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Case Report

Cerebellar ataxia after a single day of metronidazole use: Case report

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ABSTRACT

Cerebellar ataxic syndromes, although uncommon, have been reported previously in patients taking metronidazole. However, almost all cases describe instances where patients were taking prolonged or high doses of the drug. We report a 65-year-old man who consumed 400 mg of metronidazole 3 times over 1 day and presented with slurring of speech, imbalance while walking and diplopia. The symptoms developed the day after consumption of metronidazole. Examination showed slurring of speech, gaze-evoked nystagmus, and dysmetria in all limbs. MRI brain revealed symmetric hyperintense lesions in the dentate nucleus and pons on T2-weighted imaging and FLAIR, which have a well-established association with metronidazole-induced central nervous system (CNS) toxicity. On discontinuation of the drug, symptoms improved, and complete recovery was noted at follow-up 2 weeks later. This case indicates that CNS side effects of metronidazole may not necessarily occur only at high doses or after prolonged courses of metronidazole, but may occur as an idiosyncratic reaction to the drug. Reasons for variable susceptibility require further investigation.

Keywords: Metronidazole, Cerebellar ataxia, Side effect, Central nervous system toxicity, Case report

INTRODUCTION

Metronidazole is a nitroimidazole used commonly for treating protozoal and anaerobic infections. It achieves high serum concentrations following oral administration and has excellent tissue penetration. Common side effects include gastrointestinal symptoms such as nausea, vomiting, diarrhea, metallic taste, and abdominal cramping. Neurological manifestations such as peripheral neuropathy, seizures, and encephalopathy, although less common, have been reported, particularly among patients receiving high doses of the drug. Here, we report a case of cerebellar ataxia that developed after oral administration of merely 1.2 g of metronidazole.

CASE REPORT

A 65-year-old male presented with chief complaints of difficulty in speech, which he described as heaviness and slurring, causing difficulty in being understood by others. These symptoms were associated with double vision which was present in all directions of gaze but disappeared on covering either eye. He also had imbalance while walking with swaying in all directions but no associated falls. The symptoms began gradually over a day after consumption of three doses of metronidazole 400 mg which were prescribed for a presumptive diagnosis of gastroenteritis.

He had a history of hypertension for 20 years taking amlodipine 10 mg daily and diabetes mellitus since 15 years on metformin 500 mg thrice daily. He also had a history of alcohol use disorder for 20 years, and a history of beedi smoking for the past 40 years.

On examination, pulse was 86/min, regular, blood pressure: 120/76 mm Hg, and respiratory rate: 16/min. On the central nervous system (CNS) examination, he was conscious and oriented to time, place, and person. Speech was slurred, partially intelligible, with preserved syntax and grammar. He had horizontal nystagmus on the left gaze which was sustained. Tone, power, and reflexes were normal in all four limbs. Cerebellar tests revealed dysmetria and past pointing on finger nose finger test, dysdiadochokinesia, and positive heel knee test bilaterally, although features were more prominent on the left side. Sensory examination was normal. He had a broad-based gait with truncal ataxia. Romberg's sign could not be tested. Considering his age, multiple risk factors for stroke, and acute onset, initial suspicion was of a posterior circulation stroke.

Complete blood counts, liver function tests, kidney function tests, serum electrolytes, serum vitamin B12 levels, and fasting blood sugar levels were normal. CT scan of the brain was normal. MRI brain revealed bilateral symmetrical areas of altered signal intensity – hyperintensities in the dentate

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nuclei and central pons on T2WI [Figure 1a] and FLAIR imaging [Figure 1b] which appeared hypointense in T1W imaging. No restricted diffusion on DWI/ADC or blooming on GRE images was seen. MR Venography showed no signs of cerebral venous thrombosis.

Based on the history of metronidazole intake, cerebellar signs, and corroborative findings on MR imaging, a diagnosis of metronidazole-induced neurotoxicity was established. Over the next week, after discontinuation of metronidazole, the patient's dysarthria improved, nystagmus resolved and he was able to walk with minimal support. On follow-up 2 weeks later, he was able to walk without support.

DISCUSSION

Early reports on the CNS toxicity of metronidazole were in patients with malignant neoplasms treated with metronidazole as a radiation sensitizer. Patients were given high doses of metronidazole before radiation therapy but later developed seizures during the course of treatment. These patients typically received cumulative doses exceeding 20 g.[1] The first description of a cerebellar syndrome due to metronidazole was by Kusumi *et al*., where a 45-year-old female received a cumulative dose of 84 g over a period of 28 days for an anterior mediastinal abscess. She went on to develop a global cerebellar syndrome along with painful peripheral neuropathy. On discontinuation of metronidazole, her cerebellar symptoms resolved, however, the neuropathic symptoms persisted.[2]

Based on seventeen cases in the literature, doses causing neurological manifestations were found to be highly variable, with an average daily dose of 1.6 g, and an average duration of 79 days.[3] Typically, cumulative doses of more than 40 g of metronidazole have been associated with CNS side effects. Surprisingly, our patient developed cerebellar ataxia after merely 1.2 g of metronidazole, the lowest dose reported to the best of our knowledge. Serum levels of the drug were not tested since drug levels have not been shown to correlate with CNS toxicity.[1] The high variability in doses causing CNS side effects seems to suggest an individual patient vulnerability to the drug rather than a dependence on serum drug levels. This differential susceptibility may be due to a genetic predisposition; however, conclusive evidence is lacking.

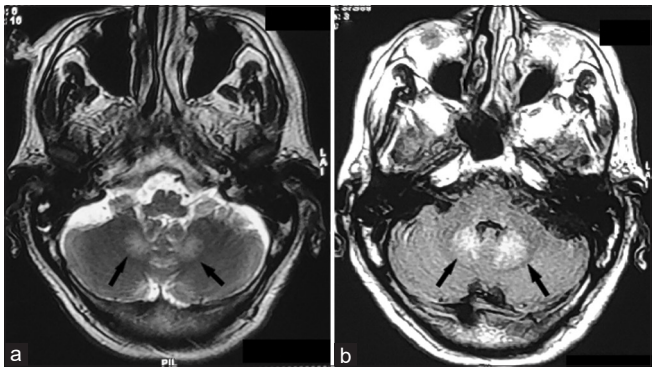

Figure 1: MRI brain in axial view at the level of the pons showing signal hyperintensities (arrows) in bilateral dentate nuclei on (a) T2-weighted imaging and (b) FLAIR imaging.

Many cases describe concomitant peripheral neuropathy with CNS toxicity; however, our patients lacked this feature. Although CNS symptoms are typically reversible on discontinuation of the drug, symptoms of peripheral neuropathy tend to persist.[2] This may suggest a different mechanism of toxicity to neurons of peripheral nerves as compared to those of the CNS. Experiments on rats to uncover mechanisms of peripheral neuropathy using radio-labeled metronidazole seemed to suggest that either metronidazole or its metabolic products bind to neuronal RNA and inhibit protein synthesis causing axonal degeneration.[4] Although mechanisms of CNS toxicity are lacking, experimental studies on dogs have shown susceptibility of the Purkinje cells of the cerebellum to high doses of oral metronidazole.[5]

Histological sections of the brains of rats treated with 800 mg/kg metronidazole have shown relatively sharp bounded, usually symmetric lesions in the nuclei of the cerebellar roof, the vestibular and cochlear nuclei, and in the superior olivary nucleus.[6] These histological features correlate well with established MRI findings reported in cases of metronidazole-induced CNS toxicity. Examination of MRI findings in seven patients with a final diagnosis of metronidazole-induced toxicity showed that all patients had bilateral symmetric hyperintense lesions in the dentate nucleus and midbrain on T2WI and FLAIR MR, along with lesions in the dorsal pons, medulla, corpus callosum, and cerebral white matter. These lesions were found to be reversible in almost all patients at 3-month follow-up.[7]

Based on the history of metronidazole use and specific MRI findings, a diagnosis of metronidazole-induced CNS toxicity can be established with high certainty. As in our case, clinicians should be able to recognize metronidazole as a possible cause of cerebellar ataxia, even at lower doses. Moreover, other signs of toxicity like GI symptoms or parasthesia may be absent. Taking into consideration the reversibility of the toxicity, early recognition may help in prompt resolution of symptoms and also circumvent the need for a lengthy workup. This case also reiterates the importance of evidence-based management of common illnesses and avoidance of overzealous antibiotic use. Finally, the MRI findings as described, although not necessary for diagnosis, can be used as strong supportive evidence.

CONCLUSION

Metronidazole, a commonly prescribed antibiotic, can rarely lead to a cerebellar ataxic syndrome, even in small doses. Hence, it should be considered in the differential diagnosis even in patients on short-course treatment. Early recognition and discontinuation of the offending agent can lead to prompt resolution of CNS symptoms; however, symptoms of peripheral neuropathy may persist. Clinicians should adhere to guideline-based prescription of metronidazole and refrain from presumptive diagnosis and treatment. When other competing differential diagnoses exist, MRI brain findings may help support or refute metronidazole as the causative agent.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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