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A Rare Case of Metronidazole Induced Encephalopathy Presenting as an Isolated Seizure Episode

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Abstract: - Metronidazole is a commonly used drug for the treatment of anaerobic and protozoal infections. Various common side effects of metronidazole include nausea, anorexia, vomiting, diarrhoea, and abdominal cramping. However, the central nervous system can rarely be affected by metronidazole toxicity. Patients mainly present with cerebellar dysfunction or altered mental status. Seizures are a rare but possible presenting feature, particularly in those receiving high doses of the drug. We present a case of metronidazole induced encephalopathy (MIE) in a 76-year-old man who experienced a seizure episode following the use of metronidazole for a post-surgical infection. The MRI findings of brain showed a focal area of signal abnormality within the splenium of the corpus callosum, seen as an area of FLAIR/T2 hyperintensity with mild restricted diffusion, which was consistent with the diagnosis of metronidazole toxicity.

Keywords:- *Flagyl, Metronidazole Side Effects, Splenium of the Corpus Callosum, New-Onset Seizure, Metronidazole Induced Encephalopathy.*

I. INTRODUCTION

Metronidazole is a 5-nitroimidazole antibiotic sold under several brand names, including Flagyl. It exhibits a limited spectrum of activity against various protozoans, including Entamoeba histolytica, Giardia lamblia, Trichomonas vaginalis, and most gram-negative and gram-positive anaerobic bacteria [1]. Although metronidazole has a high rate of therapeutic use, there are several common and uncommon adverse effects associated with its use. Among the adverse effects, those affecting the central nervous system (CNS) are typically rare, and such involvement of the CNS by metronidazole is termed as “Metronidazole induced encephalopathy (MIE).” While the presenting

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symptoms are vague, neuroimaging, particularly magnetic resonance imaging (MRI), is crucial in making the diagnosis of this unusual entity, especially in situations where there is a high index of suspicion of metronidazole intoxication [2]. Rare side effects affecting the nervous system include peripheral neuropathy, cerebellar dysfunction, dysarthric speech, encephalopathy, ataxic gait, and seizure. Seizures are a rather uncommon presenting sign of MIE given all these side effects; there are only a few studies that address this in the literature. Here, we discuss the case of a 76-year-old male patient who, after initiating Flagyl treatment for postsurgical anastomotic leak, experienced a seizure episode and was later diagnosed with an isolated corpus callosum lesion. While the clinical symptoms and neuroimaging alterations are typically reversible, there is a possibility of chronic encephalopathy with a poor long-term prognosis [3].

II. CASE PRESENTATION

A 76-year-old male patient with a past medical history significant for type 2 diabetes mellitus and hypertension presented to the emergency department after sustaining a seizure episode at home. The patient was at home with his family, having tea and snacks, when he suddenly went into a generalized tonic clonic seizure, which was witnessed by his daughter. The patient experienced generalized shaking with clenched teeth and open eyes. The episode lasted for approximately sixty seconds, after which the patient completely lost his tone while he was on the chair. The patient appeared confused for two minutes after the episode. No tongue bite or urinary incontinence was noted. His history was negative for prodromal symptoms, prior seizure episodes, family history of seizures, shortness of breath, abdominal pain, and substance abuse. He was tested for possible etiologies and prescribed levetiracetam 500 mg twice a day for seizures of unknown origin. A Computed Tomography (CT) scan of the brain without contrast was done, which effectively rules out the possibility of a stroke but no other conclusive finding was obtained. On examination, his blood pressure was 145/94 mmHg, pulse rate was 87/min, respiratory rate was 18/min, SpO2 was 97%, and temperature was 98.3 °C. The patient was alert and oriented to place, person, and time. Sensations were intact, and speech was fluent. His electrolyte levels, including sodium concentration (138 mEq/L) were within the normal range. His liver function tests and blood glucose levels were unremarkable as shown in *"Table I."* An evaluation of the patient's past medical history revealed that he had undergone a partial colectomy approximately two months prior to the seizure episode for a malignant sigmoid colon tumour and was discharged a week later. He experienced post-procedural abdominal drainage and bloody stools soon after discharge. Anastomotic leak was suspected based on a positive bacterial culture, and he was prescribed metronidazole 500 mg orally, three times a day, for 14 days. An additional course of metronidazole 500 mg orally, three times a day, for 10 days was given based on a surgical consult for his post-procedural infection. Following a neurology consultation, the patient underwent an MRI of brain with and without contrast 13 days after the seizure episode. His MRI reports showed a focal area of signal abnormality within the splenium of the corpus callosum, seen as an area of FLAIR/T2 hyperintensity with mild restricted diffusion as shown in "Fig. 1,". No abnormal enhancement or mass effect was seen. Additionally, there were diffuse FLAIR/T2 hyperintensities within the dentate nuclei bilaterally without associated enhancement. Based on the patient's medication history, which indicated the usage of metronidazole, and the findings on the brain MRI, a diagnosis of MIE (metronidazole-induced encephalopathy) was established. The medication was discontinued after the diagnosis was confirmed, and the patient has not experienced any seizure episodes since. However, we were unable to assess changes in the brain lesion following treatment discontinuation because no MRI data were available.

Table 1 Laboratory Findings

Lab Tests	Patient's value	Normal Value
Serum sodium	138 mEq/L	136-146 mEq/L
Serum potassium	4.5 mEq/L	3.5-5.0 mEq/L
Serum chloride	104 mEq/L	95-105 mEq/L
Serum bicarbonate	22 mEq/L	22-28 mEq/L
BUN	13 mg/dL	7-18 mg/dL
Serum creatinine	1.34 mg/dL	0.6-1.2 mg/dL
Blood glucose level	88 mg/dL	70-110 mg/dL
AST	Within normal range	Variable
ALT	Within normal range	Variable
ALP	Within normal range	Variable
Serum calcium	9.1 mg/dL	8.4-10.2 mg/dL

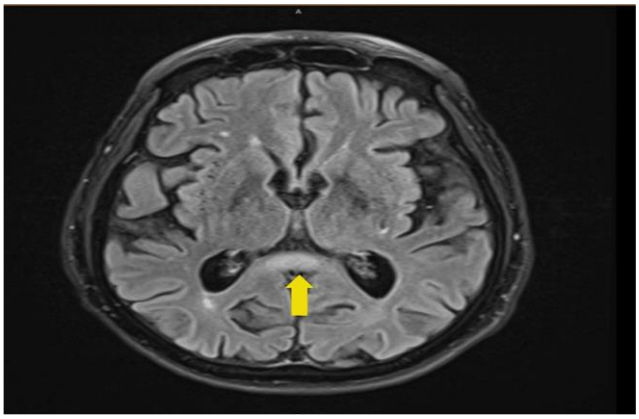

Fig 1: magnetic resonance imaging of the brain showing focal area of signal abnormality within the splenium of corpus callosum (yellow arrow).

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III. DISCUSSION

Metronidazole is a nitroimidazole antibiotic widely accepted for the treatment of a broad range of infections, such as intestinal amebiasis, liver amebiasis, joint and bone infections, infections of the central nervous system (meningitis and brain abscess), infections of the intra-abdominal cavity, and infections of colorectal surgeries [4]. The most common side effects are usually gastrointestinal-related, including metallic taste, nausea, vomiting, and diarrhoea. CNS side effects are uncommon and mainly include cerebellar dysfunction and encephalopathies.

MIE is an uncommon entity, the incidence of which is still unknown, and it is probably a condition that is underreported and underappreciated. [5]. Although the MIE mechanism has not yet been established, there are some theories that might explain it. Early research suggested that metronidazole or its metabolites might attach to ribonucleic acid (RNA) in neurons, causing axons to deteriorate [6]. In addition, localized ischemia and the potential contribution of mitochondrial dysfunction are further suggested explanations [2]. Many patients with MIE present with cerebellar signs, the most frequent being gait instability, dysarthria, and ataxia [7]. Less commonly, patients present with changes in mental state, vertigo, dizziness, seizures, and lateralizing signs. An isolated seizure as the first symptom of MIE is rarely reported. In our case, a 76-year-old patient has been prescribed metronidazole for post-surgical abdominal infection. He subsequently presented with an episode of a seizure the following month. After various investigations and a neurology consult, he was diagnosed with MIE. Moreover, the cumulative dose of metronidazole has been high in all documented cases of metronidazole-related seizures (greater than 40 grams). The etiology of this condition depends more on the cumulative dose than on the serum level [8]. In our patient, a cumulative dose of 36 grams was used, which is lower than doses given in similar reported cases. This may suggest that there is no typical therapeutic dose that may be considered to define the level at which metronidazole causes CNS toxicity. The primary method for identifying MIE in patients with metronidazole toxicity is still neuroimaging. T2 hyperintense lesions in the cerebellar dentate nuclei are most frequently seen in MIE patients on MRI scans of brain. Other impacted areas include the midbrain, dorsal pons, dorsal medulla, and corpus callosum [9]. However, in our case, the corpus callosum lesion with an associated episode of an isolated seizure is unique. Many etiologies, such as epilepsy, systemic lupus erythematosus, stroke, hypertensive encephalopathy, hypoglycemia, hyponatremia, and renal failure, can cause the T2 hyperintense lesions of the splenium of the corpus callosum [2]. Based on our patient's clinical scenario, medication history, laboratory investigations, and neuroimaging findings, we were able to reach the diagnosis of metronidazole toxicity.

IV. CONCLUSION

Metronidazole is a commonly prescribed medication used to treat a variety of illnesses. While the typical side effects are easily recognizable and treatable, rare side effects involving the CNS can be challenging to diagnose and manage. Despite extensive research on the CNS side effects of metronidazole, new cases with a wide range of signs and symptoms continue to emerge. In this report, we present a unique case of a 76-year-old male patient who experienced a seizure episode and an isolated corpus callosum lesion on the brain MRI after metronidazole usage. To prevent further complications, it is important for clinicians to be aware of CNS manifestations of metronidazole toxicity and promptly stop the medication when presented with similar clinical manifestations.

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