

Serially Changing Metronidazole-Induced Encephalopathy

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Metronidazole is a 5-nitroimidazole compound that is a fairly well-tolerated antiprotozoal and antibacterial agent. Occasionally, it can manifest adverse neurologic effects. Variable brain magnetic resonance (MR) imaging abnormalities that are a feature of metronidazole-induced encephalopathy (MIE) have been identified in the cerebellar dentate nucleus, inferior colliculus, midbrain, basal ganglia, corpus callosum, or subcortical white matter.^{1,2}

Although many cases of MIE have been reported with a focus on the reversibility or lesion distribution, we describe additional characteristic imaging findings of MIE that showed a serially changing pattern of reversible and unilateral lesions following discontinuation of metronidazole therapy, despite metabolic encephalopathy.

A 46-year-old man had been an alcoholic for 20 years but had stopped drinking four months earlier. Recently, he had been diagnosed by chest X-ray with pneumonia with pleural effusion, and he had been treated with intravenous ceftriaxone (1000 mg/day) and metronidazole (1500 mg/day) for nine days and then with 400 mg of oral moxifloxacin and 1500 mg of metronidazole per day for 15 days. Twenty-four days after taking the metronidazole medication, the patient was hospitalized with complaints of tingling sensations in both arms one day before admission and dysarthria on the day of admission. By now, the patient had consumed about 36 g of the drug. He had no history of starvation, other drug medications, or trauma.

Upon neurological examination, he was alert but confused. A cranial nerve examination was normal except for dysarthria. He presented with trivial paresthesia in both arms but did not exhibit objective sensory impairment. His motor power, deep tendon reflexes, cerebellar functioning, and gait were normal. Brain MR imaging (Intera 1.5T 10.3 version, Eindhoven, Netherlands) revealed high-signal lesions in the genu and splenium of the corpus callosum on initial diffusion-weighted images [DWI; repetition time/echo time (TR/TE), 6500/110 ms; b -values = 1000 s/mm²] with correspondingly low apparent diffusion coefficient (ADC) maps (Figure 1).

Upon physical examination, the patient's vital signs were stable, and there was no finding of malnutrition. Serum laboratory findings, including electrolytes, liver and kidney panels, and vitamin B₁, B₁₂, and folate levels, were all within normal limits. Serum anti-human immunodeficiency virus (HIV) antibody, urine, cerebrospinal fluid (CSF) studies, and culture studies, including blood, urine, and cerebrospinal fluid, all were negative.

We suspected that he was suffering from MIE, and metronidazole therapy was discontinued. On the third day following metronidazole discontinuation, his mental status

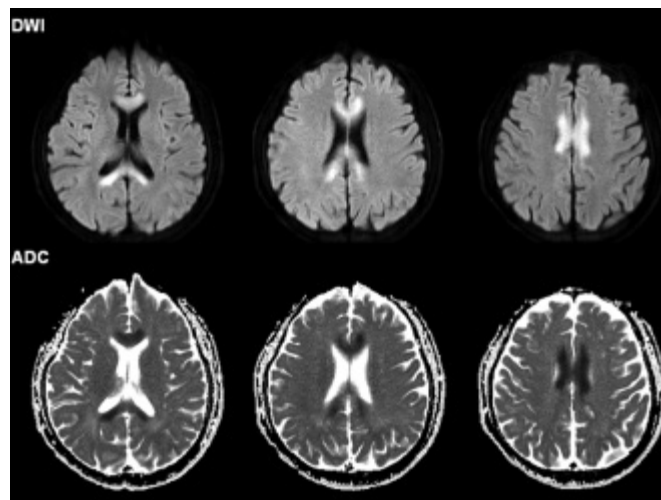


Figure 1: Initial imaging scans showing acute cytotoxic edema in the genu and splenium of the corpus callosum on diffusion-weighted images (DWIs) in the upper panel and apparent diffusion coefficient (ADC) maps in the lower panel.

showed improvement, but the patient remained disoriented. The follow-up MR imaging performed on the same day depicted that the genu and splenium lesions of corpus callosum had almost disappeared from the DWI and ADC maps, when referenced to the initial study (Figure 2). However, a newly developed high-signal lesion with a low ADC was apparent in the deep white matter along the right frontotemporoparietal region on the DWI. On T2-weighted (TR/TE, 5000/99 ms) and fluid-attenuated inversion recovery (FLAIR; TR/TE, 9,000/119 ms) images, the corresponding areas had slightly increased signal intensities. There was no hypointense or contrast-enhanced lesions visible on enhanced T1-weighted (TR/TE, 497/12 ms) images. Three-dimensional time-of-flight MR angiography (older Signa unit,

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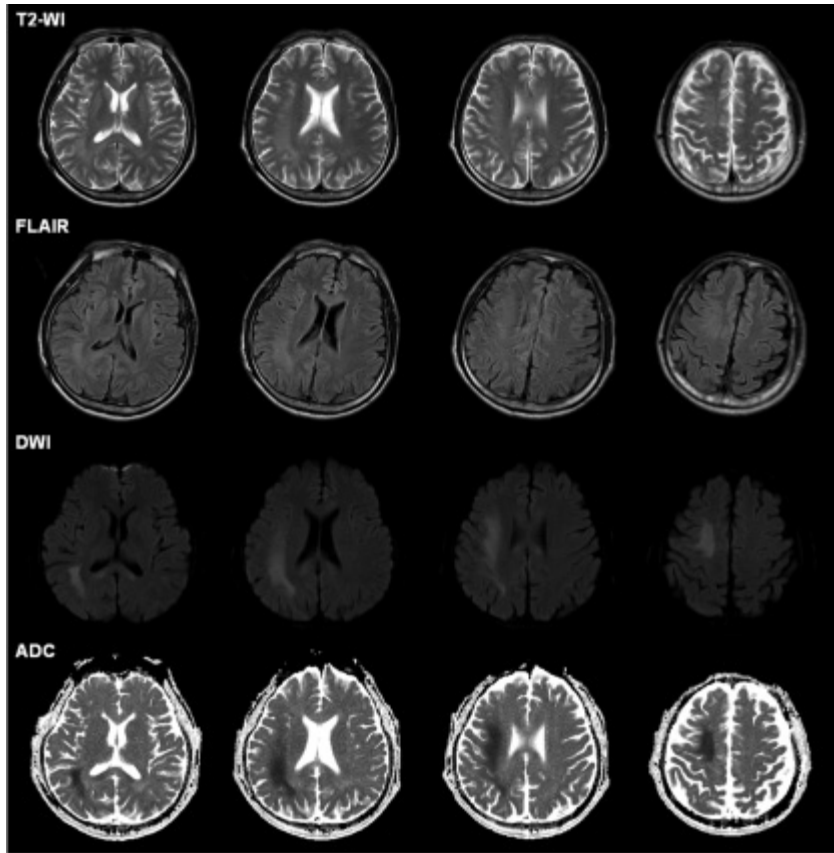


Figure 2: Three days after the cessation of metronidazole, the corpus callosal lesions had nearly resolved, but a new hyperintense lesion appeared in the right deep white matter along the frontotemporoparietal region on DWIs. The corresponding lesions showed low-signal intensity on ADC map. On T2-weighted (T2-WI) and fluid-attenuated inversion recovery (FLAIR) images, the same areas demonstrated slightly increased signal intensities.

Figure 3: Thirteen days after the cessation of metronidazole, the third follow-up imaging scan showed complete resolution of the findings on the ADC map, but a residual high-signal intensity remained in the splenium and right deep white matter on DWI and FLAIR images.

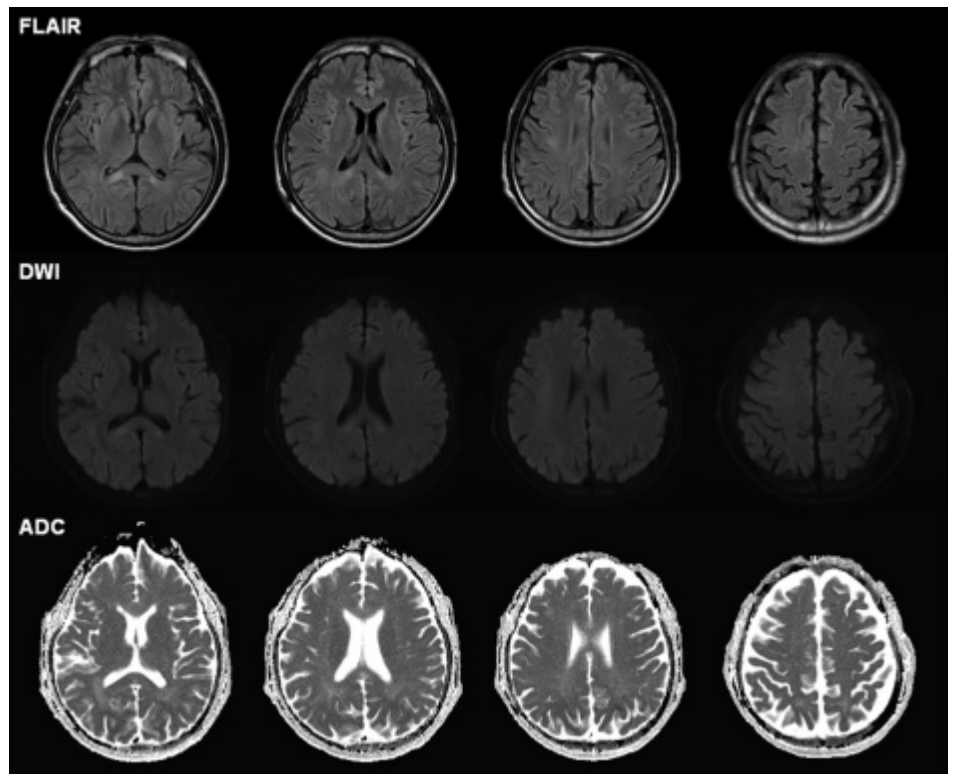


Table: Characteristics of cases of metronidazole neurotoxicity

Age/Sex	Underlying disease	Involved brain lesions	Dose (g)/Duration (d)	Reference
45/F	Cholecystitis	Bilateral dentate nuclei, genu and splenium of corpus callosum, subcortical white matter	35 g/30 d	Ahmed et al.*
74/F	Crohn's disease	Subcortical white matter, anterior commissure, corpus splenium, basal ganglia, midbrain, cerebellar white matter, and bilateral inferior olivary nuclei	180 g/180 d	Seok et al.*
31/M	Crohn's disease	Bilateral dentate nuclei and subcortical white matter	10.5 g/7 d	Kim et al.*
20/M	Ulcerative colitis	Corpus splenium	1095 g/730 d	De Bleecker et al.*
51/M	Anal fistula	Bilateral dentate nuclei, corpus splenium, periaqueductal region, and brain stem (bulbar region)	31.5 g/21 d	Hammami et al.*
20/M	Acute lymphoblastic leukemia	Bilateral dentate nuclei, dorsal pons, and medulla	Unclear/14 d	Bonkowsky et al. ³
61/M	Transplant wound infection	Bilateral dentate nuclei	92.4 g/77 d	Graves et al.*
67/M	Liver abscess	Bilateral dentate nuclei and corpus splenium	75 g/70 d	Park et al.*
43/M	Amebic liver abscess	Bilateral dentate nuclei, dorsal pons, and splenium of the corpus callosum	84 g/ 60 d	Kalia et al.*
71/M	Infectious colitis	Bilateral dentate nuclei, tectal region of cerebellum, and corpus splenium	45.5 g/31 d	Kim et al.*

*. Additional references available upon request to the corresponding author (neurocraft@kd.ac.kr). F=female, M=male, g=grams, d=per day.

TE 6.6 ms) showed no evidence of irregularity with areas of vessel narrowing and dilation suggesting vasculopathy.

At two weeks from symptom onset (13 days after cessation of metronidazole), the patient's cognition and dysarthria returned to near normal. At that time, the third follow-up imaging scan showed complete resolution of the findings on the ADC map, but a residual high-signal intensity remained in the splenium and right deep white matter on DWI and FLAIR images (Figure 3). No infratentorial lesions, such as dentate nuclei, inferior colliculi, midbrain, pons, or medulla, were apparent in the serial brain MR imagings.

DISCUSSION

Although the mechanism of metronidazole neurotoxicity remains unclear, most lesions induced by metronidazole neurotoxicity have been reported to be wholly reversible.

The previously reported cases had a lesion distribution of MIE as follows: cerebellar dentate nuclei, inferior colliculi, midbrain, corpus callosum, pons, medulla, cerebral white matter, and basal ganglia, in order of frequency.² These lesions were always bilateral and symmetric.

No cases involving the serially changing pattern of reversible lesions in a patient have been reported. Furthermore, it is noteworthy that our patient demonstrated an unilateral cytotoxic lesion during the serial imaging despite the metabolic encephalopathy. He showed no evidence of ipsilateral arterial vasculopathy on three-dimensional time-of-flight MR angiography.

In case series of MIE, DWI lesions, which involve mainly gray matter (midbrain, pons, medulla, and cerebellar dentate nuclei), showed increased ADC values and vasogenic edema, but decreased ADC values and cytotoxic edema were seen in lesions of the corpus callosum¹ and subcortical deep white matter, as in our case. Although it is unclear why lesion ADC values depend on lesion location, the mechanisms of MIE involve edema instead of ischemia, as evidenced by the reversible pattern (vasogenic edema in gray matter vs. cytotoxic edema in white matter).¹ However, another study³ showed cytotoxic edema in gray matter lesions, including dentate nuclei, dorsal pons, and medulla, on brain MR imaging, which contradicts Kim et al's study.¹

Diffusion signal-intensity changes may be related to the stage of neurotoxic injury and the time interval that has elapsed between the initial and follow-up MR imaging.¹ After the cessation of metronidazole, the high-signal lesions in the corpus callosum and deep white matter on DWI gradually resolved and regressed through two week periods, at which time our patient nearly recovered. Poor prognosis may be associated with low ADC.⁴ It is consistent that our patient recovered without any neurologic deficits considering the reversibility of his ADC intensity.

As the pattern of imaging findings in our case was not pathognomic for MIE, it is necessary to differentiate from diseases such as demyelinating or metabolic conditions. Demyelinating diseases, such as multiple sclerosis or acute demyelinated encephalomyelitis, should also be considered as a cause of unilateral white matter lesions. However, our patient developed encephalopathy following the use of metronidazole and was gradually convalescing well in cognition and dysarthria after its discontinuation. This temporal relationship, as well as normal CSF, supports the diagnosis of MIE, rather than demyelinating disease.

Because the patient had been an alcoholic for 20 years, we can also consider a possible cause of Marchiafava-Bignami disease or Wernicke encephalopathy. He had stopped drinking alcohol four months before developing the encephalopathy, had no history of starvation nor did he show malnutrition findings. A serum liver panel and vitamin B₁, B₁₂, and folate levels were all within normal limits. In particular, the possibility of Marchiafava-Bignami disease in our patient might contradict the fact that most patients presenting with the acute type of Marchiafava-Bignami disease will go into mortality. Our patient developed encephalopathy following the use of metronidazole and began to show gradual improvement after the cessation of drug intake. This temporal relationship also supports the diagnosis of MIE, although our patient did not exhibit the cerebellar lesion characteristic of MIE.⁵

It is not clear why only a few patients develop metronidazole toxicity and that they do so with therapeutic serum levels.⁵ Clinical characteristics of the reports published to date* of metronidazole neurotoxicity are summarized in the Table. The

cerebellum is the most commonly involved lesion of MIE, except for one case,* which was similar to our patient. It is noticeable that all reported patients, including our patient, were mostly Asian males: 22 Asians (88%) and 16 males (64%) among the total 25 patients.¹⁻³ and * It remains to be elucidated whether there are ethnic and gender factors that affect metronidazole susceptibility.

In conclusion, most of the previously documented brain lesions on MR images in MIE were always bilateral and symmetric, but we present another finding that metronidazole-induced cytotoxic edema might be a dynamically changeable lesion according to disease stage. In addition, MIE could manifest asymmetrical lesions without evidence of preexisting vasculopathy.

REFERENCES

1. Kim E, Na DG, Kim EY, Kim JH, Son KR, Chang KH. MR imaging of metronidazole-induced encephalopathy: Lesion distribution and diffusion-weighted imaging findings. *AJNR Am J Neuroradiol.* 2007;28:1652-8.
2. Lee SS, Cha SH, Lee SY, Song CJ. Reversible inferior colliculus lesion in metronidazole-induced encephalopathy: Magnetic resonance findings on diffusion-weighted and fluid attenuated inversion recovery imaging. *J Comput Assist Tomogr.* 2009;33:305-8.
3. Bonkowsky JL, Sondrup C, Benedict SL. Acute reversible cerebellar lesions associated with metronidazole therapy. *Neurology.* 2007;68:180.
4. Dardzinski BJ, Sotak CH, Fisher M, Hasegawa Y, Li L, Minematsu K. Apparent diffusion coefficient mapping of experimental focal cerebral ischemia using diffusion-weighted echo-planar imaging. *Magn Reson Med* 1993;30:318-25.
5. Woodruff BK, Wijdicks EF, Marshall WF. Reversible metronidazole-induced lesions of the cerebellar dentate nuclei. *N Engl J Med.* 2002;346:68-9.

* *Additional references available upon request to the corresponding author (neurocraft@kd.ac.kr)*