Damage assessment in adult IgA vasculitis. Cross-sectional results of a multicentre cohort

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ABSTRACT

Objective. *Immunoglobulin (Ig) A vasculitis affects children more commonly than adults and previous literature lacks any formal damage assessment. Our aim in this study is to investigate the disease course, relapse rates and prognostic factors in adult patients with IgA vasculitis and to evaluate the disease-related damage.*

Methods. *We assembled a retrospective cohort of adult IgA vasculitis from six tertiary Rheumatology Centres in Turkey. The demographics, clinical characteristics, treatment and outcomes of patients were abstracted from medical records.*

Results. *The study included 130 (male/female: 85/45) patients and the mean age was 42.2±17 years. Cutaneous manifestations and arthritis/arthralgia were the most common clinical manifestations. One hundred thirteen patients (86.9%) were treated with oral glucocorticoids (GC). As additional immunosuppressive (IS) agents, azathioprine was given to 44 (34.9%) and pulse cyclophosphamide to 18 (12.6%) patients. Seventy-nine patients (60%) had follow-up of median 15 (IQR 7-40) months. Twelve (15%) patients relapsed during follow-up. The mean VDI score was 0.4 in the last visit. Nineteen (24.7%) patients had at least one damage item at the end of follow-up. Most frequent damage items were renal 11 (42%), ocular 4 (15%) and cardiovascular 4 (15%).*

Conclusion. *In this cohort the most frequent damage item was renal and was related to the disease itself. Damage score was higher in patients with more severe disease and treated more aggressively. Our results suggest that more effective treatment options are needed in a subgroup of patients with IgA vasculitis to prevent the damage related with the vasculitis, especially with more severe disease.*

Introduction

Immunglobulin (Ig) A vasculitis, formerly known as Henoch Schönlein purpura (HSP), is an acute, multi-systemic, leukocytoclastic vasculitis characterised by deposition of IgA-containing immune complexes and complement components in small-vessel walls (1). The disease is characterised by palpable purpura, arthritis/arthralgia, abdominal pain and renal impairment (2). Children are affected more commonly, as it is the most common vasculitis of childhood. The incidence is 13.5-20.4/100,000 in children (3-4), which declines to 13-14 cases/100,000 in adults (5-6). The aetiology is poorly understood. IgA1 accumulation in the vascular wall and renal mesangium plays a crucial role in pathogenesis. Possible triggers of IgA vasculitis include infectious agents (especially respiratory tract infections), drugs and vaccines (7). Various genetic loci, such as MHC, IL-1r antagonist and IL-8 are implicated in the pathogenesis (5).

The prognosis is usually favourable in children, yet relapses occur with a frequency of 2.7-51.7% (9, 10). While encountered less frequently in adults, the disease tends to be more severe (11). The severity of the illness is considered to be associated with gastrointestinal and renal involvement. Earlier studies revealed that renal involvement is observed in 45 to 85% of adult-onset IgA vasculitis cases, with a 30% risk of progression to renal failure. Disease flare is usually unique and relapses occur in roughly 20% of cases in adults (12-14). The evidence is scarce about prognosis in adults and previous literature lacks any formal damage assessment. Our aim in this study is to retrospectively investigate the disease course, relapse rates and prognostic factors in adult patients with IgA vasculitis and to evaluate the disease or treatment-related damage.

Methods

Patients and registry

Data were collected retrospectively from a registry of patients with IgA vasculitis, followed in 6 tertiary rheumatology clinics across Turkey. The study included 130 patients who were at least 18 years old, diagnosed with IgA vasculitis according to the American College of Rheumatology classification criteria or 2012 International Chapel Hill Consensus (1). While 124 of the patients fulfilled the 1990 ACR criteria, and 6 of them were classified according to Chapel Hill Consensus Criteria definition as IgA vasculitis.

Clinical and laboratory data

All clinical, demographic and laboratory data were acquired from the patient charts. The standard patient form including new clinical features, laboratory, biopsy and treatment changes were filled for the diagnosis, first remission and the last follow-up visits. If relapse developed, a relapse visit was also performed. Renal failure was defined as a glomerular filtration rate (GFR) of <60 mL/minute/1.73 m2 assessed with Modified Diet in Renal Disease (MDRD) equation. Proteinuria was defined as >0.3 mg/day detected with 24 hour urine collection. Haematuria was defined as ≥5 red cells/mm^3. Results of skin and kidney biopsies were noted. The initial glucocorticoid dose (GC) and the additional immunosuppressive (IS) therapies and other medications during follow-up were recorded.

Definitions

Activity was assessed according to the Physician Global Assessment (PGA, 0-10) and Birmingham Vasculitis Activity Score (BVAS) (17). The absence of any symptoms or signs of clinical activity (BVAS=0) was defined as remission. The disease was considered refractory if there was no improvement in clinical signs or symptoms, or if any new clinical finding occurred.

A relapse was defined as the reappearance of clinical signs of vasculitis, occurring after a period that was free of symptoms (BVAS>0).

Major relapse was characterised by organ or life-threatening manifestations such as at least 30% increase in creatinine value, pulmonary haemorrhage, retinal vasculitis, acute limb ischaemia-gangrene, and mononeuritis multiplex. If none of the major relapse criteria were evident in a patient with relapse, the patient was classified as having a minor relapse.

The clinical findings which persisted to the second visit and at least three months were evaluated to document the damage with vasculitis damage index (VDI) (15). Five factor score (FFS); which include proteinuria >1 g/d, renal insufficiency (stabilised peak creatinine 140 μmol/L), cardiomyopathy, severe gastrointestinal manifestations and central nervous system involvement (29), were recorded in terms of the severity of the disease at baseline visit and at the relapse visits.

Statistics

We calculated the means of continuous variables and standard deviation when the data were distributed normally. Me-

Table I. Baseline demographics, laboratory results and clinical characteristics of IgA vasculitis patients.

Demographics	
Age at diagnosis*	42.2 ± 17
Male (n, %)	85 (65%)
ACR criteria met (n, %)	124 (95%)
Chapel Hill Consensus Definition met (n, %)	6 (5%)
Laboratory results	
Anaemia (<12 mg/dl for female, <13 mg/dl for male) (n, %)	46 (35%)
Leukocytosis (leukocyte count ≥ 11 x 10^9/L) (n, %)	65 (50%)
Erythrocyte sedimentation rate (mm/hour) *	36.2 ± 23.9
C-reactive protein (mg/l)†	18 (1-297)
Creatinine (mg/dl)*	0.85 ± 0.36
Proteinuria (>300 gm/24 hours) (n, %)	60 (46.2 %)
Haematuria (≥ 5 red cells/mm3) (n %)	60 (42%)
Clinical manifestations	**N / 130 (%)**
Constitutional manifestations	118 (91)
Fever	33 (26)
Weight loss	33 (26)
Fatigue	111 (88)
Cutaneous manifestations	123 (94.6)
Purpura	129 (99)
Ulcers	1 (0.8)
Nodules	2 (1.5)
Livedo reticularis	1 (0.8)
Musculoskeletal manifestations	
Arthritis/arthralgia	108 (83)
Myalgia/weakness/leg tenderness	53 (43)
GIS manifestations	89 (68.5)
Abdominal pain	86 (66)
Bleeding	41 (31)
Perforation	0
GIS manifestations requiring surgery	2 (1.5)
Renal	35 (27)
Peripheral extremity oedema	22 (17)
High blood pressure	2 (1.5)
Renal failure	11 (8.5)
Cardiac manifestations	2 (1.6)
Pulmonary manifestations	2 (1.6)
Ocular manifestations	2 (1.6)
Neurologic manifestations	1 (0.8)
Testicular pain or tenderness	4 (3.3)
FFS (n, %)	
0	84 (64.6)
≥1	46 (35.4)
BVAS score at diagnosis*	6 ± 4

*Mean ±SD. †Median (minimum-maximum); ACR: American College of Rheumatology; ANA: antinuclear antibody, RF: rheumatoid factor, ANCA: antineutrophilic cytoplasmic antibody; FFS: five factor score; BVAS: Birmingham Vasculitis Activity Score.

dians and first to third quartile interval were calculated for data that did not have a normal distribution.

We analysed group differences for dependent categorical variables with the chi-square or Fishers's exact test. We compared continuous variables with student t-test or Mann-Whitney U when data were skewed. A two-tailed *p*-value <0.05 was considered significant.

Results

One hundred and thirty patients were included in the study. The majority of patients (n=85, 65%) were male, and the mean age at diagnosis was 42±17 years. The baseline demographic and laboratory characteristics of the patients are presented in Table I.

The most common clinical features were constitutional (n=118, 91%), cutaneous (n=129 %99.2), musculoskeletal (n=111, 85%) and gastrointestinal manifestations (n=89, 68.5%). There were two (1.6%) patients with pulmonary involvement at the baseline and they presented with pulmonary haemorrhage. In these two patients, the diagnosis of ANCA-associated vasculitis (AAV) was also excluded. Eleven (8.5%) patients had renal failure at first admission. Clinical features are displayed in Table I.

Sixty (46%) patients had proteinuria and the median level of proteinuria was 1 g/day (Q1-Q3: 0.5-2.0). Sixty (42%) patients had haematuria at baseline. ANA positivity rate was 11.8% (n= 21/117) and hepatitis B presence 7.3% (n= 9/123).

Fifty-two (40%) patients had a preceding infection within the last six weeks (40 had upper respiratory tract, 3 urinary tract, 6 gastrointestinal and 3 other infections). Forty (33%) patients had at least one kind of drug exposure (26 antibiotics, 5 non-steroidal anti-inflammatory, and 9 other).

During diagnosis, 113 (87%) patients were treated with oral GCs. Pulse GC treatment was also given to 41 (31, 5%) patients. As additional IS agents, azathioprine was given to 44 (34.9%) and pulse cyclophosphamide to 18 (13.8%) patients. Twelve (9.2%) patients received colchicine, and five (3.8 %) patients did not receive any treatment.

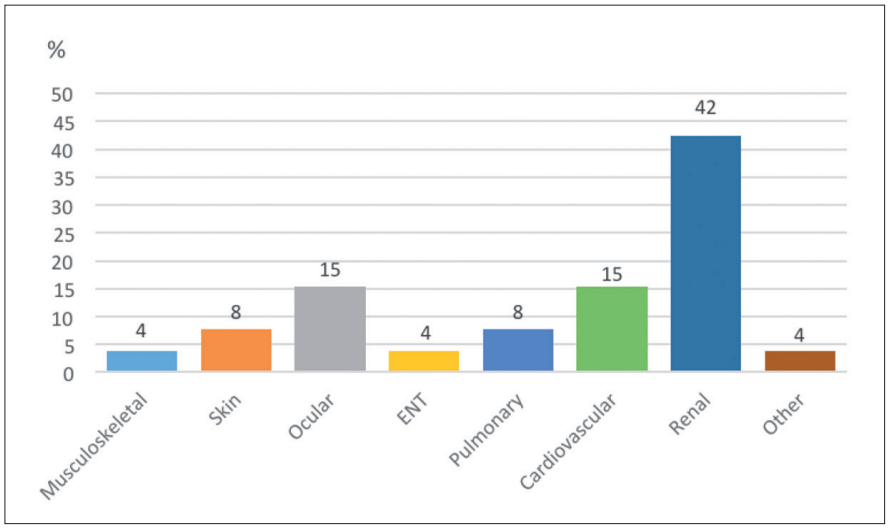

Fig. 1. Damage items in VDI assessment in IgA vasculitis patients.

The clinical features of the patients were evaluated according to the initial treatments. Those initially treated with ISs plus GCs had more renal involvement (35% *vs*. 65% *p*=0.0001) and more GIS involvement (47% *vs*. 53% *p*=0.048) than those treated with GCs alone. Other basal clinical features were similar in the treatment groups.

At the first visit mean BVAS and PGA was 6 (SD=4) and 7.3 (SD= 2.1), respectively. In the basal evaluation, there were 84 (64.6%) patients with FFS=0, 29 (22.3%) patients with FFS=1, 13 (10%0) with FFS=2, and 4 (3.1%) with FFS=3.

A total of 122 patients underwent a biopsy. Of these, 97 (79.5%) had skin, 23 (19%) had renal and 2 (1.6%) had gastrointestinal biopsies. 105 of these 122 patients had histologically confirmed IgA vasculitis in biopsy specimens.

Follow-up

Follow-up data were available for 79 (59.2%) patients. Median follow-up duration was 15 months (Q1-Q3: 7-40). Twelve (15%) patients relapsed during follow-up. Six were major, and six were minor relapses. Nine (75%) patients were still on GC treatment during the relapse. Seven (58%) patients were under IS agents, and 5 (41%) were taking both GC and ISs during the relapse.

Factors that may be related to the relapses were evaluated in patients with follow-up data. When the basal clinical characteristics of the patients with and without relapse were compared, it was determined that patients with relapse had higher acute phase responses (*p*=0.041). The relapse rate was 22.5% in GC alone treatment patient group, whereas the rate of relapse was 8% in GC+IS group (*p*=0.069), not reaching significance. There was also no statistically significant difference in other basal clinical and laboratory characteristics between the two groups.

At the last visit, disease status was judged as active or treatment failure by the treating physician in 13 patients (15%). Among 79 patients who had follow-up data, 43 (55%) patients were still undergoing GC treatment at the last visit. Eleven (25.5%) of them received a low dose (>7.5 mg/day prednisone equivalent), and 32 (74.5%) a medium or high-dose (>7.5 mg but ≤100 mg prednisone equivalent daily) GC therapy. The rate of chronic renal failure was 8.8% (n=7). Regarding the factors related to renal damage initial renal failure (*p*=0.001), proteinuria (*p*=0.004), haematuria (*p*=0.005) and IS treatment (*p*=0.003) were found to be associated with the development of renal insufficiency.

One patient died during follow-up due to pneumonia. At the end of the follow-up, the mean VDI score was 0.4, and 18 (23.5%) patients had at least one damage item. The most frequent damage item was renal 11 (42%). The rate of damage related with GC treatment

is 30%, non-related with GC treatment 70%. Distribution of damage items is shown in Figure 1.

In addition, VDI scores of the patients who were followed up at the last visit were evaluated according to the initial treatments. The rate of VDI score ≥1 was 10% in patients receiving GCs alone, whereas the rate of VDI score ≥1 of patients receiving steroid plus ISs was 38.5% (p=0.005). VDI score of those receiving GC+ISs (mean: 0.71±1.1) was also higher than those receiving GCs alone (mean: 0.11±0.31) (p=0.003).

Male gender (p=0.01), older age (p=0.006), initial renal failure (p=0.012), and proteinuria (p=0.012) were more common among patients who had a VDI score ≥1.

Discussion

Although generally accepted to be a mild vasculitis, IgA vasculitis can cause permanent organ damage, especially renal failure in adults. The present study is the largest patient series of adult IgA vasculitis from Turkey and to our knowledge, the first study including an overall damage assessment with VDI for IgA vasculitis in literature so far.

Similar to the previous reports, there was male dominance and the disease onset in fifth decade in our study (13, 18-23). When we compare our patient group with two previously published large series by Calvo-Rio *et al*. and Audemard-Verger *et al*. almost all of the patients had skin involvement as in other series. Constitutional symptom rate was greater in our patients (89% *vs*. 33%-20%). In addition, the proportion of GIS (90% *vs*. 53%-64%) and musculoskeletal (85% *vs*. 61%-60%) manifestations were higher in our series (17, 22). The number of patients presenting with renal insufficiency was lower than the Audemard-Verger *et al*. study (49% *vs*. 70%) but similar to the other studies (30-60%). This difference may be relevant as patients were enrolled only by rheumatologists in our study, whereas the French registry included many patients enrolled by nephrologists (18-24).

IgA vasculitis is thought as a self-limiting disease, particularly in children (25). In a recent cohort from Mayo Clinic, Villatoro-Villar *et al*. reported that adult patients with IgA vasculitis had more frequent skin ulcers and greater frequency of severe proteinuria compared to children (11). The treatment of severe manifestations, including severe gastrointestinal complications or proliferative glomerulonephritis, is still controversial due to lack of evidence that GCs or IS agents improve long-term outcome (26). In a prospective open-label trial by Pillebot *et al*. and in the retrospective study of the French vasculitis group, there were no differences between GCs plus cyclophosphamide and GCs alone regarding renal outcome and mortality. The rate of achieving partial or complete remission were also similar between the groups (23, 27).

Ninety six percent of all patients in our cohort initially received GC therapy. Initially 54% of patients received GC treatment alone in this study, whereas the ratios in the series of Audemard-Verger *et al*. and Calvo-Rio *et al*. were 47% and 35%, respectively. In addition, the rate of IS+GC use was higher in our series than in other two studies (45% *vs*. 5%-13%) (18, 23). Additional IS therapy (mainly azathioprine) was more given to patients with renal and GIS involvement as these manifestations are accepted as more severe spectrum at baseline. A higher percentage of patients with symptomatic disease may account for a higher GC use. Additional IS treatments may be caused by a higher inclination towards GC-sparing agents by rheumatologists.

Relapses can complicate IgA vasculitis. In previous reports, relapse rate ranges between 20-30% in adult IgA vasculitis. In our study, relapse rate was found in lower range as 15% (9, 18, 23). Higher use of GCs and other IS agents at baseline or a high rate of missing follow-up data may explain this finding.

Rigante *et al*. reported that persistent purpura is a significant predictor of relapses (28). Similarly, Shin *et al*. and Byun *et al*. observed that adult age, persistent purpura, severe abdominal pain, the presence of haematuria and severe leukocytoclastic vasculitis were associated with relapses (9, 29). In a large series (315 children and 102 adult patient) by Calvo-Rio *et al*, while previous infections seemed to be protective for relapses, the predictors of relapse were gastrointestinal and joint involvement in the whole group. However, when they analysed adults alone, only gastrointestinal manifestations were predictive for relapses (30). In our subjects initial acute phase elevation and constitutional symptoms increase the risk of relapse slightly. There was no other potential predictor for relapses in our group.

The most important severe manifestation of IgA vasculitis in adults is renal failure. At the last visit, the rate of chronic renal failure was 8.8%. Related factors were renal failure at presentation, proteinuria, haematuria, and usage of IS treatments. Patients who were initially given additional IS therapy were more likely to have renal involvement and renal failure more developing in these patients. Kang *et al*. and Pillebout *et al*. also found that renal insufficiency at presentation and proteinuria were associated with renal damage. (6, 12). In an another study by García-Porrúa *et al*., investigating factors predicting renal sequelae in adult IgA vasculitis, haematuria at disease onset and persistence of renal manifestations during the course of the disease were found to be significant indicators for renal sequelae (31). In our series, haematuria was also predictive for renal involvement. Presence of IL-1 receptor antagonist allele 2 was associated with a higher risk of severe renal manifestations and renal sequelae (32). Polymorphisms in IL-8 gene were also associated with susceptibility to renal and possibly to GI manifestations in IgA vasculitis patients (33).

In addition, Hong *et al*. indicated that late-onset disease was a significant independent prognostic factor for chronic renal insufficiency (34). Diseases such as diabetes mellitus and hypertension are common in this age group and may affect renal failure. In our study, we did not find any association between age and renal involvement.

It is well known that FFS score ≥1 is predictor of increased mortality in sys-

temic necrotising vasculitis such as AAV (35). In our study, very low mortality rate (1.2%) was observed despite the high percentage of FFS ≥1.

A formal damage assessment is lacking in previous studies of IgA vasculitis. Damage assessment is becoming a part of routine management of systemic necrotising vasculitides such as PAN and AAV. In previous reports, the mean VDI score was found 3 in AAV and 2.2 in PAN. The most frequently positive VDI items were GC-use related damage items in PAN and AAV, such as hypertension, osteoporosis and cataract (16, 36, 37). In our study, the most common VDI item was renal damage, despite the high rate of GC use in the last visit. A lower rate of GC-related damage may be explained by a short duration of GCs and young aged patient population. As we expected, the factors affecting VDI includes renal failure, proteinuria and a high initial BVAS. VDI score was also higher (mainly disease related) in patients treated IS plus GCs than patients treated with GCs alone.

The main limitation of the study is its retrospective design. The participants were only from rheumatology clinics, which may lead to an inclusion of patients with lower renal involvement rate. A short duration of a follow-up period and lack of follow-up data for some patients may also limit findings and more precise information.

In conclusion, the main cause of damage in IgA vasculitis appears to be the disease itself. Although GC treatment is given to the majority of patients, GC-related damage develops infrequently in early years of follow-up. Damage score is also higher in patients with more severe disease and treated more aggressively (IS+GCs). Despite the benign course of IgA vasculitis and some patients undergoing remission without treatment, high dose GCs and additional IS agents may be required in a small group of IgA vasculitis patients. Our results suggest that more effective treatment options are needed in a subgroup of patients with IgA vasculitis to prevent the disease-related damage, especially in patients with more severe disease.

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