Case Report

Metronidazole: A culprit to balance and speech

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ABSTRACT

In a country like India, oral metronidazole is the commonly prescribed drug of choice for entities such as amebiasis and visceral abscesses. Oral such cases, it is usually well tolerated and safe but can cause serious neurological adverse events. Peripheral neuropathy commonly encounters in practice but central nervous system toxicity is also well documented as it crosses the blood–brain barrier easily. Neurological toxicity of metronidazole may be due to prolonged administration, high doses, or high cumulative doses. Magnetic resonance imaging (MRI) of brain is the modality of choice to evaluate brain involvement. In the brain, the splenium of the corpus callosum, dentate nucleus of the cerebellum, and posterior pons involvement are commonly seen and diagnostic. Here, we have an interesting case report of a patient who was on oral metronidazole treatment for his large liver abscess, presenting with a complaint of neurological symptoms of unsteady gait, vertigo, dysdiadochokinesia, and difficulty in speech. Moreover, thus suspected as metronidazole drug toxicity and further investigated for the same, and MRI typically shows cerebellar and posterior corpus callosal involvement.

Key words: Metronidazole, Visceral Abscesses, CNS toxicity, MRI Brain, Corpus callosum, Dentate Nucleus, Pons

Metronidazole is a nitroimidazole derivative with a potent cidal activity against protozoa and anaerobes, a commonly prescribed drug for amebiasis and visceral abscesses. It is usually well tolerated and safe but can cause serious neurological adverse events, including peripheral neuropathy which is relatively common and central nervous system (CNS) toxicity as it crosses the blood–brain barrier and penetrates CNS easily. It has been suggested that neurological toxicity may be related to prolonged administration, high doses, or high cumulative doses of metronidazole [1].

Here, we report an interesting clinical case who developed slurring of speech and unsteady gait after prolonged administration of metronidazole for 2.5 months.

CASE REPORT

A 34-year-old male presented to our hospital in the 1st week of October 2021 with complaints of slurring of speech, vertigo, and instability in walking for 2 days. The patient gave a history of admission to a private hospital in the month of July 2021, 10 weeks before the present visit with chief complaints of high-grade fever associated with chills, pain in the right hypochondrium, and decreased appetite for 10 days.

On examination, he was febrile with a temperature of 104°F, and his pulse rate and blood pressure were 130/min and 112/68 mmHg, respectively. The patient was investigated and found to have an abscess in the posterior segment of the right lobe of the liver with a volume of 850 cc.

The patient was treated with parenteral metronidazole and piperacillin-tazobactam for 2 weeks and pigtail drainage was done in which, a pigtail was inserted through the right iliac fossa which resulted in the development of a fistulous tract from the right iliac fossa to sub-hepatic space, for which he was further treated with IV metronidazole for another 8 weeks.

The patient improved clinically and was discharged on oral metronidazole 800 mg thrice a day for 1 week. The total cumulative dose of metronidazole in this patient was 191.8 g over 11 weeks. The patient developed symptoms such as slurring of speech and instability of gait 2 days back for which, he presented to our hospital.

On examination, the patient had staccato speech, dysmetria, ataxic gait, dysdiadochokinesia, and pendular knee jerk past-pointing which suggested cerebellar involvement. Serial routine blood investigations were normal including complete blood count, liver function test, and kidney function test. Vitamin B12 and fasting blood sugar levels were normal.

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Non-contrast computed tomographic scan of the brain was normal. Magnetic resonance imaging (MRI) scan of the brain showed areas of hyperintense signal change in the dentate nucleus of the cerebellum, two small foci in dorsal pons and splenium of corpus callosum, respectively, suggestive of interstitial edema as no restriction in T2 FLAIR, diffusion-weighted images (DWIs), and apparent diffusion coefficient (ADC) sequences (Fig. 1). Fig. 2 (DWI and ADC) at the level of pons shows no hyperintense change in DWI and no signal loss in ADC in the dentate nucleus of the cerebellum, and Fig. 3 at the level of septum pellucidum shows a hyperintense change in DWI and loss of signal in ADC in the splenium of corpus callosum suggestive of cytotoxic edema.

Metronidazole was stopped subsequently and the patient was managed clinically. The patient got improved and was symptom free after 10 days. Follow-up MRI could not be done due to some logistic issues.

DISCUSSION

Metronidazole is an excellent antibiotic agent for anaerobic and parasitic infections. The common side effects are nausea, dry mouth, and diarrhea. Significant neurotoxic side effects of metronidazole are rare. The most commonly seen neurologic complication of metronidazole toxicity involves the peripheral nervous system predominantly as a sensory peripheral neuropathy [1].

Patients with metronidazole CNS toxicity most commonly present with dysarthria and ataxia [2]. MR is the modality of choice in identifying CNS toxicity. Structures most vulnerable to metronidazole toxicity include both cerebellar dentate nuclei but also the midbrain (tectum, red nucleus, tegmentum around the periaqueductal gray matter), dorsal pons, superior olivary nucleus, and the splenium of the corpus callosum [3].

On FLAIR and T2W images, common findings include hyperintense lesions of the cerebellar dentate nuclei, midbrain, dorsal pons, corpus callosum, and cerebral white matter. A pattern consistent with vasogenic edema is usually identified with a bright signal on DWI and high ADC. These MR findings are most conspicuous in bilateral cerebellar dentate nuclei and resolve in conjunction with clinical improvement upon drug discontinuation. Permanent residual neurologic deficits have also been reported postulated mechanisms which include axonal swelling with interstitial edema due to interference in microsomal metabolism resulting in cellular energy deprivation [4].

According to a recent case series of ten patients of metronidazole-induced neuropathy (MIN), the median age of patients with MIN was 54 (range 8–84) years and the median cumulative dose of metronidazole received was 64.5 g (range 7.5–1.380 g). Common presenting neurological symptoms were ataxia (n=6) and altered mental status (n=3). All of the

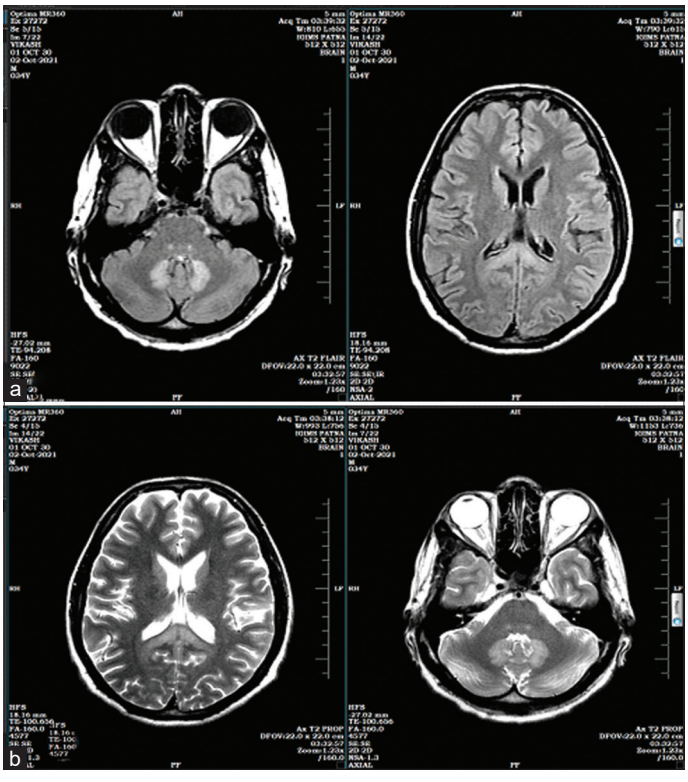

Figure 1: (a) T2 FLAIR magnetic resonance imaging (MRI) and (b) T2W MRI at the level of middle cerebellar peduncle and septum pellucidum show hyperintense signal change in dentate nucleus of cerebellum, two small foci in dorsal pons and splenium of corpus callosum, respectively, suggestive of interstitial edema as no restriction in diffusion-weighted images and apparent diffusion coefficient sequences

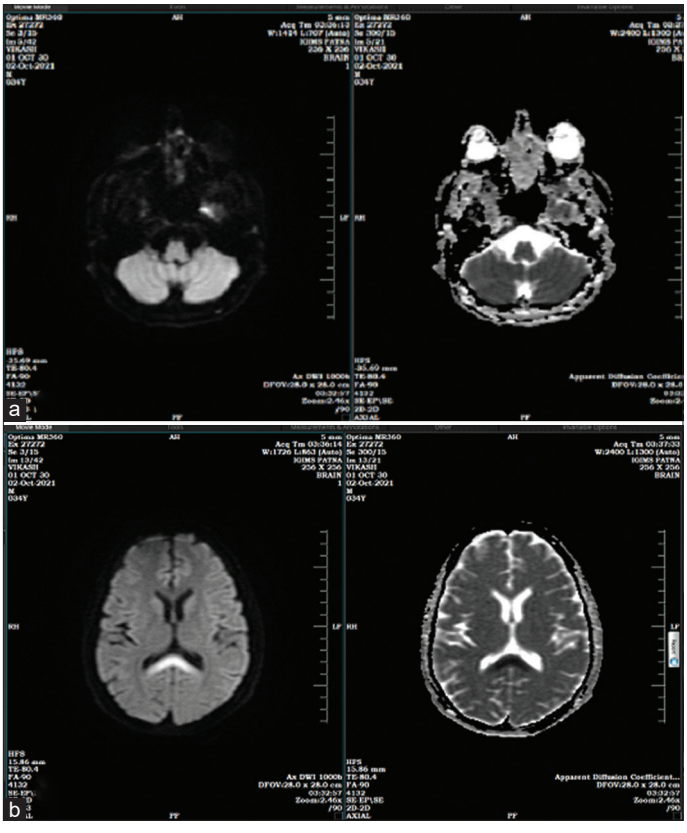

Figure 2: (a) Diffusion-weighted images (DWI) and (b) apparent diffusion coefficient (ADC) at the level of pons shows no hyperintense change in DWI (Left side image) and no signal loss in ADC (right side image) in dentate nucleus of cerebellum, and Fig 4 (below) at the level of septum pellucidum shows hyperintense change in DWI (left side image) and loss of signal in ADC (right side image) in splenium of corpus callosum suggestive of cytotoxic edema

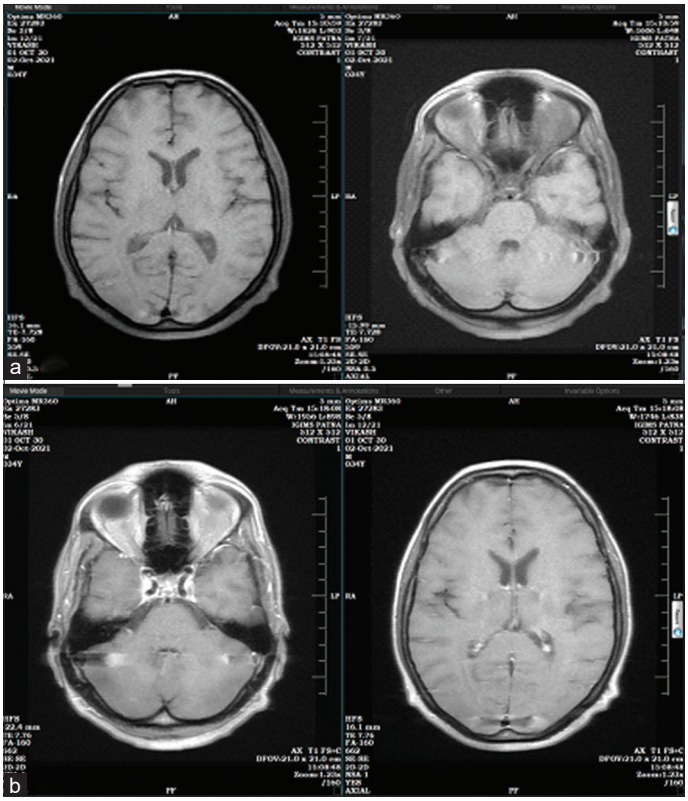

Figure 3: (a) TW1 and (b) TW1+C at the level of septum pellucidum and pons show no post-contrast enhancement of lesional areas of splenium of corpus callosum and dentate nucleus of cerebellum, respectively

patients (n=10) had symmetric T2 hyperintense lesions in the dentate nuclei at presentation. Other involved structures included the midbrain, corpus callosum, pons, medulla, basal ganglia, and supratentorial white matter. True restricted diffusion was seen in the corpus callosum (n=6). Symptoms resolved in all patients except for one. For the patients with available follow-up MRI (n=4), the observed lesions resolved [5]. Follow-up MRs demonstrated complete resolution of these abnormalities in 83% of patients. The median duration of metronidazole exposure in a review of case series was 54 days although in 26% toxicity had emerged in less than a week and in 11% in <72 h. Although generally seen with longer courses of treatment, toxicity can present in the wide range of cumulative doses from 25 to 1080 g [6].

Metronidazole crosses the blood–brain barrier and achieves therapeutic concentrations in the cerebrospinal fluid. MR defines bilateral involvement with axonal swelling and increased water content suggestive of a toxic-metabolic process [7]. Although there has been no direct correlation between blood levels and clinical toxicity, in patients with advanced liver disease, the clearance of metronidazole is reduced to 35% and the half-life extended to 280% of healthy control subjects. Beyond liver disease, there is an increased incidence of metronidazole toxicity in chronic renal failure, diabetes, hematologic, and solid organ malignancies [8].

The dentate is the largest of the cerebellar nuclei and plays an integral role in the coordination of voluntary movements. It is highly cellular and metabolically active as is the cerebellum in general which accounts for only 10% of brain volume but contains over 50% of the total neurons in the brain. The susceptibility of the dentate and dorsal brainstem nuclei is not understood but similar MR changes have been identified in maple syrup urine disease, enteroviral encephalopathies, non-alcoholic Wernicke's encephalopathy, and with other antibiotics such as isoniazid and cycloserine [9]. Isolated cases have been reported in conjunction with occupational exposure to industrial toxins such as methyl bromide and methyl iodide [10]. These diverse toxic, genetic, and nutritional disorders have been linked as "energy deprivation syndromes" with a shared toxicity that appears to be related to the disruption of metabolic pathways involved in basic glycolysis and pyruvate oxidation [11].

CONCLUSION

Frequent use of metronidazole increases its vulnerability and prompt identification of neuropathy is essential to avoid permanent damage, so physicians should be aware of these side effects. Clinicians should avoid the use of metronidazole for more than 2 weeks in case of amebic liver abscess.

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