Short-Course Self-Medication of Metronidazole Leading to Acute Toxic Encephalopathy and Ataxia

Sir,

Metronidazole, a 5-nitroimidazole, is a widely prescribed antimicrobial, believed to be generally safe and primarily used to treat infections caused by susceptible anaerobic organisms and parasites. It is a cost-effective drug with favorable pharmacokinetic properties and minor adverse effects, most commonly nausea, dry mouth, vomiting, and diarrhea. The most common neurological adverse effect is peripheral neuropathy.[1] Metronidazole-induced encephalopathy (MIE) with cerebellar toxicity is a rare but a serious adverse effect with classic findings on magnetic resonance imaging (MRI), which resolve rapidly after discontinuation of drug.

We saw an 18-year-old medical student suffering from fever, vomiting, and diarrhea 3 days before presenting to us. He had started self-medication on 1.2 g/day of oral metronidazole. He developed acute-onset ataxia with vertigo after 2 days and was admitted to a nearby hospital the next day in view of altered sensorium. His MRI brain done there was reported to show features suggestive of acute cerebellitis with brainstem involvement. He was being treated there as a case of acute cerebellitis. He was transferred to us the same day in stuporous state and was immediately put on mechanical ventilation. There was no history of seizures, headaches, history suggestive of cranial nerve involvement, dysarthria, dysphagia, weakness or sensory loss, bladder or bowel disturbances, or history of similar complaints in the past. On presentation, he was stuporous, wincing, and withdrawing to deep painful stimuli bilaterally. His pupils were left 3 mm and right 2 mm, both briskly reactive to light. Doll's eye movements were elicitable, and cough and gag reflexes were present. Deep tendon jerks were 2 + bilaterally in the upper and lower limbs. Bilateral plantar responses were extensor. MRI brain showed bilaterally symmetrical hyperintensities on T2-weighted [Figure 1] and fluid-attenuated inversion recovery (FLAIR) sequences [Figure 2] in the bilateral cerebellar dentate nuclei, medulla, dorsal pons, and midbrain tegmentum. There was restricted diffusion in bilateral cerebellar dentate nuclei as iso- to slightly hyperintense signal noted on diffusion-weighted imaging with isointense signal in apparent diffusion coefficient sequence [Figure 3].

Complete blood count, renal function test, serum electrolytes, and blood sugar levels were within normal ranges. Liver function test including serum total bilirubin (0.9 mg/dL), aspartate transaminase (27 U/L), alanine aminotransferase (19 U/L), alkaline phosphatase (52 U/L), gamma-glutamyl transferase (75 U/L), prothrombin time (13.5 s), serum albumin (4.5 g/dL), and total proteins (6.1 g/dL) were normal. Serum ammonia level was 28 μg/dL. HIV, HBsAg, anti-hepatitis C virus, and dengue NS1 antigen tests were negative. Urine examination was found to be normal. His blood cultures were sterile. Vitamin B12 (532 ng/mL) and folate levels (8 ng/mL), and serum copper (131 μg/dL) were normal. Thyroid function tests, antithyroid peroxidase (6 IU/mL), and antithyroglobulin (14 ng/mL) were within normal limits. Antinuclear antibodies, extractable nuclear antigen profile, anti-dsDNA, RA factor, c-anti-neutrophil cytoplasmic antibodies (ANCA), and p-ANCA were negative. Cerebrospinal fluid (CSF) examination revealed cell count of two cells (mononuclear), proteins 30 mg/dL, and sugar 61 mg/dL. It was negative for gram stain, ZN stain, India ink, ADA, TORCH IgM/IgG, herpes simplex virus (HSV), varicella zoster virus, and enteroviral polymerase chain reaction (PCR), and cryptococcal antigen, oligoclonal bands, and TB GeneXpert. CSF bacterial, mycobacterial, and fungal cultures were negative. Abdominal ultrasound was normal. Electroencephalogram showed generalized slowing on the first day which was normalized 4 days later. Nerve conduction studies were done to look for concurrent toxic neuropathy; however, it was normal. CSF analysis showed normal cell count, biochemistry, and was negative for TORCH IgM/IgG, HSV, and enteroviral PCR, other infective etiology, and oligoclonal bands.

Differential diagnoses kept were infective, MIE, demyelination (including acute disseminated encephalomyelitis, multiple sclerosis, neuromyelitis optica spectrum disorders), Wernicke's

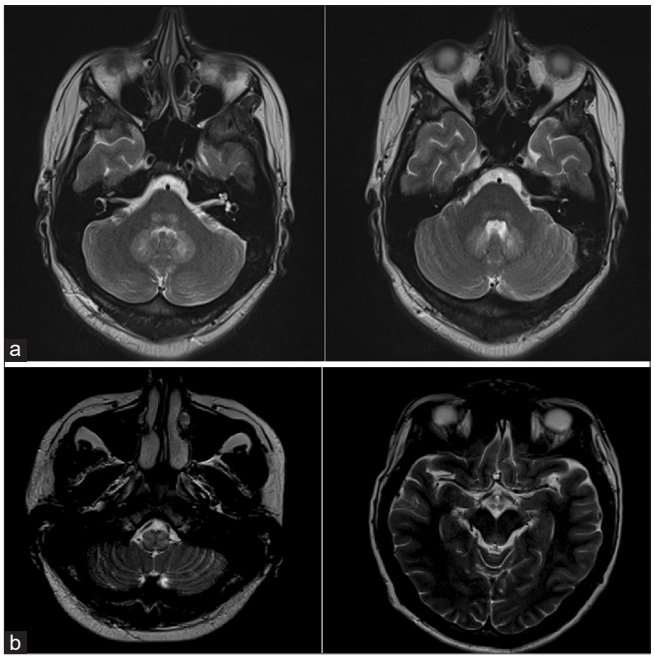

Figure 1: (a) MRI T2w images of brain showing symmetrical areas of hyperintensities in the bilateral cerebellar dentate nuclei and dorsal Pons. (b) MRI T2w images of brain showing symmetrical areas of hyperintensities in the bilateral bilateral Medulla and dorsal midbrain

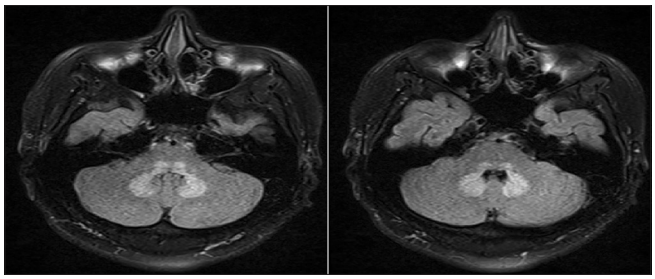

Figure 2: MRI FLAIR images of brain showing symmetrical areas of hyperintensities in the bilateral cerebellar dentate nuclei

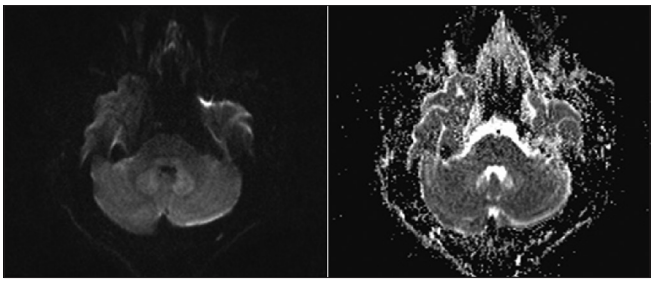

Figure 3: Bilateral cerebellar dentate nuclei showing restricted diffusion as iso to slightly hyperintense signal noted on the DWI, with isointense signal in ADC

encephalopathy, and Sarcoidosis. Patient's clinical presentation and MRI images were consistent with MIE. To develop encephalopathy with cerebellar toxicity within only 2 days and documented cumulative dose of only 2.4 g was unusual, although consistent with available literature.[2] Immediate discontinuation of metronidazole, supportive management including physiotherapy with gait training led to gradual improvement in a week. He was discharged after 2 weeks, in conscious oriented state, had normal speech, was ambulatory without any ataxia, and had only mild in-coordination of both hands.

Metronidazole is an antimicrobial and antiprotozoal with broad usage in medical and surgical patients. CNS adverse effects can range from ataxia, encephalopathy, dysarthria, and seizures to aseptic meningitis. They usually occur with prolonged therapy and generally resolve over a period of 2–8 weeks. However, peripheral neuropathy may persist for months to years.

The exact incidence of MIE is unknown. It is postulated that metronidazole and its metabolites bind to neuronal RNA and inhibit protein synthesis resulting in reversible axonal swelling.[3] Other proposed mechanisms involve modulation of gamma-aminobutyric acid receptors within the cerebellar and vestibular systems[4] and vascular spasm that could produce mild reversible localized ischemia.[5] Patients who already have risk factors such as alcoholism, severe hepatic dysfunction, and uremia are more prone to develop toxicity.[2] It is not dependent on the dosage and duration of usage and has no significant difference between the oral and intravenous routes of administration.[6] The duration of treatment before appearance of CNS toxicity is variable (1 week to 6 months),[6] and cumulative doses range from 25 to 110 g.[7] However, it can happen even with short-course therapy.[2,8] Kuriyama *et al.*[2] did a systematic review of 64 patients with MIE, in which 26% of the patients had taken the drug for less than a week and 11% had taken it for less than 3 days, with lowest dose of 0.25 g in a patient. Our patient had received 2.4 g of metronidazole over 2 days.

CSF analysis is usually unrevealing.[9] MRI brain shows T2/FLAIR hyperintensities without contrast enhancement characteristically in dentate nuclei, sometimes resembling a headphone and is called headphone sign.[10] However, midbrain, dorsal pons, dorsal medulla, and corpus callosum can also be affected.[11] The fourth cerebral ventricle gets sandwiched by bilateral cerebellar dentate nuclei, taking the form of a "chestnut," which has thus been termed the "chestnut sign."[12]

Wernicke's encephalopathy is the biggest mimicker of MIE, primarily because it also has high propensity for the dentate nuclei. Clinical findings and history of alcoholism are usually evident in these patients. Causes of dentate nuclei affection are physiological dentate calcification and Fahr's syndrome, inflammatory and infectious diseases, drug and toxin-induced (metronidazole, cycloserine and isoniazid toxicity, methyl bromide poisoning), neurodegenerative diseases, and leukodystrophies.[13]

Discontinuing metronidazole is the primary treatment. There has been no evidence of usefulness of steroid therapy for MIE. Most patients recover rapidly after stopping the drug with resolution of abnormal MRI lesions. Follow-up imaging is usually unnecessary once the clinical signs and symptoms have resolved,[5] and thus it was not repeated in our patient before discharge.

In our case, characteristic MRI brain findings and reversibility of symptoms following withdrawal of metronidazole confirmed the case as MIE. MIE should be considered in any patient receiving metronidazole therapy, who presents with acute to subacute onset cerebellar features, brainstem involvement, and altered sensorium. Our case highlights and provides a novel message that though MIE is more common with long-term usage of metronidazole, there is a need to keep high index of suspicion even with a very short course, after ruling out other obvious causes. MRI should be performed for definitive diagnosis, and findings of bilateral T2/FLAIR hyperintensities of the dentate nuclei are characteristic. Recognizing the imaging pattern is important as discontinuing metronidazole can result in rapid clinical improvement.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

Yatin Sagvekar, Virti Shah, Anshu Rohatgi, Neha Pandita, Rahul Sharma, Rajeswari Rajan, Dhrumil Shah

Department of Neurology, The Ganga Ram Institute for Post-Graduate Medical Education and Research, New Delhi, India

Address for correspondence: Dr. Anshu Rohatgi, 1242A, Neurology Office, Sir Ganga Ram Hospital, Old Rajinder Nagar, New Delhi - 110 060, India.
E-mail: yatin.sagvekar@gmail.com

References
1. Coxon A, Pallis CA. Metronidazole neuropathy. J Neurol Neurosurg Psychiatry 1976;39:403-5.
2. Kuriyama A, Jackson JL, Doi A, Kamiya T. Metronidazole-induced central nervous system toxicity. Clin Neuropharmacol 2011;34:241-7.
3. Bradley WG, Karlsson IJ, Rassol CG. Metronidazole neuropathy. Br Med J 1977;2:610-1.
4. Cecil KM, Halsted MJ, Schapiro M, Dinopoulos A, Jones BV. Reversible MR imaging and MR spectroscopy abnormalities in association with metronidazole therapy. J Comput Assist Tomogr 2002;26:948-51.
5. Thakkar N, Bhaarat, Chand R, Sharma R, Mahavar S, Srivastava S, *et al*. Metronidazole induced encephalopathy. J Assoc Physicians India 2016;64:72-4.
6. Agarwal A, Kanekar S, Sabat S, Thamburaj K. Metronidazole-induced cerebellar toxicity. Neurol Int 2016;8:6365.
7. Puri V. Metronidazole neurotoxicity. Neurol India 2011;59:4.
8. Dogra PM, Bhatt AK, Agarwal SK, Bhowmik D. Short-course metronidazole-induced reversible acute neurotoxicity in a renal transplant recipient. Saudi J Kidney Dis Transpl 2018;29:1511-4.
9. Iyer RS, Chaturvedi A, Pruthi S, Khanna PC, Ishak GE. Medication neurotoxicity in children. Pediatr Radiol 2011;41:1455-64.
10. Sudan YS, Garg A, Gupta R, Bansal AR. Headphone sign: Metronidazole-induced encephalopathy. Neurol India 2016;64:1374-6.
11. Cecil KM, Halsted MJ, Schapiro M, Dinopoulos A, Jones BV. Reversible MR imaging and MR spectroscopy abnormalities in association with metronidazole therapy. J Comput Assist Tomogr 2002;26:948-51.
12. Furukawa S, Yamamoto T, Sugiyama A, Ohira K, Aotsuka Y, Koide K, *et al*. Metronidazole-induced encephalopathy with contrast enhancing lesions on MRI. J Neurol Sci 2015;352:129-31.
13. Khadilkar S, Jaggi S, Patel B, Yadav R, Hanagandi P, Amaral LFD. A practical approach to diseases affecting dentate nuclei. Clin Radiol 2016;71:107-19.

Submission: 27.01.2019 **Revision:** 07.03.2019
Acceptance: 18.03.2019 **Published:** 25.10.2019

DOI: 10.4103/aian.AIAN_43_19