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ORIGINAL ARTICLE

Increased renal damage in hypocomplementemic patients with ANCA-associated vasculitis: retrospective cohort study

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Abstract

Introduction The complement system has an important role in the pathogenesis of vasculitis associated with antineutrophilic cytoplasmic antibody (AAV) mainly at the level of the kidneys because patients with complement deposits on the glomerular basal membrane present more aggressive disease compared with those with pauci-immune vasculitis.

Aim To analyze the association of hypocomplementemia with the clinical manifestations, laboratory data, renal histology, progress to renal insufficiency, and mortality of patients with AAV.

Methods Retrospective cohort study (2000–2007) included 93 patients with AAV. Hypocomplementemia is defined as having C3 values lower than 80 mg/dL or C4 values below 15 mg/dL. Demographic, statistical, clinical, hematological, serological, and histopathological characteristics of all the patients with and without diagnosis of hypocomplementemia were compared. In order to evaluate variable independence, a logistic regression analysis was used.

Results Ninety-three patients were studied of whom 63 (67.7%) had complement dosage at the moment of AAV diagnosis. Seven patients (11.1%) presented hypocomplementemia and a greater kidney involvement compared with normocomplementemic patients. Thirty renal biopsies were analyzed and 4 (13.3%) showed immunocomplex (IC) or complement deposits by an immunofluorescence test (IFT). Patients with "non-pauci-immune" AAV also presented terminal chronic renal disease (TCRD).

Conclusion There is an association between low complement and the degree of renal damage in patients with AAV. Patients with renal biopsies confirming IC and/or complement deposits showed more aggressive renal disease.

Key Points
- *The complement system has an important role in the pathogenesis of vasculitis associated to antineutrophilic cytoplasmic antibody.*
- *The studies in murine models confirming the complement activation by alternative pathway and particularly the receptor C5a (C5aR) is necessary for the development of glomerulonefritis.*
- *Complement deposit observed in the renal biopsies of patients diagnosed with AAV was correlated to greater kidney damage, greater proteinuria and major disease activity compared to patients diagnosed with typical pauci-immune vasculitis.*
- *The presence of hypocomplementemia at the onset of the disease was also associated with a greater organ involvement, poor prognosis and greater mortality.*

Keywords ANCA vasculitis · Complement · Kidney involvement · Prognosis

Introduction

The nature of the pauci-immune lesions typical of vasculitis associated with antineutrophilic cytoplasmic antibody (ANCA) [1] has generated the concept that complement does not play a role in the pathogenesis of this disease [2]. However, the fact that the studies in murine models confirming the complement activation by alternative pathway and particularly the receptor C5a (C5aR) is necessary for the development of glomerulonephritis made the researchers to re-evaluate the physiopathogenic role played in ANCA-associated vasculitis (AAV) [3, 4]. Complement deposit

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observed in the renal biopsies of patients diagnosed with AAV was correlated to greater kidney damage, greater proteinuria, and major disease activity compared with patients diagnosed with typical pauci-immune vasculitis [5]. The presence of hypocomplementemia at the onset of the disease was also associated with a greater organ involvement, poor prognosis, and greater mortality [6].

Our hypothesis considers that there exists greater progression to terminal renal disease and higher morbidity and mortality in hypocomplementemic patients with AAV. Our primary aim was to analyze the correlation of hypocomplementemia with the clinical manifestations, laboratory findings, progression to renal insufficiency, and mortality of patients with diagnosis of ANCA-associated vasculitis. Our secondary aim was to evaluate the renal histopathological findings and the correlation with the renal function prognosis in patients with and without hypocomplementemia.

Material and methods

Patients

A retrospective cohort study was performed including patients with AAV diagnosis evaluated in a reference center of Rheumatology in Hospital San Martín of La Plata, Buenos Aires Province, Argentina, through the years 2000 and 2017. The patients included in the present study were those with ANCA-associated vasculitis diagnosis and who satisfied the inclusion criteria of ACR 1990 or the Chapel Hill Consensus Conference Nomenclature 2012 [1]: granulomatosis with polyangiitis (GPA), eosinophilic granulomatosis with polyangiitis (EGPA), microscopic polyangiitis (MPA), ANCA-limited renal vasculitis (LRV), and with vasculitis not included in the former criteria but that evidenced typical biopsy findings and/or presented positive serology for proteinase 3 (PR3) or myeloperoxidase (MPO). Exclusion criteria were current infections and other systemic autoimmune disease that may affect the levels of complement and the results of the analysis.

Data collection

Data information was obtained through revision of medical records. At the onset of the disease, clinical and laboratory data were collected as well also histopathological findings of the renal biopsies, patient dialysis requirements, and mortality.

Demographic data (sex, age, date at vasculitis diagnosis, type of AAV, and patient follow-up during months) were evaluated. Hemoglobin, hematocrit, white blood cell count with leucocitary formula, platelet count, urea, creatinine serum and creatinine clearance, urinary sediment, 24-h proteinuria, globular erythrosedimentation (ESR), and c-reactive protein (CRP) were collected. Antineutrophil cytoplasmic and perinuclear antibodies (c-ANCA and p-ANCA) were determined by a direct immunofluorescence (DIF) technique and the specificity for PR3 and MPO by ELISA. Hypocomplementemia was defined as having C3 values lower than 80 mg/dL and/or C4 values below 15 mg/dL. The disease activity was measured using the Birmingham Vasculitis Activity Score (BVAS) [7] and the mortality prognosis by Five Factor Score (FFS) [8]. Fever was defined as having an increase of the body temperature above 38 °C. Weight loss was defined as weight loss of 4.5 kg or > 5% within a period of 6 to 12 months. At the onset of the disease, purpura and another cutaneous involvement, arthritis of small and large joints, and abdominal, cardiovascular, and neurological involvement were determined. Otolaryngologists diagnosed nose and throat lesions associated with AAV. Diffuse alveolar hemorrhage (DAH) was diagnosed based on the presence of hemoptysis and/or respiratory deficiency associated with a drop in hematocrit over 10% points and a compatible image in thorax Rx or CT. Renal involvement was defined by the presence of 24-h urine proteinuria of > 500 mg, active urinary sediment (leukocyturia > 5 white blood cells/field, hematuria > 5 erythrocytes/field, or hematic or granulocytic cylinders) and/or increase of creatinine values over 1.4 mg/dL. Rapidly progressive glomerulonephritis (RPGN) was diagnosed by the presence of hematuria, proteinuria, or urinary cylinders associated with an impairment of the renal function within weeks or months [9].

Renal histology was evaluated using light microscopy. Periodic Schiff-acid, silver methenamine, hematoxylin-eosin, and Masson trichromic stains were used. The presence of immunoglobulin and complement by was evaluated by direct immunofluorescence. Biopsies were classified into 4 categories according to 2010 histologic classification for AAV [10]. Those presenting ≥ 50% of all glomeruli globally sclerosed were sclerotic type and those with ≥ 50% normal glomeruli were classified as focal type. Those showing ≥ 50% of glomeruli with semilunar cells were classified as crescentic type and those not presenting the anterior criteria were classified as mixed type. Interstitial and tubular lesions were scored semiquantitatively on the basis of the percentage of the tubulointerstitial compartment that was affected: interstitial infiltrates (mild 0 to 25%; moderate 25 to 50%; and severe > 50%) and interstitial fibrosis and tubular atrophy (mild 0 to 25%; moderate 25 to 50%; and severe > 50%) [11]. Glomeruli number, histologic classification, tubular atrophy, vascular damage, and immune complex deposit were evaluated in the available renal biopsies. Immune complex deposit was defined as 1 or more findings by DIF for IgG, IgA, IgM, C3 or C4, and fibrinogen. Renal prognosis was evaluated according to the progression into terminal renal disease (TRD) and dialysis dependence. Overall mortality rate was also considered.

The present study was approved by the Ethics Committee following recommendations of the Declaration of Helsinki.

Being it a retrospective study, the informed consent was not considered necessary granting data confidentiality.

Statistical analysis

Values are expressed as mean ± standard deviation (SD) for continuous variables and percentages for categorical variables. Demographic, clinical, hematological, serological, and histopathological data between hypocomplementemic and non-hypocomplementemic patients were correlated. Descriptive analysis of the renal histopathological findings was done. The only patients statistically analyzed were those who presented complement registers at diagnosis of the disease. For assessing between-group differences, continuous variables were compared with the Mann-Whitney *U* test, and categorical variables were compared to the chi-square test. *P* values less than 0.05 were considered to be statistically significant. We performed statistical analyses using PASW version 25.

Results

Ninety-three patients with AAV were included; 53 were females (57%). The mean average age at the onset of the disease was 49 ± 14.9. The most frequent type of vasculitis was granulomatosis with polyangiitis with 44 cases (47.3%) followed by 23 microscopic polyangiitis (24.7%), 17 eosinophilic granulomatosis with polyangiitis (18.2%), 7 undifferentiated vasculitis (7.5%), and 1 vasculitis limited to kidney (1.07%). Patients mean average follow-up was of 46 months (range 1–180 months). At diagnosis, complement value was required in 63 patients (67.7%), and 7 presented hypocomplementemia. Patients without registered complement values were excluded. All patients were treated with usual induction and maintenance treatment schemes. Table 1

Table 1 Clinical manifestations, laboratory results, dialysis requirement, and mortality of AAV patients with normal and low complement

	Total (*n* 63)	Low complement *n* 7 (11.1%)	Normal complement *n* 56 (88.8%)	*p* value	OR (IC 95%)
Age at disease diagnosis (years)	52 (40; 62)	56 (40; 62)	53 (43; 61)	NS*	
Female, *n* (%)	36 (57.1%)	2 (28.6%)	34 (60.7%)	NS+	
GPA *n* (%)	32 (50.8%)	2 (28.6%)	30 (53.6%)	NS+	
MPA *n* (%)	15 (23.8%)	4 (57.1%)	11 (19.6%)	NS+	
EGPA *n* (%)	13 (20.6%)	1 (14.3%)	12 (21.4%)	NS+	
RLV *n* (%)	0	0	0		
ANCA C	32/56 (55.2%)	3 (42.9%)	29 (56.9%)	NS+	
ANCA P	19/56 (33.9%)	3 (42.9%)	16 (32.7%)	NS+	
PR3	19/37 (51.4%)	2 (50%)	17 (51.5%)	NS+	
MPO	14/35 (40%)	2 (50%)	12 (38.7%)	NS+	
BVAS at onset	18 (14; 23)	22 (17; 29)	17 (13; 22)	NS*	
FFS at onset	0 (0; 1)	1 (0; 1)	0 (0; 1)	NS*	
Clinical manifestations					
Fever	25 (40.3%)	3 (50%)	22 (39.3%)	NS‡	
Weight loss	29 (46%)	6 (85.7%)	23 (41.1%)	0.042‡	8.6 (1–76.4)
ORL involvement	32 (51.6%)	1 (16.7%)	31 (55.4%)	NS‡	
Renal involvement	38 (60.3%)	7 (100%)	31 (55.4%)	0.036‡	1.2 (1.1–1.4)
RPG	17 (27%)	3 (42.9%)	14 (25%)	NS‡	
DAH	17 (27%)	4 (57.1%)	13 (23.2%)	NS‡	
SNC	26 (41.3%)	3 (42.9%)	14 (25%)	NS‡	
CV disease	12 (19.7%)	1 (16.7%)	11 (20%)	NS‡	
Abdominal involvement	2 (3.2%)	0	2 (3.6%)	NS‡	
Arthritis	11 (17.7%)	0	11 (19.6%)	NS‡	
Dialysis	11/59 (18.6%)	2 (28.6%)	9 (17.3%)	NS‡	
Mortality	11/60 (18.3%)	2 (28.6%)	9 (17%)	NS‡	

Mann-Whitney *U* test, data are presented as median and interquartile ranges; + Chi-squared test; ‡Fisher's exact test. *GPA*, granulomatosis with polyangiitis; *MPA*, microscopic polyangiitis; *EGPA*, eosinophilic granulomatosis with polyangiitis; *RLV*, renal-limited vasculitis; *ANCA*, antineutrophil cytoplasmic antibodies; *PR3*, proteinase 3, *MPO*, myeloperoxidase; *BVAS*, Birmingham Vasculitis Activity Score; *FFS*, Five Factor Score; *ORL*, otolaryngologic; *RPG*, rapidly progressive glomerulonephritis; *DAH*, diffuse alveolar hemorrhage; *CNS*, central nervous system; *CV*, cardiovascular; *NS*, non-significant

shows clinical manifestations, laboratory parameters, dialysis requirement, and mortality of both groups of patients.

One group of patients with hypocomplementemia included seven patients (11.1%), of which, five were males (71.4%) with an average mean age of 56 (range 40–62) years and a mean average follow-up of 38 months (range 1–180). The predominant type of vasculitis was microscopic polyangiitis in four patients (57.1%), followed by two patients with granulomatosis with polyangiitis (28.5%), and one with eosinophilic granulomatosis with polyangiitis (14.3%). BVAS at diagnosis was 22 points (17–29) and FFS one point. The other group was represented by 56 patients with a normal complement value. Similar demographic characteristics, activity, and prognosis score were found in both groups. A statistically significant correlation was observed between hypocomplementemia and nephropathy ($p = 0.036$; OR 1.2; IC 95% 1.1–1.4). Higher prevalence of proteinuria (> 1 g/day) (57% vs. 23%), active urinary sediment (71.4% vs. 41%), and higher creatinine levels 1.4 mg/dL (71.4% vs. 32.1%) were found in patients with low values of complement compared with patients with normal complement.

Fifty-eight out of 93 patients with AAV (62.3%) presented renal involvement. Thirty available renal biopsies were classified as pauci-immune glomerulonephritis. Glomeruli average mean was 13 (IQR 7–17) with predominance of sclerosing histological class (44%). Interstitial fibrosis and tubular atrophy (52%) and vascular damage (57%) were mild. In 14 patients, DIF study was done. In four cases, immune complex deposits (IgG+), complement (C3+), or fibrinogen were observed. These four patients had renal failure with hemodialysis requirement until the end of follow-up. Patients with nephropathy and registered complement values (38/58) did not show significant differences between complement values and renal histology ($p = 0.091$). Table 2 summarizes the findings of the four patients with AAV and positive IF in renal biopsy.

Discussion

Association among hypocomplementemia, renal involvement, and morbi-mortality in 93 patients with VAA was evaluated. We observed a higher frequency of renal involvement in patients with hypocomplementemia but no difference in mortality. Eleven percent of these patients presented hypocomplementemia at the onset of the disease, a lower frequency than that reported

Table 2 Patients' characteristics with AAV and renal biopsy positive by DIF

	Patient 1	Patient 2	Patient 3	Patient 4
Sex	Male	Female	Male	Female
Age at diagnosis	63	27	66	27
Follow-up (months)	4	23	3	NA
AAV type	MPA	GPA	MPA	GPA
BVAS onset	14	18	31	23
FFS onset	1	1	2	1
Creatinine at onset	4.63 mg/dL	7.21 mg/dL	7.99 mg/dL	5.67 mg/dL
Urinary sediment	Active	Active	Active	NA
Proteinuria > 1 g/day	Yes	Yes	NA	NA
Renal disease stage	5	5	5	5
C3 low	No	NA	No	NA
C4 low	Yes	NA	No	NA
ANCA C	NA	+	–	+
ANCA P	NA	–	+	–
PR3	NA	+	–	NA
MPO	NA	–	+	NA
MPD pulses	Yes	Yes	Yes	Yes
Cyclophosphamide EV	Yes	Yes	No	Yes
Rituximab	No	No	Yes	No
Apheresis	NA	Yes	Yes	No
Dialysis	No	Yes	Yes	Yes
Mortality	Yes	No	No	No
Renal biopsy (IF)	Fibrinogen+	C3+	IgG+	C3+ IgG+

AAV, ANCA-associated vasculitis; *BVAS*, Birmingham Vasculitis Activity Score; *FFS*, Five Factor Score; *RDS*, renal disease stage; *C3*, complement 3; *C4*, complement 4, *ANCA*, anti-neutrophil cytoplasmic antibodies; *PR3*, proteinase 3; *MPO*, myeloperoxidase; *MPD*, methylprednisolone; *DIF*, direct immunofluorescence; *NA*, not available

by Fukui et al. [5] who presented an observational study of 81 AAV patients in whom 20% presented low complement. In France, Deshayes et al. [12] shows a prevalence of 5% in a retrospective cohort study with GPA and MPA patients. The prevalence found in our study is in the middle of both studies mentioned before similar to the one reported in Japanese AAV patients varying from 4.2 to 14.8% [13].

Complement is a part of innate immune system, and it participates in the elimination of pathogens activating the classical pathway, alternative pathway, or one mediated by lecithin mechanism that lead to a formation of a membrane attack complex (MAC) producing cellular lysis [13]. In AAV, complement has a role in its pathogenesis by activating the alternative pathway of the complement leading to vascular inflammation. In vitro, experiments have demonstrated that healthy human neutrophils stimulated by ANCA are capable of activating the complement, through C5aR are capable to prime neutrophils and to increase PR3 expression. An inadequate positive feedback in which neutrophils activated by ANCA activates complement increasing the presence of C5a may be important in the maintenance of the inflammatory process [14].

Eculizumab, a monoclonal antibody that inhibits the complement component C5, is now approved for the treatment of rare conditions involving complement hyperactivation as paroxysmal nocturnal hemoglobinuria and atypical hemolytic uremic syndrome (aHUS). Inhibiting C5 is a potential means of reducing glomerular inflammation in lupus nephritis or treating thrombotic microangiopathy in SLE [15]. Eculizumab was never tested as add-on therapy in AAV; Manenti L et al. [16] hypothesize that the positive effect of plasma exchange (PE) in severe AAV as well as in aHUS is due, at least in part, to the removal of activated complement factors and of powerful complement chemotaxins. This therapeutic effect may be shared by eculizumab, which could be considered more "targeted" and safer than PE as add-on therapy for AAV. Avacopan, C5aR antagonist with the capacity of blocking chemotaxis and neutrophil priming, has demonstrated that it may reduce or replace the treatment with glucocorticoids in AAV patients, being it a promising future strategy [17].

Shoichi Fukui et al. [5] compared patients with AAV with and without hypocomplementemia and observed a higher frequency of recurrent skin lesions, diffuse alveolar hemorrhage, thrombotic microangiopathy, and lower platelet count in those patients with hypocomplementemia at diagnosis. Hypocomplementemia was associated with a higher frequency of organ involvement, worse prognosis, and higher mortality. Deshayes et al. [12] demonstrated hypocomplementemia is associated with worse renal survival in ANCA-positive GPA and MPA. Our study demonstrated the association of hypocomplementemia and renal involvement with higher prevalence of proteinuria > 1 g/day in hypocomplementemic vs. normocomplementemic patient (57% vs. 23%), active urinary sediment, (71.4% vs. 41%), and higher creatinine levels above 1.4 mg/dL (71.4% vs. 32.1%). Some other studies [18, 19] have reported deposits of complement and immunocomplex in skin and kidney specimens of patients with ANCA-associated vasculitis. Patients with pauci-immune glomerulonephritis and evidence of immunocomplex deposits in biopsy presented higher proteinuria, increased hypocomplementemia, and increased glomerular hypercellularity than patients with classical pauci-immune vasculitis [19]. Scaglioni et al. [20] corroborated in 53 renal biopsies in patients with AAV the presence of immunocomplex or complement deposits in about 26.4% associating them with increased proteinuria. In our study, 4 patients showed the presence of complement and immunocomplex deposits in renal biopsies. All the patients presented creatinine values above 4.6 mg/dL and three out of 4 required hemodialysis. The association between the presence of hypocomplementemia at the onset of the disease and the presence of other extra-renal manifestations could not be demonstrated.

This study has several limitations that require consideration: first, the few numbers of patients with complement dosage at the onset of the disease, justified in part by the retrospective design; second, the tittle sample size because of the low prevalence of the disease in our country; third, the lack of renal biopsy in all patients with renal involvement and lack of DIF test in 53% of the samples that makes the pathogenic role of the complement in the AAV difficult to confirm. Thus, further prospective studies and histopathological analyses of other involved organs are needed to confirm these associations. As strengths, we can mention that our research is done in a single-center and the biopsies were read by the same team of pathologists. For our knowledge, this is the second study done in Argentina and together with Scaglioni et al. [20], both researches evaluate the complement role in AAV in an Argentinian population. This topic is not sufficiently studied in Latin American, and most of the studies come from Asia with different genetic determinants.

In conclusion, our results suggest that complement participates in renal damage of AAV patients. It is important to determine complement levels at the onset of the disease and use DIF in all renal biopsies although having pauci-immune clinicopathological characteristics. Consequently, more multicentric research studies are needed to confirm our study findings.

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Compliance with ethical standards

The present study was approved by the Ethics Committee following recommendations of the Declaration of Helsinki. Being it a retrospective study, the informed consent was not considered necessary granting data confidentiality.

Disclosures None.

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