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Original Article

Trombocytosis in childhood relapsing nephrotic syndrome

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Abstract

Background Thrombosis is a serious complication of nephrotic syndrome (NS). Long-term steroid treatment may induce thrombocytosis in relapsing NS that may predispose to thrombosis. Most children with idiopathic NS respond to steroids; however, a substantial number of patients will relapse frequently and require repeated high dose steroid therapy, thus increase the risk of thrombocytosis.

Objective To compare the occurrence of thrombocytosis between children with frequent relapses of NS (FRNS) and those with infrequent relapses (IFRNS).

Methods We reviewed the medical records of children aged 1-14 years diagnosed as FRNS and IFRNS at the Department of Child Health, Hasan Sadikin General Hospital Bandung from 2000-2005. We excluded children with iron deficiency anemia, hemolytic anemia, acute haemorrhage, malignancy, and those who received cyclophosphamide.

Results There were 33 children (26 males, 7 females) with FRNS and 33 children (27 males, 6 females) with IFRNS. The mean platelet level of children with FRNS (517,909±165,670/ml) was higher than that of children with IFRNS (416,272±145,763/ml) (P=0.005). The occurrence of thrombocytosis in children with FRNS (18) was higher than that of children with IFRNS (7) (P=0.005).

Conclusion This study shows that thrombocytosis is more common in FRNS than IFRNS, therefore we should take more precaution to the occurrence of thrombosis in FRNS. **[Paediatr Indones 2007;47:100-103]**.

Keywords: *thrombocytosis, steroid, frequent relapses nephrotic syndrome, infrequent relapses nephrotic syndrome*

Thrombosis, a serious complication in children with nephrotic syndrome (NS), occurs in 28-42% patients, 8.1% among them have recurrent episodes of thrombosis.[1,2] The risk factors of thrombosis are increased thrombocyte aggregation, increased coagulation factors, hypovolemia, corticosteroid treatment, and increased platelet count (thrombocytosis).[3]

Thrombocytosis occurs in 57.5% of NS patients.[4] In general, the risk factors for thrombocytosis include myeloproliferative disorder, malignancy, iron deficiency anemia, hemolytic anemia, chronic or acute inflammation, acute haemorrhage, surgery, cyclophosphamide, longterm steroid treatment, and nephrotic syndrome.[5]

Most children with idiopatic NS respond to initial steroid treatment; however approximately 60-80% of cases will undergo relapse and half of them have frequent relapses or steroid dependence,[3,6-8] needeing high dose steroid administration to achieve remission. During the relapse episode, NS patients tend to have increased platelet count compared to that in the initial attack. Frequent relapse nephrotic syndrome

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(FRNS) patients may need long-term steroid therapy, i.e., 6-12 months. which may increase the risk of thrombocytosis.

Previous studies have never evaluated the influence of number of relapses and duration of steroid therapy with on occurrence of thrombocytosis. This study aimed to compare the occurrence of trombocytosis between childhood nephrotic syndrom with frequent relapses those without frequent relapses.

Methods

We reviewed medical records of children aged 1-14 years diagnosed as FRNS (frequent relapse nephrotic syndrome) and IFRNS (infrequent relapse nephrotic syndrome) at the Department of Child Health, Hasan Sadikin Hospital, Bandung during year 2000-2005. FRNS was defined as the occurrence of two or more relapses within the first six months after initial response, or four or more relapses in any 12 months period. IFRNS was defined as less than two relapses within the first six months period after initial response, or less than four relapses within any subsequent 12-month period.[3] Thrombocytosis was defined as platelet count above normal value for age. We classified thrombocytosis as of mild, moderate, severe, and extreme levels according to the platelet level of 500,000-700,000/µl; 700,000-900,000/µl; 900,000-1,000,000/µl; and >1,000,000/µl, respectively.[9]

Table 1. General characteristic of study subject

Variable	IFRNS (n=33)	FRNS (n=33)
Age (mo)		
Mean	88.33	90.24
SD	38.437	37.395
Median	84.00	84.00
Minimum	24	22
Maximum	156	156
Sex		
Boys	27	26
Girls	6	7

Note: SD = standard deviation.

Results

There were 123 patients with childhood nephrotic syndrome. Fifty-one patients with anemia and six patients who received cyclophosphamide were excluded. The remaining sixty-six children available for review consisted of 33 with FRNS and 33 with IFRNS. **Table 1** shows the characteristics of subjects in both groups. There was no difference in median age and sex distribution between the two groups.

Table 2 shows that platelet level in FRNS group (517,909±165,670/µl) was higher than that of IFRNS group (416,272±145,763/µl) (P=0.005).

The occurrence of thrombocytosis in FRNS group (18) was higher than that of IFRNS groups (7) (P=0.005). The severity of thrombocytosis in both groups are listed in **Table 3**.

Discussion

Thrombosis is a potential complication in childhood that can be predisposed by increased platelet level (thrombocytosis). Our study demonstrated that the

Table 3. The severity of thrombocytosis in IFRNS and FRNS groups

Characteristics	IFRNS (n = 33)	FRNS (n = 33)	Significancy
No thrombocytosis	26	15	X^2=7.791
Thrombocytosis	7	18	P=0.005

Table 2. Platelet levels in IFRNS and FRNS groups

Platelet count (/mm^3)	IFRNS (n=33)	FRNS (n=33)	Significancy
Mean	416272.73	517909.09	t=2.646
SD	14576.35	165670.30	P=0.005
Median	430,000	506,000	CI 95% 24.898;178.375
Range	536,000	777,000	
Minimum	154,000	200,000	
Maximum	690,000	977,000	

Note: t=t test, CI=Confident interval, SD = standard deviation.

platelet level of FRNS patients was higher than that of IFRNS patients. Increased platelet level in our study was consistent with the previous studies. Wasilewska *et al*[10] published similar findings. After two weeks of steroid treatment, they found that the platelet count in NS patients was still higher than that of the control group. However, they did not explain the relationship between platelet level and repeated steroid administration in NS patients. Anand *et al*[4] studied hemostatic profiles in NS patients and revealed that thrombocytosis occurred in 57.5% cases. Our study shows that thrombocytosis was more commonly occur in FRNS patients compared to that of IFRNS patients. The higher degree of thrombocytosis would further increase the risk of thrombosis in FRNS patients.

The pathogenesis of thrombocytosis in patients with NS remains unclear. Grimbert *et al*[11] detected high NF-kB activation in $CD4^+$ T cells during relapse. NF-kB is involved in various extents of transcriptional activation of a large set of genes including IL-1, IL-6, IL-2, IL-8, TNF-α, and LT-α which are mostly increased in NS relapse.[11] IL-6 stimulates an increase of platelet production and eventually will trigger subsequent thrombocytosis.[12,13] Other factor considered to involve in the occurence of thrombocytosis is steroid treatment. To achieve remission, FRNS patients require long-term steroid treatment of about 6-12 months, whereas IFRNS patients only need steroid treatment for less than 12 weeks. In patients with short-term steroid treatment, the transcription of those cytokines regulated by NF-kB (IL-1, IL-2, and IL-6) rapidly decrease. Long-term treatment showed different results. T cells remains in the infiltrate, although transcription of IFN-α by T cells is nearly ablated. The inhibition of NF-kB independent cytokines by long-term steroid treatment suggests that additional mechanisms, perhaps inhibition of other transcription factors are involved. In contrast, macrophages continue to produce cytokines in spite of the ongoing steroid therapy.[14,15] This can explain the increase of platelet level in patients receiving long-term steroid treatment.

Many factors such as hemolytic anemia and iron deficiency anemia can cause thrombocytosis, therefore patients with anemia were excluded from this study. Other factor that should be considered to predispose thrombocytosis is infection. The presence of infection in NS patients receiving steroid is not merely suspected from high level of leukocyte count but we should also consider the differential count of leukocyte, peripheral blood morphology, and PCR examination. Those factors should be considered in evaluating thrombocytosis in patients with NS relapses.

In conclusion, thrombocytosis is more commonly found in FRNS than in IFRNS pediatric patients, therefore we should take more precaution to the occurence of thrombosis in patients with FRNS.

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