Thromboembolic complications in children with primary nephrotic syndrome: A Tunisian series

Complications thromboemboliques au cours du syndrome néphrotique primitif de l'enfant : Une série tunisienne

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Abstract

Introduction: Nephrotic syndrome is a common pathology in children. Despite its good prognosis, it can become complicated and threaten the patient's vital and functional prognosis. Thromboembolic complications are rare but serious.
Aim: To study the main thromboembolic events and their outcome during primary nephrotic syndrome in children.
Methods: It was a retrospective study of the records of children followed for primary nephrotic syndrome who presented one or more thromboembolic events
Results: Twenty thromboembolic events in 19 children were identified (15 boys and 4 girls). The average age was 5.13±3.4 years at the time of NS diagnosis. The location of the thrombosis was venous in 14 cases. Cerebral venous thrombosis was noted in seven cases, pulmonary thromboembolism in five cases. We noted deep venous thrombosis of lower limbs in three cases, occlusive mesenteric ischemia in two cases, vein portal thrombosis in one case, renal vein thrombosis in one case, and thrombosis of a peripheral artery in one case.
Conclusion: Venous and arterial thrombotic complications can occur in children with nephrotic syndrome. Clinical features may be subtle; therefore, neuroimaging and angiographic techniques are essential for diagnosis.
Key words: nephrotic syndrome, cerebral venous thrombosis, pulmonary thromboembolism, deep venous thrombosis, children

Résumé

Introduction: Le syndrome néphrotique est une pathologie fréquente chez l'enfant. Malgré son bon pronostic, des complications sévères peuvent se rencontrer et menacer le pronostic vital et fonctionnel du patient. Parmi ces complications, les accidents thromboemboliques sont rares mais graves.
Objectif : Etudier les principaux événements thromboemboliques et leur évolution au cours du syndrome néphrotique primitif de l'enfant.
Méthodes : Il s'agit d'une étude rétrospective des dossiers d'enfants suivis pour un syndrome néphrotique primitif et ayant présenté un ou plusieurs événements thromboemboliques.
Résultats : Vingt événements thromboemboliques chez 19 enfants ont été identifiés (15 garçons et 4 filles). L'âge moyen était de 5,13±3,4 ans au moment du diagnostic du SN. La localisation de la thrombose était veineuse dans 14 cas. Une thrombose veineuse cérébrale a été notée dans 7 cas, une embolie pulmonaire dans 5 cas. Nous avons noté une thrombose veineuse profonde des membres inférieurs dans 3 cas, une ischémie mésentérique occlusive dans 2 cas, une thrombose veineuse portale dans 1 cas, une thrombose de la veine rénale dans 1 cas, et une thrombose d'une artère périphérique dans 1 cas.
Conclusion : Des complications thrombotiques veineuses et artérielles peuvent survenir chez les enfants atteints du syndrome néphrotique. Les caractéristiques cliniques peuvent être subtiles ; par conséquent, les techniques de neuro-imagerie et d'angiographie sont essentielles pour le diagnostic.
Mots clés : syndrome néphrotique, thrombose veineuse cérébrale, embolie pulmonaire, thrombose veineuse profonde, enfants.

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INTRODUCTION

Nephrotic syndrome (NS) is characterized by the triad of proteinuria, hypoalbuminemia, and oedema. It is the most common nephropathy in children, its incidence ranges from 1-15 to 16-9 per 100000 children [1]. Nephrotic syndrome can lead to several complications, some of which can threaten the vital prognosis: infectious complications, iatrogenic complications secondary to prolonged corticosteroid therapy (osteoporosis, growth retardation, cataract…), and a very rare but possible evolution to end-stage renal failure, especially in steroid resistant forms. Thromboembolic disease (TE) is a serious complication, which includes deep vein thrombosis (DVT) with or without pulmonary embolism (PE) and arterial thrombosis [2-3].

The aim of our study was to remind through this pediatric series that despite their rarity, thromboembolic complications can threaten the vital prognosis. their research must be systematic in front of the least suggestive symptomatology.

METHODS

This is a retrospective study conducted in the nephrology pediatric unit of Charles Nicolle university hospital. Children included were those who had had a TE complication related to an idiopathic NS over a period of 20 years (January 1990 to March 2021).

Idiopathic nephrotic syndrome was defined according to the French society of pediatric nephrology by the presence of hypoproteinemia<60g/L, albuminemia<30 g/L associated with 24-hour proteinuria > 50 mg/Kg/day, or urine protein/creatinine ratio ≥ 2 g/g [4]. The treatment regimen consisted of prednisone (60 mg/m2/day; 2 doses; maximum 60 mg/day) given orally for 4 weeks, followed by alternate-day therapy for 8 weeks; the alternate dose was then tapered for 6 weeks and then, stopped [4]. Response to CS therapy was defined as disappearance of proteinuria (<5 mg/m^2 per day on 3 consecutive days), whereas children who had nephrotic range proteinuria and hypoalbuminemia at the end of 4 weeks of CS therapy followed by 3 boli of methylprednisolone at a dose of 1 g/1.73 m^2 were considered as steroid resistant.

Medical charts and computer-based data were evaluated to obtain detailed information about clinical risk factors, radiological imaging methods, anticoagulation treatment, and long-term outcome of the children with NS and thrombosis. Children diagnosed with secondary nephrotic syndrome were excluded from our study.

RESULTS

Among 622 children followed for primary nephrotic syndrome, thromboembolic complications (TEc) occurred in 19 children (15 boys and 4 girls). During the study period, 20 thrombotic events had occurred, with a frequency of 3.2%. The mean age was 5.13±3.4 years (range: 1-13 years) at the time of NS diagnosis.

The mean time from NS diagnosis to the first thrombosis event was 4.8± 4.4 years (range: 0-12 years). Initial presentation of NS and thrombosis occurred at the same time in 1 (5 %) child. Thrombosis occurred during the first year of NS in 8 (40 %) children and after the first year of diagnosis in the other 11 (55 %) children. The baseline characteristics of these children are summarized in Table 1.

Table 1: Baseline characteristics of the children at the time of presentation

Patient profile	Frequency
Mean age (years)	9.5±5.2
Male/Female ratio	3.75 (15/4)
Mean age at onset of NS (years)	5.13±3.4
First episode of NS	5 (26.3%)
Dependent nephrotic syndrome	12 (63.1%)
Steroid-resistant nephrotic syndrome	7 (36.8%)
Mean serum albumin (g/dl)	1.57±4.3
Hypoalbuminemia (<2 g/dl)	19 (95%)
Proteinuria (>50 mg/Kg/d)	19 (95%)
Serum cholesterol (<200 mg/dl)	1 (5%)
Serum cholesterol(200–400 mg/dl)	12 (60%)
Serum cholesterol (>400 mg/dl)	7 (35%)
Anemia (hemoglobin<10 g/dl)	3 (15%)
Hemoconcentration (hemoglobin >14 g/dl)	3 (15%)
Thrombocytois (platelets>450 *10^9/l)	2 (10%)
Prerenal azotemia (urea>40 mg/dl, creatinine>1 mg/dl)	5 (25%)
- Stage 3 of chronic kidney disease	2
- Stage 4 of chronic kidney disease	1
- Stage 4 of chronic kidney disease	2
History of arterial/venous puncture	1 (5%)
History of diuretic use	2 (10%)

Of the 20 events, episodes occurred in children with steroid-dependent NS in 12 cases (63.1%), and 7 (36.8%) episodes occurred in children with steroid-resistant NS (SRNS).

Proteinuria more than 50 mg/Kg/d was present in 19 of the 20 thrombotic events, in 1 case proteinuria was sub-nephrotic. The mean serum albumin level in our cohort was found to be 1.57±4.3 g/dl and hypoalbuminemia was seen in 95% of children. Nineteen children were on acetylsalicylic acid at the time of the thromboembolic event because of an albumin level < 2 g/dL Tests for inherited thrombophilic conditions and antiphospholipid antibodies (APLAs) were performed 6 weeks after stopping anticoagulation in 4 children with thromboembolic risk factors other than nephrotic syndrome. In another case, a thrombophilia screening test was performed on a patient who had a second thromboembolic event. None of our patients had thrombophilia abnormalities.

The clinical presentations included: Cerebral venous thrombosis (CVT) in 7 cases, pulmonary thromboembolism (PTE) in 5 cases, deep venous thrombosis (DVT) of lower limbs in 3 cases, occlusive mesenteric ischemia (OMI) in 2 cases, vein portal thrombosis (VPT), renal vein thrombosis (VRT), and thrombosis of limb artery (LA) were found in 1 case each.

CVT occurred in 7 children, strabismus was the presenting symptom in 2 children, facial paralysis with hemiplegia was noted in 2 cases, drowsiness, seizure, and headaches were present in 1 case respectively. All 6 patients had massive proteinuria with severe hypoalbuminemia, only one patient had sub-nephrotic proteinuria. the TE accident was seen on average of 324 days after the onset of NS. 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. Superior sagittal sinus thrombosis was the commonest sinus involved in 3 cases, in the other case, the thrombosis was massive and extended to all sinuses. The evolution was good in 6 cases under anticoagulant treatment; only one patient kept a sequential hemiparesis.

PTE occurred in 5 cases, it was seen on average 34 days after hospitalization in children who had presented with relapse of NS, or with edema and heavy proteinuria (extremes: 1-120 d). Breathing difficulty was seen in 4 children followed by tachycardia in 1 case. Echocardiography was performed in 5 children and was found to be normal. D-dimer, was positive in all cases. Doppler ultrasound of the lower limbs was performed in all children but was found to be normal. CT angiography performed in all cases showed involvement of the left major pulmonary artery in the 5 cases. The outcome was fatal in 3 children with severe respiratory distress secondary to massive pulmonary embolism.

DVT of the lower limb was seen in 3 cases; children had presented a disabling calf pain. ultrasound sonography showed a complete thrombosis of the right common femoral vein in 2 cases, and the sural vein in 1 case. All the children recovered following anti-coagulation.

OMI complicated relapsed nephrotic syndrome in 2 cases in two girls aged 14 years each. They were hospitalized for non-specific diffuse abdominal pain associated with vomiting. The computer tomography (CT) scan showed an extensive thrombosis of the superior mesenteric vein (SMV), and portal vein with generalized bowel wall edema in both cases. The outcome was fatal in both cases due to extensive intestinal necrosis despite appropriate treatment.

PVT was seen in 1 case with abdominal pain, the abdominal CT scan confirmed the diagnosis by showing a total thrombosis of the portal trunk, the mesenteric vein and the splenic vein. the outcome was good with a complete repermeabilization of the portal vein.

The child with RVT presented with abdominal pain, renal ultrasonography showed a left peri-renal collection. The CT scan showed a thrombosis of the left renal vein extended to the inferior vena cava.

Thrombosis of LA was seen in one case, a history of arterial puncture prior to the development of the ischemia was elicited in our patient. The child presented with pain, coldness, and pallor of the right upper limb evolving for 3 days. The diagnosis of an upper limb ischemia was made, the child recovered completely after thrombolysis followed by anticoagulation with conventional heparin and later acetyl salicylic acid given for a total of 3 months.

Final outcome was good with complete recovery seen in 14 (70%) out of 20 events, 5 children died in our cohort, of whom 3 had massive pulmonary artery thrombosis, and 2 had mesenteric ischemia by thrombosis of the mesenteric artery. One child had kept a sequential hemiparesis following a CVT. A summary of the different thromboembolic complications and their evolution is presented in Table 2.

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

Type of TEC	No of TEC	Mean age	Sex (M/F)	SDNS/ FRNS	SRNS	Recovery (%)
CVT	7 (35%)	8.7±5.7	6/1	6	1	7 (100%)
PTE	5 (25%)	8.6±7.1	5/0	2	3	3 (60%)
DVT	3 (15%)	11.2±3.8	2/1	1	2	3 (100%)
OMI	2 (10%)	14	0/2	1	1	0
RVT	1 (5%)	4.25	1/0	-	1	1 (100%)
LA	1 (5%)	4.5	1/0	1	-	1 (100%)
VPT	1 (5%)	14	1/0	1	-	1(100%)

CVT: Cerebral venous thrombosis; **PTE:** Pulmonary thromboembolism; **DVT:** Deep venous thrombosis; **OMI:** Occlusive mesenteric ischemia; **RVT:** Renal venous thrombosis; **LA:** Limb artery; **VPT:** Vein portal thrombosis

DISCUSSION

Nephrotic syndrome (NS) is associated with a high risk of TE complications [5], the hypercoagulable state in NS is multifactorial, attributed predominantly to urinary loss of anticoagulants, increased procoagulant activity, altered fibrinolytic system, thrombocytosis, and enhanced platelet activation and aggregation [6-7]. Despite the frequency of primary nephrotic syndrome in children, the incidence of thromboembolic complications remains difficult to assess. The reported incidence of TECs in adults with NS ranges from 9 to 70 % [8], while the frequency of clinically evident TECs in children, as reported in various studies is only between 1.8 and 4.4 % [9-12]. The frequency of thromboembolic complications in our study was 3.2% which is consistent with the literature. We tried to describe the spectrum, associated severe complications and outcomes of thrombosis in children with primary NS treated in our

center within a period of 31 years. The average onset age (9.5± 5.2 years) is comparable to those reported by Yan-Li et al. (9.5 ± 4 years) and Suri et al. (7.7 ± 2.7 years) [13-14]. TEC were more frequent in boys (15/4), this was similar to those reported by Yan-Li et al (21/6) [13]. In contrast to Suri's report that 14.7% of thrombosis events occurred during the first episode of NS [14], thrombosis in most of the subjects in this study occurred during the first episode of NS. A massive proteinuria was present in 19 patients, this suggesting that thrombosis occurred in most subjects during the active stage of NS. Consistent with Lilova and Suri's report, CVT were the most frequent TEC [11,14]. Patients with portal vein thrombosis, and superior mesenteric vein (SMV) thrombosis presented with non-specific symptoms, including abdominal pain, vomiting. This finding suggests that careful imaging examinations should be considered, irrespective of the symptoms, for patients at high risk of thrombosis. The mortality in our study (25%) was higher than that reported by Tavil et al (17.6%) [15]. In our study, the anatomic sites of thrombosis related to severe complications were the SMV, pulmonary artery. SMV thrombosis is a very rare but life-threatening condition. A few rare cases of acute mesenteric ischemia in patients with nephrotic syndrome have been reported. To the best of our knowledge, 4 cases of OMI were reported in children with primary NS [13,16]. This study has limitations. First, this was a retrospective study, Second, only subjects with thrombosis confirmed by imaging methods were included in the analysis, which might bias the severe complications findings.

CONCLUSIONS

Idiopathic nephrotic syndrome is a common disease in children. thromboembolic complications occurring during this disease are rare but serious and may be life-threatening. The most common sites of thrombosis were the CV and pulmonary artery. After aggressive therapy, 75% of the cases of thrombosis had a good outcome. Thrombosis in the SMV and arteries are life-threatening or organ-threatening conditions that deserve more attention and aggressive therapy.

REFERENCES

1. Banh TH, Hussain-Shamsy N, Patel V, et al. Ethnic differences in incidence and outcomes of childhood nephrotic syndrome. Clin J Am Soc Nephrol. 2016; 11:1760-68.
2. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. Clin J Am Soc Nephrol. 2012;7:513-20.
3. Kerlin BA, Haworth K, Smoyer WE. Venous thromboembolism in pediatric nephrotic syndrome. Pediatr Nephrol. 2014;29:989-97.
4. High Authority for Health. National protocol for Diagnosis and care for a rare disease. Idiopathic nephrotic syndrome in children; 2016, https://www.has-sante.fr/portail/jcms/c_2628561/fr/syndrome-nephrotique-idiopathique-de-l-enfant.
5. Christiansen CF, Schmidt M, Lamberg AL, Horvath-Puho E, Baron JA, Jespersen B, et al. Kidney disease and risk of venous thromboembolism: a nationwide population-based case-control study. J Thromb Haemost. 2014;12:1449-54.
6. Se Jin Park, Jae Il Shin. Complications of nephrotic syndrome. Korean J Pediatr. 2011;54(8):322-8.
7. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. Clin J Am Soc Nephrol. 2012;7:513-20.
8. Noone DG, Iijima K, Parekh R. Idiopathic nephrotic syndrome in children. Lancet. 2018;392(10141):61-74.
9. Rabelink JT, Zwaginga JJ, Koomans HA, Sixma JJ. Thrombosisand hemostasis in renal disease. Kidney Int. 1994;46:287-96.
10. Tinaztepe K, Buyan N, Tinaztepe B, Akkok N. The association of nephrotic syndrome and renal vein thrombosis: a clinicopatho-logical analysis of eight pediatric patients. Turk J Pediatr. 1989;31:1-18.
11. Lilova MI, Velkovski IG, Topalov IB. Thromboembolic complications in children with nephrotic syndrome in Bulgaria(1974–1996). Pediatr Nephrol. 2000;15:74-8.
12. Andrew M, Brooker LA. Hemostatic complications in renal disorder of the young. Pediatr Nephrol. 1996;10:88-99.
13. Lv YL, Guan N, Ding J, Yao Y, Xiao HJ, Zhong XH, et al. Spectrum of thrombotic complications and their outcomes in Chinese children with primary nephrotic syndrome. Ital J Pediatr. 2020; 46(1):182.
14. Suri D, Ahluwalia J, Saxena AK, Sodhi KS, Singh P, Mittal BR, et al. Thromboembolic complications in childhood nephrotic syndrome: a clinical profile. Clin Exp Nephrol. 2014;18(5):803–13.
15. Tavil B, Kara F, Topaloglu R, Aytac S, Unal S, Kuskonmaz B, et al. Case seriesof thromboembolic complications in childhood nephrotic syndrome:Hacettepe experience. Clin Exp Nephrol. 2015;19(3):506-13.
16. Gera DN, Patel J, Patel K, Kute VB. Portal vein thrombosis: a rare complication of nephrotic syndrome. Indian J Nephrol. 2018;28(3):236-9.