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Unusual Recurrence of Antituberculosis Drug-Induced Hepatotoxicity in Children: A Case Series

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Case series

Patients: Male, 4-year-old • Female, 18-month-old • Male, 2-year-and-6-month-old • Female, 13-year-old • Female, 8-year-old • Male, 7-year-old

Final Diagnosis: Recurrent ADIH

Symptoms: Nausea • vomiting • yellowish skin

Medication: —

Clinical Procedure: Liver function test examination

Specialty: Infectious Diseases • Pulmonology

Objective: Unusual or unexpected effect of treatment

Background: Antituberculosis drug-induced hepatotoxicity (ADIH) is a possible adverse event of antitubercular treatment. There are still no official guidelines for ADIH management in children. Recurrent ADIH is infrequently reported.

Case Reports: In this article, we report 6 unusual cases of recurrent ADIH in children. Five children developed ADIH during the intensive phase. Streptomycin and ethambutol were given to those with tuberculosis meningitis, urinary tract tuberculosis, and one patient with pulmonary tuberculosis with HIV infection and cardiac comorbidities. Five patients experienced a second ADIH episode after reintroduction. One patient developed ADIH symptoms again before reaching a full dose of isoniazid. The patient with pulmonary tuberculosis, HIV infection, and dilated cardiomyopathy experienced secondary episodes of ADIH and received levofloxacin and ethambutol as additional drugs.

Conclusions: Recurrent ADIH is relatively uncommon in children but may be encountered in daily practice. Reintroduction of previous treatment regimens should be tailored individually. There is an urgent need for standardized guidelines for ADIH in children.

Keywords: Antitubercular Agents • Drug-Induced Liver Injury • Tuberculosis

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Background

Antituberculosis drug-induced hepatotoxicity (ADIH) is a possible adverse event of antitubercular treatment (ATT) [1]. ADIH incidence in children varies between 3.5% and 15.2% [2-4]. There are still no guidelines for ADIH management for children. Moreover, ADIH recurrence after reintroduction of treatment is not commonly reported. We aimed to evaluate management of ADIH recurrence in our setting by reporting 6 unusual cases of children with recurrent ADIH.

Case Reports

Case 1

A 4-year-old boy with lung tuberculosis (TB) and viral encephalitis experienced ADIH 2 times during his treatment period. The second episode developed when he was on his seventh month's treatment, after being successfully reintroduced to full-dose isoniazid (INH) and rifampicin (RIF). We stopped his ATT at that point. Two weeks later, his liver enzymes normalized. We observed clinical improvement, so ATT was discontinued.

Case 2

An 18-month-old girl with pulmonary TB and congenital cytomegalovirus infection experienced a third ADIH episode when being reintroduced to full-dose INH after previously developing ADIH. We modified the treatment to anti-TB therapy with full-dose RIF monotherapy for 9 months. Clinical improvement was observed during followup.

Case 3

A 2-year-and-6-month-old boy with TB meningitis experienced 2 ADIH episodes. During his first episode, in the intensive phase, we changed his regimens to streptomycin (STM) and ethambutol (EMB). After 2 weeks, his liver function test (LFT) came back as normal. He experienced a second episode when being reintroduced to full-dose INH. We stopped the INH, decreased the RIF dose to 2/3, and continued STM and EMB. Unfortunately, he discontinued treatment for 2 months. When he started treatment again, he experienced a third ADIH episode. We changed his regimens back to STM and EMB. Currently he is on his continuation phase and showing clinical improvement.

Case 4

A 13-year-old girl with urinary tract TB experienced her first ADIH episode in the intensive phase. We changed her regimens to STM and EMB. Her LFT returned to normal after 2 weeks. She experienced ADIH again upon reintroduction of 1/3 of a dose of INH. We stopped INH and RIF, and continued STM and EMB. She is currently in the continuation phase and showing clinical improvement.

Case 5

An 8-year-old girl with pulmonary TB, HIV infection, and dilated cardiomyopathy experienced 2 ADIH episodes. When the first ADIH episode occurred, during the intensive phase, we changed her regimens to STM and EMB. After evaluation in 2 weeks, her LFT had returned to normal. When being reintroduced to a full dose of INH, she experienced a second ADIH episode. We stopped the INH and RIF, then changed the regimens into levofloxacin (LFX) and EMB. The patient then showed clinical improvement.

Case 6

A 7-year-old boy with TB meningitis experienced ADIH 3 times. The initial regimens were stopped and he was given EMB and STM. After the ADIH symptoms resolved, we began the reintroduction of RIF and INH. However, he developed ADIH symptoms again while being reintroduced to full-dose RIF and INH. This happened twice. After reintroduction for the third time was successful, we stopped the EMB and STM. He continued with full-dose RIF and INH and showed clinical improvement afterwards.

Discussion

ADIH, as a possible toxic effect of ATT, may have clinical manifestations ranging from asymptomatic increase of serum transaminases and bilirubin to acute liver failure [5]. First-line treatments for ATT (Rifampicin, Isoniazid, Pyrazinamide) are known to be potentially hepatotoxic. However, elevated liver enzymes at baseline may have been found in some patients even before initiating therapy. It is essential to rule out other causes of liver injury before establishing a diagnosis of ADIH [6].

One study conducted by Gafar et al in Padang, Indonesia, found a 15% incidence rate of ADIH [7], which was similar to a result reported by Mansukhani et al in India (15.2%) [4]. These rates are higher than those reported in Bandung, Indonesia (3.5%) [2] and Pakistan (3.8%) [3]. Gafar et al pointed out the difficulties of having no criterion standard to distinguish between true ADIH and mere hepatic adaptation, which was suspected to be the true root of the higher incidence rate observed in the study. Besides, the differential diagnosis of viral hepatitis was excluded only based on clinical anemnesis instead of viral hepatitis biomarkers [7].

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Guidelines for ADIH management have been published by the American Thoracic Society (ATS) and British Thoracic Society (BTS). There are slight differences between the guidelines. ATS does not recommend routine examination of baseline LFT, unless there are possible risks for developing ADIH, whereas BTS advises baseline LFT for all patients. Once TB treatment is stopped due to hepatotoxicity, both advise restarting ATT one drug at a time [8,9].

The ATS guidelines recommend restarting RIF followed by INH, and state that in case of any recurrence of symptoms or elevation of transaminase levels, the last drug added should be stopped. It also advises discontinuation of pyrazinamide (PZA) completely and extending the duration of RIF and INH therapy to 9 months in patients with prolonged or severe hepatotoxicity [9].

The BTS guidelines recommend the use of EMB and STM if the patient's sputum test remains positive within 2 weeks after initiating therapy. Once LFT normalizes, first-line drugs can be reintroduced sequentially, started with INH, then followed by RIF and PZA. If no further reaction develops, the standard regimens can be continued and alternative drugs can be discontinued [8].

In all our cases, we discontinued ATT immediately after we established the diagnosis of ADIH. We excluded the possibility of viral hepatitis after testing for viral hepatitis biomarkers. We have no data regarding acetylator status of these patients. Of the 6 patients diagnosed with recurrent ADIH, 5 developed ADIH during the intensive phase. Those with TB meningitis, those with urinary tract TB, and the single patient with pulmonary TB with HIV infection and cardiac comorbidities, were given STM and EMB. In all 6 patients, LFT returned to normal after 2 weeks and reintroduction of the original ATT was begun. However, all 5 of the patients who developed ADIH during the intensive phase experienced a second ADIH episode after reintroduction of ATT, and 1 even developed symptoms before reaching the full dose of INH. She therefore only received RIF.

The patient with pulmonary TB, HIV infection, and dilated cardiomyopathy experienced a second episode of ADIH and received LFX and EMB as additional drugs. Levofloxacin has been used in children with multidrug resistant (MDR) TB and for ADIH management in adults [10]. In children, both the mechanism of action and the evidence of efficacy of fluoroquinolones are still under debate [11,12]. However, in our case we observed good clinical improvement in our patients after receiving LFX and EMB for 2 weeks. Similar results were reported in India, using EMB and ciprofloxacin as anti-TB regimens [13].

The lack of standardized guidelines for ADIH management in children is causing variations in management approach. Laghari et al reported that only 55% of their patients had their ATT modified due to ADIH; instead, the major response was symptomatic treatment. There was no drug replacement or complete withdrawal; only INH was temporarily discontinued but then reintroduced again once the symptoms resolved [3]. This differs from the approaches of Yee et al, who reported discontinuation, with no later reintroduction, of INH or PZA in 6 cases [14] and Ohkawa et al, who reported drug withdrawal in 6 of 8 cases who developed hepatotoxicity. Furthermore, all drugs were discontinued completely in 1 case [15]. This lack of standardized guidelines and the resulting variations in management could lead to the more complicated clinical scenario of recurrent ADIH, as we present here.

Although it is not commonplace in children, recurrent ADIH is a condition we might encounter in our daily practice as physicians. Unfortunately, its recommended management has not been covered in either the ATS or BTS guidelines. To our knowledge, there are still no studies reporting recurrent ADIH in children. Moreover, the efficacy and safety of ATT depends on individual variability. Hence, we must tailor management to each patient individually while taking into consideration both clinical manifestations and laboratory evidence.

Conclusions

Recurrent ADIH is relatively uncommon in children but possibly encountered in daily practice. Reintroduction of ATT should be tailored individually. There is an urgent need for standardized guidelines for ADIH in children.

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Conflict of Interest

None.

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