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Orjinal Araştırma / Original Article

Scrotal Involvement in Childhood Immunoglobulin an Associated Vasculitis

Çocukluk Çağı İmmünoglobulin A ile İlişkili Vaskülitte Skrotal Tutulum

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Abstract

Aim: The aim of this study is to evaluate the demographic and clinic findings in immunoglobulin A-associated vasculitis (IgAV) patients with scrotal involvement and also to determine predictive factors for assessing the development of scrotal involvement.

Materiel and Method: The medical records of 181 boys who were diagnosed with IgAV in the Pediatric Rheumatology Clinic of our center between September 2015-January 2021 were evaluated retrospectively.

Results: A total number of 181 boys with IgAV included in the study. Twenty-seven (14.9%) of the 181 boys with IgAV had scrotal involvement. Among the scrotal-involved patients, 23 boys (85.1%) had scrotal swelling, 19 (70.3%) had erythema and 21 (77.7%) had scrotal pain or tenderness. Scrotal involvement was the first symptom of IgAV in one patient. CRP and WBC were significantly higher in the scrotal-involved group compared to the non-involved group (p=0.018, p=0.04, respectively). There were no significant differences in clinical findings and organ involvements between two groups. On ultrasonography, bilateral scrotal soft tissue thickening was observed in all patients. In 20 (74%) patients with scrotal involvement, increased vascularity was detected in the epididymis with swelling.. The size, echogenicity and vascularity of the testicles were within normal limits. Eighty-seven of the patients (48%) were given steroids, 22 of them (11.7%) nonsteroidal anti-inflammatory drug.

Conclusion: Scrotal involvement in boys with IgAV is not rare, it should be considered in the differential diagnosis in patients with scrotal pain, swelling and erythema. In addition, inflammatory markers may be higher in patients with scrotal involvement.

Keywords: Immunoglobulin A-associated vasculitis, scrotal involvement, MEFV, children

Öz

Amaç: Bu çalışmanın amacı, skrotal tutulumu olan immünoglobulin A ile ilişkili vaskülit (IgAV) hastalarında demografik ve klinik bulguları değerlendirmek ve ayrıca skrotal tutulum gelişimini değerlendirmede prediktif faktörleri belirlemektir.

Gereç ve Yöntem: Merkezimiz Çocuk Romatoloji Kliniği'nde Eylül 2015-Ocak 2021 tarihleri arasında IgAV tanısı alan 181 erkek çocuğun tıbbi kayıtları geriye dönük olarak incelendi.

Bulgular: Çalışmaya IgAV'li toplam 181 erkek çocuk dahil edildi. IgAV'li 181 erkek çocuğun 27'sinde (%14.9) skrotal tutulum vardı. Skrotal tutulumlu hastalardan 23'ünde (%85.1) skrotal şişlik, 19'unda (%70.3) eritem ve 21'inde (%77.7) skrotal ağrı veya hassasiyet vardı. Bir hastada skrotal tutulum IgAV'nin ilk semptomuydu. Beyaz küre ve C-reaktif protein, skrotal tutulumu olan grupta, tutulum olmayan gruba göre anlamlı derecede yüksekti (sırasıyla, p=0.018, p=0.04). İki grup arasında klinik bulgular ve organ tutulumları açısından anlamlı fark yoktu. Ultrasonografide tüm hastalarda bilateral skrotal yumuşak doku kalınlaşması izlendi. Hastaların 20'sinde (%74) epididimde artmış vaskülarite ile birlikte şişlik mevcuttu. Testislerin boyutu, ekojenitesi ve vaskülaritesi normal sınırlar içindeydi. Hastaların 87'sine (%48) steroid, 22'sine (%11,7) nonsteroid antiinflamatuar ilaç verildi.

Sonuç: IgAV'li erkek çocuklarda skrotal tutulum nadir değildir. Skrotal ağrı, şişlik ve eritem şikayeti olan hastalarda ayırıcı tanıda düşünülmelidir. Ayrıca skrotal tutulumu olan hastalarda inflamatuar belirteçler daha yüksek olabilir.

Anahtar Kelimeler: Çocuklar, immünoglobulin A ile ilişkili vaskülit, MEFV, skrotal tutulum

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INTRODUCTION

Immunoglobulin A (IgA)-associated vasculitis (IgAV; formerly known as Henoch Schönlein purpura) is a systemic vasculitis characterised by the deposition of IgA-containing immune complexes in the walls of small vessels such as arterioles, capillaries and venules.[1,2] IgAV is the most common childhood vasculitis, with an incidence of about 22 cases per 100,000 per year.[3,4] The majority of IgAV patients are preceded by an upper respiratory tract infection, immunizations, drugs, insect bites, and foods, suggesting potential triggers.[5,6]

IgAV is characterized by palpable purpura that predominate on the ankles and lower legs. It can have other concurrent clinical involvement such as joints, gastrointestinal (GI) tract, renal and, the central nervous system. Diagnosis of IgAV according to the European League against Rheumatism/Paediatric Rheumatology European Society (EULAR/ PRES) criteria is based on the presence of palpable purpura or petechiae with lower limb predominance (mandatory criterion) plus at least one of the flowing four features: (a) abdominal pain; (b) arthritis/arthralgia; (c) leukocytoclastic vasculitis or proliferative glomerulonephritis with predominant deposition of IgA on histology; (d) renal involvement.[7]

Approximately 50% of patients with IgAV have renal involvement, but extrarenal genitourinary manifestations of IgAV (acute scrotum, ureteritis with associated hydronephrosis, hematoma of the bladder wall, and hemorrhagic spermatic cord) develop much less frequently. Scrotal involvement of disease usually results in pain, tenderness, swelling or bruising of scrotum.[8]

Although pediatricians are well aware of the typical clinical features of IgAV, they may not be sufficiently familiar with its other rare findings such as scrotal involvement and its approach. The aim of this study is to evaluate the demographic and clinic findings in IgAV patients with scrotal involvement and also to determine predictive factors for assessing the development of scrotal involvement.

MATERIAL AND METHOD

The study was carried out with the permission of Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 16.06.2021, Decision no: E2-21-605). All procedures were performed adhered to the ethical rules and the Helsinki Declaration of Principles.

We retrospectively evaluated 181 boys of IgAV patients diagnosed at our center from September 2015 to January 2021. The diagnosis of IgAV required the fulfillment of EULAR/ PRES diagnostic criteria.[7]

Three hundred fifteen children and adolescents were diagnosed with IgAV during the study period. In total, 134 of these patients were girls. These patients were excluded from the study. The remaining 181 boys (57.5%) with IgAV were included in the study. In addition, boys who were diagnosed with IgAV during the study period but had missing data were also excluded from the study.

Patients data collected included demographic data, patient's medical history, presenting symptoms, clinical features, laboratory parameters and medications. Extensive investigations included complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum creatinine, urea nitrogen level, proteinuria, hematuria, and immunological parameters including serum C3, C4, antinuclear antibodies.

Gastrointestinal bleeding was defined as occult blood in stool, grossly bloody stools, melena, or hematochezia. Renal involvement was defined as the presence of gross or microscopic hematuria (>5 red blood cells per high-power microscopic field in a centrifuged specimen) and/or proteinuria (urine protein/ creatinine ratio <0.2 in children ≥2 year of age). Neurological involvement included headache, seizure, unconsciousness, or localizing signs. Scrotal involvement was defined as swelling, pain and tenderness in the scrotum. Symptoms or signs of scrotal involvement (scrotal swelling, pain or tenderness) were recorded. Patients with only simple purpuric rash on the scrotum were not considered to have scrotal involvement. Scrotal Doppler ultrasonography findings were evaluated.

Statistical Analysis

IBM SPSS Statistics for Windows, version 26.0 (SPSS Inc, Chicago, IL, USA) was used to perform statistical analysis. Normally distributed continuous variables were expressed as mean±standard deviation while the continuous variables that do not have normal distribution were expressed as median (minimum-maximum). Categorical variables were summarized as counts (percentages). The Chi-square test was used to compare catagorical variables and Mann-Whitney U-test was used to compare non-normally distributed continuous variables. The statistical significance level was accepted as a p-value <0.05.

RESULTS

A total number of 181 boys with IgAV included in the study. The demographic, clinical and laboratory characteristics of patients are summarized in **Table 1**. Presenting features in patients were as follows: palpable purpura in 176 (97.2%), arthritis/arthralgia in 57 (31.4%), GI involvement in 103 (56.9%), renal involvement in 50 (27.7%), and scrotal involvement in 27 (14.9%).

Twenty-seven (14.9%) of the 181 boys with IgAV had scrotal involvement. Among the scrotal-involved patients, 23 boys (85.1%) had scrotal swelling, 19 (70.3%) had erythema and 21 (77.7%) had scrotal pain or tenderness. Scrotal involvement was the first symptom of IgAV in one patient.

Patients were divided into two groups according to the scrotal involvement. The clinical differences of both groups are given in **Table 2**. CRP and WBC were significantly higher in the scrotal-involved group compared to the non-involved group (p=0.018, p=0.04, respectively). There were no significant differences in clinical findings and organ involvements between two groups (**Table 2**).

On ultrasonography, bilateral scrotal soft tissue thickening was observed in all patients. In 20 (74%) patients with scrotal involvement, increased vascularity was detected in the epididymis with swelling. The size, echogenicity and vascularity of the testicles were within normal limits. Testicular torsion was ruled out in all patients by Doppler ultrasonography.

Eighty-seven of the patients (48%) were given steroids, 22 of them (11.7%) nonsteroidal anti-inflammatory drug (NSAID). No patient underwent surgical exploration. The treatments administered, including the treatments given for organ involvements other than scrotal involvement, are summarized in **Table 1**.

Table 1. The demographic, clinical and laboratory characteristics of patients

Characteristics	
Age (mean±SD) (min.-max) (years)	7.93±3.19 (2-18)
Gender; Male /Female n (%)	181/134 (57.5/42.5)
Male Gender	
Age of disease onset (mean±SD) (min.-max) (years)	8.09±3.37 (2-18)
Triggers	
Infections n (%)	
Upper respiratory tract infection	81 (44.8)
Acute gastroenteritis	2 (1.1)
Varicella infection	1 (0.6)
Vaccinations n (%)	5 (2.2)
Clinical findings	
Rash, n (%)	176 (97.2)
Arthralgia, n (%)	42 (23.2)
Arthritis, n (%)	15 (8.2)
Localized edema, n (%)	3 (1.6)
Gastrointestinal involvement	103 (56.9)
Abdominal pain,	52 (28.7)
Occult blood positivity in stool, n (%)	50 (27.6)
Intussusception. n (%)	1 (0.6)
Renal involvement	50 (27.7)
Hematuria n (%)	24 (13.3)
Proteinuria n (%)	26 (14.4)
Testicular involvement, n (%)	27 (14.9)
Laboratory findings (mean±SD) (min-max)	
ESR (mm/hr) (0-20)	25.89±17.9 (2-83)
CRP (mg/dL) (0-8)	3.44±8,52 (0.03-101)
White blood cell (x109/L)	11441±4151 (1200-33500)
Platelets (x109/L)	386413±115500 (47900-895000)
Hemoglobin (gr/dL)	12.9±11.13 (9.6-15.7)
Treatment, n (%)	
NSAID	22 (11.7)
Steroid	87 (48)
Colchicine	5 (2.7)
Cyclophosphamide	6 (3.3)
IVIG	3 (1.6)
Plasmapheresis	1 (0.55)
ACEI	12 (6.6)
MEFV gene analysis, n (%)	27 (14.9)
M694V/M694	1 (0.55)
M694V/M680I	2 (1.1)
M694V/E148Q	1 (0.55)
M694V/-	3 (1.6)
Other heterozygos mutations	6 (3.3)
Negative	14 (7.7)
Recurrence. n (%)	8 (4.4)

SD: standard deviation, ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, ANA: Anti-nuclear antibody, NSAID: Nonsteroidal anti-inflammatory drug, IVIG: Intravenous immunoglobulin, ACEI: Angiotensin converting enzyme inhibitors, MEFV: Mediterranean fever,

Table 2. Evaluation of patients according to testicular involvement

Characteristics	Testicular involvement (n:27)	Testicular involvement (-) (n:154)	p value
Age (years)	6.99±2.48	8.28±3.47	0.06
Preceding events			
Infections n (%)	16	68	0.39
Vaccination n (%)	1	4	0.75
Clinical Findings			
Purpura, n	26	152	0.26
Joint involvement, n			0.14
Pain	8	49	
Swelling	5	37	
Intestinal symptoms, n			
Abdominal pain	8	44	0.54
Bloody stool	7	43	0.89
Intusseption	0	1	0.69
Renal involvement, n			
Hematuria	4	20	0.66
Proteinuria	4	26	0.056
Localized edema	1	2	0.71
Laboratory findings			
WBC (x109/L)	13403±3697	11097±4141	0.04
Hb ((gr/dL)	12.69±1.04	12.93±1.15	0.6
Platelets (x109/L)	417,481±140,971	380,966±110,191	0.76
CRP (0-5 mg/L)	7.17±19.95	2.81±4.19	0.018
ESR (0-10 mm/h)	25.88 ±16.24	25.89 ±18.26	0.25
Recurrence	2	6	0.057
MEFV gene positivity (n)	4	23	0.94
	M694V/- (1) E148Q/- (1) Negative (2)	M694V/M694 (1) M694V/M680I (2) M694V/E148Q (1) M694V/- (2) Other heterozygous mutations (5) Negative (12)	

ESR: Erythrocyte sedimentation rate, CRP: C-reactive protein, MEFV: Mediterranean Fever

DISCUSSION

Immunoglobulin A-associated vasculitis is the most common systemic vasculitis in childhood. The dominant clinical features are palpable purpura, abdominal pain, gastrointestinal bleeding, arthritis, and renal involvement.[1,2] However, there are rare manifestation such as myocarditis, involvement of the nervous system, respiratory system, and scrotal involvement. In this study, we evaluated 27 IgAV patients with scrotal involvement and showed that patients with scrotal involvement had higher inflammatory markers.

Acute scrotum, ureteritis, bladder wall hematoma, hemorrhagic spermatic cord, thrombosis of spermatic veins, and epididymo-orchitis may develop as extrarenal genitourinary manifestations in IgAV patients.[8] The first case of IgAV male genital involvement was published in 1960 and it was shown that 2-38% of IgAV patients may develop scrotal involvement.[9,10] In 2021, Ma et al. reviewed IgAV patients with scrotal involvement in the literature.[8] Between 1986 and 2020, 21 case reports of children with IgAV showed describing scrotal involvement. The mean age of onset of IgAV with scrotal involvement was 5.69±2.12 years. Almost all children

with scrotal involvement had scrotal pain with redness and swelling. Scrotal involvement occurred after the onset of IgAV in 14 cases (67%), before the onset of IgAV in 5 cases (24%), and simultaneously with IgAV in 2 cases (9%). Interestingly, Hardoff et al. reported that in a 4-year-old boy, recurrent scrotal swelling occurred 11 months before the diagnosis of IgAV.[11] We found that in only one of the patients in our study, scrotal findings preceded the typical findings of IgAV. The later appearance of typical palpable purpura may delay the correct diagnosis of IgAV patients presenting with scrotal involvement. These patients can be followed up with the diagnosis of epididymitis, orchitis or testicular torsion.[12] As a result, Doppler ultrasonography and typical clinical findings provide an accurate diagnosis. As is known, the sonographic findings of IgAV patients with scrotal involvement are scrotal skin thickening, epididymal enlargement, hydrocele, and normal-appearing testes with normal intratesticular blood flow. The sonographic findings of scrotal involvement of IgAV can allow distinction from testicular torsion in patients and have high sensitivity (89-100%) and specificity (97-100%).[13] It is important to distinguish between testicular torsion, which requires immediate surgical treatment, and scrotal involvement of IgAV. Because scrotal involvement in IgAV should be managed conservatively, not surgically. In all patients in our study, testicular torsion was excluded and the treatment of IgAV was managed conservatively. Scrotal involvement improved with a short-term administration of steroid therapy and/or NSAID.[12]

Ben-Sira et al. showed that 13 of 87 boys diagnosed with IgAV over a 15-year period had scrotal complaints. Sonographic evaluation was performed in seven patients to determine the extent of scrotal involvement and to consider testicular torsion. Sonographic findings included an enlarged epididymis, thickened scrotal skin, and a hydrocele. The testes themselves were sonographically normal and no signs of torsion were found in any of the patients.[14]

In our study, it was not demonstrated that any organ involvement was associated with scrotal involvement. On the other hand, Tabel et al. showed that scrotal involvement was associated with renal involvement.[15] In contrast, Ha et al. did not report a relationship between scrotal involvement and renal involvement. In addition, serum C4, CH50, IgA, IgG, IgM, IgE, anti-streptolysin O, and ANA were not found to be significantly associated with scrotal involvement.[16]

MEFV gene analysis was performed from patients in our study who had an atypical course, prolonged rash, and a family history of familial Mediterranean fever. It was observed that there was no statistical difference between the results of MEFV gene analysis in patients with and without scrotal involvement. It is known that MEFV mutations are more common in IgAV patients than in the general population. Moreover, mutation carriers may have more severe clinical manifestations and higher inflammatory response. Bayram et al. showed that 47 (43.9%) of 107 IgAV patients had one of the MEFV mutations. Homozygosity for one mutation in eight patients, heterozygosity for one mutation in 33 patients, and compound heterozygosity for two mutations in six patients. Scrotal involvement was statistically more common in patients with MEFV mutations. On the other hand, although the frequency of articular, GI and renal involvement was higher in patients with MEFV mutations in their studies, no statistically significant difference could be found.[17]

The limitation of our study is its retrospective nature and the relatively small number of IgAV patients with scrotal involvement. Multicenter studies are needed to reveal the risk factors associated with scrotal involvement.

In conclusion, scrotal involvement in boys with IgAV is not rare, it should be considered in the differential diagnosis in patients with scrotal pain, swelling and erythema. In addition, as shown in our study, inflammatory markers may be higher in patients with scrotal involvement.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara City Hospital No:2 Clinical Researches Ethics Committee (Date: 16.06.2021, Decision no: E2-21-605).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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