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ASSOCIATION BETWEEN THE PRESENCE OF ANTI-C1q ANTIBODIES AND ACTIVE NEPHRITIS IN PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

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Abstract Lupus nephritis (LN) is a severe complication of systemic lupus erythematosus (SLE). A retrospective analysis was carried out on a group of 24 patients with SLE to evaluate whether the presence of anti-C1q antibodies (anti-C1q) is related to renal involvement and to explore the behaviour of anti-C1q with respect to LN during a four-year follow-up period. A first serum sample stored at the serum bank, taken not more than three years after SLE diagnosis and one serum sample per year for the subsequent four years were used to detect anti-C1q. Lupus clinical manifestations and serological markers of activity corresponding to the date of each serum sample selected were collected from medical records. In the first serum sample, anti-C1q were found in 8 active SLE. LN was confirmed by histology in 5/8 patients who were positive for anti-C1q and in 1/16 patients who were negative for these autoantibodies (p = 0.0069). Three patients (3/8) had anti-C1q without renal involvement but with lupus skin manifestation. Anti-C1q levels decreased in 3/5 patients with LN who responded to treatment and remained higher in 2/5 patients who needed a new renal biopsy which showed severe renal disease. The 15 patients without severe kidney disease and anti-C1q negative at diagnosis did not develop LN and anti-C1q remained negative in the 4 years of follow up. Anti-C1q were found in SLE patients with active renal involvement or with lupus skin disease. The absence of anti-C1q seemed to be linked to low probabilities of renal involvement.

Key words: systemic lupus erythematosus, lupus nephritis, anti-C1q autoantibodies

Resumen ***Asociación entre presencia de anticuerpos anti-C1q y nefritis activa en pacientes con lupus eritematoso sistémico.*** La nefritis lúpica (NL) es una complicación grave del Lupus Eritematoso Sistémico (LES). Se analizó retrospectivamente en 24 pacientes con LES si la presencia del anticuerpo anti-C1q (anti-C1q) se asociaba con NL y el comportamiento del anti-C1q respecto a la NL en un período de seguimiento de cuatro años. El anti-C1q se determinó en una primera muestra de suero no distante en más de tres años del diagnóstico de LES y en una muestra por año en los siguientes cuatro años. Se obtuvo información de las historias clínicas, sobre manifestaciones clínicas de LES y marcadores serológicos de actividad para las fechas de selección de cada suero. En la primera muestra de suero se detectó anti-C1q en 8 pacientes con LES activo. NL fue confirmada por histología en 5 de ellos y en uno de 16 pacientes con anti-C1q negativos (p = 0.0069); 3 de 8 pacientes fueron anti-C1q positivos sin NL y con lesiones en piel. Los niveles de anti-C1q disminuyeron en 3/5 pacientes con NL que respondieron al tratamiento y se mantuvieron aumentados en 2/5 que necesitaron una nueva biopsia, que evidenció compromiso renal grave. Los 15 pacientes sin enfermedad renal grave y con anti-C1q negativo al diagnóstico no desarrollaron NL y el anti-C1q se mantuvo negativo en los 4 años de seguimiento. El anti-C1q se asoció en pacientes con LES a NL activa o con compromiso en piel. La ausencia del anti-C1q parecería relacionarse a un menor riesgo de desarrollar nefropatía lúpica.

Palabras clave: lupus eritematoso sistémico, nefritis lúpica, anticuerpos anti-C1q

Lupus nephritis (LN) is one of the most severe complications of Systemic Lupus Erythematosus (SLE) and affects between 40% and 80% of these patients[1, 2]. Immunosuppressive drugs used during the LN treatment and the possibility of progression to chronic renal failure and renal transplant also play an important role in the increase in morbidity and mortality in lupus patients[2, 3].

The increased levels of anti-double stranded DNA antibodies (anti-dsDNA) and hypocomplementemia are serological markers of SLE activity, but they are not enough to identify which organ will be affected[4, 5].

Several studies have described that anti-C1q antibodies (anti-C1q), antibodies against collagen-like region of first component of the classical complement pathway[6-8], might be regarded as immunological markers of SLE with renal involvement in particular[9-11]. The presence of anti-

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C1q might be associated with active renal disease[11, 12-14]. Moreover, detection of anti-C1q, either alone or in combination with other serological markers of disease activity, could give complementary information to the diagnosis of a renal flare[14, 15-17]. However, some authors question these findings. It is still debatable whether anti-C1q are associated with systemic disease activity or only with severe renal activity[19, 20]. Besides, there is no consensus about whether the presence of anti-C1q is related to one type of LN in particular[18] or whether the levels of these antibodies are useful in the follow-up of LN[16, 18-20, 21]. A retrospective analysis was carried out on a group patients using samples from a serum bank and medical records review in order to evaluate (a) the relation between presence of anti-C1q in patients with SLE diagnosed less than three years before and renal involvement, and (b) the behavior of anti-C1q with respect to LN during a four-year follow-up period.

Materials and Methods

For this study, serum samples were collected from patients over 16 years of age who fulfilled at least four of the American College of Rheumatology 1997 (ACR 97) criteria for SLE classification, with no more than three years after SLE diagnosis[22]. These serum samples were kept at the serum bank of the Immunology Unit of *Instituto de Investigaciones Médicas Alfredo Lanari* at -80 °C between January 1995 and October 2012. This serum bank contains samples collected to perform routine analysis in patients assisted in this unit. None of the samples were obtained specifically for this study. Patients included had a first serum sample taken no more than three years after SLE diagnosis. Patients diagnosed with hypocomplementemic urticarial vasculitis syndrome (HUVS) confirmed by histology were excluded. Anti-C1q analyses were performed on the first serum sample collected, and subsequently on one serum sample per year for the following four years after the first one (if available). All patients gave their written consent. This study was approved by the Institutional Review Board.
The patients´ demographics and clinical data at the time each serum sample was taken were retrospectively obtained from medical records. The ethnic groups of patients were defined according to GLADEL criteria[23]. Mestizos were those individual born in Latin America with both Amerindian and Caucasian ancestors. Caucasian were those with all Caucasian European ancestors; African-Latin Americans were born in Latin America with at least one African ancestor irrespective of whether other ancestors were Caucasian or Amerindian. Pure Amerindians were those individuals who had all autochthonous ancestors.

Lupus clinical manifestations and disease activity were defined according to Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) criteria[24]. Skin involvement was defined as the presence of lupus specific skin lesions: acute rashes (rash malar, generalized erythema and bullous lesions); subacute rashes (annular o psoriasiform); chronic rashes (discoid, lupus, lupus profundus)[25].

Renal involvement was defined based on clinical and laboratory manifestations, including proteinuria, renal function parameters and urinary sediment. It was histologically classified according to World Health Organization (WHO)[26]. Active LN was defined as 24-hour urine protein excretion > 0.5 g/day and/or active urinary sediment and/or an increase in serum creatinine levels of more than 25% from baseline[27]. Active urinary sediment was considered as the presence of hematic casts or > 5 red or white blood cells leukocytes (RBC/WBC) in the absence of alternative causes. Response to treatment was considered as the normalization of the parameters of active renal disease.

Anti-C1q IgG isotype (ORG 549, Orgentec) were measured on each selected serum sample using a commercial ELISA kit, according to instructions provided by the manufacturer. This kit consists of C1q adsorbed to microplate wells. A high salt concentration buffer is used to avoid cross reactivity with circulating immune complexes. Calibrators and positive and negative controls are included. Autoantibodies levels are expressed in U/ml with reference to a calibration curve. Cut-off value recommended by the manufacturer is 10 U/ml. The test was performed on a group of healthy individuals and the cut-off value was calculated as the mean anti-C1q titre plus two standard deviations (mean+ 2SD). The cut-off value was set in 15 U/ml. Anti-C1q detection was performed blinded to the patients' history. Laboratory parameters (corresponding to the date of each serum sample selected) were obtained from medical records. Anti-dsDNA were measured using ELISA; component complement C3 and C4 were assessed using radial immune-diffusion and hemolytic complement levels CH50% were measured by Kent and Fife's method.

Statistical analysis was performed with Stata 11.0. Fisher's test was used to compare categorical data and Mann Whitney U test, to compare numerical variables. A p value < 0.05 was considered statistically significant.

Results

Serum samples from 24 women were analyzed, median age was 27 years at the time of diagnosis (range 17-55). Nineteen were Caucasian and 5 Mestizas. The median time from SLE diagnosis to the first determination of anti C1q was 16 weeks (range 0-169). At the time of the first anti-C1q determination, the disease was clinically active in 20 patients and non-active in four patients. Six patients had LN (4 class IV, 1 class V + III and 1 class II); 5/6 had active renal disease.

At the first serum sample, anti-C1q were found in 8 of 24 patients. In Table 1 clinical manifestations and laboratory findings in patients with and without anti-C1q are compared. Clinical disease activity was observed in all patients (8/8) with anti-C1q. The four patients with non-active disease were negative for anti-C1q; 5/8 patients with anti-C1q and 1/16 without anti-C1q had renal involvement histologically confirmed. The association between the presence of the anti-C1q and renal involvement was statistically significant (p = 0.0069). The only patient with negative anti-C1q and proliferative LN (Class IV) had already received immunosuppressive treatment and she had no renal disease activity by the time the first serum sample was taken. Table 2 shows a comparison of laboratory parameters for renal disease between patients with and without anti-C1q. In 5 patients with positive anti-C1q and active renal disease, the median value of anti-C1q was 21 U/ml (range 16-128). Low complement levels were present in 5/5 and anti-ds DNA levels were high in 4/5 patients. Three of these patients were Caucasian and two were Mestizas.

Table 3 shows antibodies levels and LN evolution during a four-year follow-up in 6 patients with LN at the time of the first serum sample. When the second serum sample was analyzed (one year of follow-up), it was observed that anti-C1q levels had decreased in 3 patients while remaining high in other 2 patients. The three patients whose anti-C1q titers decreased during the follow-up to levels below the cut off value (patients 1, 2 and 3) also normalized $CH_{50\%}$ levels and remained without active renal disease, but in two of these patients their anti-dsDNA levels remained increased. In the patient with renal involvement and negative anti-dsDNA at baseline (patient 3), anti-dsDNA titers increased in the third serum sample, which coincided with an episode of lupus psychosis, but her anti-C1q remained negative. The two patients whose anti-C1q titers during follow-up were even higher than at baseline (patients 4 and 5) remained with active renal disease and underwent a new renal biopsy. One remained as class IV LN and the other one changed from class II to class IV LN. The only patient with LN and negative anti-C1q in the serum sample achieved under treatment (Patient 6) remained anti-C1q negative and without active renal disease during the follow-up period. The 15 patients without renal involvement and negative anti-C1q in the first serum sample remained negative for the antibody during the follow-up and did not develop active renal disease.

As seen in Table 1, skin involvement had a similar frequency in patients with or without anti-C1q. However,

TABLE 1.– *Clinical manifestations and serological markers of activity in 24 SLE patients with and without anti-C1q*

	Patients with positive a-C1q n = 8	Patients with negative a-C1q n = 16	p value
Age (years)[a]	29.5 (17-56)	27 (18-52)	0.900
Ethnic group (Caucasian / Mestizas)	6/2	13/3	0.460
Rash, n	5	5	0.150
Alopecia, n	2	3	0.550
Ulcers, n	0	5	0.100
Pleuresia, n	1	1	0.560
Pericarditis, n	0	1	0.670
Fever, n	1	2	0.720
Leukopenia, n	0	5	0.100
Renal disease, n	5	1	0.069
Low C3, n	3	7	0.690
Low C4, n	5	10	0.480
Low CH50%, n	7	10	0.170
High levels of anti-dsDNA, n	7	11	0.320

SLE: systemic lupus erythematosus. Low C3: C3 less than 80 mg/dl; Low C4: C4 less than 20 mg/dl; Low CH50%: hemolytic complement levels less than 150 UCH50%. High levels of anti-dsDNA: levels more than 150 UI/ml. All data are expressed as number (n) of observations. a Median (range).

TABLE 2.– *Parameters of renal activity in 24 SLE patients with and without anti-C1q*

	Patients with positive a-C1q n = 8	Patients with negative a-C1q n = 16	p value
Creatinine (mg/dl)[a]	1.19 (0.77-1.98)	0.79 (0.51-1.22)	0.007
Creatinine clearance (ml/min)[a]	62 (33-89)	94 (69-189)	0.058
Active urinary sediment, n	4	0	0.008
Proteinuria 24-hours (mg/24hs), n	5	1	0.007

SLE: systemic lupus erythematosus; n: number of patients. a Median (range).

TABLE 3.– *Nephritis evolution and behavior of different antibodies levels during the 4-year follow-up in 6 female patients with LN at the first sample*

			Baseline				Second serum sample				Third serum sample				Fourth serum sample				Fifth serum sample			
P	E	A	Anti C1q	Anti DNA	C'	Bx	Anti C1q	Anti DNA	C'	Bx	Anti C1q	Anti DNA	C'	Bx	Anti C1q	Anti DNA	C'	Bx	Anti C1q	Anti DNA	C'	Bx
1	C	46	128	3280	145	IV	16	128	160	NR	NA	15	250	NR	NA	15	220	NR	NA	15	198	NR
2	C	17	21	600	110	IV	8	138	200	NR	5	80	210	NR	5	14	185	NR	4	21	180	NR
3	C	25	16	12	90	III + V	8	72	167	NR	7	433	176	NR	6	50	167	NR	6	15	90	NR
4	M	34	17	530	130	IV	21	81	260	NR	24	265	260	IV	8	678	131	NR	8	269	260	NR
5	M	21	36	427	32	II b	213	972	35	II b	98	800	85	IV	42	828	86	NR	78	721	122	NR
6	C	18	10	173	94	IV	3	48	246	NR	4	15	200	NR	4	62	186	NR	1	86	219	NR

LN: lupus nephritis; P: patient; S: sex; F: female; E: Ethnic group; C: Caucasian; M: mestiza; A: age in years; Anti-C1q: anti-C1q levels in U/ml; Anti DNA: anti-dsDNA levels in U/ml; C': Complement hemolytic levels in CH50% ; Bx: kidney biopsy; IV: proliferative LN class IV; II: Mesangial LN class II; III: Membranous LN class II; NR: not required; NA: serum sample not available.

there were 15 patients without renal disease and negative anti-C1q and 4 out of 15 had skin disease, and the three patients who had positive anti-C1q without renal activity had skin involvement. The difference was statistically significant (p = 0.040). The values of the first anti-C1q in the three patients without renal disease activity, with anti-C1q and skin involvement were 35, 43 and 50 U/ml. Their anti-C1q levels decreased simultaneously with the improvement of the skin disease. None of them developed renal disease nor met the clinical criteria for the diagnosis of hypocomplementemic urticarial vasculitis syndrome (HUVS) during the follow-up.

Discussion

Physiologically, C1q molecule plays a role in the maintenance of self-tolerance since it is involved in the removal of apoptotic material and immune complexes, formed during the immune response[28,29]. Anti-C1q were found in the glomeruli of lupus patients. Based on these results, Mannik et al. postulated that these antibodies were involved in the pathogenesis of LN[30]. Flierman and Daha proposed a hypothesis to explain the role of anti-C1q in the development of LN. In this model, the presence of anti-C1q seems to be a necessary, although not sufficient, condition for the development of LN and it would explain why some patients develop nephritis while others do not, depending on their antibody profile[31].

Anti-C1q frequencies between 30 and 45% had been recorded in lupus patients[10, 11, 14, 32]. Clinical features, the type of nephropathy and the time of evolution of the disease might explain the variability in the reported frequencies. Also, methodological differences in the commercial ELISA used to detect anti-C1q could be associated with different frequency results. Currently, commercial standardized ELISA kits are available, but each kit estimates anti-C1q levels using different cut-off values. In this study, a higher, more specific, cut-off value for anti-C1q detection was used. In this series of patients with SLE diagnosed less than three years before, anti-C1q frequency was similar to that reported by other authors[10,11,14,32].

There were not differences in anti-C1q frequencies between Caucasian and Mestizos patients. However, a larger sample will be required for further assessment of differences related to ethnic groups. In a meta-analysis that included 31 studies from different countries and ethnic groups, only three studies were from South America (Brazil)[38].

All patients who were positive for anti-C1q showed clinical disease activity. There was an association between the presence of anti-C1q and active renal involvement. Also, at the time of the second serum sample (one year of follow-up), anti-C1q levels appeared to be related to LN evolution. The only patient with LN and negative anti-C1q was already under immune-suppressive therapy and she had no renal disease activity when the first serum sample was taken. Perhaps this could be the reason why the anti-C1q was absent in the first serum sample. Antibody levels remained undetectable during follow, and it coincided with a good response to treatment. The time chosen to take the serum sample for anti-C1q detection must be taken into account when interpreting the results in a specific case.

Even though the number of patients here studied was relatively small, a relation between anti-C1q levels and the response to treatment (defined as the normalization of the parameters of active renal disease) can be appreciated. Increased levels of anti-C1q during the treatment might be associated with active renal disease and severe renal histological lesion. An interesting finding was that the two LN patients who did not respond to treatment were both Mestizas. This result is consistent with other studies that observed a worse prognosis of renal disease in this ethnic group[33]. Increased anti-dsDNA titers or low complement

levels were detected both in patients with or without anti-C1q. These results suggest that complementary detection of anti-C1q added to other serological markers might contribute to identify patients with active renal disease. These cases should be considered to perform a kidney biopsy.

None of the anti-C1q negative patients showed severe renal disease at the time of the first serum sample or developed such a condition over the 4-year follow-up period. It is consistent with previous reports suggesting a link between absence of the antibody and a low probability of severe renal involvement[13, 34]. Long term studies will be necessary to evaluate the negative predictive value of anti-C1q for LN.

The presence of anti-C1q in absence of renal disease was associated with skin involvement as a feature of active SLE. Therefore, serum anti-C1q were found in lupus patients with active renal disease and in patients with lupus skin disease without renal disease. Renal and skin complications are the two organ systems most prone to antibodies mediated manifestations in SLE. The association between anti-C1q and skin manifestations could be explained by the relationship that exists between HUVS and SLE. HUVS occurs in 7-8% of patients with lupus and SLE develops in approximately 50% of patients with HUVS. It is still debatable if they are two distinct clinical entities or this syndrome is an atypical form of SLE[35]. The DNASE1L3 mutation has been described in familial forms of HUVS and SLE-associated HUVS, which would support considering the HUVS a variant of SLE[36]. The anti-C1q are present in 100% of patients with a diagnosis of HUVS, and Wisnieski et al. showed that the anti-C1q found in both HUVS and SLE are targeted against the same epitopes on the collagen-like region of the C1q, suggesting the same antibody identity for both conditions[37]. In this series, patients with diagnosis of HUVS confirmed by histology were excluded. However, skin biopsy would have been needed to confirm HUVS in these three patients with anti-C1q.

A recent meta-analysis that used a statistical model, hierarchical summary receiver operating characteristic (HSROC) concluded that, although anti-C1q is associated with LN, post test probabilities are not sufficiently convincing to provide reasonable certainty of the presence or absence of a history of active disease[38]. In spite of the results of this meta-analysis, in this study anti-C1q were associated to renal disease activity and severe histological lesion. However, this study has several limitations: only 24 patients had a serum sample available in the serum bank with no more than three years after SLE diagnosis and one serum sample annually collected for the subsequent four years; data obtained retrospectively from clinical records did not allow to define whether anti-C1q is superior, equal or inferior to conventional markers such as anti-dsDNA and C3 or C4 levels in terms of sensibility/ specificity to detect a flare of renal disease and for monitoring response to treatment.

This study presents the behaviour of anti-C1q, anti-dsDNA and CH50% on a group of patients with SLE over a period of four years of follow up. All LN cases have been confirmed by renal biopsy and the renal activity was scored by SAR/SAN criteria[26].

In conclusion, anti-C1q were found in the serum of SLE patients and, consistent with previous studies, this shows an association with active renal involvement and severe renal histological lesion and also with lupus skin disease. More significantly, none of the 16 patients negative for anti-C1q antibodies had or developed lupus nephritis. The absence of anti-C1q seemed to be linked to low probabilities of renal involvement. A prospective study involving a greater number of patients is needed to confirm the findings of this work and take into account the value of anti-C1q for LN follow-up and therapeutic decisions.

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