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Original article

METRONIDAZOLE INDUCED REVERSIBLE CEREBELLAR TOXICITYA CASE REPORT OF UNCOMMON SIDE EFFECTS OF COMMONLY USED DRUG

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ABSTRACT

Background : Pyogenic liver abscesses carry significant morbidity and mortality and can be difficult to treat, typically requiring drainage and broad-spectrum antibiotics to resolve. Antibiotic regimens will often take several weeks to months after drainage to clear the infection, which can put patients at significant risk for developing serious side effects from long term medication toxicity Metronidazole is a widely used antibiotic against bacteria And protozoan infections. Even though the therapeutic use of the drug is high, it is associated with some severe side effects like neurotoxicity such as optic neuropathy, peripheral neuropathy, encephalopathy and cerebella toxicity. **History** :We present a case of a 56-years male presented with dysarthria, who had positive cerebellar sign . **Conclusion** The magnetic resonance imaging findings suggestive of metronidazole induced cerebellar toxicity following metronidazole therapy for six months in a case of liver abscess. And, the symptoms resolved after cessation of metronidazole

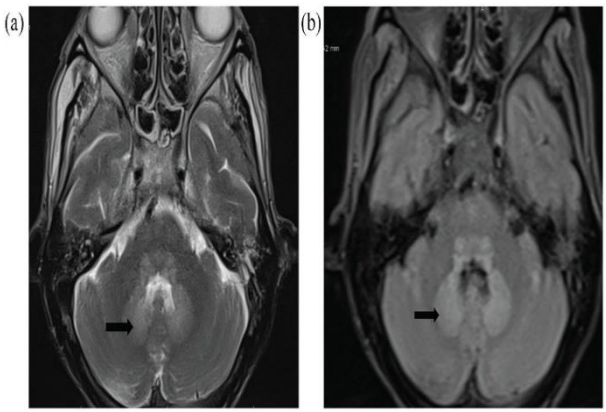
INTRODUCTION

Pyogenic liver abscesses carry significant morbidity and mortality and can be difficult to treat, typically requiring drainage and broad-spectrum antibiotics to resolve. Antibiotic regimens will often take several weeks to months after drainage to clear the infection, which can put patients at significant risk for developing serious side effects from long term medication toxicity[1] . Metronidazole is commonly used to treat liver abscess and carries a number of well-known common short term and long-term adverse effects. Common adverse effects of metronidazole include metallic taste, confusion, nausea, vomiting, diarrhea, headacheand disulfiram-like reaction [2][3].Neurotoxicity is rare, seen predominantly as peripheral neuropathy, dizziness, vertigo and headache. Cerebellar toxicity is a rare but serious side effect of metronidazole toxicity with classic findings on magnetic resonance imaging (MRI). We discuss one case of metronidazole-induced cerebellar dysfunction, presenting with signal changes of the dentate nucleus. Although the pathophysiology of metronidazole neurotoxicity remains unclear, most lesions secondary to metronidazole neurotoxicity are completely reversible. Moreover, the toxicity does not seem to be a dose- or duration-related phenomenon.

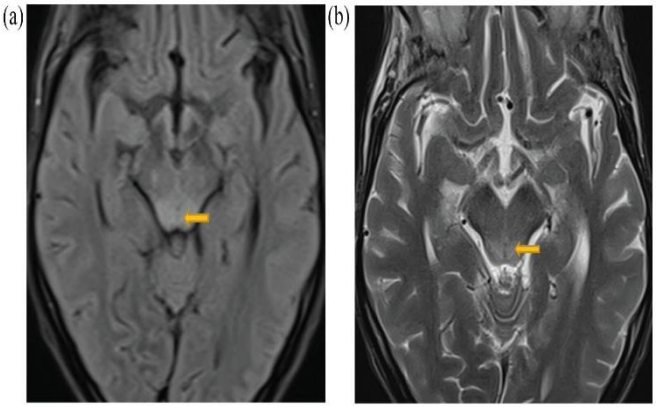
History

A 56 years old male presented to the emergency department of our hospital with the chief complaint of slurring of speech ,walkingdifficulty, imbalancedizziness since 4 day which was acute on the onset and progressive in nature. He could understand the spoken or written language and could obey the command; his comolain of dizziness is on and off. There was no history of headache, vomiting, blurring of vision, neck rigidity, facial deviation, difficulty in swallowing. He had no complaints of any abnormal body movements, focal weakness of any body parts, and stool or urinary incontinence. He was diagnosed with an amoebic liver abscess six months back for which he was taking tablet ciprofloxacin(500mg)twice a day, metronidazole (400mg) thrice a day for six month.Aspirantion of liver abscesses contentdone for 3 times in these six month time. He is anchronic smoker and chronicalcoholic since 20 yr. He stopeddrinking 6 month ago.

On examination, his blood pressure was 140/80 mmHg, pulse was 88 beats per minute, respiratory rate was 18 breaths per minute, SpO2 96% on room air. His Glassgow Coma Score was 15/15, higher mental functions were intact, signs of meningeal irritations were absent and



sensory and motor functions were intact. Cerebellar signs were elicited where dysdiadokinesia was present, tandem gait was impaired and Romberg's test was positive.and sign of dymetriafinger- nose test, Finger- finger were present.Patient was admitted to the medicine ward with the impression of cerebellar stroke. On routine investigation his random blood sugar was 121mg/dl, electrolytes were within normal range and his blood cell counts were normal while hemoglobin was 12 gm/dl. His liver function test was normal.



(a) Axial T2-weighted

(b) FLAIR images show increased signal intensities symmetrically involving the bilateral dentate nuclei, middle cerebellar peduncle, and part of the pons

(a) Fluid attenuated inversion recovery

(b) axial T2-weighted images show the increased signal intensity in the tectum of the midbrain.

For diagnosis of Posterior circulation stroke or cerebllar stroke Magnetic Resonance imaging was done .MRI Brain (plain +contrast) shows Mild restricted diffusion seen involving splenium of corpus callosum and bilateral posterior midbrain along tectal plate, both cerebellar hemisphere along periventricular white matter of 4th ventricle and bilateral postero-medial

thalami, which appears hyperintense on T2W and FLAIR images, and shows no blooming on GRE images and shows no contrast enhancement.

After diagnosis, metronidazole was discontinued and.After cessation of metronidazole patient start improving clinically within 3-4 day and cerebellar signs resolved within two weeks. Follow up MRI was not done as the symptoms of cerebellar toxicity had completely resolved.

DISCUSSION

Metronidazole is an antimicrobial and antiprotozoal with broad usage in medical and surgical patients. It is a synthetic 5-nitroimidazole which is in inactive state on administration and turns to metabolically active form on reaching the target. It is a well-tolerated drug with very low incidence of severe side effects. The most common side-effects include nausea, headaches and metallic taste in mouth. Neurological side-effects are uncommon. Vast majority being mild to moderate peripheral neuropathy. As the drug penetrates cerebrospinal fluid (CSF), it can cause central neurological (CNS) side effects[4]. This can range from seizures to diffuse encephalopathy or acute/chronic cerebellar symptomvisual impairment, vestibulo-toxicity, cochlear toxicity,. Imaging is usually not indicated in this group of patients and is usually done to rule out other intracranial pathologies. Moreover, imaging is unrevealing in most of the patients presenting with seizures or diffuse encephalopathy[5]. However, recently there have been many cases of acute/ chronic cerebellar toxicity reported in literature. Interestingly, most of the patients in this group have findings on MR imaging which includes signal changes in the dentate nucleus. Recognizing the pattern of imaging abnormality is important as terminating the usage of Metronidazole can result in rapid clinical improvement and resolution of signal changes.

The exact mechanism of cerebellar toxicity is unclear. Multiple prior studies done in animal (rats) subjects have shown axonal degeneration after treatment with Metronidazole, with symmetric lesions in the cerebellar and cochlear nuclei. It was postulated that Metronidazole and its metabolites binds to neuronal RNA and inhibit protein synthesis resulting in reversible axonal swelling[6]. Metronidazole crosses blood-brain barrier and can result in imaging and histological findings similar to Wernicke's encephalopathy. Metronidazole neurotoxicity is not dependent upon the dosage and duration of usage with no significant difference between the oral and intravenous routes of administration. IN prior studies, males and females had the same predisposition and the median duration of complications[7] . Onset from the initiation of the antibiotic was approximately 15 days (ranged from 1 to 90 days), with an average cumulative metronidazole dose of 93.4 g (g) (ranged from 0.25 to 1095 g). The development of symptoms can last from 2 to 4 weeks when cumulative dosing of metronidazole reaches 21–182 g[7]; however, few cases of toxicity have been reported with shorter treatment periods[8] . Neuropathic changes associated with metronidazole use have been found to be dose-dependent, with doses of 1000–2400 milligrams (mg) daily for at least 30 days, or, a cumulative dose of 50 g[9] . In terms of neurological symptoms, cerebellar dysfunction was found to be the most common (75 %), followed by altered mental status (33 %) and seizures (13 %) [7]. Among

cerebellar dysfunction, dysarthria, ataxia, dysmetria and nystagmus were most common findings on examination in descending order of frequency[7] .

Current literature has demonstrated patients with metronidazole toxicity exhibiting symmetrical T2W or FLAIR hyper intensities with minimal hypo-intensity on T1W images with no contrast enhancement or mass effect. Many patients also show restricted diffusion with varying apparent diffusion coefficient (ADC) value. Lower ADC values may suggest more acute nature of cell damage.The area involve are cerebellar dentate nucleus (most characteristic), midbrain (including periaqueductal region), corpus callosum splenium, dorsal pons, medulla, inferior colliculus, subcortical white matter, basal ganglia, thalamus, and middle cerebellar peduncles in decreasing order of frequency[1][3] . Lesions in the corpus callosum may demonstrate a restricted diffusion pattern[1]. Lesions are bilateral and symmetric in almost all the patients. Lesions are generally reversible with complete resolution of signal changes on follow-up imaging[8] . Cerebrospinal fluid analysis is usually unrevealing. 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 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. Other diseases such as osmotic demyelination tend to involve the basalpons and spare the dentate nuclei. Many diseases can result in increased T1-signal within the dentate, which is usually a non-specific finding and represents mineralization or calcification[10]. However, there are very few conditions which result in increased T2/FLAIR signal in the dentate. Extensive search of literature revealed very few conditions which result in such an imaging appearance. This includes Wernicke's encephalopathy and metronidazole toxicity, methyl-bromide toxicity, maple-syrup urine disease and enterovirusencephalomyelitis .Complete reversal of symptoms and imaging findings is seen in most of the cases[11][12]. Follow-up imaging is usually unnecessary once the clinical signs and symptoms have resolved.

In the majority of cases post metronidazole discontinuation, patients exhibit symptom resolution (65 %), or at least significant improvement (29 %) However, 3 % of patients may have permanent deterioration, leading to death[13]

CONCLUSIONS

To summarize, MR imaging findings of bilateral increased T2/FLAIR signal of the dentate nuclei are a very characteristic feature of metronidazole-induced neurotoxicity. Patients taking metronidazole should be watched for cerebellar ataxia, seizures, paresthesia, and neurotoxicity. On the development of such side effects the problematic drug should be discontinued. A complete reversal is usually observed.

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