Factors associated with disseminated tuberculosis in children

Factori asociați cu tuberculoza diseminată la copii

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Abstract

Background. *Tuberculosis continues to result in high morbidity and mortality in children from resource-limited settings. Disseminated tuberculosis is a fatal form, with severe clinical symptoms and complications. Hence, it is important to identify the risk factors for the early detection and treatment.*
Objective. *To identify factors associated with disseminated tuberculosis in children.*
Method. *A case-control study including children with tuberculosis below the age of 14, consulted in the period 2010-2017 in the "Dr. Soetomo" Hospital's Paediatric Outpatient Clinic. The cases were defined as children who were diagnosed with disseminated tuberculosis, miliary tuberculosis and/or tuberculous meningitis. The data were collected using simple random sampling from medical record with such a case and the control ratio was 1:1. The factors analyzed were: age, nutritional status, tuberculosis contact and BCG status, and HIV infection. The tuberculosis contact was defined as a close contact for more than two weeks with a TB patient. Age was divided into more than and below 2 years old, while nutritional status was divided into normal and malnutrition. Chi-square test and logistic regression were used to identify the risk factors.*
Results. *A total of 124 children were evaluated: 62 cases, 62 controls, 31.5% under 2 years of age, 87.9% received BCG immunization. The factors closely associated with severe tuberculosis were tuberculosis contact (OR 7.9; 95% CI; 3.3-18.7; p<0.01) and nutritional status (OR 2.9; 95% CI; 1.1-7.6; p=0.033). Age, BCG status and HIV infection were not significantly related to disseminated tuberculosis.*
Conclusions. *The history of contact and nutritional status are significant factors associated with disseminated tuberculosis in children.*
Keywords: ***tuberculosis, miliary TB, TB meningitis, children, risk factors***

Rezumat

Introducere. *Tuberculoza este o cauză importantă de morbiditate și mortalitate la copiii din țările cu resurse limitate. Formele diseminate de tuberculoză sunt de cele mai multe ori fatale, cu simptome și complicații severe. Prin urmare, este importantă identificarea factorilor de risc pentru aceste forme, pentru detecția și tratamentul precoce.*
Obiectivul *acestei lucrări este identificarea factorilor de risc asociați cu tuberculoza diseminată la copii.*
Materiale și metodă. *Studiul este de tip caz-control și include copii cu tuberculoză, sub 14 ani, consultați în Ambulatoriul Spitalului „Dr. Soetomo", din Indonezia, în perioada 2010-2017. Cazurile au fost definite ca fiind copii diagnosticați cu tuberculoză diseminată, tuberculoză miliară sau meningită tuberculoasă. Datele au fost colectate utilizând metoda simplă de randomizare din fișele pacienților, cu un raport de 1:1 caz și martor. Factorii analizați au fost: vârsta, statusul nutrițional, contactul cu tuberculoza, imunizarea BCG și infecția cu HIV. Contactul cu tuberculoza a fost definit ca un contact apropiat pentru mai mult de două săptămâni cu un bolnav de tuberculoză. Copiii au fost împărțiți în două grupuri de vârstă, sub și peste 2 ani, în timp ce statusul nutrițional a fost împărțit în status nutrițional normal și malnutriție. Testul Chi-pătrat și regresia logistică au fost folosite pentru identificarea factorilor de risc.*
Rezultate. *Din cei 506 copii evaluați în această perioadă, au fost incluși în studiu 124 de copii (62 de cazuri și 62 de control), 31,5% sub 2 ani, 87,9% au fost vaccinați BCG. Factorii asociați cu formele severe de tuberculoză au fost contactul TBC în antecedente (OR 7,9; 95% CI; 3,3-18,7; p<0,01) și statusul nutrițional (OR 2,9; 95% CI; 1,1-7,6; p=0,033). Vârsta, statusul vaccinal și infecția cu HIV nu au fost asociate cu tuberculoza diseminată.*
Concluzii. *Contactul cu un bolnav de tuberculoză în antecedente și statusul nutrițional sunt factori de risc importanți asociați cu formele de tuberculoză diseminată la copii.*
Cuvinte-cheie: ***tuberculoză, tuberculoză miliară, meningită tuberculoasă, copii, factori de risc***

Introduction

Tuberculosis (TB) among children is much more prevalent in developing countries, where resources for TB control are scarce, than in industrialized countries[1]. Miliary tuberculosis (miliary TB) and tuberculous meningitis are severe forms of disseminated TB, with high rates of disability and mortality[2,3]. Infants and young children are more likely to develop life-threatening forms of TB disease (e.g., miliary TB, TB meningitis), leading to childhood morbidity and mortality higher than in older children and adults.

The research in South Africa showed that TB was a major cause of meningitis in children[4]. There were 65 TB cases per 100,000 pediatric population reported in Romania[5]. Haghan and Nathani estimated that the death rate of patients with mild TB was ranging from 25% and reaching 100% without appropriate treatment[6]. Health office reported 3991 new tuberculosis cases detected in East Java in 2016, out of which 9% of them were in children. Most children acquire the infection from adults with whom they come in contact in their environment, so it's important to look for the source of transmission[7]. Complications such as respiratory distress syndrome, renal failure, pericarditis, shock, disseminated intravascular coagulation and acute respiratory failure have been reported[6,8].

Factors considered to increase the risk of disseminated TB are: malnutrition, absence of BCG immunization, history of tuberculosis contact, and immune disorders such as Human Immunodeficiency Virus – Acquired Immune Deficiency Syndrome (HIV-AIDS)[9,10]. Planning effective, child-focused TB interventions requires detailed evidence to guide implementation, but patient-level data are often scarce. We conducted a pre-intervention assessment to describe several factors associated with the development of disseminated forms of tuberculosis in children. The understanding the factors that increase the risk of disseminated tuberculosis is expected to allow an early intervention to prevent the severe forms of TB disease in children.

Methods

Study design: This was a retrospective analysis of data on 506 children diagnosed with tuberculosis between January 2010 and March 2017.

Study subjects: There were included children registered as patients in the pediatric pulmonology outpatient clinic aged less than 14 years old, diagnosed with tuberculosis.

Study setting: The study took place in the Paediatric pulmonology outpatient clinic of the "Dr. Soetomo" Hospital, which is located in Surabaya, East Java. The clinic serves as referral center for the Eastern regions of Indonesia.

Source of data: The patients' data were obtained from paper-based medical records of the pulmonology outpatient clinic. Data obtained at baseline, at the time of patient enrolment, included the following variables: gender, age, nutritional status, history of tuberculosis contact, BCG immunization status, and diagnosis.

Study procedure: There were included children aged between 2 months and 14 years diagnosed with tuberculosis, with complete medical records. The diagnosis of tuberculosis was based on the National Tuberculosis Guidelines for paediatric tuberculosis which includes clinical, tuberculosis scoring system, tuberculin skin test result, sputum analysis, and geneXpert. Medical records included in this study were divided into two groups, disseminated and non-disseminated tuberculosis.

Operational definitions: In this study, a child diagnosed with tuberculous meningitis and/or miliary tuberculosis was considered as a case of disseminated tuberculosis, while other forms were considered as control group. The diagnosis of tuberculous meningitis was based on head CT scan and lumbar puncture result, while the diagnosis of miliary tuberculosis was based on chest X-ray confirmed by radiologist and paediatric consultant. The age group was divided in two groups: under and above 2 years old.

The nutritional status adjusted for gender and age was determined, the weight and height were determined using the WHO chart for children less than 5 years of age and CDC chart for children above 5 years of age. A WHO weight-for-length Z score (WLZ) of < -2 or ideal body weight percentage <80% was considered as malnutrition.

Tuberculosis contact was defined as history of close contact with tuberculous patients for two weeks or more. BCG status was determined from BCG scar in the right arm and patients' immunization record. HIV infection positive means being diagnosed with HIV by a paediatrician.

Statistical analysis

The association between each independent variables and the severe tuberculosis was examined using the chi-square test. Univariate and bivariate logistic regression models were fitted to determine the risk factors for the development of severe tuberculosis. The results were expressed as odds ratios (OR) with their 95% confidence intervals (CI). The analyses were performed using SPSS software version 25 for Mac, and all tests were two-sided, with a p-value of <0.05 considered statistically significant.

Ethical approval: The study was approved by the Ethics committee of the "Dr. Soetomo" Hospital (number: 228/Panke.KKE/III/2017), Surabaya, Indonesia.

Results

Out of 506 tuberculosis patients examined in the study period in the Outpatient Clinic, 62 of them were diagnosed with disseminated tuberculosis, giving an overall severe tuberculosis prevalence of 12.3%, of which 58% suffered from miliary tuberculosis and 42% suffered from tuberculous meningitis. Then, 62 patients with non-disseminated tuberculosis were randomly chosen as controls. The total number of subjects in this study was 124. From the 124 children, the majority were males, ≥2 years of age (68.5%), with malnutrition (66.9%). Most of them had already performed BCG immunization (87.9%) and had been exposed to tuberculosis contacts (54.8%) – Table 1.

The bivariate analysis of the possible risk factors showed that nutritional status and the history of tuberculosis contact were significantly associated with disseminated tuberculosis in children (Table 2). Multivariate logistic regression analyses also showed that tuberculosis contact and malnutrition were significant risk factors of developing disseminated tuberculosis ($p<0.01$) – Table 3 and Table 4.

Discussion

Our findings support the previous studies that disseminated tuberculosis develops as a result of factors such as tuberculosis contact and nutritional status. Nutrition plays an essential role for developing the appropriate innate and Th1 immune responses against TB[11,12]. The relationship between nutritional status and the incidence of disseminated tuberculosis is owing to Th1 cells, which act as an important component in the cell-mediated immune system defence against *Mycobacterium tuberculosis* (MTB)[11]. Cell-mediated immune system is a key factor in host defence mechanism against the progression of tuberculosis infection to active TB disease[13]. Therefore, Th1 immunity against tuberculosis is impaired by malnutrition, so increases the risk of developing disseminated tuberculosis.

Table 1 Subjects characteristic

Patient characteristic	Case N (%)	Control N (%)
Gender		
Male	35 (56.5)	32 (51.6)
Female	29 (43.5)	30 (48.4)
Domicile		
Surabaya	49 (79)	44 (71)
Outer Surabaya	13 (21)	18 (29)
Age		
< 2 years old	20 (47.6)	19 (30.6)
≥ 2 years old	42 (52.4)	43 (69.4)
Nutritional status		
Underweight	31 (50)	10 (16.1)
Normal weight	31 (50)	52 (83.9)
BCG status		
Yes	52 (83.9)	57 (91.9)
No	10 (16.1)	5 (8.1)
Tuberculosis contact		
Yes	50 (80.6)	18 (29)
No	12 (19.4)	44 (71)
HIV infection		
Positive	3 (4.8)	4 (6.5)
Negative	59 (95.2)	58 (93.5)

A study in guinea pigs given a low protein diet and then exposed to MTB revealed deficits in mounting an appropriate Th1-type cell-mediated response. This includes decreased lymphocyte proliferation, higher immunoglobulin G levels, and decreased cytokines such as IL-2, TNF-α, and IFN-γ, so these animals had evidence of worse disease, with higher bacillary load in the lung and spleen[13]. Nutrition has a profound effect on the Th1 immune system's ability to defend against tuberculosis soon after infection and thus predisposes the animal to disease progression[11]. A recent study from Lienhardt discovered that severe malnutrition was shown to depress immune responsiveness to BCG, although there was some uncertainty about the effect of mild malnutrition[14].

Children who are in close contact with individuals with tuberculosis are at high risk of developing TB. Despite the former vaccination with BCG, it has been suggested that a positive tuberculin skin test (TST) in a child who has close contact with an adult with infectious TB most likely represents an infection with MTB. Sloot et al. reported the risk of coprevalent and incident TB among contacts with LTBI aged less than 5 years was about twice the risk among contacts aged 5-14 years,

Table 2 Bivariate analysis of disseminated tuberculosis risk factors in children

Variables	Cases N (%)	Controls N (%)	OR	95% CI	p-value
Age					
<2 years	20 (47.6)	19 (30.6)	0.9	0.435 – 1.981	1.00
> 2 years	42 (52.4)	43 (69.4)			
Nutritional status					
Undernutrition	31 (50)	10 (16.1)	2.9	1.1 – 7.6	0.03
Normal	31 (50)	52 (83.9)			
BCG status					
No	10 (16.1)	5 (8.1)	2.2	0.703 – 6.837	0.27
Yes	52 (83.9)	57 (91.9)			
Tuberculosis contact					
Yes	50 (80.6)	18 (29)	7.9	3.3 – 18.7	<0.01
No	12 (19.4)	44 (71)			
HIV infection					
Yes	3 (4.8)	4 (6.5)	0.2	0.291 – 6.328	0.70
No	59 (95.2)	58 (93.5)			

Table 3 Multivariate model of disseminate tuberculosis risk factors in children

Variables	Exp (B)	95% CI	p value
Age	0.999	0.398 – 2.511	0.998
Nutritional status	2.878	1.087 – 7.621	0.033
BCG immunization status	1.378	0.335 – 5.669	0.657
Tuberculosis contact	7.848	3.288 – 18.731	<0.01
HIV infection	1.356	0.291 – 6.328	0.698

Table 4 Multivariate model of disseminate tuberculosis risk factors in children

Variables	Exp (B)	95% CI	p value
Nutritional status	27.814	5.570 – 138.880	<0.001
Tuberculosis contact	155.632	28.847 – 839.656	<0.001
Constant	0.087		<0.001

and the risk among contacts aged 5-14 years was almost three times the risk among contacts aged higher than or equal to 15 years[15].

Bacille Calmette-Guerin (BCG) status coverage in this study was high. The estimated efficacy of BCG prevention from miliary TB reached 77%, but in Asian countries which already have high immunization coverage, the efficacy estimation could decrease[16]. BCG has 60-80% protective efficacy against severe forms of tuberculosis in children, particularly meningitis[16,17], and its efficacy against pulmonary diseases varies geographically, depending on the method of administration, vaccine strain used and nutritional status at the time of vaccination[18-20]. BCG does not seem to protect against disease when it is given to people already infected or sensitized to environmental mycobacteria, which could explain the geographical variation[21-23]. Surabaya, including East Java province, is located at 111°0'-114°4' East, and 7°12'-8°48' South. A study from Mangtani et al. concluded that there was no evidence of protection against infection less than 40° latitude away from the Equator[23]. A recent meta-analysis of trials, including 18 studies reporting on protection against pulmonary tuberculosis and six reporting on protection against miliary TB or tuberculous meningitis, showed no evidence that efficacy of BCG was associated with vaccination strains[24]. Future trials of candidate vaccines need to investigate the efficacy of the new vaccine against tuberculosis infection, and early and also late progression to active disease.

The age of the patient was not a significant risk factor of disseminated tuberculosis. This finding may be affected by the higher prevalence of older pediatric tuberculosis patients in this study. Marais et al. concluded that even though children with the age under 2 years old were at risk of developing miliary TB, most children suffering from tuberculosis in endemic areas were older, so there is a higher chance of children over 2 years of age for suffering from miliary tuberculosis[9]. Kruijshaar and Abubakar, from their study in UK, discovered that more cases of miliary tuberculosis occurred in older children, which indicated the possibility of reactivation of latent disease[25]. Thus, results support that those severe forms of tuberculosis are able to appear at any age.

Human immunodeficiency virus infection was not a significant risk factor for disseminated tuberculosis. This finding differs from a previous study, which stated that young age and HIV infection were significant risk factors of disseminated TB[9,26]. The discrepancy was caused by different research population. The function of immunity system, such as macrophage and T cell, was changed in HIV patients[27]. The patients with a low level of CD4 T cells could tolerate the existence of MTB, so this increases the risk of developing extrapulmonary tuberculosis.

The limitation of the study is the use of secondary data from medical records, that may create information bias.

Conclusion

The nutritional status and the history of tuberculosis contact were significant factors associated with disseminated tuberculosis in children. ■

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