Neuroimaging Highlight

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Metronidazole-Induced Encephalopathy: Case Report and Review of MRI Findings

Submitted by: Jamsheed A. Desai, Jessica Dobson, Michel Melanson, Giovanna Pari, Albert Yongwon Jin

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A 74-year-old man presented with a four week history of behavioural disturbances, upper and lower extremity numbness and impaired balance. He had been treated with metronidazole for six months for osteomyelitis of the right hallux. Examination revealed encephalopathy, and glove-and-stocking sensory loss to pinprick with reduced vibration threshold at the toe. The gait was wide based and ataxic. Nerve conduction studies showed a large fibre sensory-motor axonal polyneuropathy. Magnetic resonance imaging (MRI) revealed a solitary restricted diffusion lesion in the splenium of the corpus callosum (Figure A, B) with subtle prolongation of T2 (Figure C). The radiographic differential diagnosis included hypoglycaemia, viral encephalitis, antiepileptic drug toxicity/withdrawal and metronidazole toxicity[1]. The combination of the imaging finding with the history of prolonged metronidazole use suggested metronidazole induced encephalopathy. Metronidazole was discontinued based

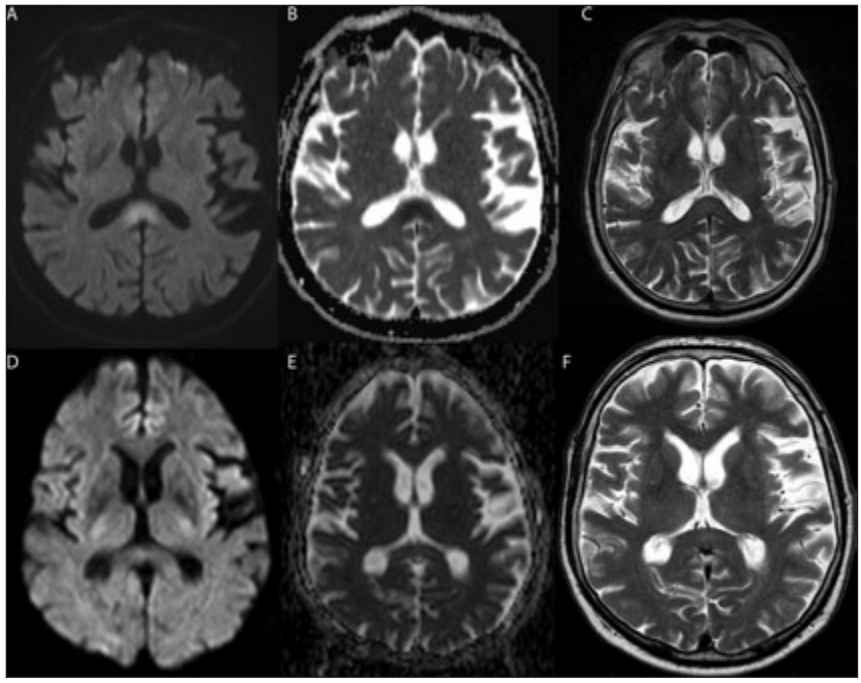

Figure: *Diffusion weighted imaging findings in a 74-year-old man with metronidazole-induced neurotoxicity. A) High diffusion weighted imaging (DWI) signal intensity; B) Low ADC in the splenium of the corpus callosum indicative of cytotoxic edema; C) Subtle T2 prolongation in the splenium of the corpus callosum; D and E) Five month follow-up DWI and ADC respectively, showing resolution of restricted diffusion; F) Mildly persistent T2 prolongation at five month follow-up.*

From the Department of Medicine (Neurology) Queen's University (JAD, MM, GP, AYJ); Queen's Medical School (JD), Kingston, Ontario, Canada.

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Correspondence to: Albert Yongwon Jin, Queen's University, Department of Medicine, Division of Neurology, Kingston General Hospital, Connell 7-76 Stuart Street, Kingston, Ontario, K7L 2V7, Canada.

on a presumptive diagnosis of metronidazole-induced encephalopathy, neuropathy, and ataxia. At six week follow-up the encephalopathy and ataxia had resolved and the lower extremity paresthesiae had improved. Follow-up MRI at five months showed resolution of the restricted diffusion lesion with subtle persistent T2 hyperintensity (Figure D, E, F).

Discussion

The MRI signal characteristics of lesions in metronidazole toxicity are varied. The lesions visualized on MRI are always bilateral and symmetric with lesions of the corpus callosum always involving the splenium[2]. Initial T2-weighted, fluid-attenuated inversion recovery (FLAIR), and diffusion weighted imaging (DWI) has been reported to show symmetric hyperintensities in various brain regions[2-7]. The most common lesion sites in metronidazole toxicity in order of decreasing frequency are the dentate nucleus, midbrain, splenium of the corpus callosum (SCC), pons, medulla, inferior colliculus, subcortical white matter, basal ganglia and middle cerebellar peduncle[2,6-8]. T1-weighted imaging demonstrates minimal hypointensity and no evidence of enhancement on post-contrast scans[4]. Initial ADC values depend on lesion location. Many authors have reported low ADC values and high DWI signal intensity suggestive of cytotoxic edema in the splenium of corpus callosum, basal ganglia, brainstem nuclei and subcortical white matter[2,5-7]. However, there are also cases involving the cerebellar dentate nuclei that show high ADC values and high DWI indicative of vasogenic edema[2,4,6]. Proton magnetic resonance spectroscopy (MRS) is usually not performed but there is one case reported of prominent lactate peak associated with metronidazole toxicity[3].

Prolonged use of metronidazole may result in ataxia, encephalopathy, and large fibre sensory-motor axonal polyneuropathy, all of which were evident in our patient. Discontinuation of metronidazole therapy results in a clinical improvement in symptoms and commonly a corresponding resolution of T2, FLAIR, and DWI hyperintensities[2-7]. One case of persistent DWI and FLAIR hyperintensity in the SCC was reported however follow-up imaging was performed on Day 3 after metronidazole discontinuation and longer term follow-up was not available[6]. Incomplete resolution of T2 hyperintensity[9] and restricted diffusion[2] have been reported with follow-up imaging performed at eight months and 15 days respectively. Here, we report a case of metronidazole-induced encephalopathy which presented with an isolated lesion in the SCC and showed persistent T2 prolongation with complete resolution of ADC at five month follow-up.

The pathogenesis of metronidazole-induced neurotoxicity is not well understood. Animal studies have shown metronidazole-induced Purkinje cell damage in dogs[10], inhibition of protein synthesis resulting in axonal degeneration in rats[11], and carbon-labelled metronidazole uptake in the cerebellum of mice[12]. Other proposed mechanisms include: damage due to semiquinone and nitro anion radicals[13]; reversible mitochondrial dysfunction[3]; and impairment of vitamin B1 action[14]. Although the pathogenesis of metronidazole-induced toxicity is incompletely understood our case confirms that discontinuation of metronidazole leads to resolution of cytotoxic edema and associated clinical symptoms.

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