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LETTER TO THE EDITOR

Metronidazole-Induced Craniocervical Myoclonus with Reversible Bilateral Dentate Nucleus Lesions

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Dear Editor,

Metronidazole is a widely prescribed drug that is used to treat bacterial and protozoal infections. Neurologic complications from metronidazole are rare but have been reported to exhibit the following syndromes: cerebellar syndrome, encephalopathy, seizures, autonomic neuropathy, optic neuropathy, and peripheral neuropathy.[1] Metronidazole-induced cerebellar syndrome is a rare adverse drug reaction, particularly when it involves lesions of the dentate nucleus; accompanying myoclonus is even more unusual.[2] Here, we report a patient who presented with craniocervical myoclonus involving bilateral dentate nucleus lesions following metronidazole use whose symptoms were reversible (including recovery of the dentate nucleus lesions) after the discontinuation of metronidazole. The development of neurologic symptoms in metronidazole users is believed to be the result of metronidazole neurotoxicity because immediate discontinuation of the drug can improve symptoms and prevent further injury.[3]

An 82-year-old man with hypertension and Alzheimer's disease presented to the emergency department complaining of jerky movements for 3 days. He had been taking metronidazole for acute cholecystitis at a nursing home for 12 days prior to presentation (500 mg three times a day, estimated cumulative dose of approximately 30 g). Rhythmic synchronous myoclonic movements involving the eyebrow, neck and bilateral upper arms were continuously observed at a frequency of 1–2 Hz. His mental status was clear and other neurological examinations were unremarkable. Repeated electroencephalography did not show any epileptiform discharges. His body temperature was normal. His glomerular filtration rate was 35 mL/min and liver function tests were normal. Cerebrospinal fluid examination was normal. Brain magnetic resonance imaging (MRI) showed high signal intensity in the bilateral dentate nuclei of the cerebellum on the T2 and T2 fluid-attenuated inversion recovery (FLAIR) scans (Figure 1A). Metronidazole was discontinued and clonazepam was prescribed (0.5 mg three times a day for 3 days), after which his myoclonus completely resolved. Clonazepam was then tapered off over the course of 3 days and the patient's myoclonus did not recur. Sixteen days after his initial MRI scan, a repeat MRI was performed, which showed a complete recovery of the signal changes that were previously observed in the bilateral dentate nuclei (Figure 1B).

Metronidazole neurotoxicity is rare but can manifest as several neurologic syndromes.[1-4] A recent systematic review of case series showed that cerebellar dysfunction (75%) and cerebellar lesions (93%) were common among patients with metronidazole neurotoxicity; furthermore, 81% of cerebellar lesions had dentate nuclei involvement.[5] Likewise, bilateral dentate nucleus lesions were evident in this case; however, our patient presented with only myoclonus without definite cerebellar dysfunction. The dentate nuclei are located within the functional circuit known as the Triangle of Guillain-Mollaret, along with the red nucleus and inferior olivary nucleus. Although any lesion that involves this circuit can produce myoclonus, only 2 cases have been reported in the current literature on metronidazole-induced neurotoxicity.[2,6] Clinical manifestations in our case included rhythmic synchronous myoclonus within the craniocervical area involving the eyebrows, neck and upper arms at a

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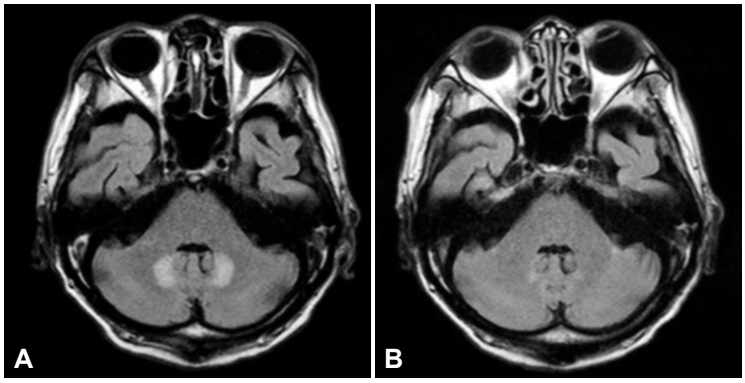

Figure 1. Brain MRI images before and after metronidazole discontinuation. A: Axial fluid-attenuated inversion recovery (FLAIR) scan showing increased signal intensity in the bilateral dentate nuclei of the cerebellum. B: Complete resolution of the high signal intensity in the dentate nuclei at day 16 after metronidazole discontinuation.

frequency of 1−2 Hz, which is similar to palatal myoclonus; however, myoclonus of the palate was not observed in this case. Intriguingly, myoclonus was the only presenting symptom in this case; neither encephalopathy nor cerebellar dysfunction were observed despite encephalopathy and cerebellar dysfunction being rather common symptoms.

Other antibiotics such as cefepime, a fourth generation cephalosporin, may also cause myoclonus. The mechanism of cephalosporin-induced myoclonus is related to inherently reduced GABAergic activity that results in neuronal hyperexcitability and epileptogenicity.[7] On the other hand, the mechanism of metronidazole-induced neurotoxicity within the central and peripheral nervous system is not well understood. Proposed mechanisms include the binding of metronidazole to RNA, DNA and inhibitory neurotransmitters as well as the induction of both vasogenic and cytotoxic edema.[4]

Except for male predisposition, factors affecting susceptibility to metronidazole-induced neurotoxicity, such as the duration of exposure or medication dose, are not well known.[5] The withdrawal of metronidazole can reverse neurologic symptoms and radiological manifestations.[5] Therefore, early suspicion and detection of metronidazole neurotoxicity and prompt cessation of the drug can yield an excellent prognosis even when myoclonus is the only presenting symptom.

Conflicts of Interest

The authors have no financial conflicts of interest.

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