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## Correspondence

# Metronidazole-induced encephalopathy: Uncommon cause of recurrent falling in a geriatric man



## KEYWORDS

Encephalopathy;  
Fall;  
Metronidazole;  
Older

Dear Editor,

Metronidazole is a widely prescribed drug used for treating protozoal and anaerobic infections,<sup>1</sup> and is often tolerated well. Adverse neurotoxicity like metronidazole-induced encephalopathy (MIE) is rarely reported. Furthermore, a misdiagnosis can be made among older adults vulnerable to falls from various etiologies.

Here, we report a 71-year-old man, who was admitted for recurrent falls. He was clear and well-oriented, but exhibited slurred speech, clumsy hands, and unsteady gait. Laboratory examinations were all unremarkable. Neurological examination indicated severe dysarthria, dysmetria and overshooting in four extremities and titubation.

The man had recently been hospitalized for a severe liver abscess. Drainage was applied, and metronidazole at 500 mg thrice daily was administered in accordance with pus and blood culture, which yielded *Bacteroides fragilis*. Metronidazole was administered for 40 days, in a cumulative dose of 61.5 g. Brain MRI revealed hyperintense lesions over the bilateral dentate nucleus in DWI (Fig. 1A) and T2-weighted FLAIR sequences (Fig. 1B). Therefore, MIE was favored. The dysarthria and gait stability gradually improved after discontinuation of metronidazole. No further falling was reported. A brain MRI 1 month later revealed near-complete recovery of the cerebellar dentate lesions (Fig. 1C and D).

Falling is common among older adults, which may arise from a wide range of etiologies such as immobility, orthostatic hypotension, or infectious illness. MIE is an under-recognized cause of recurrent falling in older adults and has an overall incidence of 0.25% at 100 days after metronidazole exposure.<sup>2</sup>

The median duration of metronidazole exposure before MIE onset was 35.0 days, and the median cumulative dose was 65.4 g.<sup>3</sup> While a wide range of cumulative doses (0.25–1095 g) may bring risk of MIE, and symptoms were found to develop in less than one week for one-fourth of the patients.<sup>3</sup> Chronic liver disease, low income, antidepressant use, and benzodiazepine use were risk factors for MIE.<sup>3</sup> The common neurological symptoms are dysarthria (63%), limb dyscoordination (53%), and altered level of consciousness (41%). Several diseases should be differentiated from its classic bilateral dentate nuclei lesions, including Wernicke encephalopathy, hypothyroidism, methyl bromide intoxication, and encephalomyelitis.<sup>3</sup>

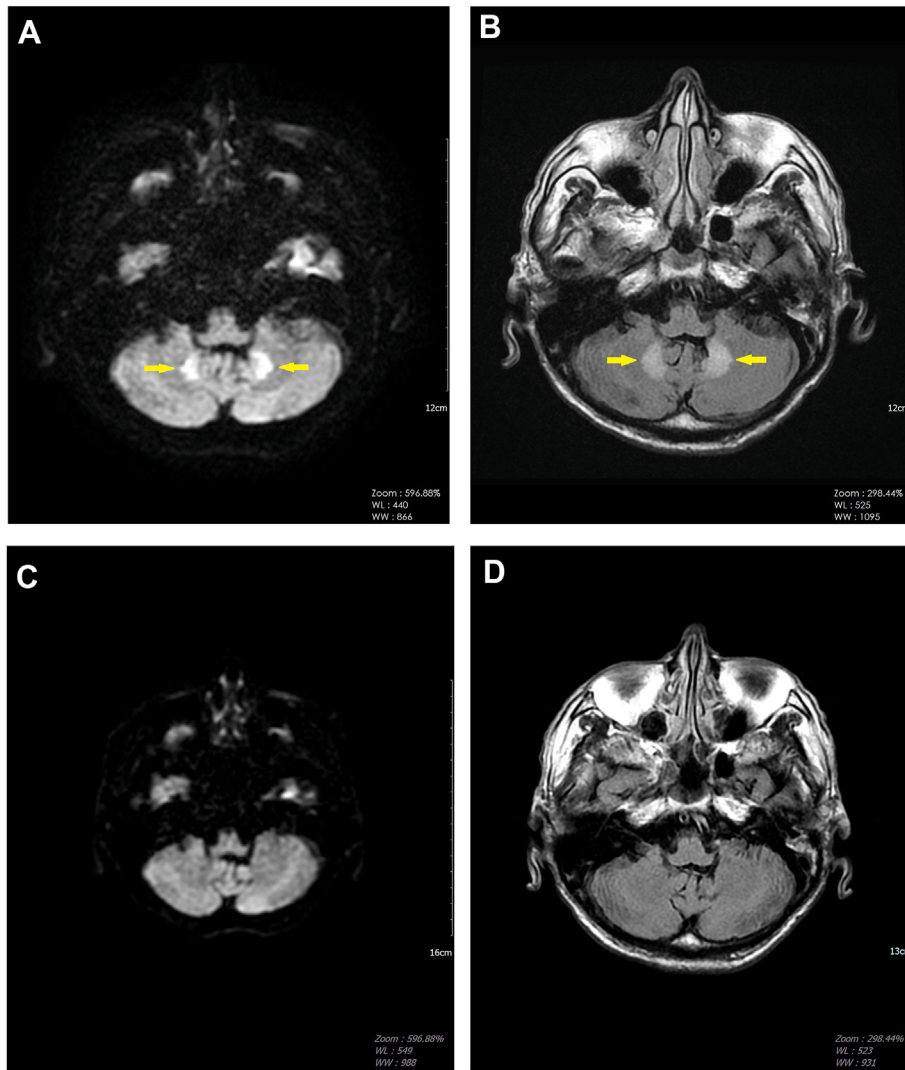
For pathogenesis, several mechanisms have been postulated, including  $\gamma$ -aminobutyric acid receptor modulation in the cerebellar and vestibular systems. Neurotransmitters, such as norepinephrine and dopamine, may be oxidized by metronidazole, leading to the formation of superoxide radicals that cause axonal swelling. Animal studies have revealed that the binding of metronidazole to DNA and RNA blocks the cell cycle, impairs protein synthesis, and thereby induces axonal loss.<sup>4</sup>

The timely cessation of metronidazole upon diagnosis mostly (92%) resulted in clinical improvements within two weeks. Radiological resolution occurs in three-fourths of cases and has a median time of 34 days from discontinuation of metronidazole. In rare instances, irreversible neurological deficits, such as vision loss, and even death, are possible.<sup>3</sup>

The present case can assist clinicians with recognizing the importance of appropriate antimicrobial stewardship,<sup>5</sup> in terms of associations of MIE with recurrent falling in older

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**Fig. 1.** Brain magnetic resonance images of a 71-year-old man with recurrent falling (A, B) and at the 1-month follow-up after discontinuation of metronidazole (C, D). Axial diffusion-weighted imaging (Fig. 1A) and T2-weighted FLAIR (Fig. 1B) sequences showed symmetric hyperintensities (yellow arrowheads) in bilateral cerebellar dentate nuclei. Near-complete recovery from hyperintense lesions was discovered in bilateral cerebellar dentate nuclei in both series (Fig. 1C and D) following 1-month cessation of oral metronidazole use.

patients. A possible MIE diagnosis should be considered for patients with neurological symptoms after recent or prolonged metronidazole use. The potential benefits and risks of prolonged metronidazole use should be weighed before it is used to treat infection in older patients. Timely discontinuation of metronidazole and caution to falsely attribute the cause to other fall-related etiologies are warranted.

### Conflicts of interest

There are no conflicts of interest to be declared by the authors.

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