

Clinical Study

Predisposing Factors for Deep Venous Thrombosis in Children and Adolescents with Nephrotic Syndrome

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Nephrotic syndrome (NS) is a state of hypercoagulability. In this paper, we sought to determine risk factors for the occurrence of deep vein thrombosis (DVT) in children with NS. The “with DVT” group included patients with decompensated NS and diagnosed with DVT. The “without DVT” group included the same patients, six to eighteen months prior to the episode of DVT, with decompensated NS but without DVT. Different prediction variables were analyzed. The odds ratio for the occurrence of DVT in patients with triglyceride levels ≥ 300 mg/dL was 3.14 (95% CI 1.14 to 8.64). For hematocrit levels $\geq 43\%$ and for the presence of infection or a severe systemic event, the odds ratio was 4.37 (95% CI 1.23 to 15.53). The presence of significant risk factors for the occurrence of DVT in children with NS may serve as a warning for the occurrence of venous thrombosis.

1. Introduction

Many studies have associated nephrotic syndrome (NS) with a multifactorial hypercoagulable state [1]. This NS-associated hypercoagulability is dependent not only on changes in pro- and anticoagulant factors but also on hemodynamic characteristics that favor thrombosis, such as the tendency toward hypovolemia and hemoconcentration. NS can result in the urinary loss of proteins that inhibit the hemostatic system (e.g., antithrombin III) and the increased synthesis of factors that promote thrombosis (factors V, VIII, and fibrinogen) [2]. Conditions such as thrombocytosis, increased levels of von Willebrand factor, and increased formation of thromboxane A₂ are also observed in patients with the disease [3]. While some studies have shown lower serum levels of protein S and reduced activity of protein C in patients with NS [3], other studies point to increased levels and activity of these proteins [4, 5], possibly due to the variability in the severity of hypoalbuminemia and proteinuria and the time since last steroid use, which may bias the results of these studies. The mentioned factors are closely associated with the occurrence of venous or arterial

thrombosis, a serious complication of NS. Thrombosis in NS has not been associated with genetic factors that lead to hypercoagulability [6].

Risk factors for thromboembolism in adult patients with NS are described as follows: a high urine protein to serum albumin ratio (predictive factor for venous thrombosis) as well as age, hypertension, diabetes, and smoking (predictive factors for arterial thrombosis) [7]. However, there are few studies concerning these risk factors in the pediatric population.

Although the incidence of DVT in nephrotic patients under the age of 18 is lower than in adults [8], thromboembolic events can have serious consequences in children and adolescents. Thus, the purpose of this study was to determine the predisposing factors for the occurrence of DVT in children and adolescents with primary NS.

2. Methods

This was a retrospective case study. It was composed of all records from children and adolescents (up to 18 years of age) with diagnoses of idiopathic NS and DVT who were regularly

TABLE 1: Baseline characteristics of cases.

Patient	Age “without DVT”/“with DVT” (in years)	Time between periods “without DVT” and “with DVT”	Gender	Response to steroid therapy	Site of thrombosis	Infection or severe systemic event—“without DVT”	Infection or severe systemic event—“with DVT”
Patient 1	6/6	6 months	M	Steroid dependent	Venous sinus	—	Periumbilical cellulitis
Patient 2	3/4	6 months	F	Steroid resistant	Left lower extremity	—	Multifocal cellulitis
Patient 3	7/7	6 months	M	Steroid sensitive	Left lower extremity	—	Right lower extremity cellulitis
Patient 4	3/4	12 months	M	Steroid sensitive	Right lower extremity	—	Peritonitis
Patient 5	7/9	18 months	F	Steroid dependent	Left lower extremity	—	Right lower extremity cellulitis and pneumonia
Patient 6	9/10	6 months	M	Steroid resistant	Venous sinus	—	Peritonitis and urinary tract infection
Patient 7	6/6	7 months	M	Steroid dependent	Venous sinus	Acute otitis media	—
Patient 8 (1st episode of DVT)	5/6	12 months	M	Steroid dependent	Right lower extremity	—	Acute pancreatitis
Patient 8 (2nd episode of DVT)	11/12	6 months	M	Steroid dependent	Right lower extremity	—	—
Patient 9 (1st episode of DVT)	9/10	12 months	F	Steroid sensitive	Subclavian vein	Lower extremities cellulites	Lower extremities cellulitis
Patient 9 (2nd episode of DVT)	11 / 12	18 months	F	Steroid sensitive	Right lower extremity	Lower extremities cellulites	Left lower extremity cellulitis

Subtitle: M: male; F: female.

monitored at the Pediatric Nephrology Unit of the University Hospital of the State University of Campinas, Brazil.

NS was defined according to the ISKDC (International Study of Kidney Disease in Children) criteria [9]. Episodes of venous thrombosis were defined via clinical diagnosis (i.e., presence of edema with asymmetric limb tightness and pain during palpation) and confirmed by Doppler ultrasound. Episodes of venous sinus thrombosis were confirmed using computed tomography or magnetic resonance angiography.

We analyzed the charts of patients with DVT at two different time points, at the time of DVT diagnosis and at the patients' most recent hospitalization (a period of six to eighteen months earlier), when patients were also hospitalized because of decompensated NS, but without the occurrence of DVT. We excluded patients who had a personal or family history of thrombophilia. Patients with DVT on presentation were included in the “with DVT” group, and patients on admission prior to the occurrence of DVT were considered the “without DVT” group.

The prediction variables analyzed are described below. Prior to admission, we looked for dehydration (48 hours before admission), diuretic use, acetylsalicylic acid use,

trauma history, and response to steroid therapy (according to the ISKDC criteria [9]). During hospitalization, the following variables were included as possible risk factors for DVT: hemoglobin and hematocrit levels, current dose of prednisone, level of lipids (total cholesterol, triglycerides and HDL), platelet number, albumin and creatinine level, infection or severe systemic event, and the use of another immunosuppressant. In addition, the weight during and after each hospitalization was collected for each patient. To obtain the percentage weight gain of the patients during hospitalization, the weight of each patient after discharge, which was the weight of the patient without edema, was used as the default value. The prednisone dose was calculated in milligrams per kilogram, and the weight of each patient after discharge, which was the weight of the patient without edema, was used.

The presence of infection that required intravenous antibiotics or serious events that required hospitalization for 48 hours or more were considered to be “severe systemic events”.

None of the “with DVT” group had indications for restraint, had vascular access in the region of the thrombosis,

TABLE 2: Results of the variable analysis between the “with DVT” and “without DVT” groups.

Variable	“With DVT” <i>M</i> ± <i>SD</i>	“Without DVT” <i>M</i> ± <i>SD</i>	<i>P</i> value
Hemoglobin (g/dL)	14.1 ± 2.7	12.9 ± 1.6	0.3
Hematocrit (%)	41.9 ± 7.1	37.2 ± 4.4	0.05
Prednisone dose/weight (mg/kg)	1 ± 0.6	0.79 ± 0.7	0.657
Total cholesterol (mg/dL)	547.3 ± 228.4	376.9 ± 210.3	0.074
Triglycerides (mg/dL)	430.6 ± 256.4	190.9 ± 94	0.008
HDL (mg/dL)	42.5 ± 4.85	36.8 ± 10.5	0.225
Platelet number (mm ³)	419545.5 ± 127513.4	400818.2 ± 120924.6	0.507
Albumin (g/dL)	1.2 ± 0.32	1.41 ± 0.5	0.959
Serum creatinine (mg/dL)	0.43 ± 0.37	0.38 ± 0.22	0.959
Weight gain during hospitalization (%)	12 ± 9.6	8.75 ± 5.6	0.248
	<i>n</i> (%)	<i>n</i> (%)	
History of dehydration	3 (27%)	0 (0%)	0.107
Use of spironolactone	6 (55%)	5 (45%)	0.5
Use of furosemide	0%	3 (27%)	0.107
Use of another immunosuppressant	2 (18%)	2 (18%)	0.707
Use of ASA	2 (18%)	1 (9%)	0.5
Trauma	0 (0%)	0 (0%)	—
Infection or severe systemic event	9 (81%)	3 (27%)	0.015

M: mean; SD: standard deviation; ASA: acetylsalicylic acid.

or was using medications that could predispose the patient to hypercoagulability.

χ^2 or Fisher tests were used to analyze categorical variables. For continuous variables, a nonparametric Wilcoxon test for related samples was used. A 95% confidence interval was used. A *P* value ≤ 0.05 was considered statistically significant. For variables with a significant *P* value, an odds ratio was calculated.

The researchers have no conflicts of interest to disclose. The study was approved by the institution’s Ethical Committee of Research.

3. Results

The earliest hospitalization occurred in 1993, and the most recent one occurred in 2009. Of the 200 charts of patients with NS that were analyzed, a total of nine medical records from patients presenting with the above criteria were studied. Of these nine, there were six males and three females. Two patients had two episodes of DVT at different times, which yielded a total of 11 cases of thrombosis (mean of 0.647 episodes of DVT per year and an absolute frequency of DVT episodes of 5.5% among all reviewed patient charts). The average age at admission prior to the occurrence of DVT was 7 ± 2.79 years, and the average age at the time of DVT presentation was 7.91 ± 3.08 years.

Concerning the location of venous thrombosis, seven occurred in the lower extremities (63%), three occurred in the cerebral venous sinus (27%), and one occurred in the subclavian vein (10%). Of the two cases in which there

was recurrence of thrombosis, no episodes occurred during anticoagulation.

Table 1 shows the profile of the patient. Table 2 presents the means and standard deviations of variables for both the “with DVT” and “without DVT” groups (relative to 11 episodes) and the *P* values obtained for each.

Of the variables in Table 2, triglyceride levels, hematocrit levels, and the presence of an infection or serious systemic event were significantly different between the “with DVT” and “without DVT” groups (*P* < 0.01, *P* = 0.05 and *P* = 0.015, resp.). These factors were increased in the “with DVT” group, compared to the “without DVT” group. There was a mean increase of 125% for triglycerides, and a mean increase of 12.63% for hematocrit. In nine episodes of DVT, the patients also had infectious complications or severe systemic events. However, only three patients from the “without DVT” group had infectious complications or severe systemic events (81% and 27%, resp.). In the “with DVT” group, there were six cases of cellulitis (in a place other than where DVT occurred), two cases of bacterial peritonitis, a case of pneumonia, a urinary tract infection, and a case of acute pancreatitis. In the “without DVT” group, there were two cases of cellulitis and one of acute otitis media.

For the variable triglyceride, no data were found for two patients. Thus, a new analysis was conducted with patients without complete data excluded, which resulted in nine episodes of DVT. In this new comparison of the potential risk factors for DVT between the two groups, there were differences between the “with DVT” and “without DVT” groups with respect to triglycerides (*P* = 0.025); the likelihood of DVT occurrence in patients with triglyceride

levels greater or equal to 300 mg/dL was 3.14 (95% CI 1.14 to 8.64). The odds ratio for the occurrence of DVT in patients with hematocrit levels greater than or equal to 43% and in patients with an infection or severe systemic event was 4.37 (95% CI 1.23 to 15.53; $P = 0.008$).

It was not possible to perform a multivariate analysis due to the small sample size.

4. Discussion

The incidence of thromboembolic events in children and adolescents with NS has been described as 1.8% to 5% [10]. In our study, the frequency of such an event was 5.5%.

In this retrospective study, we chose to consider the same patient at two different time points rather than two age- and gender-matched patients. In doing so, we were able to control for individual hereditary factors, such as the presence of proteins C and S and antithrombin III, thus preventing them from acting as confounding variables during the data analysis.

The lower extremities were the most common site of thrombosis (63%), and the prevalence of lower extremities thrombosis in our study was higher than that in other studies [10, 11]. Although cerebral venous thrombosis is considered a rare complication of NS [12], three of the eleven cases of thrombosis in our study (27%) occurred in the venous sinuses.

Thus far, no reliable predictors of the occurrence of thrombosis in children with NS have been established, and prophylactic anticoagulant therapy remains controversial [13].

The influence of the albumin levels in the pathogenesis of thrombosis in nephrotic patients is controversial. Citak et al. [4] found that nephrotic children had lower levels of antithrombin III and albumin and higher levels of fibrinogen and cholesterol, suggesting that these factors may be partially responsible for the higher incidence of DVT in nephrotic children. However, in our study, the variables albumin and cholesterol showed no significant differences between the groups.

Antithrombin III deficiency has been associated with albumin levels lower than 2 g/dL and pulmonary embolism in some studies [1, 14] but not in others [15, 16]. In our study, although albumin levels were lower, they were not associated with thrombosis, perhaps due to the high frequency in which these values are found in childhood NS. Fluss et al. [17], in a case report of nephrotic children with venous sinus thrombosis, found that not all cases had antithrombin III deficiency or an increased level of fibrinogen. They concluded that these variables were not important risk factors of thromboembolism in NS. However, the same study found hypoalbuminemia to be the only identifiable risk factor, as it induced platelet hyperaggregability and changes in the fibrinolytic system. Our study corroborates the findings of Llach et al. [18] and Velasquez Forero et al. [19], in which serum albumin levels in patients with or without thromboembolic events were not significantly different.

The use of steroids has been suggested in some studies to increase the risk of thromboembolic complications [2, 20]; however, others have not found this to be the case [17, 18]. The data presented here showed no significant differences in dose (mg/kg) between the patients with or without DVT.

This study showed that high serum triglyceride levels and hematocrit as well as the presence of infection or a severe systemic event in patients with decompensated NS were predictive of DVT occurrence in children with NS.

In a study conducted in India [21], there was a statistically positive correlation between hypercoagulability in NS, proteinuria, and increased lipid levels. In this paper, they stated that hyperlipidemia alters the platelet membrane, promoting platelet aggregation. Therefore, the results of the present study corroborate their hypothesis, as patients with triglyceride levels greater than 300 mg/dL had a higher risk of developing DVT.

The predictor hematocrit has not often been evaluated in the literature. The only study found in which this analysis was performed did not consider hematocrit to be a predisposing factor for the occurrence of DVT [22]. Theoretically, this finding may have a floor effect, as high hematocrit levels may be suggestive of hemoconcentration, a well-known predisposing factor for DVT. Thus, it should be emphasized that hematocrit values greater than 43% should increase awareness concerning an increased risk of DVT in patients with NS.

Infection is one complication of NS, and several factors predispose NS patients to infection, including decreased levels of immunoglobulins, opsonization defects, impaired production of specific antibodies, and immunosuppressive therapy [23]. This study considered only infections and severe systemic events related to the cause of the hospitalization. Thus, there was a significant association between these events and the occurrence of DVT, which was also observed by Lilova et al. [11] to be a predisposing factor for thrombosis in children with NS. However, there are few studies that have sought to assess this association.

The limitations of this study are related to its retrospective design and its small sample size, which limited the statistical analysis. As for the retrospective aspect of the study, this inconvenience has relatively little merit, as the data computed were based on objective measures and are thus less likely to have errors. However, the sample size, which is higher than that reported in the literature [4, 11, 17], can only be increased via the use of multicenter studies because DVT in nephrotic children has a low incidence.

5. Conclusion

In conclusion, the results obtained show an association between DVT in children with NS and triglycerides greater than 300 mg/dL, hematocrit greater than 43%, and the presence of infection or severe systemic event. These results have both theoretical and clinical relevance. Hence, these factors should be considered as a warning to the risk of DVT in children with NS.

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