

Defining the early stage of metronidazole-related cerebellar toxicity: A diagnostic challenge with unusual features

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Metronidazole is widely recognized as a safe and effective 5-nitroimidazole antibiotic, yet clinically significant neurotoxicity, although rare, has been increasingly documented.^[1] Neurological complications most commonly involve the cerebellum and brainstem and may clinically mimic infectious, metabolic, autoimmune, or paraneoplastic disorders. Because these symptoms can arise in patients receiving treatment for systemic infections, early recognition is challenging. While characteristic magnetic resonance imaging (MRI) abnormalities are well described, a subset of patients present with normal neuroimaging, adding further diagnostic uncertainty. Here, we describe a patient who developed a clear cerebellar syndrome shortly after metronidazole exposure despite unremarkable MRI findings, underscoring the need for clinical suspicion even without radiological abnormalities.

A 56-year-old man presented with pneumonia and was started on metronidazole 500 mg three times daily and cefuroxime 500 mg twice daily. After five days of treatment (cumulative metronidazole dose: 7.5 g), his infectious symptoms improved; however, he developed new neurological complaints, including gait instability, impaired manual dexterity, and dysarthria. His medical history included diabetes mellitus, hypertension, and bipolar disorder; medications included perindopril, metoprolol, empagliflozin, quetiapine, and lithium. Neurological examination demonstrated bilateral

dysmetria, dysdiadochokinesia, dysarthria, and marked gait ataxia, indicating a cerebellar syndrome. Routine laboratory tests, including renal and hepatic function, electrolytes, inflammatory markers, and complete blood count, were normal except for mild hyperglycemia. Lithium levels were therapeutic. Serologic testing for infectious and autoimmune causes of cerebellar dysfunction, including tuberculosis, toxoplasmosis, human immunodeficiency virus, syphilis, anti-glutamic acid decarboxylase, anti-gamma-aminobutyric acid (GABA), and anti-immunoglobulin-like cell adhesion molecule 5, was negative. Paraneoplastic antibodies (anti-Hu, anti-Ri, anti-Yo) were also negative. Electromyoneurography showed no neuropathic findings. Brain MRI was performed one week after symptom onset using a 1.5-T scanner and included axial and sagittal T1-weighted, T2-weighted, fluid attenuated inversion recovery (FLAIR), and diffusion-weighted imaging/apparent diffusion coefficient sequences with adequate posterior fossa coverage. No abnormalities were detected, including within the cerebellar dentate nuclei, as shown in Figure 1. Given the close temporal relationship between metronidazole exposure and symptom onset, the drug was discontinued. Lithium therapy was continued without dose modification, and serial renal function and lithium levels remained stable. The patient's neurological symptoms gradually improved, and he regained independent ambulation with mild gait ataxia approximately one month after

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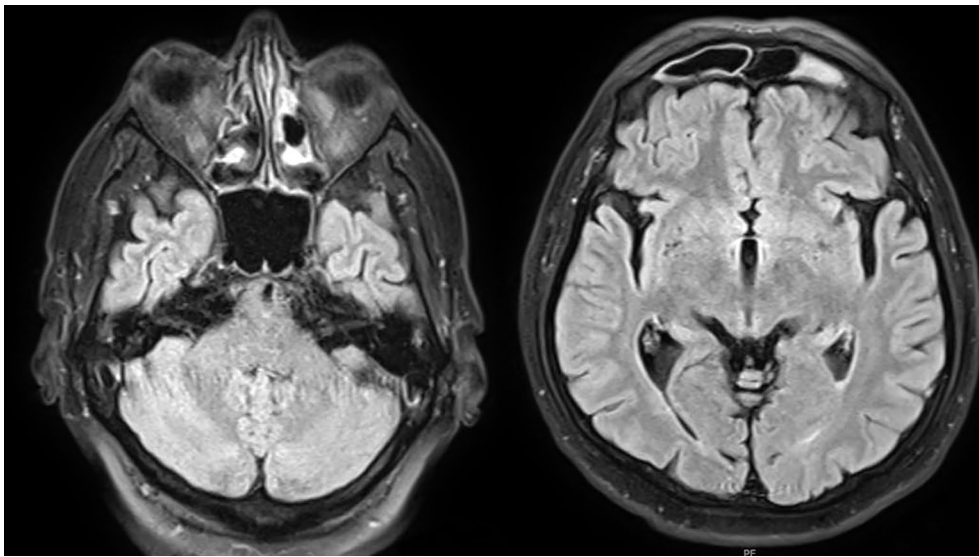


Figure 1. Axial FLAIR-weighted brain magnetic resonance imaging demonstrating no abnormal signal intensity in the brainstem or cerebellum.

FLAIR: Fluid attenuated inversion recovery.

cessation. Causality assessment using the Naranjo Adverse Drug Reaction Probability Scale yielded a total score of 6, corresponding to a probable association between metronidazole exposure and the observed cerebellar syndrome; this score was supported by a clear temporal relationship (+2), clinical improvement after drug discontinuation (+1), absence of reasonable alternative causes (+2), and prior conclusive reports in the literature (+1).^[2] A written informed consent was obtained from the patient.

The clinical manifestations of metronidazole neurotoxicity span a broad spectrum, including cerebellar and brainstem dysfunction, encephalopathy, optic neuropathy, peripheral neuropathy, and seizures, most of which improve after drug discontinuation.^[3] Peripheral neuropathy accompanies cerebellar dysfunction in nearly one-third of reported cases, highlighting the multifocal nature of toxicity.^[3] A large nested case-control study estimated the incidence of neurologic events to be 0.25%, though this likely underestimates true risk, as mild or atypical cases may go unrecognized.^[1]

The underlying pathophysiology remains incompletely understood. Proposed mechanisms include impaired neuronal RNA and protein synthesis, thiamine antagonism, altered GABAergic signaling, mitochondrial dysfunction, and free radical generation via catecholamine

interactions.^[3] Traditionally, toxicity has been associated with daily doses exceeding 2 g/day or prolonged cumulative exposure.^[4] However, many reports document toxicity at standard dosing and after short treatment durations, suggesting individual susceptibility contributes substantially. Systematic reviews indicate an average onset after 6-7 weeks of therapy, but earlier presentations, including symptoms appearing within days, have been reported.^[5] This variability underscores that dose and duration alone are unreliable predictors. In this case, the emergence of symptoms after only four days of therapy and a cumulative dose of 7.5 g is consistent with an early-onset presentation at lower-than-expected cumulative exposure within the reported clinical spectrum, reinforcing the notion that pharmacokinetics alone do not fully explain individual susceptibility. Moreover, the differential diagnosis warrants particular consideration of lithium-related neurotoxicity. Although lithium levels were therapeutic, reversible neurotoxicity has been described even within the therapeutic range. Furthermore, metronidazole has been reported to interact with lithium, potentially increasing neurotoxicity risk through pharmacokinetic or nephrotoxic mechanisms.^[6] In the present case, stable renal function, unchanged lithium dosing, and continued lithium therapy during recovery argue against primary lithium toxicity, although a facilitating interaction cannot be fully excluded.

Radiologically, the hallmark of metronidazole neurotoxicity is symmetric T2/FLAIR hyperintensity in the cerebellar dentate nuclei, often accompanied by abnormalities in the midbrain and splenium of the corpus callosum.^[7] Dentate nucleus involvement is helpful in differentiating toxicity from other cerebellar pathologies. However, delayed radiological evolution is documented: lesions may be absent early and appear only on follow-up imaging.^[5] Some patients, even those with severe symptoms, may exhibit a normal MRI.^[7] Accordingly, our findings are compatible with an early, imaging-negative stage, although the absence of follow-up imaging limits definitive conclusions.

Clinical outcomes vary, though reversibility is common. Patel et al.^[8] reported recovery within two weeks in most cases, whereas a systematic review by Sørensen et al.^[5] showed complete resolution in 56% and persistent deficits in 4%.^[8] Our patient's near-complete recovery within one month is consistent with the typically reversible course.

This case highlights several important points: metronidazole toxicity may occur at standard doses and short durations; MRI may be normal early in the disease; and prompt drug discontinuation is essential. Clinicians should maintain a high index of suspicion when new cerebellar symptoms arise during metronidazole therapy, even without risk factors or imaging abnormalities. Early recognition prevents progression and reduces unnecessary diagnostic investigations, though alternative etiologies must still be carefully excluded.

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REFERENCES

1. Daneman N, Cheng Y, Gomes T, Guan J, Mamdani MM, Saxena FE, et al. Metronidazole-associated neurologic events: A nested case-control study. *Clin Infect Dis* 2021;72:2095-100. doi: 10.1093/cid/ciaa395.
2. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 1981;30:239-45. doi: 10.1038/clpt.1981.154.
3. Sarna JR, Furtado S, Brownell AK. Neurologic complications of metronidazole. *Can J Neurol Sci* 2013;40:768-76. doi: 10.1017/s0317167100015870.
4. Kim E, Na DG, Kim EY, Kim JH, Son KR, Chang KH. MR imaging of metronidazole-induced encephalopathy: Lesion distribution and diffusion-weighted imaging findings. *AJNR Am J Neuroradiol* 2007;28:1652-8. doi: 10.3174/ajnr.A0655.
5. Sørensen CG, Karlsson WK, Amin FM, Lindelof M. Metronidazole-induced encephalopathy: A systematic review. *J Neurol* 2020;267:1-13. doi: 10.1007/s00415-018-9147-6.
6. Teicher MH, Altesman RI, Cole JO, Schatzberg AF. Possible nephrotoxic interaction of lithium and metronidazole. *JAMA* 1987;257:3365-6.
7. Altunışık E, Kurt EZS. Transient Encephalopathy with a single dose of oral metronidazole: A case report. *Turk J Neurol* 2021;27:82-4. doi: 10.4274/tnd.2020.47154.
8. Patel L, Batchala P, Almardawi R, Morales R, Raghavan P. Acute metronidazole-induced neurotoxicity: An update on MRI findings. *Clin Radiol* 2020;75:202-8. doi: 10.1016/j.crad.2019.11.002.