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NEPHROLOGY-CASE REPORT

Prophylaxis with AT III for thromboembolism in nephrotic syndrome: why should it be done?

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Abstract Children with nephrotic syndrome (NS) are at risk for sinovenous and arterial thrombosis, uncommon but serious complications of the nephrotic syndrome. Multiple factors are involved in the hypercoagulable state of patients with NS, for instance, enhanced platelet reactivity and deficiency of antithrombin III due to urinary loss of this protein. We report the case of a 7-year-old girl with relapse of nephrotic syndrome and with a clinical risk for thromboembolic complications, identified by very low AT III and albumin serum levels and high fibrinogen and cholesterol serum levels. However, having symptoms of hypovolemia, she was treated with albumin and diuretics, known risk factors for thrombotic incidents, although these drugs were both administered after prophylactic intravenous antithrombin. There are no randomized controlled clinical trials supporting prophylactic anticoagulation in the management of nephrotic syndrome. Arterial thromboses during nephrotic syndrome has been associated with thrombophilic states and the use of diuretics. It might be advisable to do laboratory monitoring for coagulation profiling and, in children at risk, prophylactic treatment with AT III before administering albumin infusion and diuretics.

Keywords Nephrotic syndrome · Therapy · Antithrombin · Thromboembolism · Child

Abbreviations
NS Nephrotic syndrome
AT Antithrombin

Introduction

Nephrotic syndrome (NS) is a renal disorder characterized by heavy urinary protein losses in association with edema, hypoalbuminemia and hyperlipidemia. However, children with NS are at risk of arterial and venous thrombosis, as recently reviewed [1]. Overall, sinovenous and arterial thrombosis are uncommon but serious complications of NS in children [2, 3]. The development of hypovolemia in the nephrotic child apparently increases the tendency to a hypercoagulable state. Furthermore, multiple factors are involved in the hypercoagulable state of patients with NS, for instance, enhanced platelet reactivity and

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deficiency of antithrombin III (AT III) due to urinary loss of this protein [4].

Several conditions other than NS are known causes of acquired AT III deficiency: liver failure, disseminated intravascular coagulation, severe trauma, and burns [5]. However, there are no guidelines establishing which individuals with acquired AT deficiency should be treated with AT concentrate.

Typically, acquired AT deficiency in NS children does not lead to an increased risk of blood clots. This may be because clotting factors other than AT are frequently also reduced. Therefore, an increased incidence of thromboembolic complications was observed when serum albumin levels went below 2.0 g/dl and AT III levels were 75% below normal [6]. Still, attention to and prevention of thromboembolic complications should be considered in children with known risk factors.

Case report

A 7-year-old girl had steroid responsive NS, with low recurrences (maximum 4 relapses of NS per year), since 5 years of age. She was admitted to the hospital because she showed pyrexia, followed by edemas of the face and fatigue. The parents had begun steroid medication at home 3 days before. At the hospital, the patient was running a temperature, was pale, and had severe edemas in the face, lower extremities, and abdomen, with increased body weight of about 6 kg over basal conditions (36 kg); she also had vomiting, tachycardia, and oliguria (0.34 ml/kg/day). Laboratory tests showed heavy proteinuria (20 g/24 h) and severe reduction of AT III and serum albumin levels. However, she had high serum protein C, fibrinogen, D-dimer, and cholesterol levels (Table 1). Still, the girl was treated with intravenous steroids on the first and second days after admission due to vomiting and then was put on oral steroids (2 mg/kg/day in two separate doses).

Since thromboembolic complications were associated with very low AT III, albumin serum levels, and high fibrinogen and cholesterol serum levels [6], the patient was considered at risk. Furthermore, having symptoms of hypovolemia (tachycardia, decreased urine output, weakness, headache, and confusion) she was treated as follows: firstly with human albumin

Table 1 Laboratory results during follow-up for NS relapse in a young girl

Variable (reference intervals)	0	1[a]	2	3[a]	4	6	8
Proteinuria (<150 mg/day)	21,000	15,170	–	–	–	120	–
Platelets (150,000–400,000/mm^3)	389,000	478,000↑	417,000↑	435,000↑	458,000↑	461,000↑	478,000↑
Urea (3.60–20.0 mg/dl)	5.90	12.3	14.2	14.5	9.90	10.40	13.1
Creatinine (0.2–0.8 mg/dl)	0.26	0.27	0.21	0.30	0.20	0.27	0.23
Albumin (3.8–5.4 g/dl)	1.54↓	1.29↓	2.03↓	1.73↓	2.41↓	2.62↓	2.79↓
PT (0.83–1.11 INR)		1.12		1.09	1.02		0.89
APTT (0.85–1.17 ratio)		1.17		1.01	0.94		0.79↓
Fibrinogen (150–400 mg/dl)		1,195↑		1026↑	593↑		417
AT III (80–120%)		37↓		52↓	61↓		>122↑
Cholesterol (<200 mg/dl)		521↑				422↑	378↑
Triglycerides (<150 mg/dl)		83				119	139
D-dimer (<500 μg/l)		979↑					319
Protein C (70–140 U/dl)		>140↑					119
Protein S (58–112%)		72					81
FVII (70–130%)		96.7					117.3
FVIII (50–150%)		>150↑					132.9
Homocysteine (<15 μmol/l)		5.4					

[a] Albumin, furosemide, and antithrombin treatments

Legend: ↑ = high level, ↓ = lower level than reference intervals, PT = prothrombin time, INR = international normalized ratio, APTT = partial thromboplastin time, FVII = factor VII, FVIII = factor VIII

20% solution (1 g/kg) and diuretic use (furosemide 1.5 mg/kg), both administered in two separate doses. The patient received intravenous antithrombin of 1,000 units (Table 1: day 1, the same treatment was repeated 2 days later).

Discussion

Risk factors for thromboembolic complications are genetic defects from protein C, protein S, AT III, factor V, factor II, and elevated lipoprotein (a) levels, besides acquired deficiencies of concentrations or functions of protein C, protein S, AT, and dysfibrinogenemia [7].

The prevalence of thromboembolism in pediatric NS is around 4% [6]. In particular, of all patients with NS, 0.5% had serious pulmonary embolism, 1.5% had deep venous thrombosis, and fewer had renal vein thrombosis. The relative risk of pulmonary embolism comparing patients with and without NS was 1.39, and the relative risk of deep venous thrombosis was 1.72 [8]. Several conditions have been established as risk factors for thromboembolic events in childhood NS, in particular blood hyperviscosity syndrome as well as an increase in erythrocyte aggregation; however, changes in the number of platelets or their function and increased fibrinogen levels were involved [9]. Furthermore, other multiple derangements of hemostasis and acquired risk factors such as AT deficiency, factor V Leiden, antiphospholipid antibodies, and low circulating levels of vitamin B6 were frequently observed [10]. Still, when the coagulation balance (pro- versus anticoagulation, pro- versus antifibrinolysis, platelet and vessel wall interactions) is altered, is difficult to evaluate the precise etiology of thrombosis diathesis in childhood NS, such as a decrease in AT or an increase in protein C. Therefore, criteria commonly used to evaluate the occurrence of thromboembolic complications are albumin, cholesterol, fibrinogen, AT III, and D-dimer levels (as molecular markers of coagulation activation). In particular, in nephrotic children elevated plasma D-dimer levels are not a rare finding in cases with pulmonary embolism. However, the factor V Leiden suggests a genetic predisposition for thromboembolic complications [6, 11, 12]. Acquired versus inherited alteration in the coagulation and fibrinolytic balance associated with NS may be of greater importance in evaluating thrombotic risk. Therefore, routine mutational screening of patients with nephrosis will not identify the majority of patients at risk for renal vein thrombosis [13].

Childhood NS is often associated with a hypercoagulable state. However, children with very low plasma AT III levels and fibrinogen levels above 750 mg/dl were at risk for deep vein thrombosis. The thrombotic risk was mainly evident at the onset of NS, when serum AT III levels were decreased [1]. Accordingly, acquired AT III deficiency was attributable to loss of intermediate-sized antithrombotic proteins in urine. Furthermore, serum AT III increased during the course of the disease. The response to steroids has been correlated with the fluctuations of AT III levels in childhood NS [1].

The therapeutic approach to thrombosis in NS may be the use of anticoagulants as a preventive measure or an attempt at thrombolysis with streptokinase, urokinase, and stanozolol [1] or simply with long-term intravenous heparin infusions following a loading dose in childhood pulmonary embolism [14]. In general, antithrombotic management during NS is done when thromboembolic events occur, corticosteroid treatment is discontinued, and patients have received AT III concentrate and heparin infusion [6]. A dramatic reduction of AT III levels in thrombophilic patients with NS may require replacement therapy using an intravenous infusion of a highly purified, human, blood-derived AT protein [7].

The hypercoagulable state in NS is characterized by increased coagulation factors (fibrinogen, factors V and VIII); it increases during thrombin action, fibrinolytic activity, platelet aggregation, and a decrease in AT III activity [15]. Therefore, treatment with antithrombotic agents is generally begun after the thromboembolic incident, also in those with known risk factors. For example, 1,000 units of AT III were administered to an adult nephrotic patient with arterial thrombosis, a serum albumin concentration of 1.5 g/dl, and severely decreased levels of serum AT III. Accordingly, several compensatory mechanisms explained the frequent absence of thrombotic incidents in children. Still the benefit of preventive antithrombotic treatment is often considered to be unsuitable. Therefore, it is very difficult to know if the absence of thromboembolism in the present case was due to the two infusions of AT III or to a response of the NS to the

steroids. At any rate, the importance of coagulation profiling in NS is emphasized by a high index of suspicion for thromboembolic complications in children with thrombocytosis, hyperfibrinogenemia, low levels of AT III, increases in protein C and protein S, and serum albumin levels below 2 g/dl [16]. In these clinical conditions, anticoagulant prophylaxis may be taken into consideration [15, 17]. Actually, prophylactic anticoagulation has been suggested only in patients with NS from membranous glomerulonephritis, in view of the higher risk of thromboembolic complications. In addition, there are no randomized clinical trials supporting prophylactic anticoagulation in the management of NS [18]. Therefore, thromboembolism in NS has been associated with thrombophilic states and use of diuretics. Still, laboratory monitoring for coagulation profiling and prophylactic treatment with AT III, alone or together, before administering albumin infusion and diuretics, may be advisable in high-risk patients. Further observational or controlled studies are necessary.

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