Received: 20 February 2017 | Accepted: 27 April 2017

DOI: 10.1002/jgf2.91

CASE REPORT

Journal of General and Family Medicine Open Access WILEY

Irreversible metronidazole encephalopathy in an elderly woman with primary biliary cholangitis

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Abstract

An 82-year-old woman with primary biliary cholangitis was diagnosed with an irreversible neurological disorder, caused by metronidazole (MNZ)-induced encephalopathy. Although the disorder is a reversible pathological condition, in rare cases, it can cause serious sequelae or could even be fatal. Therefore, medications should be administered carefully, particularly in patients who require long-term administration of large doses or those with liver dysfunction.

KEYWORDS

encephalopathy, irreversibility, liver dysfunction, metronidazole

1 | INTRODUCTION

Metronidazole (MNZ) is used as a first-line treatment for *Clostridium difficile* (CD) colitis. MNZ-induced encephalopathy is a relatively rare disease, characterized by a reversible central nervous system disorder. Generally, it is thought that the illness improves upon discontinuing medication. However, a few cases of serious residual sequelae and death have been reported, albeit in small numbers. Similarly, we have found serious residual sequelae caused by MNZ-induced encephalopathy, as reported in this study.

2 | CASE PRESENTATION

An 82-year-old woman was admitted to our hospital complaining of fevers and nausea for one month. Upon experiencing these symptoms, she consulted her previous doctor, which led to her being diagnosed with pyelonephritis. Levofloxacin was prescribed, and her symptoms improved. However, 14 days prior to hospitalization, she once again started suffering from fevers, as well as passing mushy stool. The previous doctor prescribed MNZ based on a diagnosis of CD enteritis, confirmed by a positive CD toxin test. Consequently, the fever declined; however, the persistent nausea and vomiting led to the hospitalization of the patient. She has a past medical history of primary biliary cholangitis, atrial fibrillation, and interstitial pneumonia. She was taking branched-chain amino acid, ursodeoxycholic acid, kanamycin, spironolactone, lactulose, and apixaban.

On physical examination, vital signs were as follows: JCS (Japan coma scale), 0; GCS (Glasgow Coma Scale), 4/5/6; blood pressure, 130/64 mmHg; pulse rate, 68 beats/minute and regular; body temperature, 36.8°C; peripheral capillary oxygen saturation (SpO2), 95% (O2 at 2 L/min); no neurological abnormality.

Laboratory examinations revealed the following:

Blood test: blood urea nitrogen (BUN) 23 mg/dL.

Urinalysis: white blood cells 2+, nitrate +, protein 2+.

There were no other significant findings.

Due to intravascular volume depletion, the patient was treated with fluid replacement. Consequently, although the symptoms of nausea and vomiting improved, fever and bacteriuria began 12 days after the admission of the patient to the hospital. Following this, we began

treatment to prevent the recurrence of pyelonephritis, with ceftriaxone (CTRX). However, we resumed treatment with MNZ due to recurrence of CD enteritis. Twenty-five days after admission to the hospital, a disturbance in consciousness (GCS 1/1/1) and left-sided hemiparesis occurred; in addition, left-sided Babinski reflex tested positive. A diffusion-weighted magnetic resonance imaging (DWI-MRI) of the patient's head and fluid-attenuated inversion recovery imaging revealed a high signal intensity area in the bilateral corpus callosum ampulla (Figure 1A, B) and a high signal intensity area in the right periventricular white matter. Apparent diffusion coefficient (ADC) mapping was used to detect the low signal intensity area in the same region. Subsequently, we discontinued the use of MNZ, as MNZ-induced encephalopathy was suspected. Upon reexamining the MRI on 25 days after cessation of MNZ, the lesions showed a trend toward regression (Figure 1C, D), and disturbances in consciousness showed a tendency toward improvement (GCS 4/5/6). However, left-sided hemiplegia and dysarthria remained. Although the patient was not able to make a complete recovery, brain lesions on MRI images showed a tendency toward regression. Cerebral infarction was unlikely, based on MRI findings. Wernicke encephalopathy was unlikely as the patient was administered vitamin B. Based on the clinical history of the patient, we made a diagnosis of MNZ-induced encephalopathy.

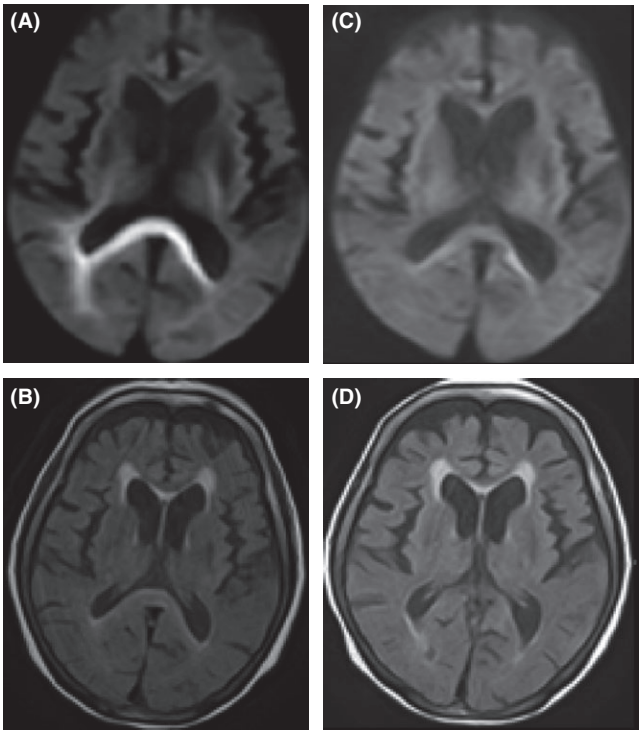

FIGURE 1 Diffusion-weighted image (DWI) and fluid-attenuated inversion recovery (FLAIR) showed high signal intensity in the bilateral corpus callosum ampulla (DWI: A, FLAIR: B). Lesions in the bilateral corpus callosum ampulla disappeared on 25 days after cessation of MNZ (DWI: C, FLAIR: D)

3 | DISCUSSION

There were two important observations made from this case: the relationship between irreversible MNZ-induced encephalopathy and cumulative doses of MNZ and the relationship between irreversible MNZ-induced encephalopathy and liver dysfunction. With regard to MNZ-induced encephalopathy, when the cumulative dose of MNZ is between 21 g and 135 g, there is a correlation between the development of the disease and the cumulative dose.[1] However, there are other studies that report correlative cumulative doses between 0.25 g and 1110 g.[2] Additionally, in cases of liver dysfunction, the clearance of MNZ has been found to deteriorate to a third of the original value.[3] MRI images of the head have previously presented bilateral and symmetrical hyperintense signal in DWI, with T2-weighted imaging (T2WI), in areas such as the cerebellar dentate nucleus, midbrain, pontine tegmentum, dorsal medulla oblongata, and corpus callosum. Signals in these areas often completely disappear, but occasionally remain. Moreover, upon comparing the MRI observations of seven cases of

TABLE 1 Case series of irreversible metronidazole-induced encephalopathy

Underlying diseases	Cumulative dose (g)/ Dosing period (d)	MRI findings (ADC)	Symptoms	References
Osteomyelitis	132/70	n/a	Disturbance of consciousness hypoventilation	5
Cholangitis, liver cirrhosis	33/22	Low in corpus callosum and white matter	Disturbance of consciousness nausea, vomiting	6
Retroperitoneal abscess	250/150	Low in corpus callosum and white matter	Cognitive impairment cerebellar ataxia	7
CDI	64.5/43	n/a	Disturbance of consciousness dysarthria, hemiparesis	8
ACTH deficiency, empyema, liver cirrhosis	42/21	n/a	Disturbance of consciousness dysarthria, gait disturbance	9
CDI, liver cirrhosis	33/22	Low in corpus callosum and white matter	Dysarthria, hemiparesis	Our case

ADC, apparent diffusion coefficient; n/a, not applicable; CDI, Clostridium difficile infection.

MNZ-induced encephalopathy, we found reports of studies indicating lesions in the cerebellum and the brainstem that did not show low signal intensity, suggestive of angioedema, whereas lesions in the corpus callosum showed low signal intensity, indicative of cytotoxic edema.[4]

In MNZ-induced encephalopathy, improvements can be seen within 4–10 days upon discontinuing MNZ medication. However, there have been five known cases of severe sequelae and deaths (Table 1).[5–9] In three of six cases (six including our own case) of irreversible MNZ-induced encephalopathy, a low ADC in the MRI of the head and in areas of the corpus callosum and white matter was detected, which lead us to suspect that the cytotoxic edema in the area was related to the irreversibility of the illness. The cumulative dose and dosing period ranged from 21 to 250 g and from 14 to 150 days, respectively. However, it should be noted that three of six cases were complicated by liver cirrhosis. In cases without comorbid conditions, the cumulative dose and dosing period were 64.5-250 g and 43-150 days, respectively. In comparison, in cases with comorbid conditions, they were 33-42 g and 21-22 days, respectively. This led us to conclude that if MNZ is administered at or over 1.5 g per day, it is necessary to keep in mind the risk of MNZ-induced encephalopathy in cases where the duration of drug administration more than one month for patients without liver dysfunction, and more than ten days for patients with liver dysfunction.

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflicts of interest in connection with this article.

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How to cite this article: Onuma Y, Oki M, Komatsu M, et al. Irreversible metronidazole encephalopathy in an elderly woman with primary biliary cholangitis. *J Gen Fam Med*. 2017;18:436–438. https://doi.org/10.1002/jgf2.91