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Case Report

A rare case of cerebellar toxicity after prolonged use of metronidazole: a case report

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ABSTRACT

Metronidazole, a commonly used antiprotozoal and antibacterial medication is usually a safe and rarely reported to cause serious side effects. Major nervous side effects are peripheral ones, while central toxicity is rare. Following the discontinuation of the medication, clinical improvement is seen in the most cases. A 62 years old female patient was presented to hospital after experiencing the symptoms of an unsteady gait, difficulty in walking, impaired coordination of arms and legs, slurring of the speech, headache, tingling and numbness of both the feet and ascending limb weakness following intake of 400 mg metronidazole TDS daily for 2 months. The motor system examination revealed reduced muscle power, and DTR (Deep tendon reflex) was found to be 2+, except ankle reflex absent, while examination of sensory system showed, decrease pain and joint vibration sense up to the neck with absent planter reflex. The axial magnetic resonance imaging study of the brain showed bilateral symmetric hyperintensity involving both dentate nuclei in FLAIR image. The patient's clinical conditions, on the other hand was deteriorated even after the discontinuation of the medication, hence injection methylprednisolone was given as an empirical therapy and was proved to be successful, and patient was recovered completely.

Keywords: Metronidazole, Cerebellar toxicity, Dentate nucleus, Methylprednisolone

INTRODUCTION

Metronidazole is the prototype 5-nitroimidazole compound. It is effective against anaerobic protozoa like Entamoeba histolytica, Trichomonas vaginalis, Giardia lamblia and has also cidal activity against numerous anaerobic and microaerophilic bacteria, such as Bacteroides, Fusobacterium group, Clostridium difficile, and Helicobacter pylori. Besides in asymptomatic cyst passers, metronidazole is the drug of choice in most forms of amoebiasis, and also indicated for the treatment of anaerobic or mixed intra-abdominal infections, vaginitis, Clostridium difficile infection, brain abscess, endocarditis and pelvic inflammatory disease.[1] It also has a radio sensitizing effect on hypoxic tumour cells.[2] It has wide utilization around the globe and is on WHO's EML (Essential Medicines List) also.[3]

Metronidazole, when used in appropriate dosage for appropriate duration, is usually a safe medication, and rarely reported to cause serious side effects. Commonly reported adverse effects with metronidazole are gastrointestinal ones, that are nausea, anorexia, diarrhoea, stomatitis, metallic taste, and mouth dryness.[4] Nervous toxicity with metronidazole is fairly rare, and seen with prolonged use of metronidazole, and manifest as a peripheral neuropathy, syncope, vertigo, dizziness, and confusion.[5] Cerebellar toxicity is even uncommon, but

serious side effect of metronidazole.[6] Neurological manifestations warrant drug discontinuation. The majority of the neurological manifestations fade away within 2-6 weeks of discontinuation of drug; however, peripheral neuropathy may persist for prolonged period. We report the case of cerebellar toxicity in 62 years old female patient following prolonged use of metronidazole.

CASE REPORT

This case concerns a 62 years old female patient who was presented to outpatient department of our hospital after experiencing the symptoms of an unsteady gait, difficulty in walking, impaired coordination of arms and legs, slurring of the speech, headache, tingling and numbness of both the feet and ascending limb weakness. There was no association with the convulsion, vertigo, dizziness, or any other cardiovascular issue. Her personal history and family history was insignificant. Her past history revealed admission in some private hospital for liver abscess, for which she was treated with IV metronidazole. She recovered well starting IV metronidazole, and was discharged and was put on 400 mg oral metronidazole TDS for one week. Patient failed to go for follow-up after discharge, and was taking oral metronidazole approximately 1200 mg per day (400 mg TDS) without consulting physician, since last two months. Starting metronidazole, she gradually developed the symptoms of ataxia, that were progressively deteriorating over the past one week, and she was presented to our hospital. Patient had no history of intake of the drugs, such as anti-epileptic drugs, barbiturates, benzodiazepines, and chemotherapeutic drugs in the last three months before presentation to our hospital except, metronidazole.

On general examination, her vitals were normal with blood pressure- 130/70 mm Hg, pulse rate-78/minute, respiratory rate-15 breathe/minute, and body temperature was 37.2 °C. Her oxygen saturation was 97 % at room air. Cardiorespiratory and elementary system examination did not reveal any abnormality. On examination, ascending weakness from both the lower limbs, extending to involve both the upper limb was found. Neurological examination revealed normal higher functions, cranial nerves were normal, tone was also normal, motor system examination showed that muscle power was diminished (2/5 in both the limbs at all joints) and DTR (Deep tendon reflex) was 2+, except absent ankle reflex, while sensory system examination showed decrease pain and joint vibration sense up to neck with absent planter reflex. The Romberg's test was negative.

The culprit medication was discontinued immediately, and patient was admitted to our hospital. Laboratory findings of hemogram, metabolic profile, urine for porphobilinogen, serum electrolytes, renal and liver profile, x-ray chest and electrocardiogram didn't reveal any abnormality. Her nerve conduction velocity study and electromyography study were suggestive of diffuse sensory and motor axonal polyneuropathy for all the limbs. Patient was subjected for MRI (Magnetic resonance imaging) brain study. Axial MRI brain study showed bilateral symmetrical hyperintensity involving both dentate nuclei of cerebellum in FLAIR image (Figure 1). No, any other lesion, intracranial haemorrhage, restricted diffusion, white matter abnormality or contrast enhancement was found in MRI brain study. Based on MRI brain findings, clinical history, examinations and history of prolonged metronidazole intake, possibility of metronidazole induced cerebellar toxicity was made.

Even after discontinuing the metronidazole, patient's neurology continued to deteriorate, she was unable to stand and walk and was ataxic. Hence, injection methyl prednisolone 1 gm diluted with 250 ml normal saline was infused as an empirical therapy daily for 3 days from third day of admission. On the 4th day after starting injection methyl prednisolone, she was remarkably improved with normal power in both the limbs and was able to walk with support. Patient was discharged on 7th day in stable condition, with oral methyl prednisolone in tapering dose, with normal limb powers, but had paresthesia of both the feet and mild ataxia. The patient was called up for follow-up after 1 month, and we found that patient was recovered totally with no paresthesia of both the feet, no ataxic symptoms, and was able to walk without support.

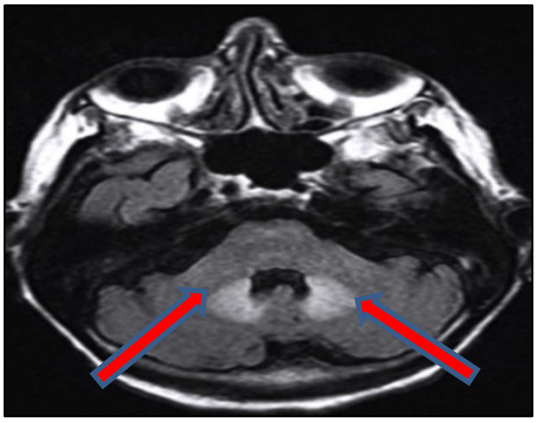

Figure 1: FLAIR sequence of axial magnetic resonance imaging of the brain showing hyperintensity (red arrows) in bilateral dentate nucleus of the cerebellum.

DISCUSSION

Metronidazole a typical antibacterial and antiprotozoal medication is normally well-tolerated, and rarely causes any serious adverse drug reaction.[7] Metronidazole for its indications is generally used for shorter duration, while its prolonged use is rare.[8] Common adverse effects of metronidazole are gastrointestinal ones.[4] Nervous toxicity which is quite rare, becomes evident on prolonged utilization of metronidazole, and appears as a peripheral neuropathy, acute encephalopathy, syncope, headache,

vertigo, dizziness, seizure, and confusion, while cerebellar toxicity is rare, which was seen in our case. Optic neuropathy, and aseptic meningitis have also been reported.[8] Central nervous system side effects become evident when the drug gain access to CSF.[6]

Nervous toxicity, following prolonged utilization of metronidazole is related to dose and duration of therapy with metronidazole. Neurological manifestations following metronidazole intake may develop with dose of 1-2.4 gm/day for at least 30 days or with a total dose of 50 gm.[8] Deenadayalu et al reported a case of dysarthria and ataxia in 50-year-old male patient, after history of metronidazole intake at even low dose than those mentioned in previous studies, that was oral metronidazole 500 mg TDS for 5 days (total-7.5 gm).[9] In our case, total dose of the metronidazole taken orally by the patient was around 72 gm and duration of drug intake was 60 days. Definite mechanism responsible for metronidazole-induced nervous toxicity is still unknown. In rats, higher dose of metronidazole has been demonstrated to cause cerebellar lesions.[10] Possible mechanism is that axonal degeneration resulting from interrupted protein synthesis by binding of metronidazole and its metabolites to neuronal RNA may be responsible for the neurological manifestations.[8] Purkinje cell lesions have been discovered in dogs following prolonged administration of metronidazole.[11]

MRI brain study is useful, and the primary sites involved in MRI brain as per recent literature, are in the form of T2W or FLAIR hyperintensity in the zones of dentate nucleus of cerebellum (most classical finding), splenium of the corpus callosum, midbrain including periaqueductal region, dorsal pons, medulla and rarely basal ganglia and thalamus.[12] In the majority of the patients, lesions are bilateral, and symmetrical. In our patient, the FLAIR sequence of axial MRI of brain, showed bilateral symmetrical hyperintensity affecting both the cerebellar dentate nucleus. The examination of Cerebrospinal fluid is normally inconclusive here.

Remission in the neurological symptoms is generally seen after discontinuation of metronidazole, and time to remission ranges from several days to weeks, but, peripheral neuropathy may persist for several months.[13] In our case, patient did not show clinical improvement in neurological symptoms even after discontinuation of metronidazole, and was ataxic. Delayed toxicity by drug accumulation may be the reason behind it. Hence, we started an empirical treatment with methylprednisolone to prevent complications. Methylprednisolone is a synthetic glucocorticoid having non-specific anti-inflammatory and immunosuppressive effects in CNS, in this manner, tissue inflammation, and cellular oedema are reduced, and micro circulatory perfusion is improved, resulting in improved local cerebral blood flow. The treatment was found to be effective, and after 3 days of injection methyl prednisolone, patient was remarkably improved. As a result, it may be a potential therapy option for patients whose symptoms worsen over time even after drug discontinuation. A follow-up MRI brain study is generally not required, once neurological symptoms are relieved.

Rechallenge study with metronidazole was not done in our case. The causality assessment for this suspected ADR (Adverse drug reaction) was done using WHO-UMC system, and it was found to be Probable ADR. Naranjo score was also measured using Naranjo algorithm, the score calculated was 8, suggesting Probable ADR. Severity of this ADR was measured using Modified Hartwig and Siegel scale, and it was found to be ‘level 4’ ADR (Moderate ADR). ADR form (version 1.3) was filled up, and this ADR was reported to the nearest ADR monitoring centre under PvPi (Pharmacovigilance Programme of India) via Vigiflow software with unique ID: IN-IPC-300510631.

CONCLUSION

Metronidazole is generally safe, when used in appropriate dosage for appropriate duration, however, prolonged utilization may lead to nervous toxicity. Metronidazole induced cerebellar toxicity should be considered in any patient presenting with cerebellar symptoms and peripheral neuropathy, with history of prolonged metronidazole intake. For definitive diagnosis, MRI brain study should be performed, and T2W or FLAIR hyperintensity in the zones of dentate nucleus of cerebellum is characteristic finding. Metronidazole should be discontinued immediately. In the majority of cases, clinical neurological manifestations and MRI finding results are completely reversed in few weeks. With persistently worsening neurological symptoms, to avoid fatal complications, early methylprednisolone intervention should be started, which can prevent progression of metronidazole-induced cerebellar toxicity and assist in neurological recovery. Further studies are needed to explore the mechanism of neurological protection by methylprednisolone in cerebellar toxicity.

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