpose of this case presentation is to describe the characteristic clinical and MR findings associated with metronidazole induced encephalopathy (MIE), relay the increased risk potential of MIE for those with cirrhosis undergoing long term treatment with the medication, and to present a unique case in which the patient’s symptoms and MR findings initially worsened after cessation of the drug.

Specialties: This report has importance for a broad audience of clinicians because Metronidazole is a commonly prescribed drug for a variety of infections. This significant but reversible toxicity has clinical manifestations that may mimic other disease processes and be not recognized unless the clinician is aware of this entity. This report is particularly relevant for radiologists, gastroenterologists, and infectious disease practitioners.
Abstract:
This is a case of Metronidazole induced encephalopathy (MIE) in a 69 year old male patient with cirrhosis treated for a brain abscess. He presented with characteristic neurologic findings and T2 hyperintensity of the dentate nuclei on MR imaging after receiving a total of 35g. After Metronidazole cessation with subsequent symptomatic improvement, the patient was discharged. This case is consistent with other studies that suggest cirrhosis may be a risk factor for MIE. The case includes characteristic imaging findings before, during, and after Metronidazole treatment that may help clinicians narrow and focus diagnosis in the appropriate clinical setting.

Introduction:
Metronidazole is a commonly prescribed antibiotic for various infections, including abscesses, *H. pylori* gastritis, protozoal infections, amebiasis, *C. diff* colitis, other anaerobic bacterial infections, sexually transmitted infections and STI post-exposure prophylaxis. While many patients take it without side effects, it has been associated with side effects such as nausea, headache, vomiting, anorexia, stomach cramping, diarrhea and constipation (1). Less commonly reported are the neurotoxic side effects, including dizziness, vertigo, peripheral neuropathy, ataxia, dysarthria and weakness. The most severe neurotoxic side effects include seizure, aseptic meningitis, and encephalopathy, which may be underreported. The exact mechanism of metronidazole-induced encephalopathy (MIE) is unknown, but most cases in the literature demonstrate cerebellar symptoms and characteristic MRI findings of bilateral T2 hyperintense lesions of the dentate nuclei of the cerebellum, the midbrain, dorsal pons, medulla, and Splenium of the Corpus Callosum (2,3). Treatment courses and cumulative doses of metronidazole in these cases vary, as well as comorbid conditions and concurrent medications. Awareness of the side effects is needed because they are reversible with discontinuation of the drug according to cases in the literature. We present a case of MIE that occurred in a patient with hepatic dysfunction after treatment with metronidazole for a brain abscess.

Case Presentation:
A 69 year old white male with a history of alcoholic cirrhosis, esophageal varices, and diabetes mellitus type 2 presented to neurosurgery follow-up clinic one month following a right parietal lobe abscess drainage. At time of treatment, the brain MR showed normal dentate nuclei of cerebellum (Image 1a.) and midbrain (Image 2a.) The patient had a 100 pack-year smoking history and quit eleven months before presentation. On presentation, he had a four day history of poor oral intake, nausea, vomiting, and progressive dysarthria. On neurological examination, he had a four day history of poor oral intake, nausea, vomiting, and progressive dysarthria. On neurological examination, the patient displayed dysmetria and dysdiadochokinesia without signs of clonus or asterixis. The patient’s sensation and musculoskeletal exams were normal. Cranial nerves were normal and patient had no meningeal signs. A noncontrast brain MRI on that day showed new bilateral Fluid-attenuated inversion recovery (FLAIR) and T2 hyperintensity in the cerebellar nuclei (Image 1b), as compared to initial imaging
(Image 1a.) at the time of abscess drainage. The patient’s medications prior to admission included acetaminophen 650 mg every 4 hours prn, cefepime 6 g/d, esomeprazole 40 mg/d, folic acid 1 mg/d, lispro 7 units before meals, lactulose 30 mL bid, levetiracetam 500 mg/d, mirtazapine 15 mg/d, omeprazole 20 mg/d, propranolol 10 mg every 8 hours, rifaximin 550 mg/d, ropinirole 2 mg/d, spironolactone 50 mg/d, thiamine 100 mg/d, oxycodone 5 mg every 6 hours prn and metronidazole 500 mg TID. The patient received 70 doses of metronidazole, totaling 35 g. Relevant labs include albumin 2.7, total bilirubin 2.8, conjugated bilirubin 1.4, alkaline phosphatase 179, PTT 41.4, PT 18.6, INR 1.70, BUN 13, Creatinine 0.79, Ammonia level 28 (normal reference range 15-50). One metronidazole blood level was obtained at presentation and was 71 mcg/mL. The lab’s recommended plasma level was 22 mcg/mL. At this point, metronidazole and cefepime were discontinued. Two days after discontinuing metronidazole, the patient showed improvement of dysmetria, dysarthria and dysdiadochokinesia. Patient was discharged home on meropenem 2g/d after the sixth day of metronidazole cessation.

The patient presented again with worsening dysarthria and altered mental status twelve days after discharge. Imaging showed slight improvement of abnormal enhancement in the dentate nuclei (Image 1c), but T2 and FLAIR images demonstrated worsening hyperintensity of white matter within the brainstem and extending from the subcortical white matter to periventricular, callosal, and basal ganglia areas (Image 2b,c). The patient was treated conservatively and discharged 5 days later, again exhibiting symptomatic improvement. The patient followed up 3 months later and had no dysarthria, dysmetria, or dysdiadochokinesia. MRI showed no residual enhancement (Images 1d, 2d).

Image 1 Axial T2-weighted images at level of dentate nuclei. 1a. prior to onset of cerebellar signs. 1b. At onset of new cerebellar signs, striking bilateral and symmetrical T2 hyperintensity in dentate nuclei. 1c. Twelve days after cessation of Metronidazole treatment, with fading but persistent T2 hyperintensity in dentate nuclei and new abnormal hyperintensity of tegmentum of pons. 1d. Normal MR findings restored at 3 month follow-up after cessation of Metronidazole treatment.
Discussion:

Metronidazole has several favorable characteristics: low resistance rates, high oral bioavailability (4), effective CNS penetration, and penetration in brain abscesses equal to serum drug concentration (5). Metronidazole undergoes glucuronidation in liver yielding metabolites with 30-65% of the parent drug’s function. 6-18% of metronidazole is excreted unmetabolized in urine(6). Metabolites also are renally excreted. Half life of metronidazole is 6-9 hours, and is not affected by renal disease. Cases of Metronidazole induced encephalopathy vary in dosing and clinical presentation with extended dosing as the recurrent theme. Cirrhosis may increase elimination half life from nine hours to 20 hours (7). Patients with liver disease likely are predisposed to this rare side effect. Several cases of metronidazole induced encephalopathy in cirrhotic patients have been reported (2,8-10).

MIE has been reported with amounts as low as 30 g (11). Our patient received 35 g of Metronidazole over 43 days and developed dysarthria, dysmetria and dysdiadochokinesia. Findings of hyperintensity of the dentate nuclei on his second brain MR were characteristic. The commonly associated findings of hyperintensity of the midbrain, dorsal pons, medulla, or splenium of the Corpus Callosum were not present initially, but were seen on third brain MR.

A defining trait of MIE is reversibility with cessation of Metronidazole, which occurred during his first MIE episode. Our case engenders interest because 12 days after discharge (two weeks after Metronidazole cessation) he developed worsening clinical features of MIE with T2 hyperintensity in the basal ganglia, brainstem, and corpus callosum on his third brain MR. Symptom resolution again followed conservative management with no further recurrence.
Considering other causes of this patient’s encephalopathy, hepatic disease is not the likely primary cause in this patient who did not have asterixis or hyperammonemia.

Medications have to be scrutinized also as potential sources of neurotoxicity and encephalopathy. 6g Cefepime was administered daily concomitantly with metronidazole and both were discontinued simultaneously. This Cefepime dosing is associated with risk of cefepime induced encephalopathy (CIE), especially with renal dysfunction (12). However, the side effects of Cefepime don’t include cerebellar symptoms, and this patient had no renal dysfunction. The patient had confusion, but not the characteristic CIE-associated hallucinations or myoclonus (12,13).

Treatment included rifaximin during each admission, a drug associated with neurotoxicity (13). However, rifaximin was continued until discharge during each admission and he showed improvement despite rifaximin therapy, making rifamilaxin not the likely primary cause of his neurological dysfunction.

Meropenem was started after metronidazole and cefepime cessation. Early after market introduction of Meropenem, it was thought to cause seizures in patients with CNS dysfunction, but more recent literature has not borne out this initial concern (14).

Reversibility of the Metronidazole induced encephalopathy may take weeks, with some persistence for months after metronidazole cessation (8,15). One publication reported two cases with irreversible supratentorial neurotoxicity. However, that lasting effect was attributed to the severity of the patients’ co-morbidities of long term total parenteral nutrition and medication overdose (15).

We think our patient's other medications and hepatic dysfunction are not likely to be the primary source of encephalopathy. We speculate an effect related to competitive binding and release of the patient’s several medications may have prolonged the presence of metronidazole and its metabolites in the patient’s system. Alterations in dose of the other medications may have displaced the Metronidazole back into the patient’s serum, resulting in recurrent symptoms. Thus, we speculate that the combination of cirrhosis, other comorbidities, and concurrent treatment with multiple potentially neurotoxic medications may help explain the unusual clinical course of initial improvement, then worsening, and finally, resolution of a classically reversible drug side effect.

**Conclusion:** Large cumulative Metronidazole doses may induce reversible encephalopathy with hyperintense, non-enhancing lesions in the inferior colliculi or cerebellar dentate nuclei. Reversal typically follows drug cessation. We speculate that more significant compromise of metabolic pathways of drug elimination may delay recovery with recrudescence of the drug side effects.

**References:**

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