CASE REPORT

Metronidazole-induced encephalopathy after prolonged metronidazole course for treatment of *C. difficile* colitis

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SUMMARY

A 65-year-old woman with a diagnosis of *Clostridium difficile* colitis undergoing prolonged treatment with metronidazole was admitted to hospital for altered mentation, slurred speech and weakness. She was diagnosed with metronidazole-induced encephalopathy, confirmed with brain MRI and improved when the offending agent was removed. This case report highlights encephalopathy as a complication of prolonged metronidazole treatment, which has become more common in clinical practice for the treatment of *C. difficile* infection.

BACKGROUND

Metronidazole is a fairly safe and well-tolerated 5-nitroimidazole antibiotic, but can cause serious adverse neurological events. Widespread use of metronidazole to treat *Clostridium difficile* infections for prolonged periods of time makes it necessary for the clinician to be aware of metronidazole-induced encephalopathy (MIE), a rare complication of metronidazole therapy, with distinctive clinical and MRI findings.

CASE PRESENTATION

A 65-year-old woman with a diagnosis of *C. difficile* colitis 2 months prior to admission presented from a nursing facility where the staff had noted alteration in mental status, slurred speech and left-sided extremity weakness. On initial physical examination, the patient was alert and able to follow simple verbal commands but required frequent redirection and her attention was noted to be poor. Her affect was flat, with a paucity of spontaneous speech. Fluency of her speech was limited, with significant word-finding difficulty consistent with aphasia. She had notable dysarthria. The remainder of the cranial nerve examination was normal, no ocular palsies or nystagmus were noted. Motor examination of the extremities revealed diffusely diminished strength without laterality or pronator drift. Bilateral dysmetria was present on finger-to-nose testing; gait was not assessed secondary to weakness. The remainder of her neurological examination was normal. Her National Institutes of Health Stroke Scale was 2, with one point for dysarthria and one point for aphasia. She was not given points for limb ataxia as this finding was judged to be in proportion to her overall weakness.

She had no history of alcohol abuse, malnutrition or hyperemesis. Review of nursing facility records indicated that the patient had been on

metronidazole 500 mg three times daily for the preceding 6 weeks which was not discontinued in error after a 14-day course for recurrent *C. difficile*.

INVESTIGATIONS

CT of the brain without intravenous contrast was normal. Brain MRI without contrast revealed abnormal signal intensity involving the region of the dentate nucleus, superior cerebellar peduncle, splenium of the corpus callosum and parietal subcortical white matter (figure 1). The lesions in the superior cerebellar peduncle, splenium and parietal white matter were associated with restricted diffusion whereas the dentate nucleus demonstrated no evidence of restricted diffusion. The reading radiologist's impression noted that this constellation of findings was consistent with MIE.

DIFFERENTIAL DIAGNOSIS

The differential diagnosis for a patient with altered mental status or encephalopathy is broad, including but not limited to infectious, neoplastic, inflammatory, ischaemic and medication-related causes. The findings of altered mentation, dysarthria and aphasia initially prompted consideration of central nervous system processes such as ischaemic stroke, neoplasms or inflammatory encephalitis and led to prompt neuroimaging with CT and MRI modalities. The constellation of prolonged metronidazole use and clinical findings consisting of acute altered mentation, aphasia, dysarthria and dysmetria in addition to discrete and symmetric MRI findings limited the differential to a handful of genetic, metabolic or toxic processes. This group of conditions which includes MIE, Wernicke's encephalopathy (WE) and Leigh's syndrome, can be described as 'energy deprivation syndromes', with their variations in topography reflecting preferential damage to structures and tissues most vulnerable to metabolic derailment.¹

In adult patients, the most important and commonly encountered condition to require differentiation from MIE is WE. The clinical diagnosis of WE rests on the classical triad consisting of ocular signs (including nystagmus, bilateral lateral rectus palsies and conjugate gaze palsies), altered consciousness and ataxia, although all three elements are present in only 16–38% of patients with WE.^{2,3} Acute WE may produce similar clinical findings and symptoms as MIE in the early course. In the present case, the patient lacked ocular signs and her limb ataxia was mild. In addition there was no history of risk factors

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Figure 1 Axial fluid-attenuated inversion recovery images with abnormal signal hyperintensity in (A) bilateral dentate nuclei and (B) splenium of the corpus callosum. Diffusion-weighted images (C) and (D) demonstrate restricted diffusion in the bilateral subcortical white matter.

for WE such as alcohol abuse, malnutrition or hyperemesis. Typical MRI findings in WE are symmetric signal intensity alterations in the thalami, mamillary bodies, tectal plate and periaqueductal area.⁴ The appearance may be so similar to MIE that some authors have questioned whether reported cases of clinical WE were in fact due to concomitant metronidazole therapy.^{5–7}

To be considered in pediatric patients with similar MRI findings are the hereditary disorders of maple syrup urine disease (MSUD) and Leigh syndrome. MSUD is a rare autosomal recessive error of branched-chain amino acid metabolism resulting in metabolic acidosis, neurological deterioration and the characteristic urine odour within the first week of life.⁸ Leigh syndrome, also known as subacute necrotising encephalomyelopathy, also presents in infancy or early childhood with psychomotor regression, lactic acidosis and inevitable death.⁹ A rare toxic exposure that causes a similar distribution of MRI abnormalities as the present case is methyl bromide, a colourless gas used as an insecticidal fumigant.^{10 11} Finally, viral encephalitis, antiepileptic drug toxicity or withdrawal, and hypoglycaemia should be considered.¹²

TREATMENT

Metronidazole was ceased, the patient's signs of inattention, aphasia, dysarthria, dysmetria and extremity weakness improved

rapidly. She was discharged to a rehabilitation facility with instructions for a repeat MRI examination as an outpatient and avoidance of future metronidazole use.

OUTCOME AND FOLLOW-UP

Follow-up MRI of the brain 4 months following discontinuation of metronidazole showed resolution of abnormal signal intensity in the cerebellar peduncles and the dentate nuclei, and interval improvement in the other involved regions of the brain with no new abnormalities. Clinically, the patient continued to improve and on follow-up examination had complete resolution of her previous neurological findings. A Naranjo Score for determining the likelihood of causality in a presumed adverse drug reaction was calculated (table 1).¹³ The Score was 7 of a possible 9, indicating a probable adverse drug event.

DISCUSSION

Neurological toxicity is well documented as a consequence of metronidazole use. Neurological adverse effects of metronidazole use include peripheral neuropathy, seizures, ototoxicity and encephalopathy.^{14 15} The clinical features of MIE commonly include altered mentation, cerebellar dysfunction and seizures.¹⁶ More than 60 cases of MIE have been reported and subsequently reviewed by Kuriyama *et al.*¹⁶ In total, 75% of patients

Table 1 The Naranjo adverse drug reaction probability scale

1. Are there previous conclusive reports on this reaction?	Yes, +1
2. Did the adverse event appear after the suspected drug was administered?	Yes, +2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	Yes, +1
4. Did the adverse event reappear when the drug was re-administered?	Do not know, 0
5. Are there alternative causes (other than the drug) that could on their own have caused the reaction?	No, +2
6. Did the reaction reappear when a placebo was given?	Do not know, 0
7. Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	Do not know, 0
8. Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	Do not know, 0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	No, 0
10. Was the adverse event confirmed by any objective evidence?	Yes, +1
Total score	7

with MIE had cerebellar dysfunction as the primary neurological manifestation, with the majority of patients exhibiting dysarthria and ataxia. Dysmetria was found in 25% of patients, and nystagmus, which was absent in the present case, was present in less than 1% patients.¹⁶ Although accelerated onset within 1 week of treatment has been reported in pediatric patients and patients with hepatic or renal dysfunction, most cases occur at total cumulative doses in the range 20–120 g over a period of 2–6 weeks.^{17–22}

Characteristic abnormalities on MRI in MIE are almost always bilateral and symmetric, and the most common site of fluid-attenuated inversion recovery hyperintensity is the cerebellar dentate nucleus, occurring in 81% of reports.¹⁶ Other structures involved include the midbrain, splenium of the corpus callosum, pons, medulla, inferior colliculus, subcortical white matter, basal ganglia and middle cerebellar peduncle.^{7 16 21 23 24}

The mechanism of MIE is incompletely understood, but several possibilities have been put forth. A rat model of metronidazole neuropathy showed that large doses bind to RNA of rat nerve cells to inhibit protein synthesis, causing axonal degradation.²⁵ It has also been proposed that the adverse neurological effects of metronidazole may be due to its action as an antagonist of thiamine. Alston *et al*²⁶ demonstrated that metronidazole undergoes conversion by enzymes in human gut flora to a structural analogue of thiamine. This analogue acts as an effective in vitro inhibitor of thiamine diphosphokinase, the enzyme responsible for the first step in thiamine metabolism. This effect on thiamine antagonism could explain why metronidazole toxicity and WE share similar histological findings. Dogs that have been fed high doses of metronidazole exhibit selective loss of Purkinje cells in the cerebellum, and alcoholics with clinical WE also show significant and selective decrease in Purkinje cell density and atrophy of the molecular layer where the dendritic trees of the Purkinje cells are found.^{27 28} Alcoholics without clinical WE, however, had no change in the density or dendritic volume of Purkinje cells. The mechanistic hypothesis of thiamine antagonism coupled with the similarities on histology and MRI have led some to question whether MIE and WE are two manifestations of derangement in a single metabolic pathway.²⁹

Metronidazole is not unique in its ability to cause neurotoxicity among antimicrobial medications. Confusion, encephalopathy, seizures, peripheral neuropathy, ototoxicity and a wide range of other neurological signs and symptoms have been reported with aminoglycosides, penicillins, cephalosporins, fluoroquinolones and other antibiotic classes.³⁰

Rising prevalence of *C. difficile* infection and recurrence increases the likelihood of prolonged metronidazole use.³¹ To date the most commonly reported indication for

metronidazole treatment in cases of MIE is abdominal abscess, followed by inflammatory bowel disease, with *C. difficile*-related treatment making up only 8% of published MIE case reports.¹⁶ Although a prolonged course of metronidazole was administered in error in the present case, extended courses of antimicrobial therapy for recurrent *C. difficile* infection have become more common in the clinical setting.³² The clinician must be aware of potential neurotoxic effects of metronidazole when considering antimicrobial choices for extended treatment in *C. difficile* infection.

Although the pathogenesis of metronidazole-induced toxicity is incompletely understood, cessation of the drug leads to improvement and in most cases complete resolution of clinical symptoms and imaging abnormalities within days to weeks. Care should be taken to ensure that metronidazole is discontinued after an appropriate course of therapy, and both patients and physicians should be aware of the signs and symptoms of this complication prior to initiation of a prolonged course.

Learning points

- ▶ Metronidazole-induced encephalopathy (MIE) is a known but rare complication of prolonged metronidazole treatment.
- ▶ MIE can be recognised by clinical findings of altered mentation, cerebellar signs and seizures and symmetric, bilateral regions of hyperintensity on brain MRI.
- ▶ Prolonged treatment with metronidazole for *Clostridium difficile* infection may increase risk of metronidazole-related neurotoxicity.
- ▶ MIE commonly improves on withdrawal of the offending agent.

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Competing interests None.

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