Metronidazole encephalopathy: Uncommon reaction to a common drug

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ABSTRACT

Encephalopathy associated with metronidazole administration is an uncommon but potentially reversible disease and depends on the cumulative metronidazole dose, and most patients with this condition recover rapidly after discontinuation of therapy. We present a case as well as a review of the literature regarding this rare but serious adverse event.

Key Words: Adverse effect, encephalopathy, metronidazole, toddy

INTRODUCTION

Metronidazole, a nitroimidazole antimicrobial agent is widely used in the treatment of anerobic and protozoal infections for more than three decades. Common side effects are nausea, vomiting, abdominal discomfort, headache, and metallic taste. Neurological effects such as ataxia, dizziness, peripheral neuropathy, and seizures were also reported. We report a rare case of metronidazole-induced encephalopathy (MIE) in order to create an awareness of this unusual entity among practitioners.

A 39-year-old male without any comorbidities was brought to the emergency department for acute onset of slurring of speech, generalized weakness, and unsteadiness. He was unable to button his shirt, and turn a doorknob due to clumsiness of hands and fingers for the past 24 hours. Four days prior to this admission, he complained of numbness and tingling sensation of toes and dorsum of both feet. Recently, he was treated for amebic liver abscess with ultrasound-guided aspiration and was given tablet metronidazole 800 mg three times a day for 2 weeks. Since repeat ultrasound revealed re-accumulation of liver abscess after 2 weeks, he was advised to continue metronidazole 800 mg three times a day orally for 2 more weeks. Thus, he had taken 67.2 grams of tablet metronidazole over a period of 28 days.

Neurologic examination revealed the patient was conscious but confused, with dysarthria, nystagmus, dysmetria on finger-to-nose test, positive Romberg’s sign; graded sensory loss to pain, temperature, touch, and proprioception over distal lower and upper extremities in a stocking and glove type, and impaired joint position and vibration sense. Clinical assessment of cranial nerve, muscular system, deep tendon reflexes, and gait was normal with absent Babinski sign. Rest of the systemic examination and vitals were essentially normal.

His hematological, metabolic panel, thyroid profile, cerebrospinal fluid (CSF) analysis, viral markers, arterial blood gas, ammonia levels, vitamin B1, B12, and folate levels were within normal limits but for mild derangement of liver function. His autoimmune work-up was negative. His magnetic resonance imaging (MRI) brain revealed symmetrical areas of altered signal intensity, appearing hyperintense on T2W and fluid-attenuated inversion recovery (FLAIR) images, and involving the dentate nuclei and splenium of the corpus callosum. There was an evidence of diffusion restriction on diffusion-weighted/apparent diffusion coefficient mapping without evidences of hemorrhage or infarct. Imaging findings were in favor of metronidazole toxicity, which was supported by the prolonged history of metronidazole intake. Moreover, his symptoms disappeared on third day after discontinuation of metronidazole, and MRI 4 months later showed...
resolution of the earlier described signal changes. The serum metronidazole levels were not estimated due to technical limitation.

MIE usually occurs at doses exceeding a total of 50 grams/month or 1.5 to 2 grams/day. Although the exact mechanisms are unknown, the possible mechanisms with experimental evidences are furnished. Metronidazole easily penetrates into the blood–brain barrier and reaches therapeutic concentrations equivalent to that of serum.[1] Furthermore, cerebellum of rats has been shown to uptake carbon labeled metronidazole.[3] In vitro, metronidazole incorporated into thiamine analogs, inhibits the phosphorylation of thiamine, thereby antagonizing vitamin B1 effect.[4] Radiolabelled metronidazole binds ribonucleic acid (RNA) in a significant manner, and inhibits neuronal protein synthesis and facilitates degeneration.[3] Catecholamine neurotransmitters are oxidized by metronidazole derivatives to produce semiquinone and nito anion radicals which are neurotoxic.[5] The case is presented so as to facilitate practitioners to recognize the symptoms and signs of metronidazole toxicity, and consider them in their differential diagnosis. It is worth to remember the potential neurological abnormalities and imaging findings of this entity, as this agent is frequently prescribed and used in clinical practice.

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