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ORIGINAL ARTICLE

Thromboembolic complications in childhood nephrotic syndrome: a clinical profile

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Abstract
Background Thromboembolism is a rare life-threatening complication of childhood nephrotic syndrome.
Methods We present the clinical profile and outcome of 34 children with 35 events of thromboembolic complications with nephrotic syndrome.
Results Cerebral venous thrombosis (CVT) was the commonest complication seen in 11 (31.4 %) children followed by pulmonary thromboembolism and deep venous thrombosis in 9 (25.7 %) and 6 (16.6 %) children, respectively. Arterial thrombosis resulting in central nervous system infarcts was observed in 7 (20 %) children and 2 children had thrombosis of the peripheral arteries. Episodes were equal in steroid-resistant nephrotic syndrome and steroid-dependent nephrotic syndrome groups. Most of the thromboembolic complications occurred with relapse but 11.4 % of children developed intracranial thrombosis during remission. The most sensitive symptom of CVT was persistent headache while unexplained respiratory distress and hypoxemia pointed towards pulmonary thromboembolism. Hypoalbuminemia was seen in 82.8 % of children, while concurrent infection was seen in 31.4 %. Coexistence of genetic prothrombotic condition was identified and merits evaluation. Early heparin therapy followed by oral anticoagulants resulted in complete recovery in 91.1 % of children. Death occurred in 3 (8.5 %) children and autopsy revealed pulmonary thromboembolism in 2 children.
Conclusion Venous and arterial thrombotic complications can occur in children with nephrotic syndrome. A high index of suspicion is required as the clinical features may be subtle. Neuroimaging and angiographic techniques help in confirming diagnosis. Early aggressive heparin therapy followed by oral anticoagulants is necessary for a favorable outcome.

Keywords Nephrotic syndrome · Cerebral venous thrombosis · Pulmonary thromboembolism · Deep venous thrombosis · Arterial thrombosis · Children

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Introduction

Thrombosis is a well-recognized complication of nephrotic syndrome (NS). The incidence of thromboembolic complications (TECs) in NS in children is reported to be approximately 3 % [1]. This percentage, however, may be an underestimate of the true incidence as unless suspected and investigated, many such events apparently go unrecognized. No prospective longitudinal studies to detect clinical or subclinical thromboembolic events are available in the pediatric age group. We describe here the clinical profile and outcome of 35 thrombotic events seen in 34 children with NS over a period of 7 years.

Patients and methods

We reviewed the case records of all children diagnosed as having NS with TECs who were admitted to the Advanced Pediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India from January 2004 to December 2010. The center serves as a tertiary care referral center for North West India and registers approximately 250–300 new children with NS every year. The management protocol is based on the Consensus Statement on Management of Nephrotic Syndrome by the Indian Pediatric Nephrology Group [2–4] and all the patients analyzed in this report were hospitalized and investigated accordingly.

Cerebral venous thrombosis (CVT) was diagnosed by contrast-enhanced computed tomography (CT) of the brain followed by CT venography or magnetic resonance venography studies. Pulmonary thromboembolism (PTE) was clinically suspected if children developed unexplained respiratory distress, cough, wheeze or hypoxemia. The initial investigation in such cases was a lung perfusion scan after an intravenous injection of 74 MBq of ^{99m}Tc-MAA. The results were interpreted as high, moderate or low probability of PTE. High probability was defined as $\geq$2 perfusion defects in the presence of normal ventilation. CT angiography of the chest was performed in children with moderate probability on ventilation perfusion scans. Deep venous thrombosis (DVT) was detected by ultrasound Doppler of the limb. Anticoagulation therapy was initiated as soon as TECs were identified. In children with intracranial arterial involvement, acetyl salicylic acid was used. Children received unfractionated heparin (70–100 U/kg) for the first 4–5 days and later overlapped with warfarin for 48–72 h. Oral warfarin was maintained as a single daily dose for a period of 6–12 months. No child received fibrinolytic therapy. Tests to identify procoagulant state were carried out during follow-up after stopping anticoagulant therapy at the Coagulation Laboratory of the Department of Hematology, PGIMER, Chandigarh. Thrombophilic work-up was not performed at admission. The tests included functional activity of protein C and protein S, antithrombin III functional activity, lupus anticoagulant, anticardiolipin immunoglobulin (Ig) G and IgM, and DNA testing for Factor V Leiden. Tests for anti-β_2-glycoprotein were not available during this period. Our laboratory is registered in the World Health Organization's United Kingdom National External Quality Assurance Scheme for Coagulation and Immunochemistry for quality control.

Results

During the study period a total 34 children (22 boys and 12 girls) had 35 thrombotic events. The baseline characteristics of these children are summarized in Table 1. CVT was the commonest complication seen in 11 (31.4 %) children followed by PTE in 9 (25.7 %) and DVT involving the peripheral limb arteries in 5 (14.2 %) children. Superior vena caval thrombosis was seen in one child. Arterial thrombosis resulting in central nervous system infarcts was observed in 7 (20 %) children and 2 children had thrombosis of the peripheral arteries (Table 2).

Patient characteristics

Age

The mean age of the children at the time of admission for the event was 7.7 $\pm$ 2.7 years (range 2.5–12 years) while the mean age at the onset of NS was 5.9 $\pm$ 4.2 years (Table 1).

Type of nephrotic syndrome

Of the 35 events, 11 episodes occurred in children with steroid-resistant NS (SRNS) and the same number of events were recorded in children with steroid-dependent/frequently relapsing NS (SDNS/FRNS) (Table 1). 7 episodes were seen in children with infrequently relapsing NS but during a relapse of disease. Notably, we recorded TECs during the first episode of NS in 5 children and it was the predominant presenting complaint in 3 of them.

Risk factors

The following factors were associated with risk of thrombotic event:

(i) Degree of proteinuria
(ii) Serum albumin levels

Table 1 Baseline characteristics of the children at the time of presentation ($n = 35$)

Patient profile	Frequency
Mean age (years)	7.7 ± 2.7 (2.5–12)
Male:female ratio	1.9:1
Mean age at onset of NS (years)	5.9 ± 4.2
Type of nephrotic syndrome ($n = 34$)	
First episode	5 (14.7 %)
Infrequent relapsing nephrotic syndrome	7 (20.5 %)
Frequent relapsing nephrotic syndrome/steroid-dependent nephrotic syndrome	11 (32.3 %)
Steroid-resistant nephrotic syndrome	11 (32.3 %)
Mean serum albumin (g/l)	1.7 + 1.2 g/l (0.1–6.6)
Hypoalbuminemia (<2.5 g/l)	29 (82.8)
Proteinuria (>40 mg/m^2/h)	29 (82.8)
Mean 24 h urinary protein (mg/m^2/h)	76 + 56
Serum cholesterol	
Serum cholesterol (<200 mg/dl)	4 (11.4 %)
Serum cholesterol (200–400 mg/dl)	19 (54.2 %)
Serum cholesterol (>400 mg/dl)	12 (34.2 %)
Concurrent focus of infection	11 (31.4 %)
Bacterial peritonitis	6
Meningitis	1
Cellulitis	2
Bacteremia	2
Anemia (hemoglobin <10 g/dl)	8 (22.8 %)
Hemoconcentration (hemoglobin >14 g/dl)	8 (22.8 %)
Thrombocytosis (platelets >450 *10^9/l)	10 (28.5 %)
Prerenal azotemia (urea >40 mg/dl, creatinine >1 mg/dl)	10 (28.5 %)
History of arterial/venous puncture	3 (8.5 %)
History of diuretic use	15 (42.8 %)

(iii) Associated infection
(iv) Thrombocytosis
(v) Anemia
(vi) Hemoconcentration

(i) Degree of proteinuria: Proteinuria (≥40 mg/m^2/h) at the time of thrombotic phenomena was seen in the majority (82.8 %) of children; however, 2 children (18.1 %) had sub-nephrotic range proteinuria, while 4 children (8.5 %) developed these complications while in remission. Of these 4 children, 3 (27.2 %) developed CVT while 1 child was diagnosed with intracranial arterial thrombosis (Table 2).

(ii) Serum albumin levels: The mean serum albumin level in the cohort was found to be 1.7 ± 1.2 g/l and hypoalbuminemia was seen in 82.8 % of children (Table 1).

Table 2 Frequency of various thromboembolic complications, clinical profile and outcome

Type of TEC	No. of TECs	Mean age years (range)	Sex female: male	First episode (%)	Infrequent relapse (%)	SDNS/ FRNS (%)	SRNS (%)	No. (%) of patients with proteinuria (>40 mg/m^2/h)	Focus of infection (%)	No. of patients with associated genetic thrombophilia (patient positive/patient tested)	Recovery (%)
CVT	11 (29.4)	7.5 ± 2.6 (3–12)	1:1.2	4 (36)	3 (27.2)	2 (18.1)	2 (18.1)	6 (54.5)	1 (9)	2/7	11 (100)
PTE	9 (25)	7.8 ± 2.3 (3.5–11)	0:9	–	2 (22.2)	4 (44.4)	3 (33.3)	9 (100)	5 (55.5)	1/4	7 (77.7)
DVT and SVC	6 (16.6)	7.3 ± 2.9 (4–12)	1:2	–	1 (16.6)	1 (16.6)	4 (66.6)	6 (100)	4 (66.6)	0/1	6 (100)
ICAT	7 (19.4)	8.1 ±3.6 (2.5–12)	1.3:1	1 (14.2)	1 (14.2)	4 (57.1)	1 (14.2)	6 (85.6)	1 (14.2)	4/5	7 (100)
LA	2 (5.5)	7.5 (3–12)	1:1			1 (50)	1 (50)	2 (100)	–	0/1	1 (50)

TEC thromboembolic complications, *CVT* cortical venous thrombosis, *PTE* pulmonary thromboembolism, *DVT* deep venous thrombosis, *SVC* superior vena cava thrombosis, *ICAT* intracranial arterial thrombosis, *LA* limb artery, *NS* nephrotic syndrome, *SDNS* steroid-dependent nephrotic syndrome, *SRNS* steroid-resistant nephrotic syndrome

(iii) Infection: Concurrent focus of infection, an important predisposing factor for TECs was found in 31.4 % of children. The site of infection identified was bacterial peritonitis in 17.1 % of children, cellulitis in 5.7 %, bacteremia in 5.7 % and meningitis in 2.8 %. *Streptococcus pneumoniae* as well as *Staphylococcus aureus* were isolated on blood culture in each of 2 children. Co-infection was identified as a risk factor in 83.3 % of children with DVT, and 55.5 % with PTE, but was identified in only 1 child (9 %) with both CVT and intracranial arterial thrombosis (Table 2).

(iv) Other factors predisposing to thrombosis like thrombocytosis and anemia were seen in 28.5 and 14.2 % of children, respectively. Hemoconcentration and azotemia were seen in 22.8 and 28.5 % of children, respectively (Table 1).

Tests for inherited thrombophilic conditions and antiphospholipid antibodies (APLAs)

These tests were performed 6 weeks after stopping anticoagulation in 18 children. 2 children with CVT were identified as having a functional protein S deficiency along with NS. The mother of one of the children had a history of DVT during pregnancy and on further evaluation was found to be protein S deficient.One child with PTE had low antithrombin functional activity. APLAs were found in 4 children who had intracranial arterial thrombosis—lupus anticoagulant was positive in 1 child while IgM anticardiolipin antibodies were positive in the other 3 children. On repeat testing, these were found to be negative in 2 children after 1 year of follow-up.

Clinical profile

The clinical presentations included:

(i) Cerebral venous thrombosis
(ii) Intracranial arterial thrombosis
(iii) Pulmonary thromboembolism
(iv) Deep venous thrombosis of lower limbs
(v) Thrombosis of deep vessels of neck
(vi) Thrombosis of peripheral arteries

(i) CVT: Headache was the most important presenting symptom in all the children with CVT, followed by vomiting in 81.1 % of children (Table 3). Focal seizures (18 %) and alteration in sensorium (18 %) occurred less commonly. A fundal change in the form of papilledema was found in 7 children (63.3 %) and was an important clue to diagnosis. Lateral rectus gaze palsy was seen in 4 (36.3 %) children. CT was the first line of investigation performed in all children. Sinus thrombosis in the form of empty delta sign was evident on contrast-enhanced CT (CCT) in all children (Fig. 1). Venography studies either by magnetic resonance imaging (MRI) or CT were performed for better delineation of venous sinuses in 54.5 % of children. Superior sagittal sinus thrombosis was the commonest sinus involved in 72.7 % of children followed by transverse, sigmoid and straight sinus. Parenchymal lesions in the form of venous infarct or bleeding were found in 4 (36.3 %) children.

(ii) Intracranial arterial thrombosis: This was less commonly seen compared to venous thrombosis. 2 children with arterial thromboembolic phenomenon presented with an acute stroke/hemiparesis-like event (Table 4). The majority of the other children (6) had seizures at the time of presentation; CT of the brain revealed parenchymal infarcts in all these children. Diffusion-weighted MRI in 3 children followed by MR angiography in 2 children revealed involvement of the basilar, vertebral and posterior cerebral artery in one child and involvement of the left middle cerebral artery in the other child. Anticoagulation therapy was initiated in 4 of these 7 children and the remaining 3 children were given acetyl salicylic acid (3–5 mg/kg/day) only.

(iii) PTE: It was demonstrable in 9 children, all boys (Table 5) with a mean age of 7.8 years, the youngest being 3.5 years. PTE was generally seen 1–9 days after hospitalization in children who had presented with relapse of NS, or with edema and heavy proteinuria. Breathing difficulty was seen in 77 % of children followed by cough in 33 %. Chest pain was observed in only 11 % of children. Tachypnoea and hypoxia (pulse oximetry $\leq$92 %) were the most consistent signs seen in 66 % of children and wheeze was identified in 33 % of children. Some children (55.5 %) were admitted for treatment of infection. Bacterial peritonitis was identified in three children and pneumococcal meningitis in one child. Of the 9 children, echocardiography was performed in 5 children and was found to be normal. D-dimer, a surrogate marker for thrombosis, was performed in only 5 children, of whom 4 were positive. Doppler ultrasound of the lower limbs was performed in all children but was found to be normal. Ventilation perfusion scans revealed high probability in 5 and intermediate probability in 2 children. The left lung was involved more frequently than the right lung. CT angiography performed in 2 children showed involvement of the left major pulmonary artery in both children.

Table 3 Clinical profile of children with cortical venous thrombosis ($n = 11$)

Patient no. Age/sex	Type of NS	Presenting complaints	Papilledema	Lateral rectus palsy	Other focus of infection	Proteinuria (mg/m^2/day)	Imaging studies	Sinus involved on imaging	Parenchymal lesions	Outcome
Patient 1 10/F	SRNS FSGS	Headache, vomiting	Present	No	No	64	CCT, CTV	Superior sagittal sinus thrombosis	No	Recovered
Patient 2 8/F	First episode	Headache vomiting	Absent	No	No	46	CCT	Cortical venous thrombosis	No	Recovered
Patient 3 6/F	SRNS	Headache vomiting, right focal seizures	Present	Yes	Bacterial peritonitis	38	CCT, MRV	Left transverse sinus and sigmoid sinus thrombosis with sagittal sinus thrombosis and occipital venous infract	Yes	Recovered
Patient 4 6/F	SDNS	Vomiting, headache inward deviation of eyes	Absent	Yes	No	No	CT, MRI, MRV	Superior sagittal sinus and bilateral transverse sinus with right frontal white matter infarct	Yes	Recovered
Patient 5 7/F	First episode	Right focal seizures altered sensorium	Absent	No	No	22	CCT	Cortical venous thrombosis	No	Recovered
Patient 6 3/M	Infrequently relapsing NS	Altered sensorium seizures,	Present	Yes	No	26	CCT, CTV	Superior sagittal sinus and straight sinus thrombosis	No	Recovered
Patient 7 11.5/M	First episode	Headache vomiting	Present	No	No	54	CCT, MRV	Superior sagittal sinus, right transverse and sigmoid sinus thrombosis	No	Recovered
Patient 8 6/M	Infrequently relapsing NS	Headache	Absent	No	No	8	CCT	Left parieto-occipital venous infarct with bleeding	Yes	Recovered
Patient 9 12/M	Infrequently relapsing NS	Headache vomiting, Altered sensorium	Present	Yes	No	44.5	CCT	Sagittal sinus thrombosis with right parietal cortical venous infarct	Yes	Recovered
Patient 10 6/M	SDNS/FSGS	Headache vomiting.	Present	No	No	No	CCT, MRV	Sagittal sinus thrombosis, right sigmoid, transverse sinus	No	Recovered
Patient 11 7/M	First episode	Headache vomiting	Present	No	No	68	CCT	Sagittal and transverse sinus	No	Recovered

NS nephrotic syndrome, *SDNS* steroid-dependent nephrotic syndrome, *SRNS* steroid-resistant nephrotic syndrome, *FSGS* focal segmental glomerulosclerosis, *CCT* contrast-enhanced computerized tomography, *CTV* computed tomography venography, *MRI* magnetic resonance imaging, *MRV* magnetic resonance venography

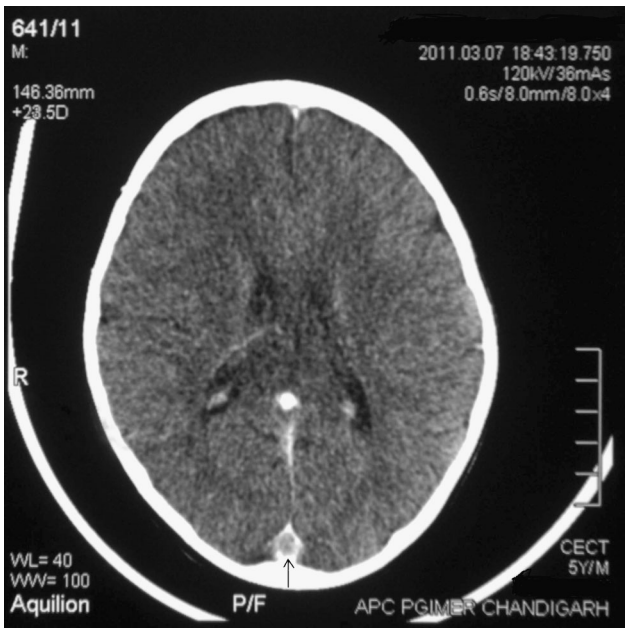

Fig. 1 Axial contrast-enhanced cranial CT shows a filling defect in the region of the venous confluence (*empty delta sign*)

(iv) DVT: This was seen in 5 children, of whom 4 had SRNS (Table 6). All children had presented in relapse of NS. Associated infection in the form of cellulitis of the lower limbs was identified in 2 children, spontaneous bacterial peritonitis in 1 child and septicemia in 1 child. Blood culture was positive in 3 children. Femoral veins were most commonly involved with unilateral and bilateral involvement in each of 2 children. Thrombus extended to involve the inferior vena cava, and common and external iliac vein in 1 child. Thrombosis of the upper limb vessels involving the right brachial and axillary vein occurred in 1 child on day 2 of hospitalization while admitted for the treatment of pneumococcal sepsis; a history of peripheral venous cannulation in the same limb was obtained. All the children recovered following anticoagulation and treatment for infection. Ventilation perfusion scans did not reveal any PTEs.

(v) Thrombosis of deep veins of neck: Thrombosis of the superior vena cava and left internal jugular vein was seen in 1 child who presented with chylopericardial tamponade. This child has been reported previously and she had improved following surgical drainage, nutritional rehabilitation and conservative management with conventional heparin [5].

(vi) Thrombosis of peripheral arteries: Involvement of the peripheral limb arteries (posterior tibial artery and the brachial artery) was seen in only 2 children; both children developed progressive gangrene of the limb and a history of arterial puncture prior to the development of gangrene was elicited in both children. Thrombectomy was performed in one child; however, the gangrene progressed and the child succumbed to septicemia and progressive gangrene. The other child recovered completely after initial anticoagulation with conventional heparin and later acetyl salicylic acid was given for a total of 3 months.

Outcome

Final outcome was good with complete recovery seen in 32 (91.4 %) out of 35 events. All children with central nervous system thrombosis as well as with DVT improved. Moreover, children in whom a diagnosis of PTE could be established antemortem also recovered. However, 3 children died in our cohort, of whom 2 had sudden death. Autopsy was performed in both children with sudden death which revealed left main pulmonary artery thrombosis in one child and bilateral pulmonary arterial thrombosis in the other child.

Discussion

Thromboembolism is a well-known but rare complication of pediatric NS. The true frequency of TECs in NS is difficult to determine as many events are subclinical/asymptomatic and go undiagnosed [6]. The reported incidence of TECs in adults with NS ranges from 9−70 % [7] while the frequency of clinically evident TECs in children, as reported in various studies is only between 1.8 and 4.4 % [8–11]. The incidence of subclinical pulmonary embolism by scintigraphic pulmonary ventilation and perfusion studies was found to be 28 % in children with NS [6]. The coagulation disturbances in children are as severe as in adults with NS [6, 12]. We recognized 35 events over a period of 7 years. To the best of our knowledge, this is the largest single center experience of TECs in children with NS.

The hypercoagulable state in NS is multifactorial, attributed predominantly to urinary loss of anticoagulants, increased procoagulatory activity, altered fibrinolytic system, thrombocytosis, and enhanced platelet activation and aggregation [6, 12, 13]. Other thrombophilic factors which also contribute are low albumin, increased cholesterol, associated infections and iatrogenic volume depletion due to inappropriate and overuse of diuretics, venepuncture and immobilization. There are few studies on the contribution of genetic prothrombotic defects in addition to acquired risk factors. Fabri et al. [14] evaluated 53 children with NS for prevalence of the Factor V mutation Arg506–>Gln (Factor V Leiden), the prothrombin variant (20210G–>A),

Table 4 Clinical profile of children with intracranial arterial thrombosis ($n = 7$)

Patient no. Age/sex	Type of NS	Presenting complaints	Focus of infection	Proteinuria (mg/m^2/day)	Type of neuroimaging	Neuroimaging findings	Therapy	Outcome
Patient 12 11/F	SDNS	Focal seizures, headache	No	103	CCT	Multifocal infarcts	Heparin, warfarin, aspirin	Improved
Patient 13 10/F	SRNS	Seizures, altered sensorium, headache	No	87	MRI	Bilateral parietal and occipital lobe infarcts	Heparin, warfarin	Improved
Patient 14 5/F	SDNS	Right focal seizures	No	96	MRI	Infarcts in left middle cerebral artery territory and thalamus	Aspirin	Improved
Patient 15 12/M	First episode	Pain abdomen, seizures	Bacterial peritonitis	54	CCT	Occipital infarcts	Heparin, warfarin	Improved
Patient 16 5/M	SDNS	Left hemiparesis, seizures	No	73	MRI, MRA	Infarcts in midbrain, pons and right cerebellar hemisphere. Thrombosis of right vertebral artery, basilar artery and post cerebral artery	Heparin, aspirin	Improved
Patient 17 8/F	Infrequently relapsing NS	Left hemiparesis with facial involvement	No	No	CCT	Right temporal and parietal lobe infarcts	Aspirin	Improved
Patient 18 7.5/M	SDNS	Altered behavior, left focal seizures	No	78	CCT	Right parietal and occipital lobe infarcts	Aspirin	Improved

NS nephrotic syndrome, *SDNS* steroid-dependent nephrotic syndrome, *SRNS* steroid-resisant nephrotic syndrome, *CCT* contrast-enhanced computerized tomography, *MRI* magnetic resonance imaging, *MRA* magnetic resonance arteriography

Table 5 Clinical profile of children with pulmonary thromboembolism ($n = 9$)

Patient no. Age/sex	Type of NS	Symptoms	Other focus of infection	Symptoms on day of hospitalization	Proteinuria ($mg/m^2/day$)	D-dimers	Ventilation perfusion scan	Outcome
Patient 19 10/M	SRNS	Respiratory distress	SBP	9	142	Positive	Segmental perfusion defects involving superior segment of left lower lobe, superior and inferior lingual segment of left upper lobe. Right lung normal. High probability	Recovered
Patient 20 11/M	SRNS	Cough	No	8	65	NA	Mild in homogeneity in mid zone, moderate size perfusion defects in post segment of upper lobe and lateral basal segment of left lung. Right lung normal. Intermediate probability.	Recovered
Patient 21 6/M	SDNS	Cough, respiratory distress	Pneumococcal peritonitis	2	308	Positive	High probability of pulmonary thromboembolism left lung, major thrombus obstructing left pulmonary artery. Right lung normal.	Recovered
Patient 22 3.5/male	SDNS	Respiratory distress, wheeze	No	1	42	Negative	Perfusion defects seen in lateral and middle basal segments of the left lung. Right lung normal. Intermediate probability.	Recovered
Patient 23 8/M	Infrequently relapsing	Respiratory distress, wheeze	Meningitis	5	68	Positive	Large perfusion defect in the posterior segment of the upper lobe and the medial segment of the middle lobe of right lung. High probability	Recovered
Patient 24 9/M	SDNS	Respiratory distress	No	9	54	NA	Large perfusion defect in superior basal segment of left lung and right lung posterior bronchopulmonary segment of upper lobe. High probability	Recovered
Patient 25 8/M	SRNS	Sudden collapse	Bacterial peritonitis	12	62	NA	–	Died, left main pulmonary artery thrombosis
Patient 26 6/M	SDNS	Cough wheeze	No	4	78	Positive	Impaired uptake in lingual and basal segments of left lung and medial segment of the middle lobe of right lung. High probability	Recovered
Patient 27 9/M	Infrequently relapsing	Seizures, shock	Septicemia, shock	7	105	ND	–	Died, bilateral pulmonary artery thrombosis

NS nephrotic syndrome, *SDNS* steroid-dependent nephrotic syndrome, *SRNS* steroid-resistant nephrotic syndrome, *NA* not available

Table 6 Clinical features of children with deep vein thrombosis lower limb ($n = 5$) and superior vena cava ($n = 1$)

Patient no. Age/sex	Type of NS	Presenting complaints	History of venous puncture	Other focus of infection	Proteinuria ($mg/m^2/h$)	Doppler study	Outcome
Patient 28 10/M	SRNS	Swelling of the body, swelling of the lower limbs	No	No	49	Thrombus in proximal inferior vena cava, bilateral external iliac and common iliac and bilateral femoral veins	Recovered
Patient 29 4/M	SRNS	Pain in leg right leg	No	Coagulase-negative *Staphylococcus* peritonitis	89	Right femoral vein thrombosis	Recovered
Patient 30 7/M	Infrequently relapsing	Pain abdomen lethargy, not feeling well, arm swelling	Yes	Pneumococcal bacteremia	142	Thrombosis right brachial right axillary vein	Recovered
Patient 31 7/M	SDNS	Relapse thigh swelling	No	Cellulitis	152	Bilateral femoral vein thrombosis	Recovered
Patient 32 12/F	SRNS	Swelling, fever, swelling left lower limb	No	*Staphylococcus aureus* cellulitis	77	Left femoral vein thrombosis	Recovered
Patient 33 4/F	SRNS/FSGS	Cough, dyspnea facial swelling	No	No	32	Superior vena cava and left internal jugular vein thrombosis	Recovered

and homozygosity for Ala677–>Val in the methylenetetrahydrofolate reductase gene and concluded that inherited thrombophilia is not a strong risk factor for the development of nonrecurrent thrombosis in children with NS [14]. Martinez and co-workers [15] also investigated the presence of genetic prothrombotic factors in patients with glomerulonephritis with or without a history of TECs and/or NS. They found an increased prevalence of heterozygous Factor V Leiden in patients with a history of thrombotic events [15].

Identification of these conditions is of clinical significance as the management is different especially with regards to the duration of anticoagulation. Among 18 children who were evaluated, we identified two children with associated inherited protein S deficiency, and one child with antithrombin III deficiency. The role of APLAs, especially with congenital NS (CNS) thrombosis, has been recognized previously [16] but its association with childhood NS has not been well recognized. We found 4 children with APLAs with intracranial arterial lesions. However, with this limited information based on single APLA test, it would be imprudent to suggest a cause-and-effect relationship between intracranial artery thrombosis and the presence of APLAs. We screened for antinuclear antibodies in all children and therefore lupus (the most important secondary cause for APLAs) can be ruled out. Therefore, our results suggest that there could be some correlation between APLAs and intracranial arterial thrombosis; however, this needs further studies in a larger group of patients.

Few centers have reported cases of CVT occurring in patients with NS. In a pooled literature analysis [17], only 21 pediatric cases were found. We treated 11 cases with a good outcome; however, it was the commonest complication encountered in our cohort. CVT was seen during the first episode as the presenting manifestation and/or was found to occur during relapse and in remission. Unlike other types of TECs, concurrent infection was not found to be a necessary trigger for CNS thrombosis. The single most sensitive symptom of CVT in our study was persistent headache. We suggest that unexplained headache in children with NS should arouse clinical suspicion of CVT warranting prompt investigations. Superior sagittal sinus was the commonest sinus involved in our children, similar to Fluss et al. [17] who also reported its involvement in all the patients in their study. Even with parenchymal lesions seen in four children the outcome was excellent.

Posterior reversible encephalopathy syndrome (PRES) is an important differential diagnosis in children with kidney disease presenting with seizures, headache and altered sensorium. Diffusion-weighted cranial MRI provides accurate diagnosis [18, 19]. Of 7 children with intracranial arterial lesions, diffusion-weighted MRI was performed in

3 children. PRES could be a possibility in other children in whom detailed imaging studies were not performed.

PTE proved to be the most important life-threatening complication and was identified as the cause of death on autopsy in two of our children. It is to be noted that signs and symptoms of this complication are subtle and require prompt recognition to prevent fatal outcomes. Unexplained tachypnoea, hypoxemia or abnormal respiratory findings should alert the physician towards this possibility [11, 20, 21]. According to the recent Prospective Investigation of Pulmonary Embolism Diagnosis III criteria, ventilation perfusion scan is still the investigation of choice to confirm a diagnosis of PTE [22]. Hence, it is a preferred modality over the more invasive CT angiography. Early ventilation scans help in the diagnosis and improving the outcome [23].

TECs are generally venous, whereas arterial thrombosis occurs less frequently. Literature on arterial thrombosis in NS is scarce. Acute subclavian and brachial artery thrombosis has been described by Witz et al. [24] while Siddiqi et al. [25] reported sustained acute thrombosis of the arterial bypass grafts in two patients with NS. Arterial punctures and associated infection predispose to this complication and were identified as additional risk factors in both cases.

Superior vena cava thrombosis has been rarely described and can result in chylopericardium and chylothorax [5, 26]. Renal vein thrombosis, also a well-known complication, is seen more frequently in adults and in patients with membranous nephropathy [27–30] while case series in children do not report it to be a frequent occurrence [9, 12]. It has been conspicuous by its absence in our series. This is one of the major differences between our study and those reported from developed countries. We do not have an adequate explanation to explain this difference but it could perhaps be a reflection of differences in genetic background between our patients and those reported from the Western world. DVT was easily detected by available methods but further tests to detect renal vein thrombosis in all the children with DVT were not performed.

The therapeutic approach to thrombosis in children is with anticoagulants, (conventional heparin infusion/low-molecular-weight heparin) with/or without fibrinolytic agents (streptokinase, urokinase, tissue plasminogen activator) [31]. Most of our children received conventional heparin with a good outcome. Fresh frozen plasma infusion may be required to correct the antithrombin III levels. Fibrinolytic therapy was not given to any of our children. Tissue plasminogen activator has been efficacious in pediatric patients; however, its risk−benefit ratio in pediatric patients remains unclear. An attempt at surgical removal of peripheral arterial thrombosis in one child was not successful. There is no consensus on the duration of anticoagulation in children [31]. All our children received oral anticoagulation for at least 6 months. Children with associated protein S deficiency may require lifelong anticoagulation.

Our literature search showed only one report concerning prophylactic anticoagulation in children with NS [9]. Prophylactic anticoagulation involves a risk of bleeding and is therefore not routinely recommended. Moreover, it was found that anticoagulation therapy failed to prevent further recurrences of renal vein thrombosis in a short series of patients [8]. One child had recurrence of TECs in our cohort and was not receiving any anticoagulation therapy at that time. The use of prophylactic anticoagulation may be considered during relapse and infections with severe hypoalbuminemia in order to prevent thrombotic complications; however, further studies are required.

Limitations

A major limitation of our study is that the exact incidence of thrombosis in our cohort of children is unclear. It is extremely difficult to classify our pediatric population into SRNS/SDNS categories as the overwhelming majority of our children have been receiving treatment for several months–years from other centers. As ours is a tertiary care center, by the time the patients reach our institute they have received several courses of different immunosuppressive therapies. Strict categorization of these patients into FRNS/SRNS groups is rather inaccurate.

Another limitation of our study is that a complete coagulation profile like D-dimer, fibrinogen assay and tests for procoagulant states could not be performed in all the children due to technical and financial constraints.

We observed that some children developed thrombotic events even when the disease was in clinical remission. We do not have an adequate explanation on the pathogenesis of this event but it is an important clinical observation from our study.

Conclusions

Although rare, TECs are life-threatening complications in children with NS. Thrombotic complications are predominantly venous, but arterial thrombosis can also occur. They are more common in SRNS or SDNS but they can also be encountered during the first episode or a relapse in infrequently relapsing NS. Thrombotic risk factors, such as severe hypoalbuminemia, infections, arterial or venous punctures and volume compromise should be identified and promptly treated. Coexistence of genetic prothrombotic condition can occur, and merits evaluation. A high index of

suspicion for thrombotic complications in a child with NS is required as the clinical features may be subtle. Neuroimaging and angiographic techniques help in confirming of diagnosis. Our experience shows that early aggressive heparin therapy followed by oral anticoagulants is required for a favorable outcome.

Conflict of interest All the authors have declared no competing interest.

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