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

Metronidazole is commonly used for brain abscess but is not well known for its neurotoxic complications. Metronidazole-induced encephalopathy (MIEP) is toxic encephalopathy associated with the use of metronidazole. We experienced a case of brain abscess which developed reversible severe MIEP during treatment period. Although MIEP occurs in typical locations, it is not easy to differentiate from other conditions such as cerebral infarction, demyelinating diseases and metabolic diseases. Neurosurgeons should be aware that severe MIEP can occur during the use of metronidazole though it is not common.

KEY WORDS: Metronidazole • Brain abscess • Toxic encephalopathy

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 right-sided 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 afebrile. 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 palsies, horizontal movement 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. Diffusion-
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\textsuperscript{1,2,5,6,8-21,24,25,28} 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\textsuperscript{11,18,21}

Most MIEP patients show favorable outcomes. However, Kim et al.\textsuperscript{16} 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\textsuperscript{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\textsuperscript{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, 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 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. First, MIEP lesions are mostly symmetric and bilateral. Second, bilateral cerebellar dentate nuclei are involved in most cases. Third, lesions of the corpus callosum almost always involve the splenium. Finally, follow-up brain MRI demonstrates lesion resolution after discontinuing metronidazole. Our case is unique in terms of unilateral lesion in periventricular white matter. Though all lesions were bilateral and symmetric in 21 reviewed cases showing MR imaging of MIEP lesion as figure, incidence of unilateral lesion in MIEP is unknown to the best of our knowledge.

Discontinuing metronidazole is the primary treatment for MIEP. Though most patients recover between 3 and 16 weeks after stopping metronidazole associated with resolution of abnormal MRI findings, irreversible severe neurologic sequelae remain in some cases. Although there has been no evidence of usefulness of steroid therapy for MIEP, we administered steroid empirically for this case.

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

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