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Case Report

Internal Medicine Section

Long-term Implication of Metronidazole Induced Reversible Cerebellar Toxicity and Peripheral Neuropathy- A Case Report

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ABSTRACT

Metronidazole Induced Encephalopathy (MIE) is rare and serious central nervous system toxicity. A 40-year-old male, on long-term self treatment with metronidazole (cumulative dose: 102 gm) presented with dysarthria, nystagmus, unsteadiness, and numbness in both legs. A Magnetic Resonance Imaging (MRI) scan of the brain revealed a symmetric hyperintensity in both the dentate nuclei of cerebellum on both T2 weighted and Fluid-Attenuated Inversion-Recovery (FLAIR) imaging. Discontinuation of metronidazole resulted in resolution of the imaging findings and clinical improvement occurred within one month. Metronidazole-induced neurotoxicity should be considered in patient who present with cerebellar symptoms and characteristic lesion on MRI in close temporal relation with metronidazole intake and drug should be discontinued to prevent permanent neurological deficit.

Keywords: Central nervous system, Dentate nuclei, Encephalopathy, Magnetic resonance imaging

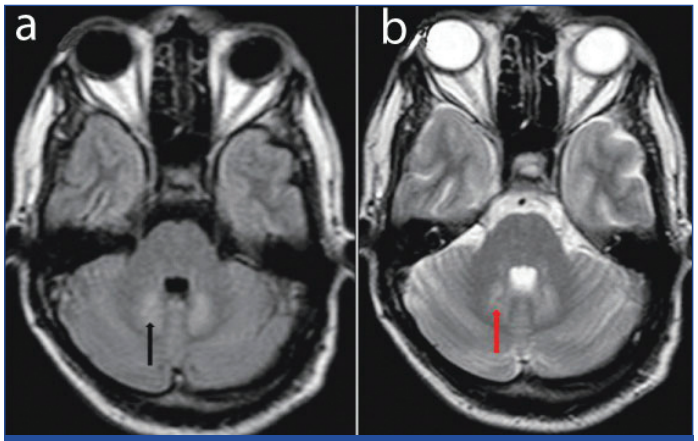
CASE REPORT

A 40-year-old male presented in the Emergency Department of a tertiary care center with complaints of sudden onset of slurring of speech, unsteadiness while walking, vomiting and numbness in both legs and arms for three days. The patient was admitted to the same hospital six weeks back with a complaint of fever and right upper quadrant abdominal pain since two weeks. He was diagnosed with amoebic liver abscess and was treated with intravenous metronidazole 2500 mg/day in divided doses for 10 days with significant improvement in symptoms. He was discharged with oral metronidazole 800 mg thrice a day for 10 more days, but he continued to take oral metronidazole for more than four weeks till readmission without any consultation and follow-up. No history of any addiction, hypertension, diabetes mellitus, and head injury was present.

On general physical examination, the patient was alert, afebrile, vitals were within normal limits, without any evidence of pallor, icterus, cyanosis, clubbing, oedema feet, or lymphadenopathy. Central Nervous System (CNS) examination revealed dysarthria, horizontal nystagmus, dysdiadochokinesia and wide-based ataxic gait without any motor deficit. Sensory examination revealed diminished pain and temperature sensation in both hands and feet and altered joint position sense in small joints of both feet. The rest of the CNS examination including fundoscopy was unremarkable.

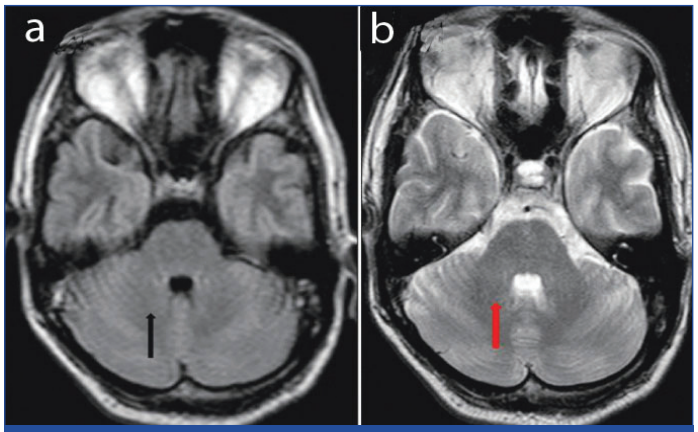
The patient underwent MRI brain which showed an altered signal intensity in bilateral dentate nuclei of cerebellum appearing hyperintense on both T2 weighted and FLAIR imaging while hypointense in T1 weighted images with mild restricted diffusion [Table/Fig-1a,b]. The radiologist suggested the cause to be toxic encephalopathy. Complete blood count, plasma glucose, liver function tests, renal function test were within normal ranges. Human Immunodeficiency Virus (HIV), Hepatitis B surface Antigen (HBsAg) and Hepatitis C serology were negative. Vitamin B12, folate levels, and thyroid function tests were within normal limits. Cerebrospinal Fluid (CSF) examination was unremarkable. Electroencephelogram (EEG) was unremarkable. Nerve conduction study revealed sensory axonal affection of bilateral sural and ulnar nerves.

Based on the clinical picture, characteristic MRI findings and temporal relation with metronidazole intake, a diagnosis of metronidazole induced cerebellar toxicity and peripheral neuropathy was made. Abdominal ultrasound revealed liquefied liver abscess and almost 250 mL anchovy sauce abscess was aspirated percutaneously guided by ultrasound. The patient was treated symptomatically with intravenous fluid, antiemetic, antihistaminic, multivitamins and metronidazole was withdrawn which resulted in gradual improvement of symptoms. On day eight of admission, the patient was discharged with advice of regular follow-up.



[Table/Fig-1]: a) Axial T2-weighted; and b) Fluid-attenuated inversion-recovery image showing characteristic hyperintense signal in bilateral dentate nuclei.

The patient was followed-up after four weeks and reported gradual improvement in numbness in his extremities. Repeat MRI brain revealed complete resolution of lesions of dentate nuclei [Table/Fig-2a,b].



[Table/Fig-2]: a) Axial T2-weighted; and b) Fluid-attenuated inversion-recovery image showing resolution of the hyperintense signal in bilateral dentate nuclei 1 month later.

DISCUSSION

Prolonged use of metronidazole may produce neurological toxicity in the form of encephalopathy, cerebellar toxicity, seizure and neuropathy. Metronidazole induced peripheral neuropathy is predominantly sensory and usually gets resolved partially or completely after discontinuation of drug [1]. Metronidazole Induced Encephalopathy (MIE) is a very rare but is a serious adverse effect of metronidazole [2].

The pathophysiology of metronidazole induced neurotoxicity is not well-known. It has been proposed that metabolites of metronidazole may inhibit protein synthesis via binding to Ribonucleic Acid (RNA), and finally result in axonal degeneration [3]. Metronidazole may modulate the Gamma Aminobutyric Acid (GABA) receptor within the vestibular and cerebellar systems [4]. Metronidazole is structurally similar to the thiazole precursor of thiamine and could thereby lead to a reduction in thiamine absorption by acting as a thiamine analog [5]. Metronidazole induced acute neurotoxic effects are possibly due to axonal swelling because of increased water content. Furthermore, possible mechanism of neurotoxicity is mild reversible localised ischemia due to vascular spasm [6].

A recent review reported that the most common clinical manifestations of MIE are dysarthria, limb dyscoordination, gait instability, and altered consciousness [7]. Various risk factors reported with metronidazole induced neurotoxicity are uremia, hepatic dysfunction, and alcoholism [8]. According to a recent review, the duration of treatment with metronidazole before the appearance of CNS toxicity is variable ranging from 3 days to 8 years (average 101.6 days), and cumulative doses range from 5 g to 2000 g (average 125.7 gm) [7]. In this case, the total dose of metronidazole that the patient received was 102 gm and the total duration was 42 days. [Table/Fig-3] shows the clinical manifestations, cumulative dose and duration of metronidazole intake, neuroimaging findings and outcome of selected cases of previously reported MIE [1,9-14].

Several characteristic MRI findings of MIE have been reported. Bilateral symmetrical T2-weighted hyperintense lesions are characteristically seen in cerebellar dentate nuclei. The midbrain, dorsal pons, dorsal medulla, and corpus callosum can also be affected. Rarely, lesions may affect the inferior olivary nucleus and the white matter of the cerebral hemispheres. Lesions are typically bilaterally symmetrical in metabolic encephalopathy [1]. The location of T2-weighted hyperintense lesions in our patient is consistent with the reported distribution of the most frequently affected regions. A recent review concluded that the lesions of the cerebral white matter may correlate with a worse prognosis [7]. Sometimes, lesions of the dentate nuclei may not be present initially but show on repeat-imaging. Therefore, serial imaging may be indicated when diagnostic uncertainty remains [15].

The differential diagnoses of symmetrical T2 hyperintensity in dentate nuclei are multiple sclerosis, disseminated encephalomyelitis, methyl bromide intoxication, enteroviral encephalomyelitis and maple syrup urine disease [16].

MIE should be considered in any patient who presents with cerebellar deficits with or without altered sensorium and peripheral neuropathy in close temporal relation to metronidazole intake. According to recent systemic review, almost one-third of patients were simultaneously present with polyneuropathy and making the clinical picture more complex [7]. Also, a history of exposure may not be immediately available in patients with altered sensorium. If the condition is suspected, the drug must be immediately withdrawn and MRI brain performed. Nerve conduction studies generally show an axonal sensory or sensorimotor polyneuropathy [7]. Patients who receive larger total doses of metronidazole may be at higher risk of peripheral neuropathy, but most cases of metronidazole-induced polyneuropathy recover with time [17].

Author and study year	Age (years)/ Gender	Indication	Clinical presentation	Cummulative dose and duration of metronidazole	MRI brain findings	Outcome
Thakkar N et al., (2016) [1]	32/M	Multiple liver abscesses	Recurrent seizures, burning feet and altered sensorium	Total 39.3 g over 42 days	T2W hyper intensities in splenium and bilateral dentate nuclei (Left>Right)	Symptoms resolved; partial resolution on repeat MRI at 10 days
Woodruff BK et al., (2002) [9]	62/M	Multiple epidural abscesses	Mild ataxia and dysarthria	Total 60 g over one month	Increased signal intensity on brain MRI	Symptoms resolved; MRI abnormalities resolved
Woodruff BK et al., (2002) [9]	74/M	Intra-abdominal abscesses	Ataxia and dysarthria	Total 42 g over four weeks	Increased signal intensity on brain MRI	Symptoms resolved; lesions resolved on repeat MRI
Seok JI et al., (2003) [10]	74/F	Rectovaginal fistula due to Crohn's disease	Dysarthria, dysphagia, gait disturbances, ataxia	Total182 g over six months	High-signal intensities on brain MRI	Symptoms resolved; lesions nearly completely resolved on repeat MRI
Ito H et al., (2004) [11]	54/F	*Helicobacter pylori* infection	Speech disturbance and gait unsteadiness	Total 66 g over 66 days	Increased signal intensities in cerebellum on brain MRI	Symptoms resolved; Complete resolution on repeat MRI at three months
Patel K et al., (2008) [12]	63/M	Submental abscess and mandibular osteomyelitis	Ataxia, recurrent fall and horizontal nystagmus	Total 42 g over six weeks	T2-hyperintense symmetric signal in cerebellum	Symptoms resolved; Complete resolution on repeat MRI at six weeks
Bottenberg MM and Hegge KA (2011) [13]	55/M	Recurrent diarrhea	Ataxia, dysarthria, vertigo, nausea, and vomiting	Total 548 g over two years	Increased signal intensities in dentate nuclei, dorsal pons, and splenium	Symptoms resolved; Complete resolution on repeat MRI at 20 days
Hou W et al., (2019) [14]	59/M	Intra-abdominal infection	Dysarthria, dysphagia, right sided weakness	Total 53 g over six weeks	Symmetrical T2W hyper intensities in the dentate nuclei and dorsal medulla	Neurological deficit improved progressively
Present case	40/M	Amoebic Liver abscess	Dysarthria, nystagmus, unsteadiness, numbness in legs	Total 102 g over 42 days	Symmetrical T2/FLAIR hyper intensity in dentate nuclei	Symptoms resolved; Complete resolution on repeat MRI after four weeks

[Table/Fig-3]: Summary of Selected Cases of Metronidazole-Induced Encephalopathy [1,9-14].

CONCLUSION(S)

Metronidazole induced neurotoxicity is a rare but serious complication with characteristic MRI features in form of bilateral symmetrical T2-weighted hyperintense lesions in cerebellar dentate nuclei. Early recognition of these imaging findings with immediate cessation of the drug improves prognosis and prevents irreversible neurological damage.

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