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Sequential MR imaging (with diffusion-weighted imaging) changes in metronidazole-induced encephalopathy

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Abstract

Metronidazole-induced neuro-toxicity, though rare, is known. A characteristic spatial distribution of lesions in cerebellar dentate nuclei and dorsal pons is known. However, temporal progression of lesions on magnetic resonance imaging (MRI) has not been described previously. We describe two such cases which presented initially with splenial hyperintesity and showed progression to characterstic lesions. Both cases improved with stoppage of metronidazole.

Key words: Magnetic resonance imaging; metronidazole; metronidazole-induced encephalopathy; splenial hyperintensity

Introduction

Metronidazole is an antibiotic, antiprotozoal, and amoebicide agent of the nitroimidazole group. It is one of the commonly used antibiotics in clinical practice and is considered safe. In the past few years, there have been few reports of metronidazole-induced neurotoxicity and characteristic pattern of bilateral symmetrical hyperintensity in the supratentorial white matter, corpus callosum, and within the cerebellum and deep cerebellar nuclei on magnetic resonance imaging (MRI).[1] However, none of these describe the temporal progression of lesions on MRI. We present two cases depicting progressive MRI changes including diffusion-weighted imaging (DWI) changes of metronidazole toxicity.

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Case History

Case 1

A 41-year-old male presented with fever for 2 days, slurring of speech, difficulty in recognition, and irrelevant talk since 1 day. No history of headache, loss of consciousness, or seizures was present. Patient was admitted 15 days back with complaints of loose motions, abdominal pain, and fever. He was diagnosed to have amoebic liver abscess and was started on metronidazole 400 mg orally thrice a day.

This time neurological examination revealed altered consciousness [Glasgow Coma Scale 14 (E4M6V4)], disorientation, bilateral reacting pupils, slurring of speech, and positive cerebellar signs with left past pointing. No cranial nerve palsy or motor weakness was seen.

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MRI brain on day 1 of the admission showed DWI hyperintensity in the splenium of corpus callosum suggesting acute infarct or toxic encephalopathy. Restricted diffusion was confirmed on apparent diffusion coefficient mapping (with ADC value of 0.5×10^{-3} mm^2/s) [Figure 1]. Gradient recovery echo images showed no evidence of hemorrhage.

The patient was started on antiplatelet, low molecular weight heparin, and other supportive treatment. Metronidazole was continued. However, there was no improvement, rather severity of ataxia increased.

MRI brain repeated on the fifth day showed hyperintensities involving the bilateral dentate nuclei in cerebellum with resolution of corpus callosal lesions suggesting toxic encephalopathy [Figure 2].

At this point, metronidazole toxicity was strongly considered. Metronidazole was immediately stopped, and the patient started showing recovery over next 3 days. He was discharged on the eighth day without any motor or cranial nerve deficit.

Case 2

A 56-year-old female presented with difficulty in speech and decreased hearing since 1 day. She was taking metronidazole 400 mg orally thrice daily since 5 days for gastroenteritis (severe vomiting and loose motions). The patient was admitted with a possibility of cerebrovascular event and investigated.

Her neurological examination revealed disorientation, altered consciousness (GCS-E4M5Vslurred), bilateral reacting pupils, slurring of speech, and positive cerebellar signs with right cerebellar ataxia. Motor examination revealed right upper limb weakness with power of 4/5 and bilateral mute plantar reflexes.

MRI brain [Figure 3] which showed hyperintensity in the splenium of corpus callosum with diffusion restriction (ADC value of 0.6×10^{-3} mm^2/s) for which radiological possibilities of infarct, metabolic, or viral encephalitis were considered. Lumbar puncture showed 3 cells, mostly lymphocytes, glucose 80mg/dl, and protein 20mg/dl.

She was started with antiplatelets, antibiotics, and other supportive treatment. Metronidazole was continued. Patient condition deteriorated over the next 48 hours, became drowsier, and was intubated. MRI brain [Figure 4] repeated after 3 days showed multiple hyperintense lesions in corpus callosum, dentate nuclei of cerebellum, brainstem, and deep white matter, suggesting toxic encephalopathy.

Possibility of metronidazole toxicity was strongly considered at this stage. Metronidazole was withheld

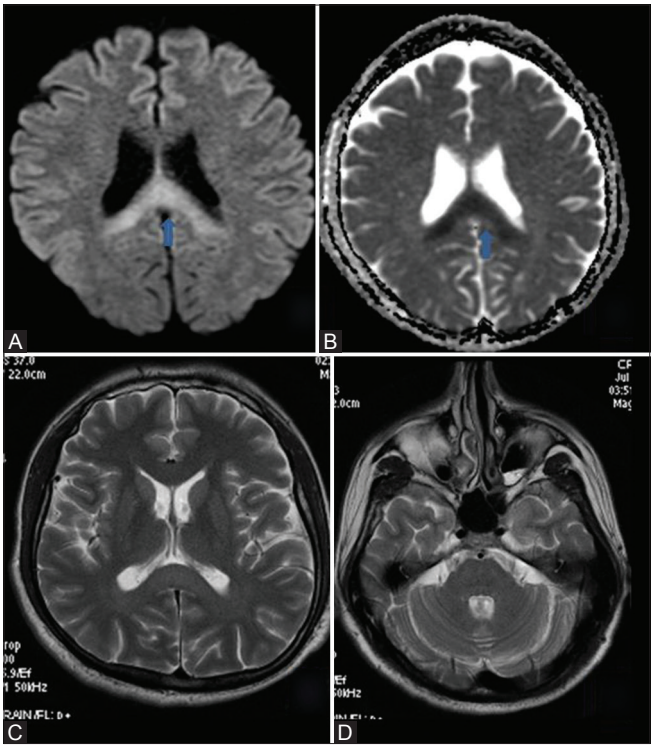

Figure 1 (A-D): Initial Magnetic resonance imaging (Brain) of case 1, showing symmetric areas of hyper intensity in splenium of the corpus callosum (arrow) on DWI (A) with restricted diffusion ADC mapping (B) (ADC value of 0.5×10^{-3} mm^2/s) and T2-weighted images, axial (C and D) no signal change in corpus callosum (C) cerebellum and pons (D)

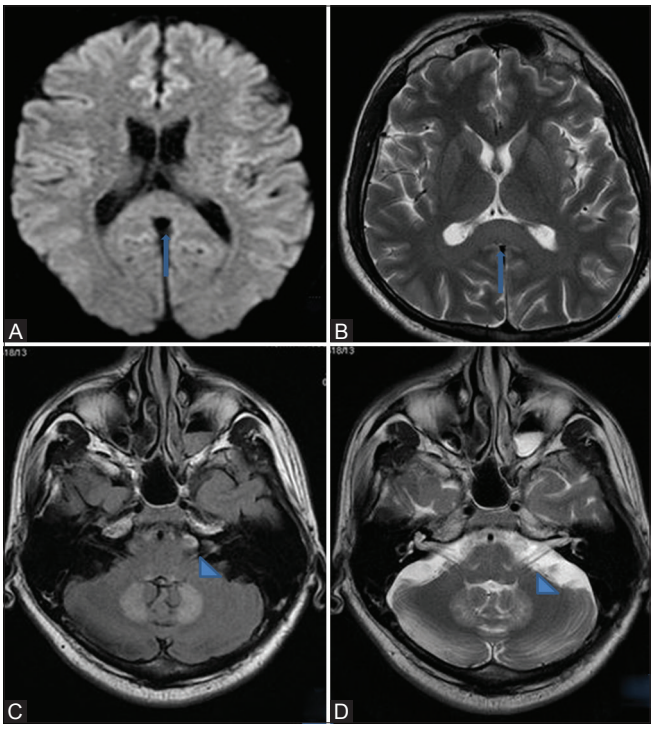

Figure 2 (A-D): Follow up MRI of case 1 after 5 days, showing resolution of hyper intensity in splenium of corpus callosum (arrow) on DWI (A) normal signal on T2W (B) and characteristic involvement of dentate nucleus on (C) Axial FLAIR and (D) Axial T2-weighted images

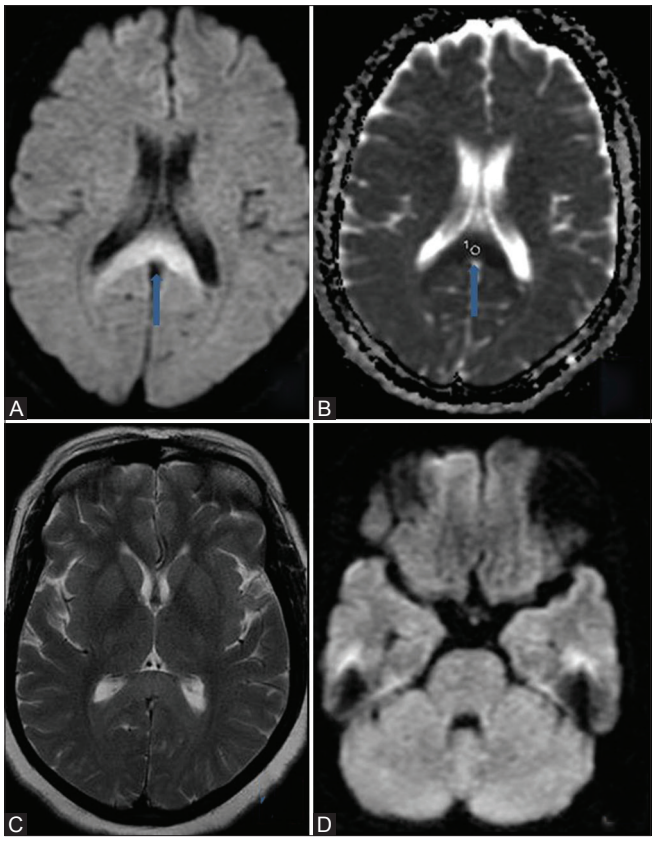

Figure 3 (A-D): Initial Magnetic resonance imaging (Brain) of case 2, showing symmetric areas of hyper intensity involving the splenium of the corpus callosum (arrow) on (A) Axial DWI with restricted diffusion (value of 0.6 × 10-3 mm^2/s) on ADC map (B), (C) axial T2-weighted images, signal change in corpus callosum (D) Axial DWI no signal change in cerebellum and pons

immediately. Patient started improving and was weaned off the ventilator over the next 3 days. Patient was discharged on the ninth day in stable condition.

Discussion

The available literature describes very few cases with imaging findings of metronidazole-induced encephalopathy and none describe the temporal progression of initial midline splenial lesions to more characteristic sites as bilateral symmetrical supratentorial white matter and deep cerebellar nuclei, as seen in both our cases.

Among the initial descriptions in literature, Ahmed *et al*.[1] were the first to describe MRI findings of metronidazole toxicity in a 45-year-old female as bilateral symmetrical, abnormal hyperintensity in the supratentorial white matter, corpus callosum, and within the cerebellum and deep cerebellar nuclei on T2-weighted images. They suggested axonal swelling with increased water content due to toxic injury or localized reversible ischemia due to vascular spasm as possible mechanism. A few subsequent case reports[2-4] have described symmetric lesions at additional sites as in

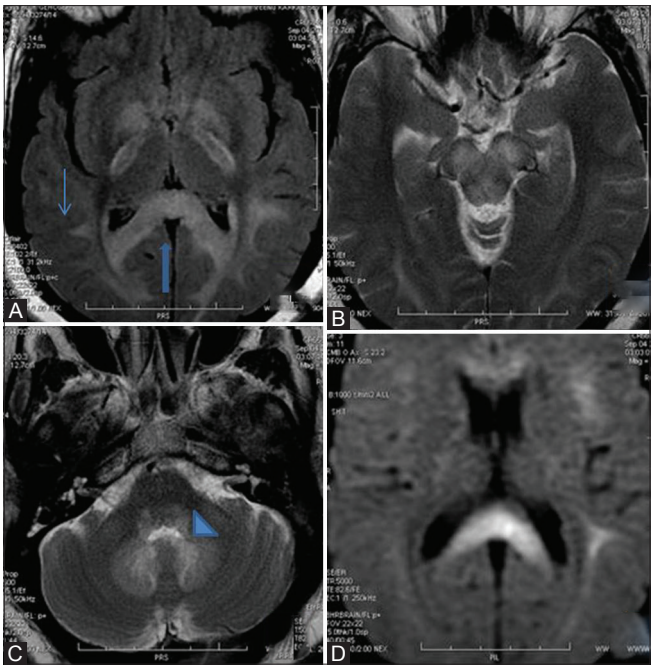

Figure 4 (A-D): Follow up MRI brain, Axial T2 (A-C) Multiple T2 hyper intense lesions at characteristic sites involving corpus callosum (bold arrow), subcortical white matter (arrow), midbrain (B), dentate nucleus (arrowhead) and dorsal pons. (D) Axial DWI showing symmetric areas of hyper intensity involving the splenium of the corpus callosum

colliculus, superior olive, and cochlear nuclei, indicating their reversibility. Other theories for signal changes including interstitial edema and ischemia as cause of signal intensity on diffusion-weighted imaging or cell damage to Purkinje cells due to binding of the drug to neuronal RNA, causing inhibition of protein synthesis, and axonal degeneration have also been postulated.[2-4]

Second MR in our cases showed similar characteristic spatial distribution of cerebellar dentate nuclei and dorsal pons in both the cases prompting us to implicate metronidazole as a causative agent. Other common causes of such multifocal hyper intensities such as multiple sclerosis, acute disseminated encephalomyelitis, Wernicke encephalopathy, and enteroviral encephalomyelitis were excluded by clinical history and investigations.

In both our cases, initial imaging showed only splenial hyperintensity on DWI. The differential diagnosis of splenial hyperintensity (or boomerang sign as it is sometimes described)[5] is vast including ischemia, infections – encephalitis (influenza, *Escherichia coli*, mumps, adenovirus, Epstein-Barr, virus and Rota virus), demyelinating lesions including multiple sclerosis, posterior reversible encephalopathy syndrome, diffuse axonal injury, Marchiafava-Bignami disease, adrenoleukodystrophy, AIDS dementia complex, lymphoma, epilepsy, antiepileptic drug usage, osmotic myelinolysis, and acute toxic

encephalopathy.[6] However, mechanism of this splenial hyperintensity is incompletely understood. Various mechanisms proposed include breakdown of the blood–brain barrier,[7] reversible demyelination or transient disturbance of energy metabolism, and ionic transport causing intramyelinic edema.[8] In both the cases, metronidazole toxicity was not considered at the onset, and the drug was continued as index of suspicion was low both radiologically and clinically. Both these cases showed restricted diffusion on initial MR indicative of cytotoxic edema as cause in initial stage, suggesting a mechanism of intramyelinic edema.

We propose a mechanism of selective vulnerability and variable affinity of neurons for metronidazole as cause of characteristic and temporal progression of lesions. Metronidazole or its immune mediator may have specific high affinities receptors on splenial axons evidenced by initial cytotoxic edema (confirmed by high ADC values), and persistent exposure might result in cell damage and involvement of other characteristic sites with lesser affinity such as cerebellar dentate nuclei dorsal pons and cerebral white matter.

These cases call attention to metronidazole toxicity as differential diagnosis of splenial hyperintensity before MRI reveals characteristic multifocal site pattern.

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Conflicts of interest
There are no conflict of interest.

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