Clinicopathologic Correlations in Henoch-Schonlein Nephritis

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Introduction. Renal involvement is the major cause of mortality and morbidity in children with Henoch-Schonlein purpura. The purpose of this study was to determine the predictive factors of Henoch-Schonlein nephritis (HSN) and correlations between clinical and pathologic findings.
Materials and Methods. Demographic characteristics and clinical manifestations of 105 children with Henoch-Schonlein purpura were retrospectively evaluated. Kidney biopsy with pathologic scoring was performed in 17 patients.
Results. Sixty-one boys and 44 girls were included in this study. The mean age at presentation was 73.0 ± 33.4 months (range, 12 to 156 months). Thirty-nine percent of patients had renal involvement. Their mean age at presentation of HSN was 87.4 ± 30.9 months, which was significantly higher than the age of those without nephritis. Age at presentation was the only predictor of renal involvement. Hematuria and proteinuria were the most common laboratory findings of HSN, followed by nephrotic syndrome and acute nephritis. The most common histologic findings were grades 3 (especially 3B) and 2 of the International Study of Kidney Disease in Children classification, respectively. Higher pathologic grades were more frequent in patients with nephrotic syndrome and acute nephritis. Similarly, there was a positive relationship between the severity of proteinuria and both pathologic grading and scoring, especially crescent formation, endocapillary proliferation, and tubular atrophy.
Conclusions. There was a significant correlation between the severity of renal involvement and pathologic grading and scoring in HSN. The severity of proteinuria was a significant determinant of renal pathologic findings.

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INTRODUCTION

Henoch-Schonlein purpura (HSP), a nonthrombocytopenic purpura, is the most common systemic vasculitis in children.[1] Renal involvement is the major cause of morbidity in HSP,[2,3] which occurs in 20% to 100% of patients.[2,4] It is more common during the first 3 weeks of HSP and rarely occurs after the improvement of clinical manifestations.[5] The majority of children do not have severe kidney disease.[3,4] Most of them present with microscopic hematuria and mild proteinuria, and rarely as acute nephritis or nephrotic syndrome.

Short-term and long-term outcomes of HSP are generally favorable, predicted by the severity of initial manifestations and renal involvement. End-stage renal disease occurs in 1% to 7% of patients with HSN. Therefore, long-term follow-up has been recommended in these patients.[1,2]

A direct correlation has been suggested between the severity of clinical manifestations, histopathologic grading, and renal outcome in Henoch-Schonlein nephritis (HSN),[3] which has been questionable in some other reports.[1,2] The aim of this study was to determine the predictive factors of

HSN and evaluate the correlation between clinical manifestations and histologic grading, compared to other populations.

MATERIALS AND METHODS

This is a retrospective medical record review of 105 patients with HSP admitted during 20 years in a children hospital in Tehran, Iran. Henoch-Schonlein purpura was defined based on nonthrombocytopenic palpable purpura, arthralgia or arthritis, and gastrointestinal manifestations with abdominal pain or bleeding and renal involvement in children aged less than 18 years.[6] Patients with systemic disorders, vasculitis, drug hypersensitivity, and incomplete data were excluded from the study.

Henoch-Schonlein nephritis was defined as the presence of gross or microscopic hematuria (more than 5 erythrocytes per high-power field in centrifuged urine) with or without proteinuria (urine protein greater than 4 mg/kg/d), nephrotic syndrome (urine protein more than 50 mg/kg/d, serum albumin less than 2.5 g/dL, edema and hyperlipidemia), and acute nephritis (hematuria plus one or more of the followings: increased serum creatinine, hypertension, and oliguria).

A kidney biopsy was performed in patients with nephrotic syndrome, acute nephritis, and gross hematuria with nonnephrotic-range proteinuria during the 1st month of presentation. In the latter group, some patients had severe gastrointestinal manifestations, treated by corticosteroids, immunosuppressive drugs, and intravenous immunoglobulin therapy. Histopathologic grading was done according to the last the International Study of Kidney Disease in Children classification as grade 1, minimal glomerular lesions; grade 2; mesangial proliferation; grade 3, mesangial proliferation with less than 50% crescents; grade 4, mesangial proliferation with 50% to 75% crescents; and grade 5, mesangial proliferation with more than 75% crescents.[1]

Pathologic scoring was done for the glomerular component (sclerosis, necrosis, endocapillary proliferation, matrix expansion, mesangial proliferation, and crescent formation), tubulointerstitial component (interstitial inflammation or fibrosis and tubular loss), and vascular component as grade 1 (< 25%), grade 2 (25% to 50%), and grade 3 (> 50%). Mesangial proliferation was classified as grade 1 (4 to 6 mesangial cells per area cells) and grade 2 (7 or more cells).

The independent *t* test was used to analyze the relationship between initial manifestations and development of renal involvement. In addition, correlations between clinical manifestations and pathologic findings were evaluated using the Spearman rank correlation test. *P* values less than .05 were considered to be significant.

RESULTS

One hundred and five children (61 boys and 44 girls) with HSP were enrolled in this study. The mean age at presentation was 73.0 ± 33.3 months (range, 12 to 156 months). All of the patients had palpable purpura followed by joint (88.6%), gastrointestinal (73.3%), and renal involvement (39%). One patient had a seizure attack. Forty-four patients (41.9%) were treated with corticosteroids to reduce abdominal symptoms.

Renal involvement was seen in 23 boys and 18 girls. The mean age at presentation was 87.4 ± 30.9 months (range, 24 to 156 months), which was significantly higher than the age of those without nephritis ($P < .001$; Table 1). Of patients with HSN, 80.5% had mixed hematuria and proteinuria, 9.7% had nephrotic syndrome, 9.7% had mixed nephritic and nephrotic syndrome, and 4.9% had acute nephritis.

Kidney biopsy was performed in 17 patients. Of those, 41.2% had hematuria and proteinuria, 23.5% had nephrotic syndrome, 23.5% had mixed nephritic and nephrotic syndrome, and 11.8% had acute nephritis. Histologic findings were grade 3 (52.9%), grade 2 (41.2%), and grade 4 (5.9%). Mesangial proliferation and matrix expansion were the most common pathologic findings, followed by endocapillary proliferation and crescent formation (Table 2).

Table 1. Clinical and Demographic Characteristics of Study Population

Characteristic	Nephritis	No Nephritis	*P*
Number of patients	41	64	…
Age, y	87.4 ± 30.9	63.7 ± 31.7	< .001
Gender			
Male	23 (56.1)	38 (59.3)	
Female	18 (43.9)	26 (40.6)	.74
Joint involvement	37 (90.2)	56 (87.5)	.66
Abdominal pain	33 (80.0)	44 (68.0)	.18

Table 2. Frequency of Pathologic Findings in Henoch-Schonlein Nephritis

Pathologic Finding	Number (%)
Matrix expansion	17 (100)
Mesangial proliferation	17 (100)
Endocapillary proliferation	11 (64.7)
Crescent	10 (58.8)
Inflammation	9 (52.9)
Sclerosis	9 (52.9)
Necrosis	7 (41.2)
Tubular atrophy	5 (29.4)
Interstitial edema	3 (17.6)

There were significant correlations between both pathologic grading and total scoring and the severity of clinical nephritis (correlation coefficient, 0.52, $P = .03$ and correlation coefficient, 0.49, $P = .04$, respectively; Table 3). In addition, there were significant relationships between the severity of proteinuria and pathologic grading and total scoring, especially with endocapillary proliferation, tubular atrophy and crescent formation (Tables 4 and 5). Demographic and clinical manifestations had no correlation with the pathologic grading (Table 4).

Table 3. Frequency of Pathologic Grades in Henoch-Schonlein Nephritis

	Pathology Grade		
Clinical Findings	Grade 2	Grade 3	Grade 4
Hematuria and proteinuria	5	2	0
Nephrotic syndrome	0	4	0
Acute nephritis	1	1	0
Nephritic-Nephrotic syndrome	1	2	1

Table 4. Clinical, Laboratory and Demographic Correlations With Pathology Grade and Score in Henoch-Schonlein Nephritis

	Final Score		Grading	
Variables	Odds Ratio	*P*	Odds Ratio	*P*
Age	0.05	.83	-0.01	.96
Gender	0.27	.29	0.36	.14
Joint involvement	0.35	.16	0.21	.39
Abdominal pain	0.04	.85	0.24	.33
Proteinuria	0.50	.03	0.49	.04

Table 5. Relationship Between Proteinuria and Various Pathologic Findings

Pathologic Finding	Correlation Coefficient	*P*
Sclerosis	0.241	.35
Inflammation	0.406	.11
Endocapillary lesion	0.621	.008
Mesangial proliferation	0.184	.48
Crescent	0.495	.04
Tubular atrophy	0.501	.04
Edema	0.315	.22

DISCUSSION

Renal involvement is the determinant prognostic factor of HSP. Children with isolated hematuria and mild proteinuria have a high recovery rates.[2] Initial kidney impairment, nephritic or nephrotic syndrome, significant proteinuria, hypertension, decreased factor XIII activity, extensive crescents, severity of glomerular necrosis and sclerosis, macrophage infiltration, hyaline arteriolosclerosis, tubular loss, and interstitial fibrosis have been suggested as significant predictors of renal survival in HSN.[2,7-10]

On the other hand, severe gastrointestinal manifestations, persistent purpura, older age at presentation, reduced level and treatment with coagulation factor XIII activity, central nervous system involvement, relapse, and corticosteroid treatment have been associated with increased risk of HSN.[4,5,6,11] Age was the only independent predictor of renal involvement in this study and patients with HSN were significantly older (more than 6 years) than those without renal involvement, as has been previously reported.[4] Children older than 4 years had a higher risk of renal involvement in Sano and colleagues' study. In another report, renal involvement and gastrointestinal complications were less likely in children younger than 2 years old.[6]

Our study showed a direct correlation between the severity of renal involvement and pathologic findings. Patients with nephrotic syndrome and acute nephritis had higher pathologic grading with increased mesangial proliferation and crescent formation. This correlation has been investigated in previous studies. Coppo and associates reported severe kidney impairment and acute nephritis as the prognostic features of severe pathologic findings in HSN.[12] Assadi showed a direct correlation between initial clinical manifestations and glomerular histologic grading. Children with mixed nephritic nephrotic syndrome had severe glomerular lesions and those with isolated hematuria or mild proteinuria had mild pathologic findings.[13]

The severity of proteinuria had also significant correlations with the pathologic grading and total scoring and consequently to clinical course and eventual prognosis in this study, as has

been reported in the previous studies.[8,9] Liu and colleagues reported severe glomerular, tubulointerstitial and vascular lesions in patients with higher grades of proteinuria, which was considered an indirect measure of HSN severity in adulthood.[14] A significant correlation has also been shown between glomerular mesangium and hematuria in HSN.[15] Halling and coworkers showed a positive correlation between urine albumin-creatinine ratio to glomerular mesangial proliferation, segmental sclerosis, and interstitial inflammation. Morphologic changes resulted in greater proteinuria, lower glomerular filtration rate, and higher blood pressure. The severity of proteinuria was a major risk factor for the progression of glomerular disease.[9]

Morphologic lesions may not be predictable from the initial presentation. Advanced pathologic lesions have been reported not only in patients with nephrotic syndrome or acute nephritis, but also in isolated hematuria or mild proteinuria, suggested kidney biopsy in persistent or increasing proteinuria.[1,9,16] However, patients with gross hematuria and mild proteinuria, even with severe gastrointestinal manifestations, had mild pathologic lesions in this study. Regarding the positive correlation between the severity of proteinuria and renal pathologic findings in this study, close clinical follow-up with kidney biopsy in patients with rising proteinuria is suggested in this group of patients. According to the limited number of kidney biopsies, increased sample volume is recommended for definite recommendation.

CONCLUSIONS

The severity of clinical manifestations of HSN was in accordance to pathologic findings and proteinuria was an important determinant of histologic grading among children with HSP.

CONFLICT OF INTEREST

None declared.

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