CASE REPORT

Metronidazole-induced encephalopathy associated with treatment for liver abscesses

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Abstract
Metronidazole-induced encephalopathy (MIE) is a rare condition in Japan. We report the case of a patient with MIE who presented with abducens paralysis and ataxia without underlying risk factors. A history of metronidazole (MNZ) administration and rapid improvement after MNZ discontinuation are important in making this diagnosis, and characteristic findings of magnetic resonance imaging support the diagnosis. MIE is expected to become common in Japan as the use of MNZ increases because of expanded insurance coverage. Therefore, MIE needs to be recognized as a differential diagnosis of the central nervous symptoms in patients taking MNZ.

KEYWORDS
abducens paralysis, ataxia, dentate nucleus, encephalopathy, metronidazole, the splenium of the corpus callosum

1 | INTRODUCTION
Metronidazole (MNZ) is widely used in many countries to treat abscesses because of its antibacterial activity against anaerobes and high tissue transitivity. After insurance coverage expanded in 2012, MNZ became more widely used in Japan.1 Unfortunately, MNZ-induced encephalopathy (MIE) occurs in patients taking MNZ. We report the case of a 67-year-old woman with MIE that was associated with MNZ used for liver abscesses.

2 | CASE PRESENTATION
A 67-year-old Japanese woman visited the emergency department with the complaint of nausea. One month before the visit, she had been hospitalized for 3 weeks for multiple culture-negative liver abscesses. During her hospitalization, she was treated with a combination of 300 mg intravenous ciprofloxacin (CPFX) every 12 hours and 500 mg oral MNZ after every meal. The patient’s liver abscesses improved without interventional drainage. She was discharged and prescribed the same dose of oral CPFX and MNZ. She experienced nausea and vomiting 15 days after discharge and visited our emergency department 17 days after discharge. She reported no diarrhea, abdominal pain/distension, headache, or weakness.

The patient had hypertension and hyperlipidemia that were well controlled with bisoprolol and pravastatin. She had an allergy to ceftriaxone. She had no history of smoking or drinking, and there was no relevant family history.

On physical examination, the patient was alert. Her temperature was 36.0°C, her heart rate was 78 beats/min, and her blood pressure was 143/78 mmHg. Her conjunctivae and sclerae were not pale or icteric. Cardiopulmonary, abdominal, dorsal, and appendicular findings were all unremarkable. Neurological examination was remarkable for the right-dominant bilateral abducens paralysis, globally accelerated deep tendon reflexes, and truncal ataxia; she could not walk because of a deviation to the right. Motor and sensory functions were normal. Despite remarkable truncal ataxia, finger-to-nose test movements were rapid and smooth. Romberg and Babinski signs were negative.

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Laboratory test results were normal. Computerized tomography (CT) scans of the head were normal, and an abdominal CT scan showed a reduction of the abscesses.

Given the combination of acute ataxia, abducens paralysis, and MNZ administration for 5 weeks, we suspected MIE. We immediately discontinued MNZ and performed magnetic resonance imaging (MRI) of the brain 35 days after initiating MNZ. T2-weighted imaging (T2WI) and fluid attenuated inversion recovery (FLAIR) on the MRI image showed a high intensity at the bilateral cerebellar dentate nucleus and midbrain tegmentum (Figure 1). Diffusion-weighted imaging (DWI) showed high intensity combined with a reduction in the apparent diffusion coefficient (ADC) at the splenium of the corpus callosum (Figure 2). (The ADCs at the cerebellar and brainstem lesions were normal.) These findings were consistent with MIE. We excluded Wernicke encephalopathy because serum vitamin B1 levels were normal.

Nausea improved the day after MNZ was discontinued, and abducens paralysis improved by 6 days after discontinuation. The patient fully recovered and was able to perform the tandem-gait test nine days after discontinuation.

We changed antibiotics to garenoxacin monotherapy to target both Gram-negative rods and anaerobes. She was discharged after a 10-day hospital stay.

The patient took garenoxacin for 8 days as the last part of the 64-day course of antibiotics for the liver abscesses. MRI T2WI was performed 43 days after MNZ discontinuation, and showed improved high intensity at the bilateral dentate nucleus and midbrain tegmentum. DWI showed persistent high intensity at the splenium of the corpus callosum, but the reduced ADC was improved. Even though DWI intensity was persistently high, the patient’s symptoms completely resolved and did not recur during a four-month follow-up.

### 3 | DISCUSSION

We report the case of a patient with MIE who presented with abducens paralysis and cerebellar ataxia. She had a typical history of long-term, high-dose MNZ administration, and symptoms improved rapidly after MNZ was discontinued, which supported the diagnosis.

Although the pathogenesis of MIE is unclear, excessive MNZ accumulation that results from insufficient metabolism probably causes MIE via injury of structures of the cerebellum, brainstem, and the splenium of the corpus callosum. MIE typically manifests as an altered mental status, headache, vomiting, and bilateral abducens paralysis. The only effective treatment is the discontinuation of MNZ. Symptoms are generally reversible and improve within 6-7 days after MNZ discontinuation. However, some patients develop serious sequelae.

MRI findings of MIE include two different key types: Cerebellar and brainstem lesions present with hyperintensity on FLAIR and T2WI, which suggests vasogenic edema. On the other hand, some cases present with concomitant changes on DWI and ADC at the splenium of the corpus callosum, which suggests cytotoxic edema. Findings at the corpus callosum reportedly persist longer than cerebellar/brainstem lesions. MRI findings of our case, including chronological changes, are consistent with typical findings of MIE. The difference in the MRI findings between the lesions may suggest different mechanisms of injury between gray and white matter, although the difference may simply reflect the different degrees of injury.
The risk of MIE correlates with the MNZ dose and administration period. The average onset period and total dose that causes MIE is reportedly 61.3 days and 95.9 g, respectively. However, this period and dose differs between reports. According to a Japanese report, the Japanese MNZ medical package insert indicates that peripheral or central nervous disorders can occur if MNZ is used for 10 days or longer, or if more than 1500 mg is administered. Given the wide range of periods and doses of MNZ, MIE should be considered as a differential diagnosis of central nervous symptoms in patients taking MNZ, regardless of the duration or total dose. Once MIE is suspected, MNZ should be immediately discontinued. A brain MRI is useful for confirming the diagnosis.

Because MIE is likely caused by MNZ accumulation from insufficient metabolism, patients with liver diseases, metabolic disorders, or low body weight are at risk. However, our patient was a female with normal weight and no underlying diseases. Our report therefore suggests that patients without risk factors can develop MIE regardless of the MNZ duration or dose. Thus, a detailed explanation of these adverse symptoms should be given to patients before they begin taking MNZ.

Because Japanese insurance coverage was expanded to include various infections with a maximum dose of 2250 mg per day in 2012, MNZ is used more frequently and at a higher dose for more types of diseases. Therefore, the incidence of MIE is also expected to increase. In fact, MIE is no longer a rare condition even in Japan. Primary care physicians should make MIE a differential diagnosis of central nervous symptoms in patients taking MNZ, regardless of the dose, duration, or presence of any underlying conditions.

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CONFLICT OF INTEREST

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

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