Sultan Qaboos University Med J, February 2022, Vol. 22, Iss. 1, pp. 149–151, Epub. 28 Feb 22
Submitted 10 Dec 20
Revisions Req. 29 Dec 20 & 14 Mar 21; Revisions Recd. 3 Jan & 21 Mar 21
Accepted 18 Apr 21
https://doi.org/10.18295/squmj.5.2021.080

INTERESTING MEDICAL IMAGE

Metronidazole Induced Neurotoxicity

A clinico-radiological diagnosis

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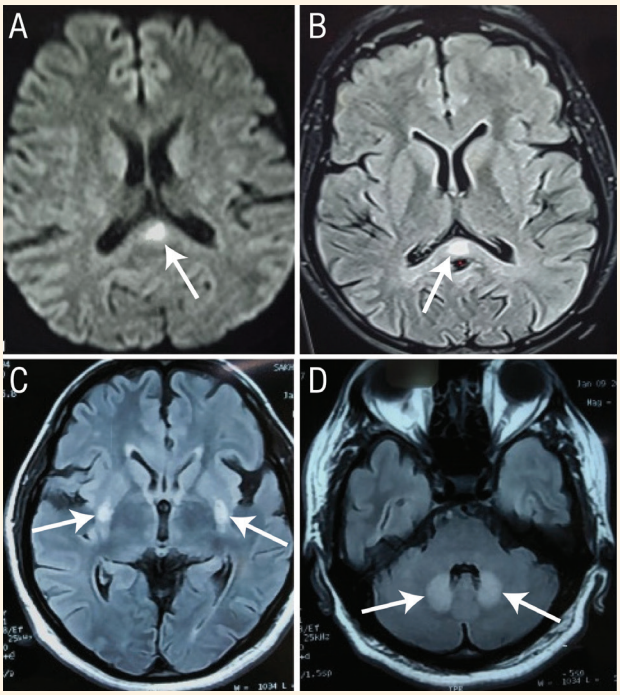

Figure 1: Magnetic resonance imaging scans of the brain of a 44-year-old male patient showing (**A**) the splenium of corpus callosum with evidence of diffusion restriction (arrow) and (**B**) hyperintensity (arrow) on fluid attenuation inversion recovery scans. Scans also showed (**C**) symmetrical areas of hyperintensity involving bilateral lentiform nucleus (arrow) and (**D**) dentate nucleus of cerebellum (arrow).

A 44-year-old male patient presented to a tertiary care hospital in Kolkata, India in 2019 with a history of subacute onset ataxia, dysarthria and episodes of generalised 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 scans of the brain, the splenium of *corpus callosum* showed evidence of diffusion restriction as well as hyperintensity on fluid attenuation inversion recovery (FLAIR) scans [Figures 1A and B]. There were also symmetrical areas of hyperintensity involving bilateral lentiform nucleus and dentate nucleus of cerebellum [Figures 1C and D].

Cerebrospinal fluid (CSF) study was non-contributory with absent oligoclonal bands (OCB). Vasculitis and infectious profiles were negative. Nutritional, paraneoplastic and autoimmune causes of cerebellar ataxia were ruled out by relevant investigations [Table 1]. Serum thiamine was not performed due to logistic issues. 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 the use of his images for publication purposes for academic interest.

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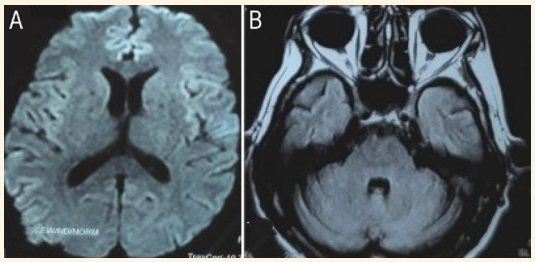

Figure 2: Magnetic resonance imaging scans of the brain of a 44-year-old male patient showing (**A**) axial diffusion weighted image with no restriction in splenium of *corpus callosum* and (**B**) axial T2 fluid attenuation inversion recovery sequence showing resolution of hyperintensities in dentate nucleus of cerebellum.

Table 1: Relevant biochemical results of the current patient

Parameter	Result	Normal range
Blood investigations		
Haemoglobin in g/L	128	120–160
Erythrocyte sedimentation rate (1st hour) in mm	27	<30
Fasting blood sugar in mg/dL	101	75–110
Anti-nuclear antibody	Negative	
Serum vitamin B12 in pg/mL	442	190–950
Plasma folate in ng/mL	11	2–20
Serum T4 in mcg/dL	7.7	5.10–14.10
Thyroid stimulating hormone in mIU/L	2.9	0.27–4.20
Serum calcium in mg/dl	9.7	9–11
Cerebrospinal fluid investigations		
White blood cell count in microL	4; all were lymphocytes	
Glucose in mg/dL	75	44–100
Protein in mg/dL	36	15–45
Adenosine deaminase level in u/L	4.2	0–9
Oligoclonal bands	Absent	

The patient did not have any objection regarding use of his images which may reveal his identity and gave permission to use them.

Comment

Metronidazole is a nitroimidazole derived synthetic antibiotic; it 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. However, Rao and Mason proposed that free radical mediated damage may be the mechanism for neurotoxicity caused by nitroheterocyclic drugs such as metronidazole.[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 current patient exhibited most of these radiological findings with additional involvement of basal ganglia. Primary central nervous system (CNS)demyelinating diseases such as multiple sclerosis and acute demyelinating encephalomyelitis can mimic these findings. However, the temporal profile, absence of OCB in CSF and reversibility of imaging findings were uncharacteristic of a demyelinating aetiology.

Wernicke's encephalopathy is the closest radiological differential of metronidazole-induced encephalopathy (MIE). As opposed to MIE, involvement of mammillary body and diencephalon are hallmark features of Wernicke's encephalopathy.[4] Brainstem lesions in MIE may mimic those of central pontine myelinolysis (CPM), with or without extra-pontine myelinolysis. However, brainstem lesions in CPM typically show restriction on diffusion weighted images.[5] Causes of focal T2 splenial hyperintensities are myriad and include encephalitis, Marchiafava-Bignami syndrome, extra-pontine myelinolysis, 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 excluded metabolic and infectious causes in the current 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.

This case highlights a severe adverse effect of metronidazole, a commonly prescribed antibiotic, on the CNS. Albeit rare, awareness about its association is important among general practitioners since the toxicity is reversible on discontinuation of the medication.

AUTHORS' CONTRIBUTION

AKD and UC contributed to conception and initial drafting of manuscript and were involved in the direct care of the patient. UC and SM helped with the collection of the images and relevant laboratory investigations necessary for the treatment as well as documentation of the case. AM and AD supervised the entire procedure of preparing the manuscript as well as supervised the treatment. AKD, UC and AC helped in the preparation of the manuscript, relevant revision and editing. All authors are in agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors approved the final version of the manuscript.

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