Metronidazole Induced Encephalopathy Mimicking an Acute Ischemic Stroke Event

Kensuke TAKADA,¹ Yoshinori MAKI,¹ Masanori KINOSADA,¹ Ryota ISHIBASHI,¹ Masaki CHIN,¹ and Sen YAMAGATA¹

¹Department of Neurosurgery, Kurashiki Central Hospital, Kurashiki, Okayama, Japan

Abstract

Metronidazole induced encephalopathy (MIE), an encephalopathy brought by an antibiotic, is characterized with cerebellar dysfunction, altered mental status and extrapyramidal symptoms. MIE can result in an acute manifestation, but MIE has not been reported as a stroke mimic. An 86-year-old patient undergoing metronidazole therapy for Clostridium difficile enteritis presented to our hospital with sudden disoriented status and motor weakness of the left extremities. Computed tomography (CT) was unrevealing of intracranial hemorrhagic change, and CT angiography did not show any apparent major occlusion or stenosis of the intracranial vessels. However, CT perfusion (CTP) revealed a decrease in peripheral blood flow in the right cerebral hemisphere, and tissue plasminogen activator was administrated for a possible acute ischemic stroke. The findings of follow-up magnetic resonance imaging (MRI) were typical for MIE, revealing areas of hyperintensity on fluid attenuated inversion recovery (FLAIR) signal intensity in the dentate nuclei, the splenium of the corpus callosum, and in the dorsal midbrain. The degree of hyperintensity was stronger in the left dentate nucleus than in the right left dentate on FLAIR and the apparent diffusion coefficient map. The asymmetric findings of the left dentate nucleus on MRI were considered to be responsible for the clinical symptoms and the findings of CTP. We report a rare case of MIE mimicking an acute ischemic stroke, and hypothesize the relationship between the findings of CTP and that of MRI based on the anatomical connection of the dentate nucleus and the cerebral hemisphere.

Key words: metronidazole induced encephalopathy, computed tomography perfusion, stroke mimic, magnetic resonance imaging, tissue plasminogen activator

Introduction

Metronidazole induced encephalopathy (MIE), an encephalopathy brought by an antibiotic for Clostridium difficile, Helicobacter Pylori, trichomobal infection and amoebiasis, can show clinical manifestations such as cerebellar dysfunction, altered mental status and extrapyramidal symptoms.¹ MIE has been reported mostly in adult cases without sex predisposition.¹ The mechanism of neurotoxicity in MIE remains unclear though several mechanisms have been proposed.¹,² Hyperintensities of the dentate nuclei, the splenium of the corpus callosum and the midbrain on fluid attenuated inversion recovery (FLAIR) are considered to be typical for MIE.¹,² The signals of the lesions related to MIE are mostly symmetric but can be asymmetric on magnetic resonance imaging (MRI),¹,³ and can show regions of hypointensity or hyperintensity on apparent diffusion coefficient (ADC) mapping.¹,² The onset of symptoms in MIE can be acute,⁴ but there has been no description in the literature of MIE mimicking an acute ischemic stroke.¹,⁴ Stroke mimic is an entity in which presentation mimicking acute ischemic stroke within the appropriate time-window from symptom onset can result in the erroneous administration of tissue plasminogen activator (t-PA), and can include cases of hypoglycemia, seizure, migraine, conversion disorder and drug intoxication.⁵ Here, we describe the first report of MIE mimicking an acute ischemic event in which t-PA was administrated.

Case Report

An 86-year-old woman on her fourth week of metronidazole therapy for C. difficile enteritis was introduced to our department. The patient was at
usual status at 18:40, but a nurse confirmed motor weakness of the left extremities and right conjugate deviation in the patient about 21:30. The patient was then transferred in our hospital at 22:18. On arrival, her Glasgow Coma Scale (GCS) was E1V2M5. We observed motor weakness predominantly in the left extremities, and in the right extremities to a lesser extent. Dysarthria was also confirmed, and an acute stroke event was suspected. National Institutes of Health Stroke Scale assessment was 23. Blood of the patient was collected on arrival for the examination. After we confirmed that apparent kidney failure did not exist with venous blood gas, the patient was soon moved for the examination of computed tomography (CT). CT did not show any apparent hemorrhagic lesions or early ischemic signs. The Alberta Stroke Program CT (ASPECT) Score was 10. CT angiography (CTA) did not demonstrate any major intracranial vascular stenosis or occlusion (Figs. 1A and 1B), and CT perfusion (CTP) showed a decreased cerebral blood flow in the right cerebral hemisphere. The blood flow seemed to decrease also in the left frontal and occipital regions (Fig. 1C). As diffuse peripheral embolic event was strongly suspected with the findings of CTP, t-PA was administrated at 22:58 after any contraindication was not confirmed with past medical history and blood examination. The neurological symptoms did not change after the administration of t-PA.

Magnetic resonance imaging on FLAIR images signal intensity performed 20 hours after the onset revealed areas of hyperintensity in the deep white matter, but did not reveal any remarkable change in the dentate nuclei. The hyperintensity in the left white matter was seen especially in the frontal and the parieto-occipital regions (Figs. 2C and 2D). The splenium of the corpus callosum and left dentate nucleus showed respectively isointensity and hyperintensity on ADC map. The deep white matter showed hypointensity corresponding to hyperintensity on DWI (Figs. 2E and 2F).

As the findings of MRIs were typical for MIE and atypical for acute ischemic stroke, we considered that the symptoms resulted from MIE, and subsequently ceased metronidazole therapy.

Hemorrhagic complications related to t-PA did not occur, but an epileptic seizure occurred on admission day 3. Levetiracetam of 2,000 mg was initiated. MRI on admission day 10 showed a decrease of hyperintensity on FLAIR, except in the splenium of the corpus callosum. The patient recovered gradually to the status of GCS E3V1M4, but the bilateral motor weakness remained. Tubal feeding was required, and she was transported to another hospital for rehabilitation therapy.

**Discussion**

We report a case of MIE mimicking an acute ischemic stroke for which t-PA was administrated. MIE was diagnosed in our case with typical findings on MRI performed 20 hours after the onset.

The administration of t-PA within 4.5 hours has become standard therapy for the treatment of acute ischemic stroke, and endovascular therapy is also strongly recommended, with CTA and CTP considered useful in determining the indications of t-PA.

---

**Fig. 1** CT images before the administration of t-PA. (A) No apparent hemorrhagic lesion was detected on computed tomography (CT). CTA (B) and CTP (C). (B) CTA demonstrating no apparent cerebral artery stenosis or occlusion. (C) CTP showing the decrease of the blood flow in the right cerebral hemisphere. The decrease of the blood flow was also seen in the frontal and occipital regions.
In our case, CTA did not show any apparent intracranial occlusion or stenosis, and we decided that endovascular therapy was not needed. However, due to the decrease of the blood flow in the right cerebral hemisphere detected on CTP, we were unable to completely eliminate an acute ischemic event from the differential diagnosis. In addition, transfer to our hospital was undertaken about 4 hours after the onset of the initial symptoms, and thus we did not have time to examine the patient with MRI. As a result, we administered t-PA. Among the cases where a t-PA was administered for a stroke mimic, hypoglycemia, seizure, migraine, conversion disorder and drug intoxication have been reported. In our case, an epileptic seizure happened after the admission. The first symptom in our case could be also seizure related to MIE. To clarify the pathology of the first symptoms in our case under emergency situation, MRI during the administration of t-PA could be considered. Electroencephalography could be also effective to detect seizure. The erroneous administration of t-PA even for the stroke mimics is not considered to be contraindicative, and instead seen as preferable to missing a true acute ischemic stroke. Because the administration of t-PA in cases of stroke mimic has been reported to result in a low occurrence of symptomatic intracranial hemorrhage, t-PA should be administered without hesitation when no contraindication of t-PA is confirmed in possible stroke patients like our case.

The relation of the radiological findings and the clinical symptoms in our case was interesting. MRI performed 20 hours after the onset showed typical findings for MIE. The lesions of the deep white matter shown as hyperintensity on DWI and hypointensity on ADC could result from cytotoxic edema related to MIE. These findings can be observed on CTP as the decrease of the blood flow in the bilateral cerebral hemispheres. Especially in the left hemisphere, the lesions of the decrease of blood flow on CTP almost corresponded to the lesions of the deep white matter confirmed on MRI. In addition, hyperintensity on FLAIR was dominantly observed in the left dentate nucleus in our case. As the left dentate nucleus did not show...
hypointensity on ADC map, vasogenic edema or inflammation due to MIE was considered.\(^1\)\(^,\)\(^2\) As the right cerebral hemisphere is anatomically connected to the left dentate nucleus,\(^3\) the cell dysfunction due to vasogenic edema or inflammation of the left dentate nucleus demonstrated on ADC mapping might have caused right cerebral dysfunction as a remote effect. The right cerebral dysfunction could be then projected on CTP as a decrease of CBF (cerebral blood flow). The laterality of the findings of CTP in our case was possibly due to the remote effect existing only in the right hemisphere. Our hypothesis can be applied to explain the laterality of motor weakness in our case. However, our speculated mechanism requires further validation, as the findings of CTP concerning MIE are still lacking.

As a rapid assessment for the administration t-PA and endovascular therapy are strongly recommended based on the findings of CTA and CTP,\(^6\) metabolic diseases including MIE can also result in a presentation mimicking stroke. Our experience should be shared as a rare case of MIE mimicking an acute stroke event.

**Conclusion**

We reported a case of MIE mimicking an acute ischemic stroke. The findings of CTP resulting in our suspicion of an acute ischemic stroke could be related to the pathology of MIE. Although the administration of t-PA in cases MIE mimicking stroke is not contraindictive, our experience should be shared as the first report of MIE mimicking an acute ischemic event.

**Acknowledgment**

We thank Paul Williams (Kurashiki Central Hospital) for his extensive proofreading of this article.

**Conflicts of Interest Disclosure**

None.

**References**

1) Roy U, Panwar A, Pandit A, Das SK, Joshi B: Clinical and neuroradiological spectrum of metronidazole induced encephalopathy: our experience and the review of literature. *J Clin Diagn Res* 10: OE01–OE09, 2016

2) 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

3) Bahn Y, Kim E, Park C, Park HC: Metronidazole induced encephalopathy in a patient with brain abscess. *J Korean Neurosurg Soc* 48: 301–304, 2010

4) Demel SL, Jovin TG, Jadhav AP: Metronidazole toxicity presenting with acute onset of aphasia and right sided weakness. *J Clin Neurosci* 22: 1199–1200, 2015

5) Tsivgoulis G, Alexandrov AV, Chang J, et al.: Safety and outcomes of intravenous thrombolysis in stroke mimics: a 6-year, single-care center study and a pooled analysis of reported series. *Stroke* 42: 1771–1774, 2011

6) Powers WJ, Derdeyn CP, Biller J, et al.: American Heart Association Stroke Council: 2015 American Heart Association/American Stroke Association Focused Update of the 2013 Guidelines for the Early Management of Patients With Acute Ischemic Stroke Regarding Endovascular Treatment: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. *Stroke* 46: 3020–3035, 2015

7) Milosević NT, Ristanović D, Marić DL, Rajković K: Morphology and cell classification of large neurons in the adult human dentate nucleus: a quantitative study. *Neurosci Lett* 468: 59–63, 2010

Address reprint requests to: Yoshinori Maki, MD, Department of Neurosurgery, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki, Okayama 710-0052, Japan. e-mail: maki0427@kuhp.kyoto-u.ac.jp