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Demographics, clinical, laboratory findings and treatment results of pediatric patients with IgA Vasculitis: single-center experiences

IgA Vaskülitli çocuk hastaların demografik, klinik, laboratuvar bulguları ve tedavi sonuçları: tek merkez deneyimi

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Abstract

Purpose: Immunoglobulin A (IgA) vasculitis (IgAV), also known as Henoch-Schönlein purpura (HSP), is a vasculitis characterized by the accumulation of IgA in the vessel walls. In this study, we purposed to evaluate the demographics, clinical and laboratory findings, and treatments and responses of patients diagnosed with IgAV/HSP in our center.

Materials and methods: The records of 201 IgAV/HSP patients who were followed up in the pediatric nephrology-rheumatology clinic were evaluated retrospectively.

Results: It was seen with the equal frequency between girls and boys. While all patients had purpura, other findings were gastrointestinal, joint, renal, subcutaneous edema, and testicular involvement, in order of frequency. The rate of patients who developed intussusception was 2.5%, and none required surgical treatment. Biopsy was performed in patients with persistent proteinuria or hematuria. Histopathological diagnoses were mesangial proliferation, crescent, and minimal change, respectively. While the rate of renal involvement was high in cases with rash and relapse (p=0.046), there was no difference in gastrointestinal and joint involvement. In the histopathological findings of the boys, the crescent was higher than in the girls (p=0.017).

Conclusion: IgAV/HSP generally has a good prognosis, but some patients suffer from renal involvement. In our study, renal histopathology in cases with renal involvement showed milder findings in girls than in boys, but there was no difference in other findings. Renal involvement was higher in relapsed patients.

Key words: IgA vasculitis, renal involvement, Henoch-Schonlein purpura, renal histopathology.

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Öz

Amaç: Henoch-Schönlein purpurası (HSP) olarak adlandırılan İmmünoglobin A (IgA) vasküliti (IgAV), damar duvarlarında IgA baskın immün birikimi ile karakterize küçük damar vaskülitidir. Bu çalışmada merkezimizde IgAV/HSP tanısı almış hastaların demografik özelliklerini, klinik ve laboratuvar bulgularını tedavilerini ve tedavi yanıtlarını değerlendirmeyi amaçladık.

Gereç ve yöntem: Çocuk romatoloji ve nefroloji kliniğinde takipli 201 IgAV/HSP hastasının kayıtları retrospektif olarak değerlendirildi.

Bulgular: Kız ve erkekler arasında hastalık eşit sıklıkta görüldü. Hastaların tamamında purpura varken diğer bulgular sıklık sırasına göre gastrointestinal, eklem, renal, subkutan ödem, testiküler tutulum idi. İnvajinasyon gelişen hastaların oranı %2,5'tu ve hiçbirinde cerrahi tedavi gerekmedi. Persistan proteinüri veya hematürisi olan hastalara biyopsi uygulandı. Histopatolojik tanıları sırayla mezengial proliferasyon, kresent ve minimal değişiklik idi. Döküntü ile relaps gelişen olgularda renal tutulum oranı yüksek iken (p=0,046) gastrointestinal ve eklem tutulum oranlarında fark yoktu. Renal tutulum olan erkeklerin böbrek histopatolojik bulgularında kresent kızlara göre daha yüksek oranda görüldü (p=0,017).

Sonuç: IgAV/HSP, genel olarak, iyi prognoza sahiptir, ancak renal tutulumdan muzdarip hastalar vardır. Çalışmamızda renal tutulum gerçekleşen olgularda böbrek histopatolojisi kızlarda erkeklere göre daha hafif bulgular gösterirken diğer bulgularda fark yoktu. Relaps gelişen olgularda renal tutulum daha fazla idi.

Anahtar kelimeler: IgA vasküliti, renal tutulum, Henoch-Schonlein purpurası, renal histopatoloji.

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Introduction

Immunoglobin A (IgA) vasculitis (IgAV), previously named Henoch-Schönlein purpura (HSP), is a small vessel vasculitis characterized by IgA-dominant immune accumulation in the vessel walls [1]. While it may occur as systemic or limited vasculitis in a single organ, skin, kidney, gastrointestinal system, and joints are frequently involved [1]. Immunoglobulin A (IgA) vasculitis/Henoch-Schönlein purpura (IgA/HSP) has an annual incidence of 20 per 100,000 [2]. It is commonly seen between 3-15 years of age. Although it is more common in males, the male-female ratio varies between 1.2:1-1.8:1. IgAV/HSP is seen especially in autumn, spring, and winter. This is explained by the relationship between IgAV/HSP and infections [3]. An upper respiratory tract infection occurs in about half of IgAV/HSP cases, but the disease is also associated with possible triggers such as vaccines and insect bites [4].

Characteristic symptoms are palpable purpura, arthritis/arthralgia, abdominal pain, hematuria, or proteinuria. Gastrointestinal (GI) involvement is seen in 10-40% and renal findings in 10-55% of patients. Renal involvement during the chronic period and gastrointestinal involvement in the acute period are major causes of morbidity and mortality [5]. IgAV/HSP is self-limited in most cases; however, renal involvement may be associated with severe glomerulonephritis, leading to end-stage renal disease. Delay in treatment can lead to fibrosis and progression to chronic kidney disease in patients with severe nephritis [6].

The diagnosis of IgAV/HSP is based on clinical and histopathological evidences. The American College of Rheumatology (ACR) defined diagnostic criteria for HSP patients, in 1990 [7]. Subsequently, the Ankara 2008 criteria were approved by the European League Against Rheumatism (EULAR), European Society of Pediatric Rheumatology (PRES), and Pediatric Rheumatology International Trials Organization (PRINTO) [8]. In accordance with Ankara 2008 criteria, palpable purpura became an obligatory feature, arthritis/arthralgia and kidney involvement were included and the age criterion was removed. Ankara 2008 criteria had a similar specificity (87.7% vs. 87%) but higher sensitivity (100% vs. 87.1%) in children compared to the ACR criteria [8].

In this study, we aimed to evaluate the demographic characteristics, clinical and laboratory findings, and treatments and responses of patients diagnosed with IgAV/HSP.

Materials and methods

The records of 201 IgAV/HSP patients in the pediatric rheumatology and nephrology outpatient clinic were evaluated retrospectively. Local ethics committee approval was obtained for the study. (2022/26-18)

The diagnosis of IgAV/HSP patients was confirmed according to the 2008-EULAR-PRINTO-PRES classification criteria [8]. The patient records, demographic characteristics, clinical laboratory findings at the time of diagnosis, treatments, treatment results, and disease course were evaluated retrospectively. Clinical findings such as abdominal pain and/or gastrointestinal bleeding (melena, hematochezia, or fecal occult blood) were considered as gastrointestinal involvement, hematuria, proteinuria, and/or increased serum creatinine renal involvement. Laboratory parameters included hemogram, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum immunoglobulin A (IgA), serum creatinine, estimated glomerular filtration rate (eGFR), fecal occult blood, and 24-hour urine protein excretion. *MEFV* gene analysis was performed in patients who had severe abdominal pain, significant acute phase response, or recurrent clinical findings.

Statistical analysis

The statistical analyzes were performed with SPSS 20.0 software. Quantitative variables were presented as mean ± standard deviation or median (minimum-maximum) values, while categorical variables were presented as number of cases and percentage. The groups were evaluated for normal distribution using the Kolmogorov-Smirnov test. Mann Whitney U and Chi-square tests were used to compare groups for mean values and to compare ratios between groups. $p<0.05$ was considered statistically significant.

Results

Of the patients diagnosed with IgAV/HSP vasculitis, 102 (50.7%) were female, 99 (49.3%) were male, and the age at diagnosis was

7.5±3.0, and the follow-up period was 27.2±26 months. While all patients had purpura, they had gastrointestinal, joint, renal involvement, scalp edema, and orchitis, in order of frequency. Preceding respiratory tract infection history was present in 87 (43.3%) patients. One or more relapses were observed during follow-up in 53 (26.4%) patients. Relapses were manifested as skin findings in 42 (20.9%) patients, renal findings in 6 (3%), and gastrointestinal findings in 5 (2.5%) patients. The demographic and clinical findings are shown in Table 1. *MEFV* gene analysis was studied in 47 patients with high acute phase response, recurrent rash, fever, and abdominal pain. At least one or more *MEFV* variants were detected in 25 patients. The most frequently seen mutation was *M694V*. The *MEFV* gene distributions of the patients are given in Table 2. Renal biopsy was performed in 39 patients with persistent proteinuria or hematuria. The pathological findings of the patients were mesangial proliferation 21 (53.8%), crescentic glomerulonephritis 12 (30.7%), and minimal change 6 (15.3%), respectively. The renal biopsy results are given in Table 3. Treatments are shown in Table 1. Spontaneous remission was observed in 79 patients, while treatment was started in 112 patients. 102 (39.3%) of these patients had complete remission, and 10 (5.0%) had partial remission. The outcomes of the patients are shown in Table 4.

The distribution of clinical and histopathological findings between male and female patients is shown in Table 5. While there was a higher rate of renal involvement in relapsed cases, this relationship was not observed in GIS and joint involvement. The relationship between relapse development and system involvement in IgAV/HSP cases is given in Table 6.

Table 1. Demographic, clinical, and laboratory data of patients Immunglubolin a Vasculitis/Henoch-Schonlein Purpura (IgAV/HSP)

Demographics	
• Number	201
• Female / Male	102/99
• Onset age (year)	7.5±3.0
• Follow-up period (month)	27.2±26.2
Clinical findings [N (%)]	
• Purpura	201 (100)
• Arthritis/arthralgia	112 (55.7)
• Gastrointestinal involvement	117 (58.2)
• Renal involvement	70 (34.8)
• Invagination	5 (2.5)
• Scalp edema	34 (16.9)
• Preceding infection	87 (43.3)
• Testicular involvement	13 (6.5)
• Relapse	53 (26.4)
• Skin	42 (20.9)
• Renal	6 (3.0)
• Gastrointestinal	5 (2.5)
Laboratory results	
• Hemoglobin (g/dL)	12.3±1.3
• Leukocytes(/mm3)	11.638±5.133
• Platelets (/mm3)	367.489±141.510
• ESR (mm/h)	28.2±21.3 (2-121)
• CRP (mg/L)	18.7±31.9 (0-233)
• IgA (mg/dL)	192.0±101.2
• Proteinuria [N (%)]	64 (31.8)
• Hematuria [N (%)]	59 (29.4)
Treatment [N (%)]	
• NSAID	20 (10)
• Corticosteroids	104 (51.7)
• Colchicine	16 (8)
• Azathioprine	18 (9)
• Mycophenolate mofetil	3 (1.5)
• Cyclophosphamide	1 (0.5)
• ACE-I	26 (12.9)
• Omega-3	19 (9.5)

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, NSAID: Nonsteroid anti-inflammatory drugs
ACE-I: Angiotensin-converting enzyme inhibitors

Table 2. Distribution of *MEFV* gene mutations in 47 Henoch Schonlein purpura patients

	N	%
No mutation	22	47
Homozygous mutation		
• M694V / M694V	3	6
• R202Q / R202Q	2	5
Compound heterozygous mutation		
• M694V / R202Q	3	6
• M694V / M680I	1	2
• E148Q / P369S	1	2
Heterozygous mutation		
• M694V / -	5	11
• E148Q / -	4	9
• R202Q / -	3	6
• V726A / -	1	2
• A744S / -	1	2
• K695R / -	1	2

Table 3. Pathological diagnosis distributions of patients who underwent renal biopsy (N:39)

	N (%)
Minimal glomerular change	6 (15.3)
Crescent	12 (30.7)
Mesangial proliferation	21 (53.8)

Table 4. The outcome of patients at two-year follow-up

Outcome	[N (%)]
Spontaneous remission	79 (39.3)
Partial remission	10 (5.0)
Complete remission	102 (50.7)

Table 5. Distribution of clinical findings and renal pathological diagnoses by gender

Clinical findings [N (%)]	Kız	Erkek	*p*
• Arthritis/arthralgia	60 (58.8)	52 (52.5)	0.225
• Gastrointestinal involvement	38 (37.2)	40 (40.4)	0.377
• Renal involvement	37 (36.2	33 (33.3)	0.386
• Invagination	2 (2)	3 (3)	0.486
• Scalp edema	15 (14.7)	19 (19.1)	0.255
• Preceding infections	49 (48.0)	38 (38.3)	0.108
• Relapse			
• Skin	18	24	
• Renal	4	2	0.550
• Gastrointestinal	2	3	
Pathological diagnoses [N (%)]	17	22	
Minimal glomerular change	5 (29.4)	1 (4.5)	
Crescent	6 (35.3)	6 (27.2)	0.017*
Mesangial proliferation	6 (35.3)	15 (68.1)	

p<0.05 significant

Table 6. Relationship between other system involvements and recurrent purpura

	Recurrence (+)	Recurrence (-)	*p*
Renal involvement	24 (34.2)	46 (65.7)	0.046*
Gastrointestinal involvement	20 (25.6)	58 (74.3)	0.494
Joint involvement	28 (26.6)	77 (73.3)	0.524

**p*<0.05 significan

Discussion

IgAV/HSP is characterized by palpable purpura, joint, GI, renal findings, and subcutaneous edema. In our study, we reported the experiences of pediatric IgAV/HSP in the tertiary pediatric nephrology-rheumatology center in the west of Turkey. IgAV/HSP is most common between 3-15 years of age and peaks between 5-7 years of age [9-11]. In studies from Turkey, the mean age of IgAV/HSP has been reported to be between 7 and 9 years [3, 6, 12-14]. In our study, the age of onset was 7.5±3.0 years, and males and females were equally affected. In the literature, besides the studies reporting gender equality, there are also studies showing male, or female dominance [3, 6, 12-14].

The etiopathogenesis of IgAV/HSP has yet to be fully elucidated. It is thought to be triggered by respiratory infections or other infectious diseases [15]. The frequent occurrence of IgAV/HSP in autumn and spring supports the idea that infections trigger the disease. Medications, vaccines, and nutrients can also be triggers [9]. In our study, 87 patients (43.3%) had a history of infection as a predisposing factor. The preceding infection history rate varies between 21.4-68.8% [6, 12, 13]. Sixty-nine patients (34%) were hospitalized at the time of admission. Almost all of the patients hospitalized were patients presented gastrointestinal findings. In two studies from Taiwan and Turkey, hospitalization rates were reported as 40.5% and 38.9%, respectively [11, 12]. The Korean study reported a lower rate of hospitalization [16]. These differences in hospitalization rates may be due to differences in disease severity and indications for hospitalization. In particular, the fact that GIS involvement is an acute condition that can result in rapid deterioration, the anxiety of the family, and the level of sensation of the disease may be the reason for this difference. The most common indication for hospitalization was GI involvement, and corticosteroid therapy was given to these patients as 30 mg/kg or 1-2 mg/kg/day methylprednisolone.

All patients had purpura, and 34 (16.9%) had subcutaneous edema (scalp edema). In other studies, this rate has been reported between 25.3-51.3% [11, 12]. Arthritis-arthralgia is the secondly common finding in IgAV/HSP [8]. Arthritis-arthralgia has been reported in 50-70% of patients with IgAV/HSP [12-14, 17]. Also, there are studies reporting higher rates of joint involvement (91.9%) [18]. In our study, the incidence of arthritis-arthralgia was 55.7%. NSAIDs were sufficient in the treatment of these patients. GI involvement was 55.8% in our cohort. The patients in this group were those with abdominal pain accompanied by occult blood in the stool or intestinal wall edema or free fluid findings on abdominal ultrasonography. There was no case of massive rectal bleeding. The rate of GI involvement in IgAV/HSP cases has been reported to be between 32-72% [3, 6, 12-14, 19]. Intussusception is the most important surgical complication in IgAV/HSP and develops in 0.7-13.6% [20]. Five (2.5%) patients had intussusception. These patients improved with corticosteroid therapy without the need for surgery or pneumatic reduction. In other studies, this rate was between 2.3-5.6% [12, 14].

It is generally recommended that patients with IgAV/HSP should be followed for at least six months to detect renal involvement [9]. Renal involvement in HSP has been reported as 20-50% in the literature [8, 21-25]. In our study, renal involvement was determined as 34.8% in the first 6-month period. Of these patients, 22 (31.4%) had nephrotic, 42 (60%) non-nephrotic proteinuria, 57 (81.4%) microscopic, and 26 (37.1%) macroscopic hematuria. Rarely, especially in patients with isolated hematuria and proteinuria, renal involvement may occur in a later period. None of our patients had renal failure or end-stage renal disease. Renal biopsy was performed in 39 patients with persistent or nephrotic proteinuria. All biopsy patients had IgAV/HSP nephritis ranging from minimal glomerular changes to diffuse crescent formation. The histopathological diagnoses of these patients were mesangial proliferation in 22 (56.4%), crescent in 12 (30.7%), and minimal change in 6 (15.3%), respectively. Karadag et al. [12] reported that six crescents, four mesangial proliferation, and three minimal glomerular changes were detected in 13 patients who underwent biopsy. They administered high-dose methylprednisolone and cyclophosphamide treatments to patients who developed IgAV/HSP nephritis. None of their patients developed end-stage renal disease or renal disease failure [12].

Testicular involvement is manifested by pain and swelling and may require evaluation by an experienced pediatric surgeon to rule out testicular torsion – this distinction is important because the former is conservative in treating, and the latter is an acute surgical emergency [19]. Testicular involvement developed in 13 patients (6.5%). In other studies, the rate of testicular involvement has been reported between 1.9-6% [6, 12, 13].

Mutation in at least one allele was detected in 25 (53.2%) patients whose *MEFV* mutation analysis was studied. The most frequently seen mutation was *M694V*. An increased *MEFV* mutation rate has been shown in the literature among patients with IgAV/HSP [26-28]. However, there is no consensus on the effect of *MEFV* gene mutations on the clinical severity of IgAV/HSP [12].

Our study did not detect any difference in the incidence of clinical findings between male and female genders. However, in renal biopsy results, while minimal glomerular changes were higher in females, mesangial proliferation was higher in males (p=0.017).

Some studies reveal the relationship between recurrence and the presence of nephritis [17, 24, 25]. The recurrence was present in 53 (26.4%) of our patients. The recurrences were seen in skin, renal, and GI. In our study, there was a significant relationship between recurrences and the development of nephritis (p=0.046). We did not observe any relationship between recurrences and gastrointestinal and joint involvement. The frequency of relapses reported in previous studies ranges from 3% to 65%, and relapses are mostly seen as skin findings [12, 17, 21, 23, 29]. Studies with higher relapse rates defined relapse as a new exacerbation of skin lesions or other clinical manifestations following the resolution of the disease for at least two weeks or one month [21, 23]. In studies with low incidence, symptoms occurring before three months were accepted as a prolonged course of IgAV/HSP, and exacerbations occurring in a more extended period were considered as recurrence [12, 17]. In our study, we considered relapse as a new exacerbation of clinical symptoms following at least two weeks or one-month resolution of the disease.

In conclusion, this study aimed to share our knowledge and experience to help better define demographic findings, risk factors, management and follow-up of the disease, and associated complications. In our patients, the most common finding and the most frequent recurrence were seen in the skin. The renal involvement rate was higher in cases with recurrence. Gastrointestinal and renal findings significantly accompanied skin findings at the onset of the disease and were the most important causes of morbidity and hospitalization. GIS and renal flare are less responsible for relapses. In cases with renal involvement, renal histopathology shows milder findings in girls than in boys. IgAV/HSP generally has a good prognosis, but some patients suffer from renal involvement. Ultimately, multicenter studies are needed to prevent and improve the long-term renal involvement results of IgAV and to develop an optimal approach to treatment and follow-up.

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Authors' contributions to the article

C.A., A.S., S.K. and M.T.B. constructed the main idea and hypothesis of the study. C.A., M.T.B. and A.S. developed the theory and arranged/edited the material and method section. C.A. and M.T.B. evaluated the data in the results section. C.A. and M.T.B. wrote, reviewed, corrected and approved the discussion section. In addition, all authors discussed the entire study and approved the final version.