Année 2023/2024 N°

Thèse

Pour le

DOCTORAT EN MEDECINE

Diplôme d'État

par

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Née le 26 août 1996. à Coulommiers (77)

TITRE

Influence du taux sérique d'Immunoglobulines A sur la présentation clinique, biologique et le pronostique de la Vascularite à IgA

Présentée et soutenue publiquement le 25 avril 2024 devant un jury composé de :

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Clinique, Faculté de Médecine –Tours

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RESUME :

La vascularite à Immunoglobuline A (VIgA) est une vascularite touchant les petits vaisseaux par dépôts de complexe immuns. Ces complexes immuns sont formés d'Immunoglobulines A (IgA). Les facteurs de mauvais pronostics connus sont l'âge, le sexe, et l'atteinte rénale à type de glomérulonéphrite identique à la néphropathie à IgA. Étant donné le rôle central des IgA dans la physiopathologie de la maladie, nous avons étudié si un taux sérique d'IgA supérieur à la norme au diagnostic influait sur la présentation clinico-biologique ou le pronostic de cette vascularite.

Nous avons étudié les données rétrospectives de patient.es adultes atteint.es de vascularite de la cohorte multicentrique française « IGAVAS ». Ce registre est constitué de 260 patient.es ; 159 patient.es ont été inclus dans l'étude (données manquantes chez 101 patient.es). Les comparaisons cliniques et biologiques ont été faites en fonction du taux sérique d'IgA (normal *versus* augmenté). En analyse univariée, les patient.es ayant un taux d'IgA augmenté étaient plus âgé.es 56 *vs* 44 ans SD, p=0,0003). Ils présentent aussi une atteinte cutanée plus sévère : lésions de type bulles hémorragiques 15,3% (n=13) vs 1,4% (n=1) (p=0.002), plus fréquemment un purpura au niveau de la muqueuse digestive 50% (n=11) vs 18,8% (n=6) (p=0,02), une atteinte rénale plus sévère (p=0.04) 28,2% (n=24) vs 12,2% (n=9) à type de néphrite interstitielle, 42 ,5% (n=17) vs 18,4% (n=7) (p=0,02). En en analyse multivarié, en ajustant sur l'âge, toutes les différences citées disparaissaient, excepté pour la présence de bulles hemorragique.

En conclusion, le taux sérique d'IgA ne semble pas influencer de façon majeur le pronostic des patient.es mais peut jouer sur la présentation clinique. L'âge apparaît lui comme le principal facteur pronostic.

Mots clés : vascularite à IgA, adulte, taux d'IgA, prognostique, presentation clinique, âge

Abstract:

Background:

Immunoglobulin A vasculitis (IgAV) is a vasculitis affecting small vessels with IgA1 dominant immune deposition. IgAV often follows a mucosal infection (lung or digestive) and leads to purpura, joint pain and kidney or digestive tract involvement. To date, prognostic factors are not enough powerfull to predict patients'outcomes. Given that IgA are highly implicated in the pathophysiology of the disease, we hypothesized that global serum IgA levels could impact the clinical presentation and/or prognosis of IgAV patients.

Objectives:

This study aimed to compare the impact of IgA serum level on the clinical presentation and/or prognosis of IgAV patients.

Methods:

We studied data of the retrospective multicenter French cohort (IGAVAS) including histologically proven IgA vasculitis. Patients were divided in 2 groups, patients with increased serum IgA level (>3.5 g/l) and patients with normal serum IgA level.

Results:

Out of the 260 patients screened, 159 patients were analyzed (missing data n=101). Of them, 74 patients presented increased value of serum IgA and 85 patients were within the ranges.

Patients with higher IgA levels were older 56 *vs.* 44 years (p=0.0003), presented with more severe skin involvement: hemorrhagic blisters 15% *vs.* 1% (p=0.002) , more gastro-intestinal mucosal purpura 50% *vs.* 19% (p= 0,02), more serious kidney failure defined as eGFR< 60 ml/min/1.73m^2: 28% *vs.* 12% (p=0.04) and more frequent tubulo-interstitial lesions on renal biopsy 43% *vs.* 18% (p=0.02).

In the multivariate analysis, most of these results lost their significant value except for the age 1.05 CI (1.02, 1.09), p=0.005 and the hemorrhagic blisters OR 11.1 CI (1.89, 21.2), p= 0.028.

Conclusion: Taken together, our results suggest that a higher IgA serum level is not associated with a more severe disease but is rather age-related.

Key words: IgA vasculitis, adult, serum IgA levels, prognosis, clinical presentation, age

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SERMENT D'HIPPOCRATE

En présence des enseignants et enseignantes
de cette Faculté,
de mes chers condisciples
et selon la tradition d'Hippocrate,
je promets et je jure d'être fidèle aux lois de l'honneur
et de la probité dans l'exercice de la Médecine.

Je donnerai mes soins gratuits aux indigents,
et n'exigerai jamais un salaire au-dessus de mon travail.

Admis(e) dans l'intérieur des maisons, mes yeux
ne verront pas ce qui s'y passe, ma langue taira
les secrets qui me seront confiés et mon état ne servira pas
à corrompre les mœurs ni à favoriser le crime.

Respectueux(euse) et reconnaissant(e) envers mes Maîtres,
je rendrai à leurs enfants
l'instruction que j'ai reçue de leurs parents.

Que les hommes et les femmes m'accordent leur estime
si je suis fidèle à mes promesses.
Que je sois couvert(e) d'opprobre
et méprisé(e) de mes confrères et consœurs
si j'y manque.

Remerciements

Merci au service de médecine interne et d'immunologie clinique du CHU de Tours pour la bienveillance et la qualité de la formation de la meilleur spécialité médicale du monde.

Merci particulièrement à Monsieur le Professeur François Maillot de m'avoir fait l'honneur de présider ce jury. Merci également de votre gentillesse permanente et de m'avoir toujours fait sentir à ma place dans votre service. Je n'ai jamais travailleé avec un chef de service plus chaleureux à mon égard que vous.

A Madame le Docteure Alexandra Audemard-Verger d'avoir été ma directrice de thèse. Ce fût un plaisir de travailler avec vous, merci pour votre accompagnement et votre entrain.

A Madame le Docteure Nicole Ferreira-Maldent d'avoir accepté de faire partie du jury de ma thèse. Toujours de bonne humeur et toujours rayonnante, un bonneur de travailler avec toi.

A Madame Le Docteure Sophie Leducq, d'avoir participé à mon jury de thèse.

A tous mes co-internes rencontrés sur tous ces semestres, avec lequels j'ai partagé toutes ces péripéties en stage, les hauts, les bas, les fous rires, avec lesquels on s'est serré les coudes jusqau'au bout. Je vous souhaite le meilleur pour la suite. A ceux, avec qui nous avons désormais lié des amitiés pour longemtps j'espère, merci de votre soutient, merci de votre présence et je sais que je peux toujours compter sur vous.

A mon groupe de lycée, on est désormais loin des uns et des autres, mais on sait toujours se retrouver heureusement !

Et enfin à ma famille, sans qui tout ceci n'aurait jamais été possible. Merci pour vos sacrifices, vous avez tous toujours crus en moi, je me suis dépassée et même au-delà. Grâce à vous, rien n'a jamais été impossible.

Note spécial à ma sœur, la plus incroyable des soeurs, c'est bientôt ton tour !

Table des matières

Impact of serum IgA levels on the presentation and prognosis of adult IgA vasculitis

Inès Nasri[1], Antoine Hankard, Alexandre Boissais[1 ;2], Chloé Giret[1 ;2], Anne Murarasu[1 ;2], Evangeline Pillebout[3], Benjamin Terrier[4], François Maillot[1 ;2], Alexandra Audemard-Verger[1 ;2] .

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Abstract:

Background:

Immunoglobulin A vasculitis (IgAV) is a vasculitis affecting small vessels with IgA1 dominant immune deposition. IgAV often follows a mucosal infection (lung or digestive) and leads to purpura, joint pain and kidney or digestive tract involvement. To date, prognostic factors are not powerful enough to predict patients' outcomes. Given that IgA are highly implicated in the pathophysiology of the disease, we hypothesized that global serum IgA levels could impact the clinical presentation and/or prognosis of IgAV patients.

Objectives:

This study aimed to compare the impact of IgA serum level on the clinical presentation and/or prognosis of IgAV patients.

Methods:

We studied the data of the retrospective multicentre French cohort (IGAVAS) including histologically proven IgA vasculitis. Patients were divided into 2 groups, patients with increased serum IgA level (>3.5 g/l) and patients with normal serum IgA level.

Results:

Out of the 260 patients screened, 159 patients were analysed (missing data n=101). Among them, 74 patients presented with increased serum IgA value and 85 patients were within the ranges.

Patients with higher IgA levels were older, 56 *vs.* 44 years (p=0.0003), presented with more severe skin involvement: haemorrhagic blisters 15% *vs.* 1% (p=0.002), more gastro-intestinal mucosal purpura 50% *vs.* 19% (p= 0,02), more serious kidney failure defined as eGFR< 60 ml/min/1.73m^2: 28% *vs.* 12% (p=0.04) and more frequent tubulo-interstitial lesions on renal biopsy 43% *vs.* 18% (p=0.02).

In the multivariate analysis, most of these results lost their significant value except for age 1.05 CI (1.02, 1.09), p=0.005 and haemorrhagic blisters, OR 11.1 CI (1.89, 21.2), p= 0.028.

Conclusion: Taken together, our results suggest that a higher IgA serum level is not associated with more severe disease but is more so age-related.

Key words: IgA vasculitis, adult, serum IgA levels, prognosis, clinical presentation, age
Word counts : 3277 ; Figure: 0 ; Table: 3
Conflict of Interests: none

Introduction:

Immunoglobulin A vasculitis (IgAV), formerly called Henoch-Schönlein purpura, is a vasculitis affecting small vessels (1). IgAV often follows on from a mucosal infection (lung or digestive) and leads to purpura, joint pain and kidney or digestive tract involvement (2). The development of digestive involvement, with risk of gastro-intestinal (GI) perforation or severe kidney damage, are key factors in the outcome of this disease. The dentification of new prognostic markers is a major challenge for guiding patient management. Indeed, the natural course of the disease is quite unpredictable, ranging from spontaneous recovery to the development of chronic glomerulonephritis with end-stage renal failure requiring extra-renal purification. To date, known factors of poor outcomes in IgAV are gender, age, renal function impairment and proteinuria level at presentation and, on renal biopsy, the degree of interstitial fibrosis, percentage of sclerotic glomeruli, and presence of glomeruli with fibrinoid necrosis (3–6). However, some of these factors are more likely markers of the severity of the disease and are not powerful enough to predict patient outcome.

IgA1 Immune complex including IgA1 deposition in skin, kidneys, joints and in the GI tract are the cornerstone of the disease in IgAV pathophysiology (1). IgA is the second most frequently produced immunoglobulin by plasma cells in the mucosa. There are predominant immunoglobulins in the mucosa, and their role is to protect the host against pathogens (7). At IgAV diagnosis, serum IgA level is increased in around half of patients (8). In IgAV patients, a particular IgA subclass named IgA1 are galactose-deficient and are responsible for immune complex deposition in non-lymphoid organs or tissues (1). Galactose-deficient IgA1 behave like auto antigens and further activate the adaptative immune system.

Given that IgA are highly implicated in the pathophysiology of the disease, we hypothesized that global serum IgA levels could impact the clinical presentation and/or prognosis of IgAV.

In this large, multicentre, retrospective study, we compared the baseline clinical and laboratory presentation and outcome of 159 adult IgA patients according to their serum IgA levels at diagnosis (normal *vs.* increased).

Methods:

Data

Our data were obtained from a French multicentre retrospective study on the clinical spectrum of IgAV and efficacy of treatments in a French patient population (IGAVAS study) (9). Inclusion criteria were patient aged >18 years old, diagnosis of IgAV between January 1990 and January 2015. The diagnosis of IgAV was retained if patients presented with purpura, histologically proven small vessel vasculitis and IgA deposits, and involvement of at least one organ from among the kidneys, joints, or gastro-intestinal tract. The patient's clinical and laboratory characteristics, treatments and outcome were compared according to their serum IgA level at disease onset. The study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the Institutional Review Board (Hopital Européen Georges Pompidou, Paris).

Data include general characteristics (age, fever, asthenia…) and details of clinical features such as type and localization of skin lesions, and gastrointestinal and joint symptoms. Laboratory parameters selected were creatinine level, albumin level, C-reactive protein (CRP) level, fibrinogen levels, and immunoglobulin A levels, presence of haematuria and proteinuria. Renal failure was described as an eGFR of < 60ml/min/1.73m2, assessed using the Modified Diet in Renal Disease equation. Renal histologic findings were classified according to Pillebout's classification (19). We also compiled data on the response to therapy, the type of treatment and relapses as previously described (9).

Statistical analysis

Descriptive analysis of the data was performed. Data were expressed as the mean ±SD for normally distributed continuous variables, as median (IQR) for non-normally distributed variables, and as percentages and frequencies for categorical variables. A comparison between patients with high IgA levels and those without was performed using the $\chi 2$ test, Fischer's exact test, Student's t test and Mann-Whitney U test for the univariate analyses, as appropriate. Elevated IgA levels were defined by a concentration higher than 3.5 g/L. Using high levels of IgA as the dependent variable, logistic regression models were employed. The multivariate analysis concerned patients with kidney involvement who had a renal biopsy. Variables of clinical interest were included in the multivariable model. They are retained to explain the

outcome if $p<0.05$. To be significant, we considered a p-value equal or inferior to 0.05. All statistical analyses were performed using GraphPad Prism version 8.0.

Results

Out of the 260 patients screened, 159 patients were included (missing data n=101). 85 of those patients had higher IgA levels (≥3.5g/L) and 74 had normal IgA levels (< 3.5g/L).

Univariate analysis

Baseline presentation according to IgA serum level

The clinical characteristics between patients presenting with increased (IgAI group) and normal (IgAN) IgA serum level are gathered in **Table 1**. In the IgAI group, 63% were male (n=53 patients, and 58% were male (n= 43) in the IgAN group, p=0.52. Patients in the IgAI group were older, 56 *vs*. 44 years, p< 0.0003. Regarding general symptoms, such as fever and asthenia, no difference was observed. No differences in purpura extension, neither in terms of skin histological findings such as IgA deposits (79% *vs.* 82%) nor leukocytoclastic vasculitis (91% *vs.* 90%) were observed. Patients in the IgAI group tended to present more skin necrosis (34% *vs*. 20%), p=0.0516. Haemorrhagic blisters were significantly more frequent (15% *vs.* 1%), p-value<0.002 in the IgAI group. Regarding renal involvement, there was no difference in frequency between the 2 groups 68% (n=58) *vs*. 64% (n=44), p= 0.53. Analysis of laboratory parameters showed that creatininemia levels were higher in the IgAI group: 81 µmol/l *vs.* 75 µmol/l (p=0.04). Rate of microscopic haematuria or proteinuria were not different in the two groups. Analysis of renal biopsies showed no differences in the two groups except for tubulo-interstitial lesions which were more frequent in the IgAI group, 43% (n=17) *vs*. 18% (n=7), p=0.02.

Besides purpura of the gastro-intestinal tract (GIT) mucosa, (p =0.02) GIT involvement was not more prevalent in any group. No differences were observed in terms of joint symptoms either, 59% *vs*. 70% (52) p=0.13.

Outcome according to IgA serum level

We thus analysed the different therapeutic regimens in the two groups in order to analyse patients' outcomes **(Table 2).** No differences in the use of glucocorticosteroids, colchicine, and angiotensin-converting enzyme inhibitors were noticed. While there was no difference regarding the use of oral Disease-Modifying AntiRheumatic Drugs (DMARDs) such

as azathioprine and methotrexate, we noticed greater use of cyclophosphamide the IgN group (8% n=5 *vs.* 21% n=12, p <0.04).

Outcome at 6 and 12 mouths was not influenced by serum IgA levels. At 12 months, 26% (n=10) of the IgAI patients relapsed versus 18% (n=7) of the IgAN patients, p=0.65. There was no more risk of acute kidney failure in the 12 months after the diagnosis, 40% (27) vs. 32% (21), p= 0.37, however we noted a tendency to persistent kidney injuries in the next 12 months for IgAI patients (n=12, 19% *vs*. 5, 8%, p=0.07).

Multivariate analysis

We then aimed to explore whether the different clinical presentations of IgA vasculitis that were significant or tended to be significant, were influenced by elevated serum IgA levels. The age difference was still significant, the odds ratio (OR) is 1.05 with a confidence interval (CI) of 1.02, 1.09, p=0.005 whereas there was no difference in terms of sex, OR 1.10, CI (0.37, 3.39), p=0.9, skin lesions and skin necrosis, OR 0.88, CI (0.38, 2.07), p=0.8 except for haemorrhagic blisters, OR 11.1 CI (1.89, 21.2), p= 0.028. We also did not observe a significant difference for the kidneys, in terms of tubulointerstitial nephritis, OR 2.06, CI (0.67, 6.66) p=0.2, or for GIT involvement , OR 0.64, CI (0.21, 1.97), p= 0.4.

Discussion

Altogether our results show that IgA serum levels do not impact the clinical presentation of adult patients with IgAV.

In a first step, univariate analysis between the two groups of patients according to their serum level of IgA showed that patients with increased IgA levels had more severe skin involvement (haemorrhagic blisters) and more severe renal involvement (impaired renal function and more tubulointerstitial lesions on renal biopsy).

In a second step, all the differences in the 2 groups (IgAN and IgAI) that emerged in univariate analysis were erased in multivariate analysis, except for the increased frequency of haemorrhagic blisters. We therefore hypothesised that the other differences between the two groups, i.e. the more severe renal and skin involvement, could be explained by the impact of age. It is noteworthy that our group has recently described the influence of age on the initial phenotype and prognosis of IgAV patients. In this study (5), which included 260 patients with IgAV, the elderly group (≥ 63 years old) had a more severe baseline vasculitis presentation in terms of both skin and renal involvement. In the elderly patients, purpura was more extensive, and more severe (necrosis). Renal involvement was more frequent and more severe with higher urine protein excretion, more renal failure and more tubulointerstitial lesions on renal biopsy. In a Japanese study published in 2018, although age is still associated with a more prevalent and less favourable outcome for IgAV nephritis, they observed that elderly patients (≥65 years old) had more frequent crescentic glomerulonephritis than younger adult patients (<65 years old). They also observed more hypertension, less remissions and a higher creatininemia levels (50% increase) during 4 years of follow-up (10).

Immunoglobulin serum levels are influenced by various factors in healthy patients, such as sex, smoking or alcohol use (11). Serum IgA levels, like other immunoglobulin levels, change over a life time. IgA levels rise during childhood and adulthood, stabilise around the fourth decade and then fall by the sixth decade (12).

IgA exists in 2 isoforms, IgA1 and IgA2, and as monomers or J chain containing polymers. In serum, 90% of the IgA is IgA1 monomer. IgAV are characterized by the deposition of poorly O-galactosylated IgA1 and only those latter immunoglobulins have been involved in

the pathophysiology of IgAV. Of note, in this study, whole serum IgA levels, including both IgA1 and 2, and both poorly and normal O-galactosylated IgA1, were monitored.

Recent studies have highlighted the prognostic value of poorly O-galactosylated IgA1 serum levels. Sunderkotter and colleagues have shown, in a small series including 16 adult IgAV patients, that the average galactodeficient-IgA1 concentration in serum was significantly higher in systemic IgAV than in skin-limited IgAV (13). Pillebout *et al.* have shown in a prospective cohort of paediatric IgAV patients that galactodeficient-IgA1 concentration in serum was correlated to severity of the disease and more precisely to kidney involvement (14).

We can therefore hypothesise that only serum galactodeficient IgA levels, and not overall IgA levels, have prognostic value in IgA vasculitis. A future study could investigate the prognostic value of serum levels of galactose-deficient IgA1 patients in our cohort. However this assay is not routinely performed, and the scope of these results would not be easily useful in medical practice.

The limit of this study is the use of a retrospective cohort, with missing data especially on cofounding factors such comorbidities.

One of the strengths of this study is the large number of patients included in the cohort, and its methodology using a multivariate analysis. Another strength is also its originality, since to date no other study has investigated a simple and available biomarker which is serum IgA levels on patient clinical presentation and/or prognosis.

Conclusion:

Altogether our results show that serum levels do not influence the prognosis of patients with IgAV but can change the clinical presentation.

Table 1. Baseline characteristics of patients at diagnosis according to IgA serum level (normal or increased). Univariate analysis.

Clinical features	IgAI n (%)	IgAN N ()%	p value
			-
Male (%)	53 (63)	43 (58)	-
Mean age (years)	56	44	-
General signs	33 (39)	28 (38)	0.8986
Fever	16 (19)	13 (18)	0.8379
Asthenia	25 (29)	16 (22)	0.2627
Skin involvement			-
Upper limbs	85 (100)	73 (99)	0.2823
Lower limbs	39 (46)	27 (38)	0.289
Abdomen	28 (33)	19 (26)	0.3166
Face	4 (5)	2 (3)	0.5085
Necrosis	29 (34)	15 (20)	0.0516
Haemorrhagic blisters	**13 (15)**	**1 (1)**	**0.002**
Leukocytoclastic vasculitis	71 (91)	61 (90)	0.79
IgA deposits in vessel walls	61 (79)	54 (82)	0.7
Joint involvement	50 (59)	52 (70)	0.13
Arthritis	12 (24)	7 (14)	0.17
Kidney involvement	58 (68)	47 (64)	0.53
AHT	11 (19)	11 (23)	0.58
Lower limb oedemas	16 (28)	12 (26)	0.81
Macroscopic haematuria	7 (12)	3 (6)	0.32
Renal biopsy	40 (69)	38 (81)	0.17
Endocapillary glomerulonephritis	17 (43)	19 (50)	0.51
Extra-capillary proliferation	20 (50)	14 (37)	0.24
Necrosis	21 (27)	16 (24)	0.53
Tubulointerstitial nephritis	**17 (43)**	**7 (18)**	**0.02**
IgA mesangial deposits	40 (100)	38 (100)	>0.99
Creatinine median μmol/L	**81**	**75**	**0.04**
eGFR<60 ml/min/1.73 m2	**24 (28)**	**9 (12)**	**0.02**
24h urine protein median (g/day)	0.80	0.54	0.35
Microscopic haematuria	31 (44)	33 (40)	0.74
GI involvement	44 (52)	48 (52)	0.10
Nausea, vomiting	6 (14)	12 (25)	0.17
Diarrhoea	12 (27)	11 (23)	0.63
Paralytic ileus	5 (11)	6 (13)	0.87
Gastrointestinal bleeding	17 (39)	14 (29)	0.34
Acute abdomen	4 (9)	2 (4)	0.34
Thickened walls	22 (73)	19 (56)	0.15
Erythematous mucosa	8 (36)	11 (33)	0.82
Mucosa petechiae	**11 (50)**	**6 (19)**	**0.02**
Erosion, endoscopically	12 (55)	17 (52)	0.83
Laboratory parameters			-
CRP mean (mg/l)	50	39	0.18
Fibrinogen mean (g/l)	4.8	4.7	0.79
Albumin mean (g/l)	32	33	0.87
IgG mean (g/l)	**12.1**	**10.0**	**0.001**
IgM mean (g/l)	0.8	0.9	0.47
Anti-nuclear antibodies	15 (19)	13 (18)	>0.99

IgAI: Patient with IgA Levels above 3.5g/L
IgAN: patient with normal IgA levels
eGFR: estimated Glomerular Filtration rate
CRP: C-reactive protein

Table 2. Results of the univariate analysis for therapeutics and outcome

	IgAI n(%)	IgAN n(%)	p value
Treatment			
Treated patients	66 (78)	56 (76)	0.85
Methylprednisolone bolus	19(29)	17 (32)	>0.99
Oral glucocorticosteroids	58 (88)	46 (82)	0.45
Cyclophosphamide	**5 (8)**	**12 (21)**	**0.04**
Azathioprine	5 (8)	5 (9)	>0.99
Methotrexate	0 (0)	0 (0)	>0.99
Colchicine	14 (21)	15 (27)	0.53
Angiotensin-converting-enzyme inhibitors/ Angiotensin II receptor blocker	21 (33)	16 (29)	0.70
Outcome			
Relapses	10 (26)	7 (18)	0.59
Treatment response at 6 months	43 (80)	40 (756)	0.65
Treatment response at 12 months	28 (70)	36 (84)	0.19
Treatment response during the 12 months	46 (74)	46 (77)	0.83
Acute kidney injury in the 12 months*	27 (40)	21 (32)	0.37
Kidney failure within the 12 months#	12 (19)	5 (8)	0.07

IgAI: Patient with IgA levels above 3.5g/L
IgAN: patient with normal IgA levels

*defined as an eGFR of ＜60 ml/minute/1.73 m2

defined as no decrease in the eGFR of more than 20% from baseline

Table 3. Multivariate analysis

Characteristic	OR[1]	95% CI[1]	p-value
Age	1.05	1.02, 1.09	**0.005**
Male	1.10	0.37, 3.39	0.9
Skin necrosis	0.88	0.38, 2.07	0.8
Haemorrhagic bullous skin lesions	11.1	1.89, 21.2	**0.028**
Tubulointerstitial nephritis	2.06	0.67, 6.66	0.2
GIT involvement	0.64	0.21, 1.97	0.4

[1]OR = Odds Ratio, CI = Confidence Interval, GIT: gastro-intestinal tract

References

1. Song Y, Huang X, Yu G, Qiao J, Cheng J, Wu J, et al. Pathogenesis of IgA Vasculitis: An Up-To-Date Review. Front Immunol. 2021;12:771619.
2. Xu L, Li Y, Wu X. IgA vasculitis update: Epidemiology, pathogenesis, and biomarkers. Front Immunol. 2022;13:921864.
3. Baud KL, Hankard A, Ramdani Y, Maisons V, Pillebout E, Augusto JF, et al. Impact of gender on baseline presentation and outcome in adult IgA vasculitis. Rheumatology (Oxford). 4 Dec 2023;kead648.
4. Pillebout E, Thervet E, Hill G, Alberti C, Vanhille P, Nochy D. Henoch-Schonlein Purpura in Adults: Outcome and Prognostic Factors. Journal of the American Society of Nephrology. May 2002;13(5):1271.
5. Audemard-Verger A, Pillebout E, Baldolli A, Gouellec NL, Augusto JF, Jourde-Chiche N, et al. Impact of aging on phenotype and prognosis in IgA vasculitis. Rheumatology (Oxford). 1 Sept 2021;60(9):4245-51.
6. Shi D, Chan H, Yang X, Zhang G, Yang H, Wang M, et al. Risk factors associated with IgA vasculitis with nephritis (Henoch–Schönlein purpura nephritis) progressing to unfavorable outcomes: A meta-analysis. PLoS One. 1 oct 2019;14(10):e0223218.
7. Wines BD, Hogarth PM. IgA receptors in health and disease. Tissue Antigens. August 2006;68(2):103-14.
8. Pillebout E, Thervet E, Hill G, Alberti C, Vanhille P, Nochy D. Henoch-Schönlein Purpura in adults: outcome and prognostic factors. J Am Soc Nephrol. May 2002;13(5):1271-8.
9. Audemard-Verger A, Terrier B, Dechartres A, Chanal J, Amoura Z, Le Gouellec N, et al. Characteristics and Management of IgA Vasculitis (Henoch-Schönlein) in Adults: Data From 260 Patients Included in a French Multicenter Retrospective Survey. Arthritis Rheumatol. sept 2017;69(9):1862-70.
10. Komatsu H, Fujimoto S, Maruyama S, Mukoyama M, Sugiyama H, Tsuruya K, et al. Distinct characteristics and outcomes in elderly-onset IgA vasculitis (Henoch-Schönlein purpura) with nephritis: Nationwide cohort study of data from the Japan Renal Biopsy Registry (J-RBR). PLoS One. 8 May 2018;13(5):e0196955.
11. Khan SR, Chaker L, Ikram MA, Peeters RP, van Hagen PM, Dalm VASH. Determinants and Reference Ranges of Serum Immunoglobulins in Middle-Aged and Elderly Individuals: a Population-Based Study. J Clin Immunol. Nov 2021;41(8):1902-14.
12. Buckley CE, Dorsey FC. The effect of aging on human serum immunoglobulin concentrations. J Immunol. Oct 1970;105(4):964-72.
13. Neufeld M, Molyneux K, Pappelbaum KI, Mayer-Hain S, von Hodenberg C, Ehrchen J, et al. Galactose-deficient IgA1 in skin and serum from patients with skin-limited and systemic IgA vasculitis. J Am Acad Dermatol. Nov 2019;81(5):1078-85.
14. Pillebout E, Jamin A, Ayari H, Housset P, Pierre M, Sauvaget V, et al. Biomarkers of IgA vasculitis nephritis in children. PLoS ONE [Internet]. 2017 [cited 27 March 2024];12(11). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5708800/

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27 pages –3 tableaux – 0 figures – 0 graphiques

Résumé : La vascularite à Immunoglobuline A (VIgA) est une vascularite touchant les petits vaisseaux par dépôts de complexe immuns. Ces complexes immuns sont formés d'Immunoglobulines A (IgA). Les facteurs de mauvais pronostics connus sont l'âge, le sexe, et l'atteinte rénale à type de glomérulonéphrite identique à la néphropathie à IgA. Étant donné le rôle central des IgA dans la physiopathologie de la maladie, nous avons étudié si un taux sérique d'IgA supérieur à la norme au diagnostic influait sur la présentation clinico-biologique ou le pronostic de cette vascularite. Nous avons étudié les données rétrospectives de patient.es adultes atteint.es de vascularite de la cohorte multicentrique française « IGAVAS ». Ce registre est constitué de 260 patient.es ; 159 patient.es ont été inclus dans l'étude (données manquantes chez 101 patient.es). Les comparaisons cliniques et biologiques ont été faites en fonction du taux sérique d'IgA (normal *versus* augmenté). En analyse univariée, les patient.es ayant un taux d'IgA augmenté étaient plus âgé.es 56 *vs* 44 ans SD, p=0,0003). Ils présentent aussi une atteinte cutanée plus sévère : lésions de type bulles hémorragiques 15,3% (n=13) vs 1,4% (n=1) (p=0.002), plus fréquemment un purpura au niveau de la muqueuse digestive 50% (n=11) vs 18,8% (n=6), (p=0,02), une atteinte rénale plus sévère (p=0.04) 28,2% (n=24) vs 12,2% (n=9) à type de néphrite interstitielle, 42 ,5% (n=17) vs 18,4% (n=7) (p=0,02). En en analyse multivarié, en ajustant sur l'âge, toutes les différences citées disparaissaient, excepté pour la présence de bulles hémorragique. En conclusion, le taux sérique d'IgA ne semble pas influencer de façon majeur le pronostic des patient.es mais peut jouer sur la présentation clinique. L'âge apparaît lui comme le principal facteur pronostic.

Mots clés : vascularite à IgA, adulte, taux d'IgA, prognostique, présentation clinique, âge

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Date de soutenance : 25 avril 2024