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Assessment of renal resistive index measurement in children with immunoglobulin A vasculitis

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Abstract

Introduction: Henoch-Schönlein purpura (HSP), also known as IgA vasculitis (IgAV), is the most prevalent systemic vasculitis. Renal involvement occurs in approximately one third of children with IgAV, while biopsy-proven nephritis could be diagnosed in only 6% of patients with prolonged proteinuria or nephritic syndrome. The renal resistive index (RRI) provides insights into intrarenal arterial resistance. The aim of this study was to assess the potential utility of RRI measurements in patients with IgA vasculitis (IgAV).

Material and methods: This cross-sectional study included 27 children diagnosed with HSP/IgAV between January 2021 and January 2023. Additionally, 27 healthy controls were included to the study. Age, sex, symptoms recorded and initial laboratory test results, including renal function tests, serum albumin levels, complete blood count, erythrocyte sedimentation rate, C-reactive protein, renal function tests, spot urine protein/creatinine and albumin/creatinine ratio were obtained at study enrollment. The RRI measurements were obtained from intrarenal arteries using color Doppler ultrasonography.

Results: Among the 27 IgAV patients (13 male, 14 female), 3 (11.1%) exhibited renal involvement, with renal biopsy performed in only one patient, revealing class IIIa nephritis. The RRI values were not significantly different between the IgAV and control groups. Additionally, RRI was 0.61 ±0.05 and 0.56 ±0.06 in patients with and without antecedent infection, respectively (p = 0.04). Furthermore, RRI was not significantly different among patients grouped based on the presence of arthritis, severe gastrointestinal symptoms, or renal involvement.

Conclusions: Our findings indicate that RRI remains unaffected in patients with IgAV, reflecting the relatively benign nature of the disease, particularly in children. Further investigations, involving a larger cohort of patients with nephritis, are warranted to elucidate the utility of RRI in assessing renal involvement in IgAV.

Key words: renal resistive index, IgA vasculitis, Henoch-Schönlein purpura, Doppler ultrasonography.

Introduction

The IgA vasculitis (IgAV) – former name Henoch-Schönlein purpura, is the most common systemic vasculitis in children worldwide. It is characterized by non-thrombocytopenic purpura often accompanied by arthralgia or arthritis and gastrointestinal (GI) involvement, ranging from mild abdominal pain to GI bleeding and intussusception [1]. Renal involvement occurs in approximately one third of children with IgAV, while biopsy-proven nephritis could be diagnosed in only 6% of patients with prolonged proteinuria or nephritic syndrome, which necessitates biopsy. Renal and severe GI involvement are significantly related to each other, and both require intensive treatment, starting with systemic glucocorticosteroids. Although there is no tool other than renal biopsy to determine the severity of renal involvement in IgAV, routine renal biopsy is not preferred due to its invasiveness [1, 2].

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The renal resistive index (RRI) is a Doppler ultrasound (US) imaging-based parameter, revealing the intrarenal arterial resistance. Therefore, it may be affected by various intrarenal pathologies, including acute renal injury, glomerulonephritis, hemolytic uremic syndrome, and renal vein thrombosis [3, 4]. The RRI was also found to be higher in patients with systemic lupus erythematosus (SLE) [5–7]. We first aimed to investigate the clinical properties of the IgAV patients. Moreover, since renal involvement is the most destructive manifestation of IgAV, and there is no single notable marker for predicting IgA nephritis, we aimed to clarify whether the RRI may be affected in patients with IgAV, related to the clinical findings and renal function tests, proteinuria level, acute phase reactants and serum IgA levels, and whether it predicts any risk for renal involvement in the future.

Material and methods

Patients

This cross-sectional study included children, diagnosed with HSP/IgAV between January 2021 and January 2023 by the Department of Pediatric Rheumatology of our medical center. The diagnosis was established in accordance with the Ankara 2008 criteria, verified by the European Alliance of Associations for Rheumatology (EULAR; formerly the European League Against Rheumatism), Pediatric Rheumatology International Trials Organization, and Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) [8].

Age, sex, symptoms recorded and initial laboratory test results, including renal function tests, serum albumin levels, complete blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), renal function tests, spot urine protein/creatinine and albumin/creatinine ratio, were obtained at study enrollment. Glomerular filtration rate (GFR) was calculated by the Schwartz formula [9]. Since RRI is affected by alterations in the renal and systemic circulation, participants with hypotension, hypertension, obesity, bradycardia and other arrythmias, a solitary kidney or significant difference in size between the kidneys and an estimated GFR calculated below 60 ml/min/1.73 m^2 were excluded from the study [10]. Vital signs, including blood pressure, heart rate and body temperature, were examined at the time of study enrollment. Patients' families were questioned for any previous infection at the first admission. Renal biopsy was utilized when nephrotic-range proteinuria or prolonged abnormal proteinuria not reaching the nephrotic range lasted at least one month. In children older than 2 years, normal protein excretion in urine is below 0.2 mg/mg creatinine. Proteinuria of 0.2–2 mg/mg creatinine is defined as prolonged abnormal proteinuria that does not reach the nephrotic range, and more than 2 mg/mg creatinine is defined as nephrotic-range proteinuria [11].

Renal biopsy results were graded by the International Study of Kidney Disease in Children (ISKDC) classification system [12]. Severe GI involvement was defined by the pediatric rheumatologist as the presence of at least one of the following: persistent abdominal pain, involuntary abdominal guarding in physical examination, overt GI bleeding or intussusception.

The control group consisted of 25 healthy children, admitted for well-child follow-up. Doppler ultrasonography (USG) was performed in the patient group at the time of diagnosis and healthy controls. Doppler USG was repeated in available patients with IgAV, 6 months after disease onset. The RRI was compared between IgAV patients and the control group. Afterward, RRI values were compared between IgAV patients, grouped according to the presence of arthritis, antecedent infection, severe GI involvement, renal involvement, nephrotic-range proteinuria, and biopsy-proven nephritis.

Ultrasonography

We performed renal USG using a high-resolution ultrasonography machine (Philips EPIQ 7) and a 5–1 MHz convex probe (Philips Health Care, Bothell, WA, USA). Ultrasonography was utilized by the same radiologist with 10 years of experience (BCP) in Doppler USG. Images were taken using grayscale B-mode USG, with at least 20 minutes on resting. Then, RRI measurements were utilized with color Doppler USG. The RRI measurements were performed from intrarenal arteries (segmental or interlobar) with the Doppler angles of 30–60° in the right and left kidneys. Repeated measurements were taken from different parts of the intrarenal arteries with Doppler USG, revealing at least five clear or acceptable waveforms. Through the selection of one of these waveforms, peak systolic velocity and end diastolic velocity were determined and RRI values were obtained automatically with the following formula: peak systolic velocity–end diastolic velocity/peak systolic velocity.

Statistical analysis

Prior to the study, a power analysis was conducted, which determined the sample size as 13 patients per group. Statistical analyses were performed using the statistical software package IBM SPSS Statistics 20.0 (IBM Corp.). Categorical variables were stated as numbers and percentages, while continuous variables were provided as mean and standard deviation or median and minimum–maximum as appropriate. The χ^2 test was used to determine the differences of categorical variables between groups. Continuous variables were

Table I. Laboratory results of patients with IgAV

Parameter	Result
Serum creatinine [mg/dl], mean ±SD	0.4 ±0.12
ESR [mm/h], median (range)	11.5 (2–52)
CRP [mg/l], median (range)	8.2 (0.7–117)
Serum IgA [mg/dl], mean ±SD	225 ±56.9
Protein/creatinine ratio in spot urine [mg/mg creatinine], median (range)	0.12 (0.05–2.1)
Albumin/creatinine ratio in spot urine [mg/mg creatinine], median (range)	6.9 (0.1–490)

CRP – C-reactive protein, ESR – erythrocyte sedimentation rate, IgA – immunoglobulin A, SD – standard deviation.

Table II. Comparison of renal resistive index between patients with IgAV and healthy controls

	HSP patients (n = 27)	Control group (n = 27)	p
RRI value	0.59 ±0.06	0.57 ±0.03	0.114

HSP – Henoch-Schönlein purpura, RRI – renal resistive index. The p-value significance level is < 0.05.

Table III. Comparison of the renal resistive index of IgAV patients grouped according to manifestations

Parameter		RRI	p
Antecedent infection (n = 17)	Yes	0.61 ±0.05	0.04
	No	0.56 ±0.06	
Arthritis (n = 8)	Yes	0.61 ±0.05	0.211
	No	0.58 ±0.06	
Severe GI involvement (n = 14)	Yes	0.57 ±0.06	0.201
	No	0.61 ±0.05	
Renal involvement (n = 3)	Yes	0.60 ±0.02	0.726
	No	0.59 ±0.06	

GI – gastrointestinal, RRI – renal resistive index. The p-value is bolded when significant (< 0.05).

investigated by using histogram, probability plots and Kolmogorov-Smirnov/Shapiro-Wilk tests to determine whether they were normally distributed. Student's *t*-test or the Mann-Whitney *U* test was used to compare continuous data between two groups, as appropriate. Multiple linear regression analysis was utilized to determine any multivariate relation between two independent continuous variables, and a positive or negative correlation was defined as weak, moderate, strong, and very strong if the Spearman correlation coefficient (*rho*) was 0.21–0.40, 0.41–0.60, 0.61–0.80 and 0.81–1.00, respectively. A *p*-value less than 0.05 (typically ≤ 0.05) was considered as statistically significant.

Bioethical standards

Written informed consent was obtained from each parent of the patients. The study was performed in accordance with the Declaration of Helsinki and approved by the Ethics Committee of the Adana City Training and Research Hospital (approval number: 109/2045, date: 04.07.2022).

Results

This study included 27 children (13 male, 14 female), diagnosed as having IgAV. Their median age was 9.1 ±3.7 years (median: 8.1 years, range: 4.1–17.1 years). Antecedent infection history was present in 17 (63%) of the patients, and all of them were encountered in the upper respiratory tract. None of the patients had pyuria or symptoms related to urinary tract infection. Twenty-one patients (77.8%) had abdominal pain, of whom 14 (51.9%) had severe GI involvement. Arthralgia and arthritis were encountered in 13 (48.1%) and 8 (29.6%) of the patients. Only 3 (11.1%) patients had renal involvement; of these, 1 had prolonged abnormal proteinuria in the non-nephrotic range, 1 had nephrotic-range proteinuria, and 1 had microscopic hematuria. Renal biopsy was performed in the patient with nephrotic-range proteinuria, which further revealed crescentic glomerulonephritis with mesangial proliferation, and IgA staining (class IIIa according to the ISKDC classification) [12]. Table I shows general characteristics of the patients.

The control group consisted of 27 healthy subjects (10 male, 17 female) with a mean age of 11 ±3.6 years (median: 10.7 years, range: 4.2–17.3 years). The age and sex did not differ between the patient and control groups (p = 0.06 and 0.583, respectively). All patients and healthy controls had normal vital signs, including blood pressure, heart rate and body temperature at the study enrollment.

Comparison of RRI values between patient and control groups are shown in Table II. None of the participants had RRI values higher than 0.7. Although RRI was found higher in IgAV patients than the control group, this difference was not statistically significant. Moreover, IgAV patients were grouped according to the clinical manifestations. Although patients with the presence of arthritis and the absence of severe GI involvement had higher RRI values, these differences were not statistically significant. Only 3 patients had renal involvement; nonetheless, RRI did not differ significantly between patients regarding the presence of renal involvement. Only patients with a history of antecedent infection had significantly higher RRI values (Table III).

Moreover, we searched for relations between GFR, serum creatinine, spot urine protein and albumin/creati-

nine ratios, ESR, CRP, serum IgA levels and RRI, which did not reveal any significant correlation. Finally, we repeated RRI measurements in 12 patients, 6 months after the initial presentation of IgAV. Although RRI was elevated in the second measurement, the difference was not statistically significant (Table IV).

Table IV. Comparison of initial and 6th month renal resistive index values in patients with IgAV

	At diagnosis	At 6th month follow-up	*p*
RRI value	0.58 ±0.06	0.61 ±0.03	0.214

RRI – renal resistive index.
The p-value significance level is < 0.05.

Discussion

In this study, we found that RRI did not differ significantly between IgAV and healthy controls. Again, there was no significant difference between patient groups regarding the presence of arthritis and severe GI involvement. On the other hand, the patients with an antecedent infection had significantly higher RRI values than other patients. Moreover, follow-up data available in 12 patients and RRI did not significantly differ at the 6th month after disease onset. Also, urinary protein excretion and GFR did not correlate with RRI.

The RRI is a promising tool for patients with several renal pathologies, including acute tubular necrosis, renal vein thrombosis and distinct glomerulopathies, such as SLE [3–6, 13, 14]. We found that the RRI was not affected in IgAV; therefore, no judgement was possible for prediction of renal involvement in IgAV. We cannot be sure whether the RRI is affected by the presence or severity of the renal involvement in IgAV due to the small number of patients with nephritis; thus, further studies are warranted in IgAV patients with renal involvement.

Additionally, we found elevated RRI in patients with antecedent infection, although inflammatory markers such as ESR or CRP were not correlated with RRI. Regarding the literature, we know that the RRI predicts risk of acute renal injury, need for dialysis and mortality in patients with sepsis and pneumonia [15–17]. However, the underlying mechanism of elevated renal resistance is not clear. Likewise, urinary infections may lead to intrarenal resistance and elevation of RRI. However, all antecedent infections were restricted to the upper respiratory system in our study [18]. There are several reports on cardiovascular effects of respiratory tract infections, but these were occult ischemic events [19, 20]. Moreover, we know that both acute and chronic inflammation increase blood viscosity substantially by elevated concentrations of acute phase reactants and hypergammaglobulinemia [21]. Therefore, we suspect that respiratory tract infections may lead to platelet reactivity, increased blood viscosity and thus subclinical ischemia and intrarenal resistance.

Study limitations

The major limitations of our study include the small proportion of patients with renal involvement and the lack of routine renal biopsy. These preliminary results may not allow general conclusions to be drawn due to the small sample size. The investigated issues may be elucidated in further studies investigating the utility of RRI in patients with IgA nephritis.

Conclusions

The present study is most likely the first one analyzing RRI measurement for detecting intrarenal resistance in IgAV. We found that the RRI was not affected in IgAV patients at admission and follow-up. However, antecedent infections may lead to intrarenal resistance in IgAV patients. Further studies are needed to reveal the utility in the presence of renal involvement in IgAV, and whether the nephritis severity correlates with the RRI measurement.

Disclosures

Conflict of interest: The authors declare no conflict of interest.
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Ethics approval: This study was approved by the Ethics Committee of the Adana City Training and Research Hospital (approval number: 109/2045, date: 04.07.2022).
Data availability: The data that support the findings of this study are available on request from the corresponding author (R.M.A.K.).

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