Epidemiology and Risk Factors for Thromboembolic Complications of Childhood Nephrotic Syndrome: A Midwest Pediatric Nephrology Consortium (MWPNC) Study

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Objectives To identify clinical variables predictive of the risk of thromboembolism (TE), and to confirm the incidence of TE in primary and secondary childhood nephrotic syndrome (NS).

Study design A comprehensive chart review identified 326 children with NS from any cause evaluated between 1999 and 2006. These patients had a total of 1472.8 patient-years of follow-up. Comparison statistics, survival analysis, and logistic regression were used to define TE epidemiology and clinical risk factors.

Results We found that 9.2% of our cohort had experienced at least 1 TE. The overall incidence was 20.4 patients with TEs/1000 patient-years. The median time to the first TE was 70.5 days after diagnosis of NS. Deep venous thrombosis was the most common TE (76%) and was frequently associated with the use of a central venous catheter (45%). Significant independent predictors of TE included age ≥ 12 years at onset of NS ($P < .0001$), severity of proteinuria ($P < .0001$), and history of TE preceding diagnosis of NS ($P < .0001$). Life- or limb-threatening TEs represented 23.7% of the events.

Conclusions Children with NS should be carefully followed for TE, particularly those who are age 12 years or older, have severe proteinuria, or have a previous history of TE. *(J Pediatr 2009;155:105-10)*.

Nephrotic syndrome (NS) is most commonly idiopathic in nature, resulting from any of several well-described primary glomerulopathies that are defined by histopathology and clinical criteria.[1] Idiopathic NS has an incidence of 2 to 7 per 100 000 children and a prevalence of about 16 cases per 100 000 children per year.[2] In addition, several well-recognized secondary glomerulopathies may result in nephrotic range proteinuria or NS.[1] Regardless of the underlying etiology, common complications of NS and its treatment include infection, cardiovascular disease, bone mineral loss, acute renal failure, and thromboembolism (TE).[2]

TE has been reported in 1.8% to 5% of children with idiopathic NS, in contrast to the much higher incidence in adults (20% to 30%).[2,3] NS-associated TE has been studied extensively in idiopathic NS, with the focus primarily on acquired hemostatic defects, such as urinary loss of natural anticoagulant proteins.[4] Our goal in the present study was to better describe the spectrum and incidence of TE in a population of children with NS, including both primary and secondary glomerulopathies. We hypothesized that specific, identifiable clinical variables would predict the risk for TE in these children. To test this hypothesis, we performed a multicenter chart review of a large number of children diagnosed with NS in an attempt to identify these variables.

Methods

Patients with NS were identified from inpatient and outpatient records at Nationwide Children's Hospital, Columbus, Ohio and the University of Michigan Health System, C.S. Mott Children's Hospital, Ann Arbor, Michigan. Probable records were identified using an ICD-9-CM search (using NS codes 581.0-581.9, 582.1, and 583.1) and reviewed for eligibility. All patients age ≤ 21 years at the onset of NS who were newly diagnosed or seen for follow-up between January 1, 1999 and March 31, 2006 (a period of 7.25 years) were eligible for inclusion. The resulting time range

APL	Antiphospholipid antibodies/ lupus anticoagulant	OR	Odds ratio
AT3	Antithrombin III	PE	Pulmonary embolism
CI	Confidence interval	PS	Protein S
CVAD	Central venous access device	SLE	Systemic lupus erythematosis
DVT	Deep venous thrombosis	SSNS	Steroid-sensitive nephrotic syndrome
FVL	Factor V Leiden	TE	Thromboembolism
MN	Membranous nephropathy	uPr:Cr	Urine protein:creatinine ratio
NS	Nephrotic syndrome		

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of NS diagnosis was October 1, 1983 to March 14, 2006 (a period of 22.5 years). NS was defined as serum albumin concentration ≤ 3.0 g/dL and nephrotic-range proteinuria (urine protein:creatinine ratio [uPr:Cr] ≥ 2.0 in a spot urine sample). uPr:Cr was not available for a few of the younger patients, but these patients were included anyway, based on the presence of both a urine protein of 4+ by dipstick and serum albumin ≤ 3.0 g/dL. The study protocol was approved by each institution's institutional review board.

Data collected from the medical records included demographic information, date of NS onset, type of NS, nadir serum albumin level, peak uPr:Cr, clinical or radiologic evidence of TE, date(s) of TE, anatomic site(s) of TE, and history of central venous access device (CVAD) use within any TE-affected vessel. At one of the institutions, all patients with TE were screened for prothrombotic risk factors according to institutional protocol. These studies included genetic evaluation for factor V Leiden (FVL) and prothrombin G20210A gene mutation; protein C, protein S (PS), and antithrombin III (AT3) activities; plasma homocysteine; and assessment for the presence of antiphospholipid antibodies or lupus anticoagulant (APL). Because of incomplete follow-up, confirmation of antiphospholipid syndrome in patients with APL using strict diagnostic criteria was not possible.[5,6] Age at onset of NS and time from onset of NS to first TE were calculated. TE events occurring within 1 week before, simultaneous with, or after diagnosis of NS were considered to be associated with NS. TE occurring more than 1 week before diagnosis of NS were evaluated as a risk factor for TE but were not considered to be associated with NS.

Histopathologic diagnoses were defined by the pathologists at each institution using standard criteria. For the purpose of analysis, the patients were divided into 2 groups based on histopathology and clinical course. The group designated "primary NS" comprised patients with primary glomerulopathies, including steroid-sensitive NS (SSNS) with no biopsy performed (n = 81), biopsy-proven minimal-change NS (n = 56), focal segmental glomerulosclerosis (n = 63), mesangial proliferative glomerulonephritis (n = 17), membranous nephropathy (MN; n = 10), membranoproliferative glomerulonephritis (n = 14), and congenital NS (n = 3). SSNS was defined as resolution of proteinuria (trace or negative protein by dipstick) on 3 consecutive days in response to oral prednisone 2 mg/kg/day.[1] The "secondary NS" group comprised patients with NS due to secondary glomerulopathies caused by other illnesses, including systemic lupus erythematosis (SLE; n = 48), Henoch-Schonlein purpura nephritis (n = 6), crescentic glomerulonephritis (n = 6), IgA nephropathy (n = 5), and various others (n = 17). The patients with SLE all met the American College of Rheumatology criteria for SLE diagnosis and had renal biopsy findings consistent with SLE glomerulonephritis.[7,8] In adults, MN is associated with increased risk for TE complications; the lower incidence of MN in children precluded a direct assessment of this risk factor.[3] Consequently, a special category, "membranous histology," including patients with either MN or class V SLE histology (which closely resembles MN histologically) was created as a surrogate to allow assessment of this possible risk factor.[9] Pulmonary embolism (PE) was defined as any thrombus within a pulmonary artery, regardless of whether or not a primary deep venous thrombosis (DVT) was identifiable.

Basic demographic comparisons were performed between patients with TE and those without TE. Two-tailed Student *t*-tests or nonparametric Wilcoxon rank-sum tests were used for continuous variables, and χ^2 tests or Fisher exact tests were used for categorical variables. The Holm step-down method was applied to control the type I error rate, using an overall level of significance of $\alpha = 0.05$. Limited multivariate logistic regression modeling was performed using forward stepwise selection to estimate the relative significance of the various potential predictors. The presence of significant 2-way interactions was determined, and odds ratios (ORs) and 95% confidence intervals (CI) were reported. Model fit and discrimination were assessed using the Hosmer-Lemeshow goodness-of-fit test and the area under the receiver operating characteristic curve, respectively. Kaplan-Meier plots were produced for survival analysis using the Mantel-Cox log-rank test. For the univariate, multivariate, and survival analyses, TE occurring within 5 years after the diagnosis of NS was considered the primary outcome. All analyses were performed using SAS version 9.1.3 (SAS Institute Inc, Cary, North Carolina) and Stata/SE 9.2 (StataCorp, College Station, Texas).

Results

A total of 370 patient charts with the appropriate ICD-9-CM codes were identified within the specified time frame and screened for inclusion. Of these patients, 326 met all of the eligibility criteria for inclusion (**Table I**). The cohort was 52% male and 69% Caucasian, with a median age of 6.5 years at NS diagnosis. Median follow-up time was 3.7 years after the onset of NS, with a total of 1472.8 patient-years of follow-up for the cohort. Patients with primary NS represented 75% of the cohort; patients with SLE comprised 59% of the secondary NS group.

Of the 326 patients in the cohort, 30 (9.2%) had a total of 38 NS-associated TEs, for an incidence of 20.4 patients with TEs per 1000 patient-years of follow-up, or 25.8 TE events per 1000 patient-years. TEs occurred in 6.6% of the patients in the primary NS group and 17.1% of those in the secondary NS group ($P < .01$) (**Table I**). The raw incidence of TE was slightly higher in females than in males (25.3 vs 15.8/1000 patient-years) and slightly higher in African-Americans than in Caucasians (28.5 vs 19.1/1000 patient-years). The sex and ethnicity differences in TE incidence did not reach statistical significance, however (**Table I**).

In the patients with TE, the median age of NS onset was 13.8 years, the median age at first TE was 15.2 years (**Table I**), and the median time from NS diagnosis to first TE was 70.5 days (**Table II**; available at www.jpeds.com). Four