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Original article

Impact of aging on phenotype and prognosis in IgA vasculitis

Alexandra Audemard-Verger [1,2], Evangéline Pillebout[3], Aurélie Baldolli[4], Noémie Le Gouellec[5], Jean-François Augusto[6], Noémie Jourde-Chiche[7], Loic Raffray[8,9], Eric Thervet[10], Alban Deroux[11], Julie Goutte[12], Aurélie Hummel[13], Bertrand Lioger[14], Sébastien Sanges[15], Patrice Cacoub[16,17], Zahir Amoura[18], Guillaume Moulis[19,20], Francois Maurier[21], Christian Lavigne[22], Geoffrey Urbanski[22], Johan Chanal[23], Stanislas Faguer[24], Sophie Deriaz[1], Nicole Feirreira-Maldent[1], Elisabeth Diot[1], Francois Maillot[1,2], Loïc Guillevin[25,26,27] and Benjamin Terrier[25,26,27]

Abstract

Objectives. Immunoglobulin A vasculitis (IgAV) is a small-vessel vasculitis most frequently benign in children while more severe in adults. We aimed to study the impact of age on presentation and outcome of adult IgAV.

Methods. We conducted a nationwide retrospective study including 260 IgAV patients. Patients were divided into four quartiles according to the age at IgAV diagnosis: <36, $36 \leq \text{age} < 52$; $52 \leq \text{age} < 63$ and ≥ 63 years. Comparison of presentation and outcome were performed according to age of disease onset.

Results. Mean age at diagnosis was 50.1 (18) years and 63% were male. IgAV diagnosed in the lowest quartile of age was associated with more frequent joint ($P < 0.0001$) and gastrointestinal involvement ($P = 0.001$). In contrast, the oldest patients had more severe purpura with necrotic lesions ($P = 0.001$) and more frequent renal involvement ($P < 0.0001$), with more frequent haematuria, renal failure, higher urine protein excretion and more frequent tubulointerstitial lesions. Patients were treated similarly in all groups of age, and clinical response and relapse rates were similar between groups. In the 127 treated patients with follow-up data for >6 months, clinical response and relapse rates were similar between the four groups. Median follow-up was of 17.2 months (9.1–38.3 months). Renal failure at the end of follow-up was significantly more frequent in the highest quartile of age ($P = 0.02$), but the occurrence of end-stage renal disease was similar in all groups. Last, overall and IgAV-related deaths were associated with increase in age.

Conclusion. Aging negatively impacts the severity and outcome of IgAV in adults. Younger patients have more frequent joint and gastrointestinal involvement, while old patients display more frequent severe purpura and glomerulonephritis.

Key words: age, IgA vasculitis, Henoch–Schönlein purpura, renal involvement, prognosis, outcome

[1]Department of Internal Medicine and Clinical Immunology, CHRU Tours, [2]University of Tours, Tours, [3]Department of Nephrology, Hôpital Saint Louis, Assistance Publique-Hôpitaux de Paris (AP-HP), Université Paris Descartes, Paris, [4]Department of Infectious Diseases, CHU de Caen, Caen, [5]Department of Internal Medicine and Nephrology, CH de Valenciennes, Valenciennes, [6]Department of Nephrology, CHU d'Angers, Angers, [7]Department of Nephrology, AP-HM, Aix-Marseille Université, C2VN, INSERM, INRAE, Marseille, [8]Department of Internal Medicine, CHU de la Réunion, La Réunion, [9]Université de La Réunion, UMR Processus Infectieux en Milieu Insulaire Tropical (PIMIT), INSERM 1187, CNRS 9192, IRD 249, La Réunion, [10]Department of Nephrology, Hôpital Européen Georges Pompidou, Assistance Publique-Hôpitaux de Paris (AP-HP), Université de Paris, Paris, [11]Department of Internal Medicine, CHU de Grenoble, Grenoble, [12]Department of Internal Medicine, CHU de St Etienne, St Etienne, [13]Department of Nephrology, Hôpital Necker, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, [14]Department of Internal Medicine, Hopital de Blois, Blois, [15]Département de Médecine Interne et Immunologie Clinique, CHU Lille, Lille, [16]Department of Internal Medicine and Clinical Immunology, Hôpital Pitié-Salpétrière, AP-HP, [17]Inflammation-Immunopathology-Biotherapy Department (DHU i2B), UMR 7211, UPMC Université Paris 06, Sorbonne Universités, [18]Department of Internal Medicine, Hôpital Pitié-Salpétrière, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, [19]Department of of Internal Medicine, CHU de Toulouse, Toulouse, [20]Clinical Investigation Center 1436, Toulouse University hospital, Toulouse, [21]Department of Internal Medicine, Hôpitaux privés, Met, [22]Department of Internal Medicine, CHU d'Angers, Angers, [23]Department of Dermatology, Hôpital Tarnier, Assistance Publique-Hôpitaux de Paris (AP-HP), Paris, [24]Department of Nephrology and Organ Transplantation, CHU de Toulouse, Toulouse, [25]Université Paris Descartes, [26]Department of Internal Medicine, Hôpital Cochin and [27]National Referral Center for Systemic and Autoimmune Diseases, Hôpital Cochin, Paris, France

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Correspondence to: Alexandra Audemard-Verger, Boulevard Tonellé, CHRU de Tours, Tours France.
E-mail: a.audemard-verger@chu-tours.fr

CLINICAL SCIENCE

Rheumatology key messages

- Aging negatively impacts the severity and prognosis of immunoglobulin A vasculitis (IgAV) in adults.
- Younger IgAV patients have more frequent joint and gastrointestinal involvement.
- Older IgAV patients display more frequent severe purpura and glomerulonephritis.

Introduction

Immunoglobulin A (IgA) vasculitis (IgAV), formerly called Henoch–Schönlein purpura, is a small-vessel vasculitis with IgA1-dominant immune deposits within the vessel wall. Disease presentation typically includes skin, joint, gastrointestinal (GI) tract and kidney involvement. IgA vasculitis is the most frequent vasculitis in childhood [1], while the disease is less common in adults [2, 3]. IgAV in children is often benign, whereas IgAV has been described as being more severe, with worse clinical features and outcome in adults. Abnormal circulating IgA1 play a pivotal role in IgAV pathophysiology [4]. IgA1 hinge regions are galactose-deficient, such modification being more prone to immune complex formation and deposition, thereby leading to enhanced inflammation [4], most likely through complement alternative pathway activation. IgA1 could also activate neutrophils via the IgA Fc receptor FcαRI (CD89), thereby inducing neutrophil migration and related tissue damage [5]. Since IgA production has been shown to increase with age [6], it raises the question of potentially more severe phenotype and poorer outcome in elderly patients compared with younger adults.

Because the impact of age on IgAV presentation and outcome has been poorly studied in the literature, we aimed to evaluate whether IgAV in elderly patients displays more severe phenotype and poorer outcome as compared with younger patients. We therefore compared clinical, laboratory and histological presentation, treatments and outcome of IgAV patients according to age at diagnosis.

Methods

Patients

This multicentre retrospective survey was conducted in 31 French university and general hospitals in departments of Internal Medicine, Nephrology, Dermatology and Rheumatology. Inclusion criteria were (i) age >18 years and (ii) a diagnosis of IgAV between January 1990 and January 2015. Patients were considered to have IgAV if they presented all of the following features: (i) purpura, (ii), biopsy-proven small vessels vasculitis, (iii) histologically proven IgA deposits, and (iv) involvement of at least one organ among kidney, joint or GI tract. Exclusion criteria were IgAV associated with a diagnosis of cancer within the 5 previous years before vasculitis onset. Patients were divided into four quartiles according to the age at IgAV diagnosis: <36, $36 \leq \text{age} < 52$, $52 \leq \text{age} < 63$ and ≥ 63 years. The study was performed in accordance with ethical standards of the Declaration of Helsinki, and was approved by the Cochin Ethical Committee (IRB) who waived the requirement for informed consent.

Clinical and biological data

Clinical and biological data were recorded for each patient at the time of diagnosis, during follow-up (6 and 12 months after initial evaluation) and at the end of follow-up by the physicians in charge of the patients with the use of a standardized form. Laboratory assessment included the determination of serum creatinine level and urinalysis to screen for haematuria and urine protein excretion. Renal function was assessed using the Modified Diet in Renal Disease equation. Renal failure was defined as an eGFR <60 ml/min/1.73 m^2 [7]. Proteinuria was defined as 24-h urine protein excretion >0.5 g/day, and haematuria as >10 red cells/mm^3 in the urine. Elevated serum IgA levels was defined as IgA >3.5 g/l.

Histological data

Histological data (skin and renal biopsies) were recorded at the time of diagnosis. Pathology reports for renal biopsies were examined by two independent nephrologists (E.T. and E.P.) blinded to the clinical features. According to the presence of focal or diffuse distribution, extracapillary proliferation, number of glomeruli involved, interstitial fibrosis, proportions of glomeruli involved by crescents, fibrinoid necrosis and global sclerosis, all biopsies were classified according to the classification previously described by Pillebout *et al.* [8].

Response to therapy

The responses to therapy were previously published [9]. They were defined by analysing the course of the following clinical manifestations: skin involvement (purpura), articular manifestations (arthralgia and/or arthritis), GI symptoms and renal involvement (normalization or improvement of eGFR, proteinuria and haematuria). Response were evaluated by two independent physicians (A.A.V. and B.T.) blinded to the treatment received. A complete response was defined as an improvement in all baseline clinical manifestations and in cases of renal involvement by a proteinuria <0.5 g/d, the disappearance of haematuria and no decrease of the glomerular filtration rate (GFR) $>20\%$ from baseline. A partial response was defined as an improvement in at least one-half of the baseline clinical manifestations, and

in cases of renal involvement as an improvement of proteinuria >50% of the baseline value, disappearance or not of haematuria, and no decrease of the GFR >20% from baseline. All other patients were classified as non-responder. Relapse was defined as the reappearance of manifestations attributable to active vasculitis, and occurring after a period free of symptoms of ≥1 month. Minor relapse was defined by increase of prednisone >20 mg/day and major relapse by addition of immunosuppressive drug or increase of prednisone >20 mg/day. Other patients were considered as having no relapse.

Statistical analysis

Descriptive statistics included the mean (S.D.) or median [interquartile range (Q1, Q3)] when appropriate for continuous variables, and frequency (percentage) for categorical variables. Spearman's correlation test was used for continuous variables and univariate analysis included the χ^2 and the χ^2 for trend to compare categorical variables and ANOVA for quantitative variables, using Prism v.6.0 (GraphPad Software, La Jolla, CA, USA).

Results

Patients' characteristics according to age at IgAV onset

Mean age at IgAV diagnosis was 50.1 (18.6) years and 63% were male. Baseline manifestations according to the quartiles of age at diagnosis are shown in Table 1.

Elderly-onset of IgAV was associated with more frequent constitutional symptoms ($P = 0.04$) and more severe and extensive purpura, i.e. reaching the abdomen ($P = 0.08$) and with necrotic lesions ($P = 0.001$). In contrast, IgAV diagnosed in the lowest quartile (younger patients) was associated with more frequent joint ($P < 0.0001$) and GI involvement ($P = 0.001$). Also, elderly-onset IgAV patients had significantly more frequent renal involvement ($P < 0.0001$) with more severe presentation, i.e. more frequent haematuria ($P < 0.0001$), more frequent renal failure at baseline with eGFR <60 ml/min/1.73 m^2 ($P < 0.0001$) and higher urine protein excretion ($P < 0.0001$).

Median serum IgA ($P = 0.005$) and C-reactive protein ($P = 0.02$) levels were significantly higher in the highest quartiles. Finally, age at IgAV diagnosis positively correlated with serum IgA levels ($R = +0.32$, $P < 0.001$) and negatively to baseline eGFR ($R = -0.58$, $P < 0.001$) (Fig. 1A and B). However, annual ΔeGFR were similar for patients regardless of their age at diagnosis (Fig. 1C).

Histological features

We next analysed histological findings on skin and renal biopsies according to patients' age (Table 1). No difference on skin biopsy was noted, except for low frequency of IgA deposits within dermal vessels in older patients. Frequencies for IgA mesangial deposits, extracapillary proliferation, fibrinoid necrosis and glomerular sclerosis on renal biopsy were comparable between quartiles of age. Also, distribution of renal involvement based on Pillebout *et al.*'s classification did not differ between groups (data not shown). In contrast, tubulointerstitial lesions increased with age ($P = 0.006$).

Therapeutic management and outcome

First-line therapeutic management was similar between the four quartiles of age for the use of glucocorticoids, cyclophosphamide and colchicine (Table 2). Of the 260 patients included in the study, 127 treated patients had available follow-up data for >6 months allowing the analysis of response to therapy. Clinical response and relapse rates were similar between the four groups. Renal failure at the end of follow-up was significantly more frequent in older patients ($P = 0.02$), but the occurrence of end-stage renal disease (dialysis or transplantation) did not differ. Finally, overall and IgAV-related deaths increased with increased age at IgAV diagnosis ($P = 0.009$). IgA-related deaths included small bowel perforation during GI involvement in two cases (one patient in the third quartile and one in the fourth quartile) and multivisceral failure (three patients in the fourth quartile).

Discussion

Providing data on the impact of age on IgAV presentation and outcome is of interest since vasculitis treatments such as glucocorticoids and immunosuppressants may be more toxic in elderly patients. In the present study, we show that age significantly impacts the phenotype and prognosis of IgAV in adults, probably because of multiple aspects, including the vasculitis itself, physiological aging and concomitant comorbidities. Such aspects may impact on both disease presentation on one hand and the outcome with the risk of sequelae on the other.

IgA vasculitis patients presented distinct clinical phenotypes according to their age at diagnosis. Late-onset IgAV had significantly more frequent and severe renal involvement at diagnosis, with more frequent renal failure and higher urine protein excretion, and on renal biopsy more frequent tubulointerstitial lesions. Vasculitis, physiological aging and comorbidities, especially arterial hypertension and other underlying chronic kidney disease, may drive these lesions and explain differences in terms of presentation and prognosis according to age. Elderly patients had similar patterns of vasculitis-related glomerulonephritis to younger patients, but they showed more severe and extensive purpura and higher serum IgA and C-reactive protein levels. These data suggest that older patients had at least as active vasculitis as younger ones and that disease phenotype was not related only to physiological aging and comorbidities.

Previously, Hong *et al.* [10] reported that patients over 60 years had worse renal outcome. However, this study

Table 1 Baseline presentation of patients with IgA vasculitis according to age-diagnosis

Characteristic	Age <36 years (*n* = 65)	36 ≤ age < 52 years (*n* = 65)	52 ≤ age < 63 years (*n* = 65)	Age ≥63 years (*n* = 65)	*P*	*P* for trend
Epidemiological						
Age at diagnosis, mean (S.D.), years	25 (5)	44 (5)	58 (3)	74 (8)	—	—
Male, *n* (%)	38 (59)	43 (66)	47 (72)	36 (55)	0.19	0.92
Clinical						
Constitutional symptoms, *n* (%)	23 (35)	17 (26)	21 (32)	26 (40)	0.40	0.44
Fever	7 (11)	11 (17)	14 (32)	7 (11)	0.24	0.81
Asthenia	13 (20)	7 (11)	13 (20)	21 (32)	**0.026**	**0.04**
Weight loss	9 (14)	4 (6)	3 (5)	6 (9)	0.24	0.31
Skin involvement, *n* (%)						
Purpura	65 (100)	65 (100)	65 (100)	65(100)	1	1
Lower limb	64 (98)	65 (100)	64 (98)	65 (100)	1	1
Upper limb	22 (34)	21 (32)	27 (42)	23 (35)	0.71	0.60
Abdomen	12 (18)	12 (18)	21 (32)	18 (28)	**<0.0001**	0.08
Face	4 (6)	2 (3)	1 (2)	1 (2)	0.38	0.10
Necrosis	5 (8)	21 (32)	19 (29)	23 (36)	**0.001**	**0.001**
Haemorrhagic blisters	2 (3)	6 (9)	5 (8)	9 (14)	0.17	**0.04**
Joints involvement, *n* (%)	56 (86)	39 (60)	34 (52)	31 (48)	**<0.0001**	**<0.0001**
Arthralgia	56 (86)	39 (60)	33 (52)	31 (48)	1	1
Arthritis	11 (17)	6 (9)	3 (5)	6 (9)	0.58	0.09
Myalgia	2 (3)	1 (2)	4 (6)	3 (5)	0.25	0.744
GI involvement, *n* (%)	43 (66)	37 (58)	31 (48)	26 (40)	**0.016**	**0.001**
Abdominal pain	43 (66)	37 (58)	30 (48)	25 (40)	0.4	0.12
Diarrhoea	12 (18)	9 (14)	8 (12)	7 (11)	0.98	0.19
Ileus	3 (5)	1 (2)	6 (9)	3 (5)	0.11	0.37
Haemorrhage	13 (20)	6 (9)	11 (17)	13 (20)	**0.004**	0.05
Surgical abdomen	3 (5)	0 0	1 (2)	2 (3)	0.37	0.72
Kidney involvement, *n* (%)	29 (47)	44 (68)	52 (80)	57 (88)	**<0.0001**	**<0.0001**
Oedema	4 (6)	10 (15)	16 (25)	19 (29)	0.21	**0.02**
High blood pressure	3 (5)	6 (9)	14 (21)	17 (26)	0.07	**0.01**
Other involvement, *n* (%)						
Peripheral neuropathy	0 0	1 (2)	1 (2)	2 (3)	0.57	0.17
Orchiepidymitis	2 (3)	0 0	2 (3)	0 0	0.25	0.36
Cardiopathy	0 0	0 0	2 (3)	0 0	0.11	0.52
Intraalveolar haemorrhage	0 0	0 0	0 0	1 (2)	0.39	0.18
Laboratory parameters[a]						
Serum IgA level, median (Q1, Q3), g/l	3.2 (2.3, 4)	3.2 (2.3, 4.3)	4 (2.3, 4.3)	4.4 (3.4, 5.8)	**0.0005**	—
Serum IgA >ULN, *n* (%)	18/46 (39)	15/33 (46)	20/37 (54)	32/43 (74)	**0.007**	**0.0007**
Creatinine, median (Q1, Q3), μmol/l	70 (61, 78)	65 (63, 95)	83 (71, 110)	95 (71, 160)	**<0.0001**	—
eGFR, median (Q1, Q3), ml/min/1.73 m^2	110 (100, 128)	96 (74, 112)	86 (60, 98)	57 (40, 89)	**<0.0001**	—
eGFR <60 ml/min/1.73 m^2, *n* (%)	0 0	0 0	16 (24)	32 (49)	**<0.0001**	**<0.0001**

(continued)

Table 1 Continued

Characteristic	Age <36 years ($n = 65$)	36 ≤ age <52 years ($n = 65$)	52 ≤ age <63 years ($n = 65$)	Age ≥63 years ($n = 65$)	*P*	*P* for trend
Albumin, median (Q1, Q3), g/l	38 (34, 41)	33 (29, 39)	31 (25, 37)	31 (26, 36)	**0.0014**	–
Haematuria, *n* (%)	25 (39)	39 (62)	41 (67)	48 (77)	**<0.0001**	**<0.0001**
Proteinuria, median (Q1, Q3), g/day	0.2 (0.1, 0.5)	0.9 (0.1, 2.5)	1 (0.2, 3)	1.3 (0.4, 2.6)	**<0.0001**	–
Skin biopsy, *n* (%)	64/65 (99)	51/65 (78)	53/65 (82)	54/65 (83)	–	–
Leukocytoclastic vasculitis	58 (91)	48 (94)	49 (92)	50 (93)	0.99	0.75
IgA deposits	56 (90)	38 (78)	30 (56)	41 (79)	0.004	**0.02**
Fibrinoid necrosis	13 (20)	14 (27)	21 (40)	11 (20)	0.07	0.57
Renal biopsy *n* (%)	20/29 (69)	40/44 (91)	43/52 (83)	41/57 (72)	–	–
IgA mesangial deposits	20 (20)	39 (98)	43(100)	40 (98)	0.66	0.71
Extracapillary proliferation	10 (50)	14 (36)	13 (30)	22 (54)	0.11	0.94
Fibrinoid necrosis	5 (25)	15 (38)	10 (23)	16 (39)	0.06	0.90
Glomerular sclerosis	8 (40)	16 (41)	8 (18)	15 (37)	0.11	0.43
median (Q1, Q3), %	13 (5, 29)	10 (5, 15)	13 (10, 20)	15 (10, 30)	0.28	–
Tubulointerstitial nephritis	4 (20)	7(18)	14 (33)	19 (46)	0.29	0.006

[a]In patient with and without renal involvement. eGFR: estimated glomerular filtration rate; GI: gastrointestinal; Q1: first quartile; Q3: third quartile; ULN: upper the limit of normal. Values in bold are significative.

had some limitations. First, patients did not have histologically proven IgAV, and second, histological data were lacking to support and explain more severe renal disease. Recently, Komatsu *et al.* [11] reported in a Japanese cohort of histologically proven IgAV that patients over 65 years presented at baseline more severe renal disease, and multivariate analysis showed that age >65 years was independently associated with renal function decline. In a retrospective Spanish study of 162 adult and children IgAV, Blanco *et al.* [12] reports that adults compared with children had more frequent and severe renal involvement supporting the hypothesis that age impacts IgAV baseline characteristics and outcome.

However, in a recent work by Hočevar *et al.* prospectively including 214 new histologically proven adult IgAV, they evaluated the role of clinical and laboratory parameters as markers predicting GI or renal involvement. Age was reported to be associated with renal involvement [odds ratio 1.02 (95% CI: 1.01, 1.04) $P = 0.023$]. However, in multivariate analysis, increasing patient age was not associated with any renal involvement nor associated with lower GI involvement [13]. In our study, besides a more severe renal disease at baseline, we did not show increased renal function decline in elderly patients, but patients' follow-up in our study was shorter than in the study by Komatsu *et al.* (<2 *vs* 4 years).

Besides physiological aging and potential comorbidities, the concept of inflammaging, defined as a chronic, sterile, low-grade inflammation, has been raised during the past decade as the long-term result of chronic physiological stimulation of the innate immune system [14]. Inflammaging is believed to accelerate many age-related diseases through the release of proinflammatory cytokines, especially IL-6 and TNF-α [12]. Importantly, the gut microbiota has been shown to have a central role in inflammaging, as it can release inflammatory products, and secretory IgA is known to play a crucial role in gut microbiota compartmentalization [15, 16]. Gut microbiota dysbiosis was reported in IgAV in children, with significant compositional and structural changes [17], but data are lacking in adults.

Given the more severe presentation and worse renal prognosis of older patients, the question of the most appropriate treatment in this population is challenging. Our findings do not support the use of less effective therapeutic strategy because of age, but considering a lower cumulative dose of glucocorticoids remains a major point in this population. In the absence of randomized controlled trials dedicated to elderly patients in IgAV, data from other vasculitis could provide important insights. In ANCA-associated vasculitis, an induction regimen limiting glucocorticoid exposure with fixed low-dose intravenous cyclophosphamide pulses showed reduction of severe adverse events in comparison with conventional therapy, without affecting the remission and relapse rates. Such a strategy could be beneficial in older patients with IgAV [18].

FIG. 1 Correlation between age at IgAV diagnosis and baseline serum IgA level (**A**), eGFR (**B**), and annualized ΔeGFR during follow-up (**C**)

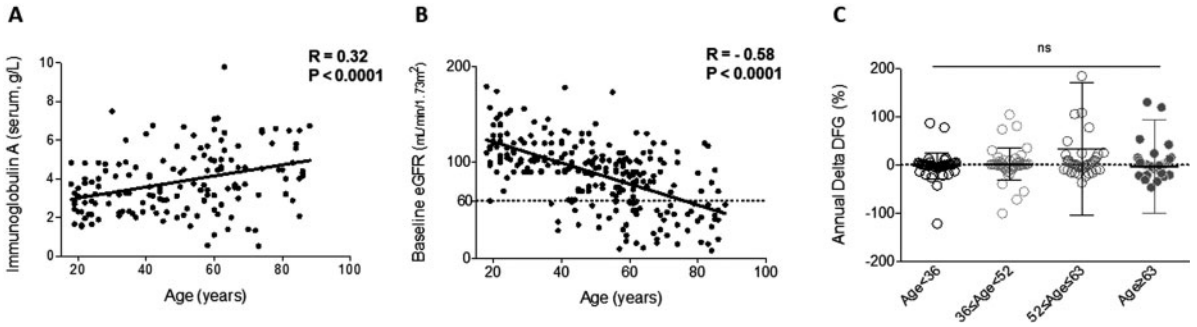

TABLE 2 Treatment and outcome of IgAV patients according to age at diagnosis

Characteristic	Age <36 years	36 ≤ age <52 years	52 ≤ age <63 years	Age ≥63 years	*P*	*P* for trend
First line treatment, *n* (%)	51/65 (78)	47/65 (72)	47/65 (72)	49/65 (75)	0.89	0.70
Oral corticosteroids, *n* (%)	41 (80)	37 (79)	39 (82)	45 (91)	0.30	0.10
Cyclophosphamide and corticosteroids, *n* (%)	9 (18)	9 (19)	11 (23)	6 (12)	0.55	0.62
Colchicine, *n* (%)	11 (22)	14 (30)	6 (13)	9 (18)	0.22	0.31
Clinical response, *n* (%)[a]						
Partial response	13/37 (46)	7/30 (23)	11/29 (38)	9/31 (29)	0.60	0.89
Complete response	19 (51)	15 (50)	12 (41)	15 (48)	0.78	0.50
No response	5 (13)	8 (27)	6 (20)	7 (23)	0.59	0.45
Follow-up, median (Q1, Q3), months	14 (7, 34)	21 (7, 50)	17 (12, 36)	17 (9, 37)	0.69	
Relapse, *n* (%)						
Minor relapse	5/30 (17)	4/29 (14)	5/32 (16)	1/28 (4)	0.41	0.18
Major relapse	3/30 (10)	1/29 (3)	3/32 (9)	2/28 (7)	0.77	0.90
No relapse	22/30 (73)	24/29 (83)	24/32 (75)	25/28 (89)	0.39	0.23
Renal outcome at last fallow-up						
Creatinine, median (Q1, Q3), μmol/l	70 (63, 80)	70 (65, 87)	81 (73, 106)	86 (69, 115)	**0.04**	—
eGFR, median (Q1, Q3), ml/min/1.73 m^2	109 (99, 120)	97 (77, 111)	71 (59, 90)	69 (47, 95)	**<0.0001**	—
End of follow-up eGFR <60 ml/min/1.73 m^2	1/43 (2)	7/47 (15)	12/41 (29)	18/48 (37)	0.002	**<0.0001**
ESRD (transplantation or dialysis)	0/53 0	5/54 (9)	0/53 0	3/54 (5)	0.03	0.52
IgAV global death, *n* (%)	0/53 0	0/54 0	2/51 (4)	6/55 (11)	**0.007**	**0.001**
IgAV-related death, *n* (%)	0/53 0	0/54 0	1/51 (4)	4/55 (7)	**0.04**	**0.009**

[a]Of the 260 patients, 127 patients were treated and had available follow-up data for >6 months. eGFR: estimated glomerular filtration rate; ESRD: end-stage renal disease; Q1: first quartile; Q3: third quartile.

Finally, limitations in our study are the lack of data on concomitant comorbidities and missing data for duration of treatment and cumulative dose of glucocorticoids, which does not allow us to perform multivariate analysis including such variables. The other main limitation is that mortality rate was not controlled for age. It is well established that renal function declines with age for several reasons, including comorbidities, which could explain the more severe renal disease at diagnosis with lower eGFR and increased proteinuria. However, as indicated previously, additional data strongly suggest also a role for the vasculitis itself.

Overall, aging negatively impacts the severity and prognosis of IgAV in adults. Younger patients have more frequent joint and gastrointestinal involvement, while old patients display more frequent and severe purpura and glomerulonephritis. Concomitant comorbidities and physiological aging probably play a role.

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Data availability statement

Original data may be made available by contacting the corresponding author (A.A.-V.).

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