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Case report

Metronidazole induced cerebellar toxicity after prolonged treatment of large multiloculated pyogenic liver abscess; A case report and literature review

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ABSTRACT

Metronidazole is a common antibiotic agent for hepatic abscesses, which require both gram-negative and anaerobic coverage. Rarely, this antibiotic has been found to induce encephalopathy. Here, we describe a 65-year-old male who was treated with metronidazole for his hepatic abscess, who presented with syncope and questionable seizure and was found to have magnetic resonance imaging (MRI) brain findings consistent with metronidazole toxicity. Our patient demonstrated striking brain MRI findings which can be used to further understand the process behind this medication-induced toxicity. Hypotheses of this mechanism include swelling of axons secondary to increased water or vasospasm leading to reversible ischemia that is localized in the brain. In terms of MRI findings, brain lesions tend to populate bilaterally with focus at the dorsal pons, midbrain, cerebellar dentate nuclei (as with our patient), dorsal medulla, or splenium of corpus callosum. Additional research is warranted regarding this rare manifestation and timely removal of the offending agent is crucial for reversal of symptoms.

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, headache, ataxia, seizures, cochlear toxicity, peripheral neuropathy, vision impairment, and disulfiram-like reaction [2,3]. Rarely, cumulative neurotoxicity can occur if the drug is used for extended periods of time [2]. Limited research has been done on neurological side effects of long-term use, so most are not well established. Here we present one such case of cumulative CNS toxicity due to long term use of metronidazole. Most studies evaluating the etiology of metronidazole-induced neurotoxicity have been conducted on animal models. Hypotheses include swelling of axons secondary to increased water or vasospasm as a result of free radical production during metronidazole metabolism leading to reversible ischemia that is localized in the brain [2]. Metronidazole freely crosses the blood-brain barrier, allowing for serum-like quantities in the cerebrospinal fluid [4]. This antibiotic's intermediate metabolites may bind to the RNA or DNA of neuronal cells [3]. In animal studies, metronidazole bonded to CNS ribonucleic acid in rats, limiting protein synthesis and leading to axonal degeneration [5]. In one study, over the course of six weeks, rats were given 800 mg/day of metronidazole, which caused symmetrical lesions in the vestibular, cochlear, and cerebellar nuclei [5]. Metronidazole-induced neuropathy could possibly be linked to the drug's capacity to generate oxygen radicals and subsequently increasing axonal swelling [6].

Case presentation

A 65-year-old male patient with a past medical history of pre-

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diabetes, dyslipidemia, benign prostate hyperplasia, cholelithiasis, and recent Klebsiella pneumoniae hepatic abscess (receiving metronidazole 500 mg three times daily and ciprofloxacin 500 mg twice daily at home for the past 3 months). The patient presented five months earlier to the ED with a complaint of epigastric pain that began one night prior to presentation. CT abdomen and pelvis (CTAP) showed a 11.9 × 13.3 cm complex cystic mass in the liver, suggestive of hepatic abscess [Fig. 2]. IR CT guided drainage was performed and Jackson-Pratt (JP) drain was placed to drain a large pocket of abscess. Blood cultures and abscess fluid cultures were positive for Klebsiella pneumoniae. Patient was treated with cefepime and metronidazole. Repeat CTAP 3 weeks after showed multiple small residual left hepatic abscesses, significantly decreased in size and number compared to the previous imaging [Fig. 2]. The patient received a total of 12 weeks of metronidazole after discharge from the hospital. Repeat CTAP 24 weeks after demonstrating areas of hepatic scarring. [Fig. 1]. During this admission, the patient presented after a fall and convulsive syncope. He denied recollection of the episode or prodromal symptoms. The family reported the patient had upper body shaking movements with an absence of lip-smacking or incontinence. In the Emergency Department (ED), the patient was hemodynamically stable. Physical exam was notable for ataxic gait and a positive right-sided Romberg sign. Patient was not receiving medication that can cause drug-drug interaction that would explain his neurological symptoms.

The patient was admitted for syncope with questionable seizure and Neurology and infectious diseases evaluations were requested. The patient underwent echocardiography, computed tomography (CT) of the head, magnetic resonance imaging of the brain (MRI Brain without contrast) and magnetic resonance imaging of the arteries (MRA) which were unremarkable in determining a cause for the patient's presentation. However, an MRI Brain with contrast demonstrated hyperenhancement of T2/FLAIR signal abnormality in the bilateral cerebellar dentate nuclei with findings concerning for metronidazole toxicity. Metabolic and cardiac etiologies were excluded upon workup. Given these findings, the patient was advised to discontinue metronidazole at home. He was then scheduled for neurology outpatient follow-up with repeat MRI to determine resolution upon cessation of antibiotics. Repeat MRI brain with and without contrast was performed 10 weeks later which showed complete resolution of the changes in the cerebellum consistent with metronidazole toxicity [Fig. 2].

Two months after hospital discharge, the patient continues to report significant improvement of his gait without ataxia or unsteady gait. Repeat MRI was obtained during neurological outpatient evaluation, which showed resolution of cerebellar changes consistent with metronidazole toxicity.

Discussion

Metronidazole induced encephalopathy was first published in 1977, and multiple cases have been reported since then, and this remains a rare phenomenon [3]. 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) [7]. The development of symptoms can last from 2 to 4 weeks when cumulative dosing of metronidazole reaches 21–182 g; 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]. In a retrospective analysis of 36 case reports, peripheral neuropathy was a common adverse effect of metronidazole when patients received over 42 g total in over 4 weeks of treatment [2]. In our patient's case, he developed seizure-like activity as well as ataxic gait in the setting of metronidazole use.

Ahmed et al. first described MRI findings of long-term metronidazole toxicity as abnormal symmetrical signals in supratentorial white matter and within the cerebellum deep gray matter. They reported almost complete resolution of said findings approximately 6 weeks after cessation of the drug [10]. In terms of MRI findings, brain lesions tend to populate bilaterally with focus at the dorsal pons, midbrain, cerebellar dentate nuclei (as with our patient), dorsal medulla, or splenium of corpus callosum [1]. Differential diagnoses which may appear similar on MRI to consider when a patient presents with suspected Metronidazole induced encephalopathy include metabolic etiologies, inflammation, or demyelinating disorders; however, unremarkable CSF findings and presence of gray matter involvement help to differentiate them [11]. Current literature has demonstrated patients with metronidazole toxicity exhibiting symmetrical T2W or FLAIR hyperintensities with minimal hypo-intensity on T1W images in the areas of 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]. The most striking aspect of this disease is the complete or near-complete resolution of the initial lesions on subsequent MRIs [1]. In our patient's case, after metronidazole was discontinued, the patient was found to have significant improvement demonstrated on radiographic imaging.

If long term therapy or multiple courses of metronidazole are being used, clinical monitoring for neurologic symptoms is essential. If patients exhibit new neurological symptoms, then metronidazole use should be considered as an etiology. Discontinuation of the drug typically results in reversal of clinical findings and of associated neurological imaging findings [2,12]. 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]. There are two case reports of patients who expired from permanent metronidazole-induced encephalopathy (MIE) despite discontinuing the medicine [13]. Groothoff et al. and Hobbs et al. observed that metronidazole has caused fatal irreversible encephalopathy [13,14]. As with most cases, our patient achieved significant neurologic symptomatic improvement following the cessation of the offending antibiotic.

CRediT authorship contribution statement

Ahmed Salem: Conception and design of study, acquisition of data, Drafting the manuscript, revising the manuscript critically for important intellectual content, Approval of the version of the manuscript to be published. **William Lewis:** Conception and design of study, acquisition of data, Drafting the manuscript, Approval of the version of the manuscript to be published. **Brooke Kania:** Conception and design of study, acquisition of data, Drafting the manuscript, revising the manuscript critically for important intellectual content, Approval of the version of the manuscript to be published. **Deniz Yucel:** Drafting the manuscript, Approval of the version of the manuscript to be published.

Ethical standards

All authors gave their informed consent before their inclusion in the study.

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Disclosures

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.idcr.2023.e01683.

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