

A Case Report of Pyrazinamide-Induced Hepatitis Complicated by Obstructive Hydrocephalus Secondary to Tubercular Meningitis in Pediatric Patient

By Jammula Mounika

Case Report

A Case Report of Pyrazinamide-Induced Hepatitis Complicated by Obstructive Hydrocephalus Secondary to Tubercular Meningitis in Pediatric Patient.

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Abstract

This case report focuses on a pediatric patient with obstructive hydrocephalus secondary to tubercular meningitis, complicated by pyrazinamide-induced hepatitis. The elevated dosages of essential antituberculosis agents for pediatric use, recommended by the World Health Organization, raise concerns about heightened hepatotoxicity risk. Drug-induced liver injury (DILI) from anti-tuberculosis drugs is defined as hepatic injury, due to anti-tuberculosis drugs as suggested by the international DILI Expert Working Group and American Thoracic society and recent evidence questions the safety profile of pyrazinamide compared to earlier

perceptions. The patient, a 10-month-old with a history of obstructive hydrocephalus due to TB meningitis, was started with anti tubercular therapy for which the baby was presented with yellowish discoloration of both eyes after 15 days of starting anti tubercular therapy. Clinical and diagnostic findings, including head to toe examination, Cerebrospinal fluid (CSF) analysis, neurosonogram, Contrast enhanced magnetic resonance imaging (CEMRI) of the brain, and abdominal ultrasound, were detailed. Laboratory investigations revealed abnormal liver function and increased inflammatory markers. Identification of pyrazinamide as the specific hepatotoxic agent was established through dechallenge and rechallenge assessments. The patient's management plan was modified to incorporate non-tubercular medications. Adjustments to the treatment regimen, including the discontinuation of pyrazinamide, were executed, resulting in an extension of isoniazid and rifampicin therapy for 9 months. The case highlights the need for a multidisciplinary approach, individualized treatment plans, and close monitoring in pediatric tuberculosis cases, particularly considering neurological and hepatic complications. Further research and awareness are crucial for refining treatment guidelines and improving overall care.

Keywords: Tubercular meningitis, pyrazinamide, Drug induced liver injury, Treatment regimen

Introduction

⁴ Tuberculous meningitis (TBM), recognized as the most devastating manifestation of tuberculosis, contributes to approximately 20% of childhood TB mortality [1]. The recent elevation in recommended ³ dosages of essential antituberculosis agents, namely isoniazid (INH), rifampicin, and pyrazinamide (PZA), for pediatric use as advised by the World Health Organization ⁸ has sparked concerns regarding the heightened risk of hepatotoxicity [2]. Anti-tuberculosis drug-induced liver injury (TB DILI), defined by the international DILI Expert Working Group and the American Thoracic Society, refers to hepatic injury resulting from the administration of anti-tuberculosis drugs [3].

PZA plays a crucial role as a cornerstone in the standard combination therapy for tuberculosis. Despite its indispensability, PZA is associated with hepatotoxicity, and the exact mechanisms driving this adverse effect remain poorly elucidated. The prevailing notion implicating PZA's hepatotoxicity in its biotransformation within the liver emphasizes the intricate nature of its impact [4]. Initially perceived as a safer alternative compared to other potentially hepatotoxic

anti-TB drugs like INH and rifampicin, recent Research has unveiled a reconsideration of PZA's safety profile. Contrary to prior beliefs, current evidence suggests that PZA might pose a higher risk of hepatotoxicity than previously understood, even surpassing the potential liver-related risks associated with both INH and rifampicin [4].

Case Study

A 10-month-old female child, born to parents with 3rd-degree consanguinity, presented with a chief complaint of yellowish discoloration of both eyes persisting for the last 3 days after starting the anti tubercular therapy. The patient had a history of obstructive hydrocephalus secondary to TB meningitis, diagnosed one month ago. Surgical interventions included the placement of a right ommaya reservoir followed by ventricular peritoneal shunting. The child was immunized up to date, with no BCG (Bacille Calmette-Guerin) scar observed. On examination, vital signs were within normal limits, and laboratory values indicated anemia and inflammation. Ultrasound of the abdomen revealed cholelithiasis and mild hepatomegaly.

History of Illness:

Two months prior, 8-month-old baby was admitted with insidious onset fever lasting for 8 days. Subsequently, the child developed a vacant stare, and difficulty recognizing individuals, and experienced recurrent fever and seizure episodes leading to readmission.

Table 1: Clinical status

Head-to-toe examination	
Head circumference	45cm (increased)
General Status	Vacant stare look noted
Neck Rigidity	Positive
Anterior Fontanelle	Bulging
Eyes	No sunset sign
Head	Macrocephaly
Extremities	Fisting of palm observed
Motor System	
Tone	Increased in both upper and lower limbs
Power	4/5 in both upper and lower limbs

Reflexes	Exaggerated in both upper and lower limbs	
CSF analysis		
CSF glucose	18 mg/dl	Decreased
CSF protein	218 mg/dl	Increased
CSF chloride	120.5 mg/dl	Increased
Neurosonogram		
Impression - Bilateral lateral and 3rd ventricles were grossly dilated, causing a significant mass effect. Corpus callosum appeared compressed and thinned. Obstructive hydrocephalus, likely secondary to tubercular etiology.		
CEMRI of brain with seizure protocol		
Impression: Partial empty sella sign with torturous optic nerve and mild indentation of posterior sclera bilaterally. Leptomeningitis with severe obstructive hydrocephalus, likely of tubercular origin.		
Ultrasound of abdomen		
Cholelithiasis and mild hepatomegaly were noted.		

Table 2: Laboratory investigations

Laboratory Values		
C- reactive protein	38.20 mg/dl	Increased
Erythrocyte sedimentation rate	34 mm/hr	Increased
Hemoglobin	6.3 g/dl	Decreased
Red blood cells	2.7 million/cumm	Decreased
Packed cell volume (PCV)	20.1%	Decreased
Mean corpuscular volume	74.5 fl	Decreased
Mean corpuscular hemoglobin	23.2pg	Decreased
Total leucocyte count	34560 cells/cumm	Increased
Neutrophils	83%	Increased
Alkaline phosphatase	88.8U/L	Increased

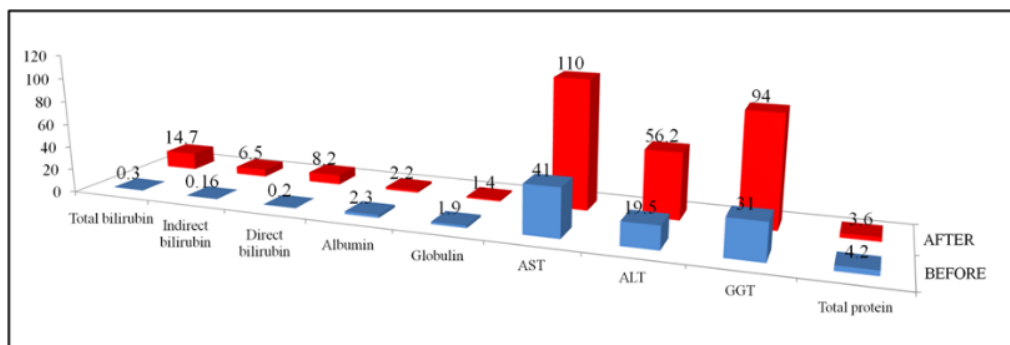


Figure 1: Liver function test values before and after Drug-induced hepatitis (DIH)

Table 3 : Treatment regimen

Anti -TB Drugs	Before DIH		After DIH	
	Dose	Frequency	Dose	Frequency
Isoniazid	50 mg	1-0-0	100 mg	1-0-0
Rifampicin	75 mg	1-0-0	150 mg	1-0-0 (alternative day)
Pyrazinamide	150 mg	1-0-0	stopped	-
Ethambutol	100mg	1-0-0	stopped	-

Dechallenge and Rechallenge Assessment:

Upon diagnosing drug-induced hepatitis, the medical team decided to discontinue the anti-tubercular drugs to identify the specific agent responsible for hepatitis. Subsequently, the treatment plan was adjusted to incorporate non-tubercular medications, including Inj. Levofloxacin 80mg (10mg/kg/dose) 1-0-1, syrup prednisolone 5mg once daily (OD), and a PCV transfusion of 160ml over 4 hours. After 15 days icterus was resolved.

Later, a rechallenge was conducted with Isoniazid, and the infant was closely monitored for the presence of icterus and liver function test (LFT) abnormalities. Similar rechallenges were performed with Rifampicin and Pyrazinamide. Notably, there were no symptoms of icterus or LFT abnormalities observed with Isoniazid and Rifampicin. However, when Pyrazinamide was readministered, icterus and LFT abnormalities reappeared, confirming that Pyrazinamide was the specific drug responsible for the drug-induced liver injury. This dechallenge and rechallenge process allowed for the precise identification of the hepatotoxic agent and informed the subsequent management of the patient's treatment plan.

Discussion

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Serious adverse events in children undergoing TB treatment are infrequent, although there have been occasional reports of severe hepatotoxic events. Donald's review [1] indicates that abnormal LFTs and jaundice were recorded in 53% and 10% of children, respectively, during treatment for TBM [5]. The three primary first-line anti-tubercular drugs—isoniazid, rifampicin, and pyrazinamide—carry the potential for causing liver injury, ranging from elevated liver enzymes without clinical symptoms to overt hepatic failure. In our study, pyrazinamide exhibited abnormal liver enzyme levels and icterus, indicating hepatic injury. The dechallenge and rechallenge process utilized in this case played a pivotal role in pinpointing pyrazinamide as the specific culprit behind the observed DILI. This approach facilitated the precise identification of the hepatotoxic agent, enabling the adjustment of the treatment plan to exclude the offending drug. The strategic shift in managing the patient's condition involved the use of alternative non-tubercular medications, such as levofloxacin and prednisolone, along with a careful transfusion regimen.

If DIH is attributed to pyrazinamide, it becomes necessary to discontinue pyrazinamide before completing the intensive phase, leading to an extension of isoniazid and rifampicin therapy to nine months. This adjustment was made in our study as well. The evolving understanding of pyrazinamide's hepatotoxic potential underscores the importance of vigilant monitoring in tuberculosis treatment protocols.

Conclusion

This case report emphasizes the importance of a multidisciplinary approach in managing complex cases of tuberculosis in pediatric patients, taking into account both neurological and hepatic complications. It also underscores the significance of individualized treatment regimens and close monitoring to ensure optimal patient outcomes. Further research and awareness regarding the hepatotoxic potential of anti-tuberculosis drugs, especially pyrazinamide, is essential for refining treatment guidelines and improving the overall care of pediatric patients with tuberculosis.

Abbreviations

DILI: Drug-induced liver injury; CSF: Cerebrospinal fluid; CEMRI : Contrast enhanced magnetic resonance imaging; TBM: Tuberculous meningitis; INH: Isoniazid; PZA : Pyrazinamide; BCG: Bacille Calmette-Guerin; PCV: Packed cell volume; LFT: liver function test; OD: once daily; DIH: Drug-induced hepatitis.

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Conflict of interest

The authors declare that there is no conflict of interest.

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