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A SINGLE CENTRE EXPERIENCE OF LOW C3/C4 LEVELS AND OTHER LABORATORY ASPECTS IN TURKISH CHILDREN WITH IMMUNOGLOBULIN A VASCULITIS

İMMÜNOGLOBULİN A VASKÜLİTLİ TÜRK ÇOCUKLARINDA DÜŞÜK C3/C4 DÜZEYLERİ VE DİĞER LABORATUVAR ÖZELLİKLERİYLE İLGİLİ TEK MERKEZ DENEYİMİ

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ABSTRACT

Objective: Immunoglobulin A vasculitis (IgAV) is the most prevalent systemic vasculitis in childhood. This intricate immune-mediated vasculitis affects the small blood vessels in several organ systems. Complements 3 and 4 (C3 and C4) are constituents of the complement system; serum C3/C4 measurements play a critical role in the diagnosis and follow-up of some immune diseases. Thus, the purpose of this study was to assess low C3/C4 levels and other laboratory results in children with IgAV.

Material and Methods: A total of 124 children—60 IgAV patients and 64 healthy controls—were assessed in this study. The C3 and C4 levels were quantified using a turbidimetric immunoassays method with manufacturer details. The extractable nuclear antigen antibody (ENA) panels were evaluated using the ELISA method. The results were evaluated statistically.

Results: The white blood cell count, neutrophil count, and neutrophil/lymphocyte ratio were higher in the patient group compared to the control group (p=0.015, p=0.013 and p=0.039, respectively). CRP, ESR, and random urine protein/creatinine ratio (RUPCR) increased in patients than controls (p<0.001, p=0.002 and p<0.001 respectively). There was no difference in the lupus anticoagulant activity and low C3/C4 levels between the groups (p>0.05).

Conclusion: IgAV, an IgA-mediated systemic small vessel vasculitis, affects many organs. As a result, it is crucial to evaluate the laboratory results in the follow-up of the patient and the possible complications.

Keywords: Immunoglobulin A vasculitis, C3, C4, immunoassay

ÖZ

Amaç: Eskiden Henoch-Schönlein purpurası olarak adlandırılan immünoglobulin A vasküliti (IgAV), çocukluk çağında en sık görülen sistemik vaskülit türüdür. Kompleman 3 ve 4 (C3 ve C4) kompleman sisteminin bileşenleridir ve bazı bağışıklık hastalıklarıyla ilişkili oldukları bulunmuştur. Bu nedenle bu çalışmada IgAV'li çocuklarda düşük C3/C4 düzeylerinin yanı sıra diğer laboratuvar bulgularını değerlendirmeyi amaçladık.

Gereç ve Yöntemler: Bu çalışmada 60 IgAV hastası ve 64 sağlıklı kontrol olmak üzere toplam 124 çocuk değerlendirildi. C3 ve C4 düzeyleri, üretici ayrıntılarıyla birlikte türbidimetrik immünoanaliz yöntemi kullanılarak ölçüldü. Ekstrakte edilebilir nükleer antijen antikor (ENA) panelleri, enzime bağlı immünosorbent analizleri (ELISA) kullanılarak değerlendirildi. Sonuçlar istatistiksel olarak değerlendirildi.

Bulgular: Hasta grubunda lökosit sayısı, nötrofil sayısı ve nötrofil/lenfosit oranı kontrol grubuna göre daha yüksek bulundu (sırasıyla p=0,015, p=0,013 ve p=0,039). Ayrıca hastalarda kontrollere göre CRP, ESR ve rastgele idrar protein/kreatinin oranı (RUPCR) artmış bulundu (sırasıyla p<0,001, p=0,002 ve p<0,001). Düşük C3/C4 seviyeleri ve lupus antikoagülan aktivitesi açısından gruplar arasında anlamlı fark bulunamadı (p>0,05).

Sonuç: IgA aracılı sistemik küçük damar vasküliti olan IgAV, öncelikle böbrekleri, eklemleri, gastrointestinal sistemi ve cildi etkilemektedir. Sonuç olarak, potansiyel hasta durumlarını izlerken laboratuvar sonuçlarının değerlendirilmesi çok önemlidir.

Anahtar Kelimeler: İmmünoglobulin A vasküliti, C3, C4, immünolojik test

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INTRODUCTION

Immunoglobulin A vasculitis (IgAV), known as Henoch-Schönlein purpura, is the most prevalent vasculitis characterised by the involvement of small blood vessels in various organ systems. Abdominal pain, arthritis, and nonthrombocytopenic palpable purpura are its hallmarks. While some demographic studies estimate an incidence rate of 0.1-0.8 per 100,000 adults, the annual incidence rate of IgAV in children and adolescents under the age of 17 varies from 6.79 to 55.9 per 100,000 children across various nations (1). IgAV is uncommon in Africa, but the disease is more common in Southeast Asia and, to a lesser extent, in Europe and North America (2). Although the exact cause of HSP is unknown, IgAV aetiology appears to include environmental, genetic, and antigenic components. The 2012 Chapel Hill Conference described the condition as vasculitis with IgA1-dominant immune deposits, highlighting the role of IgA. The immune deposits primarily damage small arteries, such as capillaries, venules, or arterioles (3). Ten to forty percent of patients have gastrointestinal involvement, and ten to fifty-five percent have renal abnormalities (4). The major causes of morbidity and mortality include gastrointestinal involvement in the acute phase and renal involvement in the chronic phase (5). While the pathophysiology of IgAV remains poorly understood, the epidemiology, clinical symptoms, and prognosis of IgAV are well known. IgA1-dominant IgA deposits in the vessel walls are the most prominent pathogenic characteristic of IgAV, as the disease's name suggests. Aberrant IgA and IgA complexes are essential for the immunopathogenesis of IgAV.

The complement system performs various effector functions related to humoral immunity and inflammation. These proteins interact with other immune system components and with each other in a carefully regulated way (6). Increased cytokine, chemokine, and other innate defence molecule synthesis results from the complement system activation. Complement activation components, such as anaphylatoxin C3a and C5a, also cause the humoral adaptive immune response, the generation of reactive T cells and antibodies, and a marked increase in the detection of antigens by follicular dendritic cells and B cells. In addition, the complement system facilitates the removal of soluble immune complexes and cell debris, both of which run the risk of triggering autoimmunity and an immunological response against autoantigen (7). Complements 3 and 4 (C3 and C4) are constituents of the complement system and function in various pathways associated with complement activation. Certain autoimmune diseases can be diagnosed based on the levels of serum C3/C4. In patients with systemic lupus erythematosus (SLE), depletion may lead to a decrease in serum C3 and C4 levels (8). Furthermore, there is mounting evidence that antineutrophil cytoplasmic antibody-related vasculitis is pathophysiologically and progressionally connected with complement system activation (9).

Therefore, this study evaluated C3/C4 levels as well as other immunological markers in children with IgAV.

MATERIAL AND METHODS

Study population

This study evaluated 60 IgAV patients who were monitored between March 2024 and July 2024 in the Paediatric Rheumatology Department of Başakşehir Çam and Sakura City Hospital. The 2010 criteria of the European League Against Rheumatism, the Paediatric Rheumatology International Trials Organisation, and the Paediatric Rheumatology European Society (EULAR/PRINTO/PRES) served as the basis for the diagnosis of IgAV. The control group consisted of 64 age- and sex-matched healthy children who were admitted during the same study period. The exclusion criteria included concurrent chronic diseases, including other autoimmune disorders, and prior use of glucocorticoids or other immunosuppressive agents. Participants underwent complete blood count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), urine protein/creatinine ratio (RUPCR), antinuclear antibodies (ANA), lupus anticoagulant activity, antibodies to double-stranded DNA, β2 glycoprotein 1, anticardiolipin, and anti-neutrophil cytoplasmic (ANCA), and extractable nuclear antigen antibodies. Prior to their participation in the study, all patients and their families provided written informed consent in accordance with the 2008 Declaration of Helsinki's ethical principles. The Başakşehir Çam and Sakura City Hospital Ethical Committee approved the Project (Date: 26.06.2024, Approval Number: E-96317027-514.10-246491516).

Laboratory

C3/C4 levels were quantified using a turbidimetric immunoassay [method/instrument used, manufacturer details], with reference ranges of 0.9-1.8 g/dL for C3 and 0.1-0.4 g/dL for C4. The urinary protein-to-creatinine ratio was calculated using spot urine samples. The extractable nuclear antigen antibodies (ENA) panel was measured using enzyme-linked immunosorbent assays (ELISA).

Statistical analysis

The OpenEpi information software package, version 3.01 (www.openepi.com), and the Statistical Package for the Social Sciences program (IBM SPSS, version 20) were used to conduct the statistical analyses. The mean±standard deviation (SD) was used to display the data. The relationship between these variances and the patients' clinical and demographic characteristics was investigated using the chi-square ($\chi 2$) test, Fischer exact test, or analysis of variance (ANOVA) statistics. To evaluate the risk factors, 95% CIs and the odds ratio (OR) were employed. Each two-tailed p-value was considered significant if it was less than 0.05.

RESULTS

A total of 124 subjects, 60 IgAV patients and 64 healthy controls-were assessed in this study. Table 1 displays the patients' demographic and clinical characteristics.

We then evaluated the laboratory findings in the groups (Table 2). The white blood cell count, neutrophil count, and neutrophil/lymphocyte ratio were higher in the patient group compared to the control group (p=0.015, p=0.013, and p=0.039, respectively). Also, CRP, ESR, and urinary protein/creatinine ratio increased in patients compared with controls (p<0.001,

Table 1. Baseline demographic and clinical features of the subjects

	Patient group (n=60)	Control group (n=64)	p
Age (months) (Mean±SD)	107.7±45.7	100.8±46.4	0.407
Gender, n (%)			
Female	31 (51.7)	35 (54.7)	0.875
Male	29 (48.3)	29 (45.3)	
Age at diagnosis (month) (Mean±SD)	108.8±43.9		
Clinical findings, n (%)			
Cutaneous	59 (98.3)		
Gastrointestinal system	24 (40)		
Arthritis/arthralgia	19 (31.7)		
Renal	5 (8.4)		
Other	1 (1.7)		
Treatment, n (%)			
Conservative	9 (15.0)		
NSAID	23 (38.3)		
Steroids	27 (45.0)		
Azothioprine	3 (5.0)		
IV Ig	1 (1.7)		
Colchicine	3 (5)		

Table 2. Laboratory features of the groups

	Patient group (n=60)	Control group (n=64)	p
Haemoglobin (gr)	12.4±1.3	12.5±1.1	0.662
White blood cell count (/mm3) Mean (min-max)	8870.0 [3670.0-20200.0]	7870.0 [4220.0-24220.0]	**0.015**
Neutrophil count (/mm3) Mean (min-max)	4860.0 [1750.0-18490.0]	3865.0 [1400.0-19140.0]	**0.013**
Lymphocyte count (/mm3) Mean (min-max)	2895.0 [940.0-7940.0]	2715.0 [1230.0-6680.0]	0.779
Neutrophil/lymphocyte ratio (/mm3) Mean (min-max)	1.8 [0.1-12.7]	1.3 [0.2-6.8]	**0.039**
Platelet count (/µL) Mean (min-max)	352500.0 [184000.0-983000.0]	338500.0 [161000.0-515000.0]	0.266
CRP (mg/dL)	3.3 [0.1-85.8]	1.0 [0.1-40.1]	**<0.001**
ESR (mm/h) Mean (min-max)	12.0 [2.0-64.0]	8.0 [2.0-65.0]	**0.002**
Proteinuria	4 (6.7)	0 (0)	0.063
RUPCR	0.2 [0.0-11.8]	0.1 [0.0-0.9]	**<0.001**
ANA (+)	4 (6.7)	7 (10.9)	0.603
ENA panel	11 (18.3)	4 (6.2)	

Ku	3	1	
Scl-70	2	--	
Sjögren's syndrome type B	1	--	
Mitochondrial M2	3	--	
DFS70	2	1	0.074
Pm-Scl	3	0	
Centromere protein-B	1	--	
Ro-52	--	1	
Jo-1	--	1	
Complements			
Low C3	1 (1.7)	0 (0.0)	0.484
Low C4	1 (1.7)	0 (0.0)	0.484
Lupus anticoagulant activity (+)	1 (1.7)	0 (0.0)	0.484

CRP: C-reactive protein; ENA: extractable nuclear antigen; ESR: erythrocyte sedimentation rate; RUPCR: urine protein/creatinine ratio

p=0.002, and p<0.001, respectively). The low C3/C4 levels, ENA panel, and lupus anticoagulant activity were not differed between groups (p>0.05).

DISCUSSION

One of the most common forms of vasculitis in children, IgAV typically appears before the age of 10 years. IgA1-predominant immunological deposits and polymorphonuclear leukocyte inflammatory infiltration of small blood arteries are its defining characteristics (10). One of the five main immunoglobulins, IgA, is the predominant antibody of immunity and is essential for maintaining mucosal homeostasis in the gastrointestinal, respiratory, and genitourinary systems. It is made up of two heavy and two light chains, as well as an Fc-tail that can engage with Fc receptors and Fab regions that bind antigens (11). Immune-mediated vasculitis (IgAV), is linked to complement deposition, neutrophil recruitment, and IgA deposition. Approximately 90% of individuals with IgAV worldwide are young people. In contrast to other forms of systemic vasculitis, IgAV typically has a self-limiting course in children. Although some chemical and viral triggers exist, the fundamental aetiology of IgAV remains unknown. It has been that some cytokines, particularly IL-8, play a role in the pathophysiology of IgAV. The chemokine required to attract neutrophils, the main effector cells in IgAV, is IL-8 (12). IgA immune complexes, which are made up of galactose-deficient IgA1 and anti-IgA1 antibodies, have the ability to trigger IL-8 (13). Remarkably, these immune complexes increase the expression of IL-8 and other pro-inflammatory cytokines by activating the complement system, including C3a and C5a (14).

Complement is a crucial component of the innate immune system, which defends against all invasive pathogens (15). Moreover the complement system is known to play a number of other immunological and immunoregulatory functions, such as: (1) opsonising and solubilising native immune complexes (IC) made up of autoantigen and self-reactive antibodies; (2) generating and releasing the anaphylatoxin C3a and C5a, which draw inflammatory cells to the complement activation site; and (3) facilitating the binding of complement receptors CR1 on erythrocytes or CR3/CR4 on phagocytic myeloid cells to opsonised IC, which helps remove IC from the bloodstream (16). There is a clear mechanistic connection between complement activation and vascular damage because it causes neutrophil adherence and the development of neutrophil-platelet aggregates in vascular endothelial cells (17). It has been demonstrated that complement proteins can be activated by IgA. The blood contains complement in its dormant form, and there are three different ways that complement might be activated (18). Because IgA does not have a C1q binding site, it is unable to activate the complement's classical pathway. Nevertheless, it has been shown that IgA can activate the complement pathway that binds mannan and other pathways (11). Clinical practice frequently uses immunoassays to assess serum complement C3 and C4 levels to identify and track complement activation. Crucially, in individuals with ANCA-associated renal vasculitis, low serum C3 levels-without hypocomplementemia per se—are a reliable indicator of a poor renal prognosis (19). To improve the sensitivity of the systemic lupus erythematosus (SLE) categorisation criteria, hypocomplementemia involving C3 and C4 was proposed as an immunological criterion in 2009 (20). Although the complement system plays a role in the pathogenesis of IgAV, serum C3 and C4 levels have been reported to be within the normal range in most patients. However, decreases in C3/C4 levels may occur because of the depletion of complement components (21). Low C3 and C4 levels can be seen in active SLE (22). Low C3 levels can be seen in post-streptococcal glomerulonephritis and C3 nephritic factor-related disease (23). Low C4 levels can be associated with C1 inhibitor deficiency (24). Lower C3 and higher C4 levels were associated with a poorer prognosis in patients with IgA nephropathy (25). Lower C3 and C4, indicating complement activation, were associated with higher coronavirus disease 19 (COVID-19) severity (26).

In this study, we evaluated low C3/C4 levels and other laboratory findings in Turkish IgAV patients. As far as we know, this

study is the first study on this subject in our country. Calvo-Río et al. reported that the most common laboratory finding in their study was leukocytosis, with a rate of 36% in Spanish children (27). We found that the white blood cell count, neutrophil count, and neutrophil/lymphocyte ratio were higher in the patients than in the control group. In our patient group, there was leukocytosis compared with the control group. We also showed that CRP, ESR, and RUPCR increased in patients compared with the control group (Table 2). Simple, quick, and sensitive, RUPCR is closely linked to kidney injury and can determine the extent of it. Traponi et al. studied 150 Italian children with IgAV epidemiologically and clinically over 5-years (28). They found low C3/C4 levels in 10% of the patients. In the study by Luciana et al. in which they evaluated serum C3/C4 levels in children, a decrease was observed in only 2.15% of the cases (29). This was lower than the previous study. Calvo-Río et al. found low C3/C4 levels to be 12.8% in IgAV patients with nephritis (27). In our study, low C3/C4 levels did not show any difference between the patient and control groups (Table 2). A low C3/C4 level was detected in 1.7% of patients. This result was lower than the two studies conducted in Italy. This difference may be due to the fact that it was evaluated at different periods of the disease. Additionally, the ENA panel and lupus anticoagulant activity were not different between the groups.

Limitations

This study had some limitations. We had a comparatively modest patient population. The follow-up findings of the patients were not evaluated in the study. However, the advantage of the study is that it reflects data from a centre with high patient potential in Istanbul.

CONCLUSION

IgAV is an IgA-mediated systemic small vessel vasculitis affecting different systems. Although IgA vasculitis is typically a self-limiting disease, patients can develop life-threatening complications. Therefore, it is crucial to evaluate laboratory findings in the follow-up of complications that may develop in patients.

Ethics Committee Approval: This study was approved by Başakşehir Çam and Sakura City Hospital (Date: 26.06.2024, Approval Number: E-96317027-514.10-246491516).

Informed Consent: Prior to their participation in the study, all patients and their families provided written informed consent in accordance with the 2008 Declaration of Helsinki's ethical principles.

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