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 trombocytosis 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 trombocytosis 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 trombocytosis in children with FRNS (18) was higher than that of children with IFRNS (7) (P=0.005).

**Conclusion** This study shows that trombocytosis 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:** trombocytosis, steroid, frequent relapses nephrotic syndrome, infrequent relapses nephrotic syndrome
(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 occurrence of thrombocytosis. This study aimed to compare the occurrence of thrombocytosis between childhood nephrotic syndrome 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. 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.

**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
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\textsuperscript{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\textsuperscript{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\textsuperscript{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-\(\alpha\), and LT-\(\alpha\) which are mostly increased in NS relapse.\textsuperscript{11} IL-6 stimulates an increase of platelet production and eventually will trigger subsequent thrombocytosis.\textsuperscript{12,13} Other factor considered to involve in the occurrence 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-\(\alpha\) 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.\textsuperscript{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.

References

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