

Pulmonary tuberculosis in childhood nephrotic syndrome (A cross sectional study)

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ABSTRACT Childhood tuberculosis persists as an important global health problem. Tuberculosis is one of the commonest important complications in children with nephrotic syndrome. Tuberculosis may interfere with the response to steroid therapy and is still being the commonest morbidity cause in children with nephrotic syndrome. To find out the prevalence, clinical features, and the impact of tuberculosis in children with nephrotic syndrome, a cross sectional study was conducted on 100 nephrotic children consisted of 63 males and 37 females at the Cipto Mangunkusumo Hospital from April 1st to October 30th, 1999. Pulmonary tuberculosis was detected on 15 cases (95% CI : 8% - 22%) , consisted of 8 boys and 7 girls. Most of them aged 10 – 16 years old (66,6%) and 86,7% were undernourished. The combination of clinical judgement, chest X-ray and Mantoux test were helpful in establishing the diagnosis. The majority of tuberculosis cases (80%) were detected on frequent relapsers and steroid dependent groups of the nephrotic syndrome. A significant correlation were noted in tuberculosis with undernutrition and unfavorable response to steroid (frequent relapser and steroid dependent cases). [Paediatr Indones 2001; 41:106-110]

Keywords: pulmonary tuberculosis, nephrotic syndrome, children

INFECTION REMAINS AN IMPORTANT COMPLICATION IN children with nephrotic syndrome (NS), especially in the developing countries, such as Indonesia. Besides being the commonest mortality cause, infection results in significant morbidity and may also be responsible for a poor response to steroid therapy or induces relapse in child who has already attained remission.^{1,2} One of the commonest infections is tuberculosis (TB).³

Childhood tuberculosis persists as an important global health problem. In 1989, it was reported that approximately 1,300,000 cases and 450,000 deaths as a result of tuberculosis occurred annually worldwide in children under 15 years old.⁴ Until now, the prevalence of tuberculosis in children with NS in Indone-

sia have not reported yet. The purpose of our study was to find out the prevalence, clinical features, and the impact of tuberculosis in children with nephrotic syndrome.

Methods

This cross sectional study was conducted on children with nephrotic syndrome admitted at the division of Nephrology, Department of Child Health Faculty of Medicine, University of Indonesia, Cipto Mangunkusumo Hospital, Jakarta. All cases aged between 1 – 16 years old which was diagnosed and followed up at least one year (i.e. those cases admitted before April 1, 1999) were enrolled to this study. Estimation of the sample size was calculated using a single sample for estimating means.⁵ All cases were diagnosed and treated according to the protocol proposed by the International Study group of Kidney Diseases in Children.⁶ Based on their response to steroid therapy, they were classified into steroid

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responsive with total remission, infrequent relapsers, frequent relapsers, steroid dependent and steroid resistant.⁷

To establish the diagnosis of pulmonary tuberculosis, all cases were investigated against peripheral blood features including hemoglobin content, white blood cell and differential count, erythrocyte sedimentation rate, Mantoux test, chest X-ray examination and culture of *Mycobacterium of tuberculosis* from gastric lavage or sputum.

The presence of two or more of the following criteria were considered as tuberculosis disease : (1) history of prolonged fever (>3 weeks), persistent cough (>2 weeks), close household contact with an adult with pulmonary TB, anorexia and recent weight loss or failure to gain adequate in weight, (2) a positive Mantoux test (>10 mm induration at 72 hours), (3) a positive chest X ray (mediastinal lymphadenopathy, unequivocal hilar or paratracheal adenopathy and / or non resolving pneumonia), (4) a positive sputum culture for *Mycobacterium of tuberculosis*.⁸ If positive Mantoux test is the only sign that occurred, the patient is diagnosed as tuberculosis infection.⁹

Close household contacts were defined as adults with recently active (within the last 12 months) pulmonary TB who lived and slept in the same house.⁸ Weight loss was defined as the loss of >10% of previous maximum weight.⁸ Failure to gain weight was defined as no weight gain for a period of 2 months if the child had been weighed on at least two occasions during this period.⁸ Tuberculin skin testing was done with 5 tuberculin units of purified protein derivate.¹⁰ Parents were requested to return for reading after 48 – 72 hours. Data were analyzed using SPSS for MS windows release 6.0 ; 95% confidence intervals was supplied. The level of significance (p) was <0.05.

Results

Subject characteristics

During the period of April 1st – October 30th. 1999, 109 children were registered but only 100 children consisted of 63 (63%) males and 37 (37%) females were eligible for evaluation. For the purpose of further analysis, cases were divided into three groups i.e., nephrotic cases associated with TB disease, TB infection and cases without TB.

TB was found in 15 (15%) cases (95% CI : 8% -

22%), consisted of 8 boys and 7 girls as shown in table 1. TB infection was found in 8 (8%) cases and NS without TB was found in 77 (77%) cases. In NS with TB disease, ten cases aged between 10 – 16 years old, and undernourished were found in 13 cases. Positive BCG scar was found in only 5 cases while the remaining 10 cases were absent. Positive Mantoux test were noted in 14 cases while in one case with miliary TB, Mantoux test was negative. Moreover, 8 cases showed positive Mantoux test without any other signs and symptoms which related to TB. These cases were diagnosed as TB infection.

Table 2 shows that all cases showed the increment of erythrocyte sedimentation rate (ESR) while leucocyte counts were all in normal range and there are no statistical difference among these three groups of study. Leucocyte differential counts were also in normal range. Mycobacterial cultures were only done in 9 cases while two cases showed a positive *Mycobacterium of tuberculosis*.

Response to steroid treatment and the presence of TB disease

The association between the response to steroid treatment and the presence of TB disease was shown in Table 3. Frequent relapsers and steroid dependent nephrotic syndrome were found in 12 out of 15 TB cases (80%) and only 37.6% among other subgroups. A significant association was noted between the unfavorable response to steroid with the presence of tuberculosis.

The association between TB disease and nutritional status

The association between TB disease and nutritional status was listed in Table 4. The table showed statistically significant association, meaning that undernourished nephrotic children were prone to suffer from TB disease when compared to well-nourished ones.

Discussion

The child with nephrotic syndrome represent an immunocompromised host. both as a result of the nephrotic state per se and as a consequence of immunosuppressive therapy.¹¹ This condition may

TABLE 1. CHARACTERISTICS OF STUDY SUBJECTS

	TB disease		NS with TB infection		Non TB	
	n	%	n	%	n	%
Sex						
male	8		8	3	3	52
female	7		7	5	5	25
Age (years)						
1 - < 5	1		1	1	1	24
5 - < 10	4		4	1	1	22
10 - 16	10		10	6	6	31
Nutritional status						
undernourished	13		13	2	2	40
wellnourished	2		2	5	5	33
obesity	0		0	1	1	4
BCG scar						
positive	5		5	3	3	25
negative	10		10	5	5	52
Close contact						
positive	9		9	0	0	0
negative	6		6	8	8	77
Mantoux test						
positive	14		14	8	8	0
negative	1		1	0	0	77
Chest X-ray						
normal	1		8	8	77	77
hilar adenopathy	13		13	0	0	0
miliary TB	1		1	0	0	0
Clinical features						
prolonged fever	5		5	0	0	1
persistent cough	2		2	1	1	4
weight loss	2		2	0	0	2
anorexia	2		2	1	1	2
Steroid response						
frequent relapsers & steroid dependent	12		12	7	7	25
infrequent relapsers & total remissions	3		3	1	1	52
Cumulative steroid dose (mg / kg BW)						
< 100	3		3	1	1	13
100 - 200	1		1	3	3	19
200 - 300	2		2	0	0	16
300 - 400	5		5	1	1	14

TABLE 2. SOME LABORATORY FINDINGS IN 100 PATIENTS WITH NEPHROTIC SYNDROME

		NS + TB	NS+TB infection	NS without TB
		(n = 15)	(n = 8)	(n = 77)
		Mean (SD)	Mean (SD)	Mean (SD)
ESR (/hour)		45,5 (20,9)	33,6 (14,3)	31,3 (16,5)
WBC	(/µl)	8593 (3330)	6775 (2626)	7510 (2551)
Segments	(%)	54,1(19,8)	65,1 (19,9)	59,1 (14,8)
Lymphocytes	(%)	41,0 (19,2)	29,6 (20,5)	35,7 (14,1)

TABLE 3. ASSOCIATION BETWEEN THE RESPONSE TO STEROID TREATMENT AND THE PRESENCE OF TB DISEASE

Steroid response	NS+TB	NS+TB infection or without TB	Total
FR & SD	12	32	44
IR & TR	3	53	56
Total	15	85	100

$\chi^2=9,3$ df = 1 p < 0,0023. OR = 6.63 (95% CI : 1,56 – 32,26)

NS = nephrotic syndrome, TB = tuberculosis, FR = frequent relapser, SD = steroid dependent; IR = infrequent relapser, TR = total remission.

TABLE 4. ASSOCIATION AMONG TB DISEASE AND NUTRITIONAL STATUS

Nutritional status	NS+TB	NS+TB infection or without TB	Total
Undernourished	13	42	55
Well-nourished	2	43	45
Total	15	85	100

$\chi^2=7.15$; df = 1; p = 0.007. OR = 6.65 (95% CI : 1.30 –45.6)

contributed to the reactivation of latent infection leading to the occurrence of the disease such as pulmonary tuberculosis. This study revealed an overall prevalence of 15% of TB disease among 100 children with nephrotic syndrome. Most of them aged 10 – 16 years old (66.6%). This finding was in accordance to the statement from literature that children under five years and teenagers were at risk of tuberculosis infection.¹² The majority of our TB cases (86.7%) were undernourished. It might be due to tuberculosis infection and its primary disease (nephrotic syndrome). On the other hand malnutrition itself could play a role as a predisposing factor leading to TB infection.¹³

The diagnosis of tuberculosis in adult cases are mostly based on bacteriological examination while in the diagnosis in children is usually epidemiological and uses indirect parameters. A high index of suspicion is required, especially in the developing country like Indonesia where the prevalence of TB infection among the population is still high. On the other hand,

lack of objective criteria can lead to overdiagnosis and overtreatment.¹⁴ To overcome this problem, WHO criteria to assist diagnosis of tuberculosis in children was helpful.⁸ Children with pulmonary TB manifested clinically with wide variety of signs and symptoms. Children may either be asymptomatic or, at other extreme conditions present with severe weight loss and wasting in cases with disseminated TB.¹⁵

The diagnosis of pulmonary tuberculosis in this study was based on clinical findings, Mantoux test and chest X-ray. Mantoux test were positive in 14 out of 15 tuberculosis cases and were all negative in non TB cases. Abnormal chest X-ray were seen in 14 TB cases (13 cases with hilar adenopathy and one with miliary TB) while in non TB cases, chest X-rays were all normal. Eight cases were diagnosed as TB infection (cases with positive Mantoux test, no clinical signs related to TB diseases and normal chest X-ray). All of these cases were covered with prophylactic treatment against tuberculosis based on the assumption that they were potentially progress to TB disease.

In our study the history of close contact with adult tuberculosis were noted in 9 cases of TB disease while in other cases, no histories of close contact were detected. Children who contact with an adult case of TB are exposed to a considerable risk of infection and disease, especially in those cases with immunocompromised condition, such as nephrotic syndrome. Positive history of close contact was considered as an important criteria in clinical judgement of TB disease.

The increment of ESR in all cases in this study could not be used as parameter to support the diagnosis of tuberculosis since nephrotic syndrome per se usually shows the same result especially in those cases with full-blown or in relapse condition. This study showed a significantly higher prevalence of TB disease among patients who received frequent course of steroids, i.e. frequent relapse and steroid dependent nephrotic syndrome in compare to those other cases with infrequent relapse and in those cases in remission state. The impaired host defense mechanism together with the immunosuppressive therapy may have contributed to the reactivation of latent infections leading to the occurrence of disease. Other factors, such as general protein deficiency, low immunoglobulin concentration, decreased level of serum factor B, a functional disorder of serum complement and mal-

nutrition might play a role as a contributing factor to those reactivation.¹⁶ Mycobacterial cultures done in nine cases revealed that only two cases showed positive *Mycobacterium of tuberculosis*. Both of these cases were from the group of nephrotic cases associated with TB disease. This result was not surprising since the positive rate of mycobacterial culture in childhood tuberculosis was usually low. Clinical judgement, Mantoux test and chest X-ray are more important for the diagnosis rather than bacteriological examination. Another interesting aspect is the impact of tuberculosis on the course of the nephrotic syndrome. It has been previously reported that the occurrence of tuberculosis associated with nephrotic syndrome may interfere with the response to steroid therapy and may also have detrimental effect on renal function.¹⁷ This is beyond the scope of this study and further study is needed to evaluate this aspect.

We concluded that the prevalence of TB disease in children with nephrotic syndrome was 15%, two thirds of them aged 10 – 16 years and 86.7% were undernourished. Chest X-ray and Mantoux test combined with high index of suspicion are most helpful in establishing the diagnosis of tuberculosis. Significant association were noted in tuberculosis with undernutrition and unfavorable response to steroid namely frequent relapser and steroid dependent cases.

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