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Hospitalized pediatric antituberculosis drug induced hepatotoxicity: Experience of an Indonesian referral hospital

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ABSTRACT

Objective: To determine the characteristics and risk factors of pediatric antituberculosis drug induced hepatotoxicity (ADIH) in Dr. Hasan Sadikin Hospital, a referral hospital in West Java, Indonesia.

Methods: Medical records of hospitalized pediatric ADIH from October 2010 to October 2015 were reviewed retrospectively through computer-based search. Descriptive data were presented as percentage. Analytical case-control study on characteristics of ADIH was conducted using *Chi*-square and Mann Whitney test.

Results: Fifty (3.5%) out of 1424 pediatric TB patients developed ADIH; 20 (40%) were boys and 30 (60%) girls. More than half were under 5 years old and 33 (66%) were malnourished. ADIH occured in 29 (58%) cases treated for pulmonary TB, 15 (30%) for extrapulmonary TB and 6 (12%) for both; 34 cases (68%) occured during the intensive phase. We identified hepatic comorbidities including CMV infection [1 (2%)] and typhoid [1 (2%)], and other diseases treated by hepatotoxic drugs such as chemotherapeutic drugs, antiepileptics, and antiretroviral drugs [9 (18%)]. Case-control analysis of 50 ADIH cases and 100 TB controls without ADIH showed that the correlation between gender, age, type of TB, nutritional status and comorbidities to occurence of ADIH was statistically insignificant (P = 0.26, 0.765, 0.495, 0.5349 and 0.336, respectively). Pediatric ADIH was treated using modified British Thoracic Society guidelines.

Conclusions: Pediatric ADIH in our hospital is quite frequent, thus identifying risk factors and development of pediatric guideline is mandatory. Further study is needed to identify other risk factors such as genetic acetylator status.

1. Introduction

Childhood TB along with the adverse effect of its treatment is a major health burden. Approximately one million children were diagnosed with TB worldwide in 2014, with Indonesia ranking second after India amongst countries with the highest burden of TB in the world[1]. Antituberculosis drugs are proved effective to eradicate TB, although they can cause some serious adverse events, namely, gastrointestinal disturbances, hepatotoxicity, rash, and fever[2,3]. Recently, the new increased dosage recommendations of the essential antituberculosis drugs (isoniazid, rifampicin and pyrazinamide) by the World Health Organization in 2010, although effective and well-tolerated by children, have also raised concerns regarding antituberculosis drug induced hepatotoxicity (ADIH)[4]. Adverse effects of antituberculosis drug such as hepatotoxicity may potentially cause significant morbidity and mortality as well as affect treatment compliance and outcome of TB treatment[3,5]. Isoniazid, rifampicin and pyrazinamide could all potentially cause varying severity of hepatotoxicity[1,3]. Hepatotoxicity, a serious and often fatal side effect of TB treatment, is otherwise known as ADIH/ATDIH[2,6], drug-induced hepatic injury[7], antituberculosis drug induced liver injury (DILI)[8,9], and antituberculosis drug induced hepatitis[10]. Clinical manifestation of ADIH could range from asymptomatic increase of serum transaminases and bilirubin, to acute liver failure[2,8,9].

The diagnosis of ADIH was made by the presence of clinical jaundice and/or raised serum total bilirubin level (> 1.5 mg/dL) and/or 3–5 fold rise of serum alanine aminotransferase (ALT) above normal levels in patients receiving antituberculosis therapy, in exclusion of known viral hepatitis (HBV, HCV), chronic liver disease, and liver dysfunction due to any other hepatotoxic

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drug[2,9,11].

It was reported that among all adverse drug reactions in children recorded in VigiBase, a worldwide database of adverse drug reactions, only 1% was drug-induced liver injury, with antituberculosis drug being one of the causative agents[7]. The occurrence of ADIH is variable, ranging from 3%–39% in children and adults[2,3,9,12,13]. Data of ADIH incidence specifically in children is still somewhat lacking. Devarbhavi[8] reported that out of all drug-induced liver injury cases during 1997–2004 in Bangalore, India, 8.7% occurred in children, of which 56.4% was due to combination of antituberculosis drugs with a high mortality rate of 50% (11 out of the 22 cases). A cohort study by Hotchandani *et al*.[6] in Pakistan over the period of September 2010 to February 2011 showed that ADIH occured in 14% of children with TB treatment. Another large case series involving 2 000 children receiving 10–20 mg/day isoniazid revealed no discontinuation of treatment due to hepatotoxicity[13].

The diagnosis and management of ADIH in children presents a major challange, especially in developing countries due to several factors. The misdiagnosis of ADIH caused by coexisting viral hepatitis in developing countries could happen if serological tests were not performed due to limited resources[14]. Management of ADIH in children such as temporary discontinuation and reintroduction regiment of antituberculosis drugs is based on adult studies extrapolated to children, thus as far as the author knows, there is no specific guideline for the management of ADIH in children[9,10]. As surveillance and reports of adverse reaction of TB treatment in resource-limited developing countries are poor, data on ADIH in children especially in developing countries is lacking[1].

The objective of this study was to determine the frequency, characteristics, risk factors and treatment outcome of ADIH in children receiving antituberculosis therapy in a provincial referral hospital in a developing country.

2. Materials and methods

This is an analytical case-control study. This study involved 50 pediatric TB patients with ADIH (case) and 110 pediatric TB patients without ADIH (control) diagnosed and treated in Hasan Sadikin General Hospital, Bandung, Indonesia from October 2010 to October 2015. Children hospitalized with ADIH who were previously diagnosed and treated for TB in Hasan Sadikin Hospital or other subsidiary hospitals then referred to Hasan Sadikin Hospital were identified retrospectively from computer-based search of inpatient medical records using combined ICD 10 code of TB (A.19) and toxic liver disease (K.71), or other diseases of liver (K.76). Medical records with both codes were reviewed and cross-checked with TB registry and directly observed treatment short course (DOTS) registry data.

Descriptive data of characteristics including gender, age, type of TB, nutritional status, liver function test, type and dosage of antituberculosis drug, and comorbidities were obtained from medical charts and presented as median or mean and percentages. Data on follow up and treatment outcome were obtained from TB and DOTS registry.

Association of gender, age, type of TB, nutritional status, hepatic comorbidities and the occurence of ADIH were determined using *Chi*-square and Mann Whitney test. Statistical significance was represented with $P < 0.05$. Statistical calculations were conducted using SPSS version 7. The study protocol was performed according to the Helsinki Declaration and approved by the Ethics Committee of Dr. Hasan Sadikin General Hospital, Bandung, Indonesia (Ethical Clearance No. LB.04.01/A05/EC/485/XII/2015).

3. Results

Subjects and characteristics could be reviewed in Table 1. The youngest patient was 5 months old and the oldest was 13 years and 5 months old. The incidence of ADIH differed only slightly with age, with 28 (54%) occurred in children under 5 years. Out of the 50 children, 29 (58%) were treated for pulmonary TB, 15 (30%) for extrapulmonary TB and 6 (12%) were treated for both. Extrapulmonary TB cases consisted of 15 tuberculosis meningitis (TBM), 2 lymphadenitis TB, 2 scrofuloderma, and 1 peritonitis TB. Pulmonary TB and lymphadenitis TB were treated with isoniazide, rifampicin, and pyrazinamide in the intensive phase, whereas TBM, peritonitis TB and scrofuloderma were treated with isoniazide, rifampicin, pyrazinamide, ethambutol and prednisone in the intensive phase. According to medical charts, 33 (66%) used standard pediatric fixed-dose combination (FDC) drugs, and the rest were given separate, pulverized drugs mostly due to inavailability of FDC in the referring hospital.

We found that 34 (68%) cases of ADIH occurred within one month of intensive phase TB treatment with rifampicin (varied, but within the range of 10–15 mg/kg BW/day) and isoniazid (varied, but within the range of 5–10 mg/kg BW/day) along with pyrazinamide for pulmonary and lymphadenitis TB, pyrazinamide and ethambutol or streptomycin for TBM, scrofuloderma, and peritonitis TB. Of all subjects, 33 (66%) were moderately and severely malnourished (defined as BB/TB or BMI/U $\leqslant$ –2SD in WHO Child Growth Standard or Growth Reference). Primary or secondary malnutrition were not determined in the scope of this study.

Hepatic comorbidities occuring in these patients were 2 (4%) hepatic involvement in CMV and typhoid; 9 (18%) used other hepatotoxic drugs such as antiepileptics, antiretrovirals and chemotherapeutics. These patients were excluded from the statistical analysis. Twenty eight cases were complicated with underlying diseases including sepsis [5 (10%)], congenital heart diseases [4 (8%)], cerebral palsy [4 (8%)], nephrotic syndrome [3 (6%)], acute leukemia [2 (4%)], systemic lupus erythematosus [2 (4%)], autoimmune hemolytic anemia [2 (4%)], non Hodgkin's malignant lymphoma [1 (2%)], HIV [1 (2%)], epilepsy [1 (2%)], thalassemia [1 (2%)], congenital pulmonary airway malformation [1 (2%)] and brain tumor [1 (2%)].

All cases received antituberculosis reintroduction regiment of rifampicin and INH; 34 (68%) completed treatment, and 12 (24%) were lost to follow up and 4 (8%) died during treatment. None of the mortality was caused by hepatic failure due to ADIH. Mortality of the subject was due to TBM, acute renal failure in systemic lupus erythematosus, and sepsis in acute leukemia and non Hodgkin's lymphoma. Twelve (24%) cases were lost to follow up, among which 2 patients were discharged against medical advice, and 10

discontinued polyclinic visits and treatment and were untraceable.

Table 1
Characteristics of hospitalized children with ADIH.

Characteristics		No. of subjects (%)
Sex	Girls	30 (60%)
	Boys	20 (40%)
Age	< 5 years old	28 (56%)
	5–14 years old	22 (44%)
Type of tuberculosis	Pulmonary	29 (58%)
	Extrapulmonary	15 (30%)
	Pulmonary and extrapulmonary	6 (12%)
Occurence of ADIH	Within 2 months of therapy	34 (68%)
	After 2 months of therapy	16 (32%)
Nutritional status	Malnourished	33 (66%)
	Normal	17 (34%)
Hepatic comorbidities	Other hepatitis (CMV, typhoid)	2 (4%)
	Other drug induced liver injury (antiepileptic drugs, chemotherapeutic drugs, antiretroviral drugs)	9 (18%)
Other Underlying Diseases	Sepsis	5 (10%)
	Congenital heart disease	4 (8%)
	Cerebral palsy	4 (8%)
	Nephrotic syndrome	3 (6%)
	Acute leukemia	2 (4%)
	Systemic lupus erythematosus	2 (4%)
	Autoimmune hemolytic anemia	2 (4%)
	Non Hodgkin's malignant lymphoma	1 (2%)
	HIV	1 (2%)
	Epilepsy	1 (2%)
	Thalassemia	1 (2%)
	Congenital pulmonary airway malformation	1 (2%)
	Brain tumor	1 (2%)
Outcome	Completed treatment	34 (68%)
	Loss of follow up	12 (24%)
	Demise	4 (8%)

Correlation between characteristics and occurence of ADIH was analyzed using *Chi*-square test (Table 2). Statistical analysis using Pearson's *Chi*-square test found no significant correlation between characteristics and occurence of ADIH. Due to the small number of subjects and insignificant correlation, multivariate analysis to determine risk factors of ADIH could not be conducted.

Table 2
Correlation between characteristics and occurence of ADIH.

Variable		ADIH cases (n = 50) (%)	Controls (n =110) (%)	P^*
Gender	Male	30 (60%)	45 (40.9%)	0.269
	Female	20 (40%)	65 (59.1%)	
Age	<5 years	28 (56%)	60 (54.5%)	0.765
	>5 years	22 (44%)	50 (45.5%)	
Type of tuberculosis	Pulmonary	29 (58%)	70 (63.6%)	0.495
	Extrapulmonary	15 (30%)	29 (26.4%)	
	Both	6 (12%)	11 (10%)	
Nutritional status	Malnourished	33 (66%)	78 (71%)	0.534
	Normal	17 (34%)	32 (29%)	

*: Pearson *Chi*-square analysis.

4. Discussion

Antituberculosis drug induced hepatotoxicity needs more attention because it could lead to discontinuation of therapy, therapy drop out, increase in drug resistance, and general raise in the morbidity and mortality of TB.

This study revealed that the incidence of ADIH was 3.5%, which is lower than other studies conducted in other high-burden TB countries such as Pakistan (14.1%) and India (8.7%)[6,8]. On account of high number of pediatric TB cases diagnosed in our hospital, the overall incidence of ADIH is low. However, the high frequency of ADIH cases (50 cases in 5 years) in our hospital warrants more attention in the diagnosis, treatment and follow up in such cases. A guideline for diagnosis and treatment of pediatric ADIH is yet to be determined.

A previous study by Mansukhani and Shah[15] showed that ADIH was associated with younger patients[7]. A study in Indonesia with similar setting revealed 67% of ADIH cases in early childhood (age 1–5 years)[16]. This finding is based on the premise that complication of TB therapy mostly occurred in children under 5 years old due to the immature organic ion uptake mechanism which yielded hepatotoxic metabolites in the liver[2,3,7]. This study also showed that ADIH occurred more frequently in younger patients (54% in children under 5 years old), although the difference was slight. Taking into account that the data were taken from hospitalized patients, we could assume that younger children are at risk for higher morbidities and more complications of the disease, thus more likely to be hospitalized.

Previous findings showed that gender was not associated with ADIH[6,10,15]. This study showed that ADIH occured more frequently in girls than boys, although the difference was not significant, thus supporting previous studies. As data of association between sex chromosome or sex hormones and ADIH could not be found, this finding could be incidental.

Type of TB was not found to be associated with ADIH, because all ADIH cases, despite of the type of TB, were treated with first line antituberculosis drugs such as rifampicin, isoniazid and pyrazinamide, which were metabolized by the liver, thus potentially hepatotoxic[17]. Hepatotoxicity is often potentiated by multiple drug regiment, enhancing the toxic effects on the liver caused by INH, rifampicin and pyrazinamide given together in this study[18]. Although the type of TB was not associated with the incidence of ADIH, this study showed that more severe type of TB such as tuberculous meningitis contributes to more severe liver damage as shown by higher ALT or direct bilirubin.

Most ADIH cases occurred in the first month of TB therapy, whether it was pulmonary or extrapulmonary[2,3,8]. This is likely due to the antituberculosis agents used in intensive phase of both pulmonary and extrapulmonary TB such as rifampicin, isoniazid and pyrazinamide. This study showed that more pulmonary TB cases developed ADIH, which could be due to pulmonary TB occuring as comorbidity of other diseases needing hospitalization, such as acute leukemia, nephrotic syndrome, and HIV.

Malnutrition, which still remains a major problem in developing countries, greatly contributes to disease severity and development of ADIH. Several studies from India showed association between malnutrition and hypoalbuminemia with development of ADIH[19,20]. This study concurred with previous findings, which showed that 33 (66%) of pediatric ADIH patients were malnourished, although

statistical significance could not be established.

Data on mortality of ADIH in children have not been widely reported. In this study, 4 mortalities were not associated with liver failure due to ADIH; they were due to the severe TB disease (TBM), acute kidney failure in SLE, and sepsis.

There were several limitations in diagnosing and management of pediatric ADIH in Hasan Sadikin Hospital. First, due to limited resources, we didn't perform phenotypic assay of acetylation rate. Previous studies found that slow acetylators experienced more hepatotoxicity and experienced more severe ADIH than fast acetylators[21,22]. Thus, acetylation status might be useful in detecting more severe cases of ADIH and treating them accordingly. As far as the author knows, study investigating acetylator status in pediatric ADIH has never been performed in Indonesia.

To this day, there are no guidelines on therapy of pediatric ADIH worlwide, thus management is based on modified adult guidelines on ADIH from American Thoracic Society (ATS) and British Thoracic Society (BTS), which is to stop antituberculosis drugs altogether followed by reintroduction therapy. Follow up of treatment was ascertained by DOTS registry data, which showed a quite high rate of loss of follow up in 12 (24%) ADIH cases. Previous study by Nataprawira and Wonoputri in Hasan Sadikin Hospital concluded that factors contributing to loss of follow up in pediatric TB patients include financial issues, time clash with parents' work schedule, and far dwelling[23].

A few difficulties were present in data collecting of this study. As electronic medical record filed based on the ICD 10 code had only been started in this hospital from 2010, we were unable to collect further data from a longer period of time due to technical difficulty in finding the medical records. As a pediatric guideline for ADIH was apllied only from 2013 in our hospital, the treatment for ADIH before that time was still varying depending on the clinical judgement.

The main limitation of this report is the small number of subjects, unidentified exact dose of antituberculosis drug from previous health care facilities in several cases, and failure to identify the main risk factor of ADIH which is genetic acetylator state. Further studies with larger scope and number of subjects are needed to determine the risk factors of ADIH. Although the incidence is quite low, due to the potential harm of pediatric ADIH, a guideline for the diagnosis and management of pediatric ADIH should be developed especially for high-burden TB countries.

Conflict of interest statement

We declare that we have no conflict of interest.

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