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Predictors of peritonitis in children with nephrotic syndrome

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Abstract Patients with nephrotic syndrome (NS) are at increased risk for infection. Peritonitis is difficult to diagnose in the absence of peritoneal fluid analysis and empiric therapy carries significant risks. We identified factors present at initial presentation that are associated with an increased risk for the later development of spontaneous bacterial peritonitis in children with NS. A case-control study of patients admitted to Children's Hospital and Regional Medical Center, Seattle from 1989 to 1999 with a diagnosis of NS was conducted; 8 cases of NS and peritonitis (aged 20–113 months) and 24 controls with NS alone (aged 10–193 months) were identified and matched on year of diagnosis of NS. Medical charts were reviewed and laboratory values at the time of initial presentation of NS were recorded. Odds ratios (OR) were estimated, Fischer's exact test was used to obtain *P* values, and 95% exact confidence intervals (CI) were also calculated. Cases tended to be younger than controls (mean age 50.5 months vs. 65.3 months), and were more likely to be white and male. There was a suggestion of an association between serum albumin level at presentation and the risk of subsequent peritonitis. Those patients with a serum albumin level less than or equal to 1.5 g/dl at initial presentation were estimated to have a 9.8-fold (95% CI 0.93, 472; *P*=0.06) increase in the odds of developing peritonitis than those with an initial albumin greater than 1.5 g/dl. A platelet count greater than 500 cells/mm^3 tended toward a reduced risk (OR=0.12, 95% CI 0.002,1.29; *P*=0.10) for subsequent peritonitis when compared with patients with a platelet count less than 500 cells/mm^3, but was not statistically significant. Hypertension, hematuria, or normal serum complement levels (C3, C4) at the time of initial diagnosis were not associated with an increased risk of subsequent peritonitis. Low serum albumin (≤ 1.5 g/dl) at presentation was associated with an increased risk of peritonitis among children with NS at our institution.

Keywords Nephrotic syndrome · Peritonitis

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Introduction

The risk of infectious complications among children with nephrotic syndrome (NS) is well described. The mortality rate from infection is high: an estimated 1.5% of children with NS died from overwhelming infection during follow-up [1]. Spontaneous bacterial peritonitis (SBP), one of the more serious and common infections, affecting 1.4%–3.7% of children with NS, carries a 9% case fatality [2]. SBP occurs primarily within the first 2 years after the diagnosis of NS [3, 4, 5]. Previous episodes of SBP also place children at increased risk for subsequent episodes [2, 3]. Both gram-positive and gram-negative organisms have been implicated as causative agents [6, 7].

In many cases of SBP, a diagnostic paracentesis is not obtainable and patients are treated empirically with 2 weeks of intravenous, broad-spectrum antibiotics. There are several potential disadvantages to this approach. Patients with NS are already at increased risk for thromboembolic events and the presence of an indwelling line can further potentiate this risk [8, 9]. The use of broad-spectrum antibiotics can lead to antibiotic resistance and can enhance the growth of fungi and other organisms, further complicating the course in these patients.

Previous research has hypothesized that defects in humoral immunity and a decrease of proteins in the complement pathway at the time of active disease with and without concomitant infection may explain why patients with NS are at increased risk for infection [3, 10,

11]. Even if these hypotheses are correct, these parameters are not routinely measured in patients with NS. To our knowledge, this is the first study designed to identify potential laboratory abnormalities present at initial presentation for NS that may predict the subsequent development of SBP. Given the significant mortality and morbidity associated with SBP, if patients can be identified who are at greatly increased risk, they may benefit from the administration of prophylactic antibiotics covering both gram-positive and gram-negative organisms.

Patients and methods

Medical charts were reviewed encompassing a 10-year period from 1 July 1989 to 30 June 1999 for all patients admitted to Children's Hospital and Medical Center, Seattle, (Wash., USA) with a diagnosis of NS and peritonitis. Of the initial 43 cases, the majority (33) were excluded because they had congenital NS, a secondary underlying condition such as systemic lupus erythematosus, or because the initial diagnosis of NS was made elsewhere and initial admission data were not obtainable. Two cases were excluded due to lack of a firm diagnosis of peritonitis: a paracentesis was not performed, and there was no documentation of fever or peritoneal signs. This left 8 cases that were matched with controls by year of diagnosis. Three controls for each case were chosen from patients admitted during the same time period with a diagnosis of NS only. In the present study, a diagnosis of peritonitis required a positive paracentesis demonstrating >250 leukocytes/mm^3 in the peritoneal fluid. Signs of peritoneal inflammation and a history of fever were present in all cases. NS was defined by the presence of hypoalbuminemia (<2.5 g/dl), proteinuria (3+ or greater on dipstick), and edema.

Variables that were potentially relevant [12] were extracted from the medical charts at the time of the initial diagnosis of NS and included date of birth, date of diagnosis of NS, date of diagnosis of peritonitis, clinical history, blood pressure, urinalysis with microscopic examination, complete blood count, electrolytes, blood urea nitrogen, creatinine, albumin, total protein, C3, and C4. The laboratory values at the time of presentation were recorded. Hypertension was defined as systolic and diastolic blood pressure ≥95th percentile for age, sex, and height as standardized and published elsewhere [13].

Point estimates for odds ratios (OR) were calculated. Fischer's exact test was used to obtain *P* values, and exact methods were used to obtain 95% confidence intervals (CI). Where possible, laboratory values were dichotomized at some generally accepted cut-off value. For some, percentiles were used as critical values based on their distribution in this data set. Variables examined were serum albumin (>1.5 g/dl, ≤1.5 g/dl); platelet count (≤500 cells/mm^3, >500 cells/mm^3); hypertension (yes, no); glomerular filtration rate (<80 ml/min per 1.73 m^2, ≥80 ml/min per 1.73 m^2) as calculated using the Schwartz formula; C3 (90–137 mg/dl, 138–252 mg/dl); C4 (17–30 mg/dl, 31–98 mg/dl); and microscopic evaluation for hematuria (0–5 RBC, 6–100 RBC/hpf). Age was divided into two groups, < and ≥4 years of age. Race was characterized as white and non-white. The non-white group included black, Asian, Hispanic, and "other" categories. OR were adjusted for potential confounders; only those adjusted OR that were changed by greater than 10% from the crude OR are presented. All analyses were performed using the STATA statistical software package (STATA, College Station, Tex., USA).

Table 1 Demographic characteristics of 8 children with nephrotic syndrome (NS) and peritonitis (cases) and 24 children with NS (controls)

	Cases (%)	Controls (%)
Age (years at time of NS diagnosis)		
<4	6 (75%)	11 (46%)
≥4	2	13 (54%)
Gender		
Male	7 (87.5%)	15 (62.5%)
Female	1 (12.5%)	9 (37.5%)
Race		
White	7 (87.5%)	13 (61.9%)
Non-white	1 (12.5%)	8 (38.1%)

Results

Of the 8 cases, 6 developed SBP within the 1st year after diagnosis of NS. On average, the cases were younger than controls and somewhat more likely to be male and white (Table 1). Of 8 children with SBP, 7 had a serum albumin level less than 1.5 mg/dl when first diagnosed with NS, in contrast to 10 of 24 controls (OR=9.8; 95%CI 0.93, 472) (Table 2). Platelet count greater than 500 cells/mm^3 was associated with a reduced risk of the subsequent development of peritonitis (OR=0.12; 95%CI 0.002, 1.29). The 1 case with an elevated platelet count and the 1 with a serum albumin level greater than 1.5 g/dl were not the same person. The OR did not change appreciably after adjusting individually for age, gender, or race. The presence of hypertension or hematuria at the time of initial diagnosis was not associated with an increased risk of subsequent peritonitis. Normal serum levels of C3 and C4 were also not associated with an increased risk of peritonitis (Table 3).

Discussion

This study was designed to identify characteristics at initial presentation of NS that were predictive of the subsequent development of peritonitis. Chart reviews carried out at various institutions, comparing children admitted with NS and peritonitis with children admitted with NS alone, have found that black children were more prevalent in the peritonitis subgroup [3, 5]. Mannennbach et al. [14] found a racial predilection to repeated episodes of peritonitis, but no difference between races for single episodes of peritonitis. While we observed a relatively lower proportion of non-whites in peritonitis cases compared with controls, the small number of cases argues for a very cautious interpretation of this observation. We found a predominance of males in the peritonitis subgroup, which likely reflects the distribution of NS. Age, gender, and underlying renal pathology were not found to be significantly different between the children with

Table 2 Unadjusted odds ratios of developing peritonitis associated with selected laboratory parameters assessed at the initial diagnosis of NS (*RBC/hpf* red blood cells per high-power field, *GFR* glomerular filtration rate, *CI* confidence interval)

Variable	Cases (%)	Controls (%)	Odds ratio	95% CI
Serum albumin (mg/dl)				
>1.5	1 (12.5%)	14 (58.3%)	1.0 (referent)	
≤1.5	7 (87.5%)	10 (41.7%)	9.8	0.93–472
Mean (range)	1.1 (0.5–2.1)	1.5 (0.6–2.1)		
Platelet count[a] (cells/mm^3)				
≤500	6 (85.7%)	10 (41.7%)	1.0 (referent)	
>500	1 (14.3%)	14 (58.3%)	0.12	0.002–1.29
Mean (range)	401 (317–513)	495 (243–811)		
Hypertension				
No	4 (50%)	9 (37.5%)	1.0 (referent)	
Yes	4 (50%)	15 (62.5%)	0.6	0.08–4.16
Urine microscopy[a]				
0–5 RBC/hpf	4 (57.1%)	14 (58.3%)	1.0 (referent)	
6–100 RBC/hpf	3 (42.9%)	10 (41.7%)	1.05	0.12–7.80
GFR (ml/min per 1.73 m^2)[a]				
≥80	7 (100%)	19 (79.2%)		
<80	0 (0%)	5 (20.8%)		
Serum C3 (mg/dl)[a] (normal 83–293)				
90–137	2 (28.5%)	13 (59.1%)	1.0 (referent)	
138–252	5 (71.5%)	9 (40.9%)	3.61	0.44–43.9
Serum C4 (mg/dl)[a] (normal 16–52)				
17–30	3 (42.8%)	7 (31.8%)	1.0 (referent)	
31–98	4 (57.2%)	15 (68.2%)	0.62	0.08–5.52

[a] Data missing for 1 subject, 2 controls were also missing C3 and C4 levels

Table 3 Comparison of mean values of cases and controls

	Cases	Controls
Variable	Mean (range)	Mean (range)
Serum albumin	1.1 (0.5–2.1)	1.5 (0.6–2.1)
Platelet count	401 (317–513)	495 (243–811)
Serum C3	146 (97–176)	140 (102–252)
Serum C4	33 (20–50)	37 (17–98)
GFR	191.3 (118–433)	136.4 (55.9–275)

NS who develop peritonitis and the children with NS who do not develop peritonitis [3, 5, 6]. However, the majority of our children with SBP were less than 4 years of age, which is similar to the findings of Speck et al. [4].

While hypoalbuminemia is necessary for the diagnosis of NS, relatively more severe hypoalbuminemia may predispose these patients to develop ascites, in turn predisposing them to SBP. However, of 21 patients 0–13 years of age who were admitted to Hadassah University Hospital with a diagnosis of NS, no difference was found in the albumin levels between those patients with ascites and those without ascites [15]. Gulati et al. [16] analyzed the spectrum of infections in 154 children with NS from 1990 to 1992 seen at their institution. They found that the 59 patients (38%) with NS who developed infectious complications (urinary tract infection, peritonitis, and tuberculosis primarily) had significantly lower serum albumin and total protein levels than children with no infections. (Data for peritonitis were not separated from other infections.) There was no difference in age, duration of NS, proteinuria, or serum creatinine between the two groups. However, because serum albumin levels were recorded at the time of infection, it is difficult to determine the role of the infectious process in lowering serum albumin and total protein.

The initial low serum albumin level may indicate patients who are prone to losing proteins such as IgG and factors I and B, proteins that have been shown to be low in the serum of patients with NS at times of active disease. These factors are important proteins in the alternate pathway of the complement system that help in opsonization, phagocytosis, and host defense [10]. Various studies have found a significantly greater urinary excretion of factors I and B and lower serum levels of these factors in patients with NS and a history of infection or NS and active infection compared with patients with NS only and healthy controls [10, 11]. The low serum levels correlate with increased urinary excretion of these factors in those patients with a history of infection [10]. In those patients with relapse and infection, there is a positive correlation between factor I and albumin levels [11]. McLean et al. [17] demonstrated a relationship between low serum factor B levels and opsonization of *Escherichia coli* in patients with active NS.

Krensky et al. [3], in his chart review of 351 children admitted with NS, found that those NS patients with peritonitis had lower levels of IgG in their serum than patients with NS only in relapse. The groups were matched for age, gender, morphological diagnosis, disease activity, and steroid therapy. Researchers have found decreased levels of C3, C4, IgG, and IgM in the ascitic fluid of patients with NS compared with peritoneal fluid removed from women undergoing laparoscopy for different reasons. They postulate that the decreased levels in the fluid lead to a decreased bactericidal activity in patients, rendering them more susceptible to infection [18]. Perhaps the association between hypoalbuminemia and SBP reflects relatively greater capillary permeability with loss of these immunological proteins into the urine.

The reduced risk of SBP associated with a high platelet count that we observed, if not due to chance, is difficult to interpret. Platelets are acute-phase reactants and are often elevated at times of illness. Some investigators have attempted to correlate the platelet count with splenic function and have postulated that decreased splenic function increases the susceptibility to infection in patients with NS [19, 20]. In a prospective study of nine children with NS, four patients were found to have splenic dysfunction by radionuclide scan. They experienced bacterial infections and had elevated platelet counts compared with the five NS patients without splenic dysfunction. Over the 2-year observation period of the study, the five children with normal splenic function did not develop any bacterial infections. The authors hypothesized that an elevated platelet count may serve as a surrogate marker for splenic dysfunction [19]. Other studies have refuted the presence of splenic dysfunction in nephrotic patients as a reason for infection. Berns et al. [20] counted the number of packed red blood cells (a sign of asplenia) in a smear of the peripheral blood of patients with NS. They found all 19 children had normal values on multiple studies at times of relapse with and without therapy and remission, including 2 patients who had peritonitis at the time of study.

Throughout the literature, both hypertension and hematuria have been considered indicators of a poor prognosis in patients with NS. They are often thought to be suggestive of focal segmental glomerulosclerosis (FSGS) or membranoproliferative glomerulonephritis (MPGN), more aggressive forms of NS [12]. It is thought that these patients are at increased risk of infection because of prolonged periods of active disease requiring prolonged steroid use and potentially other immunosuppressive agents [1]. However, we found no association between hematuria and hypertension, symptoms much more common in children with FSGS and MPGN, and the subsequent development of peritonitis in this study.

The major limitation of this study is the small sample size, and the resulting low power to detect differences. In addition, only data at the initial presentation of NS were used and we were limited by the data present in the charts. Since cases and controls were matched within 1 year of diagnosis, changes in the management of patients should not have influenced the results. Some patients may have been admitted to another hospital with peritonitis. These cases would be missed or they may have been included in the control group if there was no documentation of the admission in the chart. Given the patterns of care for NS in our geographic region, this is unlikely.

The associations we have identified are reasonably strong and need to be confirmed in larger studies. In the absence of a diagnostic paracentesis, knowledge of factors associated with the development of SBP would help restrict the use of broad-spectrum antibiotics to those patients at increased risk for developing SBP. Despite improvements in treatment, the mortality from peritonitis remains high, and recognition and early diagnosis are necessary to improve the outcome in these patients.

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