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ISONIAZID INDUCED BILATERAL DENTATE NUCLEI HYPERINTENSITY

Radiology

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ABSTRACT

CEREBELLITIS occurring as a drug induced neurologic complication with isoniazid therapy is relatively rare but when seen, usually occurs in patients with renal function impairment. Here, we report the case of a patient on long term anti-tuberculosis therapy for Multi drug resistance pulmonary tuberculosis with recent onset renal function impairment, presenting with acute cerebellar signs. On magnetic resonance imaging, isolated bilateral dentate nucleus T2 hyperintensities with restriction on diffusion weighted images were seen.
Although metronidazole toxicity has most commonly been implicated with such signal changes on magnetic resonance imaging, the association in patients on isoniazid with renal function impairment has been described in a handful of cases.

KEYWORDS

bilateral dentate nuclei hyperintensities, drug-induced cerebellitis, isoniazid.

INTRODUCTION

In developing countries where tuberculosis (TB) is prevalent, Isoniazid (INH) is commonly included as part of the four drug regimen for tuberculosis.[1] An increased incidence of side effects associated with anti-tuberculosis therapy (ATT) have been reported in patients with impaired renal function, owing to reduced renal clearance.[2] Neurotoxic complications of INH though well known, the occurrence however of cerebellitis as such is rare.[1,3]

The largest of the deep cerebellar nuclei, the dentate nucleus is affected by a few pathologies, metronidazole toxicity induced cerebellitis being the most common drug induced cause.[4-6] The findings in INH induced cerebellitis on magnetic resonance imaging (MRI) is classically seen as isolated bilateral dentate nucleus signal alterations, and is often considered a diagnosis of exclusion.[3]

CASE STUDY

A 43-year-old male patient presented to the outpatient department of Vasantrao Pawar Medical College, Hospital and Research centre, Nashik, India, with complaints of dizziness and bilateral lower limb weakness for the past ten days. The patient, at the time of evaluation was already on ATT for previously diagnosed pulmonary tuberculosis for the past 4 months.

On examination he had mild pyrexia and appeared distressed. He had no history of headaches, nausea or vomiting. No known history of hypertension, diabetes or alcohol intake. Examination of the central nervous system (CNS) revealed bilateral cerebellar signs. Investigations showed elevated serum creatinine (2.0 mg/dl) without electrolyte imbalance. His liver function tests were normal. Ultrasound (USG) examination showed mild hepatomegaly and features of bilateral medical renal disease in the form of mildly raised renal cortical echogenicity with normal kidney size.

Next, in view of the positive cerebellar signs and episodic dizziness, MR imaging of the brain was performed, which showed areas of bilateral, symmetrical hyperintensities in the dentate nuclei of the cerebellum on T2 WI (Figure A) with hypointensities on T1 WI (Figure B). Corresponding areas also showed hyperintensity in diffusion weighted imaging (DWI), without any signal changes in apparent diffusion coefficient (ADC) (Figure C and D).

Metronidazole toxicity and enteroviral encephalitis, ie, the reported causes were ruled out as there was no associated drug or retrospective clinical history.

Possibility of cerebellitis due to INH neurotoxicity owing to the build up of drug, secondary to altered renal function was thence considered. Accordingly, INH administration was stopped, alteration in ATT regime and administration of high-dose pyridoxine (100 mg/ day) was started. A significant improvement was seen in the patient within a few days, further confirming the diagnosis.

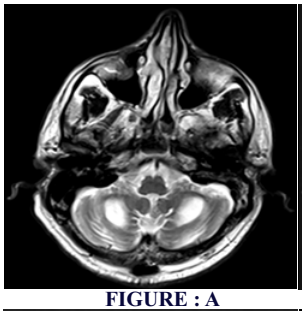

FIGURE : A

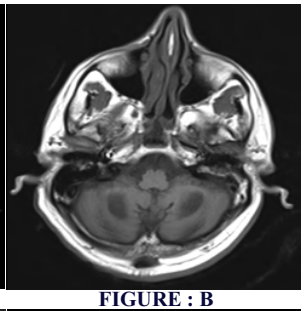

FIGURE : B

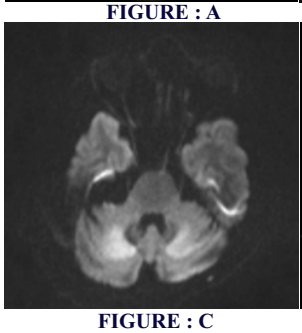

FIGURE : C

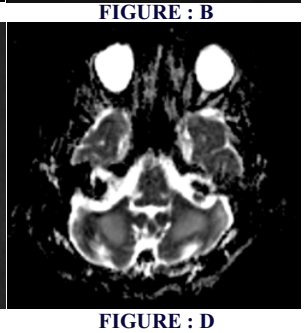

FIGURE : D

Axial T2 W image shows bilateral symmetrical hyperintense signal in dentate nuclei of cerebellum **(Figure A)**; Axial T1 W image shows bilateral symmetrical dentate nuclei hypointensities **(Figure B)**; Diffusion restriction seen on axial DW image **(Figure C)** with no signal changes in ADC **(Figure D)** in the corresponding areas**.**

DISCUSSION

The diagnosis of drug toxicity, ie, INH induced cerebellitis is usually made by process of exclusion, and is described in literature in the background of renal function impairment.[2,3,8] The drastic improvement observed in our patient on INH cessation and initiation of pyridoxine therapy further strengthened the diagnosis of drug-induced cerebellitis. Differential diagnoses of T2-weighted bilateral dentate nuclei hyperintensities on MR imaging include metronidazole toxicity, enteroviral encephalopathies, methyl bromide intoxication, maple syrup urine disease.[5,6] All of the aforementioned pathologies, including other causes of cerebellitis such as excessive alcohol intake, stroke, vaccinations and infective aetiologies were ruled out in our case on the basis of patients medical history and clinical investigations. On investigation, our patient was diagnosed with medical renal disease, a condition which may have caused the reduced the clearance

of INH (which has a primarily renal route of excretion) and contributed to higher levels of INH, leading to neurotoxicity. The neurotoxic effects of INH usually manifest in the form of peripheral neuropathy, due to interference with pyridoxine metabolism (inhibition of pyridoxine phosphorylation) and resulting in vitamin deficiency, therefore, pyridoxine supplementation is advised.[3,7,9] Cerebellum involvement although rare, does occur and can involve the bilateral dentate nuclei with resultant edema due to reduced gamma‐aminobutyric acid (GABA) levels and down regulation of N‐methyl‐D‐aspartate (NMDA) receptors.[3,8,10]

CONCLUSION

INH‐induced cerebellitis should be considered in the differential diagnosis of bilateral dentate nuclei hyperintensity, more so in patients presenting with neurological complaints after starting ATT. As a preventive strategy, treatment initiation with high-dose pyridoxine should be started in especially in patients with altered renal function/renal impairment. Clinical suspicion with early diagnosis and treatment in the form of INH withdrawal and pyridoxine supplementation can potentially reverse the edema and cause dramatic improvement in the patient's symptoms, potentially lower the risks of long term effects.

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