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Case Report

A potential new role for ASL perfusion imaging: Diagnosis of metronidazole induced encephalopathy – Two companion cases

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ARTICLE INFO

Article history:

Received 6 September 2019

Revised 4 October 2019

Accepted 6 October 2019

Keywords:

Metronidazole

Encephalopathy

Arterial spin labeling

ABSTRACT

Metronidazole induced encephalopathy (MIE) is a rare condition due to prolonged high dose administration of metronidazole. MIE with corresponding increased perfusion on MRI arterial spin labeling (ASL) of the involved regions of the brain appears not to have been reported in the literature to date. We present two such cases, a 59-year-old male with recurrent *C difficile* colitis with classic MR imaging characteristics of MIE, and a companion case of a 65-year-old female with gangrenous cholecystitis also presumed to have MIE. Despite aggressive medical management, both patients expired. Our cases demonstrate a correlation with ASL hyperperfusion to affected brain regions thought to be due to edema or inflammation. Perfusion imaging may play a role in diagnosis of MIE.

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Background

Metronidazole induced encephalopathy (MIE) is a rare form of medication related neurotoxicity seen with the administration of this antibiotic. Metronidazole is of the nitroimidazole class of antibiotics, often used in clinical practice for treatment of anaerobic infections [1] and in the setting of Crohn's disease [2]. MIE is characterized by dysarthria, extremity weakness, gait abnormalities, altered mental status, and

visual disturbances [2]. Most commonly, MIE is a reversible phenomenon with complete recovery after cessation of the medication [3]. However, studies have suggested a dose dependency, although research has been inconsistent to date [3]. Irreversible cases have been reported when dosages of 1.5 g/day or higher [4] are administered for longer periods with some studies suggesting a total dose ranging from 20–120 g for 1–12 week duration [5].

The distinguishing magnetic resonance imaging (MRI) features of MIE have been well characterized and reported in

Abbreviations: MIE, Metronidazole induced encephalopathy; ASL, Arterial spin labeling; DWI, Diffusion weighted imaging; IV, Intravenous; HBV, Hepatitis B virus; MRI, Magnetic resonance imaging; CBF, Cerebral blood flow; CTP, Computer tomography perfusion.

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the literature. Classically, MIE manifests as T2 hyperintense lesions in the splenium of the corpus callosum along with symmetric T2 lesions within the dentate nucleus and/or brainstem [2],[6–10]. The pathophysiology of T2 lesion in MIE is unknown, though it has been postulated that the lesions correspond to areas of vasogenic edema. The proposed mechanism of vasogenic edema is due to metronidazole's propensity to induce oxidation of norepinephrine, dopamine, and catecholamines to form oxygen radicals, thus reducing tissue oxygen levels. This may subsequently lead to increased cellular water content and axonal swelling [11]. Alternatively, studies have noted that T2 lesions also exhibit restricted diffusion on diffusion weight imaging, suggesting cytotoxic edema as a potential underlying cause as well [2].

In conjunction with conventional sequences on MRI with which MIE has been diagnosed, arterial spin labeling (ASL) has become an important physiological sequence in assessing several other diseases such as stroke, seizure, migraines, and neoplasms [12–16]. ASL is a noninvasive noncontrast perfusion method where inflowing blood protons are magnetically labeled in the neck, and sampled in the brain. This allows for adding a physiological measurement of cerebral blood flow to the conventional anatomic analysis in MRI [14]. However, to date, no reports exist in the literature demonstrating ASL's potential role in diagnosing MIE. In this report, we present 2 companion cases of MIE with ASL correlates.

Case presentation 1

We present a 59-year-old male with end stage liver disease secondary to cirrhosis who initially presented with recurrent bouts of *Clostridium difficile* (C diff) colitis requiring a prolonged hospital stay. The patient was treated with metronidazole 500 mg every 8 hours intravenously (IV) for the colitis through his inpatient stay. Six weeks after the initial presentation, the patient acutely deteriorated, presenting with altered mental status and hypotension with systolic blood pressures in the 70s. His vital signs demonstrated tachycardia and tachypnea with an elevated white blood cell count of $23.1 \times 10^9/l$, decreased hemoglobin (Hb) of 8.0 g/dl, and borderline ammonia level at $35 \mu\text{mol/l}$ (ref [11–25] 35). Remainder of the labs, including sodium and magnesium levels, were within normal range. The patient was subsequently stabilized with vasopressors in the intensive care unit. Given the encephalopathic symptoms, CT was performed which did not reveal an acute abnormality. Clinical exam was remarkable for diarrhea and bloody stools. Subsequent CT imaging of the abdomen and pelvis, however, demonstrated large pelvic abscesses which were then drained. During this episode and because of the history of recurrent C diff colitis, the patient was continued on intravenous (IV) metronidazole at 1.5 g per day, which was the same dose that was administered in the 6 weeks prior to his initial admission. He persisted to have altered mental status and an MRI performed 3 days after the CT demonstrated symmetric T2/FLAIR hyperintensities with corresponding increased ASL signal involving the bilateral dentate nuclei and splenium (Fig. 1). There was no corresponding restricted diffusion on diffusion weighted imaging or

enhancement on contrasted enhanced T1 images. MIE was diagnosed based on the MRI and metronidazole was subsequently discontinued. Unfortunately, due to continued complications from rectal bleeding and coagulopathy, the patient expired 1 week after the MRI.

Case presentation 2

We present a 65-year-old female with history of treated hepatitis B cirrhosis complicated by esophageal banding and recurrent hepatic encephalopathy. She was found to have acute gangrenous cholecystitis with portal vein thrombosis at an outside hospital, for which she was subsequently transferred to our institution for management. At the time, she was treated with oral metronidazole at 1.5 g per day for management of the cholecystitis and then discharged after stabilization. One month after the initial presentation, the patient presented with acute altered mental status and lethargy suspicious for hepatic encephalopathy. Vital signs were normal. Labs, however, were remarkable for decreased white blood cell count of $2.9 \times 10^9/l$, decreased Hb at 9.4 g/dl, and elevated liver enzymes. The remainder of the labs were within normal range. Head CT showed no acute abnormality. The patient was continued on IV metronidazole at her previous dosage of 1.5 g per day. She continued to demonstrate progressive altered mental status with intermittent unresponsiveness. An MRI was then performed demonstrating symmetric T2/FLAIR hyperintensities with increased ASL signal within the dentate nuclei and splenium (Fig. 2). Similar to the prior case, there was no associated restricted diffusion or contrast enhancement. Despite discontinuing the metronidazole therapy and aggressive medical management, the patient's encephalopathy continued to progress, and the patient also expired 2 weeks after the MRI was performed.

Discussion

Metronidazole is a broad-spectrum antibiotic used for anaerobic infections and Crohn's disease. When administered in high dosages, generally 1.5 g/day or higher or for long periods, this medication can rarely induce an encephalopathy (MIE) characterized by altered mental status, gait abnormalities, dysarthria, extremity weakness in addition to other findings. Although most often reversible after medication cessation, there have been reports of irreversible encephalopathy as well. [17]·[5]·[18] The incidence of MIE is still unknown but generally considered rare. [2] MRI findings of MIE have been previously well characterized, however no cases to date exist within the literature demonstrating a correlation with ASL and few discussing correlation with perfusion imaging. Our companion cases would be the first report to demonstrate ASL correlation with classic findings of MIE.

The mechanism for MIE is still being elucidated, although some studies have suggested that the radiological findings are due to vasogenic edema. [10]·[11]·[18] Alternatively, Takada et al also postulated that these findings may be related to

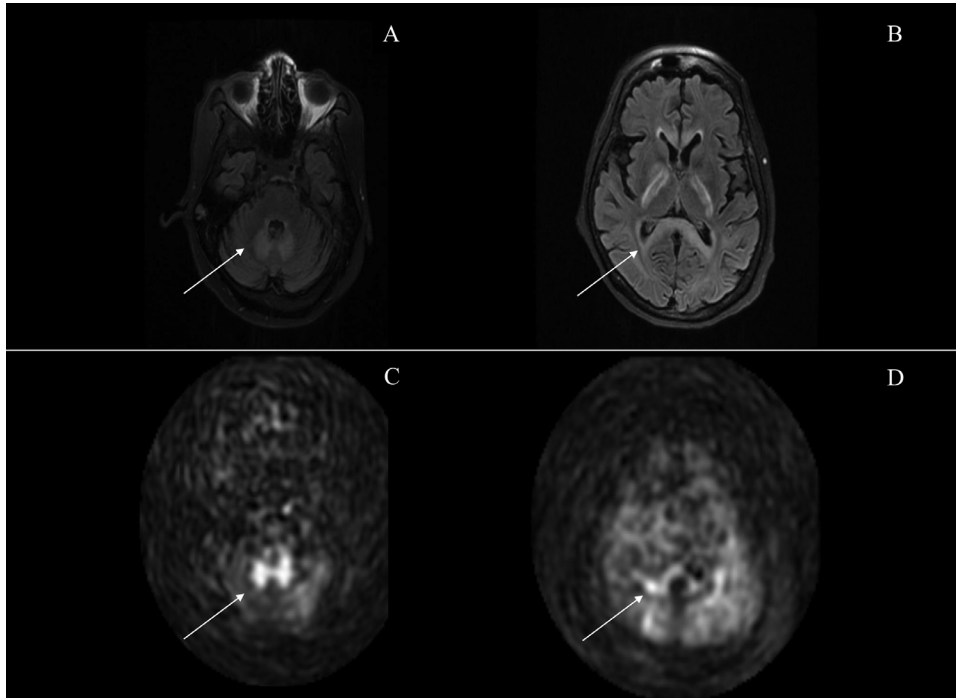


Fig. 1 – A 59 year old male with history of recurrent *C difficile* colitis treated with high dose metronidazole for a long duration. A-B) FLAIR hyperintensities are seen within the dentate nuclei and splenium most compatible with MIE. C-D) ASL hyperperfusion is demonstrated in the corresponding regions.

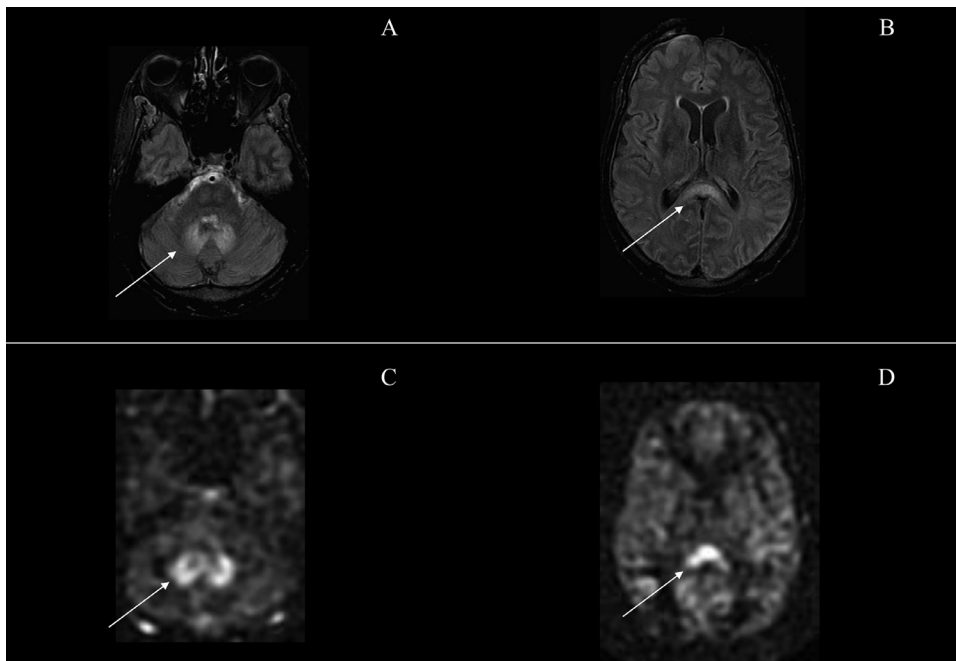


Fig. 2 – A 65 year old male with history of hepatitis B related cirrhosis treated with high dose metronidazole for acute cholecystitis. A-B) FLAIR hyperintensities are seen within the dentate nuclei and splenium again most compatible with MIE. C-D) ASL hyperperfusion is demonstrated in the corresponding regions.

inflammation or cytotoxic edema. [19] Takada et al also describe decreased cerebral blood flow in CT perfusion in a cerebral hemisphere mimicking stroke, however, they did not note any perfusion abnormality within the dentate nuclei or splenium as seen in our case series. [19] Given the increased ASL signal in our reported cases, these findings are thought to represent hyperperfusion which could be related to underlying edema or secondary inflammatory factors potentially due to axonal swelling from oxygen radicals. [11] Further studies are necessary to elucidate the exact mechanism.

Although MIE demonstrates characteristic imaging findings, it is also essential to exclude other diagnoses which can present similarly. Other metabolic conditions, namely Wernicke's encephalopathy (WE) and osmotic demyelination syndrome (ODS), are most commonly included in a differential diagnosis with MIE. Rarer conditions such as methyl bromide intoxication, maple syrup urine disease, or enteroviral encephalomyelitis (EV 71) can also be considered in the appropriate clinical context. [2] Although WE can rarely show symmetric dentate nuclei involvement, this condition classically affects the mammillary bodies, medial thalami, and periaqueductal gray matter with a clinical history of longstanding alcoholism and corresponding thiamine deficiency. [2] As reported by Kim et al, previous cases of nonalcoholic WE showed similar imaging characteristics, however, long-term metronidazole was administered in both previous reports and MIE was not evaluated for in either case, although later suspected. [2] [20] [21] Kim et al also noted that dentate nuclei lesions are not supportive of WE upon pathological analysis. [2] Perfusion imaging has not been well explored in WE, however, Bhan et al demonstrated a case of bithalamic bolus hyperperfusion on CT perfusion in WE mimicking stroke, but did not note perfusion abnormalities in the dentate nuclei or splenium. [22] Additionally, Lyu showed ASL hyperperfusion in the frontal cortices in WE but also did not note perfusion abnormalities in the dentate nuclei or splenium. [23] In our companion cases, in conjunction with the imaging findings, there was no supporting evidence of thiamine deficiency or alcoholism to consider WE.

ODS can also affect the dentate nuclei but typically involves the pons in the setting of rapidly corrected sodium, although the rarer subtype of extrapontine myelinolysis can be considered in such cases. Bolus MR perfusion imaging can play a role in diagnosing ODS where there is increased cerebral blood volume in the affected region of the pons only in the acute stage as seen in Guo et al [24]. Of note, no studies to date have correlated ASL in ODS. In our report, the sodium levels were normal and hyperperfusion was not seen in the pons in either case, which made extrapontine ODS unlikely in both.

Given the extensive gastrointestinal disease history of both patients in our cases, EV71 could have been considered. EV71 characteristically affects the brainstem, thalami, and putamina in association with hand foot mouth disease as described by Shen et al [25]. However, given that this condition more commonly affects the pediatric population and with the differing imaging characteristics, this diagnosis was not considered in our companion cases. Similarly, methyl bromide intoxication and maple syrup urine disease also did not have supporting evidence in both cases to be considered.

Therefore, a final diagnosis of MIE was made in both cases with the characteristic imaging findings, include novel ASL correlates, in conjunction with the supportive clinical histories of long-standing metronidazole administration.

MIE is a well described clinical condition seen in when metronidazole is administered in high doses for long periods. MRI findings typical of MIE have been more recently elucidated, often characterized by lesions within the dentate nuclei, splenium, and brainstem. [2] [3] [17] Our companion cases demonstrate increased ASL signal corresponding to the dentate nuclei and splenium in patients with presumed MIE, of which there are no descriptions in the literature to date. These findings show that noncontrast perfusion imaging could have a potential role in diagnosis of MIE.

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