Cardiology in the Young

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Hypersensitivity myocarditis induced by isoniazid overdose in a 15-year-old girl: a case report

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Brief Report

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Abstract

Introduction: Myocarditis represents a diverse group of inflammatory diseases affecting the heart muscle, with both infectious and non-infectious etiologies. Among the non-infectious causes, drug-induced hypersensitivity reactions are rare but serious. Isoniazid, a cornerstone in tuberculosis treatment, is known for its hepatotoxicity but has rarely been documented to cause hypersensitivity myocarditis. *Case report:* We present a case of a 15-year-old girl from Eastern Turkmenistan who was admitted to our emergency department with altered consciousness and seizure activity. She was diagnosed with status epilepticus and treated accordingly. The patient, with no prior medical history, was found to have hypotensive shock and myocarditis upon further examination. A detailed history revealed she had ingested 45 tablets of expired isoniazid in a suicide attempt. She was treated with pyridoxine and supportive therapies, resulting in a gradual recovery. *Conclusion:* This case underscores the critical need to consider drug-induced hypersensitivity myocarditis in the differential diagnosis of myocarditis, especially in patients with recent medication use. Prompt recognition and appropriate treatment with pyridoxine, steroid, and supportive cardiac care can be lifesaving. This case also highlights the importance of awareness regarding the potential cardiotoxic effects of isoniazid overdose.

Introduction

Myocarditis encompasses a spectrum of inflammatory diseases of the heart muscle with diverse aetiologies. While infectious agents are well-recognised causes, non-infectious factors also play a significant role. These non-infectious triggers include autoimmune diseases, systemic inflammatory conditions, medications (e.g., procainamide, isoniazid, and hydralazine), alcohol abuse, exposure to heavy metals, and hypersensitivity reactions to vaccines or toxins.[1] In Turkey, tuberculosis remains a highly prevalent infectious disease.[2] The cornerstone of tuberculosis treatment involves a combination of medications, including isoniazid, rifampicin, ethambutol, and pyrazinamide. Isoniazid, in particular, holds an irreplaceable position as a first-line anti-tuberculosis drug due to its potent efficacy against *Mycobacterium tuberculosis* .[3] Introduced in 1955, isoniazid continues to be a mainstay of tuberculosis therapy due to its remarkable effectiveness. However, its use is not without side effects. Hepatotoxicity is a frequent concern, with approximately 20% of patients experiencing elevated liver enzymes (aspartate aminotransferase and alanine aminotransferase) following isoniazid administration. In a smaller subset (around 1%), severe hepatocyte injury can occur.[4,5]

Mechanistically, isoniazid is thought to exert its cardiotoxic effects by inducing oxidative stress and apoptosis in cardiomyocytes (heart muscle cells).[6] Isoniazid is a narrow therapeutic window medication used for tuberculosis treatment. With an estimated LD50 (lethal dose for 50% of the population) of 50 mg/kg in dogs, it requires careful dosing. Isoniazid comes in various forms, including elixirs, injections, syrups, and tablets (ranging from 50 mg to 300 mg strengths). A crucial aspect of its mechanism of action involves the depletion of gamma-aminobutyric acid in the brain and pyridoxine (vitamin B6) within the central nervous system. Pyridoxine serves as a precursor for the coenzyme pyridoxal phosphate, essential for the function of glutamic acid decarboxylase, an enzyme involved in gamma-aminobutyric acid synthesis. Isoniazid overdose can lead to life-threatening complications such as seizures, metabolic acidosis, and coma. Pyridoxine administration acts as a direct antagonist to isoniazid, mitigating its toxic effects.[7]

Drug-induced hypersensitivity myocarditis is a rare but recognised adverse reaction to medications. However, current literature lacks documented cases of antitubercular drugs causing hypersensitivity myocarditis.[8]

In this case report, we present a 15-year-old patient who developed status epilepticus and hypersensitivity myocarditis associated with isoniazid, and who recovered with B6, steroid, and cardiopulmonary supportive therapies.

Case report

A 15-year-old girl from Eastern Turkmenistan presented to our emergency department with altered consciousness and seizure activity. During observation, she experienced a seizure and was administered 0.1 mg/kg of intravenous midazolam. Given the recurrence of seizures, she was provisionally diagnosed with status epilepticus and treated sequentially with 40 mg/kg intravenous levetiracetam and 20 mg/kg intravenous phenytoin. Due to hypotensive blood pressure, she was started on adrenaline at 0.1 mcg/kg/min, titrated up to 0.3 mcg/kg/min, and norepinephrine at 0.1 mcg/kg/min was added. The patient was intubated and transferred to our paediatric ICU.

She had no prior medical history. On physical examination, the patient's general condition was poor with a Glasgow Coma Scale score of 7, and there was no neck stiffness. Heart sounds were faint, extremities were pale and cold, capillary refill time was 4–5 s, central pulses were weak, and peripheral pulses were absent. Hepatomegaly (5 cm) was noted. Laboratory test results are presented in Table 1.

With a provisional diagnosis of meningoencephalitis, empirical antibiotic therapy was initiated with 50 mg/kg intravenous cefotaxime three times a day, 20 mg/kg intravenous vancomycin three times a day, and 10 mg/kg intravenous acyclovir three times a day. A lumbar puncture was performed, and cerebrospinal fluid analysis was sent. Due to the presence of widespread infiltration on chest X-ray and a history of her father's death from tuberculosis, tuberculosis tests were conducted. The laboratory findings showed a high rate of eosinophilia, elevated troponin, Creatine Kinase MB levels, and echocardiography revealed an ejection fraction of 24% with more hypokinetic mid-wall segments, leading to a diagnosis of myocarditis. Consequently, treatment with 0.5 mcg/kg/h intravenous milrinone, 100 mg oral aspirin, 0.1 mg/kg oral enalapril, and 2 mg/kg/day intravenous furosemide was initiated.

Upon a reduction in the need for inotropic support and mechanical ventilation, the patient was extubated on the fourth day and transitioned to non-invasive ventilation. On the sixth day of follow-up, as the patient regained consciousness, a detailed history was obtained. It was revealed that she had ingested 45 tablets of isoniazid (100 mg each, equivalent to 90 mg/kg) in a suicide attempt. The medication belonged to her father, who had passed away six months prior, and had expired. Although the patient did not have a skin rash, the high rates of eosinophilia along with the presence of fever and malaise further support the diagnosis of drug-induced hypersensitivity myocarditis in this case. Treatment included 100 mg of intramuscular pyridoxine and 0.6 mg/kg of dexamethasone due to suspected isoniazid-associated hypersensitivity myocarditis. The patient's antibiotic therapy was discontinued due to a sterile cerebrospinal fluid culture, negative cerebrospinal fluid polymerase chain reaction (PCR) test and autoimmune panel. The patient was evaluated by child psychiatry and social services following the suicide attempt.

On the day of admission, the patient's ejection fraction was 24%. Before the administration of steroids and B6 treatment, it was 30% on the 6th day, and after the pyridoxine and dexamethasone treatment, it increased to 40% on the 8th day and to 55% on the 10th day of hospitalisation. As a result, the patient was started on 0.25 mg oral digoxin and transferred to the paediatric ward.

Discussion

This case underscores the complex interplay of neurological and cardiac complications following acute isoniazid overdose in a previously healthy adolescent. Initial symptoms included altered consciousness and recurrent seizures, necessitating aggressive treatment with intravenous midazolam, levetiracetam, and phenytoin to manage status epilepticus. Despite intensive anti-seizure therapy, the patient's condition deteriorated, leading to profound hypotension requiring escalating vasopressor support and mechanical ventilation, ultimately resulting in admission to paediatric ICU.

Further evaluation confirmed myocarditis based on echocardiographic findings showing severe myocardial dysfunction with an ejection fraction of 24% and hypokinetic mid-wall segments. The myocardial involvement was likely multifactorial, attributed to direct toxicity from isoniazid and possibly an immunologically mediated hypersensitivity reaction similar to previously documented cases.[8] While hypersensitivity myocarditis due to isoniazid is rare, it is a severe complication documented by Dhochak et al.,[8] who highlighted cases associated with antitubercular therapy.

The patient's history of ingesting a large quantity of expired isoniazid tablets as a suicidal gesture underscores the critical importance of promptly recognising and managing acute isoniazid toxicity. Isoniazid overdose can lead to significant central nervous system depression and seizures, necessitating aggressive supportive care and antidotal therapy with pyridoxine to mitigate neurotoxic effects.[7] Additionally, clinical suspicion of meningoencephalitis prompted empirical antibiotic therapy and cerebrospinal fluid analysis, although subsequent findings did not confirm an infectious aetiology, suggesting primarily toxic encephalopathy secondary to isoniazid overdose. Acute isoniazid toxicity commonly presents with altered mental status or seizures, as observed in our case.[7] Prompt recognition and treatment with pyridoxine are crucial to mitigate neurotoxic effects.[7] While our case involved hepatic involvement, highlighting the spectrum of isoniazid toxicity,[4] severe hepatotoxicity requiring discontinuation of isoniazid did not occur. However, similar cases in the literature stress the importance of monitoring liver enzymes and promptly addressing signs of hepatotoxicity.[4] Early detection and management of hepatotoxicity are essential to minimise morbidity and mortality associated with isoniazid therapy.[4]

This case provides several clinical insights relevant to managing acute isoniazid toxicity and associated myocarditis in adolescents. Management of myocarditis included pharmacological support with milrinone, aspirin, enalapril, and furosemide to stabilise cardiac function amidst ongoing haemodynamic instability. The prompt administration of steroids in our case underscores the pivotal role of early intervention in managing isoniazid-induced hypersensitivity myocarditis. Dhochak et al. reported diverse outcomes among their cases, highlighting the unpredictable nature of this complication.[8] Our patient's positive response to treatment, characterised by progressive improvement in cardiac function and resolution of shock, aligns with successful outcomes reported in the literature.[8] Echocardiographic monitoring showed notable improvement in myocardial contractility during hospitalisation, with the ejection fraction increasing to 58%, allowing for the discontinuation of inotropic support and transition to oral cardiac medications.

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Table 1. The patient's laboratory levels

	On admission	The worst levels	On discharge day	Normal range
Kidney function				
Urea	20	136.20	1109	18–45 mg/dl
Creatinine	0085	1.05	0043	0.24–0.41 mg/dl
Liver function				
AST	45	71	34	<40 U/L
ALT	7	16	2	<40 U/L
LDH	312	436	228	120–300 U/L
Inflammatory markers				
CRP	36	169	5	308–504 g/dL
Procalcitonin	29	42	0.18	4–67 µg/L
Albumin	29	29	34	3.5–5.5 g/dl
Fibrinogen	635	688	400	200–400 µg/L
Blood gas				
pH	6.75	6.75	7.45	7.35–7.45
pCO_2	48.8	60.9	35	35-45 mmHg
HCO_3	5.4	5.4	24	21–24 mmol/L
Lactate	17	17	1.1	0.5–2 mmol/L
Base excess	−25	−25	1.7	mmo/L
Complete blood count				
WBC	40,130	40,130	13,100	4–10 10^3/µL
Neutrophils	25,070	25,070	9850	1.5–6.1 10^3/µL
Lymphocytes	12,200	400	2100	2-6 10^3/µL
Haemoglobin	10	7.1	9	11–14 g/dL
Platelet	679000	360000	713000	150–400 10^3/µL
Eosinophils	490	490	210	0.04–0.36 10^3/µL
Coagulation				
PT	19	19	13	11–1608 s
APTT	33	81	13	24–35 s
INR	1.6	1.6	1	
Cardiac markers				
Troponin-T	145.9	145.9	17	<14 ng/L
Pro-BNP	2807	2807	513	<83 ng/L
Immunoglobulins				
Total IgE	2736	2736	612	<100 kU/L
CSF				
Culture	Negative			
PCR multiplex*	Negative			
Autoimmune panel**	Negative			

AST = Aspartate aminotransferase, ALT = Alanine Aminotransferase, APTT = Activated Partial Thromboplastin Time, CRP = C-reactive protein, CSF = Cerebrospinal Fluid, LDH = Lactate Dehydrogenase, INR = International Normalised Ratio, Pro-BNP = Pro-Brain Natriuretic Peptide, PT = Prothrombin Time.

*PCR Multiplex pathogens: Human parechovirus, *Haemophilus influenzae*, *Streptococcus pneumoniae, Cryptococcus neoformans/gattii, Cytomegalovirus, Enterovirus, Escherichia coli* K10, *Herpes simplex virus*, *Herpes simplex virus, Human herpesvirus, Varicella-zoster virus, Listeria monocytogenes, Neisseria meningitides, Group B Streptococcus (GBS), Herpes simplex virus (HSV)* 1 *PCR, Herpes simplex virus (HSV)* 2 PCR.

**Autoimmune Panel: Anti-NMDA (N-methyl-D-aspartate), Anti-AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), Anti-GABA (gamma-aminobutyric acid) B and A receptor antibodies, Anti-LGI1 (Leucine-rich glioma-inactivated 1) antibodies, Anti-CASPR2 (Contactin-associated protein-like 2) antibodies, Anti-DPPX (Dipeptidyl-peptidase-like protein 6) antibodies, Anti-VGKC (Voltage-gated potassium channel) antibodies.

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Psychiatric consultation and involvement of social services were crucial, addressing the underlying psychological distress and facilitating long-term support for the patient and her family following the suicide attempt.

A multidisciplinary approach was essential, involving intensive care for neurological and cardiac support. Empirical antibiotic therapy for suspected meningoencephalitis was initiated given the patient's presentation and epidemiological factors.[3] Echocardiography-guided therapy with milrinone and aspirin contributed to gradual improvement in cardiac function.[8]

The variability in outcomes among reported cases underscores the unpredictable nature of isoniazid toxicity and emphasises the importance of individualised treatment approaches. Nahid et al. stress the role of comprehensive guidelines in managing drug-susceptible tuberculosis, advocating for early recognition of adverse effects to optimise treatment outcomes.[3] Our experience reinforces these principles, emphasising the critical role of multidisciplinary care and continuous monitoring in mitigating complications associated with isoniazid therapy.

This case highlights the critical need to consider drug-induced hypersensitivity myocarditis in the differential diagnosis of myocarditis, particularly in patients with recent medication use. Prompt recognition and appropriate treatment with pyridoxine, steroid, and supportive cardiac care can be lifesaving. Clinicians should maintain a high index of suspicion for hypersensitivity myocarditis in patients receiving antitubercular therapy who present with cardiac symptoms.

While this case report provides valuable insights into the potential cardiotoxic effects of isoniazid overdose, it is important to acknowledge its limitations. The single-case nature of this study restricts the ability to draw definitive conclusions about the prevalence and clinical course of isoniazid-induced hypersensitivity myocarditis. Further research involving larger cohorts and controlled settings is warranted to establish a more comprehensive understanding of this rare but potentially fatal complication.

Additionally, the patient's history of suicide attempt introduces a confounding factor that could have influenced the presentation and clinical course. The psychological distress and potential use of other medications or substances might have contributed to the observed symptoms and outcomes.

Despite these limitations, this case report serves as a reminder of the importance of vigilance and thorough evaluation when dealing with drug-induced adverse effects, particularly in the context of antitubercular therapy. Early recognition and prompt intervention can significantly improve the chances of a favourable outcome.

Competing interests. The authors declare no conflict of interest.

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