Case Report

Metronidazole-induced Cerebellar Neurotoxicity

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Abstract

Unintentional overuse of commonly prescribed medications can prove catastrophic. A 30-year-old man presented with difficulty in speaking and walking since 10 days. Examination revealed ataxic gait and bilateral cerebellar signs. During a recent admission for amoebic liver abscess, he was managed with the percutaneous aspiration of abscess and metronidazole which he continued for more than 2 weeks. During the current presentation, brain imaging showed confluent hypodensities in the bilateral dentate nucleus suggestive of metronidazole toxicity. Two weeks after discontinuation of the offending agent, the patient improved clinically with complete radiological resolution of lesions.

Keywords: Amebic liver abscess, cerebellar toxicity, metronidazole, neurotoxicity, overuse, toxicity

Introduction

Metronidazole is a nitroimidazole and is the mainstay drug to treat a variety of common anaerobic infections. Side-effect profile includes common gastrointestinal complaints such as nausea, vomiting, diarrhea, abdominal pain, and sometimes diffuse rash over the skin. Neurological adverse effects usually are peripheral; however, rarely, central neurotoxicity features such as gait imbalance, difficulty in speech, sensory form of peripheral neuropathy, and encephalopathy have also been reported.[1] Predilection to involve dentate nucleus, dorsal part of pons, midbrain, splenium of corpus callosum, and medulla has been found in imaging of the patients found to have metronidazole-induced neurotoxicity (MIN).[2] Herein, we report a case of a young man who presented with cerebellar signs after excessive intake of metronidazole prescribed for treatment of amebic liver abscess, with dentate nucleus lesions on imaging. Our patient improved clinically within 3 days of cessation of the offending drug with resolution of lesions on imaging as well.

Case Presentation

A 30-year-old man, assistant in an account's firm, developed progressive slurring of speech and swaying while walking, 7–10 days before he visited the emergency department. The patient complained of the swaying of trunk and difficulty in maintaining balance while walking. His wife had also noticed tremors in the neck whenever he used to get up from lying down position. He also reported loss of work hours as he faced difficulty in holding up pen and writing due to intentional tremors. He denied heavy alcohol consumption, recent toxin exposure, fever, rash, trauma, or vaccination. His past medical history revealed an admission 6 weeks ago with a diagnosis of amoebic liver abscess. During hospitalization percutaneous aspiration of the abscess was done and he was discharged with prescription of oral metronidazole 800 mg thrice daily for 3 weeks.

At presentation, he had a blood pressure of 100/60 mm of Hg, pulse rate of 82 per minute, temperature 37°C and saturation 98% while breathing room air and random blood sugar of 107 mg/dL. On examination, the patient was well oriented and had mild right hypochondrial tenderness. The findings of cranial nerves, motor, and sensory examination were normal. He had bilateral

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cerebellar signs manifested as staccato speech, neck titubation, ataxia, dysdiadochokinesia, bilateral pendular knee jerk (right>left), and impaired coordination in all four limbs. The finding of rest of the systemic examination was unremarkable.

In this setting of acute onset ataxia and dysarthria with positive cerebellar signs, our possible diagnosis included metabolic encephalopathy, central nervous system (CNS) infections, cerebellar abscess, posterior circulation stroke, substance abuse/withdrawal, and drug toxicity. Fundus examination was normal without any disk edema or atrophic changes.

Routine investigations revealed a normal profile except for anemia (hemoglobin 8.4 g/dL). Renal and liver functions were normal except for raised aspartate transaminase 72 U/L (AST normal range 10–40 U/L) and alkaline phosphatase 265 U/L (ALP normal range 30–150 U/L). Viral markers were nonreactive. Blood, urine, and abscess pus cultures were sterile. Vitamin B12 was in the normal range. Ultrasonography of abdomen was suggestive of the enlarged liver with a size of 15.5 cm with large heterogeneously enhancing hypoechoic well-defined lesion measuring 11 cm × 9.8 cm × 11.9 cm in the right lobe of liver with predominant liquefied contents. It was managed with single-time percutaneous aspiration.

Upon re-evaluation of history, it was discovered that the patient had inadvertently continued tablet metronidazole for an additional 2 weeks of prescribed duration. Till the time of readmission, he had consumed a cumulative dose of 108 g of metronidazole. Magnetic resonance imaging (MRI) brain was contraindicated due to an incompatible left forearm implant. Noncontrast CT (NCCT) showed confluent hypodensities in the bilateral dentate nucleus [Figure 1].

Taking into consideration excess metronidazole use and specific pattern of lesion on head imaging patient was identified as a case of MIN. Nerve conduction studies showed evidence of sensory-motor polyneuropathy, predominantly affecting the lower limbs and axonal neuropathy. Sensory nerve action potential (SNAP) of bilateral lower limb was absent and had decreased amplitude in upper limb. Compound motor action potentials (CMAPs) of bilateral LL/UL were normal and *F* waves were normal.

The offending drug was discontinued immediately and clinical improvement was seen within 3 days of cessation. Repeat imaging performed after 2 weeks (16 days) showed almost absolute resolution of dentate nucleus hypodensities previously detected [Figure 2]. The patient was discharged home with a minimal burning sensation in both feet and imbalance while walking. These symptoms were followed over the telemedicine outpatient department (OPD). The patient reported gradual improvement in his symptoms and was able to resume his job as before without any major difficulties. Timeline of events is described in Figure 3.

Discussion

Metronidazole is used in infections with *Entamoeba histolytica*, *Giardia lamblia*, *Helicobacter pylori*, *Clostridium difficile*, and anaerobic organisms.[3] Metronidazole is neurotoxic. CNS toxicity may present as cerebellar dysfunction (75%), altered mental status (33%), and seizures (13%). Nystagmus, gait imbalance, difficulty in speech, and abnormal finger-to-nose tests were common abnormalities.[4] Drugs such as valproate, carbamazepine, lithium, phenytoin, tacrolimus, cytarabine, cyclosporine,

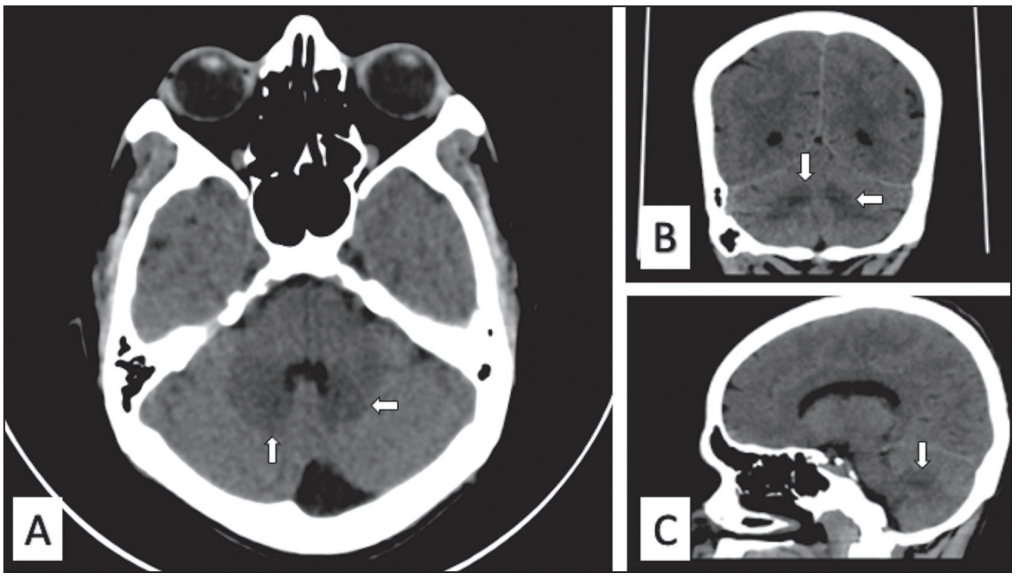

Figure 1: Noncontrast computed tomography (NCCT) brain in axial (A), reconstructed coronal (B), and sagittal sections (C) showing confluent hypodensity in the dentate nucleus of bilateral cerebellar hemisphere (white arrows). No signs of mass effect/compression were noted

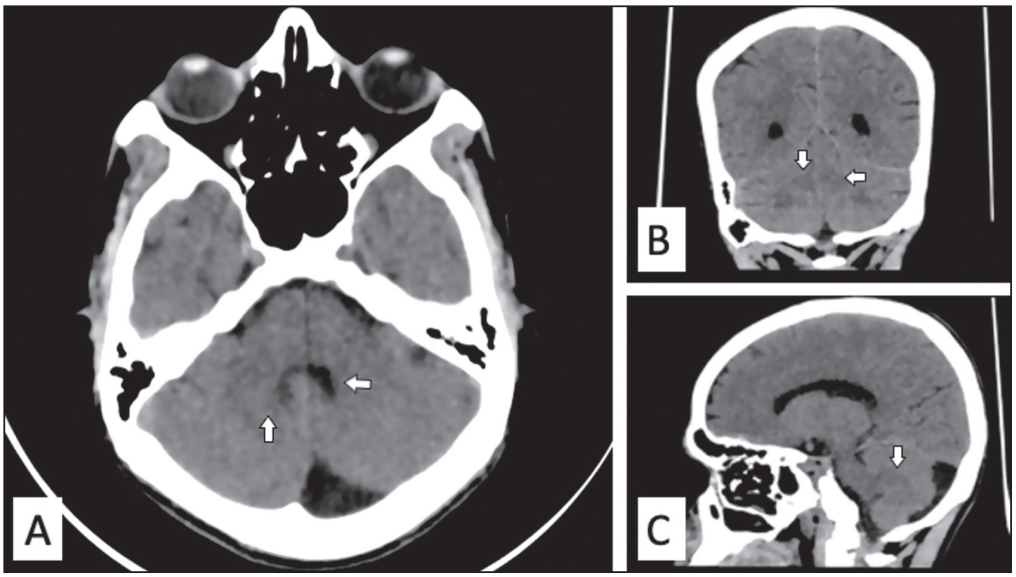

Figure 2: Follow-up NCCT (all three planes) after 16 days showing near complete resolution of the hypodensities (arrows) in the dentate nucleus and reduction in the exaggerated gray white matter differentiation as seen in Figure 1

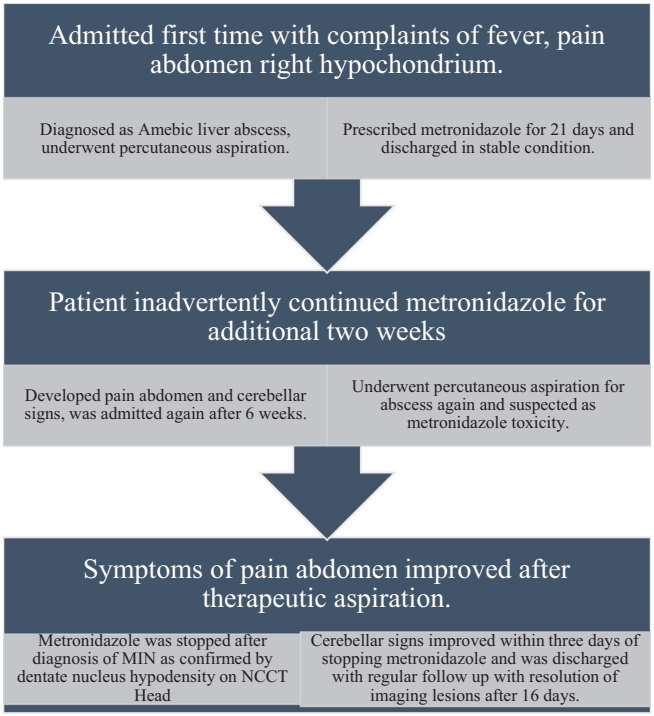

Figure 3: Timeline of events

and antihelminthic like piperazine have also been found to cause ataxia rarely.

Hari *et al.*[5] described a similar case of cerebellar ataxia and seizures in a 31-year-old man. He took metronidazole for 4 months and had hyperintense signals on T2 and FLAIR imaging in the dentate nucleus bilaterally and splenium of the corpus callosum. The features were resolved within 10 days of drug withdrawal.[5] Another patient with brain abscess received metronidazole for 10 weeks and developed hoarseness, dysarthria, and ataxic gait with typical lesions on MRI. He improved within 4 days of drug cessation with normalization of MRI at 2 weeks.[6]

The clinical concept of MIN was reported for the first time approximately 20 years ago but specific imaging patterns that are reversible have been elaborated recently. These patients have a predilection to involve cerebellar dentate nucleus and the inferior colliculus and lesions are bilaterally symmetric T2 hyperintense. Other areas that can be involved are anterior commissure of the splenium, basal ganglia, subcortical white matter, midbrain, inferior olivary nuclei, and cerebellar white matter.[2] The lesions appear as nonenhancing, hyperintense on T2-weighted, and FLAIR images with absence of mass effect. The diffusion-weighted (DW) image signal is high with variable apparent diffusion coefficient values. MRI brain features of MIN are graded as shown in Table 1.[7]

Mishra *et al.*[8] first described a similar case of liver abscess in a 30-year-old man who developed slurring of speech, vertigo, instability in walking, and burning sensation in the feet after 6 weeks of metronidazole intake. Radiological features have been described in a cirrhotic patient who self-medicated himself with an unknown cumulative dose of metronidazole and had a complete resolution in follow-up scan done after 7 weeks.[9] Cerebellar toxicity with metronidazole has been seen across a wide spectrum of time period of therapy and dosage. Time interval from as early as 28 days to 3 months and cumulative dose ranging from 25 g to 90 g has been reported in the literature.[10] Majority of the patients show complete improvement of the symptoms

Table 1: Grading of CNS findings in MIN[7]

Grade	Severity	Extent of brain involvement
Grade 1	Minimal	Symmetric involvement of one lobe (frontal, temporal, parietal, or occipital) without involvement of the corpus callosum, basal ganglia, thalami, or internal capsules
Grade 2	Mild	Symmetric involvement of two lobes, or of one lobe plus symmetric involvement of one of the corpus callosum, basal ganglia, thalami, or internal capsules
Grade 3	Moderate	Symmetric involvement of two lobes plus symmetric involvement of one of the corpus callosum, basal ganglia, thalami, or internal capsules
Grade 4	Severity	Symmetric, extensive, and confluent involvement of three or all lobes from the ventricular margin to the subcortical white matter, or of two lobes plus symmetric involvement of two of the following: corpus callosum, basal ganglia, thalami, or internal capsules

after discontinuation of metronidazole. The timeline in which the radiological abnormality resolves still remains to be elaborated.

Conclusion

New-onset neurological complaints warrant exploration of detailed drug history along with routine workup. Our case was prescribed metronidazole for 3 weeks at a dose of 800 mg three times a day; however, he self-prescribed the same dose for another 2 weeks due to persistent pain abdomen and a local practitioner's advice. Neurotoxicity associated with metronidazole, though rare, should be suspected in any patient presenting with neurological dysfunction. Treatment involves stopping metronidazole and improvement of symptoms should be expected within 3–4 weeks.

Presentation(s) or awards at a meeting

This case report was not presented previously as an abstract in any congress or symposium.

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Conflicts of interest

There are no conflicts of interest.

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.

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