Metronidazole-Induced Cerebellar Dysfunction

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ABSTRACT

Metronidazole, a nitroimidazole compound, is a frequently utilised antimicrobial medication employed in the management of a wide range of bacterial and protozoal infections. Metronidazole can rarely cause neurological side effects such as encephalopathy, cerebellar dysfunction, and peripheral neuropathy. This case report describes a 62-year male who developed cerebellar ataxia after five weeks of metronidazole treatment for an amoebic liver abscess. MRI findings showed hyper-intense signals in the bilateral dentate nuclei of the cerebellum. Discontinuation of metronidazole led to rapid symptom improvement within 48-72 hours, with complete resolution of MRI abnormalities after eight weeks. In Pakistan, metronidazole stands as an easily accessible and frequently used over-the-counter (OTC) medication. Despite its extensive utilisation, a considerable number of its adverse effects remain under-recognised. This case underscores the importance of recognising metronidazole-induced neurotoxicity to avoid unnecessary investigations and ensure timely management.

Key Words: *Metronidazole, Cerebellar dysfunction, Magnetic resonance imaging.*

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INTRODUCTION

Metronidazole, a nitroimidazole compound, is a frequently utilised antimicrobial medication used in the management of a wide range of bacterial and protozoal infections. Nitroimidazole is categorised as a pro-drug, necessitating reductive activation under the conditions of reduced-oxygen tension. This activation process results in the fragmentation of the imidazole moiety, contributing to its cytotoxic effects.[1] The neurological manifestations associated with metronidazole encompass encephalopathy, cerebellar dysfunction, and peripheral neuropathy, with an estimated incidence rate of approximately 0.25% among the exposed individuals.[2] The classical magnetic resonance imaging (MRI) brain findings associated with metronidazole-induced neurotoxicity include bilateral symmetrical hyper-intense lesions within the cerebellar nuclei, genu, and splenium of the corpus callosum on T2-weighted images.[3] The mechanism underlying the development of neurological toxicity includes inhibition of thiamine phosphorylation, inhibition of neural protein synthesis, and oxidation of catecholamines leading to quinone radical formation and cell death.[4] In Pakistan, metronidazole is easily accessible and is frequently used over-the-counter (OTC) medication. Despite its extensive utilisation, its adverse effects remain under- recognised.[5]

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In this context, we report a case highlighting a reversible cerebellar syndrome as a side effect associated with the use of this medicine.

CASE REPORT

A 62-year male, a professional driver with no known comorbidities or addictions, presented to the emergency department reporting sudden onset of speech and walking difficulties for two days. Speech impairment included slurred and fragmented speech, while walking difficulty involved balance issues and lateral swaying. Five weeks earlier, the patient had been hospitalised for an amoebic liver abscess and was on metronidazole (2.4 g/day).

Neurological examination revealed intact higher cognitive functions, normal cranial nerves, and absence of meningeal irritation signs. However, the patient exhibited a wide-based gait and difficulty with tandem walking. Motor and sensory functions were normal. A plain computed tomography (CT) scan of the brain showed age-related cerebral atrophy but no evidence of haemorrhagic stroke. The cerebrospinal fluid (CSF) analysis yielded normal results. Bilateral carotid Doppler and echocardiogram (ECHO) examinations were also within normal limits. The patient was initiated on antiplatelet therapy; however, within the subsequent 48 hours, his condition deteriorated. He developed incomprehensible speech and had difficulty maintaining posture even while seated. MRI of the brain was performed, revealing hyper-intense signals on T2-weighted and FLAIR images in the bilateral dentate nuclei of the cerebellum (Figure 1). Metronidazole administration was stopped, leading to immediate improvement, with significant resolution of symptoms over 48-72 hours. After

eight weeks, a repeat MRI brain showed resolution of hyper-intense signals in the cerebellum (Figure 2).

DISCUSSION

Drug-induced cerebellar ataxia can result from various classes of medications. The most common groups associated with this adverse effect are antiepileptic medications, benzodiazepines, and anti-neoplastic medicines. Several reports identify metronidazole as a significant causative agent of cerebellar syndrome among antimicrobial drugs. The manifestations comprise dysarthria and ataxia, often accompanied by peripheral neuropathy. The adverse effects appear to correlate with the cumulative dose administered.[6] Metronidazole-induced neurotoxicity was first reported in 1977, in which a young female experienced disorientation and memory loss after treatment with metronidazole for trichomonas infection.[7] Symptom onset typically occurs around 6-7 weeks on average, although wide variability exists, as demonstrated in the present case where the patient presented after five weeks of treatment. The median cumulative dose reported is 65.4g, yet considerable variability exists, ranging from 5-2000g. In the current case, the cumulative dose was 84 g. Although symptom recovery typically occurs within two weeks on average, individual patient responses are contingent upon multiple variables, including the involvement of the central, peripheral, or autonomic nervous systems.[8,9] Recent literature related to MRI brain findings in metronidazole-induced neurotoxicity suggests that all patients showed symmetrical hyper-intense lesions in the dentate nuclei on T2-weighted images. Additionally, the midbrain, corpus callosum, pons, medulla, basal ganglia, and supratentorial white matter may be involved. True diffusion restriction was seen in the corpus callosum in a few cases. Symptoms usually resolve in the majority of patients after stopping the drug.[10] Consistent with the literature, our patient's MRI brain exhibited similar findings with complete resolution in interval imaging. In this case, the patient experienced rapid symptom resolution, with almost complete resolution within 72 hours of medicine cessation. Given the rarity of cases with a classical presentation, we deemed it pertinent to report this case.

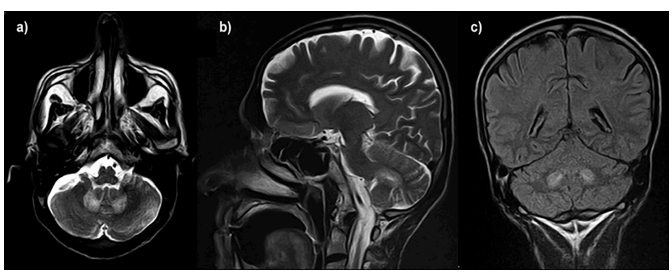

Figure 1: MRI brain prior to stopping metronidazole demonstrating hyper-intense signals in the dentate nuclei on T2-weighted axial (a), sagittal (b), and FLAIR images (c).

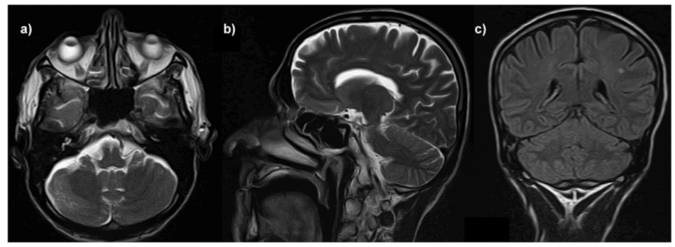

Figure 2: MRI repeated at 8 weeks after stopping metronidazole showed resolution of hyper-intense signals of the dentate nuclei in T2-weighted axial (a), sagittal (b), and FLAIR images (c).

In conclusion, physicians should be mindful that metronidazole, as one of the most commonly utilised OTC medicine in this country, can cause a rare but reversible side effect of cerebellar toxicity. This consideration is particularly important to prevent unnecessary investigations.

PATIENT'S CONSENT:

Written informed consent was obtained from the patient.

COMPETING INTEREST:

The authors declared no conflict interest.

AUTHORS' CONTRIBUTION:

RK, FS, JL: Contributed to the design, drafting, and critical revision of the manuscript.

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