

## Case Report

# Successful diagnosis of hyperpyrexia induced by isoniazid in a child with suspected extra-pulmonary tuberculosis

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**Abstract:** A 9-year-old boy received a rifampicin-isoniazid-ethambutol regimen for suspected extra-pulmonary tuberculosis, and glucurolactone and vitamin B6 to provide liver protection and decrease neurotoxicity associated with isoniazid. Baseline serum aminotransferase and total bilirubin levels were within normal limits before anti-tubercular treatment. After 4 days of treatment, the patient's body temperature increased (from 38.0 °C to 40.1 °C) and on the 11th day of treatment, serum chemistry results showed 400 U/L aspartate transaminase, 535 U/L alanine aminotransferase and 76.8 μmol/L total bile acid, which likely indicated drug-induced hepatic injury. After discontinuing isoniazid or administering anti-tubercular therapy without isoniazid, hyperpyrexia gradually resolved; hyperpyrexia reappeared following rechallenge with isoniazid. The patient's liver function returned to normal after symptomatic treatment. Thus, hyperpyrexia that accompanied hepatic injury was considered to be related to isoniazid. This case indicated that hyperpyrexia could also appear during anti-tubercular treatment owing to its hepatotoxicity.

**Keywords:** Adverse drug reaction, isoniazid, hyperpyrexia, hepatotoxicity, suspected extra-pulmonary tuberculosis

### Introduction

Undesirable effects may appear during anti-tubercular treatment. Common side effects, such as dizziness, nausea or vomiting, abdominal pain and headache, generally do not affect the continuation of treatment. However, serious adverse drug reactions (ADRs), such as renal failure, fulminant liver failure and drug hypersensitivity syndrome, can result in discontinuation of anti-tubercular therapy or hospitalization [1-3]. Because *Mycobacterium tuberculosis* is resistant to first line anti-tubercular agents, combination drug therapy is often required. In addition, anti-tubercular agents have common side effects, such as hepatotoxicity, fever and rash. Therefore, timely identification of the causative agent without affecting the continuation of other anti-tubercular agents is difficult but important, and it can affect successful completion of anti-tubercular treatment.

Isoniazid is an important anti-tubercular agent, and its reported side effects include hypersensitivity rash, peripheral neuropathy and hepatotoxicity [1, 4, 5]. However, hyperpyrexia associated with isoniazid has been rarely reported. Here, we report the first case of a 9-year-old boy who developed hyperpyrexia that was accompanied by isoniazid-associated hepatic injury. This report provides useful information to recognize the causative agent during anti-tubercular treatment.

### Ethical approval

No ethical approval was required for this case report.

### Case description

A 9-year-old boy weighing 35 kg was admitted to the Third Affiliated Hospital of Sun Yat-sen University, China reporting repeated hyperpyrexia for one week. He had abnormal liver func-

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**Table 1.** Results of therapeutic regimen after admission

Days after admission	Treatment protocol	Improvement of clinical symptoms or laboratory examination results
1-3	Cefoperazone sodium and sulbactam sodium (drip, 1.5 g, bid), polyene phosphatidylcholine (drip, 0.233 g, bid)	Hyperpyrexia gradually resolved, accompanied by heavy perspiration; the patient had abdominal pain and diarrhea; liver function improved (AST 107 U/L, ALT 329 U/L).
4	Ethambutol (po, 0.25 g, bid), isoniazid (po, 0.3 g, qd), polyene phosphatidylcholine (drip, 0.233 g, bid)	Hyperpyrexia reappeared.
5-13	Ethambutol and isoniazid were suspended, polyene phosphatidylcholine was continued	Liver function continued to improve (AST 39 U/L, ALT 165 U/L); hyperpyrexia gradually resolved, accompanied by heavy perspiration; but mild fever in the afternoon and night sweats continued.
14-16	Ethambutol treatment was administered again and polyene phosphatidylcholine was continued	Liver function approached normal (AST 23 U/L, ALT 38 U/L); the patient's condition tended to be stable without hyperpyrexia.
17	Isoniazid (po, 0.3 g, qd) was added, and ethambutol and polyene phosphatidylcholine treatment were continued	Hyperpyrexia reappeared with chills.
18	Isoniazid was stopped, and ethambutol and polyene phosphatidylcholine treatment were continued	Hyperpyrexia gradually resolved, accompanied by heavy perspiration; but mild fever in the afternoon and night sweat remained.
19-21	Rifampicin (po, 0.3 g, qd) was added, and ethambutol and polyene phosphatidylcholine treatment were continued	Normal temperature with improved abdominal pain and diarrhea. The patient's condition was stable.
22-23	The dose of rifampicin was increased to 0.45 g, qd, and ethambutol and polyene phosphatidylcholine treatment were continued	The patient's condition stabilized with normal temperature and normal liver function, and improved abdominal pain and diarrhea.

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tion test results that were obtained at an outpatient clinic. His medication history revealed that, for 11 days, he had been receiving an oral anti-tubercular regimen of rifampicin (0.3 g once daily), isoniazid (0.3 g once daily) and ethambutol (0.75 g once daily) for suspected extrapulmonary tuberculosis (TB), and glucurolactone (0.2 g every 8 h) and vitamin B6 (20 mg every 8 h) were also prescribed to provide liver protection and decrease neurotoxicity associated with isoniazid. The patient had a mild fever (38°C) in the afternoon with night sweats and he had lost 5 kg of body weight in 1 month, which was accompanied by abdominal pain and diarrhea. One week of antibacterial and antiviral therapy resulted in little improvement in his symptoms. However, outpatient clinic ultrasonography showed a normal appendix but swollen lymph nodes in the mesenteries, retroperitoneum, bilateral pars cervicalis and axillary cavity. A chest X ray film showed no meaningful results. Tubercle bacillus antibody test results were positive. He was suspected of having lymph node TB or intestinal TB.

On hospital admission, physical examination results showed an elevated body temperature of 40.1°C and second-degree of tumefaction in the tonsils with pus above them, as well as swelling lymph nodes in the anterior cervical triangle and on the bilateral chin. On the second day after admission, abnormal serum chemistry results included: aspartate transaminase (AST) 400 U/L, alanine aminotransferase (ALT) 535 U/L, total bile acid (TBA) 76.8 µmol/L, lactate dehydrogenase (LDH) 378 U/L, immunoglobulin G (IgG) 24.379 g/L, serum total complement (CH50) 62.0 U/mL, C-reactive protein (CRP) 33.5 mg/L and erythrocyte sedimentation rate (ESR) 67.0 mm/h. These results indicated probable drug-induced hepatic injury especially because the patient's liver function was normal before anti-tubercular treatment. On the same day, other laboratory examination results showed a normal blood count and normal blood clotting function, and stool examination results were also normal. The patient had no history of hepatitis and serological tests for hepatitis A, B, C and E virus, human immunodeficiency virus and Epstein-Barr virus were negative, and autoimmune antibody tests were also negative. An additional tubercle bacillus antibody test result was positive.

Based on the patient's clinical symptoms such as mild fever in the afternoon with night sweats, abdominal pain and diarrhea, laboratory examination results and ultrasonography examination results, he was suspected of having intestinal TB, but lymph node TB could not be excluded. Anti-tubercular agents were suspended because of their hepatotoxicity, antibacterial agents were prescribed and liver protection treatment was strengthened. Three days later, the patient's peak body temperature gradually reduced, which was accompanied by improving liver function. However, mild fever in the afternoon still remained. The regimens were gradually introduced based on the patient's clinical symptoms for diagnosis, which are shown in **Table 1**.

On the 13<sup>th</sup> day after admission, electronic enteroscopy and pathological results showed medium to severe chronic active inflammation with erosion and ulceration in the ileum and ileocecal valve areas, transverse colon and sigmoid colon. Based on the patient's clinical symptoms and medication history during his hospital stay as well as other laboratory examination results, the patient was diagnosed with suspected intestinal TB, an isoniazid-induced drug fever and drug-induced liver injury. Therefore, the patient's anti-tubercular regimen was adjusted to rifampicin (0.45 g once daily) and ethambutol (0.25 g every 12 h). He was discharged after 23 days of hospitalization. Similar hyperpyrexia did not occur at the 2-week follow-up in an outpatient clinic.

### Discussion

To date, the four main anti-tubercular agents that are commonly used include rifampicin, isoniazid, ethambutol and pyrazinamide. Two of these four agents (isoniazid and pyrazinamide) are major hepatotoxins. The remaining two agents are rarely hepatotoxic [6]. Drug-induced liver disease is a well-known side effect of anti-tubercular agents. Hepatotoxicity can range from asymptomatic elevation of serum transferases to hepatic failure, which is the main cause of terminating anti-tubercular treatment, and even death.

We found that hyperpyrexia and hepatotoxicity resulted from isoniazid treatment probably. According to the Naranjo Adverse Drug Reactions Probability scale [7], a hyperpyrexia

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score of 9-10 for isoniazid indicates a definite ADR, and a hepatotoxicity score of 6-8 for isoniazid indicates a probable ADR in our patient. First, there was temporal causation because the ADR occurred after anti-tubercular agents were administered. Hyperpyrexia and hepatotoxicity were also recorded as potential adverse reactions in the isoniazid package insert. Second, discontinuation of isoniazid or using a regimen without isoniazid resulted in complete resolution of hyperpyrexia or absence of hyperpyrexia and improved liver function. This also suggests that hyperpyrexia and hepatotoxicity were drug-induced adverse reactions. Third, underlying causes that may induce hyperpyrexia or hepatic injury were also ruled out, because the patient did not have other preexisting bacterial or viral infectious diseases and there was no serological evidence of infection with hepatitis A, B, C or E, and markers for autoimmune hepatitis were also negative, which indicated something other than chronic hepatitis. Fourth, hyperpyrexia reappeared following additional doses of isoniazid. Finally, other concomitant anti-tubercular agents, such as rifampicin, can also potentially cause hepatotoxicity [8, 9]. Therefore, there is strong support for the hypothesis that hyperpyrexia was induced by isoniazid, but it is more difficult to definitively attribute the hepatotoxicity to isoniazid.

Possible mechanisms by which the serious ADR of hyperpyrexia accompanied by hepatic injury occurred are discussed below. First, induction of the rifampicin liver enzyme can enhance the toxicity of some of the isoniazid toxic metabolites, since it has been reported that rifampicin-induced CYP 2E1 induction accounts for the exacerbation of isoniazid hepatocyte toxicity [8, 9]. Second, idiosyncratic or allergic and immune-related reactions may play a role in this patient. Third, the patient may be a rapid acetylator, and thus more acetylhydrazide was generated in the liver, which resulted in liver toxicity and allergic or immune-related reactions. Finally, the patient was still in a developmental stage and he may be sensitive to the side effects of anti-tubercular agents because the ability of his kidney to excrete toxic metabolites may have been limited.

### Conclusion

The long anti-tubercular treatment duration, the general combination drug regimen and the

high incidence of ADRs resulted in poor adherence and failure of the anti-tubercular treatment after hospital admission, which had a substantial impact on TB control [10]. This case suggests an efficient method for identifying the causative agent in a timely manner. However, the peak body temperature, liver and renal function and changes in other organs can provide a rapid and timely differential diagnosis of possibly serious ADRs. Careful management of ADRs is important for improving anti-tubercular treatment compliance and to control TB, especially at the beginning of treatment. However, it is important that clinical pharmacists work together with clinicians to provide patients with relevant medication information and instructions for regular monitoring to improve pharmaceutical care and safety.

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### Disclosure of conflict of interest

None.

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