Evaluation of Epidemiological, Clinical, and Laboratory Findings in Pediatric Patients with IgA Vasculitis (Henoch-Schönlein Purpura)

IgA Vasküliti (Henoch-Schönlein Purpurası) Olan Pediatrik Hastaların Epidemiyolojik, Klinik ve Laboratuvar Bulgularının Değerlendirilmesi

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ABSTRACT

Objective: Immunoglobulin A vasculitis (Henoch-Schönlein Purpura) is the most common systemic vasculitis of childhood involving the skin, joints, gastrointestinal tract, and kidneys, and less frequently affects other systems. In this study, we aimed to evaluate the epidemiologic, clinical, and laboratory findings of pediatric patients with IgA vasculitis.

Material and Methods: In this study, 366 patients diagnosed with IgA vasculitis (Henoch-Schönlein Purpura) in the pediatric nephrology clinic were retrospectively analyzed. Demographic characteristics, clinical findings, system involvement, and laboratory findings were recorded.

Results: Of the patients in the study, 57.9% (212) were male and the male-to-female ratio was 1.37. The most common age group was found to be between 5-9 years of age. A statistically significant correlation existed between age and renal involvement ($p<0.001$). It was found that renal involvement increased with increasing age. Gastrointestinal system involvement was statistically significantly higher in the male gender ($p=0.003$). A statistically significant correlation existed between increased leukocyte counts, gastrointestinal system involvement, and renal involvement ($p=0.001$, $p=0.009$, respectively).

Conclusion: Age and increased leukocyte count were found to be risk factors for renal involvement. Male gender and increased leukocyte count were found to be risk factors for gastrointestinal system involvement.

Key Words: Child, IgA Vasculitis, Gastrointestinal involvement, Henoch-Schönlein Purpura, Renal involvement

ÖZ

Amaç: IgA vasküliti (Henoch-Schönlein purpurası) çocukluk çağının en sık görülen sistemik vasküliti olup deri, eklemler, gastrointestinal sistem ve böbrekleri tutar ve daha az sıklıkla diğer sistemleri etkiler. Bu çalışmada, IgA vaskülitli çocuk hastaların epidemiyolojik, klinik ve laboratuvar bulgularını değerlendirmeyi amaçladık.

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Gereç ve Yöntemler: Bu çalışmada, pediatrik nefroloji kliniğinde IgA vasküliti tanısı alan 366 hasta retrospektif olarak analiz edildi. Demografik özellikler, klinik bulgular, sistem tutulumu ve laboratuvar bulguları kaydedildi.

Bulgular: Çalışmaya katılan hastaların %57.9'u (212) erkekti ve erkek/kadın oranı 1.37'di. En sık görülen yaş grubu 5-9 yaş arası olarak saptandı. Yaş ile böbrek tutulumu arasında istatistiksel olarak anlamlı bir korelasyon vardı (p<0.001). Yaş arttıkça böbrek tutulumunun arttığı saptandı. Gastrointestinal sistem tutulumu erkek cinsiyette istatistiksel olarak anlamlı derecede yüksekti (p=0.003). Lökosit sayısındaki artış ile gastrointestinal sistem tutulumu ve böbrek tutulumu arasında istatistiksel olarak anlamlı bir korelasyon vardı (sırasıyla p=0.001, p=0.009).

Sonuç: Yaş ve artmış lökosit sayısı böbrek tutulumu için risk faktörü olarak bulunmuştur. Erkek cinsiyet ve artmış lökosit sayısı gastrointestinal sistem tutulumu için risk faktörü olarak bulunmuştur.

Anahtar Sözcükler: Çocuk, IgA vasküliti, Gastrointestinal tutulum, Henoch-Schönlein Purpurası, Renal tutulum

INTRODUCTION

Henoch-Schönlein purpura (HSP), newly defined as Immunoglobulin A (IgA) vasculitis, is the most common systemic vasculitis in childhood, involving the skin, joints, gastrointestinal (GI) tract, and kidneys, and less commonly affecting other systems. It is characterized by IgA1 deposition in small-diameter blood vessels, especially in postcapillary venules (1). The cause is not known for certain. It is frequently seen in children between the ages of 3 and 15, and seasonally it is more common in the fall and winter months (2,3). Classification criteria include palpable purpura, arthritis or arthralgia, abdominal pain, renal involvement, or a skin biopsy with predominantly IgA deposition. Palpable purpura is a "sine qua non" among these criteria and is often the first finding (4). In addition, central nervous system (CNS) involvement, cardiac involvement, and pulmonary involvement can also be seen more rarely during the disease. Although IgA vasculitis is generally a self-limiting disease with a good prognosis, in the presence of renal involvement, morbidity, and mortality may increase about the severity of involvement.

This study aimed to retrospectively evaluate the epidemiologic, clinical, and laboratory findings of patients diagnosed with IgA vasculitis.

MATERIALS and METHODS

In this study, the files of 366 patients who were admitted to the Pediatric Nephrology outpatient clinic of Dr. Sami Ulus Obstetrics, Gynecology, Pediatrics Training, and Research Hospital between January 2009 and January 2013 and diagnosed with HSP according to EULAR/PRINTO/PRES criteria were retrospectively reviewed. This Study Dr. Approved by the academic board of Sami Ulus Child Health and Diseases Training and Research Hospital (E-73799008-799-222825118). Patients were identified from automation records and analyzed retrospectively. Patients with insufficient file data were not included in the study. Demographic data (age, gender, anthropometric measurements), physical examination findings at the time of diagnosis, laboratory findings, and treatments administered were evaluated. Age groups are categorized as 2-5 years, 5-9 years, 10-14 years and 15 years and above. Triggering factors (such as previous infection, vaccination, insect bites), region of residence, and season of the disease were investigated. Blood urea nitrogen (BUN), creatinine, complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), antistreptolysin O titer (ASO), complete urinalysis and urine microscopic examination, fecal occult blood values were evaluated. Normal values of leukocyte count according to age, platelet count 150.000-450.000/mm^3, ASO value 0-200 IU/ml, CRP 0-8 mg/l, ESR 0-20 mm/h were considered normal. Skin involvement was determined as palpable purpura, petechiae and ecchymosis. Joint involvement was classified as arthralgia and arthritis. Abdominal pain, including pain occurring within 2 weeks before the onset of palpable purpura, vomiting, hematemesis, hematochezia, melena, or occult blood presence in the feces, acute abdomen, or increased intestinal wall thickness on ultrasonographic examination, is considered significant for GI involvement. Renal involvement includes microscopic hematuria (more than 5 erythrocytes in a centrifuged urine sample at 40 magnification), macroscopic hematuria, proteinuria (spot urine protein/creatine ratio >0.2 mg/mg or >4mg/m^2/hour), nephrotic syndrome (spot urine protein/creatine ratio >2 mg/mg or protein in 24-hour urine >40mg/m^2/hour hypoalbuminemia: 2.5 g/dl, hyperlipidemia and edema), nephritic syndrome (hematuria and/or proteinuria, edema, hypertension, oliguria and azotemia), presence of nephritic-nephrotic syndrome. Indications for renal biopsy were nephrotic proteinuria, persistent hematuria or persistent nephritic proteinuria, and acute kidney injury according to KDIGO (Kidney Disease: Improving Global Outcomes) criteria (7). In order to assess system involvement, the study investigated the influence of age and gender. The relationship between baseline acute phase markers (leukocyte count, ESR, CRP) and system involvement was analyzed. The relationship between patients with GI involvement and other system involvement was evaluated. The type, dose, and duration of treatment were recorded. The treatments administered were grouped as antihistamine treatment, nonsteroidal anti-inflammatory drug (NSAID) treatment, steroid treatment (oral and/or intravenous (IV) bolus), and steroid and other immunosuppressive treatments.

SPSS 15.0 for Windows program was used for statistical analysis. Descriptive statistics were given as numbers and percentages for categorical variables and mean and standard

deviation for numerical variables. For independent categorical variables, Chi-Square was used for pairwise and multiple group comparisons, Fisher's Exact Test was used for pairwise comparisons when the Chi-Square condition was not met, and Monte Carlo Simulation was used for multiple comparisons. Logistic Regression Analysis was used to determine the risk factors affecting involvement. The statistical significance level was accepted as a p-value less than 0.050.

RESULTS

In our study, 57.9% (212) of the patients were male and 42.1% (154) were female, with a male-to-female ratio of 1.37. The most common age group was found to be between 5-9 years of age (n=212, 57.9%). Approximately two-thirds of the patients were diagnosed in the fall and winter months. Possible factors that may play a role as a triggering factor in the etiology of IgA vasculitis were analyzed and upper respiratory tract infection was observed in 168 patients (45.9%). Elevated ASO was found in 50 (32.7%) patients and group A β-hemolytic streptococcus was grown in the throat cultures of 28 (10.1%) patients. Demographic and etiologic characteristics of the patients are summarized in Table I.

All patients had skin involvement. When other system involvement was analyzed, it was observed that joint involvement was the most common (59.7%). This was followed by GI involvement (25.4%), renal involvement (19.9%), scrotal involvement (6.8%), and CNS involvement (3.8%). System involvements are summarized in Table II. Purpura was found in all patients. The rashes were classified according to their anatomical localization. The majority of patients had rashes on the lower extremities (56.8%) and lower extremities and buttocks (30.3%). Joint involvement was present in 59.7% of patients. Arthritis was present in 70.6% of patients with joint involvement. Approximately 75% of the patients had single joint involvement. Ankle joint involvement was most common (64.9%), followed by knee joint (20.1%). Multiple joint involvement was found in 7.8% of patients. GI involvement was present in 25.4% of patients. Fecal occult blood positivity was detected in 59.1% of these patients. The main complaint of patients in this group was abdominal pain. Among patients with GI involvement, 11.8% had intussusception and 1.1% had intestinal perforation. Renal involvement was present in 19.9% of patients. Among patients with renal involvement, 83.5% had hematuria (80.8% microscopic and 2.7% macroscopic hematuria). Proteinuria was present in 66.0 of these patients. Mild proteinuria was found in 41.1%, isolated microscopic hematuria in 27.3%, isolated macroscopic hematuria in 2.7%, nephritic in 17.8%, nephrotic in 8.2% and mixed nephritic and nephrotic syndrome in 2.7%. Renal biopsy was performed in 5.8% of patients with renal involvement. In all of these patients, diffuse mesangial proliferation was detected on light microscopy, and IgA precipitates were detected in the mesangium on immunofluorescence examination. Crescentric involvement was not detected. The characteristics of patients with renal involvement are summarized in Table III. All patients with CNS findings had prolonged headaches. Convulsions were not observed in any of the patients.

Table I: Demographic and Etiologic Distribution of Patients

Patients' Characteristics	n (%)
Sex	
Female	154 (42.1)
Male	212 (57.9)
Age	
2-5 years	48 (13.1)
5-9 years	212 (57.9)
10-14 years	89 (24.3)
15 years and older	17 (4.6)
Season	
Spring	67 (18.3)
Summer	62 (16.9)
Autumn	158 (43.2)
Winter	79 (21.6)
Possible trigger factors	
Upper Respiratory tract infection	168 (45.9)
Surgery	8 (2.2)
Unknown	190 (51.9)

Table II: System involvement of patients

System involvement	n (%)
Skin involvement	366 (100)
Gastrointestinal involvement	93 (25.4)
Scrotal involvement	25 (6.8)
Central nervous system involvement	14 (3.8)
Renal involvement	73 (19.9)
Joint involvement	218 (59.7)

Table III: Distribution of patients with renal involvement

Characteristics of renal involvement	n (%)
Isolated microscopic hematuria	20 (27.3)
Isolated macroscopic hematuria	2 (2.7)
Mild proteinuria	30 (41.1)
Nephritic syndrome	13 (17.8)
Nephrotic syndrome	6 (8.2)
Mixed nephritic/nephrotic syndrome	2 (2.7)

No statistically significant relationship was found between age and joint involvement, GI involvement, scrotal involvement, and CNS involvement. The rates of involvement were similar in all age groups (p=0.448, p=0.103, p=0.577, respectively). However, there was a statistically significant relationship between age and renal involvement, and renal involvement increased with increasing age (p<0.001) (Table IV). The relationship between gender and system attitudes was evaluated and GI involvement was statistically significantly higher in males than in females (p=0.003). The effects of baseline white blood cell counts on system involvement were analyzed. A statistically significant

Table V: The relationship between age and system involvement

System involvement	2-5 years*	5-9 years*	10-14 years*	15 years and older*	p
Gastrointestinal system involvement	1 (11.1)	38 (23.6)	40 (26.0)	14 (33.3)	0.448
Scrotal involvement	2 (22.2)	14 (8.7)	8 (5.2)	1 (2.4)	0.103
Renal involvement	2 (22.2)	14 (8.7)	41 (26.6)	16 (38.1)	<0.001
Central nervous system involvement	0 (0.0)	5 (3.1)	6 (3.9)	3 (7.1)	0.577
Joint involvement	2 (22.2)	99 (61.9)	89 (57.8)	28 (66.7)	0.084

***:** *n(%)*

association was found between patients with increased leukocyte counts and GI involvement and renal involvement (p=0.001, p=0.009, respectively). No significant correlation was found between other system involvement and increased leukocyte values. When the relationship between baseline ESR and CRP values and system involvement was evaluated, no statistically significant relationship was found. The rate of renal involvement was statistically significantly higher in patients with GI involvement (p=0.012). No significant correlation was found between GI involvement and other system involvement.

In terms of the treatments administered, 68.3% of the patients received supportive treatment consisting of anti-inflammatory drugs and/or antihistamines. Oral steroids or IV steroids were administered to 27.1% of the patients. Steroid treatment was administered in patients with severe GI symptoms, significant testicular involvement and renal involvement presenting with nephrotic syndrome. The preferred steroid type was prednisolone. Steroid treatment was given to 73.0% of patients with GI involvement, 60.0% of patients with scrotal involvement, and 29% of patients with renal involvement. IV pulse steroid treatment was given to 3.0% of the patients who were steroid-refractory and continued to have proteinuria. Cyclophosphamide and/or azathioprine treatment was given to 4 patients who were steroid-refractory and continued to have proteinuria after pulse steroid treatment was stopped and interrupted. The results of the renal biopsy were also evaluated.

All patient's recovered with survival. In terms of renal involvement, nephritic proteinuria persisted in only two patients. None of the patients developed chronic kidney disease.

DISCUSSION

HSP, now also known as IgA vasculitis, is the most common type of systemic blood vessel inflammation in children. It is identified by a rash with palpable purpura on the skin, joint pain, stomach issues, and kidney problems, often seen in the lower parts of the body (6,7). In this study, we aimed to evaluate the demographic, clinical, and laboratory findings, treatments administered, and follow-up results of 366 IgA vasculitis cases in our center. As a result of our study, we showed that increased leukocyte count and the presence of GI involvement were risk factors for renal involvement, and the risk of renal involvement increased with increasing age. In terms of GI involvement, we found that increased leukocyte count and male gender increased the risk of GI involvement.

It has been reported that IgA vasculitis is generally observed 1.5-2 times more frequently in males than in females (8). Yang et al. (9) from Taiwan reported a male/female ratio of 1.11 in their study including 2759 children with IgA vasculitis. In our study, 154 (42.1%) of the patients were females and 212 (57.9%) were males and the male/female ratio was similar to that reported in the literature.

The most common age range in which IgA vasculitis is observed is reported to be between 3 and 15 years (10). In our study, the mean age of our patients ranged between 7.95±3.27 years by these data. In studies reported from our country, IgA vasculitis was reported to vary mostly between the ages of 7-10 years and our findings are compatible with the data from our country (11). In the literature, it has been reported that IgA vasculitis is observed more frequently in the fall and winter months (12). However, different seasonal distributions have also been reported; there are also publications reporting that the disease is most frequently seen in spring (13,14). In our study, it was found that the cases were most frequently seen in the fall months (43.2%), followed by the winter months (21.6%).

Although nearly 2 centuries have passed since the description of HSP, now called IgA vasculitis, the etiology is still unclear. Many agents have been blamed for the etiology of IgA vasculitis. The common opinion is that the disease may start after an upper respiratory tract infection and group A beta-hemolytic streptococcal infection (15). The fact that the disease is observed more frequently in the fall and winter months is attributed to the increase in the frequency of upper respiratory tract infections in these seasons (12). In our study, it was found that 45.9% of our patients had a history of upper respiratory tract infection before the diagnosis of IgA vasculitis and seasonally, it was observed mostly in the fall and winter months as previously mentioned. Elevated ASO was found in 50 (32.7%) of the patients with a history of upper respiratory tract infection, and group A β-hemolytic streptococcus was grown in the throat culture of 28 (10.1%) patients. However, no significant relationship was found between this growth and the disease. In the literature, there are studies indicating that streptococcal infections play a triggering role in the etiology of

IgA vasculitis but a definite cause-effect relationship could not be determined (16).

All patients (100.0%) had rash at presentation. Skin biopsy was performed in 19 (5.2%) of the patients at presentation due to atypical clinical findings and atypical rash. Histopathologic examination of the skin biopsy revealed leukocytoclasis on light microscopy and a typical image of IgA deposition on immunofluorescence microscopy. Our findings of skin involvement were similar to the literature (15,17). Joint involvement was found in 59.7% of the patients. Of these patients, 70.6% had arthritis. Joint involvement was transient in all patients and left no sequelae. Our findings regarding the frequency of joint involvement and involved joints were compatible with the literature (8). In our study, the rate of GI involvement was 25.4%. Intussusception was observed in 11 patients with GI involvement and intestinal perforation developed in 1 patient. In the literature, the rate of GI tract involvement is reported to be 50-76% (18). One of the reasons why the number of patients with GI involvement was lower in our study compared to the literature may be that complaints such as abdominal pain, nausea, and vomiting were not questioned sufficiently when GI involvement was questioned. It has been shown in the literature that GI involvement is more common in boys. Karadağ et al.(11) from our country also showed that GI bleeding was more common in boys than in girls. In our study, it was shown that the frequency of GI involvement was higher in boys by the literature. In some studies, the presence of abdominal symptoms and GI involvement were found to be risk factors for renal involvement (11,19, 20). In our study, renal involvement was statistically significantly higher in patients with GI involvement. We think that patients with GI involvement should be followed up more closely in terms of renal involvement.

Scrotal involvement in IgA vasculitis has been reported with a rate of 2.0-38.0% (21). This rate was found to be 6.8% in our study. IgA vasculitis with scrotal involvement constitutes 3.0% of all acute scrotum cases. The acute scrotum is an urgent clinical picture and is in the differential diagnosis of testicular torsion requiring urgent surgical intervention. In acute scrotal involvement associated with IgA vasculitis, treatment is symptomatic. Since the treatment approaches are completely different from each other, scrotal involvement should be evaluated very carefully in boys with IgA vasculitis to avoid unnecessary surgical interventions (22).

Although IgA vasculitis is usually a self-limiting disease with a good prognosis, the most important factor determining prognosis is renal involvement. In our study, renal involvement was observed in 73 patients (19.9%). It has been reported that renal involvement is observed in approximately 20-80% of pediatric IgA vasculitis cases (23,24). The reason for this wide distribution may be related to the differences in the definition of renal involvement in various studies. Microscopic hematuria was found in 80.8% of our patients, macroscopic hematuria in 2.7%, and proteinuria in 66%. Renal biopsy was performed in 21 (5.8%) patients with nephrotic proteinuria, persistent hematuria, and persistent proteinuria. In all patients who underwent renal biopsy, diffuse mesangial proliferation was detected on light microscopy, and IgA precipitates were detected in the mesenchyma on immunofluorescence. In our study, the persistence of proteinuria at nephritic level was found in two patients and no patient developed end-stage renal failure.

Central nervous system involvement has been reported with a rate of 2- 32% in IgA vasculitis; CNS symptoms develop secondary to vasculitis, metabolic changes, bleeding disorders and hypertension developing as a result of renal involvement. Headache, changes in consciousness and convulsions are the most common neurologic findings (25). In our study, the number of patients with CNS symptoms was 14 (3.8%). All patients had headaches that started with the symptoms of HSP and regressed after the active phase of the disease. Convulsions and altered consciousness did not occur.

IgA vasculitis has no specific laboratory findings. Moderate leukocytosis and left shift may be observed in some cases. In our study, leukocytosis was found in 32.2% of the patients. When we investigated the relationship between leukocytosis and system involvement, the relationship between leukocytosis and renal involvement and GI involvement was found to be significant. In the literature, there are studies showing that decreased lymphocyte, increased platelet and increased leukocyte values are associated with the risk of GI bleeding in patients with IgA vasculitis (18,26). Ekinci et al. (27) showed that increased neutrophil count may be associated with severe GI involvement and nephritis. In all these studies, it has been suggested that especially increased neutrophil count may be associated with a more severe immune system response and therefore may be associated with more severe involvement such as GI and nephritis (18,26,27).

In our study, the relationship between the age of the patients and the presence of system involvement was investigated and it was shown that the frequency of renal involvement increased with increasing age and this was statistically significant. In a study reporting multivariate analyses of clinical findings and renal morphologies of IgA vasculitis at the initial stage of the disease, it was reported that renal involvement was higher in older children and adults (28). In another study comparing pediatric and adult patients with IgA vasculitis, it was found that chronic renal failure developed with a frequency of 15.8% in adults and 7.0% in children (9). In another study in which clinical and laboratory findings of IgA vasculitis in adults and children were compared, it was reported that renal involvement was more frequent and more severe in adults (29).

The most important limitation of this study is that it was performed retrospectively and the follow-up period of some of our patients was limited. We think that the most important strength of this study is that it provides important information

due to the high number of patients for a single center and the wide patient distribution profile.

CONCLUSION

In conclusion, we found that GI involvement and advanced age were risk factors for renal involvement in IgA vasculitis. At the same time, a significant correlation was found between the increase in leukocyte count at baseline and GI involvement and renal involvement. We believe that these results will contribute to the definition of clinical and laboratory findings in IgA vasculitis in terms of system involvement, especially GI and renal involvement, and to the evaluation of risk factors.

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