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Metronidazole toxicity presenting with cerebellar ataxia

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Abstract

Metronidazole is used world wide very commonly. Minor adverse reactions to metronidazole include nausea, mouth dryness, vomiting and diarrhoea. Neurotoxicity is rare and seen predominantly as peripheral neuropathy, dizziness, vertigo and headache. Cerebellar toxicity is quite rare and serious side effect of metronidazole toxicity.We are reporting a rare case of metronidazole toxicity which presented with cerebellar atxia .

Keywords: Metronidazole toxicity,Cerebellum, Ataxia, Dentate Nucleus.

Introduction

Metronidazole (MNZ), is an antibiotic and antiprotozoal medication[1]. It is used either alone or with other antibiotics to treat pelvic inflammatory disease, endocarditis, and bacterial vaginosis. It is effective for dracunculiasis, giardiasis, trichomoniasis, and amoebiasis. The typical side effects are gastrointestinal symptoms including nausea, anorexia, abdominal cramping, diarrhoea, and vomiting. Long-term use can cause neurotoxicity, including encephalopathy, seizure disorder, peripheral neuropathy, autonomic neuropathy and optic neuropathy. Cerebellar toxicity is a rare but serious side effect of metronidazole toxicity. The neurological features usually become apparent when the drug is used in a dose exceeding 2 g/day for prolonged periods.

Most CNS adverse effects usually resolve over a period of 2-8 weeks. However, peripheral neuropathy may persist for months to years. Specific magnetic resonance imaging(MRI) findings are suitable tools that facilitate diagnosing metronidazole induced central nervous system toxicity.

Case Report

60 years old hypertensive and diabetic male patient presented in emergency with h/o acute onset of slurring of speech, vertigo and difficulty in walking for 2 days. He had no history of headache, loss of consciousness, or seizures and previous cardiovascular problem..Personal history was suggestive of chronic alcohol intake. Family history was insignificant. His past history was suggestive of admission in some hospital for liver abscess 3 months back, for which he took I.V metronidazole along with third generation cephalosporinson. He recovered well and was put on oral metronidazole for one week after discharge.But he never came for follow up and was using oral metronidazole without advise approximately 1600 mg from last three months. Labortory findings of hemogram, serum electrolytes , renal and liver profile revealed no abnormality except Random blood sugar 210 mg/dl and HbA1 c 8.5%.On general physical examination blood pressure was 170/90 mmhg. A neurologic examination revealed positive bilateral finger-nose-finger dysmetria, bilateral heel-knee-shin ataxia, dysarthria, downbeat nystagmus, a rebound phenomenon, pendular knee jerk, and preserved joint position sense, normal deep tendon reflex, and full muscle power. Conservative treatment with I/V mannitol, ceftriaxone ,antihypertensive, sugar control using S/C insulin started.

From clinical history and underlying risk factors, differential diagnosis of posterior fossa stroke, Wernicke encephalopathy, demyelinating diseases, metabolic, infectious, inflammatory processes and drug toxicity was kept. MRI of the brain showed symmetrical areas of increased T2/FLAIR signal involving the dentate nuclei .There was no restricted diffusion, intracranial hemorrhage or abnormal parenchymal enhancement. Based on the clinical and drug histoy of prolonged metronidazole intake, possibility of metronidazole induced cerebellar toxicity was made. After discontinuing metronidazole, nystagmus improved after 5 days and gait also started improving on sixth day. Patient was discharged in stable conditions and he is now under regular follow- up with no fresh complaints.

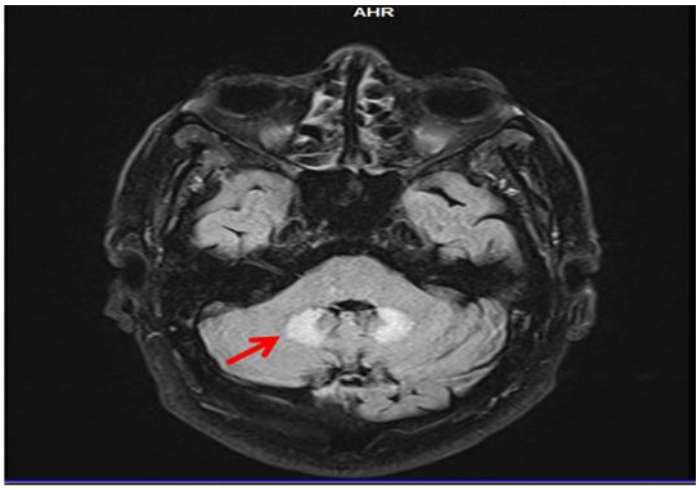

Figure: Axial T2 FLAIR image revealed symmetric increased signal intensity in bilateral dentate nuclei (red arrow)

Discussion

The typical side effects of metronidazole toxicity are gastrointestinal symptoms including nausea, anorexia, abdominal cramping, diarrhoea, and vomiting. Long-term use can cause neurotoxicity, including encephalopathy, seizure disorder, peripheral neuropathy, autonomic neuropathy , and optic neuropathy and cerebellar toxicity[2]. Cerebellar ataxia is quite a rare side effect in patients using metronidazole.

Cerebellar toxicity is related to wide ranges in the total dose (from 25 to 1080 g)[2] and therapeutic duration (from 5–730 days) of metronidazole use[3]. Deenadayalu et al described a 50- year-old a man who developed ataxia and dysarthria after taking a metronidazole dose even lower than that mentioned in previous studies (7.5 g total, 500 mg orally 3 times daily for 5 days)[4]. Both intravenously and orally administered metronidazole at a daily dose averaging 1.6 g can lead to neurologic toxicity.

The exact incidence of metronidazole-induced neurological toxicity is unknown and the underlying mechanism for brain injury has not been completely understood. Ahmed *et al*. who first described the imaging findings of metronidazole toxicity showing symmetrical, bilateral, abnormal hyperintense signal in the supratentorial white matter, corpus callosum, and within the cerebellum and deep cerebellar nuclei on T2W images[5]. It was postulated that metronidazole and its metabolites bind to neuronal RNA and inhibit protein synthesis resulting in reversible axonal swelling[6]. Other theories that have been put forward include: (1) interstitial edema and ischemia manifesting as increased signal intensity on diffusion-weighted and apparent diffusion coefficient mapping or (2) Purkinje cell damage after high dose of metronidazole due to binding of the drug to neuronal RNA, causing inhibition of protein synthesis and resulting in axonal degeneration.

MRI is the investigation of choice which was done in our case . MRI may reveal increased signal intensity on T2W/fluid-attenuated inversion-recovery images in the cerebellar dentate nuclei, midbrain, dorsal pons (the vestibular nucleus, abducens nucleus, and superior olivary nucleus), splenium of the corpus callosum, and the dorsal medulla. Unusual sites are the inferior olivary nucleus and cerebellar white matter. According to Seok *et al*.,[7] in addition to the above mentioned abnormalities, increased signal intensity may also be seen in the anterior commissure and bilateral inferior olivary nuclei with hypertrophic change.

MRI of the brain in our patient showed symmetrical areas of increased T2/FLAIR signal involving the dentate nuclei .The diagnosis of metronidazole toxicity was made clinically and was supported by the MRI findings.

The differential diagnosis includes demyelinating diseases, and metabolic, infectious, and inflammatory processes. Multiple sclerosis and acute disseminated encephalomyelitis may present with similar MRI findings, but involvement of the gray matter and the temporal profile make these possibilities unlikely. Wernicke encephalopathy is another differential diagnosis, but the involvement is predominantly of the diencephalon and midbrain. Atypical non-alcoholic Wernicke's encephalopathy can sometimes present with MRI findings of T2 hyperintensity involving the dorsal medulla and cerebellum[8]. Heat stroke can also rarely involve the cerebellum but the predominant involvement is of the thalami and external capsules. The differential diagnosis of T2 hyperintense, bilaterally symmetrical dentate nuclei includes methyl bromide intoxication, maple syrup urine disease and enteroviral encephalomyelitis[9]. The differential diagnosis of T2 hyperintense lesions in the splenium of the corpus callosum includes Marchiafava-Bignami disease, encephalitis (demyelinating, influenza, *Escherichia coli*, mumps, adenovirus, Epstein-Barr virus and Rota virus), osmotic myelinolysis, acute toxic encephalopathy and anti-epileptic drugs[9].

It is important to rule out other pathologies which tend to involve the brainstem and cerebellum including demyelination pathologies, toxic and metabolic encephalopathies. Wernicke's encephalopathy[10] is the biggest mimicker of metronidazole induced cerebellar toxicity, primarily because it also has high propensity for the dentate nuclei.

Clinical findings and history of alcoholism is usually evident in these patients. As in our case patient was also chronic alcohlic ,differential of Wernicke"s encephalopathy was kept in mind,but signs and symptoms improved within fourth day of admission after stopping metronidazole.Patient was discharged in stable condition and is under regular follow up.

Conclusion

Metronidazole induced toxicity should be considered in any patient who presents with seizures, cerebellar features, altered sensorium, symptoms of distal pure sensory involvement and is receiving prolonged therapy with metronidazole. MRI should be performed for definitive diagnosis.Metronidazole should be immediately discontinued. Complete reversal of symptoms and imaging findings is seen in most of the cases. Follow-up imaging is usually unnecessary once the clinical signs and symptoms have resolved.

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