



Renal Involvement in Children with Henoch-Schönlein Purpura

Henoch-Schönlein Purpuralı Çocuklarda Renal Tutulum

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Abstract

Objective: Henoch-Schönlein purpura (HSP) is the most common systemic vasculitis in childhood. In this study, we aimed to retrospectively analyze the clinical and laboratory findings and treatment results in terms of renal involvement features in pediatric patients diagnosed with HSP who were hospitalized or applied to our outpatient clinic.

Method: This study included 50 patients who were diagnosed with HSP, admitted to the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Pediatrics Clinic between 2012 and 2015, and followed up regularly for at least 9 months.

Results: The patients included in the study were between the ages of 3 and 16 years (mean age 6.9 years). Thirty-one patients with kidney involvement were between the ages of 5 and 16 years (mean age 10.1 years). 30% of the cases were female (n=15) and 70% were male (n=35). Of the patients with kidney involvement, 11 (35%) were female and 20 (65%) were male. The disease was more common in males, consistent with the literature (p<0.05). The season in which the disease occurred was determined as winter in 10 cases (20%), spring in 11 cases (22%), summer in 10 cases (20%), and autumn in 19 cases (38%). Skin involvement was found in the form of petechiae purpura in all cases (100%), gastrointestinal involvement in 29 patients (58%), joint involvement in 21 patients (42%), kidney involvement in 31 patients (62%), and neurological involvement in 1 (2%) patient. During the follow-up, recurrence was detected in 13 (26%) of the patients. Renal findings developed in 64.6% of the patients within the first 4 weeks and in 35.4% of the patients in the later period. Hematuria was found in all 31 patients with renal involvement, proteinuria in 5 (10%) patients, massive proteinuria in 2 (4%) patients, urea and creatinine elevation in 2 (4%) patients, and high blood pressure in 4 (8%) patients. Renal involvement was found in 23 (79%) of 29 patients with gastrointestinal involvement. Renal involvement was detected in 8 (38%) of the remaining 21 patients. These results were significant in terms of gastrointestinal involvement and renal involvement (p<0.05).

Öz

Amaç: Henoch-Schönlein purpurası (HSP) çocukluk çağıının en sık görülen vaskülitidir. Biz bu çalışmada kliniğimizde yatarak tedavi gören veya poliklinik takibine aldığımız HSP'li çocuklarda özellikle renal tutulum başta olmak üzere klinik bulguları, laboratuvar bulgularını ve tedavi sonuçlarını retrospektif olarak incelemeyi amaçladık.

Yöntem: Bu çalışmada, 2012-2015 tarihleri arasında Sağlık Bilimleri Üniversitesi, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi Çocuk Sağlığı ve Hastalıkları Kliniği'ne başvuran ve HSP tanısı alan ve en az 9 ay izlemi yapılan 50 hasta yer aldı.

Bulgular: Çalışmaya alınan hastalar 3-16 yaş aralığındaydı (ortalama 6,9). Böbrek tutulumu olan 31 hasta ise 5-16 yaş aralığında (ortalama 10,1) idi. Olguların %30'u kız (n=15), %70'i erkek (n=35) idi. Böbrek tutulumu olan hastaların ise, 11'i (%35) kız, 20'si (%65) erkekti. Hastalık literatürle uyumlu olarak erkeklerde daha sık gözlemlendi (p<0,05). On olguda (%20) hastalığın görüldüğü mevsim kış, 11 olguda (%22) ilkbahar, 10 olguda (%20) yaz, 19 olguda (%38) sonbahar olarak belirlendi. Olguların tamamında peteşi purpura şeklinde deri tutulumu (%100), 29 hastada gastrointestinal tutulum (%58), 21 hastada (%42) eklem tutulumu, 31 hastada böbrek tutulumu (%62) saptandı. Hastalarımızdan 32 no'lu olgu ilk olarak santral sinir sistemi tutulumu ile başvurdu. İzlemde hastaların 13'ünde (%26) nöks saptandı. Renal bulgular hastaların %64,6'sında hastalığın ortaya çıktığı ilk 4 haftada belirirken %35,4'ünde daha sonra ortaya çıktı. Renal tutulumu olan 31 hastanın tamamında hematüri, 5'inde (%10) proteinüri, 2'sinde (%4) masif proteinüri, 2'sinde (%4) üre, kreatinin yüksekliği, 4'ünde (%8) yüksek kan basıncı saptandı. Gastrointestinal tutulum saptanan 29 hastanın 23'ünde (%79) renal tutulumun da mevcut olduğu saptandı. Geriye kalan 21 hastanın 8'inde (%38) renal tutulum saptandı. Bu sonuçlar gastrointestinal tutulum ve renal tutulum birlikte görülmesi açısından anlamlı bulundu (p<0,05).

Sonuç: HSP'nin üst solunum yolu enfeksiyonlarının artış gösterdiği sonbahar mevsiminde sık görülebileceği, purpurik döküntüden sonra en sık rastlanan bulgunun renal tutulum olduğu, renal tutulumun da hematüri,



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Conclusion: The most common finding of HSP after purpuric rash is renal involvement, and renal involvement may develop with hematuria, proteinuria, nephrotic syndrome, hypertension, and acute kidney failure. It was determined that renal involvement occurred especially in the first 4 weeks, and the probability of renal involvement increased in patients with gastrointestinal involvement. Considering the wide spectrum of renal involvement in patients with HSP, it was emphasized that the importance of follow-up and monitoring for possible serious renal disease in proteinuria and hypertensive patients, together with angiotensin receptor blocker treatment, as in IgA nephropathy, can yield extremely positive results.

Keywords: Children, Henoch-Schönlein purpura, renal involvement

Introduction

Henoch-Schönlein purpura (HSP) is the most common vasculitis of childhood. This disease, which is characterized by leukocytoclastic vasculitis, progresses with the deposition of immunoglobulin A (IgA) in the small vessels of the skin, joints, gastrointestinal tract, and kidneys (1). Although the exact etiology is not known, it has been reported that it is seen after allergen contact in some cases and after upper respiratory tract infection caused by streptococcus or other microorganisms in some cases (2). The annual incidence of HSP in children is 14-20/100,000. The disease is more common in children than adults, and more often in boys than girls. The incidence in boys and girls was reported as 1.2/1-1.8/1, respectively. 90% of HSP cases seen in childhood are seen between the ages of 3 and 10 years (1). HSP usually occurs in autumn, winter, and spring. It can rarely be seen in summer (3). The disease is seen at a lower incidence in black children compared to white Asian children (4).

HSP is a syndrome that includes non-thrombocytopenic purpura, arthritis, arthralgia, gastrointestinal symptoms, and nephritis. Palpable purpura or accompanying abdominal pain and/or joint pain is the first finding in more than 70% of the patients (5). Typically, skin rashes in the form of palpable purpura appear first on the gluteal regions and lower extremities. Rarely, rashes can be seen on the body and face. Oligoarthritis is present in the large joints of the lower extremities (ankles and knees) in 50-80% of the patients (6-9). These findings usually heal within a few days without any sequelae but may recur later on. Gastrointestinal manifestations occur in 50-75% of cases. Bleeding in the intestinal wall causes colic-like pain and melena. Invagination and perforation are rare. Renal involvement may occur in 20-40% of cases. Oliguria, hematuria, hypertension, nephrotic syndrome, and rarely

proteinüri, nefrotik sendrom, hipertansiyon, akut böbrek yetmezliği gibi tablolarla ortaya çıkabileceği görüldü. Renal tutulumun özellikle ilk 4 hafta içerisinde ortaya çıktığı, gastrointestinal tutulumu olan hastalarda renal tutulum olasılığının arttığı saptandı. HSP'li hastaların renal tutulumun geniş spektrumu da dikkate alınarak takiplerinin önemi ve proteinüri, hipertansif olgularda olası ciddi renal hastalık yönünden izlem ile birlikte IgA nefropatisinde olduğu gibi anjiyotensin reseptör blokleri tedavisi ile son derece olumlu sonuçlar alınabileceği vurgulanmıştır.

Anahtar kelimeler: Böbrek tutulumu, çocuk, Henoch-Schönlein purpurası

chronic renal failure can be seen (6). In this study, we aimed to retrospectively analyze the clinical and laboratory findings and treatment results in terms of renal involvement features in pediatric patients diagnosed with HSP, who were hospitalized or admitted to our outpatient clinic.

Materials and Methods

This study included 50 patients who were diagnosed with HSP and were followed up in an outpatient or inpatient clinic at the University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital Pediatrics Outpatient Clinic, Pediatric Emergency Outpatient Clinic, Pediatric Service and Pediatric Nephrology Outpatient Clinic between the years of 2012 and 2015. For the diagnosis of HSP, the diagnostic criteria determined by the European Rheumatism Union in 2006 (10) were used. These were as follows:

Mandatory criterion: The presence of rash in the form of palpable purpura, which is common especially in the lower extremities, was determined as the absolute criterion.

Other criteria:

Abdominal pain

Histopathological findings (leukocytolastic vasculitis or proliferative glomerulonephritis with excessive IgA deposition)

Arthritis/arthralgia

Renal involvement (proteinuria; >0.3g/24 hours or albumin/creatinine >30 mmol/mg or microscopic hematuria or erythrocyte count >5 at high magnification).

Criteria required for diagnosis: The diagnosis was made by the presence of at least one of the above 4 criteria, especially palpable purpura in the lower extremities, the absolute criterion.

System involvements in the patients were evaluated as skin involvement, joint involvement, gastrointestinal system involvement, kidney involvement, and other system involvements according to physical examination and laboratory findings. Fifty cases included in the study were those who did not have underlying kidney, gastrointestinal, primary immunological, endocrine or other systemic diseases, and other causes of purpura were excluded. Children aged 2-15 years were included in the study. Data about identity information, age, gender, weight, height values, detailed physical examinations, blood pressure, and season of the disease were recorded for patients diagnosed with HSP. Complete blood count, complete urinalysis, proteinuria amount in 24-hour urine, serum urea, serum creatinine, serum albumin liver function tests, (aspartate aminotransferase) alanine aminotransferase), gama glutamyl transferase, C-reactive protein, sedimentation, and occult blood in the stool were evaluated. The presence of more than 5 erythrocytes at 40° magnification in the urine sample centrifuged at 3000 rpm, macroscopic hematuria, proteinuria (under 4 mg/m²/hour in 24-hour urine, 4-40 mg/m²/hour and 40 mg/hour in patients with strip protein positive m²/h), serum albumin level in patients with proteinuria, measurements above the 95th percentile and deterioration in renal function tests (increase in serum creatinine, deterioration in creatinine clearance) were evaluated with reference to the Report of the Second Task Force on Blood Pressure Control in Children for High Arterial Blood Pressure.

Ethical approval for the study was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcilar Training and Research Hospital (date: 16.06.2016, number: 2016/481).

Statistical Analysis

In this study, statistical analyses were performed with NCSS (Number Cruncher Statistical System) 2007 Statistical Software (Utah, USA) package program. In addition to descriptive statistical methods (mean, standard deviation) in the evaluation of the data, independent t-test was used in the comparison of paired groups, and chi-square test was used in the comparison of qualitative data. The results were evaluated at the significance level of p<0.05.

Results

Fifty patients aged 3-16 years (mean 6.9±3 years) were included in the study. Thirty-one patients with renal involvement were between the ages of 5 and 16 years (mean

age 10.1 years). There was no significant difference between the mean age of the patients without kidney involvement and the patient groups with kidney involvement (p=0.359).

30% of the cases were girls (n=15) and 70% were boys (n=35), and the female-male ratio was 0.43 (Table 1). On the other hand, 11 (35%) of the patients with kidney involvement were female and 20 of them (65%) were male. There was no significant difference in gender distribution between those with and without kidney involvement.

The season in which the disease occurred was determined as winter in 10 cases (20%), spring in 11 cases (22%), summer in 10 cases (20%), and autumn in 19 cases (38%) (Table 1).

Skin involvement in the form of petechiae purpura was found in all cases (100%), gastrointestinal involvement in 29 patients (58%), joint involvement in 21 patients (42%), and kidney involvement in 31 patients (62%). The case numbered 32 of our patients first applied with central nervous system involvement. During the follow-up, recurrence was detected in 13 (26%) of the patients (Table 1).

In the treatment of the patients, those with skin involvement were followed up by suggesting rest without medical treatment. Non-steroidal anti-inflammatory drugs were started to reduce pain in those with joint involvement.

Table 1. Clinical features of patients with Henoch-Schönlein purpura

		All groups	
Season of disease occurrence	Winter	10	20.00%
	Spring	11	22.00%
	Summer	10	20.00%
	Autumn	19	38.00%
Gender	Female	15	30.00%
	Male	35	70.00%
Rash	Yes	50	100.00%
Arthritis	No	29	58.00%
	Yes	21	42.00%
Gastrointestinal involvement	No	21	42.00%
	Yes	29	58.00%
Renal involvement	No	19	38.00%
	Yes	31	62.00%
Recurrence	No	37	74.00%
	Yes	13	26.00%
Treatment	Follow-up	27	54.00%
	Steroid	21	42.00%
	Angiotensin receptor blocker	2	4.00%

Hydration and short-term steroids were given to those with gastrointestinal involvement. In patients with renal involvement, angiotensin receptor blocker (ARB) was started in patients with high blood pressure and/or massive proteinuria. The treatment of the case having central nervous system involvement with corticosteroids was successfully completed (Table 1).

Onset of renal findings was at the first week of the onset of the disease in 15 patients (48.3%), at the second week in 2 patients (6.4%), at the third week in 1 patient (3.2%), at the fourth week in 2 patients (6.4%), and in later period in 11 patients (35.4%) (Table 2).

Urea and creatinine levels were found to be high in 2 (4%) patients. Elevated blood pressure was found in 4 (8%) of the patients. Hematuria was detected in 31 cases (62%), proteinuria in 5 cases (10%), and massive proteinuria in 2 cases (4%) (Table 2).

Table 2. Features of renal involvement in children with Henoch-Schönlein purpura

		n	%
Time of appearance of renal findings	1 st week	15	48.39
	2 nd week	2	6.45
	3 rd week	1	3.23
	4 th week	2	6.45
	>5 week	11	35.48
Blood pressure	Normal	27	87.10
	High	4	12.90
Creatinine	Normal	31	100.00
Urea	Normal	30	96.77
	High	1	3.23
Albumin	Normal	30	96.77
	Low	1	3.23
Hematuria	Yes	31	100.00
	No	24	77.42
Proteinuria	Yes	7	22.58

The urea, creatinine, serum albumin and blood pressures of cases numbered 9, 17 and 24 were normal. Proteinuria disappeared spontaneously in the follow-up of patients with proteinuria less than 500 mg/m²/day.

Case numbered 26 had proteinuria of 3.4 g/m²/day. ARB was started for the patient. In the follow-up, urea and creatinine values returned to normal and proteinuria disappeared.

In case numbered 29, high urea and creatinine levels were also present along with high blood pressure. The patient was started on a short-term anti-hypertensive (ARB). In the follow-up, urea creatinine values and blood pressure regressed to normal.

Case numbered 32 with neurological involvement was admitted to our emergency department with confusion and convulsions. The disease-specific rash appeared after neurological involvement. Renal involvement (hematuria) and high blood pressure were also present. Steroids were started for central nervous system involvement. Blood pressure returned to normal without the need for antihypertensive use and renal involvement improved in the follow-up. ARB was started in case numbered 14 because of high blood pressure and proteinuria (1.76 gr/m²/day). In the follow-up, blood pressure returned to normal and proteinuria disappeared. In case numbered 15, high blood pressure resolved spontaneously without the need for antihypertensive use.

No recurrence was observed in 12 (57%) of 21 patients who were given steroids, and in 9 (31%) of 29 patients who were not given steroids. It was found that the steroid did not have a significant role in preventing recurrence (p=0.2).

While recurrence was detected in 12 (41%) of 29 patients with gastrointestinal involvement, recurrence was found in 1 (4%) of 21 patients without gastrointestinal involvement. It was found that the disease recurred more in cases with gastrointestinal involvement (p=0.004). Recurrence was

Table 3. Comparison of the relationship of recurrence with age, treatment, gastrointestinal involvement, and gender

		Relapse (-) n=37		Relapse (+) n=13		p
Age		9.54±3.71		10.54±2.90		0.384
Treatment	Follow-up	23	62.16%	4	30.77%	0.062
	Steroid	12	32.43%	9	69.23%	
	ARB	2	5.41%	0	0.00%	
Gastrointestinal involvement	No	20	54.05%	1	7.69%	0.004
	Yes	17	45.95%	12	92.31%	
Gender	Female	11	29.73%	4	30.77%	0.944
	Male	26	70.27%	9	69.23%	

ARB: Angiotensin receptor blocker

Table 4. Examination of the relationship between kidney involvement and age, the season of onset of the disease, gender, rash, arthritis, gastrointestinal involvement, recurrence, and treatment

		Renal involvement (-) n=19		Renal involvement (+) n=31		p
Age		9.21±3.75		10.16±3.38		0.359
Season of disease occurrence	Winter	2	10.53%	8	25.81%	0.043
	Spring	5	26.32%	6	19.35%	
	Summer	1	5.26%	9	29.03%	
	Autumn	11	57.89%	8	25.81%	
Gender	Female	4	21.05%	11	35.48%	0.281
	Male	15	78.95%	20	64.52%	
Rash	Yes	19	100.00%	31	100.00%	
Arthritis	No	10	52.63%	19	61.29%	0.547
	Yes	9	47.37%	12	38.71%	
Gastrointestinal involvement	No	13	68.42%	8	25.81%	0.003
	Yes	6	31.58%	23	74.19%	
Relapse	No	16	84.21%	21	67.74%	0.198
	Yes	3	15.79%	10	32.26%	
Treatment	Follow-up	15	78.95%	12	38.71%	0.019
	Steroid	4	21.05%	17	54.84%	
	ARB	0	0.00%	2	6.45%	

ARB: Angiotensin receptor blocker

found in 4 (26%) of 15 female patients, while it was found in 9 (25%) of 35 male patients. There was no significant relationship between relapse and gender ($p=0.062$) (Table 3).

Renal involvement was also found in 23 (79%) of 29 patients with gastrointestinal involvement. Renal involvement was detected in 8 (38%) of the remaining 21 patients. These results were found to be significant in terms of gastrointestinal involvement and renal involvement ($p<0.05$) (Table 4).

Joint involvement was found in 9 (47%) of 19 patients without kidney involvement, and in 12 (38%) of 31 patients with kidney involvement. These results were not significant in terms of joint involvement and kidney involvement ($p=0.567$) (Table 4).

Recurrence was detected in 3 (15%) of 19 patients without kidney involvement and in 10 (32%) of 31 patients with kidney involvement, showing that there was no significant relationship between these results and the incidence of renal involvement and recurrence ($p=0.198$) (Table 4).

Discussion

HSP is a disease, the frequency of which increases in winter, spring, and autumn (11-13). However, in our cases, autumn (38%) stood out as the season in which this disease

was observed most commonly. Considering that upper respiratory tract infections, which are thought to play a role in the etiology of the disease, increase in this season (14,15), the prominence of the autumn season can be considered significant.

It was reported that HSP was 1.5 times more common in boys than in girls (16). However, in the present study, the incidence in boys was found to be higher than that in the literature (male/female: 2.3). Renal involvement is also common in males, but the male/female ratio was found to be 1.85.

HSP is known as a vasculitic syndrome that generally concerns young children and peaks around the age of 4-7 years (15,17). The mean age of our cases was found to be 6.9 ± 3 (3-16) years. However, the disease can also be seen in adults and has a more serious clinical course especially in terms of renal involvement (18). The mean age of our patients with kidney involvement was found to be 10.1 (5-16) years. The fact that the mean age of patients with renal involvement is older may be significant in terms of more serious clinical course and the emergence of renal findings as the age increases.

Renal involvement in HSP is reported as 20-100% in the literature, and renal involvement occurs in the first four weeks of the disease in 80% of the cases (19-22). In our study,

renal involvement was detected in 62% of our patients. On the other hand, the time of appearance of kidney findings was observed in the first 4 weeks (64.6% of the patients) in line with the literature.

According to a study investigating the factors affecting the prognosis in HSP, it was claimed that while the probability of renal involvement increased in patients with severe gastrointestinal involvement, persistent purpura, and decreased Factor XIII activity, steroid therapy reduced renal involvement (15). Gastrointestinal involvement was detected in 29 (58%) of our patients. Renal involvement was present in 23 (79%) of the cases. Detection of renal involvement in 8 (38%) of the remaining 21 patients was found to be significant in terms of the coexistence of serious symptoms such as gastrointestinal involvement and renal involvement.

On the other hand, it has been suggested that one of the most important factors affecting the prognosis in HSP is the initial findings of renal involvement. According to a study in which it was found that 20% of patients with renal involvement developed chronic renal failure in a 20-year follow-up, end-stage renal disease was initially found in 5% of cases with only microscopic hematuria, in 15% of cases with proteinuria that did not reach the nephrotic level or in nephritic syndrome, in 40% of cases with nephrotic syndrome, and in 50% of cases with both nephrotic and nephritic syndrome (23). It was reported that 1.7% of all children followed in the renal replacement program in Europe were caused by HSP nephritis (4). In our study, no chronicity was detected in the cases we followed up for at least 9 months of follow-up.

However, the absence of a definite specific treatment for HSP nephritis is an important problem. There are also studies suggesting ARB, as in IgA nephropathy, with corticosteroids, immunosuppressives such as cyclophosphamide, and possible severe renal disease in proteinuria and hypertensive cases (19,23,24).

Proteinuria was found in 5 of the cases in our study. In 3 of them, proteinuria was $<500 \text{ mg/m}^2/\text{day}$, and urea, creatinine, albumin and blood pressure values were normal. In the follow-up, the proteinuria of these patients resolved spontaneously without the need for any treatment. In one of the other 2 cases, proteinuria and urea and creatinine levels were also high. Serum albumin and blood pressure values were normal. In the follow-up of the patient who was started on ARB, urea and creatinine values returned

to normal and proteinuria disappeared. In the other case, blood pressure was high together with proteinuria. Urea, creatinine and albumin values were normal. Blood pressure and proteinuria improved in the follow-up of the patient who was started on ARB.

The recurrence rate reported for HSP in the literature varies and is given as 15-35% (24,25). In our study group, recurrence was found to be 26% (13 in 50 cases), which is consistent with the literature. Recurrence was detected in 32% (10 cases) of 31 patients with renal involvement. No recurrence was observed in 12 (57%) of 21 patients who were given steroids and in 9 (31%) of 29 patients who were not given steroids. In our study, it was observed that steroids could not prevent recurrence.

Study Limitations

The limitation of our study is that it is retrospective.

Conclusion

The most common finding of HSP after purpuric rash is renal involvement, and renal involvement may occur with hematuria, proteinuria, nephrotic syndrome, hypertension, and acute kidney failure. It was determined that renal involvement occurred especially in the first 4 weeks, and the probability of renal involvement increased in patients with gastrointestinal involvement. Considering the wide spectrum of renal involvement in patients with HSP, it was emphasized that the importance of follow-up and monitoring for possible serious renal disease in proteinuria and hypertensive patients, together with ARB treatment, as in IgA nephropathy, can yield extremely positive results.

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ethics Committee of University of Health Sciences Turkey, İstanbul Bağcılar Training and Research Hospital (date: 16.06.2016, number: 2016/481).

Informed Consent: Written informed consent was obtained in accordance with the Declaration of Helsinki.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Concept: S.U., Ö.Y., Design: S.U., Ö.Y., Data Collection or Processing: S.U., Analysis or Interpretation: S.U., Writing: S.U., Ö.Y.

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