

## EVALUATION OF HEMOSTATIC FACTORS IN CHILDREN WITH NEPHROTIC SYNDROME

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### ABSTRACT

**Objective:** Thromboembolism (TE) is one of the serious complications of nephrotic syndrome (NS). The aim of this study was to evaluate the haemostatic factors in children with nephrotic syndrome.

**Methodology:** Plasma level of protein C, Protein S, fibrinogen and antithrombin III (AT III) were evaluated in thirty nephrotic children at relapse and remission period and the results were compared with those of 30 healthy children.

**Results:** The mean age of patients was 5.38±3.07 years. Plasma level of protein S and AT III during relapse were significantly lower than their level in remission period and in control group. The mean fibrinogen level during relapse was significantly higher than its level in remission period and in control group. There was no significant difference in protein C levels at relapse with remission period and with control group. Serum albumin levels during relapse were positively correlated with AT III levels. There was no correlation between urinary protein excretion and the haemostatic factors.

**Conclusions:** Despite reduced levels of AT III and protein S and increased levels of fibrinogen, none of our patients revealed thromboembolism. It seems that coexistence of several factors is necessary to induce TE.

**KEY WORDS:** Nephrotic Syndrome, Hypercoagulability, Thromboembolism.

Pak J Med Sci April - June 2008 (Part-II) Vol. 24 No. 3 356-359

### How to cite this article:

Mortazavi F, Majidi J. Evaluation of hemostatic factors in children with nephrotic syndrome. Pak J Med Sci 2008;24(3):356-9.

### INTRODUCTION

The incidence of thromboembolism (TE) in children with nephrotic syndrome (NS) is 1.8-5%.<sup>1</sup> Although most thromboembolic complications have been reported in adults with membranous nephropathy, the real frequency

of TE among children with NS is difficult to determine because many of them are asymptomatic and subclinical. Hoyer et al evaluated 26 nephrotic children in remission period with pulmonary ventilation/perfusion test and found that 28% had evidence of pulmonary embolism.<sup>2</sup> These findings reveal the high frequency of asymptomatic TE in children. Both arterial and venous thromboses have been reported in NS. The most common sites are deep leg veins followed by inferior vena cava.<sup>3</sup> Primary arterial thrombosis is less common, but it has been reported in the pulmonary artery as a cause of sudden death,<sup>4</sup> in the abdominal aorta<sup>5</sup> and even coronary arteries.<sup>6</sup> Depending on the location of thrombosis, various clinical presentations have been reported such as hemiparesis, seizure and stroke due to cerebral

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\* Received for Publication: January 11, 2008

\* Accepted: May 2, 2008

sinovenous thrombosis,<sup>7-9</sup> chylothorax due to superior vena cava thrombosis,<sup>10</sup> budd chiari syndrome due to inferior vena cava thrombosis<sup>11</sup> and short bowel syndrome due to mesenteric thrombosis.<sup>12</sup> Asymptomatic intracardiac thrombosis also has been reported in literature as a rare presentation of TE.<sup>13,14</sup>

The hypercoagulability state in NS has been attributed to low serum concentrations of plasminogen, antithrombin III, protein C and protein S due to urinary loss and elevated serum levels of some coagulative factors such as macroglobulins, fibrinogen, thromboplastin, factors II, V, VII, VIII and X.<sup>4,7,13</sup> According to relatively high incidence of TE in NS and its potentially hazardous nature, identification of the risk factors leading to TE is crucial. The aim of this study was to evaluate the haemostatic factors in nephrotic children at relapse and remission and compare the results with healthy control group.

### METHODOLOGY

Thirty patients with primary NS, who were admitted in Tabriz Children's Hospital, from 2005-2007, participated in this case-control study. The control group consisted of 30 healthy children who were age and sex matched with study group. NS was defined as massive proteinuria (urine protein  $>1\text{gr}/\text{m}^2/\text{day}$ ), hypoalbuminemia (serum albumin  $<2.5\text{g}/\text{dl}$ ), hypercholesterolemia (serum cholesterol  $>250\text{mg}/\text{dl}$ ) and edema. Patients with signs of secondary NS and those who had gross hematuria, persistent hypertension, renal insufficiency, and hypocomplementemia were not included. Nephrotic patients between the ages of 1-11 years who did not fit into exclusion criteria were assumed as minimal change NS, and entered the study group. In all patients in study group protein C, protein S, antithrombin III (AT III) and fibrinogen were measured at relapse period and again in remission period after the termination of CS therapy. These parameters were also measured in control group. Treatment consisted of oral prednisolone  $60\text{mg}/\text{m}^2/\text{day}$  in three divided doses for 4-6 weeks, followed by  $40\text{mg}/\text{m}^2$  as alternate day for four weeks. Then the CS was tapered

over four weeks and stopped. Patients who had proteinuria more than  $4\text{mg}/\text{m}^2/\text{hr}$  after 6 weeks of CS therapy were considered as steroid resistant and excluded from the study. Heparinized blood samples from study group before and after treatment and from control group were processed in same laboratory. Plasma level of protein C, Protein S and AT III were measured by ELIZA. Fibrinogen level was measured by hematologic clotting kits. The research ethics committee of Tabriz University of Medical Sciences approved the study and informed consent was obtained from the parents.

Statistical analyses was performed using SPSS 14 for windows. Paired t-test, independent t-test and pearson correlation coefficient were used for comparison of the results and correlations.

### RESULTS

Study group included 30 patients (23 boys and 7 girls) with a mean age of  $5.38\pm 3.07$  years (range: 1.4-11 years). Control group included 30 children (21 boys and 9 girls) with a mean age of  $5.43 \pm 2.96$  years (range: 1.5-11 years). There was no statistically significant difference between mean age and sex of the study group and control group ( $P>0.05$ ). Table-I shows the results of laboratory findings of study group at admission at relapse period. Thrombocytosis (platelet  $>400000/\text{ml}$ ) was found in 50% of patients.

Table-II shows the haemostatic factors in study group and control group. There was no significant difference between mean protein C activity at relapse period with remission period and with control group ( $P>0.05$ ). The mean activity of protein S and AT III at relapse period was significantly lower than their levels in remission period and in the control group ( $P<0.05$ ). The mean fibrinogen level at relapse was significantly higher than its level in remission period and in the control group ( $P<0.05$ ). Correlations between changes in haemostatic parameters and biochemical findings were also investigated. There was no statistically significant correlation between serum albumin levels during relapse period with protein C,

Table-I: Laboratory findings of 30 nephrotic children before treatment

	Mean $\pm$ SD	Range
Albumin gr/dl	2.3 $\pm$ 0.2	1.7-2.4
Cholesterol mg/dl	489.2 $\pm$ 135.2	(277-792)
Triglyceride mg/dl	446.2 $\pm$ 277.3	82-1217
Platelet / mm <sup>3</sup>	419520 $\pm$ 111396.5	250000- 643000
Urine protein gr/day	4.03 $\pm$ 3.1	1.03-13.44

Protein S and fibrinogen levels ( $P>0.05$ ). But serum albumin levels were positively correlated with AT III ( $P<0.05$ ). There was no correlation between 24 hour urinary protein excretion with haemostatic parameters ( $P>0.05$ ).

## DISCUSSION

The hypercoagulability state in nephrotic syndrome is due to an imbalance between thrombotic and antithrombotic factors. Some low molecular weight proteins are excreted in urine and high molecular weight proteins like fibrinogen are increased because of compensatory protein synthesis in liver. Elevated level of fibrinogen in NS has been confirmed by many studies.<sup>15-17</sup> In our study mean fibrinogen level in relapse was significantly higher than its level in remission period and in the control group that is similar to other studies.

Although some authors have emphasized on diminished protein C levels in NS,<sup>4,7,13</sup> but there are conflicting reports concerning changes in functional activity of protein C. Anand et al showed that protein C was significantly elevated in onset of NS as compared with control group and the levels became normal with remission of the disease.<sup>15</sup> Citak et al observed that protein C levels were significantly higher

in nephrotic children than in the control group and remained so after corticosteroid therapy.<sup>16</sup> Ozkayin et al concluded that significant increase in protein C activity may have a protective effect against TE.<sup>17</sup> Yermiahu et al showed that plasma levels of protein C and protein S were within the normal range in nephrotic children.<sup>18</sup> We didn't find any significant difference in protein C levels in our patients before and after treatment with its level in control group.

Decreased AT III level at the onset of NS has been confirmed by most studies.<sup>15,16,19,20</sup> Wygledowski et al observed that activity of protein S and AT III were significantly decreased at the onset of NS as compared with control group and increased during the remission state<sup>19</sup> which is compatible with our findings. In this study plasma AT III levels correlated well with serum albumin. This relationship is explained by the molecular weight and charge of AT III that are similar to those of albumin. Elidrisy et al showed that during relapse urine AT III levels were of the same magnitude as plasma AT III, while during remission no AT III was detected in urine.<sup>20</sup> An increased incidence of TE has been reported with AT III levels lower than 75% of normal.<sup>16</sup> However TE may occur with normal AT III activity. Also some patients with low AT III level have not thromboembolic complications.<sup>19</sup> Nine of our patients (30%) had AT III levels below 75% normal. But none of them had clinically evident thrombosis. So the contribution of individual derangement of coagulant factor triggering TE is not yet known and coexistence of several factors may be necessary to induce TE. Thrombocytosis is one of the most important

Table-II: Comparison of hemostatic parameters between nephrotic patients and control group

	Study group before treatment	Study group after treatment	Control group	P <sup>1</sup>	P <sup>2</sup>
Protein C	99.4 $\pm$ 15.5%	99.8 $\pm$ 17.2%	94.3 $\pm$ 23.4%	$P>0.05$	$P>0.05$
Protein S	88.4 $\pm$ 16.7%	98.6 $\pm$ 14.8%	103.9 $\pm$ 22.6%	$P<0.05$	$P<0.05$
Antithrombin III	81.7 $\pm$ 18.3%	105.1 $\pm$ 11.7%	104.4 $\pm$ 15.2%	$P<0.05$	$P<0.05$
Fibrinogen	374.5 $\pm$ 46.1 mg/100	228.1 $\pm$ 42.9 mg/100	218.8 $\pm$ 57.1 mg/100	$P<0.05$	$P<0.05$

P<sup>1</sup>: Study group: before and after treatment

P<sup>2</sup>: between study group (before treatment) and control group

thrombotic risk factors which detected in 50% of our patients and 57.5% in Anand's study. Other contributing factors for hypercoagulability state include volume depletion, platelet hyperaggregation, hypercholesterolemia and infections. Also numerous iatrogenic factors like immobilization, trauma, multiple vein punctures, diuretics and steroid therapy increase the risk of thrombosis.<sup>3</sup>

Some authors recommend prophylactic use of anticoagulative drugs such as warfarin or aspirin with plasma albumin level less than 2gr/dl, fibrinogen level more than 600mg/dl or an AT III level below 70% of normal.<sup>4</sup> However many clinicians use prophylactic anticoagulation only in patients who have history of TE in previous relapses.

In conclusion we found some biological abnormalities including thrombocytosis, reduced levels of protein S and AT III and increased fibrinogen level in our patients, but none of these patients showed clinically evident TE. So there is no absolute correlation between biological abnormalities and the occurrence of TE. However it is of great importance to closely observe the nephrotic patients for TE, especially those with severe hypoalbuminemia. It should be kept in mind that prevention of iatrogenic risk factors such as volume depletion, immobilization, forced diuresis and infections is crucial in decreasing the incidence of TE.

We would like to express our thanks to research committee of Tabriz University of Medical Sciences for financial supporting of this study.

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