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Letter to the Editor: New Observation

Downbeat Nystagmus in Metronidazole Neurotoxicity

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We report a case of downbeat nystagmus due to metronidazole-induced neurotoxicity and its implications.

A 74-year-old woman presented with subacute onset of disequilibrium, nausea, imbalance, and falls. She also complained of vertical oscillopsia, transient diplopia, limb incoordination, dysarthria, and distal paresthesias. She had longstanding ulcerative colitis with prior colectomy and internal pouch and had been taking metronidazole continuously for 12 years. Examination revealed DBN in all directions of gaze (including upgaze). Saccades and pursuit were normal apart from interruptions by nystagmus. There was mild dysarthria, subtle left upper limb dysmetria, and dysdiadochokinesia. Ankle reflexes and distal lower extremity vibration sense were reduced, and she walked with a narrow base with occasional veering to either side and was unable to perform tandem gait.

Other medical history included hypertension. There was no previous history of liver or kidney disease, diabetes, or cancer. There was no family history of neurological disease.

MRI brain revealed multiple T2/FLAIR hyperintensities within the splenium of the corpus callosum (Figure 1a-c). These lesions demonstrated restricted diffusion. There were additional T2/FLAIR hyperintensities in the periventricular, subcortical, and deep white matter which did not restrict diffusion and were in keeping with chronic microangiopathic disease.

Additionally, the following tests were normal/negative: complete blood count, fasting glucose, HbA1c, electrolytes, creatinine, liver function tests, thyroid stimulating hormone, vitamins B1, B6, B12, and E, magnesium, antinuclear antibodies, extractable nuclear antigen panel, antineutrophil cytoplasmic antibodies, anti-GAD65 antibodies, anti-tissue transglutaminase antibodies, deamidated antigliadin antibodies, full paraneoplastic antibody panel and genetic testing for common spinocerebellar ataxias, routine CSF testing and oligoclonal bands, and whole body PET scan.

Discontinuation of metronidazole led to significant improvement in gait and speech within 8 months although the oscillopsia, disequilibrium, and DBN did not resolve after discontinuation. Similarly, there was no improvement with 4-aminopyridine, clonazepam, gabapentin, baclofen, or memantine.

MRI brain done 2 years following discontinuation of metronidazole showed complete resolution of the callosal signal change with only the mild periventricular white matter microangiopathic changes persisting (Figure 1d-f). This complete resolution of the callosal hyperintensities (which are common in metronidazole toxicity), along with the clinical improvement in speech and ataxia, confirmed the diagnosis of metronidazole-induced neurotoxicity.

Metronidazole can rarely cause neurotoxicity and has been associated with cerebellar dysfunction, brainstem deficits, encephalopathy, peripheral neuropathy, optic neuropathy, and seizures, with many of these syndromes resolving on discontinuation of the drug.[2] Ocular motor disturbances including gaze-evoked nystagmus, diplopia, abducens palsy, saccadic pursuit, and gaze palsy have been reported.[3] However, only a single case has specifically described metronidazole-associated DBN.[1]

The pathogenesis of this neurotoxicity remains uncertain but proposed mechanisms include metabolites of metronidazole interfering with neuronal RNA protein synthesis, conversion of metronidazole to a thiamine antagonist, dysregulation of GABA neurotransmission in cerebellar/vestibular pathways, reversible mitochondrial dysfunction, or generation of toxic free radicals from reactions with catecholamine neurotransmitters.[2,4] The suggestion that gut flora may convert metronidazole to a thiamine antagonist has led to similarities being drawn with Wernicke's encephalopathy (which classically demonstrates upbeat nystagmus transitioning to DBN).[5] However, whether thiamine administration could mitigate neurotoxic effects in cases of metronidazole-associated neurotoxicity is unknown.

Prolonged use and/or high cumulative doses were once thought to be facilitating but evidence for this is conflicting.[2] A systematic review of 64 cases concluded that dose and duration of treatment were not correlated with neurotoxicity, and mean duration of metronidazole treatment before presentation was 54 days (95% CI, 21.2–87.9).[6] It is unclear why our patient developed symptoms of toxicity much later than other reported cases. She had not been taking drugs which could have affected metronidazole metabolism, nor did she have any predisposing medical conditions such as hepatic/renal failure.

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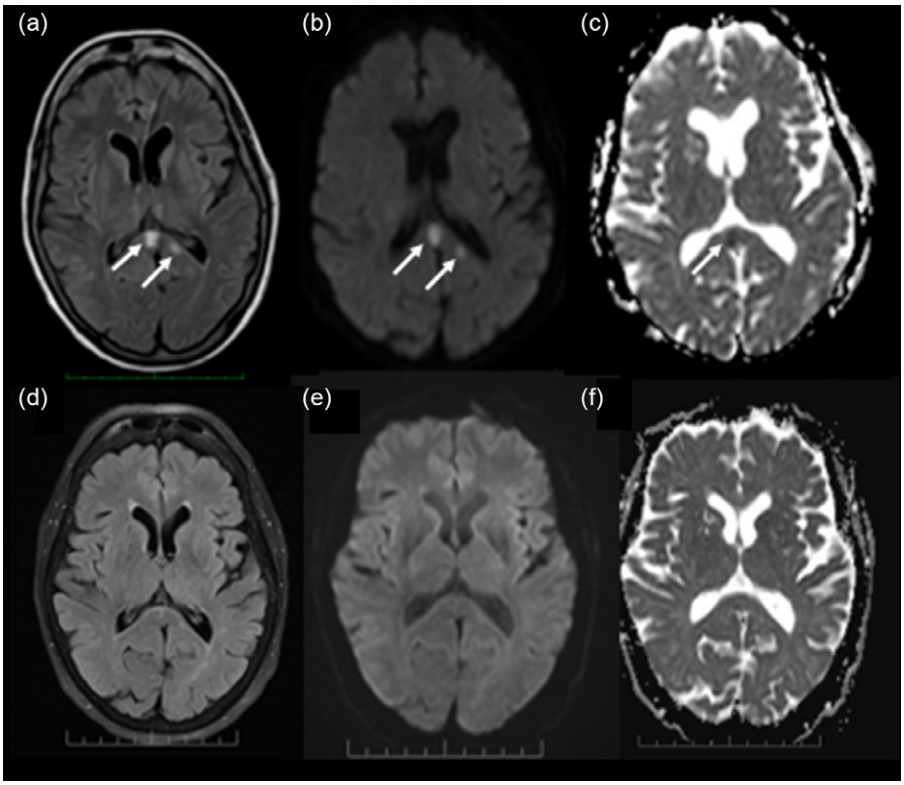

Figure 1: MRI brain on presentation demonstrating FLAIR hyperintensities (arrows) in the splenium of the corpus callosum (a), which demonstrate restricted diffusion on diffusion-weighted imaging (b), and one of which is hypointense on apparent diffusion coefficient sequence (c). These hyperintensities resolved completely following the discontinuation of metronidazole (d-f).

The classic radiological findings in acute metronidazole-induced neurotoxicity are symmetric T2/FLAIR hyperintense lesions, most commonly of the cerebellar dentate nuclei (almost invariably present, but absent in our case), midbrain (66%), and corpus callosum (44–60%).[7] Although these lesions are usually also hyperintense on diffusion-weighted imaging, only callosal lesions appear hypointense on apparent diffusion coefficient (ADC) sequences, suggesting that these may represent cytotoxic edema in contrast to lesions in other locations which are usually ADC-hyperintense and more consistent with vasogenic edema.[7] Complete or near-complete resolution is seen in 79% of cases.[3]

Imaging changes may be seen in the corpus callosum without changes in the dentate nuclei. Of 136 patients in one study, 12 lacked dentate lesions and two-thirds of those had lesions in the corpus callosum.[3] Callosal lesions are often isolated, with the splenium appearing particularly susceptible (96% of callosal lesions).[3]

In the previously reported case of metronidazole-associated DBN, MRI brain demonstrated reversible T2/FLAIR and diffusion-restricting lesions in the dentate nuclei and tectal midbrain, but not the corpus callosum.[1] The DBN also resolved with cessation of metronidazole, although the total duration of treatment was 6 weeks (unlike our patient).

Although radiological and clinical reversibility is the general rule, with symptoms often resolving within days of metronidazole discontinuation, a systematic review found that complete resolution occurred in just 56% of patients, while residual severe neurological deficits were found in 4%.[3] In our patient, following metronidazole cessation, the axial and appendicular ataxia and dysarthria resolved. However, in spite of radiological resolution, the DBN, the attendant vertical oscillopsia, and disequilibrium persisted and resisted multiple treatment attempts.

DBN typically results from damage to the cerebellar flocculonodular lobe or its projections leading to uninhibited activation of superior vestibular nuclei.[5] This suggests pathology in our patient relating to metronidazole-induced neurotoxicity beyond the reversible MRI changes seen. Disorders demonstrating DBN and ataxia include mitochondrial diseases such as MELAS, several spinocerebellar ataxias, episodic ataxias, celiac disease, paraneoplastic cerebellar ataxia, autoimmune cerebellar ataxia with anti-GAD antibodies, multiple system atrophy, and metabolic disturbances (hypomagnesemia, vitamin B1 deficiency, vitamin B12 deficiency) all of which were excluded in our patient.[8]

Toxic causes of DBN include phenytoin, carbamazepine, lamotrigine, lithium, alcohol, amiodarone, opioids, toluene, and ciguatoxin.[5] Metronidazole is generally not cited as a cause. Given that metronidazole-induced neurotoxicity is generally rapidly reversible on drug discontinuation, this particular neurotoxic syndrome may go unrecognized. We therefore propose that metronidazole-induced neurotoxicity should be included among the toxic causes of DBN.

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Statement of Authorship. Conception and design (CF; FT), data collection (CF; FT), manuscript preparation (CF); review of the manuscript and critical appraisal (CF; AES; RPM; AF; FT).

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