

AN ANALYSIS OF THE RELATIONSHIP BETWEEN DIFFERENT AUTOANTIBODIES AND CLINICAL FINDINGS IN A GROUP OF TURKISH PATIENTS WITH SYSTEMIC LUPUS ERYTHEMATOSUS

N. Defne ALTINTAŞ¹, A. Olcay TIRYAKI², Hüseyin TUTKAK², Nurşen DÜZGÜN²

ABSTRACT

Purpose: To study the prevalence of different anticardiolipin antibody isotypes (aCLs), anti-C1q antibodies (anti-C1q), and anti-b2-glycoprotein 1 IgG antibodies (anti-b2GP1 IgG) in a group of Turkish SLE patients and their association with lupus nephritis and extra-renal involvement.

Materials and Methods: SLE patients who were evaluated in Ankara University Faculty of Medicine, Department of Clinical Immunology and Rheumatology between May 2001 and May 2002 were included in the study, unless they were also hemodialysis patients. Disease duration, medications, organ involvement, disease complications and follow-up laboratory results were recorded. Disease activity was evaluated with SLEDAI; a score of ≥ 4 indicated active disease. Antibody titers were determined using the enzyme immunoassay method.

Results: A total of 62 patients (51 women, 11 men) were included. The mean age was 37. Average duration of illness was 104 months. Of the patients, 55% had a SLEDAI score of ≥ 4 . Renal involvement was present in 76%, with active nephritis in 49%. Thrombosis was present in 11%, 16% had obstetric complications, 37% had neurologic findings, 26% had thrombocytopenia, and 45% had Raynaud's phenomenon. None of the antibodies were related to renal involvement. Patients with SLEDAI ≥ 4 had significantly increased total aCL positivity ($p < 0.05$). There was no relation between disease duration and antibody positivity. Anti-b2GP1 IgG and aCL IgG were significantly related to thrombosis ($p < 0.05$). The negative predictive value of aCL for thrombosis was high, 94%. A significant association between thrombocytopenia and aCL IgG positivity was observed ($p = 0.026$). Anti-b2GP1 IgG positivity showed a significant correlation with all aCL isotypes. None of the antibodies had a significant relationship with obstetric complications, neurologic findings, or Raynaud's phenomenon.

Conclusions: The findings that aCL IgG positivity was closely associated with thrombotic events and thrombocytopenia, and anti-b2GP1 IgG was closely associated with aCL levels and thrombosis were in accordance with the general literature. No relation between anti-C1q and renal involvement, renal flare, or proliferative nephritis was demonstrated in this group of Turkish patients.

Key Words: Anti-C1q, Anticardiolipin Antibodies, Anti-b2-glycoprotein 1, Systemic Lupus Erythematosus, Nephritis.

SİSTEMİK LUPUS ERİTEMATOZUSLU BİR GRUP TÜRK HASTADA FARKLI OTOANTİKORLAR VE KLİNİK BULGULAR ARASINDAKİ İLİŞKİNİN İNCELENMESİ

ÖZ

Amaç: Sistemik lupus eritematozuslu (SLE) bir grup Türk hastada farklı antikardiyolipin antikor izotiplerinin (aCL), anti-C1q antikor (anti-Cq1) ve anti-beta2-glikoprotein 1 IgG (anti-b2GP1 IgG) antikor sıklığının ve lupus nefriti ve ekstra-renal tutulum ile ilişkisinin incelenmesi.

Hastalar ve Yöntemler: Ankara Üniversitesi Tıp Fakültesi, Klinik İmmünoloji ve Romatoloji departmanında Mayıs 2001 – Mayıs 2002 tarihleri arasında değerlendirilen SLE'li hastalar çalışmaya dahil edildi. Hemodiyaliz ihtiyacı olanlar çalışma dışında tutuldu. Hastalık süreleri, ilaçları, organ tutulumları, hastalık komplikasyonları ve laboratuvar sonuçları kaydedildi. Hastalık aktivitesi SLEDAI ile değerlendirildi; skorun ≥ 4 olması aktif hastalık olarak kabul edildi. Antikor titreleri enzim immunoassay yöntemiyle değerlendirildi.

Bulgular: Toplam 62 hasta (51 kadın, 11 erkek) çalışmaya alındı. Ortalama yaş 37; ortalama hastalık süresi 104 aydı. Hastaların %55'inin SLEDAI skoru ≥ 4 'tü. Renal tutulum %76'sında, aktif nefrit %49'unda saptandı. Tromboz %11'inde, obstetrik komplikasyonlar %16'sında, nörolojik komplikasyonlar %37'sinde, trombositopeni %26'sında, Raynaud fenomeni %45'inde mevcuttu. Antikorların hiçbirini renal tutulum ile ilişkili bulunmadı. SLEDAI ≥ 4 olanlarda toplam aCL pozitifliği anlamlı olarak yüksekti ($p < 0.05$). Hastalık süresiyle antikor varlığı arasında ilişki yoktu. Anti-b2GP1 IgG ve aCL IgG anlamlı olarak trombozla ilişkili bulundular ($p < 0.05$). Tromboz için aCL'nin negatif prediktif değeri yüksek bulundu, 94%. Trombositopeni ve aCL IgG varlığı arasında anlamlı ilişki vardı ($p = 0.026$). Anti-b2GP1 IgG varlığı tüm aCL izotipleriyle anlamlı korelasyon göstermekteydi. Antikorların hiçbirini obstetrik komplikasyonlar, nörolojik bulgular ya da Raynaud fenomeni ile ilişkili değildi.

Sonuç: aCL IgG varlığının trombotik olaylar ve trombositopeniyle ilişkili bulunması; anti-b2GP1 IgG'in aCL düzeyleri ve trombozla ilişkili bulunması literatürle uyumluydu. Ancak Anti-C1q ile renal tutulum, aktif renal hastalık ve proliferatif nefrit arasında hiçbir ilişki gösterilemedi.

Anahtar Kelimeler: Anti-C1q, Antikardiyolipin Antikorları, Anti-beta 2-glikoprotein 1, Sistemik Lupus Eritematozus, Nefrit.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a multi-systemic collagen vascular disease of unknown cause, probably due to a regulation disorder in the immune system. 1 Different groups have reported prevalences of 40 to 565 per 100,000 women. 1 This is about ten times the prevalence in men. With more accurate diagnostic techniques and increasing experience with the use of immunosuppressive agents, the prognosis is improving. Renal and central nervous system involvement are factors still adversely affecting the prognosis. 2-4

Lupus nephritis is defined as renal involvement with clinical and laboratory findings such as hypertension, nephritic or nephrotic syndrome, chronic renal failure or proteinuria, and hematuria with no other cause in patients with SLE. 5 However, it must be kept in mind that in patients with SLE renal involvement may be present with no apparent serum or urine findings. 1,6 Therefore, a marker to detect asymptomatic as well symptomatic lupus nephritis is being sought.

Anti-C1q antibody (anti-C1q) presence has been proposed as a marker of lupus nephritis. 7 C1q is a part of the complement system. It has a role in the binding and clearing of the immune complexes that are circulating or bound to the tissues. It has been reported that C1q has a role in the clearing of apoptotic cell material even in the absence of antibodies. 8 In rats with C1q deficiency that show a high risk of renal involvement with SLE development, many apoptotic bodies in the glomeruli are shown, which supports the idea that apoptosis may have a role in nephritis development. 9

The term antiphospholipid syndrome (APS) was first defined by Hughes as the hypercoagulability syndrome in the presence of antiphospholipid antibodies. 10 Antibodies such as anti-b2-glycoprotein 1 antibodies (anti-b2GP1), low titer anticardiolipin IgG, anticardiolipin IgM and anticardiolipin IgA antibodies (aCL IgG, aCL IgM, aCL IgA, respectively), and other antiphospholipid antibodies are commonly present in patients with APS. It was demonstrated that in patients with APS antiphospholipid antibodies that can bind cardiolipin require a factor called b2-glycoprotein 1, and it is suggested that these groups of antibodies may be important in predicting thrombotic events.

b2-glycoprotein I is a glycoprotein that is normally present in the plasma, but its physiologic significance is unknown. In vitro, it is shown to inhibit prothrombinase activity, contact pathway activation, ADP induced thrombocyte aggregation, and factor Xa formation by thrombocytes. Therefore, it is a weak, natural anticoagulant. 11,12 In SLE, b2-glycoprotein I has autoantigenic properties for both B and T lymphocytes. 13,14

In a multi-center study in Europe, medium-high titers of aCL IgG and anti-b2GP1 were found to be associated with thrombosis,

¹ Hacettepe Üniversitesi Tıp Fakültesi İç Hastalıkları Anabilim Dalı Ankara

² Ankara Üniversitesi Tıp Fakültesi İç Hastalıkları Anabilim Dalı Klinik İmmünoloji ve Romatoloji Bilim Dalı Ankara

medium-high titers of aCL IgG levels were associated with thrombocytopenia, medium-high titers of aCL IgM were associated with hemolytic anemia and cerebrovascular events, and medium-high titers of aCL IgA were associated with reticularis and Raynaud's phenomenon.¹⁵ In another study, Frampton et al. demonstrated a relation between antiphospholipid IgG antibody and glomerular capillary thrombosis during active illness.¹⁶ In addition, in SLE, the presence of aCLs with increased anti-ds-DNA and anti-C1q levels were reported to have a high specificity for glomerulonephritis.¹⁷ The presence of renal microthrombi was found to have a strong association with the presence of aCLs.¹⁸

Recent publications have reported that different antibodies in SLE patients may be responsible for the different patterns of organ involvement and the different course of the disease in different patients.^{15,17,19} Despite conflicting results, all antibodies are reported to be associated with disease flare,^{15,17,20,21} and yet each is found to be responsible for a different clinical presentation.^{2,15,16} With the clarification of these associations, the management plan for the patients at risk may change. The conflicting results in the literature prompted us to study the prevalence of these antibodies in the Turkish SLE population and their association with lupus nephritis and extra-renal involvement.

MATERIALS and METHODS:

Patients: Patients satisfying the American Rheumatology Association (ARA) criteria for SLE²² who were admitted to the Clinical Immunology and Rheumatology Department wards or were seen in the ambulatory clinics between May 2001 and May 2002 were included in the study. Informed consent was obtained. End stage renal failure patients were excluded. Hospital ethics committee approval was obtained.

All patients were interviewed and their medical records were examined for the date of diagnosis, treatments given, thrombotic events, miscarriages, and stillbirths. Disease activity scores were calculated. Patients were evaluated for organ involvement (skin, mucosa, joint, serosal surfaces, CNS, kidney, bone marrow). Laboratory results obtained for routine follow-up, such as anti-ds-DNA, erythrocyte sedimentation rate, thrombocyte count, and C3c and C4 levels, were recorded. Pathology results of patients with prior renal biopsies were recorded in accordance with the classification system recommended by WHO.

SLEDAI score was used for the evaluation of disease activity.²³ Since the study had a cross-sectional design and the patients were seen only once, disease flare could not be defined as an increase in the SLEDAI score.²⁴ However, a SLEDAI score of 4 or higher was considered to indicate active disease.²⁵

Renal involvement was defined as hematuria (>5 RBC/hpf), proteinuria (>0.5 g/day), or an increase in the creatinine levels at the time of diagnosis or later. Patients with hematuria (>5 RBC/hpf), proteinuria (new onset or increasing), pyuria

not related to infection, casts or an increase in the serum creatinine levels at the time of inclusion in the study were considered to have active renal involvement. Decreasing or stable levels of proteinuria, hematuria, or creatinine indicated inactive lupus nephritis.

Severe headaches, depression, epilepsy, and psychotic disorders that could not be explained by another etiology (i.e. intracranial lesions, infection, metabolic derangement, and steroid use) were regarded as signs of neurologic involvement.

Twenty sex- and age-matched healthy volunteers were enrolled as a control group. Blood for serum samples was drawn and frozen at -20 °C after centrifugation.

Determination of aCL IgG, aCL IgA, aCL IgM, anti-b2GP1, and anti-C1q titers:

Serum samples were defrosted and anti-b2GP1 IgG and anti-C1q titers, and aCL IgG, aCL IgA, and aCL IgM titers were determined using the enzyme immunoassay (EIA) method.

EIA kits for aCL isotypes and anti-b2GP1 IgG were EUROIMMUN labeled (Medizinische Labordiagnostika GmbH, Germany). For anti-C1q determination IMTEC labeled (Immundiagnostika GmbH, Germany) kits were used. All EIA determinations were performed using a fully automatic Tecan Genesis RMP 100 (Switzerland). Each serum sample was studied in two wells, and the mean value recorded for each antibody titer. The procedures were performed as described in the manufacturers' instructions.

The control and standard samples to check the reliability of the test were provided by EUROIMMUN. The upper limit of the normal range was regarded as >12 GPL U/mL, >12 APL U/mL, and >12 MPL U/mL for aCL IgG, aCL IgA, and aCL IgM, respectively. Titers of >20 RU/mL and >20 U/mL were regarded as positive results for anti-b2GP1 IgG and anti-C1q, respectively.

Statistical analysis:

Statistical analysis was performed using SPSS v.11.0 (SPSS Inc., IL, USA). The Mann-Whitney U test was performed to compare nonparametric variables such as age and antibody titer levels between the control and patient groups. Fisher's exact test and Pearson's chi-square were used to compare categorical variables. Spearman's rank correlation coefficient was used to assess the relation between aCL isotypes, and anti-C1q and anti-b2GP1 IgG levels.

RESULTS

Evaluation of the patient group:

A total of 62 (51 women, 11 men) patients were included in the study. The mean age was 37, ranging between 16 and 67. The control group comprised 18 women and 2 men and their mean age was 37 (range 24-63). Patient SLEDAI scores ranged between 0 and 49 and had a median score of 4. Of

Table 1: Patient characteristics.

Patient characteristics	n (%) / median [interquartile range]
Male sex	7 (11.3%)
Age	37 [26.00-47.25]
SLEDAI	4 [0-14.50]
SLEDAI \geq 4	34 (54.8%)
Duration of illness (months)	103.8 (2-335)
Renal involvement	47 (75.8%)
active renal involvement	23 (48.5%)
known proliferative nephritis (Class III-IV)	13 (20.9%)
History of thrombosis	7 (11.3%)
pregnancy complications	10 (16.1%)
neurologic involvement	23 (37%)
thrombocytopenia	16 (25.8%)
Raynaud's phenomenon	28 (45.2%)

Table 2 - Frequency of positive testing in patient and control groups.

	Cutt-off values*	Patient (n=62) (%)	Control (n=20) (%)
aCL IgG	>12 GPL U/mL	11 (17.7%)	0 (0.0%)
aCL IgA	>12 APL U/mL	1 (1.6%)	0 (0.0%)
aCL IgM	>12 MPL U/mL	5 (8.1%)	0 (0.0%)
Anti-β2GP1 IgG	>20 RU/mL	8 (12.9%)	0 (0.0%)
Anti-C1q	>20 U/mL	41 (66.1%)	7 (35%)

* As provided by the kit's manufacturer.

the patients included in the study, 34 (54.8%) had a SLEDAI score higher than or equal to 4. Average duration of illness was 103.8 months. Total duration of illness ranged between 2 months and 335 months. Of the 62 patients, 47 (75.8%) had renal involvement and 23 (48.9%) had findings of active nephritis. Of the patients with renal involvement, 13 had biopsy proven proliferative nephritis (class III or IV). Seven patients (11.3%) had a history of thrombosis, 10 (16.1%) had pregnancy complications, 23 (37.0%) had neurologic findings, 16 (25.8%) had thrombocytopenia, and 28 (45.2%) had Raynaud's phenomenon (Table 1).

Prevalence of the aCL isotypes, anti-b2GP1 IgG, and anti-C1q:

The frequencies of positive test results for the aCL isotypes, anti-b2GP1 IgG, and anti-C1q in the patient and control groups are shown in Table 2. Except for anti-C1q (7 positive results in the control group), none of the antibody tests passed

the positivity threshold in the control group. When the two groups were compared using the Mann-Whitney U test, except for aCL IgM, all antibody titers were significantly higher in the patient group (Table 3). When the patients with and without renal involvement were compared, no statistically significant difference was shown (Table 4). There was no significant relation between the presence of proliferative nephritis and anti-b2GP1 IgG, anti-C1q, and aCL presence.

aCL IgG: anticardiolipin antibody IgG, aCL IgA: anticardiolipin antibody IgA, aCL IgM: anticardiolipin antibody IgM, anti-b2GP1 IgG: anti-b2-glycoprotein 1 IgG, anti-C1q: anti-C1q antibodies.

IQR: interquartile range, aCL IgG: anticardiolipin antibody IgG, aCL IgA: anticardiolipin antibody IgA, aCL IgM: anticardiolipin antibody IgM, anti-b2GP1 IgG: anti-b2-glycoprotein 1 IgG, anti-C1q: anti-C1q antibodies.

Table 3: Median and interquartile ranges for the antibody titers of the two groups.

	Patient (n=62) Median [IQR]	Control (n=20) Median [IQR]	P values
aCL IgG (U/mL)	3.18 [2.39-5.57]	1.90 [1.57-2.69]	<0.001
aCL IgA (U/mL)	3.39 [2.54-5.10]	2.15 [2.03-2.50]	<0.001
aCL IgM (U/mL)	2.96 [2.19-5.38]	2.97 [2.39-4.09]	0.957
Anti-β2GP1 IgG (RU/mL)	4.00 [3.17-5.94]	3.19 [2.82-4.10]	0.027
Anti-C1q (U/mL)	30.93 [15.17-79.06]	11.86 [6.78-21.70]	<0.001

Table 4: Antibody levels in patients with nephritis and without nephritis.

	With renal involvement (n=47) Median [IQR]	Without renal involvement (n=15) Median [IQR]	p values
aCL IgG (U/mL)	3.18 [2.41-7.33]	3.14 [2.12-5.30]	0.323
aCL IgA (U/mL)	3.37 [2.57-5.09]	3.66 [2.44-5.35]	0.928
aCL IgM (U/mL)	2.93 [2.19-5.16]	3.45 [2.25-6.00]	0.282
Anti- β 2GP1 IgG (RU/mL)	3.97 [3.47-6.11]	4.08 [3.04-5.33]	0.628
Anti-C1q (U/mL)	29.62 [15.20-55.41]	43.90 [15.08-150.48]	0.712

IQR: interquartile range, aCL IgG: anticardiolipin antibody IgG, aCL IgA: anticardiolipin antibody IgA, aCL IgM: anticardiolipin antibody IgM, anti-b2GP1 IgG: anti-b2-glycoprotein 1 IgG, anti-C1q: anti-C1q antibodies.

When the relation between SLEDAI scores and antibody titers was evaluated, anti-b2GP1 IgG ($r=0.260$, $p=0.04$) and aCL IgA ($r=0.300$, $p=0.016$) had a statistically significant, weak relation with SLEDAI. However, this relation was not seen when antibody titer positivity was evaluated in patients with SLEDAI ≥ 4 . When aCL positivity as a whole (IgA, IgG, and IgM together) was evaluated, patients with SLEDAI ≥ 4 had significantly increased total aCL positivity ($p<0.05$). A weak but statistically significant relation between SLEDAI and anti-C1q was determined ($r: 0.351$, $p=0.005$).

No relation between disease duration and anticardiolipin isotypes, and anti-C1q and anti-b2GP1 IgG positivity was found.

The relation of disease process with aCL and anti-b2GP1 IgG:

When patients with thrombosis were evaluated (7 patients), 4 had (57.2%) aCL IgG positivity, 2 had (28.6%) aCL IgM positivity, 1 had (14.3%) aCL IgA positivity, 4 had (57.2%) anti-b2GP1 IgG positivity, and 3 had (42.9%) anti-C1q positivity. Anti-b2GP1 IgG and aCL IgG were significantly related with thrombosis ($p<0.05$). When aCLs were evaluated as a whole, 3 (6.1%) of the patients without aCLs had thrombotic events, whereas 4 (30.8%) of the patients with aCLs had thrombotic events ($p<0.05$). The positive predictive value of aCL presence was low, 30.8%, but the negative predictive value was high, 93.9%.

Of the 16 patients with thrombocytopenia, 4 (25%) had anti-b2GP1 IgG positivity, 10 (62.5%) had anti-C1q positivity, 5 (31.3%) had aCL IgG positivity, and 2 (12.5%) had aCL IgM positivity. None of the patients with thrombocytopenia had aCL IgA. There was a statistically significant association between the presence of thrombocytopenia and aCL IgG positivity ($p=0.026$).

None of the studied antibodies showed a statistically significant relation with pregnancy complications, neurologic findings, or Raynaud's phenomenon.

Renal involvement and anti-C1q positivity:

No significant relation between anti-C1q and renal involvement was demonstrated ($p=0.243$). The negative predictive value of anti-C1q for renal involvement was 26.3%, and the positive predictive value was 76.7%. When patients with renal involvement were examined, no significant relation between active nephritis and anti-C1q positivity was seen ($p>0.05$).

Anti-ds-DNA presence had a significant relation with active renal involvement ($p=0.006$).

The relation between aCL isotypes and anti-b2GP1 IgG positivity:

Anti-b2GP1 IgG showed a statistically significant correlation with aCL IgG, IgA, IgM, and anti-C1q ($r=0.741$, $p<0.001$; $r=0.375$, $p=0.003$; $r=0.332$, $p=0.008$; $r=0.345$, $p=0.006$, respectively). There was also a statistically significant relation between anti-C1q and aCLs IgG and IgA; between aCLs IgG, IgA, and IgM; and between aCL IgA and aCL IgM. There were no patients with anti-b2GP1 IgG positivity without aCL positivity. Only one patient was positive for all aCL isotypes and anti-b2GP1 IgG. This patient had had deep vein thrombosis 7 years before, and had active renal involvement and Raynaud's phenomenon. Two patients had anti-b2GP1 IgG, aCL IgG, and aCL IgM positivity. One of these patients had a history of deep vein thrombosis and thrombocytopenia, and the other had active renal involvement and thrombocytopenia.

When the 7 patients with thrombosis were examined, none were negative for aCLs and positive for anti-b2GP1 IgG. There were 3 patients with thrombosis who were negative for aCLs and anti-b2GP1 IgG. The other 3 patients with thrombosis were positive for both aCL IgG and anti-b2GP1 IgG.

When the 10 patients with pregnancy complications were studied, 6 (60%) had both aCL IgG positivity and anti-b2GP1 IgG positivity. Two patients (20%) had only anti-b2GP1 IgG positivity. Two (20%) were negative for both antibodies. Antiphospholipid antibody presence was not related to pregnancy complications.

DISCUSSION

The aim of this study was to examine the relation between the clinical characteristics of patients with SLE and their serum levels of aCL isotypes, anti-b2GP1 IgG, and anti-C1q with special emphasis on the nephritogenic and thrombo-

nic antibody profile. A strong relation between aCL IgG and anti-b2GP1 IgG and thrombosis and APS has been reported in the literature.^{2,15,19,26} Similarly, a strong relation between thrombosis and aCL IgG and anti-b2GP1 IgG positivity was also demonstrated in our patient group.

All patients who were positive for anti-b2GP1 IgG were also positive for aCL IgG. Of the patients positive for aCL IgG, 3 (27.2%) were negative for anti-b2GP1 IgG. This finding raised suspicion about the additional clinical value of routine determination of anti-b2GP1 IgG levels. Similarly, Tubach et al. also reported no additional benefit of anti-b2GP1 IgG determination in the diagnosis of APS.¹⁹ The data indicate the futility of routine screening for anti-b2GP1 in the presence of aCL and lupus anticoagulant positivity in patients with SLE. On the other hand, Segovia et al. reported 5 patients who fulfilled APS clinical criteria but were negative for aCL and positive for anti-b2GP1 IgG.²⁷ Similarly, there is a recent report of a patient with bilateral retinal vein thrombosis and APS, who tested negative for aCL and lupus anticoagulant but positive for anti-b2GP1 IgG.²⁸ In a study by Cabiedes et al., it was reported that anti-b2GP1 has a more significant relation with thrombotic events than aCLs.²⁹ In another study, of 47 patients with APS only 6 were aCL negative, and the authors concluded that anti-b2GP1 IgG determination could have some diagnostic value, but it could not precede that of other tests.³⁰

The international consensus statement to define the classification criteria for definite APS states that anti-b2GP1 IgG positivity is common with this syndrome, but since there is not enough standardization for the test and because of the need for further studies to clarify its clinical significance, it has been agreed not to include it in the diagnostic criteria yet. In a prospective study analyzing the relation between aCL and anti-b2GP1 IgG presence with thrombotic events, it was shown that aCL positivity could change with time, but positivity of anti-b2GP1 IgG was more stable during the period of follow-up.³¹ Similarly, in a study by Voss et al., anti-b2GP1 IgG had a stronger relation with thrombotic events when compared to aCLs.³² For this reason, it was proposed that anti-b2GP1 IgG determination could be more beneficial for prognostic and follow-up purposes. Audrain et al. have also reported that anti-b2GP1 IgG had a higher positive predictive value for APS and yet that determination of this antibody would be inutile in patients who do not have APS findings and are negative for aCLs.³³ In the report by Audrain, prophylactic aspirin administration is recommended for patients with anti-b2GP1 IgG positivity. We could not comment on this, since our study did not have a prospective design. In our patient population, the negative predictive value of anti-b2GP1 IgG for thrombosis determination was 94.4%, and the positive predictive value was 50%. We suggest testing for anti-b2GP1 IgG when patients present with APS but test negative for aCL and lupus anticoagulant.

In our study, aCL positivity was related to disease activity. Likewise, after a 3-year follow-up study of patients with SLE with no previous APS, it was concluded that aCL posi-

tivity was not helpful in predicting APS, but aCL titers were directly related to disease activity.²⁰ However, it should be kept in mind that completion of the criteria for APS takes a certain period of time. In a follow-up study by Perez-Vazquez et al., antiphospholipid prevalence was found to be 10% at 7.5 months, 21% at 3.1 years, and 23% after 15-18 years.³⁴ It was demonstrated that an average of 10 years was required for the patients to complete the criteria for APS. An important factor increasing the prevalence across the years was completion of the clinical criteria. At the end of this study, it was concluded that it was not possible to predict clinically the number of patients who would develop APS if the disease course were left uninterrupted.

Besides the thrombotic events, it is reported that events such as thrombocytopenia, neurologic involvement, pregnancy complications, and Raynaud's phenomenon are commonly associated with the presence of antiphospholipid antibodies. For this reason, we analyzed the frequency of these clinical conditions and their relations with the presence of aCL isotypes and anti-b2GP1 IgG. There was a significant relation between thrombocytopenia and aCL IgG in our study. Similar results were reported in the literature.^{2,15} However, when the patients were evaluated for pregnancy complications, neurologic involvement, and Raynaud's phenomenon, no relation was seen with either aCL isotypes or anti-b2GP1 IgG. aCL IgA or aCL IgM positivity had no demonstrable relation with thrombotic events. However, Sebastiani et al. reported aCL IgM to be related to cerebrovascular events and aCL IgA with Raynaud's phenomenon.¹⁵ In accordance with our results, Bertolaccani et al. showed that the determination of aCL IgA was of no clinical benefit.³⁵ In a study by Gunnarsson et al., all patients with proliferative nephritis had increased production of anti-C1q, especially of the IgG subtype. In these patients with proliferative glomerulonephritis, anti-C1q IgG and anti-ds-DNA antibodies reached the highest levels.³⁶ In another study, by Mannik and Wener, it was shown that anti-C1q antibodies are deposited in the kidneys.⁶ In a study by Siegert et al. that studied anti-C1q, complement levels, and anti-ds-DNA antibodies, anti-ds-DNA levels increased before all disease flares, but increases in anti-C1q levels were related to proliferative glomerulonephritis development.⁷ Anti-C1q antibodies show a rise before the start of nephritis.⁹ These studies and other relevant data in the literature suggest that proliferative nephritis has a significant relation with anti-C1q levels,^{7,36-38} and that the change in the titers of anti-C1q could be helpful in predicting lupus nephritis.²¹ In addition, Trendelenburg et al. stated that although anti-C1q positivity was not specific for lupus nephritis it had a significant negative predictive value.³⁹ Yet, Kumar et al. reported that anti-C1q levels were not specific for organ involvement, but could be helpful in predicting disease flares in anti-ds-DNA negative patients.⁴⁰ Recently, a similar result was reported by Cortes-Hernandez et al.²⁵ They found increased levels of anti-ds-DNA, anti-C1q, and anti-histone in patients with a flare.

We studied anti-C1q prevalence in our patient population since prior studies reported that anti-C1q determination

could be helpful in the determination of patients with renal involvement.⁴¹ In the literature, anti-C1q positivity is reported to be less than 10%,^{21,42} whereas in our study this number is higher, 35%. We demonstrated anti-C1q positivity in 66.7% of our patients without renal involvement and in 70% of our patients with renal involvement. Siegert et al. reported anti-C1q positivity in 27% of SLE patients without nephritis and in 58% of SLE patients with nephritis.⁴²

Although Trendelenburg et al. reported the significance of the negative predictive value of anti-C1q titers,³⁹ in our study the negative predictive value of anti-C1q for renal involvement was only 26.3%.

In our patient group, we did not see any relation between anti-C1q positivity and renal involvement or active renal involvement. In our study, among patients with renal involvement, 78.2 % (18/23) of the patients with active nephritis were positive for anti-C1q, whereas 62.5% (15/24) of the patients without active renal involvement tested positive. The difference was not statistically significant. Anti-C1q levels did not show any relation with disease activity. Moroni et al. reported that anti-C1q positivity could be sign of flare in renal involvement.²¹ Kumar et al. and Cortes-Hernandez et al. reported that anti-C1q presence is not specific for renal involvement, but it could be used in predicting disease flare, especially in patients negative for anti-ds-DNA.^{25,40}

Loizou et al. reported that the presence of increased anti-ds-DNA, aCL, and anti-C1q is very specific for glomerulonephritis.¹⁷ According to this study, anti-C1q presence is significantly related to the presence of nephritis. Siegert et al. reported similar results.⁷ However, in our patient population, we only demonstrated that increased anti-ds-DNA antibodies were related to active renal involvement. When patients with renal involvement were analyzed, of anti-ds-DNA antibody positive patients 77.8% (14/18) had active nephritis, whereas of anti-ds-DNA antibody negative patients 31.0% (9/29) had findings of active nephritis.

No relation between renal involvement and aCL isotypes or anti-b2GPI IgG was seen in our study, and this was in accordance with a group of studies.^{16,21,26} In the study by Huong et al., no relation between aCL positivity and presence of nephritis was shown.⁴³

A relation between anti-C1q and proliferative nephritis has been reported in many studies.^{7,36} Moreover, deposition of anti-C1q in renal glomeruli has been shown.⁴⁴ On the other hand, in a prospective study by Gunnarsson et al. with 18 patients with lupus nephritis, there was no relation between renal biopsy results and anti-C1q positivity.⁹ In that study, there were patients with no anti-C1q although they had proliferative nephritis or patients with stable anti-C1q titers despite treatment and improvement. In our patient population, no relation between proliferative nephritis and anti-C1q positivity was seen. Furthermore, there was no relation between aCL isotypes and the presence of proliferative nephritis. This result was in accordance with the results of the study by Fofi et al., who concluded that the WHO classification of renal involve-

ment and antiphospholipid antibodies had no demonstrable relation.⁴⁵

In general, the findings in this group of Turkish patients were in accordance with the general literature. aCL IgG and anti-b2GPI IgG positivity had a close relation with thrombotic events, similar to another study.⁴⁶ There was also a significant relation between aCL positivity and thrombocytopenia.

However, with anti-C1q determinations, both the control and patient groups had higher results than those generally reported. Yet, because the definitions across the studies are not standardized, patient groups are small, and different cut-off values are used across different laboratories, it is difficult to compare and analyze our results with regard to the current literature.

In the light of these findings, it can be concluded that SLE is a disease in which different autoantibodies can lead to different disease patterns and different ethnicities may have a role. Prospective studies with larger populations of patients, taking into regard different ethnicities, may help provide data to design treatment protocols to spare major organ functions.

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Correspondence Address

N. Defne ALTINTAŞ

Kenedy Cad. 72/13 06660 K.esat – Ankara

Tel: 0 312 4369292 - 0 532 6640331

Fax: 0 312 311 0072

Email: defne98hac@yahoo.com

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