MRI of Metronidazole-Induced Encephalopathy

Hyojeong Mulcahy, M.D., and Shashi K.B. Chaddha, M.D.

We report the magnetic resonance imaging (MRI) findings of metronidazole-induced encephalopathy in a 58-year-old man who was treated with metronidazole for hepatic encephalopathy. MRI is likely to be helpful in confirming the diagnosis of metronidazole toxicity in clinically suspected cases.

Introduction

Metronidazole (Flagyl) is a common antimicrobial agent used in the treatment of anaerobic and protozoal infections. For the patients with hepatic encephalopathy, metronidazole is used to remove the nitrogenous load in the gastrointestinal tract. Dose and duration of metronidazole should be minimized as much as possible to avoid side effects such as peripheral neuropathy, cerebellar dysfunction, and seizures [1-2]. We present a case of metronidazole-induced encephalopathy.

Case Report

A 58-year-old man presented with a chief complaint of increasing confusion, intermittent episodes of imbalance, and episodes of abnormal behavior. His medical history was significant for cirrhosis and hepatic encephalopathy secondary to congenital hepatic fibrosis. On neurologic examination, he had a horizontal nystagmus, demonstrated dysmetria on finger-to-nose test, and Romberg's sign was positive. He was on metronidazole 500 mg, orally twice a day, at home for his hepatic encephalopathy, and the dose was increased during admission to 750 mg orally twice a day.

CT scan of the brain showed mild atrophy (not shown). The patient went on to further evaluation with MRI. MR imaging demonstrated strikingly increased signal intensity symmetrically involving the dentate nuclei bilaterally on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images (Fig 1A & B), with isointensity on T1-weighted images and no evidence of enhancement following administration of gadolinium (Fig 2A & B). Diffusion weighted imaging demonstrated corresponding high signal intensity within the dentate nuclei on the isotropic diffusion images (Fig 3). An apparent diffusion coefficient (ADC) map demonstrated an increase in the value of the diffusion coefficients in the regions of diffusion signal intensity abnormality, consistent with T2 shine-through (not shown).

Discussion

Metronidazole (Flagyl) is a common antimicrobial agent used in the treatment of anaerobic and protozoal infections. For the patients with hepatic encephalopathy, metronidazole is used to remove the nitrogenous load in the gastrointestinal tract, and it’s generally administered
MRI of Metronidazole-Induced Encephalopathy

Figure 1. 58-year-old man with metronidazole-induced encephalopathy. Axial T2-weighted (A), and FLAIR (B) MR images show markedly increased signal intensity symmetrically involving the dentate nuclei bilaterally without surrounding edema or mass effect.

at 250 mg every 8 to 12 hours (500 to 750 mg daily) [3]. Dose and duration of metronidazole should be minimized as much as possible to avoid side effects associated with its long-term use such as peripheral neuropathy, cerebellar dysfunction, and seizures[1-2]. Although this phenomenon has been described as a manifestation of drug toxicity, it is not clear why metronidazole causes these lesions in a small number of patients, and cases have been reported in which the serum levels of metronidazole were within the therapeutic range[4]. No serum or cerebrospinal fluid level of metronidazole was obtained in our patient, and the diagnosis of metronidazole toxicity was made clinically and supported by the MR imaging findings.

Depending on their severity and chronicity, liver diseases have variable neurologic manifestations, and it is becoming widely recognized that patients with chronic liver disease exhibit typical abnormalities on MRI. High signal intensities in the globus pallidus on T1-weighted images have been established as a characteristic finding on MR images in chronic hepatic encephalopathy, and recent data have shown that white matter abnormalities can also be detected[5,6]. However, cerebellar lesions have rarely been observed on MRI studies, and there are a few reports describing abnormal T2 high signal intensities in superficial and deep cerebellar white matter including the brachium pontis in patients with acquired hepatocerebral degeneration[7,8].

After Ahmed et al first described the imaging findings of metronidazole toxicity[9], there are only several reported cases describing imaging findings of metronidazole toxicity in literature. Imaging abnormalities associated with metronidazole toxicity have identified lesions in the dentate nuclei of the cerebellum, corpus callosum, basal ganglia, and frontal and subcortical white matter, and MR imaging findings of bilateral involvement of the dentate nuclei are a very characteristic feature of metronidazole-induced encephalopathy[4,9-12]. In our case, it was the only demonstrated lesion on MR imaging.

The mechanism of metronidazole toxicity has not been elucidated, and the apparent preferential involvement of the dentate nucleus remains puzzling. The signal intensity changes observed on the diffusion weighted images most likely represent interstitial edema[9,11], even though it could represent cytotoxic edema in lesions of the corpus callosum[12]. The findings on MR spectroscopy suggest the possibility of a reversible mito-
MRI of Metronidazole-Induced Encephalopathy

Figure 2. 58-year-old man with metronidazole-induced encephalopathy. Axial pre- (A), and post-gadolinium (B) T1-weighted MR images show T1 isointensity and no evidence of enhancement following administration of gadolinium.

Figure 3. 58-year-old man with metronidazole-induced encephalopathy. Axial isotropic diffusion-weighted MR image shows corresponding high signal intensity within the dentate nuclei.

Mitochondrial dysfunction as a cause of the abnormalities in susceptible patients[13]. The imaging, spectroscopy, and clinical findings reverse after discontinuation of metronidazole therapy[4,9-12].

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MRI of Metronidazole-Induced Encephalopathy

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