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The Frequency of Thromboembolic Complications in Pediatric Nephrotic Syndrome

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Abstract

Background: Nephrotic syndrome (NS) is a common renal disease in the pediatric population, which can be complicated with venous thromboembolic events.
Objectives: In the present study, the researchers evaluated the risk factors of venous thrombotic events in children with nephrotic syndrome.
Methods: In this descriptive cross sectional study, the researchers evaluated 43 cases of NS including 35 uncomplicated and eight complicated patients with venous thrombotic events, who were admitted to the nephrology ward of Ali-Asghar Children Hospital from 2011 to 2015. Two groups were matched for age onset of NS. Data were recorded on age, gender, body mass index (BMI), histopathologic varieties of NS, and serum albumin level.
Results: The mean age of cases with venous thrombotic events was 7.31 $\pm$ 4.1 years. There were six females. Of eight cases with venous thrombotic events, five cases suffered of pulmonary thromboembolism (PTE) and five cases of deep vein thrombosis (DVT). The mean serum albumin level in the thrombotic group was 1.87 $\pm$ 0.4 g/dL. The histopathologic results showed two cases of membranous proliferative glomerulonephritis (MPGN), three cases of minimal change disease (MCD) and one case of focal segmental glomerulosclerosis (FSGS). The researchers found significant differences between mean serum albumin level and histopathologic results in the case and control groups.
Conclusions: Venous thrombosis and pulmonary emboli are important complications in pediatric NS. The risk of VTE increases with lower serum albumin level. The risk of VTE increases with lower serum albumin level. The researchers suggest the use of antithrombotic agents as prophylaxis in nephrotic patients with serum albumin level of less than 2 g/dL.

Keywords: Nephrotic Syndrome, Venous Thromboemboli, Albumin Level, Pediatric

1. Background

Nephrotic syndrome (NS) is a disease defined as massive proteinuria, edema, hypoalbuminemia, and hyperlipidemia. It is associated with hypercoagulability and venous thromboembolic events (VTEs). Thromboembolic events are important complications of NS, including pulmonary emboli (PE), deep vein thrombosis (DVT) and renal venous thrombosis (RVT). The different parameters are known as risk factors for VTEs. In the adult population, VTEs occur more frequently in NS with membranous nephropathy, in the first six months of disease presentation, in cases with low serum albumin level, antithrombin activity deficiency, and high level of ionized calcium. Most studies regarding thromboembolic events in NS patients are done on the adult population and there are a few studies on children (1-6).

2. Objectives

This study aimed at determining demographic, histopathologic, and laboratory findings in children with NS complicated by VTE.

3. Methods

This was a descriptive cross sectional study including eight cases of idiopathic nephrotic syndrome admitted to the nephrology ward of Ali-Asghar Children's Hospital of Tehran, Iran from 2011 to 2015. They had VTE as an NS complication. Diagnosis of idiopathic NS was done by the center nephrologist due to clinical manifestation of edema, hypercholesterolemia, hypoalbuminemia, and proteinuria more than 50 mg/kg per day. The secondary NS and also the congenital NS cases were excluded. These

cases were admitted because of the first presentation of NS or due to its relapse. Another group of 35 primary idiopathic NS patients without VTE were chosen as the control group. These two groups were matched according to the mean age of disease onset.

Collected data included age, gender, BMI, serum albumin level (SAL), histopathologic result, and the sort of VTE. All data were obtained from medical records and collected through inventories. Statistical analysis was performed using SPSS V. 18. The student *t*-test and Pearson correlation were employed for comparing variables. P values of less than 0.05 were considered as significant. The project was approved by the Ethics Committee of Iran University of Medical Sciences.

4. Results

The mean age of onset of NS of the eight patients in the case group was 3.81 years (± 2.6 y/o) and that of the control group was 3.17 years (± 2.0 y/o) without a significant difference (P = 0.53). There was no significant difference between the groups' mean age and weights, and BMI (P = 0.05) (Table 1).

The mean age of the case group at the study time was 7.3 years (± 4.1 y/o) and 4.7 (± 3.8 y/o) in the control group and this difference was significant (P = 0.03). There were six females in the case group (75%) and 15 females in the control group (43%). pulmonary emboli (PE) occurred in three cases and five patients had deep vein thrombosis (DVT). No case of renal vein thrombosis (RVT) was found. None of the cases had VTE at the first six months of their NS presentation. The BMI in case and control groups were without a significant difference. The mean serum albumin level in the case group was 1.86 g/dL (± 0.4 g/dL) and in the control group, this was 2.41 g/dL (± 0.4 g/dL) with a significant difference (P = 0.01 and 95% CI: -0.91 and -0.15). There was a significant difference between groups' mean albumin levels (P = 0.05) (Table 2).

The histopathologic feature of focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN) and minimal change disease (MCD) were distinguished in one, two, and three cases in the VTE group, respectively (two cases did not undergo renal biopsy), while in the control group, there were eight FSGS, five MCD, and no MPGN with a significant difference between these two groups (P = 0.01 and 0.01 for FSGS and MPGN, respectively). The mean serum albumin level in MPGN was lower than the other patients. Mean albumin level was 1.60 ± 0.56 g/dL in the MPGN patients yet in other pathologic varieties, the mean serum albumin level was more than 2 g/dL (P = 0.05).

5. Discussion

Most studies about the frequency and risk factors of VTEs in nephrotic syndrome have been done on adult patients and the studies in pediatric age group are scarce. Study on pediatrics can make better insight on this group.

According to the results of this study, the mean age of patients' complicated with venous thrombosis is about 3.2 years more than nephrotic patients without VTE. This shows that VTE in NS is not a frequent event at a very young age and by increase in age, the rate of these events will be more in nephrotic patients.

In the present study, the number of VTE in female patients was significantly more than male patients, while in Ismail et al.'s study, the VTE were more frequent in male adult patients. This needs bigger retrospective or prospective studies on pediatric and adult patients (7).

Table 1. Demographic Features of Two Groups

Group	N	Mean ± SD	Std. Error Mean
BMI			
Case	8	18.35000 ± 2.5253005	0.8928286
Control	35	18.88000 ± 3.8615602	0.6527228
Weight			
Case	8	27.62500 ± 12.4290846	4.3943450
Control	35	20.92857 ± 8.6080869	1.4550322
History			
Case	8	2.00 ± 0.000	0.000
Control	35	1.97 ± 0.169	0.029

Table 2. Group Statistics; Mean Ages, Mean Albumin, and GFR Level

Group	N	Mean ± SD	Std. Error Mean
Age			
Case	8	7.31 ± 4.166	1.473
Control	35	4.60 ± 3.053	0.516
Age onset			
Case	8	4.00 ± 2.646	0.935
Control	35	3.17 ± 2.083	0.352
GFR			
Case	8	91.62 ± 28.804	10.184
Control	35	99.54 ± 18.979	3.208
ALB			
Case	8	1.862500 ± 0.4867898	0.1721062
Control	35	2.400000 ± 0.4814195	0.0813747

Serum albumin level in the thromboembolic group of this study is significantly lower than the control group. This finding is similar to other studies, mostly done on adult patients (7-9). In the current study, the mean serum albumin level of thromboembolic group was 1.87 g/dL. Some studies consider serum albumin level less than 2.5 g/dL and some less than 1.5 g/dL as a higher risk for VTE (7, 10). This finding can suggest the use of intensification of prophylactic anti-thrombotic treatment in nephrotic patients with severe hypoalbuminemia.

This study showed that there was a relationship between the mean serum level of albumin and the histopathologic varieties. As the results of this study found that the mean serum albumin level in MPGN is less than the other pathologic features, therefore there is greater risk for VTE. Previous studies showed that membranous nephritis (MN) is the most frequent variety that had a direct relationship with VTE (10). This discrepancy between the current study and previous studies could be due to the population of studies; the current population of nephrotic was children under 14 years old yet others were mostly on adult populations, therefore, it seems that more studies are needed on pediatric population.

Regarding the kind and site of VTE, some study results on the adult population with NS, especially with membranous nephropathy, have shown that renal vein thrombosis is the most frequent VTE, especially in the presence of severe hypoalbuminemia (9, 10) Zhang et al. showed that 35% of NS cases had PE or RVT. According to this study PE were more common than RVT. Furthermore, PE in 84% of cases was asymptomatic. According to this study, most PE cases were asymptomatic and older age is a risk factor (11). In Kayali et al.'s study, RVT is more common than PE in NS (12). Li et al. in a study on 100 cases of NS, reported that RVT is more common than PE. It seems that asymptomatic PE cases were the reason of this discrepancy (13).

According to the current study, RVT did not occur. According to Medjeral-Thomas et al.'s study incidence of VTE in MN is more than other forms of NS (14). This difference between previous and the present study might be due to the difference between the age of the population, as membranous nephropathy in adults are frequent but not in pediatrics.

5.1. Conclusions

The result of the current study showed that there is a close relationship between serum albumin level and VTE presentation in pediatric nephrotic syndrome. The researchers could suggest the use of anti-thrombotic agents as prophylaxis in nephrotic patients with serum albumin level less than 2 g/dL. However, the limitation of the current study was the number of patients with VTE. More studies in this field on a larger pediatric population are needed.

Supplementary Material

Supplementary material(s) is available here [To read supplementary materials, please refer to the journal website and open PDF/HTML].

Footnotes

Authors' Contribution: Study concept and design and statistical analysis: Nasrin Hoseiny Nejad; acquisition of data: Malihe Tahoori; analysis and interpretation of data and administrative, technical, and material support: Rozita Hosseini; study supervision: Hasan Otukesh; drafting of the manuscript and critical revision of the manuscript for important intellectual content: Maryam Saboute.

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References

1. Chesney RW. The idiopathic nephrotic syndrome. *Curr Opin Pediatr*. 1999;**11**(2):158–61. [PubMed: 10202626].
2. Llach F. Hypercoagulability, renal vein thrombosis, and other thrombotic complications of nephrotic syndrome. *Kidney Int*. 1985;**28**(3):429–39. [PubMed: 3906225].
3. Singhal R, Brimble KS. Thromboembolic complications in the nephrotic syndrome: Pathophysiology and clinical management. *Thromb Res*. 2006;**118**(3):397–407. doi: 10.1016/j.thromres.2005.03.030. [PubMed: 15990160].
4. Barbour SJ, Greenwald A, Djurdjev O, Levin A, Hladunewich MA, Nachman PH, et al. Disease-specific risk of venous thromboembolic events is increased in idiopathic glomerulonephritis. *Kidney Int*. 2012;**81**(2):190–5. doi: 10.1038/ki.2011.312. [PubMed: 21918501].
5. Lionaki S, Derebail VK, Hogan SL, Barbour S, Lee T, Hladunewich M, et al. Venous thromboembolism in patients with membranous nephropathy. *Clin J Am Soc Nephrol*. 2012;**7**(1):43–51. doi: 10.2215/CJN.04250511. [PubMed: 22076873]. [PubMed Central: PMC3265338].
6. Cherng SC, Huang WS, Wang YF, Yang SP, Lin YF. The role of lung scintigraphy in the diagnosis of nephrotic syndrome with pulmonary embolism. *Clin Nucl Med*. 2000;**25**(3):167–72. [PubMed: 10698409].
7. Ismail G, Mircescu G, Ditoiu AV, Tacu BD, Jurubita R, Harza M. Risk factors for predicting venous thromboembolism in patients with nephrotic syndrome: Focus on haemostasis-related parameters. *Int Urol Nephrol*. 2014;**46**(4):787–92. doi: 10.1007/s11255-013-0574-0. [PubMed: 24078010].
8. Glassock RJ. Prophylactic anticoagulation in nephrotic syndrome: A clinical conundrum. *J Am Soc Nephrol*. 2007;**18**(8):2221–5. doi: 10.1681/ASN.2006111300. [PubMed: 17599972].

9. Bellomo R, Wood C, Wagner I, Agar J, Dowling J, Thomson N, et al. Idiopathic membranous nephropathy in an Australian population: The incidence of thromboembolism and its impact on the natural history. *Nephron*. 1993;**63**(2):240–1. doi: 10.1159/000187197. [PubMed: 8450923].
10. Kerlin BA, Ayoob R, Smoyer WE. Epidemiology and pathophysiology of nephrotic syndrome-associated thromboembolic disease. *Clin J Am Soc Nephrol*. 2012;**7**(3):513–20. doi: 10.2215/CJN.10131011. [PubMed: 22344511]. [PubMed Central: PMC3302669].
11. Zhang LJ, Zhang Z, Li SJ, Meinel FG, Nance JW Jr, Zhou CS, et al. Pulmonary embolism and renal vein thrombosis in patients with nephrotic syndrome: Prospective evaluation of prevalence and risk factors with CT. *Radiology*. 2014;**273**(3):897–906. doi: 10.1148/radiol.14140121. [PubMed: 25072187].
12. Kayali F, Najjar R, Aswad F, Matta F, Stein PD. Venous thromboembolism in patients hospitalized with nephrotic syndrome. *Am J Med*. 2008;**121**(3):226–30. doi: 10.1016/j.amjmed.2007.08.042. [PubMed: 18328307].
13. Li SJ, Guo JZ, Zuo K, Zhang J, Wu Y, Zhou CS, et al. Thromboembolic complications in membranous nephropathy patients with nephrotic syndrome-a prospective study. *Thromb Res*. 2012;**130**(3):501–5. doi: 10.1016/j.thromres.2012.04.015. [PubMed: 22633211].
14. Medjeral-Thomas N, Ziaj S, Condon M, Galliford J, Levy J, Cairns T, et al. Retrospective analysis of a novel regimen for the prevention of venous thromboembolism in nephrotic syndrome. *Clin J Am Soc Nephrol*. 2014;**9**(3):478–83. doi: 10.2215/CJN.07190713. [PubMed: 24334865]. [PubMed Central: PMC3944768].