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Case Report

MRI findings of metronidazole neurotoxicity in a pediatric patient with chronic diarrhea

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ABSTRACT

Neurotoxicity is a rare side effect of metronidazole therapy. Shown here are findings of metronidazole toxicity in a patient, who received chronic metronidazole as prophylaxis for pseudomembranous colitis following bowel resection as an infant. Findings depicted include increased T2 signal in the dentate nuclei and brainstem. Discontinuing the medication resulted in reversal of the findings.

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Introduction

Metronidazole is a commonly used antibiotic in the management of anaerobic and protozoan infections including *Clostridium difficile* colitis. Metronidazole is toxic to microbes through its production of free radicals [1]. The drug is cost-effective, generally well tolerated, and deemed safe for use in the pediatric population. The most common side effects of metronidazole therapy are gastrointestinal in nature and include nausea, anorexia, vomiting, and abdominal cramping. Drug-associated neurologic symptoms are less common and include peripheral neuropathy, vertigo, and headache [1–3]. Metronidazole-induced cerebellar dysfunction is rare, but

can present as ataxia, nystagmus, and/or tremor. The neurotoxic effect is reversible upon removal of the medication and does not seem to be dose or duration-related [3–4]. Previously reported central nervous system findings observed on magnetic resonance imaging (MRI) have included T2 hyperintense lesions in the dentate nuclei that resolve after cessation of the drug [4–5]. Presented here is a case in which a patient on metronidazole therapy presented with cerebellar dysfunction. Subsequent MRI demonstrated increased T2 signal in the dentate nuclei and brainstem.

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Fig. 1 – Axial FLAIR images of the brain at the level of the pons reveal symmetric foci of increased T2 signal in the dorsal pons (white arrow), and there is diffuse increased T2 signal throughout the dentate nuclei (black arrow).

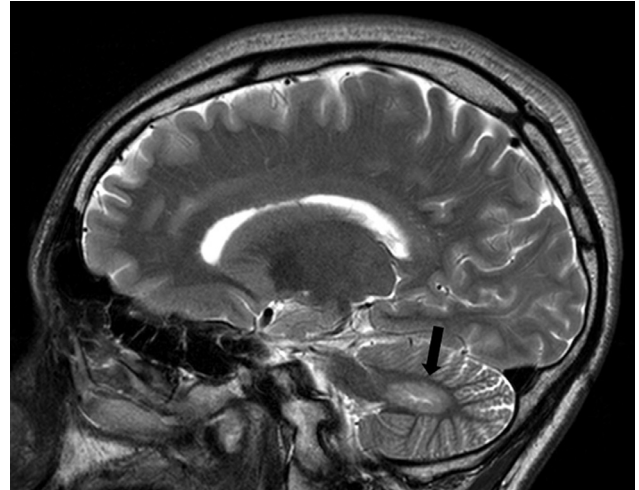


Fig. 2 – Sagittal T2-weighted images of the brain show increased T2 signal throughout the dentate nuclei (black arrow). No T2 signal abnormalities were present in the supratentorial brain.

Case report

A 17-year-old autistic male presented to clinic with a 1-day history of ataxia characterized by falling, an abnormal unilateral lean, and lack of balance. He was afebrile and denied sick contacts. His past medical history was significant for Hirschsprung's disease, and he had chronic diarrhea following bowel resection during the first week of life. The patient was taken by his mother to an outside hospital, where a chest radiograph and Computed tomography (CT) of the head computed tomography with angiography were normal. He was then transferred from the outside hospital for further evaluation. Thyroid studies, urinalysis, alcohol level, cerebrospinal fluid analysis, and a comprehensive metabolic panel were unremarkable. MRI of the brain was obtained and showed symmetric foci of T2 prolongation in the dorsal pons including the facial nuclei (Fig. 1), dorsal medulla (Fig. 2), and dentate nuclei (Figs. 1 and 3). There was no enhancement following intravenous administration of gadolinium (Fig. 4). The provisional diagnosis was rhombencephalitis; however, concern was raised for a metabolic or toxic insult due to the pattern of the imaging findings, as the cerebellar folia were relatively spared. After an extensive infectious, metabolic, autoimmune workup, and minimal clinical improvement after a 5-day course of high-dose IV methylprednisolone, a review of the patient's medical record showed long-term metronidazole therapy to treat chronic diarrhea. The medication was discontinued, and the patient's mental status and CNS symptoms of ataxia improved following cessation of the medication.



Fig. 3 – Axial FLAIR images of the brain demonstrate symmetric areas of increased T2 signal in the dorsal medulla (white arrow).

Decreased signal abnormalities were observed on follow-up MRI obtained 4 days after the initial exam (Fig. 5). The patient was discharged from the hospital and had returned to baseline at his outpatient neurology follow-up appointment.

Discussion

An unexplained change in mental status or a new focal neurologic symptom often prompts imaging evaluation. Recogn-

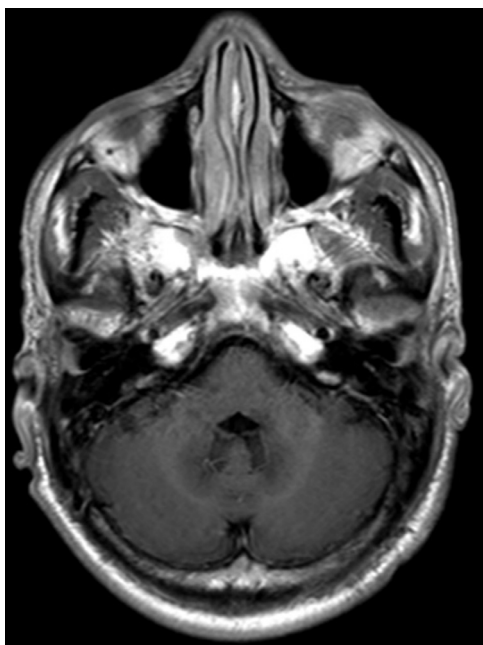


Fig. 4 – Axial T1-weighted images following intravenous administration of gadolinium exhibit no contrast enhancement associated with the T2 signal abnormalities.



Fig. 5 – Axial FLAIR images of the brain at the level of the pons obtained 4 days after the MRI in figure 1 reveal interval decreased abnormal T2 signal in the dorsal pons (white arrow) as well as decreased abnormal T2 signal throughout the dentate nuclei (black arrow).

nitiation of the imaging findings and correlation with the patient's medication list is crucial for early identification and treatment. Metronidazole is safe for pediatric use, serves as a primary medication to treat or prevent pseudomembranous colitis, and treats other anaerobic organisms and protozoans. Nervous system side effects are often mild such as headache, vertigo, headache, and peripheral neuropathy. In rare circumstances, however, dramatic side effects such as cerebellar dysfunction can manifest. In such clinical settings, MR imaging is commonly used to aid in diagnosis. Imaging findings presented in this study such as bilateral increased T2 signal in the dentate nuclei, pons, and cerebellum, may provide a diagnostic clue to this reversible condition.

A case of metronidazole-associated cerebellar ataxia was described by Hari et al. in 2013 [6] in which a 31-year-old male with an amebic liver abscess developed gait instability after 4 months of metronidazole therapy. MRI findings included a strikingly similar appearance to the case presented here with symmetric nonenhancing punctate foci of increased T2 signal in the pons bilaterally, facial nuclei, and dentate nuclei [6].

Another 43-year-old male with a liver abscess due to *Entamoeba histolytica* was reported in 2010 [7]. After 2 months of metronidazole use, he presented to the hospital with slurring of speech, weakness, and ataxia. Again, similar to the case above, signal abnormalities such as symmetric punctate foci of increased T2 signal in the dorsal pons and dentate nuclei were identified [7]. There were additional findings of increased T2 signal in the splenium of the corpus callosum. Enhancement characteristics were not discussed in this case.

A case presented by Chandak et al. discussed a 45-year-old patient undergoing 4 weeks of metronidazole therapy for a liver abscess, who presented with staccato speech and ataxia. MRI demonstrated abnormal increased T2 signal in the dentate nuclei as well as the midbrain tectum [8]. As with the case reported by Kalia et al. [7], enhancement characteristics were not discussed.

In a pediatric case described by Chatzkel et al., a 15-year-old female with inflammatory bowel disease received metronidazole for only 7 days before developing ataxia and dysmetria. MRI of the brain was again remarkable for increased T2 signal in the dentate nuclei without contrast enhancement.

Symptoms of cerebellar dysfunction in the setting of metronidazole toxicity are potentially dramatic but reversible. In the case reported here, clinical symptoms and imaging findings quickly improved upon cessation of metronidazole therapy. MRI signal abnormalities have been reported to improve upon withdrawal of the medication as soon as 3 days [8] and are known to resolve completely [9], though a distinct time to achieve complete resolution has not been defined. The case presented in this manuscript confirms that symptoms of cerebellar dysfunction and MRI findings improve upon cessation of the drug within 4 days.

Current mechanisms of neurologic injury are unknown, however, axonal swelling, Purkinje cell damage due to neuronal RNA binding/interference with protein synthesis, and ischemia have been postulated [8].

Conclusion

Metronidazole neurotoxicity is rare, but can result in signal changes in the brainstem and cerebellum on MRI. Symmetric foci of abnormal increased T2 signal in the dorsal pons and facial nuclei in combination with abnormal increased T2 signal throughout the dentate nuclei of the cerebellum are important diagnostic clues to this debilitating but reversible side effect.

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