

Henoch schönlein purpura in children: Clinical features and risk factors of renal involvement

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Abstract

Objective: This study aimed to evaluate the clinical and laboratory features of children diagnosed with Henoch Schönlein purpura (HSP), risk factors of renal involvement and their effect on prognosis.

Methods: A total of 80 pediatric HSP patients (44 males and 36 females) between ages 2 to 13 (average age 7.68±3.09) admitted to the Pediatrics Clinic and follow-up cases from the Pediatric Rheumatology and Nephrology Clinic of the Istanbul Medeniyet University, Göztepe Training and Research Hospital, between April 1998 and June 2003 were enrolled for the study. In order to precisely evaluate glomerular and tubular function, urinary β 2 microglobulin, microalbumin and tubular reabsorption of phosphorus (TRP) were determined.

Results: A retrospective evaluation of the HSP patients showed that 26 (32.5%) had symptoms of renal impairment. In terms of renal function, 20 (25%) out of the 54 asymptomatic children initially subjected to routine renal tests had renal involvement. In terms of age, there was a significant difference ($p < 0.016$) in developing renal involvement between patients above 5 years old and those younger than 5 years.

Conclusion: It was therefore suggested that long-term follow-ups in addition to examinations such as routine kidney function tests, tubular reabsorption of phosphate (TRP) and microalbumin levels should be conducted in order to detect the early phase of renal damage.

Keywords: Henoch Schönlein purpura, risk factors, renal involvement

Introduction

Henoch-Schönlein Purpura (HSP) is the commonest small-vessel vasculitis in childhood with non-thrombocytopenic purpura, joint, gastrointestinal system (GIS), renal, genitourinary and central nervous system involvement as clinical features of the disease. Basically, it is characterized by the deposition of an immune complex containing immunoglobulin A (IgA) and complement part in the capillary wall (1,2). Despite its prevalence at every age in childhood, its incidence is twice more in boys than in girls and between the ages of 5 and 7 (3,4,5). Its annual incidence was reported as 10-22/100000. Although its etiopathogenesis is not exactly known, it has been reported that infections (bacterial, viral, parasitic), medicines, vaccines, tumors, bug bite and some foods may trigger the disease (6).

Although HSP is a benign self-limited disease, the most important factor determining its prognosis in the long term is renal involvement which is not manifested in all HSP patients. However, when renal involvement occurs, severe nephrotic proteinuria, macroscopic hematuria and kidney failure are the clinical manifestations (2,7). It is crucial to know the risk factors of renal involvement beforehand. In order to prevent the onset of complications, measures such as long-term follow-up of the patients should be conducted. To this end, this study aimed to present clinical and laboratory features of HSP patients following diagnosis at the Pediatric Clinic of Göztepe Training and Research Hospital, risk factors of renal involvement and their effect on prognosis in comparison with relevant literature.



Material and Methods

A total of 80 HSP patients admitted to the Pediatrics Clinic (Internal Diseases) and follow-up cases from the Pediatric Rheumatology and Nephrology polyclinic of the Göztepe Training and Research Hospital, Istanbul Medeniyet University between April 1998 and June 2003 were enrolled for the study. The study was approved by the Ethics committee of the Göztepe Training and Research Hospital. Informed written consent were obtained from parents/guardians of the children. HSP diagnosis was made according to the American College of Rheumatology (ACR) criteria (8). The clinical features of HSP are; 1. palpable purpura, 2. diagnosis at <20 years old, 3. stomachache, and 4. skin biopsy showing the presence of leukocytoclastic vasculitis.

In the study, factors such as age, gender, complaints, drug intake and history of infection in the patients were determined. Secondary data were obtained from patient's medical records such as gender, age, clinical features of the skin, joint, kidney, GIS and other organs/systems. In patients with severe stomachache and/or positive fecal occult blood, GIS involvement was detected. During follow-up in patients with hematuria (proteinuria, edema, hypertension and decreased glomerular filtration rate (GFR), renal involvement was detected.

From the retrospective study, complete blood count, antistreptolysin O antibody (ASO), serum c-reactive protein (CRP), complement C3, rheumatoid factor (RF), antinuclear antibody (ANA), sedimentation, throat culture, immunoglobulins, fecal occult blood, skin biopsy findings, complete urinalysis, creatinine, Na, K, Ca, P, GFH levels and renal ultrasonography were determined.

Patients whose renal functions were examined after 2.5 ± 0.5 mean years of follow-up and diagnosed with HSP were called-in for a check-up and renal function, TRP, β -2 microglobulin and microalbumi levels were evaluated. In the evaluation of renal functions, in

The control group for the study included 20 health children comprising 11 males and 9 females aged between 3-17 years (average age 10.5 ± 4.6).

In this study, blood and urine, urea, creatinine, Na, K, Ca, P analysis were carried out with Auto analyzer (Olympus AU-5200, Japan) at the biochemistry laboratory of the hospital while β -2 microglobulin and microalbumin in 24-hour urine test were analyzed using the Turbitimer method with Cobas Mira (Roche Diagnostic Systems Incorp., USA) in the Sonomed biochemistry laboratory.

Data obtained were analyzed using SPSS (Statistical Package for Social Sciences) software. Mann-Whitney U and Kruskal –Wallis tests were used for data comparison. In the Kruskal –Wallis and Mann-Whitney U tests, P values of <0.05 and <0.016, respectively were considered as significant.

Results

Of the patients included in the study were, 44 males (55%) and 36 females (45%); that is, male:female ratio of 1.22. Mean hospital length of stay was 6.63 ± 4.4 days. 75% of the patients were >5 years old (mean 7.68 ± 3.09). 26 patients (32.5%) had upper respiratory tract infection (URTI) and 4 (5%) had gastroenteritis with no history of vaccination and medication intake. When the seasonal distribution of the cases was examined according to their date of admission, the study showed that 29 (36.2%) cases were admitted in winter, 23 (28.7%) cases in spring, 29 (23.7%) cases in autumn, and 9 (11.2%) cases in summer.

The most common clinical features reported in the study were rash (80; 100%), arthralgia (47; 58.7%) and edema (30; 37.5%). Other symptoms included: stomachache, vomiting, arthritis, scrotal edema, headache, diarrhea, hepatomegaly and invagination. Elevated blood pressure of >95% percentile was reported (4 cases) in the study. Of the 80 cases, 3 cases were diagnosed with having only rash.

In terms of etiological assessment, the study showed increased ASO in 13 (16.2%) patients, mycoplasma in 2 (5%), Epstein barr virus in 2 (2.5%), Giardia intestinalis in 2 (2.5%), measles in 2 (2.5%), amebiasis in 2 (2.5%), group A beta streptococcus (GABS) in throat culture in 1 (1.2%), mumps in 1 (1.2%), leptospira in 1 (1.2%), and parvovirus infection in 1(1.2%) patient. Consequently, etiological cause was reported in 27 cases (33.7%). Fecal occult blood (FOB) was positive in 41 (51.2%) patients while GIS involvement was reported in 35 (85.3%) patients of >5 years.

A. Retrospective Evaluation of the Symptoms of Renal Involvement in the Patients with Henoch-Schönlein Purpura (With Routine Renal Function Tests)

When the findings of renal involvement were retrospectively evaluated from 80 patient-files, renal involvement was reported in 26 (32.5%) patients. Upon hospital admission, renal involvement was observed in 21 patients. However, within the first 3 months, renal involvement developed in 5 more patients (Table 1). Meanwhile, GIS involvement was found in 16 (61.5%) patients with renal involvement.

Due to post follow-up prolonged hematuria and proteinuria (3 months), renal biopsy was carried out on 3 males. The renal biopsy showed endocapillary proliferation of glomeruli with lesions close to 50% in 2 patients. However, in the third case, due to nephritic proteinuria and prolonged microscopic hematuria, there was mild mesangial cell proliferation in the biopsy.

An evaluation of findings from the first hospital admission of patients with HSP and laboratory results of those with renal involvement within 3 months and GIS involvement showed increased sedimentation ASO in the patients with GIS and renal involvement than the others.

B. Prospective Evaluation of Renal Function in Patients with Henoch-Schönlein Purpura After 2.5 Years of Follow-up (with Routine Renal Function Tests, Microalbumin, β -2 Microglobulin, and TRP)

1. Evaluation of patients (Group I) on first admission to hospital with asymptomatic findings of renal involvement

When the cases were evaluated in terms of renal functions on average 2.5 years of follow-up after HSP diagnosis of, renal involvement was found in 20 (25%) of 54 patients initially evaluated as asymptomatic with routine renal tests (Table 2). GIS involvement was also found in 8 patients who were previously asymptomatic.

2. Evaluation of patients (Group II) whose findings of renal involvement were positive during their first admission to hospital

The 17 of 26 patients were found with renal involvement (65.3%) in their first hospital admission (Table 3).

The comparison between HSP patients with positive renal involvement after 2.5 years of follow-up and the healthy control group showed a significant difference between TRP and microalbumin/Cr levels ($p < 0.05$). However, there was no significant difference between β -2 microglobulin/Cr levels and the control group ($p > 0.05$) (Table 4).

The study also showed a significant difference in developing renal involvement among HSP patients ($p < 0.016$) between patients aged >5 years and <5 years. However, no significant difference was seen in terms of gender ($p > 0.016$). When the relationship between HSP patients with and without renal involvement with GIS involvement was statistically examined, there was a significant difference between microalbumin/Cr levels in patients with renal involvement ($p < 0.016$). CRP and sedimentation increased moderately in 14 and 5 patients, respectively. Leukocytosis was reported in 27 patients (33.7%) while leukopenia was found in 2 (2.5%). Serum complement (C3) level and other immunoglobulins were normal, antinuclear antibodies (ANA) and rheumatoid factor (RF) were negative while IgA increased in 1 case (430 mg/dl).

Table 1: Retrospective Evaluation of Renal Involvement Symptoms in Henoch-Schönlein Purpura Patients

| Symptoms | N | % |
|---------------------------------------|----|------|
| Microscopic hematuria | 11 | 13.7 |
| Proteinuria | 3 | 3.7 |
| Hypertension + Microscopic hematuria | 3 | 3.7 |
| GFH reduction + Microscopic hematuria | 3 | 3.7 |
| Decrease in urine density | 2 | 2.5 |
| Proteinuria + Microscopic hematuria | 2 | 2.5 |
| Hypertension + proteinuria | 1 | 1.2 |
| Microscopic +macroscopic hematuria | 1 | 1.2 |

GFH: Glomerular filtration rate, N: Number of patients = 29.

Table 2: Prospective evaluation of renal function in patients with asymptomatic renal involvement on first admission (Group I) to hospital

| Renal function | N | % |
|--|----|------|
| Decreased TRP | 10 | 12.5 |
| Increased Microalbumin / C ratio | 7 | 8.4 |
| Microscopic hematuria | 2 | 2.5 |
| Decreased TRP + Increased Microalbumin / C ratio | 1 | 1.2 |

TRP: Tubular reabsorption of phosphorus, Cr: Creatinine, N: Number of patients = 20

Table 3: Evaluation of patients with positive renal involvement (Group II) at first admission to the hospital.

| Renal function | N | % |
|--|----|------|
| Improvement | 17 | 65.3 |
| Increased Microalbumin / C ratio | 3 | 7.6 |
| Increased Microalbumin / C ratio + Decreased TRP | 2 | 7.6 |
| Microscopic hematuria | 2 | 7.6 |
| Decreased GFH + Increased Microalbumin / C ratio | 1 | 3.8 |
| Decreased GFH | 1 | 3.8 |

GFH: Glomerular filtration rate, TRP: Tubular reabsorption of phosphorus, N: Number of patients = 26

Table 4: TRP, β -2 microglobulin/creatinine, microalbumin/creatinine levels of the healthy control group and HSP patients with renal involvement (after 1 -year follow-up)

| Groups | TRP (%) | p | Microalbumin/Cr (μ gr/gr) | P | β 2 Microglobulin/Cr (μ gr/gr) | p |
|-------------------------------------|------------------|-------|--------------------------------|-------|---|--------|
| HSP patients with renal involvement | 68.1 \pm 4.8 | 0.045 | 1.7 \pm 0.89 | 0.01 | 3.23 \pm 2.8 | 0.60 |
| Control group | 82.45 \pm 5.75 | <0.05 | 0.25 \pm 0.21 | <0.05 | 2.77 \pm 1.65 | p<0.05 |

HSP: Henoch Schönlein purpura, TRP: Tubular reabsorption of phosphorus Cr: Creatinine

Table 5: Comparison of literature with Henoch Schönlein Purpura (HSP) and laboratory with clinical characteristics of patients in the current study

| Source no | * | 9 | 10 | 11 | 12 | 13 | 14 |
|----------------------------|--------------------------|--|-------------|--|--------------------------|--|----------------------------|
| No. of patients | 80 | 535 | 151 | 168 | 212 | 162 | 186 |
| Time of observation | 2.5 years | 6 years | 15.6 months | 6-66 months | 0 | 6 months | 16.9 months |
| Gender F/M | 45/55 | 42/57 | 61/90 | 66/102 | 95/117 | 77/85 | 89/97 |
| Age (mean years) | 7.68 | 6.9 | 7.4 | 8.8 | 6.93 | 7.5 | 7.4 |
| Season | Winter | | Winter | | Winter | Autumn | |
| Etiology (%) | | | | | | | |
| URTI | 32.5 | | 21.8 | 44 | | 58 | |
| Drug | 0 | | | | | 0 | |
| Vaccine | 0 | | 0.1 | 2 | | 0 | |
| Gastroenteritis | 5 | | 1.3 | 6 | | 0 | |
| Affected system (%) | | | | | | | |
| Purpura | 100 | 100 | 100 | 100 | 98.1 | 100 | 100 |
| Joint | 62.5 | 57.6 | 57.6 | 35 | 69.8 | 68.9 | 94 |
| GIS | 51.2 | 49.7 | 73.5 | 20 | 75 | 76.5 | 55 |
| Renal involvement | 32.5 | 49.9 | 27.1 | 20 | 26.9 | 56.2 | 28 |
| İzole Hematuria(%) | 13.7 | 5.2 | 25 | 59 | 9.9 | 24 | 6.9 |
| Proteinuria (%) | 3.7 | 77.5 | 16 | 35 | 1.9 | 2.5 | 2.7 |
| Recurrence (%) | 17.5 | | 4 | 11.9 | 5.2 | | |
| Risk factors | >5year + GIS involvement | >6year + Atypical rash + occult blood in the stool | year | >7 year+ GIS involvement + long duration of rashes | >7 year+ GIS involvement | low albumin occult blood in the stool + diarrhea | >10 year +Female sex+> CRP |

*: Current study, GIS: Gastrointestinal system, CRP: Serum reactive protein, URTI: Upper respiratory tract infection

Discussion

Although the clinical course is usually good in HSP, life-threatening complications rarely develop. Similar results have been reported in terms of epidemiology, clinical features, organ involvement, and prognosis of HSP in similar studies. Long-term prognosis of HSP is associated with kidney involvement, and while only microscopic hematuria was observed in some of patients, permanent kidney damage may develop in others (15).

In this study, the clinical features of HSP patients and risk factors of renal involvement were compared with 6 studies on HSP from different countries (Table 5). Along with the patient number in this study and from the 6 studies, a total of 1494 patients were obtained.

16, 17 and 18 reported that HSP is most commonly seen in male children of age 7.7 (). However, a few studies (19) reported that it occurs more in females.

In the current and retrospective studies, we reported a higher prevalence in males while the average age was in agreement with the literature.

In terms of seasonal distribution of HSP in the literature, patients presented more frequently in winter and autumn while some studies reported spring (20,21). The results of this study were similar to the literature as 36.2% patients presented in winter while 28.7% in spring. In the 6 studies we examined, 2 reported winter while 1 was in autumn; no season was stated in the other studies.

Although the etiology of HSP is not completely known, frequent respiratory tract infections have been implicated. For the first time in 1948, Gairdner showed that HSP developed in association with GABS infection. In the study, 50% of patients' throat culture tested positive for GABS infection (22). In a study of children with HSP by Al-Sheyyab et al., they reported increased ASO titer compared to the control group (23). Of the 6 studies we examined, there was respiratory tract infection varying between 22-58% in 3 of them. In our study, URTI was at the rate of 32.5%, and we found increased ASO in 13 patients (16.2%).

The possibility of HSP patients developing permanent impairment in renal functions, even if rarely, is a major source of concern for clinicians. In the literature, the incidence of renal involvement in HSP varies between 20-54% (24). This variation is assumed to arise from the differences in criteria determining renal involvement. The incidence of HSP nephritis is gradually increasing as the main cause of chronic kidney failure in the pediatric patient group and this rate is increasing towards 5-15% chronic kidney failure in children with HSP nephritis (25). Although the pathogenesis of HSP nephritis is not completely explained, it is reported that cellular and humoral immune dysfunction may be the cause (26).

Microscopic hematuria is the most common finding. However, HSP nephritis can manifest itself in a wide range varying from mild proteinuria or isolated microscopic hematuria that may last for a couple of weeks and improve spontaneously to rapidly progressive glomerulonephritis (27). In our study, hematuria was also the most common finding. In the 6 studies we examined, 5.2- 59% isolated hematuria was reported.

In the literature, it is emphasized that the most important factor determining HSP prognosis is the initial severity of renal symptoms (28). Previous studies have reported that chronic purpura, severe abdominal pain, older age, corticosteroid therapy, previous allergic condition, density and severity of renal symptoms and low serum coagulation factor XIII level significantly affect renal involvement (29,30). It is emphasized that renal symptoms are more severe especially in children at and above the age of 5 (31). Clear or obvious development of bloody stool is a risk factor of renal disorder (32). Renal involvement risk increases by 4 times in patients with abdominal pain and 7.5 times in patients with bloody stool (33). In our study and in the 6 studies examined, average age was above 5, and there was GIS involvement in 4 of the studies. Since

our study showed GIS involvement in 85.3% and renal involvement in 80.4% HSP patients above 5 years, we suggest that these be followed for a longer time and more frequently. There was renal involvement in 20 patients initially asymptomatic and prospectively evaluated 2.5 years after diagnosis. However, GIS involvement was previously seen in 8 of them. Thus, asymptomatic GIS involvement can be a risk factor for patients in terms of renal involvement after years.

Similarly, in a 162-case series conducted by Kızıldağ, it was reported that patients with positive fecal occult blood presented with severe HSP nephritis and underwent kidney biopsy. BUN and creatinine levels were higher in this group of patients (13).

When the cases were evaluated in terms of renal functions 2.5 years after HSP diagnosis, 17 of 26 patients reported with renal involvement in the first 3-month period improved (65.3%). Renal involvement was found in 20 (25%) of the 54 patients who were previously evaluated as asymptomatic with routine renal tests. In the study on 66 HSP patients by Sönmez et al. at the end of a 3-year follow-up, there were minor urinary findings in 15 patients, active renal disease in 4 and renal failure in 1 patient (34). At the end of our 2.5-year follow-up, there was minor disorder in 25 and active renal disease in 4 patients.

In a 36-case study by Muller et al., 24-hour urinary N-acetyl-beta-D-glucosaminidase (NAG) and alpha-1-microglobulin were examined. When the levels in patients on their first hospital admission and after 1, 6 and 12 months were compared, tubular proteins increased especially in the early and late phases of HSP (35). However, in these studies, TRP, microalbumin and β -2 microglobulin were not examined in the evaluation of renal function. At the end of long-term follow-up, glomerular proteins increased in patients who initially had symptoms of renal involvement. However, tubular function was most affected in the patients developing symptoms of renal involvement at the end of follow-up. Urinary β -2 microglobulin levels were normal in all the patients in our study. Normal urinary β -2 microglobulin level is associated with the fact that β -2 microglobulin is an unstable substance.

Conclusion

Finally, in terms of prognosis, knowing the renal involvement incidence of HSP patients at the beginning and determining whether there is minimal glomerular and tubular damage in patients with asymptomatic renal involvement are crucial. Long-term follow-up of asymptomatic patients with and without renal involvement initially is required during their adulthood. It is suggested that for long-term follow-ups, it will be more useful to conduct examinations such as routine kidney function tests, TRP and microalbumin levels to detect the early phase of renal damage.

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Ethical issues: All Authors declare originality and ethical approval of research. Responsibilities of research, responsibilities against local ethics commission are under the Authors responsibilities. The study was conducted under defined rules by the Local Ethics Commission guidelines and audits.

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