

# Metronidazole-induced Encephalopathy: Case Report and Review Literature

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## Abstract-

**Purpose:** Neurotoxicities resulting from various medications are under diagnosed; Metronidazole-induced encephalopathy is one of them. Here we present two patients with a history of metronidazole use and discuss neuroimaging findings.

**Case Report:** We report two patients suffering from acute neurological symptoms associated with metronidazole use. A 70-year-old female who received a cumulative dose of 41.25g of metronidazole within one month, developed seizure. Brain magnetic resonance imaging (MRI) showed T2 hyperintensity over bilateral dentate nuclei and dorsal midbrain. A 56-year-old female suffering from acute onset of central vertigo with metronidazole use, took a total dose of 24g. The brain MRI showed T2 hyperintensity over dorsal midbrain and dorsal medulla, which disappeared in the following neuroimaging 50 days later. Metronidazole-induced encephalopathy (MIE) was suspected in both patients.

**Conclusion:** Metronidazole-induced encephalopathy is an uncommon but potentially reversible disease in patients with acute neurological deficits from the use of metronidazole. Nonalcoholic Wernicke's encephalopathy may share a similar metabolic pathway with MIE, resulting in difficulties in diagnosis.

**Key words:** metronidazole, Wernicke's encephalopathy, magnetic resonance imaging

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## INTRODUCTION

Metronidazole is an antimicrobial, antiprotozoal agent that has been widely used in the treatment of a variety of infections. It is believed to penetrate cerebrospinal fluid (CSF) and the central nervous system easily. There are case reports showing that metronida-

zole also causes neurotoxicity<sup>(1,3-9)</sup>. Peripheral neuropathy is the most common adverse effect of metronidazole use<sup>(8)</sup>, but varies in the central nervous system ranging from seizures to encephalopathy and cerebellar syndrome<sup>(1,3-9)</sup>. We present two cases of encephalopathy probably caused by metronidazole and discuss neuroimaging findings.

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## CASE REPORT

### Patient 1

A 70-year-old female was a patient of cervical cancer status post modified hysterectomy and bilateral salpingo-oophorectomy in 1997 and had recurrent cervical cancer with pelvic invasion status post concurrent chemoradiotherapy in 2007. In March, 2008, she was admitted due to pneumaturia and colovesical fistula was confirmed after serial examinations. Therefore, she received Hartmann's procedure and bladder repair. After the operation, she experienced a period of nothing per os for more than one week and metronidazole was administered for one month to cover intra-abdominal infection, with a total dose of 41.25g.

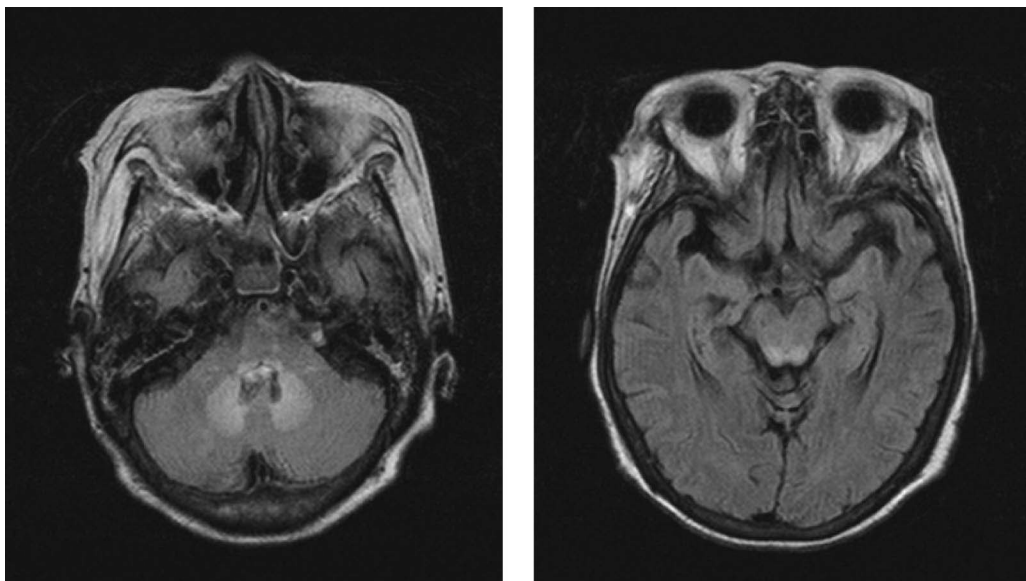
However, one week after administration of metronidazole, she developed a brief period of consciousness disturbance with facial twitching and deviated eyes to left side. On examinations while consciousness regained, there was no newly developed limbs weakness, nor abnormal cranial nerve function except presence of conjugated rotational nystagmus and bilateral appendicular dysmetria. No obvious metabolic derangement was

found. The sodium concentration was 130mEq/L. Two days later, the brain MRI revealed high signal intensity in bilateral dentate nuclei, dorsal midbrain and surrounding the 4th ventricle with some old lacunar infarcts in the right corona radiata and in left basal ganglion. (Fig. 1) Severe medical comorbidities and sepsis with organ failure developed in the following days, so the CSF study could not be performed. She expired on the 29th day after admission. Follow up neuroimaging was impossible.

### Patient 2

A 56-year-old female, with rectal tubulovillous adenoma patient status post radical proctectomy, was admitted due to severe ileus and she received resection of the small bowel with anastomosis and lysis of peritoneal adhesions on the 25th day after admission. Throughout the whole course, metronidazole (1500mg/d) had been administered since the 9th day after admission for more than 2 weeks, with a total dose 24g and she also experienced nothing per os for one month.

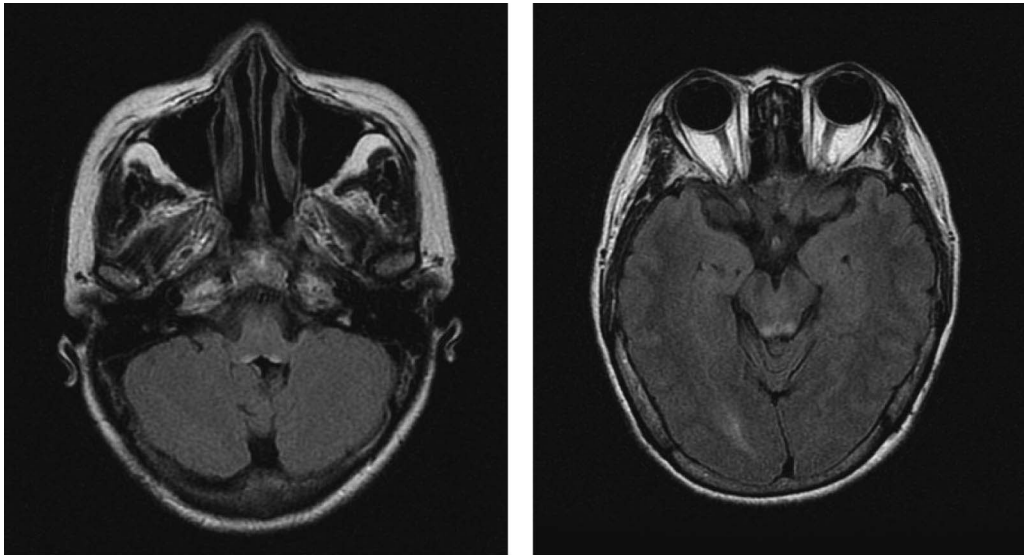
However, she developed acute onset of severe vertigo with vomiting and spontaneous nystagmus on the



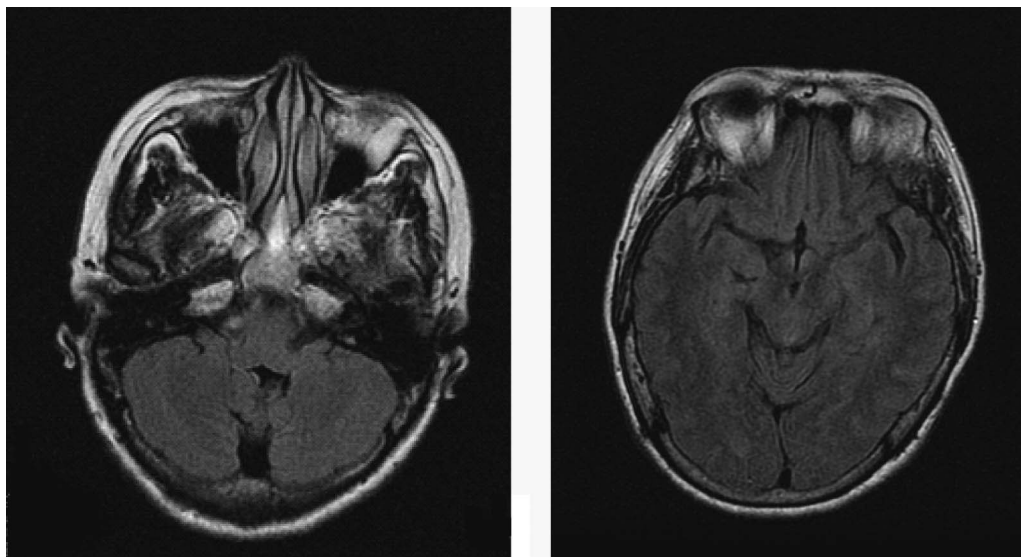
**Figure 1.** The T2 FLAIR images of Patient 1 performed 2 days after symptom onset revealed high signal intensity in bilateral dentate nuclei, dorsal midbrain and surrounding the 4th ventricle. Follow up neuroimaging was impossible because of severe sepsis with multiple organ failure.

37th day after admission. There were no additional neurological deficits and central vertigo was suspected. The brain MRI on the next day showed high signal intensity in the dorsal midbrain and dorsal medulla on T2 FLAIR images. (Fig. 2) The CSF study showed no pleocytosis and normal protein level. The associated biochemistry profiles were within normal limit. The sodium concen-

tration was 133mEq/L. Her vertigo subsided after symptomatic treatments and nystagmus also disappeared few days later. After discharge, a follow up brain MRI performed 50 days after the onset of central vertigo revealed disappearance of the T2 hyperintensity previously seen in dorsal pons and dorsal medulla. (Fig. 3)



**Figure 2.** The T2 FLAIR images of Patient 2 performed the day after symptom onset revealed high signal intensity in dorsal midbrain and dorsal medulla.



**Figure 3.** The T2 FLAIR images of Patient 2 performed on the 50th day after symptom onset showed disappearance of the T2 hyperintensity previously seen in dorsal pons and dorsal medulla.

## DISCUSSION

Cerebellar syndrome, encephalopathy, seizures, and autonomic, optic and peripheral neuropathies have been associated with the use of metronidazole<sup>(1,3-9)</sup>. The exact mechanisms of metronidazole neurotoxicity remain unclear.

Ahmed et al.<sup>(1)</sup> first described reversible neuroimaging in metronidazole-induced encephalopathy in 1995 and explained the reversibility by axonal swelling with increased water content rather than a demyelinating process. Most brain lesions induced by metronidazole are reversible. Once the medication is discontinued, the syndrome may improve within days and be resolved within several weeks.

Longer duration of metronidazole therapy with more cumulative doses has greater opportunity to cause neurotoxicity<sup>(2)</sup> but differences of metronidazole use between intravenous and oral forms are undetermined.

Involving lesions of metronidazole-induced encephalopathy (MIE) are typically located at cerebellar dentate nucleus, midbrain, dorsal pons, medulla, and splenium of the corpus callosum bilaterally and symmetrically<sup>(4)</sup>. Cerebellar dentate nuclei are involved in most cases<sup>(1,3-9)</sup> and inferior colliculus lesions can be considered as the characteristic for MIE, next to dentate nuclei involvement<sup>(5)</sup>. Other uncommon sites include white matter of cerebral hemispheres<sup>(1)</sup> and inferior olivary nucleus<sup>(4)</sup>. The lesions appear as non-enhancing, hyperintense on T2-weighted and FLAIR images without evidence of mass effect. The diffusion-weighted image signal is high with variable apparent diffusion coefficient values.

It is necessary to differentiate demyelinating diseases and other metabolic and toxic disease such as Wernicke's encephalopathy and osmotic myelinolysis with pontine or extra-pontine damage. Among the differential diagnoses, Wernicke's encephalopathy (WE) is probably the most common and confusing one. Considering WE, although it shows a predilection for midbrain and diencephalon and is associated with chronic alcoholics, it is still difficult to separate it from MIE completely. Kim et al.<sup>(4)</sup> described brain MRI findings

from 7 patients treated with metronidazole retrospectively. Besides involvement of bilateral dentate nuclei, there are selective involvements of cranial nerve nuclei (vestibular, abducens and facial) as well as atypical manifestations in nonalcoholic patients affected by Wernicke's encephalopathy reported by Bae et al.<sup>(10)</sup> and Kang et al.<sup>(11)</sup>. In a previous in vitro study<sup>(12)</sup> and a prospective study to evaluate metronidazole toxicity<sup>(2)</sup>, metronidazole was thought to be sufficiently nucleophilic to be enzymatically incorporated into a thiamine analog, which can inhibit pyrophosphorylation of thiamine, leading to a reduction in thiamine absorption from the gut and causing variable neurotoxicities. We may speculate about MIE and nonalcoholic WE with atypical MR manifestations may share similar metabolic pathways<sup>(13)</sup>.

To our knowledge, metronidazole-induced encephalopathy occurs during therapy and almost disappears a few days to weeks after discontinuing the offending medication. Patient 1 presented typical temporal relationship to metronidazole therapy but had no follow up brain MRI. However, Patient 2 developed symptoms 12 days after discontinuing metronidazole with relatively low cumulative doses and relatively uncommon brain MRI findings involving dorsal midbrain and dorsal medulla rather than bilateral dentate nuclei. This raised concerns of other possible differential diagnosis such as Wernicke's encephalopathy or demyelinating disease. However, there were no abnormalities in her blood and CSF examinations and the follow up brain MRI showed complete remission of previous brain lesions. MIE is still the probable diagnosis and accompanied nutritional causes or history of cancer may render her more susceptible to toxicity<sup>(9)</sup>.

## CONCLUSION

Metronidazole-induced encephalopathy is a relatively rare entity, but needs to be considered because of the broad use of metronidazole in both medical and surgical patients. Neurologists should be aware of MIE when facing patients with acute neurological deficits with concurrent use of metronidazole, especially those in long term

therapy and those with poor nutritional status and medical chronic illness, which may render patients more susceptible to toxicity. Early diagnosis by using brain MRI and prompt cessation of the medication bring most benefits to patients. Nonalcoholic Wernicke's encephalopathy is an important differential diagnosis and may share a similar metabolic pathway with MIE, resulting in difficulty in diagnosis.

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