A Case of Isoniazid Induced Cerebellitis in a Patient with Chronic Renal Failure

Sir,

There is a relationship between chronic kidney disease (CKD) and tuberculosis. CKD patients are prone to develop tuberculosis, as well as side effects of antituberculosis therapy, more common in patients on hemodialysis. Neurological complications are well known in CKD patients who are treated with isoniazid-based ant tuberculous therapy (ATT), more common in dialysis-dependent. Cerebellitis is rarely seen and it has been reported only in CKD patients on dialysis[1] with characteristic magnetic resonance imaging (MRI) changes.[2]

We had a 65-year-old man, presented to outpatient department with complaints of sudden onset of slurring of speech and mild clumsiness in the right upper limb for 3 days. He had no history of giddiness, nausea, vomiting, or headache. He was a known case of hypertension for 20 years and CKD stage 4 with estimated glomerular filtration rate (eGFR) of 18 ml/min/m^2 for 1 year not on dialysis. Ten days before the presentation, he was started on the directly observed treatment short course (DOTS) category 1 weight-based regimen without renal dose modification for left axillary lymph node tuberculosis which was biopsy-proven. For 75 kg, he was receiving five tablets/day having a dosage of 375 mg isoniazid (INH), 750 mg rifampicin, 2 gm pyrazinamide and 1375 mg of ethambutol. He was not on pyridoxine. His pulse was 70/min with BP of 140/90 mmHg on admission. He was conscious, oriented. The central nervous system examination showed dysarthria with subtle impairment in the right finger nose test. Other cerebellar signs were absent and gait was normal. Cranial nerve, motor, and sensory examination were normal. Posterior circulation stroke was kept as a provisional diagnosis given sudden onset of cerebellar symptoms.

Investigations revealed raised erythrocyte sedimentation rate (ESR) of 110 mm/hr, deranged renal function test with a creatinine of 4.2 mg/dl and normal hemogram, liver function test, and electrolyte. The chest radiograph was normal. Ultrasonography (USG) abdomen showed bilateral small kidneys with loss of corticomedullary differentiation suggestive of chronic renal parenchymal disease. MRI brain showed symmetrical diffusion restriction in bilateral dentate nuclei with T2 and fluidattenuated inversion recovery (FLAIR) hyperintensity with no evidence of haemorrhage [Figure 1]. CSF analysis was normal. Differential diagnosis of bilateral dentate nuclei diffusion restriction with T2 and FLAIR hyperintensity are Leigh disease, maple syrup urine disease, methyl bromide intoxication, Wernicke's encephalopathy, enteroviral encephalitis, metronidazole, and cycloserine toxicity.[2] All differential diagnoses were ruled out in our case based on history and relevant investigations. Therefore, by exclusion, INH-induced cerebellitis was considered as a provisional diagnosis. Partial recovery occurred with pyridoxine 40 mg which remained static for 1 week. Hence, INH was stopped and the patient was discharged on modified antitubercular therapy with rifampicin 600 mg/day, ethambutol 1200 mg, and pyrazinamide 1500 mg thrice a week and levofloxacin 250 mg/day. On follow-up

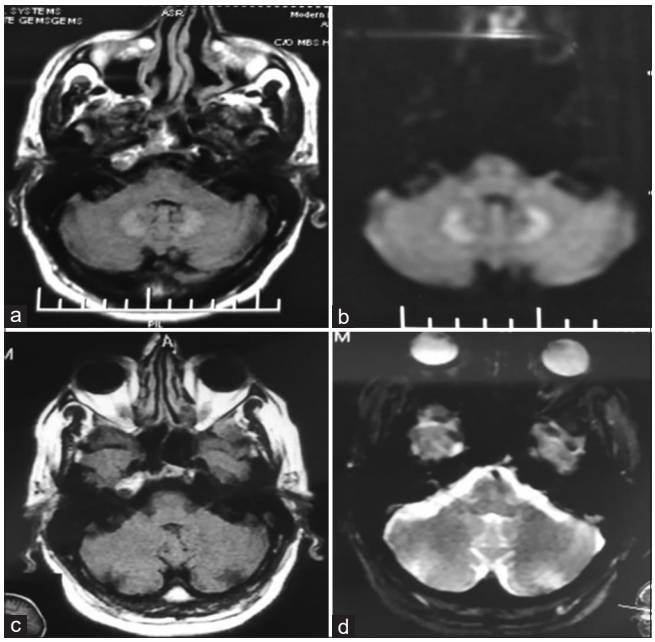

Figure 1: (a) - MRI FLAIR image shows bilateral dentate nuclie hyperintensity, (b) - Diffusion restriction in bilateral dentate nuclie, (c) - Normal MRI FLAIR image after 3 weeks of treatment, (d) - Normal DW image after 3 weeks of treatment

after 3 weeks, he had complete neurological recovery with no neuro deficit. Repeat MRI showed the disappearance of old changes.

Primary metabolism of isoniazid occurs in the liver which finally excretes via kidney. The recommended dose of INH in all stages of CKD is 300 mg/day irrespective of acetylation status.[3] Common neurological side effects of INH range from peripheral neuropathy, encephalopathy, seizures, and psychiatric manifestations. However, cerebellitis is rare. Neurotoxicity due to INH is due to interference with phosphorylation of pyridoxine, resulting in decreased production of pyridoxal-5-phosphate, a coenzyme involved in multiple metabolic functions including neurotransmission via gamma-aminobutyric acid (GABA). Because GABA is the primary inhibitory neurotransmitter in cerebellar Purkinje cells, its deficiency can explain cerebellar signs caused by INH toxicity. Also, pyridoxine deficiency is well documented in chronic kidney disease patients, more common in patients undergoing hemodialysis.[1] It occurs due to interference with normal pyridoxine metabolism to active pyridoxal phosphate by uremic toxin.[4] INH-induced cerebellitis has not been seen in a patient with normal renal function which favors the above theories for cerebellitis in CKD patients.

Siskind *et al*.[1] have reported three patients with cerebellar toxicity and other neuropsychiatry symptoms due to INH in end-stage renal disease patients on hemodialysis and was also receiving pyridoxine dose between 10 and 50 mg/day. They noticed partial recovery of patients after increasing pyridoxine dose to 100 mg/day, needed discontinuation of INH for complete recovery. Bhowmik *et al*. and[5] Pathania D *et al*.[6] have reported patients of antitubercular treatment-induced isolated cerebellitis which improved after stopping INH.

Our patient was on 375 mg INH/day which is higher than the recommended dose for CKD patients. On top of that, he was not on pyridoxine. These might be possible explanations of cerebellitis in our case. The above theories were strengthened with a pattern of recovery seen in our patient who partially improved after the introduction of pyridoxine 40 mg/day but complete recovery occurred within 2 weeks only after stopping INH.

This case is worth reporting as not only it brings out a very rare neurological complication of INH, it also highlights the importance of the addition of pyridoxine to the INH-based ATT regimen in CKD patients. It further emphasizes the need for renal dose modification of antitubercular drugs in CKD patients. We have taken all efforts to rule out all other possible causes of cerebellitis and followed up the case to ensure that there is complete recovery both clinically and radiologically. This highlights that INH-induced cerebellitis is reversible if suspected and managed judiciously.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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Submitted: 03-Nov-2019 **Revised:** 19-Nov-2019 **Accepted:** 20-Jan-2020
Published: 05-Jun-2020

DOI: 10.4103/aian.AIAN_547_19