International Journal of Advances in Medicine
Mahmud S. Int J Adv Med. 2023 Jun;10(6):471-474
http://www.ijmedicine.com
pISSN 2349-3925 | eISSN 2349-3933
DOI: https://dx.doi.org/10.18203/2349-3933.ijam20231455

Case Report

A case report of metronidazole-induced encephalopathy in Bangladesh

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Received: 24 April 2023
Accepted: 09 May 2023

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ABSTRACT

Metronidazole-induced encephalopathy (MIE) is a rare disorder that can be reversible but fatal if not recognized early. Here, the author presents a case of encephalopathy in a 36-year-old patient who took 500 mg of metronidazole three times daily for three weeks. The patient was classified as a probable MIE case on the Naranjo causality assessment scale. An interesting neuroimaging finding in this patient was an isolated dentate nucleus signal abnormality. Author aims to report reversible clinical and radiological features of MIE in this patient and compare them with documented cases in recent and old literature. Data from this case report may guide clinicians to make judicious considerations in the early detection of MIE and may influence future researchers to focus on identifying critical mechanisms of devastating adverse effects, predictability of neurotoxicity.

Keywords: Metronidazole, Encephalopathy, Dentate nucleus hyperintensity, Neurotoxicity

INTRODUCTION

Metronidazole, a nitroimidazole-derived agent, is indicated against a limited range of infections.[1,2] This drug is available for self-medication as an over-the-counter (OTC) drug in Bangladesh, a Southeast Asian country.[3] Furthermore, metronidazole has frequently been purchased OTC without a physician's prescription in Bangladesh, resulting in irrational use.[4] In addition, irrational antibiotic use is seen in other parts of Southeast Asia, which possesses a significant risk of resistance among world health organization (WHO) regions.[5] Exposure to this nitroimidazole agent has increased globally.[6] It can be due to irrational use and infection burden.[5,7] The first administration of metronidazole was in 1959.[8] More than 35 years later after the first use, the association between metronidazole and encephalopathy with supportive evidence of reversible neuroimaging features was documented in a 45-year-old patient, who exposed to metronidazole 750 mg three times daily for about 30 days.[9] Subsequently, several cases of MIE have been documented in the literature; however, knowledge of MIE has been limited, probably because of under-recognition of the condition.[1]

Here author presents a 36-years-old male patient, who exhibited isolated reversible dentate nucleus signal abnormality on neuroimaging. His clinical and radiological features were categorized as a probable case of MIE on the Naranjo probability scale. The insights from this unique case discussion guide early detection of MIE and may lead future researchers to focus on the fundamental mechanisms of adverse events and predictability of neurotoxicity.

CASE REPORT

A 36-year-old male patient presented to my hospital's emergency department accompanied by his father for evaluation. Patient had a five-day history of mental state alteration, dysarthria, gait instability, and ataxia without physical injury. Upon reporting to the emergency room, he opened his eyes spontaneously, was confused, and responded slowly to verbal commands, with ataxia and dysarthria. He also had recent onset mild headache, loss of

appetite, nausea, vertigo, and heartburn; however, he did not experience fever, vomiting, impaired swallowing, neck pain, and visual difficulty.

The patient's father informed the emergency medical staff that he had been diagnosed with diarrhea-predominant irritable bowel syndrome (IBS) for two years and was otherwise in good health without any personal or family history of neurological and liver disease. The patient had gone on a trip seven weeks ago and experienced abdominal pain and persistent diarrhea without any associated symptoms of weight loss or blood in the stool while traveling. His symptoms were typical of previous IBS episodes. However, due to his prior experience of self-medication and recovery from infectious diarrhea several times, he took OTC metronidazole 500 mg three times daily for three weeks without a physician's prescription. In the recent past or during the trip, he had no exposure to a sick patient or unsafe food habits. There was no other history of substance use, including herbal supplements, or other OTC medications. After three weeks of taking metronidazole, he developed neurological symptoms.

At the time of admission, the patient's diarrhea was resolving. The medical staff examined the patient and found normal vital signs. Physical examination revealed a Glasgow coma scale (GCS) score of 13; intact memory; unsteady gait; impaired initiation and fine control of voluntary movements; slurring of speech; normal tone and intact strength of all muscle groups; normal pain, temperature, and vibratory sensation in all extremities; normal response to the plantar reflex; absence of signs of meningitis and focal neurological abnormalities. In addition, the remaining general and systemic physical examination findings were unremarkable.

Following hospitalization, a team composed of physicians from the internal medicine, neurology, and radiology departments, took charge of prompt management. The team initially counselled the patient and his family members on proper IBS management, and ruled out infectious diarrhea in collaboration with the gastroenterology department. He followed the advice and stopped taking metronidazole. Cerebrospinal fluid (CSF) analysis, random blood sugar (RBS), serum cyanocobalamin, serum folate, serum calcium, serum electrolytes, blood urea nitrogen (BUN), serum creatinine, complete blood count (CBC), liver function test (LFT), thyroid function test (TFT), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Coronavirus disease screening, malaria screening, tuberculosis screening, HBsAg, rapid plasma reagin (RPR), urinalysis, stool test for ova and parasites, antinuclear antibody (ANA) tests were unremarkable. Echocardiography (ECG), non-contrast computerized tomography (CT) scan, and magnetic resonance imaging (MRI) of the brain were performed. However, electroencephalogram (EEG), carotid duplex ultrasound, and serum metronidazole concentration were not tested. Although ECG and CT scan findings were unremarkable, MRI showed isolated symmetrical hyperintense signal abnormalities in the cerebellar dentate nuclei (Figure 1 A).

On the third day of hospitalization, the patient was feeling relatively better and did not raise any concerns. After a complete workup, the medical team assessed the patient's presentation thoroughly. They excluded the differential diagnosis judiciously, and agreed to counsel the patient and the patient's family about the probable diagnosis and management of MIE. Therefore, the medical team continued metronidazole withdrawal and ensured supportive treatment. Following the fifth day of discontinuation of metronidazole and regular monitoring with nursing assistance, the patient exhibited improvement with minimal neurological deficits. He fully recovered on the seventh day of drug discontinuation and was discharged home. Upon follow-up after four weeks, a repeat brain MRI was negative for abnormal signals in the dentate nucleus confirming complete resolution (Figure 1 B).

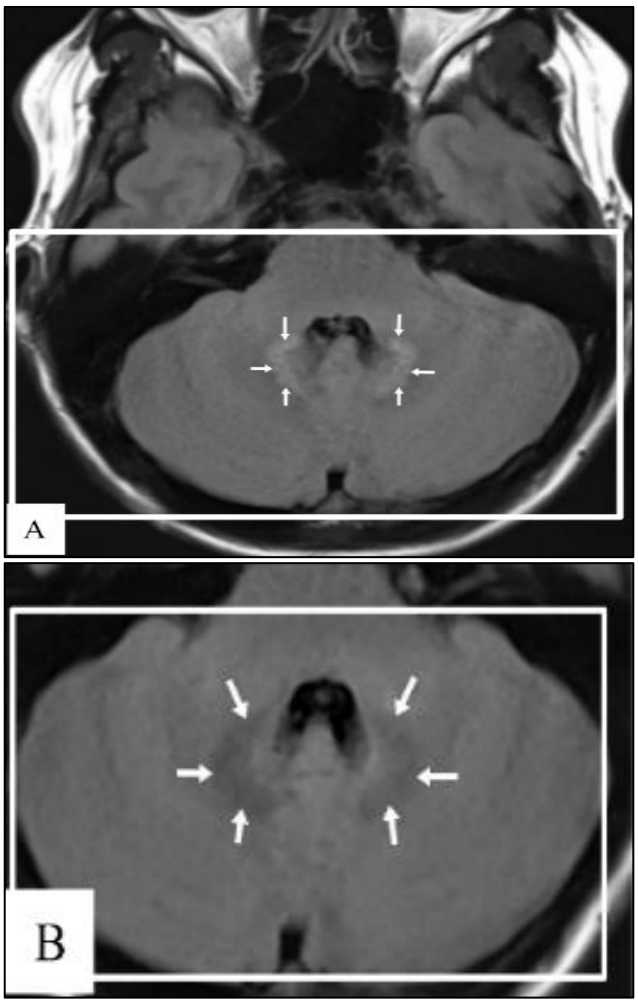

Figure 1 (A and B): Axial fluid-attenuated inversion recovery (FLAIR) MRI of the brain. Exhibits symmetrical increased signal intensity in the cerebellar dentate nuclei (arrows). Exhibits resolution of signal abnormality (arrows).

Though the team did not use any causality assessment method during his hospital stay, the team scored the patient's condition based on the Naranjo scale at this follow-up visit. The patient's total score on this scale was seven. This score indicated him as a probable case of MIE as there was no other reasonable explanation; the patient's presentation aligned with the temporal sequence and recognized response after metronidazole exposure; confirmation of the disease was done by metronidazole withdrawal but not by re-administration (Table 1).

Table 1: Assessment of causality association between metronidazole and encephalopathy in a 36-years-old patient based on the Naranjo probability scale.

Criteria	Score
Encephalopathy appeared after metronidazole exposure	+2
Encephalopathy improved after metronidazole withdrawal	+1
There were no alternative causes of encephalopathy	+2
MRI revealed objective findings of the metronidazole toxicity	+1
There is conclusive evidence of MIE in the literature	+1
The appearance of symptoms was not tested by metronidazole re-administration	0
A placebo was not administered to the patient	0
Metronidazole concentration in the patient body fluids was not assessed	0
Drug reaction was not tested by increasing or decreasing the metronidazole dose	0
The patient had no reaction to the same or similar drug in the past	0
Total score	7

The patient was symptom-free on two consecutive follow-ups at two-month and three-month intervals. He also successfully achieved compliance with patient education and rational IBS management.

DISCUSSION

Metronidazole is an effective nitroimidazole-derived agent that causes degradation of deoxyribonucleic acids and cell death of various protozoans like *Entamoeba histolytica*, *Giardia lamblia*, and many anaerobic bacteria unless the drug is resistant to activation intracellularly.[2] Unfortunately, among all the WHO regions, in many parts of Southeast Asia, including Bangladesh, many patients irrationally use antimicrobials because of easy accessibility to OTC drugs without prescription.[3] In a cross-sectional study in Bangladesh, metronidazole was the most frequently used self-medicating antibiotic among 1300 patients.[4] Therefore, there is a growing need for an effective action plan, antibiotic stewardship, and patient education to contain irrational exposure, especially in Southeast Asia.

The most common reasons for self-medication are fever, upper respiratory tract, and gastrointestinal symptoms.[4] Nausea, vomiting, abnormal taste sensation, gastrointestinal upset, and headache are common problems patients complain about after metronidazole administration.[10] In addition, unusual adverse events may include genomic instability.[6] Physicians should use widely accepted, consistent, and structured causality assessment scales in specifying the likelihood of adverse drug reactions; for example, the World Health Organization collaborating center for international drug monitoring, the Uppsala monitoring center (WHO-UMC), and the Naranjo probability scale. Naranjo probability scale causality terms can be divided into four groups: total score ≥9 (definite); total score 5 to 8 (probable); total score 1 to 4 (possible); total score ≤ 0 (doubtful). Metronidazole, as a cause of encephalopathy was categorized as a probable cause based on the total score.[11] Nevertheless, metronidazole is acknowledged for its less documentation of adverse reactions.[6,10] It is advantageous in the treatment or prophylaxis of various diseases.[11,12]

The crucial mechanism of MIE is still undefined, though several proposals have been documented.[1,13,14] Metronidazole might cause acute oxidative stress and neuroinflammation and drive pathological changes by hampering the brain antioxidant level, inducing mediators, and inhibiting inhibitors of neuronal cell death.[13] There is no evidence of demyelination.[9] Metronidazole and its metabolites bind to neuronal ribonucleic acids and disrupt the protein translation process to cause toxic insults.[14] Other proposed mechanisms include possible vascular spasm-induced reversible focal ischemia.[9] In this case report, patient experienced encephalopathy symptoms after about three weeks of drug exposure. It is crucial to note that MIE is evident in the literature after various dosing, treatment length, and in patients with variable characteristics and comorbidities.[1] It may indicate no predictable pattern of MIE. Additionally, it may draw attention to future researchers to focus on identifying the fundamental mechanisms of MIE and risk factors, including patient susceptibility to dose, treatment length, genome characteristics, and diverse factors to guide rational medication, predictability of toxicity, and antibiotic stewardship, as the knowledge of MIE has been grossly confined to the literature.

Similar to this case, the notable features of MIE in the recent and old literature were reversible dysarthria, ataxia, and signal changes in the cerebellar dentate nuclei without any evidence of demyelination on MRI.[1,9,15] Alteration of mental status was noted in several cases.[1] It could be explained by a metronidazole-induced non-convulsive state and dentate nucleus functional abnormality.[16,17] The majority of MIE patients may also exhibit signal abnormalities in the splenium of the corpus callosum and different parts of the brain stem.[1,9,15] However, unlike most cases, the interesting finding in this patient was isolated dentate nucleus signal abnormality, which could be due to early patient reporting and timely drug withdrawal. The

increased signal intensity of the dentate nucleus on axial fluid-attenuated inversion recovery (FLAIR) can also be observed in Canavan disease (CD), Maple syrup urine disease (MSUD), and glutaric aciduria (GA) type 1 (Bond et al).[17] Hence, they warrant exclusion. Diagnosis of this rare condition also requires a high suspicion index and exclusion of other conditions, such as stroke, Wernicke's encephalopathy, substance abuse, acute disseminated encephalitis, Marchiafava-Bignami disease (MBD), tuberculous (TB) encephalopathy, autoimmune encephalitis, lupus encephalitis, organ failure (liver and kidney), and functional disorders. Management includes the withdrawal of suspected agents with supportive treatment, follow-ups, and monitoring till recovery. Radiological follow-up should be made at least a few weeks after recovery to confirm the resolution, as a few cases may exhibit residual deficits and may require monitoring and prevention of further insult to the brain.[15]

CONCLUSION

This case illustrates that clinicians need to exhibit a judicious suspicion, perform radiologic evaluation, and use the causality assessment method with a complete workup to confirm the diagnosis of MIE. Encephalopathic patients without any reasonable causality should be screened for metronidazole exposure, especially in high-risk WHO regions of irrational drug use. Furthermore, this case suggests that future studies should focus on identifying the crucial mechanisms and predictability of neurotoxicity.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

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Cite this article as: Mahmud S. A case report of metronidazole-induced encephalopathy in Bangladesh. Int J Adv Med 2023;10:471-4.