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Metronidazole Induced Neurotoxicity

A clinico-radiological diagnosis

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A 44-year-old gentleman presented to our facility in 2019 with a history of subacute onset ataxia, dysarthria, and episodes of generalized tonic clonic seizures for two weeks. He had a history of prolonged intake of over-the-counter metronidazole tablets for irritable bowel syndrome. He did not have a history of hypertension or diabetes. Neurological examination revealed bilateral gaze evoked nystagmus and positive cerebellar signs. Basic laboratory parameters were within normal limits. In magnetic resonance imaging (MRI) of brain, splenium of corpus callosum showed evidence of diffusion restriction (yellow arrow) as well as hyperintensity (red arrow) on fluid attenuation inversion recovery (FLAIR) scans. (**Figure 1A, 1B**) There were also symmetrical areas of hyperintensity involving bilateral lentiform nucleus (orange arrow) and dentate nucleus of cerebellum (white arrow). (**Figure 1C, 1D**) Cerebrospinal fluid (CSF) study was non-contributory with absent oligoclonal bands (OCB). Vasculitis and infectious profile were negative. Nutritional, paraneoplastic, and autoimmune causes of cerebellar ataxia were ruled out by relevant investigations. Serum thiamine was not performed due to logistic issues. The summary of the relevant blood and CSF parameters is shown in **Table 1**. The patient was

advised to discontinue metronidazole and upon follow-up six months later, most of his symptoms had resolved. Repeat brain imaging after one year revealed complete resolution of previous abnormalities. (**Figure 2**)

An informed written consent was obtained from the patient after full explanation regarding his images being published for academic interest. The patient did not have any objection regarding use of his images which may reveal his identity and gave due permission to use them.

Comment

Metronidazole is a nitroimidazole derived synthetic antibiotic, which is mainly used in the treatment of various anaerobic bacterial infections, and protozoal infections, such as intestinal amoebiasis, giardiasis and trichomoniasis.[1] Mechanisms of neurotoxicity have not been properly elucidated. Previously, Rao et al. had proposed a free radical mediated damage.[2] Other proposed mechanisms include RNA binding by metronidazole and its derivatives causing inhibition of protein synthesis.[3] Peripheral neuropathy, optic neuropathy and encephalopathy are reported adverse effects occurring with prolonged usage. Metronidazole induced central and peripheral neurotoxicity is potentially debilitating.[3]Characteristic imaging findings include bilateral, symmetric T2/FLAIR hyperintensities of dentate nulcei, dorsal aspect of pons and medulla and genu and splenium of corpus callosum.[4]The patient in question exhibited most of these radiological findings with additional involvement of basal ganglia. Primary CNS demyelinating diseases such as multiple sclerosis (MS) and acute demyelinating encephalomyelitis (ADEM) can mimic these findings. However, the temporal profile, absence of OCB in CSF and reversibility of imaging findings were uncharacteristic of a demyelinating etiology.

Wernicke's encephalopathy is the closest radiological differential of metronidazole induced encephalopathy (MIE). As opposed to MIE, involvement of mamillary body and diencephalon are hallmark features of Wernicke's encephalopathy.[4] Brainstem lesions in MIE may mimic those of central pontine myelinosis (CPM), with or without extra-pontine myelinosis. However, brainstem lesions in CPM typically show restriction on DWI.[5] Causes of focal T2 splenial hyperintensities are myriad and include encephalitis, Marchiafava-Bignami syndrome, extra-pontine myelinosis, demyelinating lesions including drugs and toxic encephalopathies.[4] Normal

plasma folate and serum vitamin B12 level, electrolytes level, thyroid function tests and CSF studies effectively ruled out metabolic and infectious causes in this patient. Concurrence of symmetric radiological findings with affection of deep cerebellar nuclei, history of preceding drug intake and resolution of symptoms following drug cessation, established the diagnosis in this case.

We highlight a severe adverse effect of metronidazole, a commonly prescribed antibiotic, pertaining to the central nervous system. Albeit rare, awareness about its association is important amongst general practitioners since the toxicity is reversible on discontinuation of medication.

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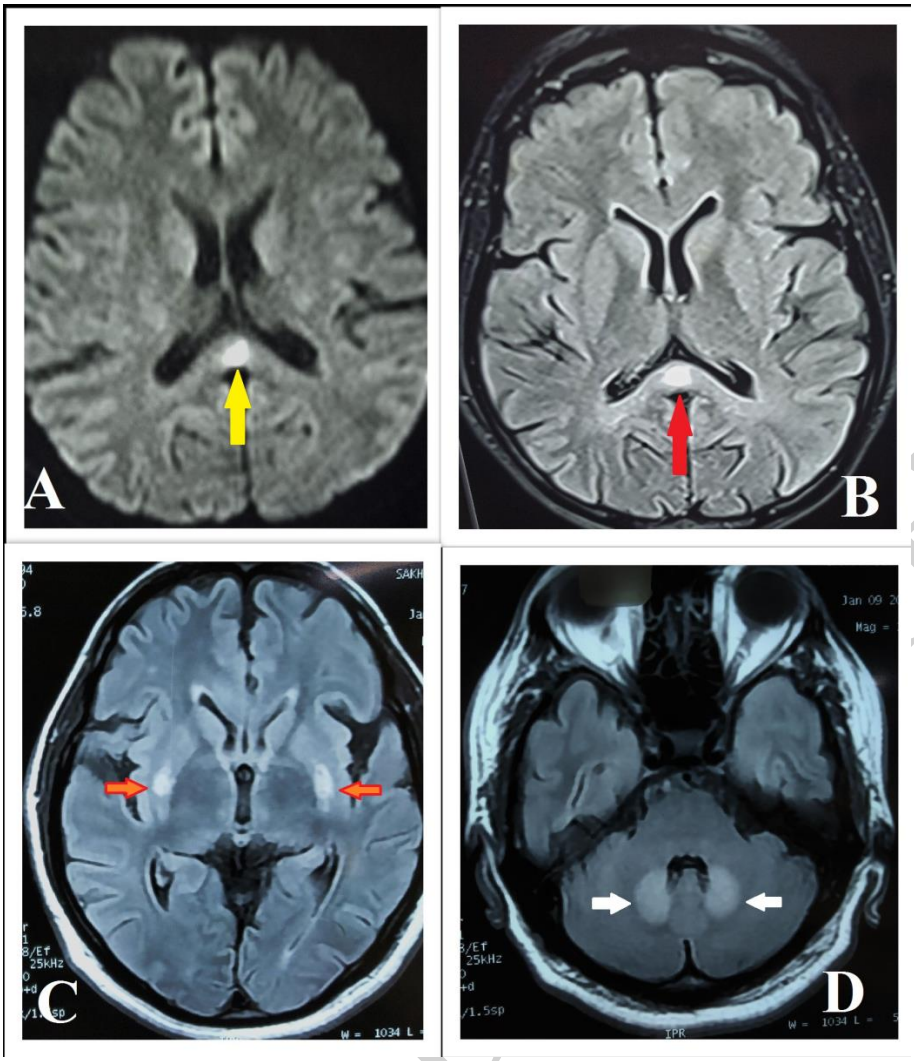

Figure 1: Splenium of corpus callosum shows evidence of diffusion restriction (yellow arrow) as well as hyperintensity (red arrow) on fluid attenuation inversion recovery (FLAIR) scans (**Panel A, B**); symmetrical areas of hyperintensity involving bilateral lentiform nucleus (orange arrow) and dentate nucleus of cerebellum (white arrow) (**Panel C, D**)

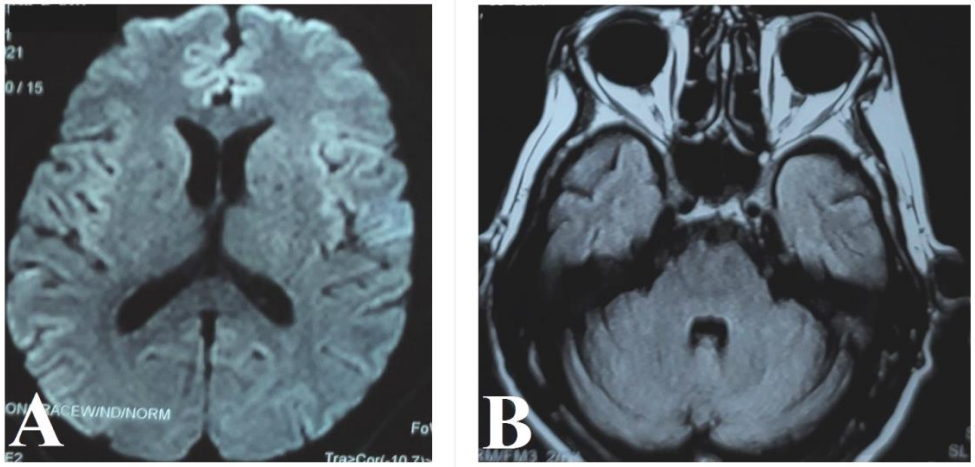

Figure 2: MRI brain showing axial diffusion weighted image (DWI) of brain with no restriction in splenium of corpus callosum **(Panel A)**; axial T2 FLAIR sequence showing resolution of hyperintensities in dentate nucleus of cerebellum **(Panel B)**

Table 1: Summary of relevant blood and CSF parameters

Blood parameters	Results	Reference range
Hemoglobin	128	120-160 g/L
Erythrocyte sedimentation rate (1st hour)	27	<30 mm
Fasting blood sugar	101	75-110 mg/dl
Anti-nuclear antibody (ANA)	Negative	
Serum vitamin B12	442	190-950 pg/mL
Plasma folate	11	2-20 ng/mL
Serum T4	7.7	5.10-14.1 mcg/dl
Thyroid stimulating hormone (TSH)	2.9	0.27-4.2 mIU/L
Serum calcium	9.7	9-11 mg/dl
CSF Examination	Results	Reference range
Cell Count	WBC count 4 /microL, all are lymphocytes	
Glucose	75 mg/dl	44-100 mg/dl
Protein	36 mg/dl	15-45 mg/dl
Adenosine deaminase	4.2 u/L	0-9 u/L

(ADA)		
Oligoclonal bands (OCB)	Absent	