Isoniazid-induced encephalopathy in an end-stage renal disease patient – A case report and literature review

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SUMMARY

Patients with end stage renal disease have higher risk of tuberculosis due to lower cell-mediated immunity. Standard regime of anti-tuberculosis contains isoniazid where neurological side effects such as seizure and encephalopathy have been documented. We present a case of isoniazid-induced encephalopathy in a haemodialysis patient. A literature review on isoniazid-induced encephalopathy was done. Recognition of this condition is important as it is reversible with cessation of isoniazid and institution of high dose pyridoxine.

INTRODUCTION

End stage renal disease (ESRD) patients have higher risk of tuberculosis (TB).[1] Standard anti-TB regime consists of isoniazid, rifampicin, pyrazinamide and ethambutol. Besides peripheral neuropathy, Cheung et al., reported that isoniazid caused neurological side effects such as seizures and encephalopathy although the frequency was not clearly defined.[2] In this report, we present a case of isoniazid-induced encephalopathy in an ESRD patient.

CASE REPORT

A 51-year-old woman was diagnosed with diabetes mellitus, hypertension and ESRD, and she was started on haemodialysis (HD) since January 2012. She was diagnosed with smear-negative pulmonary TB (PTB) in October 2017 and was initiated on intensive phase of anti-TB. In January 2018, after two months of intensive phase of anti-TB, she was switched to maintenance phase consisting of rifampicin and isoniazid. She then presented with sudden onset of confusion associated with auditory and visual hallucination. She denied fever, headache, vomiting, blurring of vision, seizure or substance abuse. She was on oral rifampicin 600mg (10mg/kg), isoniazid 300mg (5mg/kg) daily, and pyridoxine 20mg daily during presentation. No new medications were added recently that could explain her altered mental status.

Clinically she was confused. Glasgow coma scale (GCS) was 13/15 (Eye 3, Motor 6, Verbal 4). Vital signs were normal and she was afebrile. Neurological and systemic examinations were unremarkable. Blood investigations were normal (Table I). She was empirically covered for meningoencephalitis with intravenous (IV) ceftriaxone 2g twice daily and IV acyclovir 500mg daily. Urgent contrast-enhanced computed tomography (CECT) brain was normal with no features of tuberculous meningitis. Lumbar puncture opening pressure was at 10mmHg and cerebrospinal fluid (CSF) biochemistry analysis was normal. After eight days of treatment, we found no improvement in terms of her consciousness level. Electroencephalogram performed showed generalised slowing with polymorphic delta activity suggestive of encephalopathic changes. With the negative cultures and normal serial C-reactive protein (Table I), a differential diagnosis of isoniazid-induced encephalopathy was considered. Isoniazid was withheld and she was given IV pyridoxine 50mg daily. She recovered within three days and remained afebrile since admission. The diagnosis of smear-negative PTB was revised and anti-TB was not restarted after consultation with respiratory consultant (chest radiographs were reviewed again and sputum culture for Mycobacterium tuberculosis was negative). She was discharged well with oral pyridoxine 50mg daily for two weeks. She remains well and undergoes regular haemodialysis sessions with no recurrence of any neurological symptoms.

DISCUSSION

Patients with ESRD are susceptible to Mycobacterium tuberculosis infection. There are reports where TB risk is increased 3 to 25 fold in ESRD patients compared with general population depending on demographic characteristic.[1] This may be due to impaired cell-mediated immunity of ESRD patients.

Isoniazid is one of the first line drugs in the treatment of TB. Unlike pyrazinamide or ethambutol, there is no need for renal-adjusted dose for isoniazid in patients with chronic kidney disease. Patients are usually prescribed a dose of 5mg/kg of isoniazid with maximum dose of 300mg per day.

Following oral administration, isoniazid is metabolized by polymorphic arylamine N-acetyltransferase 2 (NAT2), which differs among ethnic groups as it is genetically determined. Slow metabolizer may exhibit higher peak serum concentrations and vice versa as shown in a case report by Constantinescu et al.[3] Although metabolised in the liver, major route of isoniazid elimination is the kidney where it is excreted in the urine in both free and acetylated forms.4 Hence ESRD patients on isoniazid may have higher serum concentration of isoniazid.

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Table I: Investigations Results

Laboratory parameters	Results	Normal reference value
Haemoglobin (g/dL)	10.7	11.5-16.5
TWBC, x 10^3 cells/ml	6.1	4-11
Platelet count, x 10^3cells/µL	232	150-400
Serum urea	8.5	1.7-8.3
Serum sodium, mmol/L	130	135-145
Serum potassium, mmol/L	3.5	3.5-5.1
Serum creatinine, µmol/L	570	<110
Serum aspartate aminotransferase, U/L	23	10-31
Serum alanine aminotransferase, U/L	6	10-32
Serum albumin, g/L	37	35-42
Random plasma glucose, mmol/L	6.6	4-11
Serum inorganic phosphate, mmol/L	2.04	0.81-1.45
Serum corrected calcium, mmol/L	2.5	2.1-2.6
Intact parathyroid hormone, pg/mL	7	15-68
C-reactive protein, mg/L	11	<5
Creatinine kinase, IU/L	70	50-167
Erythrocyte Sediment Rate, mm/Hr	60	<20
CSF opening pressure, cm H_20	10	<20
CSF FEME, Gram stain, cell count	Clear, colourless	
CSF glucose, mmol/L	5.5	
CSF culture and sensitivity	No growth	
CSF indian ink & latex agglutination	Negative	
CSF mycobacterium tuberculosis PCR	No growth	
CSF herpes simplex PCR	Not detected	
CSF total protein, g/L	0.54	
Blood culture	No growth	
HIV, Hepatitis B, Hepatitis C serology	Non-reactive	
Sputum Mycobacterium tuberculosis culture	No growth	
Sputum Mycobacterium tuberculosis PCR	Not detected	

* CSF, cerebrospinal fluid; PCR, polymerase chain reaction; HIV, Human Immunodeficiency Virus

Although uncommon, isoniazid may induce encephalopathy despite on pyridoxine, particularly in haemodialysis patients.[2-4] Isoniazid induces neurological symptoms via reduction of pyridoxal-5-phosphate (the active form of pyridoxine) concentration, a co-factor in many metabolic reactions.[4] Apart from that, chronic haemodialysis patients have severe deficiency in pyridoxal-5-phosphate due to altered pyridoxine metabolism and extensive removal of pyridoxal phosphate by haemodialysis making them at risk for isoniazid toxicity.[3]

The provisional diagnosis of isoniazid-induced encephalopathy in our patient is supported by the close temporal relationship between withholding isoniazid and rapid resolution of the neurological symptoms, albeit with the addition of high dose pyridoxine. Apart from that, blood, septic parameters and imaging were normal.

With increasing prevalence of tuberculosis in ESRD patients, it is important that ESRD patients treated with anti-TB be monitored closely during the course of therapy. The role of higher doses of pyridoxine in the treatment or prevention of isoniazid-induced encephalopathy is not well established. Numerous case reports showed that once isoniazid is withdrawn and pyridoxine dose increased, patients recovered well neurologically, as shown by our case too.[2-4] Apart from that, we would suggest NAT2 genotyping to help determine the dose of isoniazid in high-risk population. This approach has been recently validated in a large trial where NAT2 genotype guided regimen reduced the risk of anti-TB toxicity and treatment failure.[5]

In conclusion, isoniazid-induced encephalopathy should be considered when ESRD patient on anti-TB treatment containing isoniazid presents with neurological symptoms, provided infectious and metabolic causes are ruled out. Awareness of this condition is vital as it is reversible with the cessation of isoniazid and institution of high dose pyridoxine.

CONFLICT OF INTEREST

All authors have no conflict of interest to declare.

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