Metronidazole-Induced Encephalopathy and Inferior Olivary Hypertrophy

Lesion Analysis With Diffusion-Weighted Imaging and Apparent Diffusion Coefficient Maps

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Background: Although several cases of metronidazole-induced encephalopathy have been reported, to our knowledge, there is no previous report of brain changes in anterior commissure, basal ganglia, cerebellar white matter, and inferior olivary nuclei on magnetic resonance images. The precise mechanisms of action of metronidazole-induced encephalopathy have not been determined.

Objectives: To report a unique case of metronidazole-induced encephalopathy extensively involving multiple lesions and to determine the precise mechanism of action of metronidazole-induced encephalopathy.

Setting: University hospital.

Patient: A 74-year-old woman hospitalized with complaints of progressive dysarthria, dysphagia, and gait disturbance 3 months after the initiation of metronidazole therapy.

Intervention: Brain magnetic resonance imaging and discontinuation of metronidazole therapy.

Main Outcome Measures: We observed changes of multiple lesions found on magnetic resonance imaging and analyzed apparent diffusion coefficient map values.

Results: Initial fluid-attenuated inversion recovery brain magnetic resonance images showed high signal intensities in diffuse subcortical white matter, anterior commissure, splenium, basal ganglia, midbrain, cerebellar white matter, and bilateral inferior olivary nuclei. These lesions were resolved after discontinuation of metronidazole therapy. However, the lesions in the inferior olivary nuclei were not resolved; rather they became hypertrophic. Apparent diffusion coefficient map values in the symptom period decreased and were normalized after discontinuation of metronidazole therapy.

Conclusions: We describe a patient with metronidazole-induced encephalopathy involving reversible lesions in the anterior commissure, basal ganglia, and cerebellar white matter, which have not been reported previously. We observed inferior olivary hypertrophy, believed to be the result of lesions in the midbrain and cerebellar white matter rather than the result of lesions induced by metronidazole therapy. By using diffusion-weighted imaging and apparent diffusion coefficient maps, we found that metronidazole-induced encephalopathy might be caused by cytotoxic edema.

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ter, anterior commissure, splenium, basal ganglia, midbrain, and cerebellar white matter and resulted in inferior olivary hypertrophy. To our knowledge, this is the first report of brain changes on MRI in the anterior commissure, basal ganglia, and cerebellar white matter and inferior olivary hypertrophy in a patient with metronidazole toxicity.

REPORT OF A CASE

A 74-year-old woman was hospitalized with complaints of progressive dysarthria, dysphagia, and gait disturbance for 3 months. Six months prior to admission, she was treated with oral mesalamine (2000 mg/d), metronidazole (1000 mg/d), and ciprofloxacin hydrochloride (1000 mg/d) for rectovaginal fistula associated with Crohn disease. Three months after initiation of metronidazole, she felt unsteady and had difficulty walking. Dysarthria and dysphagia were added to the diagnosis and progressed. Her medical history was unremarkable except for a 30-year history of well-controlled diabetes mellitus.

On examination, she was alert and well oriented. Her Mini-Mental State Examination score was 19 of 30. Cranial nerve examination findings revealed severe dysarthria and lateral gaze-evoked nystagmus. Muscle strength was symmetrically grade IV+ in 4 extremities. Reflexes were normal in the upper extremities and decreased in the lower extremities. There were no pathologic plantar responses. Sensation was decreased to all modalities, especially position and vibration. Cogwheel rigidity and moderate dysmetria were observed in 4 extremities. She could not sit or stand without support. There was no abnormal involuntary movement such as palatal tremor or tremor of extremities.

Laboratory evaluation revealed a low serum vitamin B12 level (72 pg/mL [53 pmol/L]; reference range, 211-911 pg/mL [155-672 pmol/L]). Her blood liver enzyme levels (aspartate aminotransferase /alanine aminotransferase, 40/49 U/L; reference range, 0-40 U/L) and fasting blood sugar level (156 mg/dL; reference range, 70-110 mg/dL) were slightly elevated. Other routine biochemical test results, including white blood cell count with differential, hemoglobin, electrolytes, serum folate, and urinalysis, were normal. Markers of autoimmunity such as thyroid antibodies, antinuclear antibodies, and anti-dsDNA antibodies were not detected. Paraneoplastic antibodies were not checked. A lumbar puncture revealed clear cerebrospinal fluid under normal pressure with normal levels for protein, glucose, and cell count. A nerve conduction study showed sensorimotor polyneuropathy. T2-weighted and fluid-attenuated inversion recovery (FLAIR) brain MRI showed high signal intensities in the diffuse subcortical white matter (A, arrows), splenium (B, arrow), anterior commissure (C, black arrow), and basal ganglia (C, white arrows), midbrain (D, arrows), cerebellar white matter (E, arrows), and inferior olivary nuclei (F, arrows).
Because of low serum vitamin B₁₂ levels, we started cyanocobalamin therapy. She received injections of 1000 µg twice a week for 2 weeks. This was followed by injections once a week for 3 months. After 3 months of treatment, regardless of much higher than normal vitamin B₁₂ levels (21 228 pg/mL [15 666 pmol/L]), her symptoms and abnormal findings on MRI persisted (Figure 2B and E). We rediagnosed her as having metronidazole-induced encephalopathy and discontinued metronidazole therapy. Her symptoms and lesions found on MRI nearly resolved within 4 months (Figure 2C and F). However, the lesions on the inferior olivary nuclei did not change. Instead, the hyperintense olivary nuclei became hypertrophic (Figure 3).

Apparent diffusion coefficient map values were significantly decreased to mean±SD 0.605±0.055×10⁻³ mm²/s at the time of symptom onset (P=.003) and did not change (0.629±0.010×10⁻³ mm²/s) after cyanocobalamin therapy (P=.001, paired t test, compared with the recovery period). After discontinuation of metronidazole therapy, the ADC map values were normalized (0.736±0.023×10⁻³ mm²/s) (Table).

Statistical analysis was performed with a software program (SPSS version 10.0; SPSS Inc, Chicago, Ill).

**COMMENT**

Our patient's symptoms, including dysarthria, dysphagia, rigidity, and ataxia, can be explained by the lesions found on MRI, including lesions in the diffuse white matter, basal ganglia, midbrain, and cerebellar white matter. With respect to differential diagnosis, vitamin B₁₂ deficiency can be ruled out because of the persistence of her symptoms regardless of normalizing the serum vitamin B₁₂ levels and because of lesions involving the deep gray matter, which are unusual in vitamin B₁₂ deficiency. Symmetric multiple lesions found on MRI, the absence of autoimmune antibodies, and the absence of multiple stenosis of cerebral arteries on findings from magnetic resonance angiography reduce the possibility of cerebral vasculitis associated with autoimmune conditions.

In our patient, symptoms and lesions found on MRI nearly resolved after discontinuation of metronidazole therapy, which strongly suggests metronidazole-induced encephalopathy. Another possible explanation is that the patient had both vitamin B₁₂ deficiency and metronidazole neurotoxicity, the latter potentiating the former and possibly preventing efficacy of the cyanocobalamin therapy. However, the fact that only discontinuation of metronidazole without further cyanocobalamin therapy improved her symptoms and lesions found on MRI lessens the possibility of vitamin B₁₂ deficiency.

There have been several reported cases in which abnormalities of the brain on MRI were associated with metronidazole treatment: lesions involving the subcortical white matter, splenium, midbrain, and cerebellar dentate nuclei.⁴⁷ Corresponding to our case, all the re-

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**Figure 2.** Sequential magnetic resonance imaging scans before and after discontinuation of metronidazole treatment. Axial fluid-attenuated inversion recovery (FLAIR) (A-C) and diffusion-weighted images (D-F) show abnormal high signal intensities in the subcortical white matter, including splenium, during the symptom period (A and D) and after 3 months of receiving cyanocobalamin therapy (B and E). There is resolution of abnormalities in the same regions 4 months after discontinuation of metronidazole therapy (C and F).
ported cases showed a reversible manner of metronidazole-induced lesions. Of interest, our patient’s MRI showed more extensive lesions, including in the anterior commissure, basal ganglia, cerebellar white matter, and inferior olivary nuclei.

All lesions except for those in the inferior olivary nuclei improved after discontinuation of metronidazole therapy. Therefore, increased signal intensity and hypertrophic change of inferior olivary nuclei are inferred to be the result of lesions that interrupt the circuit of Guillaumet-Mollaret triangle rather than the result of lesions induced by metronidazole therapy. To our knowledge, there have been no reports on inferior olivary hypertrophy associated with metronidazole-induced encephalopathy. Our patient had inferior olivary hypertrophy without palatal tremor, and a previous study suggested that generation of a symptomatic tremor is not correlated with inferior olivary hypertrophy.8

The exact mechanisms of action underlying the pathogenesis of metronidazole-induced neurotoxicity are not completely understood. Rao and Mason9 reported that catecholamine neurotransmitters reduce the efficacy of 5-nitroimidazole drugs such as metronidazole and generate both semiquinone radicals and nitro anion radicals. These radicals are proposed to cause nervous tissue damage. Study of metronidazole in rats has shown metronidazole toxicity in histologic specimens from the brainstem and cerebellar lesions, which appear similar to those from patients with Wernicke encephalopathy.10 A study of Wernicke encephalopathy suggests that brain abnormalities found on MRI might be caused by cytotoxic edema.11

In our case, high signal intensities on DWI and decreased ADC map values indicate the presence of cytotoxic edema. According to a study by Wardlaw et al,12 patients with lower ADC map values experience more severe strokes and worse functional outcomes. Therefore, we can predict indirectly the severity and reversibility of metronidazole-induced encephalopathy by using the ADC map values. To our knowledge, this is the first report on the use of ADC map values to predict tissue viability in metronidazole-induced encephalopathy.

In conclusion, our case demonstrates that metronidazole-induced encephalopathy may involve multiple brain structures, including anterior commissure, cerebellar white matter, and basal ganglia, and can cause inferior olivary hypertrophy in addition to lesions on subcortical white matter, splenium, midbrain, and cerebellar dentate nuclei. Abnormalities on DWI in our patient indicate that met-
ronidazole-induced encephalopathy might be caused by cytotoxic edema. Our findings suggest that DWI and ADC map values can be used as a tool for understanding the pathogenesis of metronidazole-induced neurotoxicity and for predicting the outcome with drug discontinuation. According to our case, physicians need to be aware that metronidazole therapy can cause variable neurologic signs and symptoms as well as brain lesions.

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