CASE IN POINT

# Acute Encephalopathy Following Hyperbaric Oxygen Therapy in a Patient on Metronidazole

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This case describes a patient who presented to the emergency department for an acute onset of encephalopathy following hyperbaric oxygen treatment and antibiotic therapy for radiation-induced osteonecrosis of the jaw.

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Altered mental status (AMS) is a common presentation to the emergency department (ED) for older patients and is often due to underlying drug-associated adverse effects (AEs), medical or psychiatric illness, or neurologic disease. EDs often have protocols for diagnosing and managing AMS to assess the underlying etiology. A formal assessment with a full history and physical examination is paramount to diagnosing the cause of AMS.

Oral metronidazole is a commonly used antibiotic for anaerobic bacterial infections and *Clostridium difficile*-associated diarrhea and colitis.[1] Metronidazole produces cytotoxic intermediates that cause DNA strand breakage and destabilization, resulting in bactericidal activity in host cells.[2] Common AEs include gastrointestinal symptoms such as nausea, vomiting, and diarrhea; less common AEs can involve the nervous system and include seizures, peripheral neuropathy, dizziness, ataxia, and encephalopathy.[3,4] A pattern of magnetic resonance image (MRI) abnormalities typically located at the cerebellar dentate nucleus midbrain, dorsal pons, medulla, and splenium of the corpus callosum have been associated with metronidazole usage.[5]

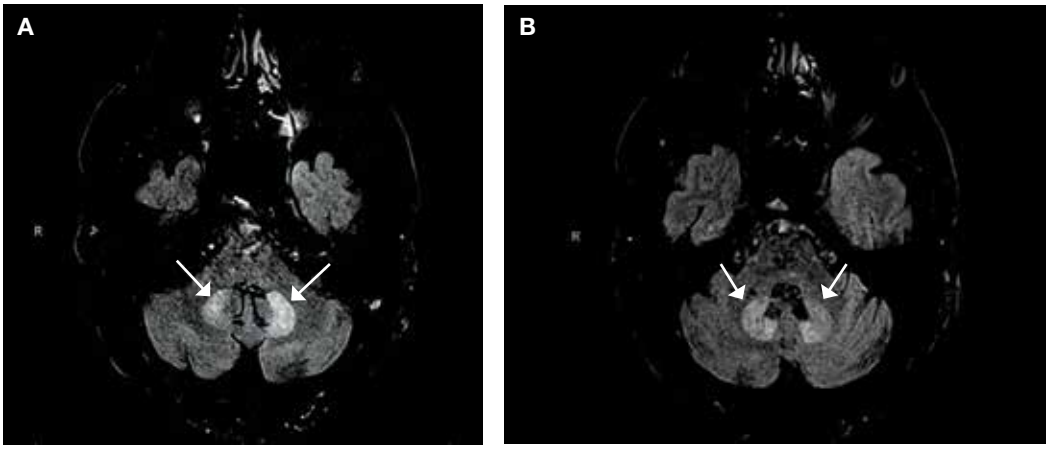
Hyperbaric oxygen therapy (HBOT) is a treatment modality used as the primary therapy for decompression sickness, arterial gas embolism, and carbon monoxide poisoning. HBOT is used as adjuvant therapy for osteonecrosis caused by radiation or bisphosphonate use.[6,7] HBOT increases the partial pressure of oxygen in plasma and increases the amount of oxygen delivered to tissues throughout the body.[8] *Hyperoxia*, defined as an elevated partial pressure of oxygen leading to excess oxygenation to tissues and organs, increases production of reactive oxygen and nitrogen species, which are signaling factors in a variety of pathways that stimulate angiogenesis.[8] AEs of HBOT include barotrauma-related injuries and oxygen toxicity, such as respiratory distress or central nervous system (CNS) symptoms.[9] Severe CNS AEs occur in 1% to 2% of patients undergoing therapy and manifest as generalized tonic-clonic seizures, typically in patients with preexisting neurologic disorders, brain injury, or lowered seizure threshold.[7,8,10] There have been no documented incidences of HBOT inducing acute encephalopathy.

## CASE PRESENTATION

A 63-year-old male smoker with no history of alcohol use presented to the ED with an acute onset of lightheadedness, confusion, and poor coordination following his second HBOT for radiation-induced osteonecrosis of the mandible. The patient reported chronic, slowly progressive pain and numbness of the feet that began 4 years earlier. He noted marked worsening of pain and difficulty standing and walking 3 to 4 months prior to presentation.

Ten years prior, the patient was diagnosed with cancer of the right tonsil. A tonsillectomy with wide margins was performed, followed by 35 rounds of radiation

**FIGURE 1** Axial-Fluid Attenuated Inversion Recovery Magnetic Resonance Image of Brain Showing Increased Signal in the Dentate Nucleus Bilaterally (arrows).




treatment and 2 rounds of chemotherapy with cisplatin.

In May 2017, the patient presented with a lump in the right cheek that was diagnosed as osteonecrosis of the mandible. An oral surgeon prescribed metronidazole 500 mg qid and amoxicillin 500 mg tid. The patient was adherent until presentation in November 2017. Following lack of improvement of the osteonecrosis from antibiotic therapy, oral surgery was planned, and the patient was referred for HBOT with a planned 20 HBOT preoperative treatments and 10 postoperative treatments.

Following his first 2-hour HBOT treatment on November 13, 2017, the patient complained of light-headedness, confusion, and incoordination. While driving on a familiar route to his home, he collided with a tree that was 6 feet from the curb. The patient attempted to drive another vehicle later that day, resulting in a second motor vehicle accident. There was no significant injury reported in either accident.

His partner described the patient's episode of disorientation lasting 6 to 8 hours, during which he "looked drunk" and was unable to sit in a chair without falling. The following morning, the patient had improved mental status but had not returned to baseline. His second HBOT treatment took place that day, and again, the patient acutely experienced light-headedness and confusion following completion. Therapy was suspended, and the patient was referred to the ED for further evaluation. Mild facial asymmetry without weakness, decreased sensation from toes to knees bilaterally, and absent Achilles reflexes bilaterally were found on neurologic examination. He exhibited past-pointing on finger-to-nose testing bilaterally. He was able to ambulate independently, but he could not perform tandem gait.

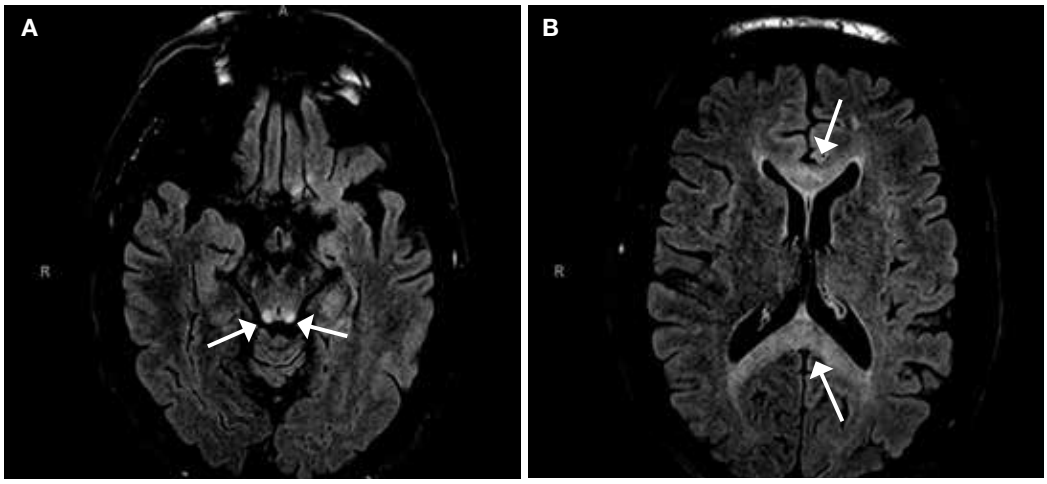
An MRI of the brain showed abnormal T2 hyperintensity found bilaterally at the dentate nuclei and inferior colliculi. The splenium of the corpus callosum also showed mild involvement with hyperintense lesions. Laboratory tests of the patient's complete blood count; comprehensive metabolic panel; vitamins $B_1$, $B_6$, $B_{12}$; and folic acid levels had no notable abnormalities and were within normal limits.

Metronidazole and HBOT therapy were discontinued, and all of the patient's symptoms resolved within 2 weeks. A repeat examination and MRI performed 1 month later showed resolution of all the patient's clinical findings and MRI abnormalities. HBOT was resumed without the recurrence of previously described symptoms.

## DISCUSSION

This patient's encephalopathic symptoms correlate temporally with the onset of HBOT. There is no medical literature suggesting a relationship between HBOT and encephalopathic symptoms with MRI abnormalities, and in fact, some studies suggest HBOT as a treatment for hypoxic-ischemic encephalopathy in neonates.[11]

**FIGURE 2** Axial Fluid-Attenuated Inversion Recovery Magnetic Resonance Image of Brain




(A) Increased signal in the inferior colliculi (arrows). (B) Increased signal in the corpus callosum (arrows).

This led us to believe that the HBOT may have exacerbated some underlying condition, evidenced by the specific MRI findings of T2 fluid-attenuated inversion recovery (FLAIR) hyperintensities in the dentate nuclei and inferior colliculi (Figures 1 and 2). The location of these lesions, specifically the dentate nuclei, which is involved in voluntary motor function, may explain the patient's symptoms of ataxia.[12]

Differential diagnoses for T2 hyperintense lesions in the dentate nuclei include metronidazole toxicity, acute Wernicke encephalopathy (WE), and methyl bromide intoxication. Diseases that would have presented in infancy with similar MRI findings (Canavan disease, maple-syrup urine disease, and glutaric aciduria type 1) were not considered plausible.[12-14] We excluded methyl bromide intoxication since it is not used regularly in the US, and the patient denied use of any insecticides. Therefore, the most likely causes of a underlying condition that was exacerbated by HBOT were metronidazole toxicity or WE.

Despite his denial of alcohol use, the patient was at risk for malnutrition secondary to his mandibular lesion and difficulty eating. Clinically, he presented with episodes of confusion and ataxia, consistent with 2 of the classic triad of symptoms of WE (no ocular abnormalities noted on exam). Typical MRI findings in WE include signal intensity alterations (including T2 hyperintensities) in the medial thalami, mammillary bodies, collicular bodies, and periaqueductal and periventricular regions.[14,15] Atypical MRI findings in WE include symmetric signal intensity changes in the cerebellum, dentate nuclei, caudate nuclei, red nuclei, cranial nerve nuclei, and splenium.[14] Of note, atypical MRI findings were more common in patients without alcohol use disorders and WE, and typical MRI findings were more common in patients with alcohol use disorders.[14] However, this patient's report of no alcohol use and the serum thiamine level being within normal limits (173 nmol/L; range 78-185 nmol/L) made acute WE less likely than metronidonazale-induced encephalopathy (MIE).

The most common neurologic AE of metronidazole is distal symmetric sensory polyneuropathy, which also can have motor or autonomic features.[16,17] While our patient had a history of peripheral neuropathy, he noted marked worsening of foot pain 3 months after initiating metronidazole therapy. A potential mechanism involves metronidazole or its cytotoxic intermediates binding neuronal ribonucleic acids, thus inhibiting protein synthesis and resulting in degenerative neuronal changes and reversible axonal swelling (as opposed to the DNA interference attributed to the drug's mechanism of bactericidal action).[18] Neuropathies may result from prolonged high-dose metronidazole therapy (cumulative dose > 42 g),[3] but they also have been seen in short-term use of high dosages.[17]

CNS AEs are much rarer and are thought to be associated with metronidazole's ability to cross the blood-brain barrier. These patients present as a toxic encephalopathy with cerebellar dysfunction (dysarthria, ataxia) as the most common presentation, followed by AMS and seizures.[4] Our patient presented with acute confusion and ataxia. Animal studies suggest that γ-aminobutyric acid (GABA) receptor modulation in the cerebellar and vestibular systems may contribute to this neurotoxicity, but no definitive mechanism of injury has been found.[19]

On MRI, MIE most commonly presents with hyperintense lesions in the bilateral cerebellar dentate nucleus on T2-weighted and FLAIR images.[5,20] The midbrain, dorsal pons, medulla, and corpus callosum also can show increased signal intensity.[5] This AE does not seem to be dose- or duration-dependent, and most cases report complete or partial resolution of symptoms following discontinuation of the drug, though this is not absolute.[4,13,21] The patient's MRI findings were highly consistent with MIE (Figure 2).

## CONCLUSION

This patient's highly specific MRI findings, neurologic examination consistent with confusion, ataxia, length-dependent sensory neuropathy, and 360-g cumulative dose of metronidazole over the previous 6 months suggest he experienced MIE. The mechanism of how HBOT precipitated the patient's altered mental status, incoordination, and worsening of peripheral neuropathy is unknown. Although encephalopathy with MRI abnormalities as described is not a reported AE of HBOT, it may be unrecognized. It is possible that without HBOT the patient would have remained asymptomatic apart from his peripheral neuropathy.

We propose HBOT may exacerbate or increase the risk of a patient developing MIE. Our patient was able to safely resume HBOT after metronidazole was discontinued, suggesting that the combination was the causation for the development of encephalopathy. We do not believe any similar cases have been reported.

## Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

## Disclaimer



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