Henoch Schönlein Purpura / Ig A Vasculitis in Children and Risk Factors for Renal Involvement

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https://doi.org/10.32552/2021.ActaMedica.585

Received: 13 April 2021, Accepted: 3 May 2021,
Published online: 30 August 2021

ABSTRACT

Objective: Henoch Schönlein Purpura also known as IgA vasculitis is the most common form of pediatric vasculitis and renal involvement is responsible for the mortality and long-term morbidity. We aimed to describe the epidemiological, clinical, and laboratory characteristics of patients with IgAV and analyze the predicting factors associated with renal involvement.

Materials and Methods: This study included 188 children diagnosed with IgA vasculitis. Demographical and clinical data were retrospectively reviewed from the patient files.

Results: Of the 188 IgA vasculitis patients, 51.6% were female. The mean±SD age at diagnosis was 8.49±3.35 years, and 66% of them were diagnosed before 10 years of age. All the patients had palpable purpura, 35.6% had arthritis, 34.6% had gastrointestinal system involvement, 12.2% had renal disorders, at the time of diagnosis. Besides 23(12.2%) patients presented with renal involvement, 42(22%) patients developed renal involvement at follow-up. Patients under 10 years of age had significantly more arthritis, patients over 10 years of age had significantly more renal involvement. Among laboratory work-up, erythrocyte sedimentation rate levels were found significantly higher in patients with renal involvement. In multivariate analysis, the occurrence of renal involvement was not associated with any of the defined demographic and clinical characteristics of the disease. Although erythrocyte sedimentation rate levels showed a higher risk ratio, it has only borderline significance.

Conclusion: Although IgA vasculitis is a self-limiting disease, renal involvement can cause serious complications. In the presented study, being older than 10 years of age and having high levels of erythrocyte sedimentation rate at the time of diagnosis could serve as a possible predictor of renal involvement.

Key words: Henoch Schönlein purpura, IgA vasculitis, IgA vasculitis nephritis, renal involvement
INTRODUCTION

Henoch Schönlein Purpura (HSP) is the most common form of pediatric vasculitis (3-26.7/100 000) [1, 2]. HSP, also named IgA Vasculitis (IgAV) characterized by the aggregation of immunoglobulin A (IgA) immune complexes into the small vessels [3]. The classical tetrad of the disease is palpable purpura, arthritis/arthritis, abdominal pain, and renal disorders[4].

Renal involvement, which is responsible for the mortality and long-term morbidity occurs in about 1/3 of the patients. Although IgAV is a self-limited disease; renal involvement can be occurred in the form of severe glomerulonephritis and may cause chronic kidney disease [5]. IgAV nephritis usually begins without any clinical symptoms, thus it requires active urine screening and monitoring. If undiagnosed, persistent renal inflammation, may progress to renal damage and scarring[6]. IgAV nephritis usually develops within 4-6 weeks of the initial presentation. However, it may develop months later. Therefore, renal monitoring for 6–12 months is very crucial in the follow-up [7].

Several studies have been conducted to predict the risk of renal involvement. Older age at disease onset, gastrointestinal symptoms, persistent purpura, relapse, elevated WBC count, elevated platelet count, and low C3 levels, central nervous system involvement, angioedema have been found to be associated with renal involvement[8-12].

In this study, we aimed to describe the epidemiological, clinical, and laboratory characteristics of patients with IgAV and analyze the predicting factors associated with renal involvement.

MATERIALS and METHODS

This study was performed among patients with IgAV who were followed up between January 2006 and January 2016 in Medeniyet University Göztepe Training and Research Hospital. Patients were diagnosed with IgAV according to the European League Against Rheumatism, Pediatric Rheumatology International Trials Organization, and Pediatric Rheumatology European Society (EULAR/PRINTO/PRES) endorsed Ankara 2008 criteria [13]. Demographical, clinical, and laboratory results were retrospectively reviewed from the patient files. Patients, who followed less than 6 months were excluded.

Abdominal involvement was defined if the patient had abdominal pain and/or hematemesis, and/or melena and/or intussusception. Renal involvement was defined if the patient had any of the following findings: hematuria (> 5 red blood cells/high power field), red blood cell casts in urinary sediment, proteinuria > 4 mg/m2/h urine protein, hypertension (systolic and/or diastolic blood pressures ≥ 95th percentile for gender, age, and height on ≥ 3 occasions), nephrotic proteinuria (> 40 mg/m2/h), and renal insufficiency. Renal biopsy was performed in the patients who had nephrotic syndrome, nephrotic-range proteinuria, or persistent non- nephrotic proteinuria. Ethical approval was obtained from Institutional Review Board of Medeniyet University Göztepe Training and Research Hospital (25.06.2013-2013/0001), and was conducted according to the tenets of the declaration of Helsinki.

SPSS software version 25 was used to evaluate the statistical analysis. Continuous data were described as mean, standard deviation (SD) medians, minimum (min), and maximum (max) values and categorical variables as percentages. The variables were investigated using visual (histogram, probability plots) and analytic methods (Kolmogorov–Smirnov–Shapiro–Wilk’s test) to determine whether or not they are normally distributed. Categorical variables were compared with the chi-square test or Fisher’s exact test where appropriate. Student t-test or Mann–Whitney U test was used to compare the continuous data between the two groups where appropriate. Forward stepwise logistic regression was used for multivariate analysis. A p-value of less than 0.05 was considered to show a statistically significant result.

RESULTS

Of the 188 IgAV patients, involved in this cohort, 51.6 % (n=97) were female and 48.4 % (n=91) were male. The mean ± SD age at the time of IgAV diagnosis was 8.49 ± 3.35 years, and 66% of them (n=124) were under 10 years of age. The median follow-
up time was 18.1 months (range, 6–48 months). Thirty-six percent of patients (n=68) had a history of respiratory tract infection, 6.9% (n=13) had gastrointestinal infection, 3.1% (n=6) had urinary tract infection and 1.59% (n=3) had vaccination preceding the vasculitis. Thirty one percent (n=59) of patients had the disease onset in winter, 30.3% (n=57) in spring, 25% (n=47) in autumn, and 13.3% (n=25) in summer.

At the time of IgAV diagnosis, all patients had typical palpable purpura, 35.6% (n=67) had arthritis, 34.6% (n=65) had gastrointestinal system involvement, 12.2% (n=23) had renal disorders and among male patients 2.2% (n=2) had scrotal involvement (Figure 1). Four percent of the cases had bullous rash. Among patients with gastrointestinal system involvement, 3% (n=2) had presented with invagination, 23% (n=15) had GI bleeding in the form of hematochezia or melena. Both of the patients presented with invagination were treated with hydrostatic reduction.

MEFV mutation analysis was performed in 55 (29.2%) patients. Three (5.4%) of them had homozygous, 7 (12.7%) of them had compound heterozygous and 16 (29%) of them had heterozygous mutations. The most common MEFV gene allele was M694V (34.6%), followed by E148Q (29.2%), M680I (24.1%), and V726A (11%), respectively. The clinical and demographic features of patients were summarized in Table 1.

Besides 23 (12.2%) patients presented with renal disorders, and 42 (22%) patients developed renal involvement during follow-up. Of them, 21 occurred within 1 month, 19 occurred within 1-3 months, and 2 occurred within 4-6 months (Figure 2).

Among all the 65 patients with renal involvement, %22.9 (n=43) had microscopic hematuria, 4.8% (n=9) had macroscopic hematuria, 18.1% (n=34) had proteinuria. Of them, 12 had nephrotic range proteinuria and 22 had nephritic range proteinuria. Nephritic syndrome was observed in 2 patients, nephrotic syndrome was observed in 4 patients, and mixed nephritic and nephrotic syndrome were observed in 8 patients. None of the patients developed acute/chronic kidney disease during follow-up. Thirteen patients underwent renal biopsy. Two patients had minimal glomerular abnormalities without crescents (stage 1), 5 patients had mesangial proliferation without crescents (stage 2), 4 patients had mesangial proliferation with crescents in <50% of glomeruli (stage 3), and 2 patients had mesangial proliferation with crescents in <75% of glomeruli (stage 5).

Among patients with renal involvement 36 patients received only oral and/or iv steroid treatment, 5 patients received oral cyclophosphamide and pulse MPZ (3-6 doses), and 4 patients received Azathioprine and oral and/or iv steroid treatment. In 25 (38%) patients proteinuria and/or hematuria resolved within 3 months, in 22 (33%) patients

![Figure 1](image_url). The frequency of system involvements in IgA Vasculitis patients

GIS: Gastrointestinal system
*Among male patients

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between 3th and 6th months, in 12 (18%) patients between 6th and 12th months, and in 6 (9%) patients between 12th and 24th months (Figure 3).

When we divided the patients into 2 groups according to the age, we found that patients under 10 years had significantly more arthritis (p=0.008) and patients over 10 years had significantly more renal involvement (P=0.026) (Table 2). There was no difference for organ involvement between the patients based on gender except GI involvement, which was observed more frequently in males than females (p=0.021) (Table 3).

We also grouped our patients according to the presence of renal involvement. There were no significant differences in gender, age, and clinical manifestations between patients with and without renal involvement Among laboratory work-up at the time of IgAV diagnosis, ESR levels were found significantly higher in patients with renal involvement (Table 4).

To predict the risk factors of future renal involvement, we performed a multivariate analysis after excluding patients presented with renal involvement. The occurrence of renal involvement was not associated with any of the defined demographic and clinical characteristics (male sex, IgAV diagnosis over 10 years old, gastrointestinal system involvement, arthritis, ESR, WBC, and PLT levels at the time of IgAV diagnosis) of the disease. Although ESR levels showed a higher risk ratio, it has only borderline significance (4.13 (0.91- 11.54) p: 0.055) (Table 5).

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**Table 1.** The clinical and laboratory findings of the patients

| Age at IgAV diagnosis (mean ± SD) | 8.49±3.35 |
|----------------------------------|-----------|
| IgAV diagnosis before 10 years of age % (n) | 66 % (124) |
| Female % (n) | 51.6 % (97) |
| Male % (n) | 48.4 % (91) |
| Palpable purpura % (n) | 100 % (188) |
| Arthritis % (n) | 35.6 % (n=67) |
| Gastrointestinal system involvement % (n) | 34.6% (n=65) |
| Invagination % (n) * | 3% (n=2)* |
| Hematochezia or melena % (n) * | 23% (n=15)* |
| Renal involvement% (n) | 34.5% (n=65) |
| Microscopic hematuria % (n) ** | 966 % (n=43) |
| Macroscopic hematuria % (n) ** | 14% % (n=9)** |
| Nephrotic proteinuria % (n) ** | 18% % (n=12)** |
| Non-nephrotic proteinuria % (n) ** | 33% % (n=22)** |
| Nephritic syndrome % (n) ** | 3% % (n=2)** |
| Nephrotic syndrome % (n) ** | 6% % (n=4)** |
| Mixed nephritic-nephrotic syndrome | 12% % (n=8)** |
| Hemoglobin (g/dl) (mean ± SD) | 11.75±1.19 |
| WBC (103/mm3) (mean ± SD) | 9.95±3.8 |
| Platelet (103/mm3) (mean ± SD) | 351.74±117.26 |
| Urea (mg/dl) (mean ± SD) | 23.43±6.19 |
| Creatinine (mg/dl) (mean ± SD) | 0.59±0.17 |
| Albumin (g/dl) (mean ± SD) | 4.03±0.46 |
| C3 (mg/dl) (mean ± SD) | 128.44±22.51 |
| C4 (mg/dl) (mean ± SD) | 23.91±6.11 |
| ESR mm/h (mean ± SD) | 37.74±19.80 |

IgAV: IgA Vasculitis, WBC: White blood cells, PLT: Platelet, ESR: Erythrocyte sedimentation rate
* Among patients with GIS involvement
**Among patients with renal involvement

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Figure 2. The frequency of patients with renal involvement according to the time of renal involvement

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DISCUSSION

In the presented study, we reported 188 children with HSP/IgAV. The median follow-up time was 18.1 months (range, 6–48 months). Of them, 34.6% developed renal disease and the vast majority occurred within 3 months after the IgAV diagnosis. Patients presented over 10 years of age had significantly more renal involvement (p=0.026). The erythrocyte sedimentation rate (ESR) levels of patients with IgAV nephritis were significantly higher than patients without renal involvement. In multivariate analysis, we did not find a significant association between the demographic and clinical characteristics of the disease and the development of future renal involvement.

IgAV can present at any age during childhood, but it could occur more frequently around 4–6 years old. Compatible with recent studies from our country, which showed a disease onset between 7.4–9.3 years, we found that the mean age at diagnosis was 8.49 ± 3.35 years [14-16] in our patient population. IgAV is more frequently seen in males than females with reported male-to-female ratios of 1.2 to 1.8 [1, 17-19]. In our study, we have shown a slight female predominance. The male to female ratio was 0.93 which is also similar to the recent studies from our country [14, 15].

IgAV demonstrates a seasonal tendency. Cold seasons have been more associated with the development of IgAV supporting those viral infections could trigger the development of this
small vessel vasculitis. In our study, 46% of patients reported a history of an infection preceding the vasculitis. Although autumn and winter have been shown as the most frequently seen seasons of IgAV [18, 20-22], some studies reported case series that presented mostly in spring [23]. Similar to these studies, most of our patients had presented in the spring and winter.

Nonthrombocytopenic palpable purpura is the mandatory criteria of IgAV diagnosis [13]. All of our patients had typical purpura at the time of diagnosis. In addition to the skin findings, gastrointestinal, musculoskeletal, and renal systems could be involved [13]. In our patient cohort, gastrointestinal system involvement was observed in 34.6%, arthritis in 35.6%, renal disorders in 35.6%, and scrotal involvement (among male patients) in 2.2%

Several studies reported that older age at disease onset is associated with a more severe disease course [8, 24]. In the presented study, joint involvement was significantly higher in patients under 10 years of age and renal involvement was significantly higher in patients over 10 years of age. Akgün et al. emphasized that the risk of renal involvement increased as the age of the patient increased, however there was no significant association of

| Table 4. The difference of demographic, baseline clinical, and laboratory characteristics between patients with and without renal involvement |
|-----------------|-----------------|-----------------|
| Renal involvement (-) | Renal involvement (+) | p-value |
| Age at IgAV diagnosis (mean±SD) | 8.17±3.31 | 9.10±3.37 | 0.072 |
| Gender (F/M) | 58/65 | 39/26 | - |
| Rash n(%) | 123 (%100) | 65 (%100) | - |
| Arthritis n(%) | 45 (%36.6) | 22 (%33.8) | 0.831 |
| GIS involvement n(%) | 42 (%34.1) | 23 (%35.4) | 0.993 |
| Scrotal involvement n(%)* | 2 (%2.2)* | 0 (%0.0) | 0.554 |
| Hemoglobin (g/dl) (mean±SD) | 11.75±1.19 | 11.98±1.52 | 0.253 |
| WBC (10³/mm³) (mean±SD) | 9.95±3.8 | 10.10±4.04 | 0.798 |
| PLT (10³/mm³) (mean±SD) | 351.74±117.26 | 328.54±103.19 | 0.346 |
| IgA (mg/dl) (mean±SD) | 225.92±121.84 | 270.53±118.74 | 0.166 |
| IgG (mg/dl) (mean±SD) | 1358.62±1166.91 | 1207.29±300.02 | 0.913 |
| C3 (mg/dl) (mean±SD) | 128.44±22.51 | 122.62±29.57 | 0.320 |
| C4 (mg/dl) (mean±SD) | 23.91±6.11 | 24.79±14.21 | 0.754 |
| ESR (mean±SD) | 37.74±19.80 | 45.27±22.07 | 0.048 |

*Among male patients

IgAV: IgA Vasculitis, GIS: Gastrointestinal system, WBC: White blood cells, PLT: Platelet, ESR: Erythrocyte sedimentation rate

| Table 5. Odds ratios for the risk of the development of renal involvement in IgAV patients |
|-----------------|-----------------|-----------------|
| Defined Variables | OR (95% CI) | P value |
| IgAV dx over 10 years old | 0.9 (0.87 – 3.53) | 0.114 |
| Gender | 0.6 (0.49 - 13.91) | 0.912 |
| GIS involvement | 0.71 (0.64 - 4.72) | 0.163 |
| Arthritis | 0.47 (0.06 – 7.29) | 0.46 |
| ESR | 4.13 (0.91 - 11.54) | 0.055 |
| WBC | 0.95 (0.63 - 5.77) | 0.071 |
| PLT | 0.73 (0.72 - 6.83) | 0.537 |

OR: Odd’s ratio, CI: Confidence interval, GIS: Gastrointestinal system, WBC: White blood cells, PLT: Platelet, ESR: Erythrocyte sedimentation rate
age with other system involvement [25]. In a study comparing adult and pediatric IgAV patients, it was reported that renal involvement was more frequent and severe in adult patients, but joint involvement and GIS involvement were observed in equal frequency in children and adults[26].

We also investigated the association of gender and system involvement. It has been reported that the male gender is a risk factor for GIS and renal involvement[27]. Similarly, in our study, a significant association was found between gastrointestinal system involvement and the male gender. Interestingly, although it does not reach statistical significance, renal involvement was more common in females than males (40% vs 29%).

Renal involvement is seen in approximately 30-50% of patients and most of whom have mild symptoms [28, 29]. However, a small minority of patients with persistent renal involvement may progress to renal failure. The most common finding is microscopic hematuria followed by non-nephrotic proteinuria. Consistent with the literature among patients with renal involvement, 29.2% had microscopic hematuria and 22.9% had non-nephrotic proteinuria, 4.8% had macroscopic hematuria, nephritic syndrome was observed in 3.1%, and nephrotic syndrome was observed in 6.2%. Although IgAV is a self-limited disease; renal involvement can occur after the acute phase of the disease. Most studies reported that renal involvement was observed most frequently in the first 2-3 months [8, 11, 18]. In a retrospective study of 261 IgAV patients, renal involvement was found most frequently (98%) within 4 weeks after the onset of IgAV [30]. In our study, renal disease was observed in 23 (35.4%) patients at the time of IgAV diagnosis, in 21 (32.3%) patients within the first month, in 19 (29.2%) patients between 1th-3th months, and only in 2 (3.1%) between 4th and 6th months. Therefore, renal monitoring for 6–12 months is very crucial in the follow-up.

Since renal involvement is the only leading cause of long-term morbidity, there was an effort to predict the risk factors of renal disease and poor renal prognosis. Several studies found severe abdominal symptoms, persistent purpura, decreased coagulation factor XIII activity, older age onset, relapse number as risk factors for renal involvement in IgAV.[8-12, 31-34]. On the other hand, Scharer et al. reported that presenting with renal failure or nephrotic syndrome, and the frequency of crescents in the glomeruli were the only factors affecting the renal prognosis. In this study, age, gender, baseline hypertension, and recurrent purpura were not considered as a prognostic factor [35]. When we compared baseline clinical and laboratory characteristics of patients, we found that patients with renal involvement had significantly higher ESR levels. We performed a multivariate analysis to predict the possible risk factors of renal involvement. However, we could not find any significant association between the defined demographic and clinical characteristics and the occurrence of future renal involvement. ESR levels showed a higher risk ratio, but it did not reach statistical significance.

The major limitation of our study was the retrospective design. Particularly, it could lead to misinterpretation of the possible prognostic factors in patients with renal involvement.

In conclusion, although IgAV is a self-limiting disease with an excellent prognosis in most of children, renal involvement can cause serious complications. In our cohort, renal involvement was observed in 34.6% of patients. And the vast majority of them in the first 3 months. Although rare, IgAV nephritis may occur months later. Pediatricians and rheumatologists should keep in mind that these patients should be follow-up at least 6 months. In the presented study, being older than 10 years of age and having high levels of ESR at the time of diagnosis could serve as a possible predictor of renal involvement.

**CONFLICT of INTEREST**

The authors declare no conflict of interest.
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