Metronidazole Induced Encephalopathy

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Abstract

Metronidazole is an antimicrobial used for the treatment of anaerobic bacterial and protozoal infections. Neurological toxicity due to metronidazole use has been a matter of concern and many case reports of neurotoxicity are being published. We report here a case of a 32 years old male chronic alcoholic with multiple liver abscesses and history of 6 weeks use of metronidazole presenting with multiple episodes of seizures, burning sensation of feet and altered sensorium. MRI Brain revealed characteristic and reversible involvement of dentate nuclei and splenium of corpus callosum, typical of metronidazole induced encephalopathy (MIE).

Introduction

Metronidazole, tinidazole, secnidazole and ornidazole are 5-nitroimidazole group of drugs which are widely prescribed, believed to be safe and primarily used to treat infections caused by susceptible anaerobic organisms such as Bacteroides, Fusobacterium, Clostridium, Peptostreptococcus and Prevotella species and parasite such as Entamoeba histolytica, giardia and trichomonas vaginalis.1

Serious nervous system adverse effects like ataxia, encephalopathy, dysarthria, seizures, aseptic meningitis, and peripheral neuropathy, usually with prolonged therapy have recently been reported, though reviews suggest that they are reversible. The most common neurological complication caused by metronidazole is peripheral neuropathy.1 Caution should be used when prescribing metronidazole in patients with history of seizure disorder. Mild central nervous system effects include dizziness, headache, confusion, vertigo, and insomnia. Other, rare and serious adverse effects seen with metronidazole therapy include Stevens-Johnson syndrome, hemolytic uremic syndrome, pancreatitis, ototoxicity, and ophthalmologic toxicity.2

MRI has proven to be the most important diagnostic tool and reversibility is the most important feature of MIE, with reversal of both CNS effects and MRI findings. Most CNS adverse effects usually resolve over a period of 2-8 weeks. However, peripheral neuropathy may persist for months to years.

Case Report

A 32 year old male was diagnosed as a case of multiple unresolving liver abscesses and treated with metronidazole for a duration of 42 days in 2 different hospitals prior to admission with us. He presented to us with multiple episodes of seizures since 13 days, burning sensation of feet (hypersesthesia) since the last 9 days and altered sensorium since 1 day. There was a history of daily consumption of 120-150 ml of alcohol since approximately 10 years. There was no other relevant drug history nor any history of high risk behaviour.

On general physical examination, patient was afebrile, vitals were within normal limits and there was no evidence of pallor, icterus, cyanosis, clubbing, edema feet or lymphadenopathy. At the time of presentation, patient was confused, drowsy, uncooperative, not oriented to time, place and person. Re-examination following improvement in his sensorium after 3 days, revealed dysarthria, ataxic gait, impaired coordination on the left side of body and bilateral grade I horizontal nystagmus suggestive of left sided cerebellar involvement. Sensory examination revealed hyperesthesia in both soles and altered joint position sense in small joints of both feet. Rest of the CNS examination including fundus examination was normal and there was no neck rigidity. Abdominal examination revealed tender hepatomegaly and there was no ascites.

Complete blood count, renal function test, serum electrolytes, blood sugar, liver function test including serum bilirubin, serum transaminases, prothrombin time and serum proteins were normal. Urine examination was found to be normal. Serum ammonia level was 36 µg/dl. HIV, HBsAg and Hepatitis C tests were negative. Vitamin B12 and folate levels were normal. Thyroid function tests were within normal limits.

CSF examination revealed cell count less than 5 cells, all being mononuclear cells, proteins- 41 mg/dl and sugars-66 mg/dl. Abdominal ultrasound showed presence of multiple liver abscesses, one of which was aspirated and found to be sterile on culture.

EEG was suggestive of generalized epileptiform discharges. Nerve conduction study showed sensory axonal affection of bilateral sural nerves and right ulnar nerve. Since the patient’s metabolic parameters were normal, clinical examination, normal LFT and serum ammonia levels ruled out hepatic encephalopathy, prolonged metronidazole use was thought to be cause of the neurological features.

MRI Brain done on the day of admission showed hyper intensities in splenium of corpus callosum with restricted diffusion, ill defined hyper

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of CNS toxicity is variable (1 week to 6 months), and cumulative doses range from 25 g to 110 g. Patients with severe hepatic dysfunction are at an increased risk of accumulation and may be at an increased risk of metronidazole-induced encephalopathy, even with short-course therapy. In our case, total dose of metronidazole that the patient received was 39.3 gm and total duration was 42 days. It has been suggested that metabolites of metronidazole may bind to RNA instead of DNA, possibly inhibiting RNA protein synthesis, which could potentially lead to axonal degeneration. Another proposed mechanism involves the modulation of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) receptor within the cerebellar and vestibular systems. Although the mechanism of metronidazole neurotoxicity remains unclear, most lesions induced by metronidazole neurotoxicity may be reversible. The reversible changes associated with the acute toxic effects of metronidazole are most likely due to axonal swelling with increased water content rather than a demyelinating process. Another suggested mechanism involves vascular spasm that could produce mild reversible localized ischemia.

Characteristic MRI Brain findings are best visualised in T2 weighted images. Hyperintense lesions most commonly involve the cerebellar dentate nuclei. The midbrain, dorsal pons, dorsal medulla, and corpus callosum can also be affected. Uncommon locations include the inferior olivary nucleus and the white matter of the cerebral hemispheres. Lesions are always symmetric and bilateral, a pattern typical of metabolic encephalopathy. The differential diagnosis of, bilaterally symmetrical hyperintense lesions in T2 weighted image (Figure 1). These MRI findings were consistent with the diagnosis of metronidazole induced encephalopathy.

Metronidazole 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 and reversibility of lesion in MRI should be looked for.

Fig. 1: MRI brain showing T2-hyper intensities in corpus callosum and cerebellum

Metronidazole therapy was discontinued following which there was a considerable improvement in his sensorium and he was able to walk with support in 4 days and without support in 10 days. Seizures were controlled by phenytoin but peripheral neuropathy persisted.

A follow up MRI after 10 days showed resolution of hyper intensities of dentate nuclei with reduced hyper intensities in splenium of corpus callosum (Figure 2) suggestive of reversibility and further confirming the likelihood of Metronidazole being the culprit.

Discussion

Metronidazole is available for treatment in anaerobic infections but may produce a number of neurologic side effects particularly after prolonged use, such as cerebellar involvement, encephalopathy, seizures, autonomic neuropathy, optic neuropathy, and peripheral neuropathy. The neuropathy induced by metronidazole is predominantly sensory. Symptoms of neuropathy may recover completely or partially after discontinuation of metronidazole.

The incidence of MIE is unknown. Patients who already have risk factors like alcoholism and uremia are more prone to develop metronidazole toxicity. The duration of treatment with metronidazole before appearance of CNS toxicity is variable (1 week to 6 months), and cumulative doses range from 25 g to 110 g. Patients with severe hepatic dysfunction are at an increased risk of accumulation and may be at an increased risk of metronidazole-induced encephalopathy, even with short-course therapy. In our case, total dose of metronidazole that the patient received was 39.3 gm and total duration was 42 days. It has been suggested that metabolites of metronidazole may bind to RNA instead of DNA, possibly inhibiting RNA protein synthesis, which could potentially lead to axonal degeneration. Another proposed mechanism involves the modulation of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) receptor within the cerebellar and vestibular systems. Although the mechanism of metronidazole neurotoxicity remains unclear, most lesions induced by metronidazole neurotoxicity may be reversible. The reversible changes associated with the acute toxic effects of metronidazole are most likely due to axonal swelling with increased water content rather than a demyelinating process. Another suggested mechanism involves vascular spasm that could produce mild reversible localized ischemia.

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Metronidazole should be...
immediately discontinued. Increased awareness among physicians may enable early recognition of potentially reversible neurotoxicity and avoid unwarranted prescription of such medications.

Fig. 2: MRI brain after 10 days showing reduction in the hyper intensities seen previously

References


2. Mandell, Douglas, and Bennett’s Principles and Practice of Infectious Diseases 8th ed p 350-356


