Vol 24 No. 3 July 2018

p-ISSN 0854-4263
e-ISSN 4277-4685

INDONESIAN JOURNAL OF CLINICAL PATHOLOGY AND MEDICAL LABORATORY

Majalah Patologi Klinik Indonesia dan Laboratorium Medik

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RESEARCH

INDONESIAN JOURNAL OF
CLINICAL PATHOLOGY AND MEDICAL LABORATORY
Majalah Patologi Klinik Indonesia dan Laboratorium Medik

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p-ISSN 0854-4263 | e-ISSN 2477-4685
Available at www.indonesianjournalofclinicalpathology.org

ACTIVATED PARTIAL THROMBOPLASTIN TIME AND FIBRINOGEN IN PEDIATRIC NEPHROTIC SYNDROME DURING RELAPSE AND REMISSION

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ABSTRACT

Nephrotic Syndrome (NS) is a complicated kidney disease disorder, one of the most important complications is thromboembolism which can affect the circulation, either arterial or venous in both pediatric and adult patients. Patients at risk of thromboembolism should have an angiography examination for diagnosis. There have been several studies conducted on patients with a nephrotic syndrome showing the risk of thromboembolism. This study included twelve patient of pediatric nephrotic syndrome consisting of males and females. The patient experiences a period of relapse and became a remission. Patients participating in the study were 3 to 17 years old. There were significant differences in fibrinogen in which the fibrinogen content of NS patients in children at relapse was higher compared with the time of remission (390.08 ± 164.87 vs. 273.17 ± 150.56; p=0.042). There was no significant difference in Activated Partial Thromboplastin Time (APTT) results in SN patients in relapse compared to remission (34.17 ± 5.65 vs. 30.08 ± 8.49; p=0.236). The high levels of fibrinogen in the relapse period indicate the presence of hypercoagulable state, along with other examinations such as high cholesterol and low albumin. In this study, there was no significant difference in APTT among SN patients during relapse compared with remission while in the fibrinogen examination a significant difference was found. Therefore, fibrinogen examination is important to be analyzed in order to avoid SN complications.

Key word: Nephrotic syndrome, activated partial thromboplastin time, fibrinogen

INTRODUCTION

Nephrotic Syndrome (NS) is a disorder of the kidney that has many complications. A first study by Addis in 1948 stated that thromboembolic complications were one of the most critical cases in nephrotic syndrome. Ozkaya *et al.* said that about 5% of patients with nephrotic syndrome had the thromboembolic disease. Kerlin *et al.,* reported that the incidence of idiopathic nephrotic syndrome was 2 out of 7 from 100,000 children and had a prevalence of about 16 cases in 100,000 children per year.[1,2]

Mahmodi *et al.* mentioned that thrombosis was the most common cause of death in patients with nephrotic syndrome.[3] Complications of venous thrombosis are more common than arteries. Thrombosis is multifactorial, and may be suspected there is hypercoagulability due to changes in the levels of various factors involved in coagulation and fibrinolytic systems, changes in platelet function, blood vessel stasis, hemoconcentration and possibly due to the use of steroids and diuretics.

In the Yalcinkaya study *et al.*, there was no difference in Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT) in pediatric patients with nephrotic syndrome and during relapse compared with healthy children.[4] Meanwhile, based on Ueda et al. APTT elongation occurred in relapse of nephrotic syndrome patients compared with patients with remission nephrotic syndrome, while PT in relapse and remission patients had no difference. Thromboembolism is one of the complications of nephrotic syndrome that must be observed. The risk of thromboembolism can be judged by the high risk of hypercoagulability in hemostasis examination.[5]

This study aimed to find out the picture of APTT and fibrinogen differences in relapsing SN children compared to remission so as to raise awareness about complications of one complication in nephrotic syndrome is thromboembolism.

METHODS

The study was conducted at the Adam Malik General Hospital Medan. The inclusion criteria in this study were pediatric patients diagnosed early with SN diagnosis of children based on NS criteria (proteinuria, hypoalbuminemia, edema, and hypercholesterolemia) and experienced a relapse period followed by remission. The age of patients included in this study was ages 3-17 years.

The exclusion criteria in this study were pediatric patients who had previously received anticoagulant/antiplatelet, pediatric patients with a prior history of blood clotting disorders e.g. hemophilia, and pediatric patients with complications such as diabetes mellitus.

All study patients followed the procedures of research such as informed consent and ethical clearance from the

Research Ethics Committee of the Medical Field Faculty of Medicine, University of North Sumatra from December 2016 to March 2017.

Laboratory examinations were performed in the Clinical Pathology Laboratory of Adam Malik General Hospital Medan. Semiautomatic Cobas U411 measured the examination of proteinuria. Serum albumin and cholesterol examination were examined using the Architect ci4100. Investigation of APTT and Fibrinogen using Coatron A6 instrument.

Statistical analysis was performed using the SPSS-based computer program. The difference APTT in SN children during relapse and remission using paired T-test, while Fibrinogen used the Wilcoxon test.

RESULT AND DISCUSSION

During the study period, researchers observed 30 patients with NS. Eighteen of them did not return for control (loss of follow-up) so at the end of the study only 12 patients could be observed in this study. The results of the research variables are shown in Table 1. From Table 2 the difference in the examination of NS patients in relapse compared to remission can be seen.

Table 1. Results of research variables

Variable	sample (n = 12)
Sex	
Boy	10 (83.33%)
Girl	2 (16.67%)
Age (years)	9.58 ± 4.42
Heigh (cm)	129.0 ± 22.29
Systole (mmHg)	105.0 ± 12.43
Diastole (mmHg)	71.67 ± 8.34

Table 2. Differences in SN patient patient examination during relapse and remission

Varible	Relapse	Remission	P
Weight**	34.17 ± 5.65	30.08 ± 8.49	0.236
Cholesterol*	413.75 ± 201.33	271.42 ± 136.45	0.027
Albumin**	2.22 ± 1.14	3.57 ± 0.85	0.001
Fibrinogen**	390.08 ± 164.87	273.17 ± 150.56	0.042
APTT*	34.17 ± 5.65	30.08 ± 8.49	0.236

*Paired T-test
**Wilcoxon test

After statistical analysis using Spearman correlation test, there was no significant relationship between APTT and albumin (r - 0.196; p = 180). There was a significant negative association between fibrinogen and albumin (r - 0.460; p = 0.012) (Table 3).

Table 3. The relationship between parameters with albumin

Variable	Albumin
APTT	r – 0.196
	p=180
Fibrinogen	r – 0.460
	p=0.012

There was a significant negative correlation between fibrinogen and albumin, the lower the albumin the more fibrinogen increased (Figure 1). There was no correlation between APTT and albumin in this study (Figure 2).

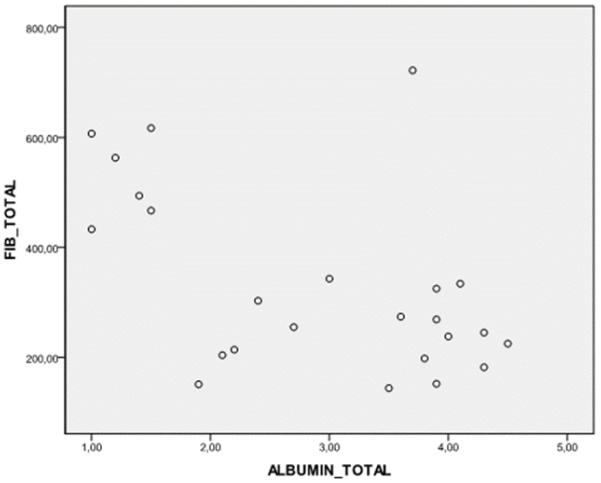

Figure 1. Scatterplot relationship of fibrinogen and albumin

Thromboembolic complications are less commonly found in pediatric NS (1.8 to 5%) than in adult NS (40%).6 Thromboembolic complications are associated with high fibrinogen, high cholesterol, and plasma protein content.[6,7]

In this study, there were 12 NS patients with more males than females (83.33% vs. 16.67%). Similarly, in Mittal et al., out of 29 patients of SN patients, 23 males and 6 females patients (79.3% vs. 20.7%) were found.[8]

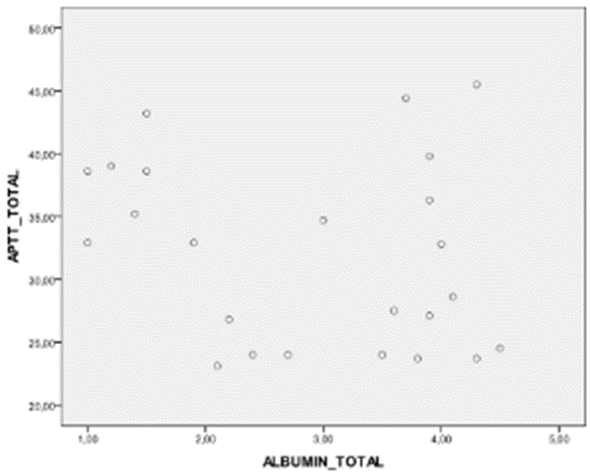

Figure 2. Scatterplot relationship of APTT and albumin

Changes also occured in the fibrinolysis system in patients with NS. Changes in concentrations of some components of both fibrinolysis and antithrombin system may occur. The reduced level of plasminogen activator (92kD) and activator plasminogen tissue (tPA: 72kD) was mentioned to be associated with low albumin and the magnitude of proteinuria. While the increase in α2-antiplasmin and α2-macroglobulin (725kD) was reported to rise, as α2-antiplasmin is an inhibitor of fibrinolysis.[2,9]

An increase in plasma fibrinogen is due to increased hepatic synthesis in line with leakage in the urine. The description of hyperfibrinogenemia in SN patients may increase platelet aggregation.[10]

Based on in vitro studies, patients with NS showed hyperaggregation.[11-13] Many factors can cause hyperaggregation and are associated with low albumin hypercholesterolemia and hyperfibrinogenemia.[14]

In this study there were significant differences in fibrinogen in NS patients during relapse and remission (390.08 ± 164.87 vs. 273.17 ± 150.56; p = 0.042). There was also a significant relationship between fibrinogen and albumin levels (r - 0.460; p = 0.012). Rani also found significant differences in fibrinogen of pediatric SN patients at relapse and remission (572.6 ± 94.78 vs 307 ± 65.00; p <0.001).[15]

The hypercoagulable state in SN is associated with changes in blood clotting cofactors, changes in fibrinogen concentration, changes in fibrinolysis system and coagulation inhibitor factor. Some studies show that the hypercoagulable state is characterized by changes in the concentration and activity of clotting factors FIX, FXI, and XII decrease with urine leakage due to their small molecular size.[9] The FII, FV, FVIII, FVIII, FX, and FXIII levels are described as increasing, along with the increase in cofactors of blood coagulation (FV and FVIII) as a result of increased hepatic synthesis due to hypoalbuminemia.[9,16] Such changes are predicted to increase the coagulation cascade that may produce a prothrombotic state.[8,9]

In this study, there was no significant difference in APTT in NS patients in relapse compared to remission (34.17 ± 5.65 vs. 30.08 ± 8.49; p = 0.236). Farid *et al*, found no significant difference in APTT of NS patients relapsing children compared to remission (34.93 ± 1.67 vs. 35.00 ± 1.46, p = 0.91). [17]

Mittal *et al.*, found a significant difference in NS patients in relapse compared to remission (36.21 ± 2.2 vs 39.3 ± 4.5, p <0.05). Despite significant APTT elongation, this may not be clinically significant, as there was no evidence of bleeding in these patients.

Lijfering et al. said that the pathophysiology of thrombogenesis in nephrotic syndrome is highly multifactorial.[18] The first thing to consider is the patient's genetic background, which may not be related to kidney disease but affects the likelihood of thromboembolism. These genetic disorders include deficiency of congenital antithrombin or factor V Leiden.[2] These factors are combined with environmental thromboembolic risk factors, for example, inflammation, drugs.[2,5,9]

The pathophysiology of concern for NS is the study of diseases associated with hemostasis disorders. Because primary NS of the glomerular damage results in leakage of high molecular weight proteins, many important hemostasis proteins are also excreted.[2,9] Also, the loss of essential coagulation regulatory proteins includes antithrombin III and protein S.[2,8,9,18]

The hypercoagulable state in NS patients is associated with a shortening of APTT values at relapse compared to remission, in which leakage of coagulation factors occurs during the active period. As a result, during the active nefrotic proteinuria, there is a shift in the hemostatic equilibrium to the protrombotic.[19] In this study, there was a shortening of APTT value, but not significant enough. This was due to several things: the selected sample had not experienced thromboembolic complications so it can be understood that the researchers did not get a hypercoagulable state. Also, a small sample size will affect the aPTT and albumin values compared with controls (thromboembolism has occurred).

CONCLUSION AND SUGGESTION

No significant difference in APTT was found between NS patients in relapse compared with remission. However, there was a significant difference in fibrinogen between SN patients in relapse versus remission.

Based on the results of this study it can be suggested that the examination of fibrinogen should be a mandatory examination for NS patients in children so that the incidence of SN complications may decrease.

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