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Case Report

An Unusual Cause of Cerebellitis - Case Report

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Abstract

In countries where tuberculosis is still very common, millions of patients are placed under Anti-tuberculous treatment, of which Isoniazid is a component. The unfortunate co-occurrence TB in end-stage renal disease patient influences the metabolism and excretion of isoniazid and increases the chances of adverse effects. We wish to present one such patient of ours on ATT who returned to our care with neurological symptoms. Both the disease of tuberculosis and its treatment are fraught with occurrence of neurological involvement and complications. Diligent neurological examination pointed towards cerebellar pathology, possibly posterior circulation stroke. Ensuing MRI brain exhibited possible features indicative of drug (Isoniazid) induced cerebellitis. Consumption of the other two drugs, metronidazole and cycloserine, was excluded. Blood and CSF examinations did not show any abnormality. INH induced cerebellitis being our most possible diagnosis, high dose pyridoxine (100mg/day) therapy was initiated. Withing a week there was significant neurological improvement, and he was eventually discharged with modified ATT. Learning from this experience we would suggest to consider cerebellitis in patients with neurological symptoms on Isoniazid therapy and institute high dose pyridoxine therapy as a preventive measure in such patients.

Introduction

End Stage Renal Disease (ESRD) and Tuberculosis (TB) interrelation association had been proven. The reported prevalence [1] of patients with TB & ESRD on Maintenance Haemodialysis {MHD} is around 10.5 %. Isoniazid (INH) an antituberculosis drug, induced cerebellitis, though rare, is a possible condition that we should be aware of. Patients with ESRD are more prone to develop INH toxicity due to reduced clearance of isoniazid and its metabolites. The classical history of initiation of ATT for tuberculosis and onset of cerebellar symptoms in a CKD patient, should promptly raise the suspicion of INHinduced cerebellitis. Endowed with several co-morbidities, twenty days into ATT, this patient returned to our care with vague neurological features along with ataxia.

Case Report

A 65year aged gentleman, known diabetic, hypertensive, ischemic heart disease status post PTCA, CABG, and ESRD on MHD was recently diagnosed with extrapulmonary TB (July 10th 2022). Initially he presented on July 10th with generalised weakness, loss of appetite and enlarged axillary lymph nodes for which axillary lymph node biopsy was done which proved to be extrapulmonary tuberculosis. He was started on anti-tuberculous therapy (ATT) category I since July 20th which included Isoniazid(300mg/OD), rifampicin (450mg/OD), pyrazinamide (1250mg every alternative day) and ethambutol (800mg every alternate day) and supplemental low dose pyridoxine(20mg/OD).

He presented on 30th July with history of imbalance during walking since that afternoon. He was dialysed the same day morning, went home after dialysis and found it difficult to balance himself and was unable to walk steadily. He also presented with history of slurred speech since the same day afternoon. There is no history of any focal neurological deficits, headache, visual symptoms, numbness/paraesthesia's, seizures, deviation of eyes, fever/headache/vomiting's, chest pain/sob, cough/expectoration, trauma, weight loss. He was a known smoker and alcoholic and was on antiplatelets, statins and antihypertensives, ie, moxonidine 0.1mg, carvidelol 12.5 mg.

On arrival to Emergency Room, his airway was patent and was breathing spontaneously on room air. His HR was 110/min, blood pressure was 140/90mmHg, peripheries were warm. USG lungs screening showed A profiling of lungs, screening 2D ECHO revealed good LV function, IVC was collapsing (max- 1.2cm and min-0.7cm). On general examination he was conscious, coherent, cooperative, there was no pallor, icterus, clubbing, cyanosis and lymphadenopathy. Cervical and lumbar spine was normal. No neck rigidity/photophobia. No bruit over carotid arteries. No postural hypotension. **Ataxic gait was noted**. Respiratory system, cardiovascular system and gastrointestinal system examinations were normal. Central nervous system examination revealed normal higher intellectual function tests, memory was retained, emotionally stable but there was dysarthria. B/L pupils was normal in size, reacting to light. Cranial nerve examination was normal. Motor examination revealed normal tone, power 4/5 in all limbs and no abnormal movements. Sensory examination was normal. Reflexes were normal. Cranial nerve examination was normal. Examination for coordination revealed impaired right finger nose test, impaired Romberg's test. Examination to elicit heel knee test, toe finger test, Dysdiadokinesis, rebound phenomenon, past pointing and Barany's pointing test was normal. Based on the positive findings from the history and clinical examination which included slurred speech, imbalance and coordination during walking, impaired right finger nose test, impaired Romberg's test, posterior circulation stroke was kept as a provisional diagnosis and was sent for MRI as he is post window period for thrombolysis {8hrs from clinical symptom onset}.

MRI Brain revealed bilateral symmetrical T2 and flair hyperintensities showing mild diffusion restriction in dentate nucleus, pointing towards possible drug (Isoniazid) induced cerebellitis. Figure 1

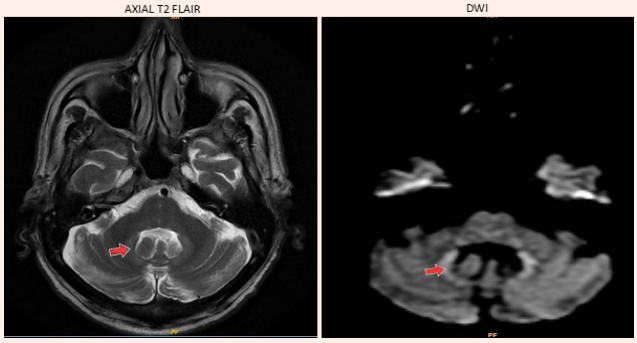

Figure 1

Since MRI was not suggestive of Posterior circulation stroke we started looking for other differential diagnosis like meningitis or meningoencephalitis, Wernicke's encephalopathy and did lumbar puncture for Cerebrospinal Fluid (CSF) analysis which also showed normal cytology and biochemistry, meningoencephalitis panel Adenosine Deaminase {ADA} & GeneXpert were also negative. He didn't have previous gadolinium exposure.

Meanwhile in his laboratory Investigations, complete blood picture revealed anaemia of chronic disease, normal Liver Function Tests (ALT- 11U/L, AST – 9U/L), electrolytes in normal range (sodium – 138 mmol/L, potassium- 4.2 mmol/L, chloride – 100 mmol/L), ammonia within normal limits (46ug/dl), creatinine was elevated (3.18mg/dl), normal vitamin B12 levels (250 pg/ml), and ultrasound KUB revealed small sized kidneys and loss of corticomedullary differentiation.

A wide spectrum of diseases with variable clinical symptoms affects the dentate nuclei. The causes relevant to our case discussion in view of T2 flair hyperintensity with diffusion restriction [2,3] are mostly *Metabolic, toxin, and drug induced* have been grouped in figure 2 and 3.

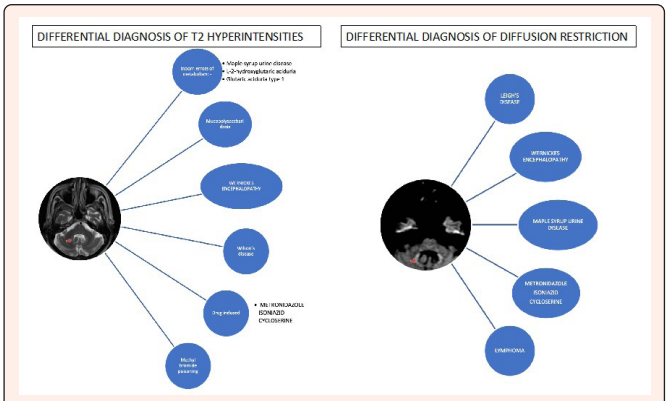

Figure 2 and Fgure 3

After reviewing patients' medical history, we suspected possibility of drug induced cerebellitis. No definitive drug intake history of metronidazole and cycloserine were found. Having ruled out other differential diagnosis, through process of exclusion, we have made a diagnosis of INH induced cerebellitis and the drug was discontinued. Anti-platelets, statins and anti-hypertensives were continued. High dose pyridoxine (100mg/day) was initiated. The patient started to show dramatic improvement clinically within a week. He was discharged with modified anti tubercular therapy which included rifampicin, pyrazinamide and ethambutol. A 2 week follow up review showed complete resolution of cerebellar symptoms.

Discussion

A diagnosis of drug toxicity is made primarily through a process of exclusion. To make such a diagnosis, it is important to demonstrate a close association between the onset of drug usage and the onset of symptoms, as was evidenced in our patient. Other than the close association observed, our patient also demonstrated dramatic improvement in her symptoms as soon as the drug was discontinued, and after the initiation of pyridoxine therapy. This further strengthened the diagnosis of drug induced cerebellitis. The close temporal relationship between the onset of confusional state and the initiation of INH therapy (4-14 days), resolution of symptoms after stopping the drug and reproducibility of symptoms on drug rechallenge was shown by cheung et al [1]. The deep cerebellar nuclei are vital structures of cerebro–cerebellar circuit which relays information from cerebellum to supratentorial cortical and subcortical targets [3]. Dentate nucleus is the largest and most lateral among all the 4 deep cerebellar nuclei. It is located adjacent to vermis and roof of 4th ventricle on either side. Dentate nuclei are involved in sensory processing, higher level cognition, planning and execution of voluntary movements. A wide spectrum of diseases with variable clinical symptoms affects the dentate nuclei and radiological T2 flair hyperintensities and diffuse restriction in dentate nucleus gives a pivotal role to search for drug and toxin induced cerebellitis [2,3].

The incidence of extrapulmonary TB is high in ESRD patients in view of abnormalities in cell mediated immunity associated with uremia [4].

Isoniazid is one of the important anti tubercular drug. Isoniazid is metabolised by N-acetyltransferase to inactive drug in the liver and is excreted through kidneys. Pharmacokinetic studies on hemodialysis have found that only 9.2% of INH is recovered through dialysate and it suggests that primary clearance of INH is through hepatic system. No dose modification is generally required in patients with kidney disease. Recommended dose of INH in all stages of ESRD is 300mg/day. INH is both hepatotoxic and neurotoxic. CNS involvement in the form of encephalopathy is due to a metabolite known as isonicotinylhydrazide. Isoniazid therapy is associated with neurotoxic syndrome which can occur in 1-2% of general population receiving doses in the range of 3-5mg/kg/day [5]. This syndrome can present as peripheral neuropathy with paraesthesia's, ataxia, muscle weakness and paralysis. CNS manifestations such as dysarthria, irritability, seizures can occur. Cerebellitis is rare form of INH neurotoxicity due to interference with phosphorylation of pyridoxine. It results in decreased production of pyridoxal 5 phosphate. Pyridoxal 5 phosphate is a coenzyme and is involved in multiple metabolic functions including neurotransmission via GABA. GABA is a primary inhibitory neurotransmitter in cerebellar purkinje cells. Pyridoxine deficiency explains signs caused by INH toxicity which included edema due to reduced GABA levels and down regulation of NMDA receptors. Risk factors for developing neurological manifestations include diabetes, alcoholics, malnourished patients and patients who are slow acetylators of isoniazid. In ESRD patients on hemodialysis pyridoxine deficiency is more common [6]. Pyridoxine deficiency cannot be attributed to vitamin losses during dialysis but rather it is due to inhibition of conversion of pyridoxine to pyridoxine-5-phosphate by uremic toxins. Pyridoxal-5-phosphate is more rapidly eliminated through dialysis in ESRD patients: Hence, patients with CKD are more prone to INH induced cerebellitis. The risk is also increased in patients who are slow acetylators of isoniazid.

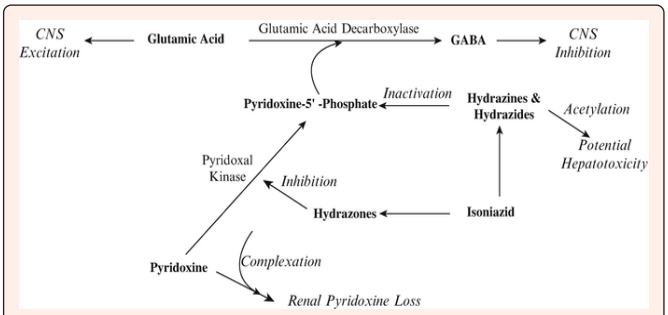

Figure 4

Review of literature showed case reports by Siskind *et al.* [6] who reported three patients with cerebellar toxicity and other neuropsychiatry symptoms due to INH in end-stage renal disease patients on haemodialysis and were also receiving pyridoxine dose between 10 and 50 mg/day. They noticed partial recovery of patients after increasing pyridoxine dose to 100 mg/day. They needed discontinuation of INH for complete recovery. Rutsky and Rosland [7] reported a 20% incidence of mild peripheral neuropathy in dialysis patients who were treated with INH 300-500mg/day. Bhowmik *et al.* [8] and Pathania D *et al.* [9] have reported patients of antitubercular treatment-induced isolated cerebellitis which improved after stopping INH. Blumberg

and Gil [10] published a report of reversible INH -associated cerebellar dysfunction in a patient with CRF, in which case, cerebellar toxicity was completely reversed after giving pyridoxine and reducing the INH dosage.

Conclusion

Isoniazid induced cerebellitis is a rare and reversible condition which often needs high index of suspicion in patients on ATT and has typical MRI findings of dentate nucleus hyperintensity with diffusion restriction. A preventive strategy with high dose pyridoxine may be beneficial in these patients.

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