Hematology, February 2007; 12(1): 69–73

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healthcare

REVIEW

Thromboembolism in childhood nephrotic syndrome: A rare but serious complication

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(Received 11 July 2006; accepted 14 August 2006)

Abstract
The main clinical features of nephrotic syndrome (NS) are heavy proteinuria, hypoalbuminemia, hyperlipidemia and edema. In addition, multiple abnormalities in the coagulation pathway may be a consequence of the NS. Both arterial and venous thromboembolic complications (TEC) are relatively common and serious consequences of NS. In addition, arterial and venous thrombosis might be unexpected events during an exacerbation of NS. Embolic episodes may manifest in different regions of the body such as the brain or the lung. Hence, predisposing factors, personal and family history of TEC, thrombosis location and evolution should be always investigated in children with NS.

Keywords: *Nephrotic syndrome, thrombophilia, children*

Abbreviations: *NS, nephrotic syndrome; ATIII, antithrombin III; TEC, thromboembolic complications*

Introduction

Venous and arterial thromboembolic complications (TEC) are relatively infrequent during infancy and childhood but still cause significant morbidity [1,2]. Several conditions such as cancer, chemotherapy, cardiac diseases, central venous lines, surgery, infections, trauma, congenital thrombophilia and nephrotic syndrome (NS) may predispose children to TEC. Additionally, in several cases these risk factors may interact with each other and enhance the likelihood of developing thrombotic episodes. Conditions that predispose patients to TEC (e.g. NS, inflammatory bowel disease, diabetes, obesity, etc.) may themselves induce thrombosis by contributing to its clinical onset in patients with true thrombophilic states [3].

Heavy proteinuria, due to an abnormal increase in glomerular permeability, is associated with NS. Proteinuria occurs in association with primary or secondary glomerular disorder, and combined forms of glomerulonephritis. The main clinical features of NS are heavy proteinuria, hypoalbuminemia, hyperlipidemia and edema. Coagulopathy and disturbances in haemostasis leading to a high risk of TEC have been reported in NS [4]. Massive proteinuria and severe hypoalbuminemia have predictive value for high thrombotic risk [5]. Therefore, a lower incidence of TEC has been showed in children compared to adults with NS [6]. Autopsy analysis has shown that 38% of children with renal vein thrombosis were associated with NS [7]. Subclinical pulmonary embolism was found in 28% of children with NS by scintigraphic pulmonary ventilation and perfusion studies [8]. This incidence appears to be fairly high. Therefore, recommendations and frequency of the investigations in children during the acute episodes of NS should be accomplished.

The present review critically accesses the available information about this relatively infrequent but serious complication of NS during childhood.

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ISSN 1024-5332 print/ISSN 1607-8454 online
DOI: 10.1080/10245330600940048

Table I. Acquired and inherited thrombophilia in children with NS.

Acquired thrombophilia	Conditions	Pathophysiology
ATIII	Serum reduction	Urinary loss
Protein S	Serum reduction	Urinary loss
Protein S	Raised activity	Increased hepatic synthesis
Protein C	Raised activity	Increased hepatic synthesis
Fibrin network	Hypofibrinolysis	Abnormal conformation
Proteins S and C levels	Serum reduction	Increased binding proteins
Platelets	Dysfunctional, Increased activation	Increased number, increased synthesis of thromboxane
tPA, PAI-1	Increased concentration	Cyclosporine A
Inherited thrombophilia		
Protein C, protein S, ATIII		Defect
Lipoprotein (a)		Raised
Coagulation factors V and II		Gene mutations
Factor V Leiden		Presence
Prothrombin variant (20210G → A)		Presence
MTHFR gene		Gene mutation

Pathogenesis

Multiple abnormalities in the coagulation pathway are observed in NS. The hypercoagulable states and the TEC in NS are attributable to a loss of intermediate-size antithrombotic proteins (ATIII) in the urine as a direct result of heavy proteinuria. However, there is a increase in the pro-coagulant serum proteins (factors I, II, V, VII, VIII, X, and XIII) due to their increased hepatic synthesis [9]. A significant increase in protein C activity in NS patients represents a protective mechanism against thrombosis. The fibrinolytic system also plays an important role in preventing thrombosis in these patients [10]. In addition, congenital abnormalities of coagulation factors and NS may simultaneously be associated [11]. Hypercoagulable states can be classified as acquired, for example, if they arise as a consequence of the heavy proteinuria, or inherited, if only causally associated to NS. The acquired and inherited conditions leading to predisposition to TEC in childhood NS are shown in Table I.

Acquired thrombophilia

Several studies have focused on the abnormalities of the coagulation pathways in NS patients. The TEC in NS have been attributed to low plasma ATIII levels. Plasma ATIII levels have been shown to correlate with albumin levels and degree of proteinuria in NS [12]. However, the excess thrombin generation played a part in the development of the acquired deficiency of ATIII in NS [8].

A reduction of ATIII in NS may also be associated with low free serum protein S levels. Peripheral arterial thrombosis was reported in a child with longstanding NS with low acquired serum ATIII and protein S levels [13]. Acquired ATIII and protein S deficiency appeared to be one of the many risk factors for TEC in children with NS [14]. Therefore, TEC could be due to combined low plasma ATIII, protein S and protein C deficiency, albumin, high fibrinogen and cholesterol levels [5]. The levels of protein S, protein C and ATIII are frequently decreased in NS because of their loss in the urine [8]. Furthermore, anticoagulant proteins S and protein C in the serum may also remain functionally inactive because of an increase in the hepatic synthesis of binding proteins for protein S and protein C [15].

TEC may result from an increase of both the plasma fibrinogen levels and platelet counts. Abnormal fibrin network conformation may be involved in hypofibrinolysis. Therefore, albumin supplementation partially restores normal fibrin architecture and increases the rate of fibrinolysis [16]. However, platelets are dysfunctional and often increased in number in NS. Increased activation of blood platelets may be an independent risk factor of TEC in the early stages of the NS relapse. Increased platelet hyperaggregability may be due to increased platelet synthesis of thromboxane in response to the hypoalbuminemia [17,18].

An important cause of thrombosis in NS, that should be always borne in mind, is volume depletion, especially iatrogenic through over vigorous diuresis [19]. The risk of TEC in NS is increased by hyperviscosity of the blood caused by hyperfibrinogenemia, and intravascular volume depletion resulting from the inappropriate use of diuretics [20,21].

Inherited thrombophilia

Genetic prothrombotic defects in protein C, protein S and ATIII deficiency, mutations of coagulation factors II and V, elevated lipoprotein (a) are established risk factors for TEC [22]. The acquired hypercoagulability in NS may coincide with an underlying inherited thrombophilia. Furthermore, TEC may be associated with ATIII deficiency, increased concentrations of fibrinogen, factors V and VIII, and platelet hyperaggregability

[23]. The prevalence of the factor V mutation Arg506 → Gln (factor V Leiden), prothrombin variant (20210G → A), and homozygosity of Ala677 → Val in the methylenetetrahydrofolate reductase gene (MTHFR) in children with NS were assessed. Although TEC occurred in 11% of the children with NS, none of the known inherited risk factors has been identified [23]. These data support the hypotheses that there is a low incidence of inherited thombogenic factors in NS patients with thrombosis. Likewise a child with steroid-dependent NS and a homozygous mutation of MTHFR gene developed thrombosis in superior mesenteric artery [24] has been reported. In addition, a young male with concomitant deep vein thrombosis, idiopathic NS and resistance to activated protein C, the factor V Leiden was found to increase the risk of thrombosis [25]. Martinez and co-workers investigated the presence of genetic prothrombotic factors of patients with glomerulonephritis with or without a history of TEC and/or NS. They found an increased prevalence of heterozygous factor V Leiden in patients with a history of thrombotic events. These patients at risk of thrombosis may benefit from TEC prophylaxis [26].

Clinical features

The incidence of TEC in children may be linked to pronounced hypoalbuminemia and proteinuria [27]. The incidence of TEC in children with severe NS is high (1.8–5%), but frequently underestimated [22]. TEC (arterial or venous thrombosis, pulmonary embolism) were reported in 5.4% of children with NS [28].

Arterial and venous thrombosis may be an unexpected event during exacerbation of the NS. Children with membranous nephropathy may have a higher than previously recognised risk of TEC [29]. Embolic episodes may manifest in different regions of the body, such as the brain or the lung. Deep venous thrombosis and pulmonary embolism were found to be secondary to the acquired protein S deficiency in a paediatric case of the NS [30]. Two patients with NS developed venous thromboses without the presence of predisposing factors or coagulation abnormalities [29].

An uncommon, but known complication of NS is pulmonary thrombosis. Pulmonary embolism can lead to persistent tachypnea in childhood NS [31]. Therefore, pulmonary thrombosis may present with subtle symptoms and requires prompt diagnosis and treatment to prevent fatal outcomes [32]. Physicians should be alert to the possible complications of pulmonary embolism when treating the clinical symptoms of NS patients. The occurrence of thrombotic events is not always correlated with the clinical or laboratory severity of the NS, except for the association with elevated levels of fibrinogen and ATIII. Serial ventilation/perfusion lung scans may provide valuable clues during evaluation of these patients [33].

Cerebral venous thrombosis is a rare complication of NS. Appenzeller and co-workers showed that the aetiology of the cerebral venous thrombosis could be determined in 88% of the patients of all ages (from childhood to adulthood) but only in 4% of the patients with NS [34]. The possible presenting symptoms may include headaches and facial palsies remitting with heparin therapy [35]. Subtle symptoms may be alerting manifestations. A young boy with NS, presented with dehydration, and vague neurological symptoms with decreased serum ATIII levels. Subsequently, he developed seizures and cerebral sinovenous thrombosis [36]. Magnetic resonance imaging with venography was important in the early diagnosis of the cerebral sinus thrombosis. Anticoagulation therapy has been shown to be effective in improving the neurological outcome in children with NS [37].

Acute subclavian and brachial artery thrombosis are rare complications of NS [38]. Siddiqui and co-workers reported sustained acute thrombosis of the arterial bypass grafts in two patients with NS [39]. TEC are generally venous, whereas arterial thrombosis occurred less frequently. Hypercoagulability caused by acquired NS is not considered a frequent cause of acute thrombosis of the arterial bypass grafts [39].

Weisz and co-workers reported an asymptomatic intracardiac thrombus in a child with frequently relapsing steroid-sensitive NS and a ventricular septal defect [40]. Persistent hyperlipidemia in membranous nephropathy may increase the risk of cardiovascular diseases [41]. Furthermore, acute myocardial infarction, probably due to arterial thrombosis attributable to a hypercoagulable state resulting from the NS, was observed in a young adult [42].

Laboratory investigation

Predisposing factors, personal and family history of TEC, thrombosis location and the evolution of the disease should be always investigated in children with NS. Potential underlying prothrombotic conditions in childhood include acquired antiphospholipid antibodies or the lupus anticoagulant and hyperhomocysteinemia, abnormalities of the inherited anticoagulant factors including protein C, protein S, ATIII and factor V Leiden. Other abnormalities may result in increased lipoprotein (a) and hyperprothrombinemia due to prothrombin G20210A mutation [43,44].

Treatment

The therapeutic approach to thrombosis in children is with anticoagulants (low molecular weight heparin) and/or with fibrinolytic agents (streptokinase, urokinase, tissue plasminogen activator (tPA)) [26]. High

dosage heparinization may be necessary in children with deep vein thrombosis. Budd–Chiari syndrome resolved after immediate heparin infusion in a very young boy with NS due to hepatic vein and inferior vena cava thrombosis [45]. Satisfactory thrombolysis of an arterial leg thrombosis after 4 days of continuous catheter-directed low-dose alteplase was achieved in a patient with relapsing NS [46]. Therefore, the most widely used thrombolytic agent used from many years is tPA [47,48]. TPA treatment in children was first reported in 1990 [49]. TPA has shown efficacy in thrombolysis in paediatric patient and was not contraindicated in cases of NS [50]. However, no studies assessing its efficacy and safety in children is available [51].

The correction of diminished ATIII levels, by substitution of ATIII concentrates, is beneficial in cases in which is necessary to interrupt an enhanced coagulation process [52]. Theoretically, low-dose aspirin therapy should compensate for the low ATIII levels, although controlled trials of aspirin therapy in NS have not been performed [24].

Pulmonary embolism should be considered in children with tachypnea, especially when other venous thromboembolic risk factors are present, to avoid delay in anticoagulant treatment and a potentially fatal outcome [37]. Pulmonary thrombosis in two tachypneic young girls, presenting with severe oedema in NS relapse, was diagnosed with CT pulmonary angiography. They were treated with continuous heparin infusion with resolution of the pulmonary thromboembolism [36]. The mortality rate in NS patients with lung TEC may increase if treatment is delayed. The importance of lung perfusion scan, performing thrombolytic therapy (streptokinase, heparin and warfarin) and follow-up therapy should be emphasized [52].

To ensure optimal outcome in cerebral sinovenous thrombosis the essential measures are anticoagulant therapy with heparin and fresh frozen plasma for correcting the ATIII levels [40]. Thrombosis of the superior sagittal and straight sinus, leading to thalamic stoke, were successfully treated with subcutaneous low-molecular-weight heparin and warfarin in children with steroid-resistant NS [41,53,54].

Conclusions

The risk of TEC in patients with NS should not be underestimated. Although rare, the TEC are among the most-serious life-threatening complications in children with NS. TEC occur less commonly in paediatric than the adult patients. The most commonly involved vessels in vascular thrombosis are the deep veins of the legs, the inferior vena cava, renal veins, superior vena cava, the mesenteric artery, hepatic veins and the middle cerebral arteries. Iatrogenic thrombotic risk factors (diuretics, dehydration, and infections) should be avoided, whereas inherited risk factors should be investigated. Adequate therapy with anticoagulants and fibrinolytic drugs should be recommended in children with acute symptoms, inasmuch as prophylaxis is necessary in relapsing patients.

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