Metronidazole Induced Encephalopathy in a Patient with Brain Abscess

Yoochang Bahn, M.D., Eunyoung Kim, M.D., Chongoon Park, M.D., Hyung-Chun Park, M.D.
Department of Neurosurgery, Inha University Hospital, Inha University College of Medicine, Incheon, Korea

INTRODUCTION

Metronidazole-induced encephalopathy (MIEP) is a toxic encephalopathy associated with the use of metronidazole. Metronidazole is efficacious in treating trichomoniasis, amebiasis, and giardiasis and in infections caused by obligate anaerobes and microaerophilic bacteria. It has been used for treatment of brain abscess, because anaerobic and microaerophilic bacteria constitute the most common pathogens. We report our experience of treating a patient with metronidazole for brain abscess, who subsequently developed severe MIEP during the treatment period, and review the clinical characteristics of MIEP and its prognosis.

CASE REPORT

A 52-year-old man presented with disorientation and rightsided weakness. He had no symptoms of upper respiratory tract infections and the only remarkable surgical history was cardiac surgery conducted 30 years previously. On examination, he was apyrexic. Heart and lung auscultation examinations were unremarkable. He was confused and disoriented in time and place. His pupil was isocoric and positive for light reflex. He had no dysfunction in other cranial nerves, but showed mild frontal lobe dysfunction as evidenced by the presence of abulia and Broca’s aphasia, as well as grade IV right hemiparesis. Magnetic resonance imaging (MRI) revealed a thin-walled, smooth, regular cavitated lesion associated with edema in the left frontal lobe. The wall was isointense on T2-weighted image and enhanced on enhanced image (Fig. 1A, B). Its interior was hyper-intense on T2-weighted image, hypointense on T1-weighted image, and hyper-intense on diffusion-weighted image (Fig. 1A, C, D).

The MRI appearance was consistent with that of a brain abscess, for which he was treated with stereotactic aspiration. There was no bacterial growth on blood and aspirated pus cultures. Intravenous ceftriaxone (daily dosage, 8 g; duration, 49 days) and metronidazole (daily dosage, 2 g; duration, 24 days) were commenced empirically. On the twentieth day of antibiotics treatment, the patient experienced new onset tinnitus, diplopia, dizziness, swallowing difficulty and left-sided weakness. Neurological examination revealed bilateral sixth cranial nerve palsy, horizontal direction nystagmus, dysphagia and grade II left hemiparesis. Repeat brain MRI and MR angiography (MRA) were conducted to exclude brain abscess progression and its complications, and other newly developed conditions, such as cerebral infarction.
weighted MR images showed high signal intensity in medulla, pons, the splenium of corpus callosum and periventricular white matter around the right trigone (Fig. 2A, B, C). These lesions showed low signal intensity on apparent diffusion coefficient (ADC) map image (Fig. 2D). On FLAIR image, high intensity signals were seen in both dentate nuclei of cerebellum (E), and in the splenium of corpus callosum (F).

MRA findings excluded vascular abnormality. Based on the location and MR characteristics, the lesions were assumed to be MIEP, rather than cerebral infarction. Metronidazole was subsequently discontinued and intravenous ceftriaxone was maintained for further 25 days. Intravenous dexamethasone (daily dosage, 2.5 mg-15 mg; duration, 15 days) was empirically commenced. The patient's neurological abnormalities began to improve after discontinuing metronidazole and almost resolved by week 4. Follow-up MRI demonstrated resolution of MIEP-related lesions (Fig. 3). He was neurologically normal at the one-year follow-up review.

DISCUSSION

The true incidence of MIEP is not known, although some published reports\(^1^,^2^,^4^,^6^,^8^,^21^,^24^,^25^,^28^\) presented cases of metronidazole's neurotoxicities. Among 31 MIEP patients reported in the publications, only 3 patients presented with brain abscess as their primary pathology\(^1^,^4^,^18^,^21\). Most MIEP patients show favorable outcomes. However, Kim et al.\(^1^,^6^\) reported two patients whose neurological symptoms persisted during long-term follow up. Their neurological sequelae included cognitive dysfunction, learning and memory dysfunction, and decreased consciousness. Through the review of previous cases\(^1^,^2^,^4^,^6^,^8^,^21^,^24^,^25^,^27\), patient's underlying condition such as brain abscess necessitating metronidazole treatment does not seem to affect the outcome of MIEP. Metronidazole is commonly used in the treatment of brain abscess to cover anaerobes and MIEP can lead to irreversible neurologic sequelae. Therefore, MIEP should always be borne in mind when administering metronidazole for the treatment of cerebral abscess.

The mechanisms that underlie metronidazole's neuronal toxicity remain unclear. Several studies\(^5^,^7^\) suggested the following mechanisms; 1) metronidazole's intermediate metabolites modulate inhibitory neurotransmitter GABA receptor especially within the cerebellar and vestibular systems, and 2)
the reactions with catecholamine neurotransmitter generate semiquinone and nitro anion neurotoxic radicals. On the previous reports 1-8, metronidazole induced neuropathy developed in the case consuming 21-135 g of metronidazole. Further study may need to clarify whether MIEP is dose-related or not.

Published reports 1-8,9-27 described the MIEP lesion distributions in descending order of incidence: cerebellar dentate nuclei, midbrain, corpus callosum, pons, medulla, cerebral white matter and basal ganglia. In our patient, MIEP lesions developed in most of reported frequent locations.

Most patients included in the published case series presented with various degree of cerebellar, cranial nerve and cerebral dysfunction 1 to 12 weeks following metronidazole administration. Our patient had diverse severe symptomatology, including tinnitus, diplopia, dizziness, swallowing difficulty and hemiparesis.

MIEP lesions appeared as non-enhancing, hyper-intense lesions on T2-weighted and FLAIR images without evidence of mass effect. These lesions appear as high signal intensities on DWI. In addition, a few radiologic features help to distinguish MIEP from other lesions 18. First, MIEP lesions are of mass effect. These lesions appear as high signal intensities in both dentate nuclei of the cerebellum (D). MIEP: metronidazole-induced encephalopathy.

CONCLUSION

Neurosurgeons dealing with brain abscesses should be aware that severe MIEP can occur during the use of metronidazole to prevent permanent neurological deficit.

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References

1. Ahmed A, Loes DJ, Bressler EL: Reversible magnetic resonance imaging findings in metronidazole-induced encephalopathy. Neurology 45: 588-589, 1995
2. Arik N, Cengiz N, Bilge A: Metronidazole-induced encephalopathy in a uraemic patient: a case report. Nephron 89: 108-109, 2001
3. Bradley WG, Karlsson IJ, Rassol CG: Metronidazole neuropathy. Br Med J 2: 610-611, 1977
4. Cecil KM, Halsted MJ, Schapiro M, Dinopoulos A, Jones BV: Reversible MR imaging and MR spectroscopy abnormalities in association with metronidazole therapy. J Comput Assist Tomogr 26: 948-951, 2002
5. Dow SW, LeCouteur RA, Ponn ML, Beadleston D: Central nervous system toxicosis associated with metronidazole treatment of dogs: five cases (1984-1987). J Am Vet Med Assoc 195: 365-368, 1989
6. De Bleecker JL, Leroy BP, Meire VI: Reversible visual deficit and Corpus callosum lesions due to metronidazole toxicity. Eur Neurol 53: 93-95, 2005
7. Evans J, Levesque D, Knowles K, Longshore R, Plummer S: Diazepam as a treatment for metronidazole toxicosis in dogs: a retrospective study of 21 cases. J Vet Intern Med 17: 304-310, 2003
8. Frytak S, Moertel CH, Childs DS: Neurologic toxicity associated with high-dose metronidazole therapy. Ann Intern Med 88: 361-362, 1978
9. Galvez M, Braham J, Miranda M: Movement disorders as a manifestation of metronidazole-induced encephalopathy in a patient with chronic liver disease. Movement Disorders 24 (12): 1864-1866, 2009
10. Graves TD, Condon M, Loucoidou M, Perry RJ: Reversible metronidazole-induced cerebellar toxicity in a multiple transplant recipient. J Neurol Sci 285: 238-240, 2009
11. Hammami N, Drissi C, Sebai R, Arzar M, Maatallah Y, Belghith L, et al.: Reversible metronidazole-induced encephalopathy. J Neuroradiol 34: 133-136, 2007
12. Heaney CJ, Campeau NG, Lindell EP: MR imaging and diffusion-weighted imaging changes in metronidazole (Flagyl)-induced cerebellar...
toxicity. AJNR Am J Neuroradiol 24: 1615-1617, 2003
13. Horlen CK, Seifert CF, Malouf CS: Toxic metronidazole-induced MRI changes. Ann Pharmacother 34: 1273-1275, 2000
14. Huh SY, Kim JK, Kim MJ, Yoo BG, Kim KS, Lee JH: Reversible encephalopathy induced by metronidazole. J Korean Geriatr Soc 12: 176-178, 2008
15. Ito H, Maruyama M, Ogura N, Fujioka T, Iwasaki Y, Aikawa A, et al.: Reversible cerebellar lesions induced by metronidazole therapy for helicobacter pylori. J Neuroimaging 14: 369-371, 2004
16. Kim DS, Jung JW, Kim JY, Kim JH, Kim EK, Kim SE: Reversible MRI findings in metronidazole-induced cerebellar dysfunction. J Korean Neurol Assoc 17: 904-907, 1999
17. Kim DW, Park JM, Yoon BW, Baek MJ, Kim JE, Kim S: Metronidazole-induced encephalopathy. J Neurol Sci 224: 107-111, 2004
18. 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 28: 1652-1658, 2007
19. Kim KH, Choi JW, Lee JY, Kim TD, Paek JH, Lee EJ, et al.: Two cases of metronidazole-induced encephalopathy. Korean J Gastroenterol 45: 195-200, 2005
20. Kusumi RK, Plouffe JF, Wyatt RH, Fass RJ: Central nervous system toxicity associated with metronidazole therapy. Ann Intern Med 93: 59-60, 1980
21. 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 33: 305-308, 2009
22. Olson EJ, Morales SC, McVey AS, Hayden DW: Putative metronidazole neurotoxicosis in a cat. Vet Pathol 42: 665-669, 2005
23. Scharer K: [Selective alterations of Purkinje cells in the dog after oral administration of high-doses of nitroimidazole derivatives (author's transl)]. Verh Dtsch Ges Pathol 56: 407-410, 1972
24. Seok JI, Yi H, Song YM, Lee WY: Metronidazole-induced encephalopathy and inferior olivary hypertrophy: lesion analysis with diffusion-weighted imaging and apparent diffusion coefficient maps. Arch Neurol 60: 1796-1800, 2003
25. Snively SR, Hodges GR: The neurotoxicity of antibacterial agents. Ann Intern Med 101: 92-104, 1984
26. von Rogulja P, Kovac W, Schmid H: [Metronidazole encephalopathy in rats]. Acta Neuropathol 25: 36-45, 1973
27. Woodruff BK, Wijdicks EF, Marshall WF: Reversible metronidazole-induced lesions of the cerebellar dentate nuclei. N Engl J Med 346: 68-69, 2002
28. Wright KH, Tyler JW: Recognizing metronidazole toxicosis in dogs. Vet Med 98: 410-418, 2003