The Journal of Emergency Medicine, Vol. ■, No. ■, pp. 1–5, 2016

0736-4679/$ - see front matter

http://dx.doi.org/10.1016/j.jemermed.2016.05.038

Clinical Communications: Adult

METRONIDAZOLE-INDUCED ENCEPHALOPATHY IN ALCOHOLIC LIVER DISEASE: A DIAGNOSTIC AND THERAPEUTIC CHALLENGE

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□ **Abstract—Background: Acute encephalopathy in a patient with alcoholic liver disease (ALD) is a commonly encountered emergency situation occurring most frequently due to liver failure precipitated by varying etiologies. Acute reversible cerebellar ataxia with confusion secondary to prolonged metronidazole use has been reported rarely as a cause of encephalopathy in patients with ALD. Case Report: We describe a decompensated ALD patient with recurrent pyogenic cholangitis associated with hepatolithiasis who presented to the emergency department with sudden-onset cerebellar ataxia with dysarthria and mental confusion after prolonged use of metronidazole. Magnetic resonance imaging (MRI) of the brain was suggestive of bilateral dentate nuclei hyper intensities on T2 and fluid-attenuated inversion recovery sections seen classically in metronidazole-induced encephalopathy (MIE). Decompensated liver cirrhosis resulted in decreased hepatic clearance and increased cerebrospinal fluid concentration of metronidazole leading to toxicity at a relatively low total cumulative dose of 22 g. Both the clinical symptoms and MRI brain changes were reversed at 7 days and 6 weeks, respectively, after discontinuation of metronidazole. Why Should an Emergency Physician Be Aware of This?: A patient with ALD presenting with encephalopathy creates a diagnostic dilemma for the emergency physician regarding whether to continue metronidazole and treat for hepatic encephalopathy or to suspect for MIE and withhold the drug. Failure to timely discontinue metronidazole may worsen the associated hepatic encephalopathy in these patients. Liver cirrhosis patients have higher mean concentration of metronidazole and its metabolite in the blood, making it necessary to keep the cumulative dose of metronidazole to < 20 g in them.**

□ **Keywords—metronidazole-induced encephalopathy; alcoholic liver disease; cerebellar; ataxia; recurrent pyogenic cholangitis**

INTRODUCTION

Metronidazole is a widely used drug in day-to-day gastroenterology practice. It is prescribed for conditions like Crohn's disease, intra-abdominal abscess, infection with *Helicobacter pylori*, hepatic encephalopathy, and recurrent pyogenic cholangitis (RPC). Its common adverse reactions include nausea, dysgeusia, anorexia, and abdominal cramping (1). Neurotoxicity with metronidazole has been rarely reported. Presenting symptoms range from headache, incoordination, and ataxia to convulsive seizures, optic neuropathy, encephalopathy, and peripheral neuropathy (1). Only a handful of cases of metronidazole-induced encephalopathy (MIE) in patients with chronic liver disease have been reported. We describe a case of acute-onset cerebellar ataxia with

RECEIVED: 6 March 2016; FINAL SUBMISSION RECEIVED: 6 May 2016;
ACCEPTED: 17 May 2016

dysarthria and confusion secondary to prolonged intravenous metronidazole use in a patient with RPC with hepatolithiasis and decompensated alcohol-related liver cirrhosis. Prompt identification and differentiation from hepatic encephalopathy were crucial in the management of this patient. Liver cirrhosis reduces the threshold for metronidazole-induced toxicity, as hepatic pathway contributes to 30%–60% of clearance of the drug (2,3). The exact pathogenesis of metronidazole-induced cerebellar toxicity is not known, but various theories have been proposed that are discussed in this article, together with a review of literature regarding this rare clinical scenario.

CASE REPORT

A 50-year-old male patient presented with progressively worsening difficulty in talking, imbalance during walking, mental confusion, headache, and paraesthesia of extremities over the past 3 days. The patient had a known case of decompensated alcohol-related cirrhosis of liver with ascites, portal hypertension, and a history of recurrent hepatic encephalopathy. RPC associated with widespread hepatolithiasis was diagnosed recently. At presentation, his medical records showed that he was on day 18 of broad-spectrum intravenous antibiotics, which included ceftriaxone (1 g twice daily) and metronidazole (400 mg three times daily). His medications included tablet propranolol, rifaximin, fish oil, and ferrous sulfate. Endoscopic biliary decompression with biliary stenting did not provide adequate relief from cholangitis. Ascites precluded percutaneous transhepatic biliary drainage. Surgery was delayed by the patient's poor general condition.

On examination he was icteric, febrile with temperature of 38.3°C, pulse rate of 102 beat/min, and blood pressure of 110/70 mm Hg. The patient was drowsy with mild mental confusion, but was easily arousable and oriented in time, place, and person. There was mild right hypochondrium tenderness and fluid thrill on abdominal examination. Neurologic examination revealed dysarthria, bilateral horizontal gaze nystagmus, positive Romberg's sign, positive bilateral finger nose test, wide base stance and gait, and impaired tandem walking suggestive of cerebellar-type ataxia. Asterixis was absent. Significant laboratory parameters on admission were: total leukocyte count of 16,500/mm^3 (neutrophils 90%), total bilirubin 8 mg/dL, direct bilirubin 5 mg/dL, serum alkaline phosphatase 550 IU/L (normal up to 310 IU/L), aspartate aminotransferase 180 IU/L (normal up to 40 IU/L), alanine aminotransferase level 110 IU/L (normal up to 40 IU/L), arterial ammonia was 40 μM/L (normal up to 80 μM/L), serum albumin 2.8 g/L, prothrombin time 15 s, with international normalized ratio of 1.1. Blood and ascitic fluid culture did not reveal any growth. Ascitic fluid routine and microscopic examination revealed total cell count of 120 (80% lymphocytes, 20% neutrophils), total protein 1.8 g/dL, albumin 0.9 g/dL, and sugar 50 mg/dL. His serum sodium level was 140 mmol/L (normal 135–145 mmol/L) and potassium was 4.2 mmol/L (normal 3.5–4.5 mmol/L). Blood urea nitrogen was 10 mg/dL (normal 0–20 mg/dL) and serum creatinine was 0.8 mg/dL (normal 0.5–1.5 mg/dL). Child-Turcott-Pugh score was 9/15 (B) and Model for End-Stage Liver Disease score was 16. Stool examination was normal. Ultrasonography of abdomen revealed ascites, splenomegaly, and coarse echotexture of liver with bilobar intrahepatic biliary radicle dilatation with evidence of intrahepatic biliary calculi. Magnetic resonance cholangiopancreatography revealed multiple small punctate T2 hypointense foci seen within the dilated biliary radicles suggestive of hepatolithiasis (Figure 1). Computed tomography of brain did not show any evidence of hemorrhage or infarct. Magnetic resonance imaging (MRI) of brain in axial T2 weighted, axial, and coronal T2 fluid-attenuated inversion recovery sequences through posterior fossa showed striking hyper-intense signal in bilateral dentate nuclei (Figure 2A–C). These findings were suggestive of an ongoing toxic or metabolic damage to the neurones. We suspected metronidazole-induced cerebellar toxicity in view of prolonged metronidazole use and classical involvement of dentate nuclei. Metronidazole was discontinued and physiotherapy was started. Two days later, his dysarthria and ataxia began to improve and he was able to walk without imbalance on the 7th day. All his cerebellar signs had disappeared by that time. Subsequent MRI done at 6 weeks after cessation of metronidazole therapy showed complete resolution of

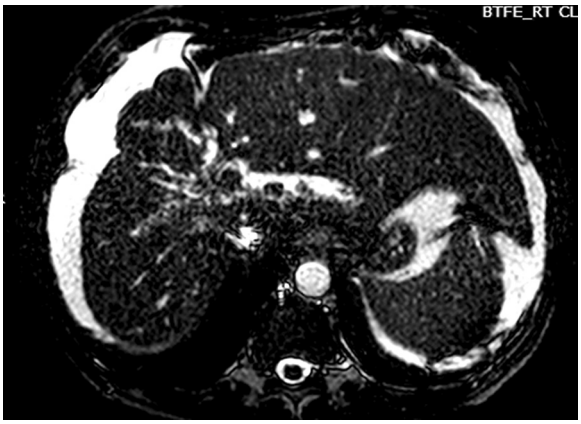

Figure 1. Magnetic resonance cholangiopancreatography showing multiple small punctate T2 hypo-intense foci within the dilated biliary radicles of both right and left hepatic lobes, suggestive of hepatolithiasis.