Childhood Henoch-Schonlein Nephritis

A Multivariate Analysis of Clinical Features and Renal Morphology at Disease Onset

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Introduction. Risk factors of renal involvement in Henoch-Schonlein nephritis (HSN) have been extensively studied, but their relations with the severity of glomerular lesions at the disease onset are much less known.

Materials and Methods. Data were collected retrospectively on 45 patients (age range, 2 to 15 years) with HSN to identify the initial clinical and laboratory features that most accurately correlate with histological findings. Nephritic syndrome was defined as hypertension, proteinuria, hematuria, and a creatinine clearance of 60 mL/min/1.73 m^2 or less. Kidney biopsy findings were graded according to the International Study of Kidney Disease in Children classification for HSN.

Results. Purpura was present in all the 45 children, arthritis in 73.3%, abdominal symptoms with or without bleeding in 68.6%, and a high serum IgA level in 24.4%. Hematuria was present in 88.6% of the patients, hematuria and proteinuria (not in nephrotic range) in 66.7%, nephrotic syndrome in 17.8%, acute nephritic syndrome in 8.9%, and nephritic-nephrotic syndrome in 13.3%. Grades II (33.3%) and III (22.2%) lesions were the most common pathologic findings on kidney biopsy followed by grades IV (17.8%), V (15.6%), and I (11.1%) lesions. Univariate analysis demonstrated that nephrotic syndrome, acute nephritic syndrome and a creatinine clearance less than 30 mL/min/1.73 m^2 were all associated with a significantly increased risk of developing grades IV and/or V lesions. multivariate analysis showed nephritic-nephrotic syndrome as significant independent predictors of severity of glomerular disease at onset.

Conclusions. The severity of renal symptoms at onset determines the intensity of glomerular lesions.

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INTRODUCTION

Henoch-Schonlein purpura (HSP) is a systemic vasculitis of the small blood vessels which is characterized by the tissue deposition of immunoglobulin A (IgA)-containing immune complex.[1-3] The classic clinical symptoms include purpuric rash, abdominal pain, arthralgias, and hematuria which can develop in any order and at any time over a period of several days to several weeks.[4,5] Renal involvement is not typically related to the severity of extrarenal involvement, but if occurs, it is typically noted within a few days to 1 month after the onset of systemic symptoms.[4,5] Renal manifestations occur more commonly in older children and adults and tend to be more severe than in children.[5,6]

The clinical and laboratory features of HSP in children are quite variable, in part because of different criteria used to define renal involvement and variability in the length of follow-up after the onset of the acute illness.[4,7] The highly variable clinical course of Henoch-Schonlein nephritis (HSN) is also related in significant part to the marked variability in its histopathologic presentation, with glomeruli ranging from histologically normal to showing diffuse proliferative and crescentic lesions.[4,8,9] Children with asymptomatic hematuria, mild proteinuria, and slightly elevated serum creatinine level usually have mild renal involvement or focal mesangial proliferation, whereas patients with heavy proteinuria, hypertension, and acute renal failure have more marked cellular proliferation and, if nephrotic, crescent formation.[10-15]

The aim of this study was to identify the initial clinical and laboratory features that most accurately correlate with the renal biopsy findings at the disease onset in a cohort of children with HSN.

MATERIALS AND METHODS

We performed a retrospective study on 129 children hospitalized for HSP between January 1997 and December 2007 at duPont Hospital for Children, in Wilmington, Delaware, and Rush University Medical Center, in Chicago, Illinois. The Investigational Review Board approval was obtained and informed consent was not deemed necessary given the retrospective nature of the study. For each hospitalized patient, we abstracted data from review of electronic and paper medical records. Patient's data consisted of demographic characteristics (age, sex, and weight) as well as clinical and laboratory data including blood pressure, serum creatinine level, serum IgA levels, urinalysis, and urinary protein excretion level. The study database also included information on kidney biopsy findings including descriptions of renal involvement.

Patients were eligible if they were 18 years and younger and had biopsy-proven HSN in the absence of any other diseases or medication known to cause hypersensitivity-related HSN enzyme inhibitors.[9] The mean time period between presenting signs and symptoms and kidney biopsy procedure was 12 days (range, 7 to 18 days). Also excluded were patients with clinical and/or laboratory evidence of microscopic polyangiitis, Wegener granulomatosis, systemic lupus erythematosus, antiphospholipid syndrome, recent serious systemic infection, clotting disorders, and liver disease.

In our analyses, we defined hematuria as urine red blood cells more than 3 per high-power field, and proteinuria as protein-creatinine ratio higher than 0.3 on a random urine sample. Hypertension was diagnosed when the average systolic and/or diastolic blood pressure was higher than the 95th percentile values for the patient's sex, age, and height.[16] The mean arterial pressure was defined as the diastolic pressure plus one-third of the pulse pressure (systolic pressure – diastolic pressure).[17] Nephrotic syndrome was defined as hypoalbuminuria greater than 2.5 g/dL and urine protein-creatinine ratio higher than 3.0. Creatinine clearance was estimated by the Schwartz formula.[17,18] Definitions of clinical outcome were a chronic association of nephritic-nephrotic syndrome, clinical features of rapidly progressive glomerulonephritis, or irreversible progression to end-stage renal disease.

Kidney biopsy tissues were examined by a renal pathologist at each institution and graded according to the International Study of Kidney Disease in Children classification for HSN.[19] In this classification, grade I is defined as minimal alterations; grade II, as pure mesangial proliferation; and grade III to V, as focal segmental (a) or diffuse mesangial proliferation (b) with less than 50%, 50% to 75%, or greater than 75% crescents formation, respectively. Grade VI is associated with glomeruli with a membranoproliferative pattern of injury.

Statistical analysis was performed using the SAS software (version 8.2, SAS Institute, Cary, North Carolina, USA). Continuous variable were presented as mean ± standard deviation. Categorical variables were presented as relative frequencies. Standard parametric or nonparametric tests were used to compare continuous variables between groups. The Pearson correlation coefficient test was used to examine which independent variables had a significant univariate association with renal lesions. Multivariate analysis was performed to examine the independence of clinical variables as a continuous outcome and changes in glomerular morphology as an ordinal variable after controlling for other potential confounders. Differences in outcome variables were compared by the Mann-Whitney test for continuous variables and by the

chi-square test or Fisher exact test for categorical variables. A 2-sided *P* value of less than .05 was considered statistically significant.

RESULTS

Patients

Of 129 children who were screened, 45 met the inclusion criteria and enrolled in the study. All of them had findings on kidney biopsies consistent with HSN (predominant IgA mesangial deposits). The patients' mean age at the time of biopsy was 6.2 ± 2.5 years (range, 2 to 15 years) with a 1.5:1 ratio of male preponderance. Table 1 lists the initial clinical and laboratory characteristics of patients at baseline, before the kidney biopsy procedure. Palpable nonthrombocytopenic purpura was present in all the 45 children. In addition, 33 children (73.3%) had arthritis, 31 (68.9%) had abdominal symptoms with or without bleeding, 11 (24.4%) had a serum IgA level greater than 350 mg/dL.

Table 1. Baseline Clinical and Laboratory Characteristics of 45 Children with Henoch-Schonlein Nephritis*

Characteristics	Values
Mean age, y	6.2 ± 2.5
Sex	
Male	27 (60.0)
Female	18 (40.0)
Mean arterial pressure, mm Hg	77.0 ± 14.0
Hypertension	32 (71.1)
Purpura	45 (100)
Arthritis	33 (73.3)
Serum IgA level > 350 mg/dL	11 (24.4)
Abdominal pain	24 (53.3)
Gastrointestinal bleeding	7 (15.6)
Renal Disorders	
Microscopic hematuria	28 (62.2)
Gross hematuria	12 (26.7)
Hematuria and proteinuria†	30 (66.7)
Nephrotic syndrome‡	8 (17.8)
Acute nephritic syndrome	4 (8.9)
Nephritic-nephrotic syndrome	6 (13.3)
Creatinine clearance < 30 mL/min/1.73 m^2	7 (15.6)

*Values are mean ± standard deviation for quantitative variables and number (percent) of patients for dichotomous ones.
†Proteinuria is within non-nephrotic range for this parameter.
‡Nearly all patients with nephrotic syndrome also had hematuria.

Renal Manifestations

Microscopic or gross hematuria was present in 40 patients (88.9%). Thirty children had hematuria and proteinuria (not in nephrotic range) and other proteinuria patterns were seen a smaller portion of the patients (Table 1). Nine children (20.0%) presented with a creatinine clearance between 30 mL/min/1.73 m^2 and 60 mL/min/1.73 m^2, and severe kidney failure (creatinine clearance less than 30 mL/min/1.73 m^2) was present in 7 (15.6%). Six of these patients had a creatinine clearance less than 20 mL/min/1.73 m^2 and required dialysis therapy, and 3 of whom developed end-stage renal disease and became dialysis dependent. In contrast, none of the children with hypertension, hematuria with or without proteinuria, or a creatinine clearance of 30 mL/min/1.73 m^2 or greater developed chronic kidney failure. Proteinuria, hematuria, and hypertension resolved and renal function returned to normal in all except for 3 with end-stage renal disease, after a mean follow-up of 23 months.

Pathologic Features

We identified 3 distinct groups of children with HSN: those with grades I and II lesions (11.1% and 33.3%, respectively), presenting with minimal urinary abnormalities; those with grade III lesion (22.2%), having moderate active kidney disease; and those with grades IV and V lesions (17.8% and 15.6%, respectively), presenting with nephrotic and/or nephritic syndromes (Table 2). The percentage of renal injury seemed to parallel the clinical severity of the glomerluar lesions.

Univariate analysis demonstrated that hematuria (*P* = .01), hypertension (*P* = .05), heavy proteinuria

Table 2. Correlation of International Study of Kidney Disease in Childhood (ISKDC) Pathologic Grade With Clinical Features at Admission in 45 Children With Henoch-Schonlein Nephritis*

ISKDC Classification	Minor Urinary Abnormalities	Nephrotic Syndrome	Nephritic Syndrome	Nephritic- Nephrotic Syndrome	Total
Grade I	5 (11.1)	0	0	0	5 (11.1)
Grade II	7 (15.6)	8 (17.8)	0	0	15 (33.3)
Grade III	0	9 (20.0)	1 (2.2)	0	10 (22.2)
Grade IV	0	0	2 (4.4)	6 (13.3)	8 (17.8)
Grade V	0	0	4 (8.9)	3 (6.7)	7 (15.6)

*Values in parentheses are percents in proportion to all the 45 children.

(P = .03), nephrotic syndromes (P = .01), acute nephritic (P = .01), a creatinine clearance less than 30 mL/min/1.73 m^2 (P = .01), and nephritic-nephrotic syndrome (P < .001) were all associated with a significantly increased risk of developing diffuse proliferative glomerulonephritis with crescents in 50% or more of the glomeruli (grades IV and V lesions). There was no correlation between the severity of renal morphology lesions and frequency of hematuria, hypertension, low serum albumin concentration, or elevated serum IgA level at presentation in any of the 45 patients.

By multivariate analysis, nephrotic and nephritic syndromes were the significant independent predictors of severe glomerular disease (P < .001; odds ratio, 2.42; 95% confidence interval, 1.21 to 4.32 and P < .001; odds ratio, 2.51; 95% confidence interval, 1.23 to 5.41). The degree of interstitial fibrosis (r = 0.53; P = .02), percentage of crescentic glomeruli (r = 0.61; P = .03), and presence of glomeruli with fibrinoid necrosis (r = 0.53; P = .03) correlated inversely with creatinine clearance.

DISCUSSION

This study examined the relationship between clinical and histological findings at the disease onset in a cohort of children with HSN using multivariate analysis. The result suggested that the long-term morbidity of HSP is predominantly attributed to the intensity of renal involvement at presentation and that patients with HSN should be followed for longer periods of time. We found a direct correlation between the severity of the renal symptoms and the percentage of glomerular injury on kidney biopsy, similar to the findings reported by other investigators.[20,21] We also found a positive correlation between the percentage of crescent glomeruli and presence of nephrotic-range proteinuria and renal insufficiency at diagnosis, which are in line with the results of other studies.[10-15] Crescentic glomerulonephritis was encountered in less than 5% when the patients manifested with hypertension, hematuria, and heavy proteinuria (not in nephrotic range), and more than 30% when nephrotic and/or nephritic syndromes were associated.

Nephritis in HSP is the primary cause of morbidity and mortality and it represents 5% of all new cases of end-stage renal disease in children.[22] The incidence of renal involvement in HSP varies from 20% to 100% of all kidney biopsies.[12,22-24] The lack of using appropriate diagnostic criteria possibly explains why the proportion of patients presenting with renal involvement varies considerably among different studies (eg, the number of red blood cells required to define hematuria, isolated hematuria versus hematuria with proteinuria or hypertension or from a delay that can occur between the initial clinical manifestation and renal symptoms).[12,22-24]

In this study, the overall severity of renal pathology was worse than that in reports from many other studies.[9,12,22,25-28] Crescentic glomerulonephritis (grades III, IV, and V) was the most frequent pathologic finding on kidney biopsy (55.6%). The discrepancy between the findings of the present study and those of other investigators is likely due to differences in the study design, time of referral to nephrologists, criteria for performing kidney biopsy, and also racial characteristics of the studied cohorts.

CONCLUSIONS

In summary, this study suggests that children with HSN presenting with acute nephritis and/or nephrotic syndrome are at a higher risk of developing severe glomerular lesions. Identification of risk factors in HSN may justify indications for early kidney biopsy and aggressive treatment at the disease onset to prevent progression of chronic kidney failure.

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CONFLICT OF INTEREST

None declared.

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