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Metronidazole-Induced Neurological Dysfunction: A Rare Side Effect of a Common Drug

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Abstract

Metronidazole is a commonly used antibiotic and antiprotozoal drug for the treatment of anaerobic and protozoal infections and is generally considered safe. However, prolonged or unmonitored use can lead to rare but serious neurological adverse effects, including cerebellar toxicity. We report a young male with an amoebic liver abscess who continued standard-dose metronidazole for five months without medical follow-up and presented with a subacute onset of gait ataxia, dysarthria, and severe painful sensory symptoms. Magnetic resonance imaging of the brain showed symmetrical T2-FLAIR hyperintensities involving the bilateral dentate nuclei, brainstem, and cerebellum, consistent with metronidazole-induced neurotoxicity. After discontinuation of the drug, cerebellar symptoms and MRI abnormalities resolved; however, painful sensory symptoms persisted. Nerve conduction studies revealed a diffuse axonal sensory neuropathy, suggesting irreversible peripheral nerve involvement. This case highlights the dual manifestation of reversible central nervous system toxicity and irreversible peripheral neuropathy due to prolonged metronidazole use and emphasizes the importance of early recognition, timely drug withdrawal, and close monitoring to prevent permanent neurological sequelae.

Keywords: Metronidazole; Neurotoxicity; Cerebellar ataxia; Peripheral neuropathy; MRI; Dentate nucleus.

Introduction

Metronidazole, a widely used antibiotic and antiprotozoal medication, is known for its efficacy in treating a variety of infections. However, its use can be associated with rare but potentially severe neurological complications, including cerebellar toxicity. Metronidazole-induced cerebellar toxicity is characterized by a spectrum of symptoms ranging from mild ataxia to severe neurologic impairment, often presenting as acute or subacute onset of gait disturbances, dysarthria, and tremors. Understanding the mechanisms underlying this toxicity, its clinical manifestations, and appropriate management strategies is crucial for healthcare professionals to recognize and effectively address this severe but potentially reversible side effect of this commonly used medication.

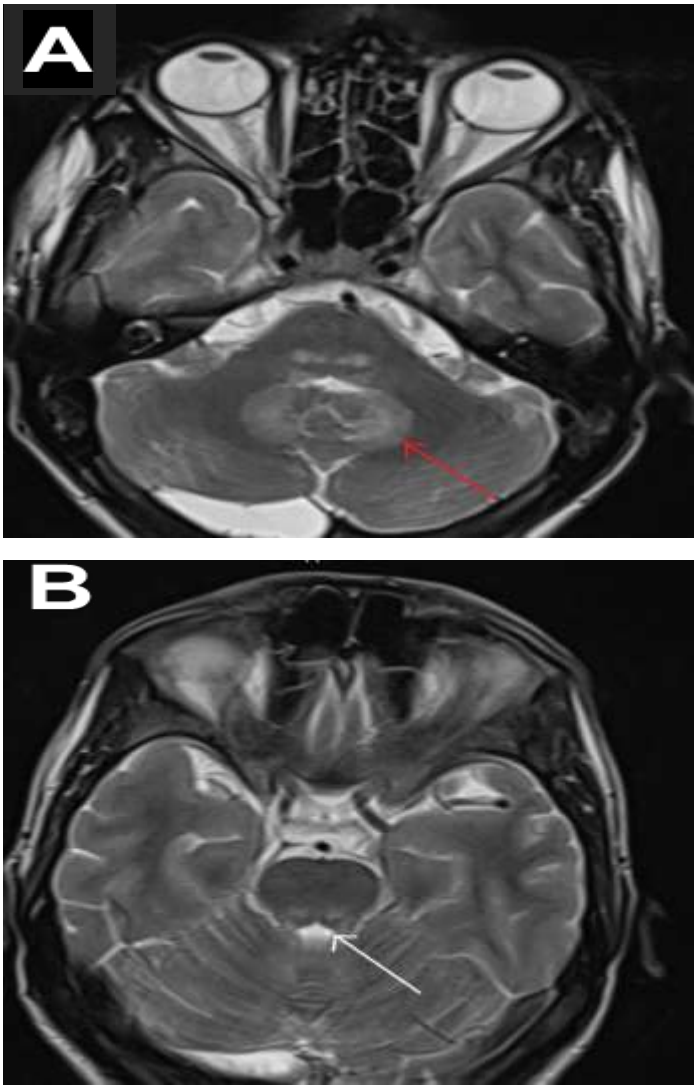
Case Description

A 32-year-old male with a history of chronic alcoholism was referred from the surgical outpatient department to the emergency unit due to complaints of subacute onset ataxia, dysarthria, and severe burning pain in both the upper and lower extremities. He reports that these symptoms have persisted for the past five days, progressively worsening to the extent that he has become bedridden. The patient was diagnosed with an amoebic liver abscess five months ago and underwent drainage of the abscess. He was prescribed an antiprotozoal agent, metronidazole, at a dosage of 400 mg every eight hours. However, he was lost to follow-up and subsequently presented to the hospital upon the emergence of new-onset symptoms. On examination, he had stable vital signs and

demonstrated coherent orientation to time, place, and person. A neurological assessment revealed a wide-based ataxic gait accompanied by cerebellar signs, including scanning speech, intentional tremors, multi-directional gaze-evoked nystagmus, dysmetria, and a rebound phenomenon.

The neurological manifestations were most consistent with a toxic–metabolic etiology. Accordingly, targeted evaluation for nutritional deficiencies, including vitamin B12, thiamine, and pyridoxine, as well as screening for heavy metal exposure (copper, lead, and mercury), was undertaken; all of which yielded normal results (Table-1). A brain CT scan was performed, revealing no abnormalities. Based on the patient's history and clinical examination, a provisional diagnosis of metronidazole-induced adverse effects was established, leading to the discontinuation of the medication. On the third day of admission, an MRI of the brain was performed, revealing areas of symmetrical T2/FLAIR hyperintensities involving the bilateral dentate nuclei of the cerebellum, the superior olivary nucleus of the midbrain, and the dorsal aspect of the pons and medulla (Figure A , area of hyperintensity involving the bilateral dentate nucleus , B, area of hyperintensity involving the dorsal aspect of the pons). These regions appeared isointense on T1 and hyperintense on T2/FLAIR, with some restriction noted on DWI, suggesting metronidazole-associated neuronal toxicity (Figure-1,2).

Figure A , area of hyperintensity involving the bilateral dentate nucleus , B, area of hyperintensity involving the dorsal aspect of the pons.



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The medication was withdrawn. On the seventh day of hospitalization, his cerebellar symptoms diminished significantly, particularly dysarthria and ataxia; however, the manifestations of peripheral neuropathy persisted. The patient was discharged on pregabalin (75 mg every 12 hours). Two weeks post-discharge, the patient exhibited no cerebellar signs or symptoms; however, he reported persistent aching pain, accompanied by tingling and numbness in both the upper and lower extremities. An electrodiagnostic evaluation was conducted, revealing universally diminished conduction velocities in the sural, common peroneal, median, ulnar, and radial nerves, indicative of axonal-type sensory neuropathy. The nerve conduction velocity assessment demonstrated a reduced amplitude of the compound muscle action potential (CMAP) and a similarly diminished amplitude of the sensory nerve action potential (SNAP) (Table-2). The patient also underwent a follow-up MRI of the brain, which revealed a resolution of the previously noted hyperintensities.

Table 1- Main biochemical investigations IF, immunofluorescence; IU, international unit; TSH, thyroid-stimulating factor

Test	Value	Reference	Unit of measure
Blood glucose fasting	74	100-125	mg/dL
HbA1C	5.1	4-5.6	%
TSH	2.28	0.70-6.4	microIU/dL
Cobalamin	440	180-914	pg/mL
Serum Folate	10	>5.38	ng/mL
Pyridoxal-5 -phosphate	32	12.60-45.20	microgm/L
Serum Calcium	9.86	8.8-10.60	mg/dl
Serum Potassium	3.95	3.5-5.10	milliEq/L
Serum Sodium	138	136-146	milliEq/L
Antinuclear antibodies IF	Negative	-	-
RA factor	5	<15	IU/mL
Anti-citrulline antibodies	0.3	<5	U/mL
Viral markers	Negative	-	-
Serum copper	80	70-140	microgm/dL
Serum zinc	75	75-291	microgm/dL
Serum selenium	23	23-190	microgm/L
Serum lead	3	<5	microgm/dL
Serum aluminum	8	<15	microgm/L

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Table -2 Nerve conduction study (NCS) parameters in the patient: CMAP,Compound Muscle Action Potential;SNAP,Sensory Nerve Action Potential; CV,Conduction Velocity; mV,millivolt; microV microvolt; ms,millisecond; m/s,meters per second

Nerve	Parameter	Right	Left	Normal	Interpretation
Median motor	CMAP (mV)				Axonal
Median sensory	SNAP (microV)	Decreased	Decreased	>15	Sensory axonal loss
Ulnar motor	CMAP (mV)	Decreased	Decreased	>6	Axonal
Ulnar sensory	SNAP (microV)	Decreased	Decreased	>10	Sensory axonal loss
Sural	SNAP (microV)	Absent	Absent	>6	Severe sensory axonal loss
Peroneal	CMAP (mV)	Decreased	Decreased	>2	Axonal
Tibial	CMAP (mV)	Markedly decreased	Markedly decreased	>2	Severe axonal
Sensory CV	m/s	Normal	Normal	>45	No demyelination
F -wave latency	M/s	Normal	Normal	<55 ms (upper limb) <60 ms (lower limb)	No proximal demyelination

In light of its applications as both an antibiotic and an anti-protozoan agent, metronidazole is extensively used in the treatment of medical and surgical patients. This pharmaceutical compound is FDA-approved for the management of protozoal infections, including Trichomonas vaginalis, Entamoeba histolytica, Giardia lamblia, Blastocystis, and Balantidium coli. It is also FDA-approved to treat anaerobic bacterial infections caused by Bacteroides species, Fusobacterium species, Clostridium species, Gardnerella vaginalis, Helicobacter pylori, Prevotella species, Porphyromonas species, and Biophilia Wadsworth [1]. It is 2-methyl-5-nitroimidazol-1-ethanol which is in an inactive state and turns to a metabolically active form upon reaching the target. After entering the organism, it inhibits protein synthesis by interacting with DNA and causes a loss of helical DNA structure and strand breakage. Therefore, it causes cell death in susceptible organisms [2].

Metronidazole is associated with a broad spectrum of adverse effects, most commonly involving the gastrointestinal and nervous systems. Frequently reported manifestations include nausea, vomiting, diarrhea, metallic taste, dizziness, headache, and mucocutaneous irritation. Infectious complications such as candidiasis and upper respiratory tract infections have also been described. . A disulfiram-like reaction may occur when metronidazole is consumed concurrently with alcohol, manifesting as flushing, tachycardia, palpitations, nausea, and vomiting; therefore, alcohol avoidance is recommended during therapy and for up to two weeks after drug discontinuation. Rarely, there are reports of transient leukopenia and neutropenia as well [3,4].However, the occurrence of neurologic

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symptoms, particularly peripheral neuropathy that is prevalent in the lower limbs, during prolonged therapy with metronidazole is rarely reported [5,6].

Metronidazole has good cellular penetration and is believed to penetrate CSF and the central nervous system easily [7].It is also comparatively safe when used at appropriate dosages, but it can produce peripheral neuropathies and cerebellar dysfunction, especially at dosages exceeding 2 g/day for prolonged periods [8,9].This neuropathy is a known but less common complication of metronidazole therapy, often occurring after prolonged use. In a retrospective analysis of thirty-six case reports, peripheral neuropathy was a common adverse effect of metronidazole when patients received over 42 g total in over 4 weeks of treatment [6]. Electrodiagnostic evaluation confirmed axonal sensory neuropathy with universally decreased conduction velocities across multiple nerves. The neuropathic symptoms persisted even after cessation of metronidazole, indicating irreversible damage to peripheral nerves. The exact mechanism of metronidazole- induced hello peripheral neuropathy is unclear, but it is believed to involve direct neurotoxic effects on peripheral nerves, possibly through disruption of axonal transport or mitochondrial dysfunction.

It is essential to rule out other conditions that affect the brainstem and cerebellum, such as demyelinating diseases and toxic and metabolic encephalopathies. Wernicke's encephalopathy, which also commonly affects the dentate nuclei, is the most significant condition that can mimic metronidazole-induced cerebellar toxicity. Other extremely rare causes for dentate T2-signal changes include methyl bromide toxicity, maple syrup urine disease, and enteroviral encephalomyelitis [10,11].However, there was no history of acute binge of alcohol and symptoms resolve after stopping metronidazole. Chronic alcohol use can exacerbate the neurotoxic effects of metronidazole and increase susceptibility to neurological complications.

Management of metronidazole-induced neurological toxicity involves prompt recognition and discontinuation of the offending drug. In cases of reversible cerebellar toxicity, symptoms typically improve within days to weeks after cessation of metronidazole. However, irreversible peripheral neuropathy may require long-term symptomatic management with medications such as pregabalin, as demonstrated in this case.

Conclusion

This report underscores the importance of considering metronidazole-induced neurological complications in patients presenting with subacute onset of cerebellar dysfunction or peripheral neuropathy, especially in those with prolonged or high-dose exposure to the drug. Healthcare providers should be vigilant in monitoring patients on metronidazole therapy and promptly address any neurological symptoms to prevent irreversible damage and improve patient outcomes.

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