

A Rare Presentation of Isoniazid-Induced Cerebellitis in a Patient with Chronic Kidney Disease-Unraveling the Clinical Complexity

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Abstract: Cerebellitis is a rare complication of drug Isoniazid. It is more pronounced in patients with chronic kidney disease. The dentate nuclei of cerebellum is affected by conditions like leucodystrophies, toxins, drugs, some metabolic and inflammatory conditions. Our case report is a drug induced cerebellitis, caused by isoniazid with characteristic MRI findings showing symmetrical T2 and flair hyperintensity seen in bilateral dentate nuclei. Common drug causing, cerebellitis is metronidazole. Our patient is a elderly female with chronic kidney disease, who was recently initiated on anti tuberculosis therapy for tubercular lymphadenitis. Symptoms resolved after withdrawal of isoniazid, short course of steroid (Dexamthasone) and pyridoxine supplimentation. Repeat MRI brain showed resolution of T2 FLAIR hyperintensities in bilateral dentate nuclei.

Keywords: Isoniazid-induced cerebellitis, Isoniazid neurotoxicity, Chronic kidney disease, Cerebellar toxicity, Tuberculosis, Antitubercular therapy, Dentate nuclei, Encephalopathy, Pyridoxine deficiency, Drug-induced neurotoxicity.

1. Introduction

Cerebellitis is a rare inflammatory syndrome characterised by cerebellar dysfunction. It can present as, trunk and limb ataxia, fever, abnormal eye movements, dysarthria, headache, nausea, vomitings, sleep disturbances and altered sensorium. It can be associated with multiple conditions. It is seen in para infectious, post infectious, post vaccination, toxin induced, antibody induced conditions and rarely secondary to drugs^[1]. Acute cerebellitis has been associated with a large number of infectious agents, such as: coxsackievirus, echovirus, enteroviruses, Epstein-Barr virus, Hepatitis A, Herpes simplex virus I, Human herpesvirus 6, Measles, Rubella, Mumps, Parvovirus B19, Borrelia burgdorferi (Lyme disease), Malaria, Mycoplasma pneumoniae, and Typhoid fever^{[2][3][4]}. Acute cerebellar ataxia following vaccination for Varicella, Hepatitis B, and Rabies has been reported.

Antibodies associated with cerebellitis are GAD 65 ab^[5], anti YO antibody^[6], anti Homer 3 ab^[7] and MgluR1 antibodies^[8]. Environmental toxins associated with cerebellitis are mercury, lead, managanese, toluene and benzene. Abuse of cocaine, heroin and phencyclidine are also linked with cerebellitis. Individuals with underlying chronic diseases such as CKD have a higher risk of acquiring TB. The global TB incidence in patients with CKD is estimated as 3718 per 100,000 patients with CKD^[9]. Isoniazid is a first line anti tubercular drug. It is associated with many side effects, including, hepatotoxicity, peripheral neuropathy, fever, skin rashes, drug induced SLE, thrombocytopenia, anemia, tinnitus, GI discomfort and rarely cerebellitis causing psychosis and seizures. History of onset of cerebellar symptoms after initiation of 4 drug regimen of ATT {isoniazid, rifampicin, pyrazinamide and ethambutol}, should rise suspicion of INH induced cerebellitis. Although INH toxicity is more common in children, patients with chronic kidney disease (CKD) are more prone to its toxicity due to reduced renal clearance. This case report aims to contribute to the growing knowledge isoniazid-induced cerebellitis by presenting a detailed analysis of a unique clinical case. Cerebellitis is

rarely seen with use of isoniazid and it has been reported only in CKD patients with characteristic magnetic resonance imaging (MRI) changes. This is often a diagnosis of exclusion and symptoms can potentially be reversed after withdrawal of INH and pyridoxine supplementation. Both the clinical and imaging findings are reversible.

2. Case History and Image Findings

This is a case of 55 year old female, who is a known case of systemic hypertension, type 2 diabetes mellitus, hypothyroidism and chronic kidney disease stage 4 on medical management. She initially presented with pain abdomen. Upon evaluation with CT abdomen, multiple enlarged lymphnodes with retroperitoneal fibrosis noted. CT guided biopsy done and it showed Tubercular lymphadenitis. She was started on 4 drug regimen with HRZE. She was started on Isoniazid 300mg/day, Rifampicin 600mg/day, Pyrazinamide 750mg/day and Ethambutol 400mg/day with Pyridoxine 40mg/day (Dosage adjusted as per weight). In 2 weeks of starting therapy, she presented with sleep disturbances, irritability and irrelevant talk and gait ataxia. CSF analysis done to rule out TB meningitis and was negative for meningitis. MRI Brain done. It showed, symmetrical T2 and FLAIR hyperintensity in bilateral dentate nuclei, with no diffusion restriction and no gross mass effect. After excluding all other causes and reviewing the literature, diagnosed to have Isoniazid induced cerebellitis. Isoniazid was withheld, started on Levofloxacin 500mg once daily and Pyridoxine supplementation continued. Empirical therapy with short course of steroid (Dexamethasone) given. Patient improved symptomatically. Repeat MRI Brain was done after 4 weeks and it showed resolution of the changes.

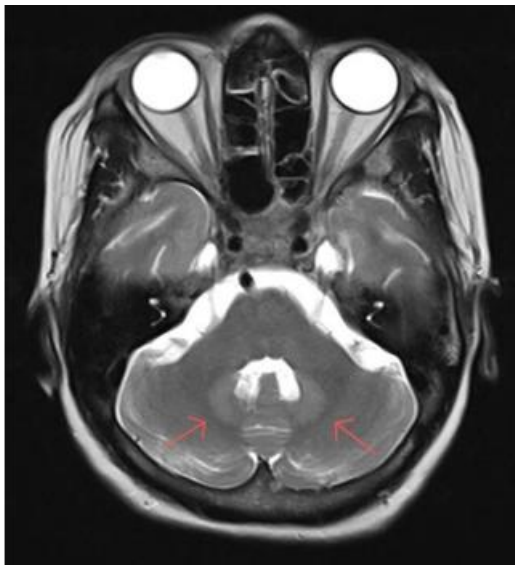


Figure 1 (A): Axial T2 W image shows bilateral symmetrical hyper intense signal in dentate nuclei of cerebellum

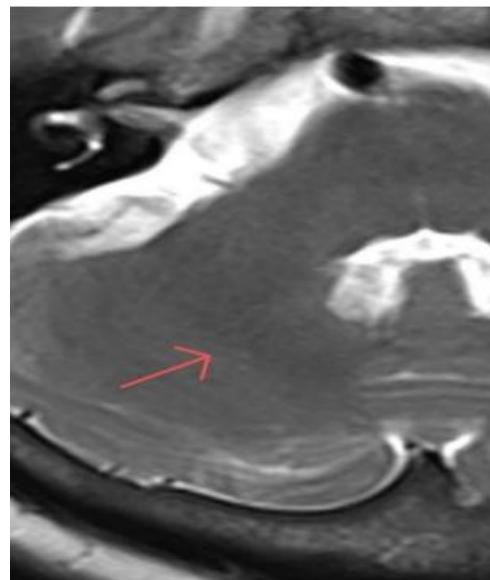


Figure 2 (B): Axial T2 W image show hyperintense signal in bilateral de cerebellum

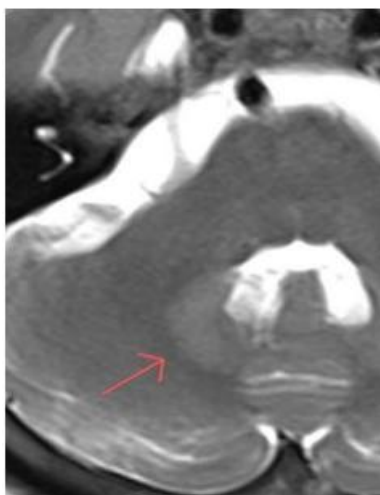


Figure 1 (B): Axial T2 W image show symmetrical hyperintense signal in of cerebellum

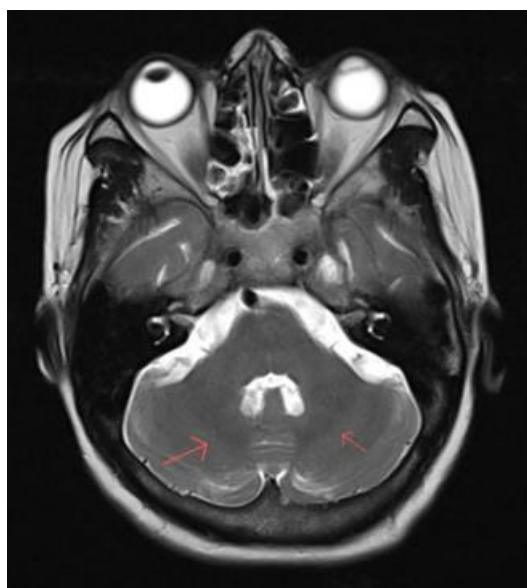


Figure 2 (A): Axial T2 W image shows resolution of hyperintense signal in bilateral dentate nuclei of cerebellum

3. Discussion

Isoniazid-induced cerebellitis is basically diagnosed clinically by the excluding other infective causes or metabolic disturbances. In this patient, the diagnosis is strongly supported by temporal relationship between the onset of symptoms and the initiation of INH therapy (4–14 days), completed recovery (within 2-3 weeks) after cessation of the drug. The clinical features and investigations must be done for the diagnosis of other conditions like septicemia, electrolyte imbalance, hypertensive encephalopathy, Wernicke's encephalopathy, aluminum toxicity, uremic encephalopathy, hepatic encephalopathy, acute disequilibrium syndrome, and cerebrovascular diseases. INH treatment may also increase the risk of developing pellagra by reducing the conversion of tryptophan to niacin. Pellagra psychosis may be mistaken for INH-induced encephalopathy where typical dermatitis or diarrhea is absent^[10]. Though plasma levels of INH and acetylator status were not determined in our patient, her Asiatic origin does not render her to fall under slow acetylator phenotype. The mechanism of INH-induced encephalopathy is still obscured. It may be caused by INH-induced deficiency of pyridoxine and pyridoxal phosphate, which act as the coenzymes for the production of synaptic transmitters^[11]. Predisposing factors for developing neuropsychiatric complications of INH include old age, diabetes, hepatic insufficiency, alcoholism, malnourishment, hyperthyroidism, slow acetylators, brain damage, past or family history of psychiatric illness, use of high dose of INH (>5 mg/kg daily), and concomitant administration of monoamine oxidase inhibitors^[11]. INH-induced encephalopathy can develop any time between first few days to 5 months after initiation of INH therapy. On the contrary, recovery is more predictable, usually within 1 week of stopping of INH^[12]. In spite of using prophylactic pyridoxine, INH-induced cerebellitis can occur. There are case reports that describe the development of encephalopathy and cerebellar syndrome in patients with CKD while on regular pyridoxine.

The decreased isoniazid clearance in chronic renal failure is

caused in minor part by the decreased renal excretion of isoniazid and in major part by the depressed hepatic N-acetylation of isoniazid^[11]. So, the role of pyridoxine in preventing isoniazid-induced encephalopathy is uncertain though the useful effect of pyridoxine on INH-induced peripheral neuropathy is well established^[12]. Nevertheless, its recommended to supplement with higher dose of pyridoxine to prevent INH-induced cerebellitis in CKD patients^[13].

4. Conclusion

Cerebellitis though a rare complication of isoniazid, it must be thought of in a patient with new onset cerebellar symptoms after initiation of isoniazid. Early recognition of such diagnosis can be crucial because cessation of the drug can result in complete recovery of the patient.

Even the radiological changes are mostly reversible with stopping the isoniazid and pyridoxine supplementation.

Informed consent:

Informed consent was obtained from all individual participants included in the study.

Financial support and sponsorship:

Nil.

Conflicts of interest:

There are no conflicts of interest

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