Clinical Features of Children With Henoch-Schonlein Purpura
Risk Factors Associated With Renal Involvement

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Introduction. This study aimed to evaluate renal involvement and factors affecting the prognosis in patients with Henoch-Schonlein purpura (HSP).

Materials and Methods. The outcomes of 107 children diagnosed with HSP who had been followed up for at least 6 months were reviewed.

Results. Renal involvement was observed in 26.1% of the patients. The mean age of the patients with renal involvement was 8.8 ± 4.0 years as compared to 7.1 ± 2.9 years in the patients without renal involvement (P = .02). The risk of renal involvement was found to be significantly higher in the patients who were 10 years old and over (P < .001). In the group with renal involvement, the frequency of scrotal involvement was significantly higher than that of the group without renal involvement (P = .02). The mean serum immunoglobulin A level of the patients with renal involvements was significantly higher (P = .04) and the mean serum complement C3 levels was significantly lower (P = .04) than those of the patients without renal involvement. None of the patients with renal involvement reached end-stage kidney failure. No significant relationship was observed between the development of renal involvement and early steroid treatment.

Conclusions. This study proposes that in old children with HSP, elevated serum immunoglobulin A levels, decreased serum complement C3 levels, and scrotal involvement are associated with renal involvement. We failed to find any effect of steroid treatment on development of renal involvement.

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INTRODUCTION

Henoch-Schonlein purpura (HSP) is one of the most common vasculitides of childhood whose major manifestations include nonthrombocytopenic purpura, arthritis or arthralgia, abdominal pain, and renal involvement.[1] The disease is characterized by the deposition of immunoglobulin A (IgA)-containing immune complexes and complement components within small vessel walls, and often within the renal mesangium.[2] The annual incidence of HSP is reported to be approximately 14 to 18 per 100 000 in children.[3] It is more common in males and more frequently occurring during the winter months. The etiology is unknown, although there is often a history of a preceding upper respiratory tract infection. Twenty-five percent of the patients have positive throat cultures of group A beta-hemolytic *Streptococcus* (GABHS).[4]

The prognosis of HSP is usually good; however, patients with severe gastrointestinal and renal

manifestations should be carefully treated and followed. During the acute period, massive gastrointestinal bleeding and intussusceptions, which might be life threatening, may be observed.[5] Long-term prognosis is usually associated with the severity of renal involvement.[6,7]

In this study, we evaluated the frequency of skin, joint, gastrointestinal, and renal involvement in HSP patients. Also, we retrospectively evaluated the treatment protocols, the clinical follow-up, and the prognosis of renal involvement.

MATERIALS AND METHODS

Patients and Collected Data

This is a retrospective study of the children with HSP, at the Department of Pediatric Nephrology, Inonu University, from December 2005 to January 2010. The European League against Rheumatism/Paediatric Rheumatology European Society criteria, published in 2006,[8] were used for diagnosis of HSP, which include palpable purpura (a mandatory criterion) in the presence of at least one of the following: (1) diffuse abdominal pain, (2) any biopsy showing predominant IgA deposition, (3) arthritis or arthralgia, and (4) renal involvement (hematuria and/or proteinuria). A retrospective analysis of all the data of the selected patients was performed by reviewing the medical files. The recorded signs and symptoms of the 107 patients were evaluated and the frequency of skin, joint, gastrointestinal, and renal manifestations were determined and compared between 2 age groups (< 10-year-old and ≥ 10-year-old children). The frequencies of anemia, leukocytosis, increased IgA level and antistreptolysin O titer, altered levels of complements C3 and C4, and the existence of a positive throat culture for GABHS were determined.

In the patients with kidney disease, the frequency of hematuria, proteinuria, hypertension, and nephritic and nephrotic syndromes were determined. Nephrotic syndrome was defined as the presence of proteinuria (> 40 mg/m^2/h) and a serum albumin level less than 2.5 g/dL, together with edema. Acute nephritic syndrome was defined as the presence of hematuria together with at least 2 of the conditions from the set of hypertension, raised serum urea or serum creatinine, and oliguria. Hypertension was defined as a systolic or a diastolic blood pressure greater than the 95th percentile for the specific age, based on the Pediatric Task Force Recommendation.[9]

Henoch-Schonlein nephritis patients were classified into 5 grades according to the initial clinical presentation. The modified Meadow classification[10] was used as follows: Meadow 1, microscopic hematuria; Meadow 2, persistent mild proteinuria (< 20 mg/m^2/h) and/or hematuria; Meadow 3, nephritic syndrome; Meadow 4, nephrotic syndrome; and Meadow 5, mixed nephritic-nephrotic syndrome.

Renal biopsy was performed for the patients with nephrotic syndrome or nephrotic-range proteinuria and macroscopic hematuria with hypertension or acute kidney failure. The histological grades of the renal biopsy samples were evaluated according to the classification defined by the International Study of Kidney Disease in Children.[11] Age, gender, clinical syndrome, histopathological class, treatment protocols, duration of the treatment, and clinical progression of the disease were analyzed in detail for the patients whose biopsies were obtained.

The procedures were in accordance with the ethical standard for human experimentations established by the Declaration of Helsinki of 1975, as revised in 1983. The study was approved by the Ethics Committee of Inonu University.

Statistical Analyses

The SPSS software (Statistical Package for the Social Sciences, version 16.0, SPSS Inc, Chicago, Ill, USA) was used for the statistical analysis. Quantitative variables were reported as mean ± standard deviation. Normality for quantitative variables in groups was determined by the Shapiro-Wilk test. Categorical variables were expressed as percentages. Continuous variables were analyzed by the unpaired *t* test. Categorical variables were analyzed by the chi-square (Pearson) and Fisher exact tests. Relative risks were calculated for factors by age group. A *P* value less than .05 was considered significant.

RESULTS

The study group consisted of 107 children, 61 boys (57%) and 46 girls (43%), with the ratio of boys to girls to be 1.32:1. The mean age was 7.56 ± 3.40 years. Seventy-nine of the children (73%) were 10 years old and younger and 28 (27%) were older than 10 years. According to the onset date, the seasonal distribution of the patients with HSP

was evaluated. Of 107 patients, 42% presented in the autumn, 27% in the spring, 17% in the winter, and 4% in the summer.

Skin, joint, and gastrointestinal manifestations were observed in 100%, 67.3%, and 41.1% of the children, respectively. In addition 28 of the 107 patients (26.1%) had renal involvement. The mean age of the patients with renal involvement was significantly higher than that of patients without renal involvement (8.8 ± 4.0 years versus 7.1 ± 2.9, $P = .02$). Renal involvement was significantly more frequent in patients older than 10 years ($P < .001$). In the group with renal involvement, the frequency of scrotal involvement was significantly higher than that of the group without renal involvement ($P = .02$). The frequencies of skin, joint, gastrointestinal, and renal involvement according to age groups are shown in Figure 1. No significant differences were found in these manifestations between the age groups. The distribution of the patients according to multisystem involvement is shown in Table 1.

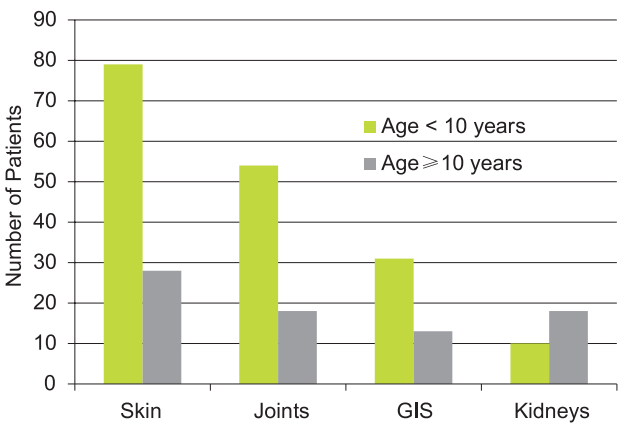

Figure 1. Comparison of different manifestations of Henoch-Schonlein purpura between different age groups.

Table 1. Classification of Patients With Henoch-Schonlein Purpura by Multisystem Involvement*

System involvement	Number (%)
Skin	17 (15.9)
Skin and GIS	7 (6.5)
Skin and joints	34 (31.7)
Skin and kidneys	4 (3.7)
Skin, joint, and GIS	21 (19.6)
Skin, GIS, and kidneys	7 (6.5)
Skin, joints, and kidneys	8 (7.5)
Skin, GIS, joints, and kidneys	9 (8.4)

*GIS indicates gastrointestinal system

The distribution of clinical findings in 28 patients with renal involvement is shown in Figure 2 according to the Meadow classification. The comparisons of the patients with HSP with or without renal involvement in terms of the gastrointestinal system, joints, and scrotal involvement are shown in Table 2.

The laboratory findings in the patients with HSP with or without renal involvement were evaluated. The mean serum IgA levels of the patients with renal involvements were statistically significantly higher than that of the patients without renal involvement ($P = .04$). Serum C3 levels was significantly lower in patients with renal involvement than that of the patients without renal involvement ($P = .04$).

The patients with renal involvement were classified according to the emergence time of renal involvement. Signs of renal involvement were detected in 6 patients at the time of diagnosis. Renal involvement was detected in 18 patients in the first month (85.7%), 3 patients in 1 to 3 months (10.7%), and 1 patient in 4 to 6 months (3.5%). The

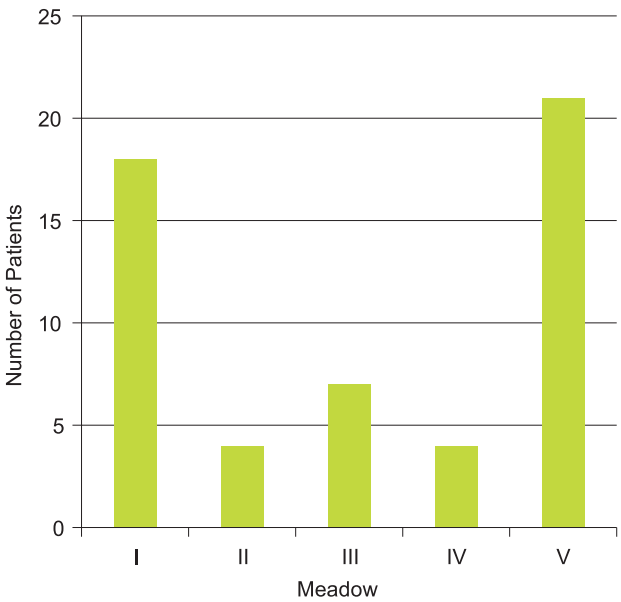

Figure 2. Renal involvement in patients with Henoch-Schonlein purpura according to the Meadow classification.

Table 2. Other Systems Involvements in Patients With Henoch-Schonlein Purpura With and Without Renal Involvement

	Renal Involvement		
Other Involved Systems	Yes (%)	No (%)	*P*
Gastrointestinal system	15 (53.6)	29 (36.7)	.70
Joints	15 (53.6)	57 (72.2)	.10
Scrotums	3 (10.7)	0	.02

distribution of the patients with HSP according to the emergence time of renal involvement is shown in Table 3.

Eight patients underwent kidney biopsy, most of whom were 10 years old and over (P = .004). One patient with stage IIA, 3 patients with stage IIIB, 2 patients with stage IVA, and 2 patients with stage VI were determined according to the classification by the International Study of Kidney Disease in Children.

The rate of development of renal involvement in the follow-up period according to the initial treatment approach was determined. Steroid treatment was applied at a dose of 1 mg/kg/d to 2 mg/kg/d for 7 to 10 days to 48 patients. After the removal of 6 patients with renal involvement from the study group at the time of referral, 11 patients with renal involvement, those were detected during the follow-up, used steroids and the remaining 11 did not use steroids. We did not detect any effects of steroid treatment on renal involvement.

Excluding patients with renal involvement at the time of diagnosis (n = 6), the remaining patients were evaluated for the development of renal involvement during the follow-up period according to their gender. It was determined that of the patients with the development of renal involvement during the follow-up, 15 patients (26.3%) were male and 7 patients (15.9%) were female. No significant relationships were determined between gender and the development of renal involvement during the follow-up. In the other 6 patients with renal involvement, followed-up due to mixed nephritic-nephrotic syndrome, improvement was seen in the symptoms of renal involvement after 6 to18 months. Symptoms of renal involvement in the patients with persistent mild proteinuria with or without hematuria improved in a year. Symptoms of renal involvement in the patients with macroscopic hematuria improved in 8 months. No end-stage kidney failure was determined in at least 6-month follow-up of the 28 patients with renal involvement.

Table 3. Classification of Patients With Henoch-Schonlein Purpura by the Time of Renal Involvement

Time of Renal Involvement	Number (%)
At diagnosis	6 (21.4)
At 1 months	18 (64.3)
At 1 to 3 months	3 (10.7)
At 4 to 6 months	1 (3.6)

DISCUSSION

The aim of this study was to evaluate the initial clinical features of children with HSP, as well as to investigate the prognostic risk factors of renal involvement. Henoch-Schonlein purpura is the most common vasculitis of childhood. It can be diagnosed in children older than 6 months and in adults; however, the majority of the cases are diagnosed between the ages of 2 and 10 years.[12] Although it has been reported in the literature that the ratio of boys to girls numbers ranges between 1.3:1 and 2:1, some studies also suggested that among girls, it is observed more frequently than the boys.[13-15] In the present study, 73% of the patients were under the age of 10 years, and the age at onset was 7.56 years. The ratio of boys to girls was 1.32:1, which is similar to the reports in the literature.

It has been reported that HSP has seasonal characteristics, and it occurs mostly in the autumn, in winter, and in the spring.[16] In our study, the seasonal distribution rate was determined as 42% in the autumn, 27% in the spring, 17% in the winter, and 14% in the summer. Similarly, in our study, it was seen that the disease was more common in the autumn and in the spring.

Henoch-Schonlein purpura is mainly characterized with the involvements of the skin, joints, gastrointestinal tract, and the kidneys. Systemic symptoms are seen in 80% of the patients, and the most common symptom is skin rash.[17] Nevertheless, it is only seen in 50% of the patients as an initial symptom.[18] Despite these data, the diagnosis of HSP without purpuric skin rash might be missed by the family and the physicians. Skin involvement, which was determined in 100% of our patients, supports this finding. Joint involvement is seen in about 60% to 84% of the patients.[18] In our cohort, in accordance with the literature, the rate of joint involvement is approximately 67%. The most common gastrointestinal symptom is severe and intermittent colicky abdominal pain, and it may be seen in more than 80% of the patients with gastrointestinal involvement.[19] Of our patients, 41% had gastrointestinal involvement and 2% had scrotal involvement. The distribution of our patients according to multisystem involvement is shown in Table 1 in detail.

Potentially, the most dangerous involvement in HSP with the most serious sequel is renal involvement. Renal involvement percentage

in HSP has been reported to be 20% to 50% and in approximately 40% in random patient groups in various studies.[20] Varying criteria and laboratory parameters used for the detection of renal involvement are considered to be the most important reason for this difference. The spectrum of renal manifestations ranged from more usual microhematuria to less common nephrotic syndrome, and those with nephrotic syndrome suffered from prolonged disease courses.[21] The distribution of renal involvement of our patients according to Meadow classification is shown in Figure 2 in detail. Renal involvement usually appears within the first three months following the initial appearance of purpura. It develops within the first 4 weeks in 80% of the patients, while it appears within the second and the third months in the remaining 20%.[22] Of our 107 patients, 28 (26.1%) had renal involvement at the beginning or at least within the 6 months of the follow-up period. When the patients with renal involvement were classified according to the time of renal involvement; renal involvement was detected in 6 patients at the time of diagnosis, in 18 patients (85.7%) in the first month, in 3 patients (10.7%) between the first and the third months, and in only 1 patient (3,5%) between the fourth and the sixth months.

Laboratory tests are not considered to be diagnostic for HSP.[23] In the literature, increased serum IgA and decreased complement levels are reported to be in the range of 20% to 50% and 10% to 20%, respectively.[24,25] In our study, both increased serum IgA and decrease C3 levels were similar to the reports in the literature.

Sano and colleagues[22] reported some risk factors related to kidney disease. In that study, the ratio of renal disease was 49% and multifactorial analysis revealed that age at onset older than 4 years, persistent purpura longer than 1 month, more than 80% decrease in the factor 13 level, and severe gastrointestinal disease were related to the frequency of renal disease. The most important prognostic factor was the severity of the symptoms of renal disease at onset and the long-term prognosis was the worst in patients with nephrotic proteinuria.[26] According to our study; age older than 10 years, elevated serum IgA levels, low C_3 levels, scrotal involvement are the risk factors for renal involvement. However, some studies revealed that the long-term prognosis depends on the histological findings in renal biopsy rather than the symptoms at onset.[2] Renal biopsy was performed in 8 of 28 patients. Most patients (62%) had histopathologically class III or IV kidney disease.

It has been proposed that the early use of corticosteroids in children with HSP could prevent chronic renal disease. Unfortunately, these studies had drawn weak conclusions with methodological flaws, and the only few prospective studies failed to use appropriate randomization or a placebo.[27] Thus, the overall results are contradictory and confusing, and the question of whether early treatment with corticosteroids reduces the risk of subsequent renal involvement in HSP remains unsettled. The rate of development of renal involvement in our patients during the follow-up according to the initial treatment approach was determined. After the removal of 6 patients with renal involvement from the study group at the time of referral, it was determined that 11 of the patients with renal involvement, those were detected during the follow-up, used steroids, and the remaining 11 did not use steroids. We did not detect any effects of steroid treatment on renal involvement.

During the study period, none of the patients had ESRD presentation. Of 6 patients with renal involvement and followed-up due to mixed nephritic-nephrotic syndrome, improvement was seen in the symptoms of renal involvement after 6 to18 months. Symptoms of renal involvement in a patient with persistent mild proteinuria and hematuria improved in a year, and symptoms of renal involvement in a patient with macroscopic hematuria improved in 8 months.

CONCLUSIONS

According to our study; in patients who are 10 years old and over, elevated serum IgA levels, decreased serum C3 levels, and scrotal involvement are the risk factors for renal involvement. No effects of steroid treatment on renal involvement were detected. The major limitation of this study is the nature of the retrospective design. We suggest that systematic and careful long-term follow-up of all HSP patients is warranted.

CONFLICT OF INTEREST

None declared.

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