CASE REPORT

Reversible metronidazole-induced encephalopathy

Encéphalopathie réversible au métronidazole

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Abstract

We report the neuroimaging findings of a case of reversible metronidazole-induced encephalopathy. Magnetic resonance imaging (MRI) demonstrated lesions in highly suggestive locations. Follow-up imaging performed 1 month after cessation of metronidazole therapy demonstrated resolution of imaging findings.

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Introduction

Metronidazole is a 5-nitroimidazole compound that has potent activity against anaerobic bacteria and several protozoa. The most common side effects of metronidazole include nausea, headaches and a metallic taste. Adverse neurologic effects including seizures, encephalopathy, cerebellopathy and peripheral neuropathy are rare.

We recently encountered a case of metronidazole-induced encephalopathy with normal apparent diffusion coefficient (ADC) that had a good outcome.

Observation

A 51-year-old male patient with a history of multiple surgeries for anal fistulas was hospitalized for a rapid onset of gait unsteadiness with difficulty in walking and severe vertigo with an altered health status. The last surgical procedure was performed at the beginning of January 2006 and the patient was prescribed metronidazole (Flagyl\textsuperscript{®} 250 mg) at a dose of two tabs three times per day. Three weeks later, after consuming a total of more than 30 g of metronidazole, he developed the symptoms. The patient denied any headaches or fever. The patient had habits of smoking and occasional drinking.

On examination, the patient presented a cerebellar syndrome, a vestibular syndrome, a posterior cordonal syndrome and a pyramidal syndrome of the lower limbs. A lumb-
bar puncture revealed clear CSF under normal pressure with normal protein, glucose and cell count. A head CT without and with contrast was normal. Laboratory analysis on admission was unremarkable. Vitamin E and B1 serum levels were normal. Electromyography demonstrated severe axonal neuropathy in the four limbs. MR imaging of the brain was performed without and then with gadolinium and demonstrated markedly increased signal intensity symmetrically involving the cerebellar dentate nuclei bilaterally on T2-weighted and FLAIR images, with minimal associated T1 hypointensity and no evidence of enhancement following administration of gadolinium. Similar changes in signal were found in the splenium of the corpus callosum, the locus niger, the periaqueductal region and in the bulbar region (Figs. 1–4). DW imaging demonstrated hyperintensities within the splenium (Fig. 5) and the dentate nuclei with a mean ADC in the corresponding regions \((0.680 \times 10^{-3} \text{ mm}^2/\text{s})\) appreciably

Figure 1  Axial T2-weighted MR image at the level of the brain stem demonstrates increased signal intensity of bulbar region.

Figure 1  Image axiale pondérée en T2 passant par le tronc cérébral montrant une hyperintensité de la région bulbaire.

Figure 2  Axial T2-weighted MR image at the level of the midcerebellum demonstrates symmetrically increased signal intensity of the dentate nuclei.

Figure 2  Image axiale pondérée en T2 au niveau de la protubérance montrant une hyperintensité bilatérale et symétrique des noyaux dentelés.

Figure 3  Axial T2-weighted MR image at the level of the lateral ventricles demonstrates increased signal intensity of the splenium.

Figure 3  Image axiale pondérée en T2 au niveau des ventricules latéraux montrant une hyperintensité du splenium.

Figure 4  Sagittal T2-weighted MR image shows increased signal intensity within the periaqueductal region.

Figure 4  Image sagittale pondérée en T2 montrant une hyperintensité périaqueduculle.
equal to the ADC of the normal cerebral parenchyma ($0.709 \times 10^{-3} \text{ mm}^2/\text{s}$) (Fig. 6).

The patient’s clinical presentation and imaging changes were thought to be most consistent with metronidazole toxicity. Metronidazole was discontinued and the patient’s condition improved.

A repeat MR imaging examination of the brain performed 4 weeks after discontinuation of metronidazole showed complete resolution of the previously noted T2 and FLAIR high signal intensities (Figs. 7 and 8).

Figure 5  DWI (b1000) shows high signal intensity of the splenium of the corpus callosum.

Figure 5  Imagerie de diffusion (b 1000) montrant une hyperintensité du splenium du corps calleux.

Figure 6  ADC map: normal diffusion in the splenium.

Figure 6  Cartographie ADC : diffusion normale au niveau du splenium.

Figure 7  Axial FLAIR MR images at the level of the midcerebellum shows complete resolution of the hyperintensity within the dentate nuclei.

Figure 7  Image axiale pondérée en T2 (a) et FLAIR (b) passant par la protubérance montrant la disparition totale des anomalies de signal des noyaux dentelés

Figure 8  Axial FLAIR MR images at the level of the lateral ventricles demonstrate normal signal intensity within the splenium.

Figure 8  Image axiale FLAIR passant par les ventricules latéraux montrant la disparition totale des anomalies de signal du splenium.
Discussion

Neurotoxicity is one of the most important adverse effects of metronidazole therapy. The exact mechanism of metronidazole toxicity has not yet been elucidated. Rao and Mason [7] 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. Ahmed et al. [1] speculated that, because of the reversibility of the MR imaging changes, the cause of the changes were most likely due to “axonal swelling with increased water content”, not axonal demyelination.

Ahmed et al. [1] first described the imaging findings of metronidazole toxicity in 1995 in a 45-year-old woman who developed nausea, vomiting, dysarthria, and confusion after consuming 35 g metronidazole over a 30-day course of therapy. MR imaging of the brain demonstrated symmetric abnormal signal intensity within the corpus callosum and within the dentate nuclei. A follow-up MR imaging of the brain revealed near-complete resolution of findings 6 weeks after discontinuation of metronidazole. Since then, 10 cases have been reported [2-6,8].

In each of the cases, including ours there was symmetrical increased T2 signal intensity in the deep cerebellar nuclei. Other areas are represented by sub-cortical white matter, splenium of corpus callosum and mesencephalon [1-6,8]. The deep cerebellar nuclei are likely to be most sensitive to the effects of metronidazole toxicity and are the most specific observed imaging manifestation of metronidazole toxicity [2].

The lesions appear on MRI as high signal intensities on T2-weighted and FLAIR images with no mass effect. Usually there is no enhancement of the lesions. Viju et al. [8] reported a case of an abnormal enhancing lesion of dentate nuclei induced by metronidazole toxicity with complete resolution after discontinuation of the drug.

These lesions appear as high signal intensities on DW imaging with an ADC that varies. It can be increased, consistent with an axonal swelling with increased water content (T2 shine-through effect) [2] or low, indicating that there is restricted diffusion [5,6]. Explanations of the restricted diffusion pattern are yet unsatisfactory. Poor prognosis may be associated with the low ADC with persistent neurologic abnormalities for several months after discontinuation of the treatment [5] and irreversibility in some cases [6]. Kim et al. [6] reported two cases of metronidazole-induced encephalopathy with restricted diffusion and low ADC associated with incomplete recovery. They assumed that the signal increase on DW imaging with low ADC results from cytotoxic edema caused by disease states other than ischemia.

The MRI abnormalities usually resolve a few weeks after discontinuation of the drug [1,2,4,5].

With respect to differential diagnosis, Wernicke’s encephalopathy is the principal diagnosis because it shows high signal intensities on DW images with low ADC but it tends to show a predilection for the midbrain and diencephalon [6].

Conclusion

Metronidazole-induced encephalopathy is associated with signal changes of characteristic topography that usually resolve after discontinuation of the treatment.

DW imaging may have a role in the diagnosis and in the prediction of a poor prognosis in the cases with a restricted diffusion.

References