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Lack of association between antiphospholipid antibody and WHO classification in lupus nephritis

C. Fofi, M.J. Cuadrado, T. Godfrey, I. Abbs, M.A. Khamashta, G.R.V. Hughes

Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London, U.K.

C. Fofi, MD; M.J. Cuadrado, MD, PhD; T. Godfrey, MD, FRACP; I. Abbs, MD, FRCP; M.A. Khamashta, MD, PhD; G.R.V. Hughes, MD, FRCP.

Please address correspondence and reprint requests to: Dr. Munther A. Khamashta, Lupus Research Unit, The Rayne Institute, St Thomas' Hospital, London SE1 7EH, UK.
E-mail: 106404.2325@compuserve.com

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ABSTRACT

Objective

To study the prevalence of antiphospholipid antibody (aPL) in patients with biopsy proven lupus nephritis (LN) and to investigate if there is any association between the presence of serum aPL and WHO classes.

Methods

Seventy-one patients (68 female and 3 male, mean age 31 years, range 10-67) meeting ACR criteria for the classification of SLE and with biopsy proven LN were included. For every patient, we evaluated anticardiolipin antibodies, lupus anticoagulant and renal biopsy classified according to the WHO classification criteria (activity and chronicity scores were included). Twenty-four hour urinary protein at the time of biopsy was considered.

Results

Twenty-nine patients had class V LN, 27 had class IV, 11 had class III, 3 had class II and 1 had class I. Twenty-seven (40.2%) patients were aPL positive. The prevalence of aPL positive patients was 45% in class V, 33.3% in class IV and 45.6% in class III. We did not find any significant association between the presence of aPL and the WHO class ($p = 0.61$ with class V, $p = 0.31$ with class IV and $p = 0.73$ with class III). There was no association between the presence of aPL and activity ($p = 0.52$) or chronicity scores ($p = 0.42$). We also did not find any association between proteinuria and the presence of aPL ($p = 0.3$).

Conclusions

Our results suggest that there is no association between the presence of aPL and the different WHO classes. The presence of these antibodies does not seem to be related to histological activity or the chronicity of lupus nephritis nor proteinuria.

Introduction

Antiphospholipid antibodies (aPL) have been strongly related to arterial and venous thrombosis and fetal loss. This association is known as the antiphospholipid syndrome (APS). The kidney is a major target organ in APS and the presence of aPL in serum has also been described in primary chronic glomerulonephrits (GN), acute nephropathies such as acute post-streptococcal GN and in non-immune-related renal diseases such as nephroangiosclerosis (1). The role of these antibodies in lupus nephritis (LN) is still controversial. They have been associated with intraglomerular capillary thrombi which may lead to glomerular ischaemia and predispose to subsequent sclerosis with progressive deterioration in renal function (2, 3). Other studies did not find any association between glomerular thrombosis and aPL positivity (4, 5). A more rapid decline in renal function has been observed in aPL positive SLE patients than in aPL negative SLE patients (6, 7).

There are few studies regarding the relationship between aPL and WHO classes in LN and their results are quite controversial. The aim of this study was to assess the prevalence of aPL [anticardiolipin antibodies (aCL) and lupus anticoagulant (LA)] in our SLE patients with biopsy proven LN and to investigate if there is a correlation between aPL and the different WHO classes.

Patients and methods

We retrospectively studied our population of 71 patients (68 female and 3 male) with biopsy proven LN. The median age was 31 years (range 10-67). All patients fulfilled SLE classification criteria (8). Renal biopsies were evaluated according to the WHO classification criteria. The information about biopsies was taken from the pathologist's report. Activity (0-24) and chronicity (0-12) indices were derived from the sum of the scores for individual active or chronic lesions within the biopsies, according to the method of Austin (9). The presence of aPL was reviewed in each patient at the time of biopsy and we considered patients to be positive for aPL when they had at least 2 positive tests separated by more than 8 weeks. aCL was measured by ELISA (10) and LA by the activated partial thromboplastin time (APTT) and the dilute Russell Viper Venom Time (dRVVT). The presence of APS was also investigated. Twenty-four hour urinary protein at the time of biopsy was measured. For our analysis we divided

Table I. Correlation between aPL status and WHO classification in lupus nephritis.

WHO class	n	aCL+	LA+	aPL+	p values*
III	11	3/11	4/11	5 (45.6%)	0.73
IV	27	7/27	6/27	9 (33.3%)	0.31
V	29	10/29	9/27	13 (45%)	0.61
Total	67	20	19	27 (40.2%)	

*When the presence of aPL was correlated with any WHO class.

patients into 2 groups, with 24-hr urinary protein > 3 gm or < 3 gm.

The association between the presence of aCL and LA, APS and the WHO class, activity and chronicity scores in renal biopsies were analysed. We also studied the correlation between aCL and LA and 24-hr urinary protein. Data were processed with the Stat view-J4.02 program using the Chi-square and Fisher tests. The level of significance was $p < 0.05$.

Results

Twenty-nine patients (40.8%) had class V LN, 27 (38% %) had class IV LN and 11 (15.4%) had class III LN. The aPL frequency among the different WHO classes is given in Table I. Four patients (one with WHO class I LN and 3 with class II) were excluded from the statistical analysis because of the small size of the sample. Twenty-seven out of 67 patients (40.2%) were aPL positive (aCL and/or LA). Data about the presence of APS were available in 67/71 patients. Six patients with class V LN, 5 with class IV and 3 with class III had APS. The prevalence of aPL positive patients was 45% in class V, 33.3% in class IV and 45.6% in class III. We did not find any significant association between the presence of aPL and the WHO class ($p = 0.61$ with class V, $p = 0.31$ with class IV and $p = 0.73$ with class III). The activity and chronicity indices were available in 45 patients. Two out of 6 patients with class III LN had an activity score of 10 and no patient had a chronicity score of 5; 11/17 patients with class IV had an activity index of 10 and none had a chronicity index of 5. Three out of 19 of patients with class V had an activity index of 10 and 8/19 had a chronicity index of 5.

Only 1 patient biopsy (class IV LN) showed thrombotic microangiopathy. The description of renal lesions were not available in 10 patients as the biopsy had been performed in other hospitals.

There was no association between the presence of aCL and/or LA and the activity score ($p = 0.52$) or the chronicity score ($p = 0.42$). We did not find any association between proteinuria and the presence of aCL and/or LA ($p = 0.3$). Patients with APS did not have higher chronicity or activity indices when compared with patients without APS.

Discussion

The presence of aPL in SLE and non-SLE patients has been associated with several characteristics of renal impairment, but the pathogenetic role of these antibodies is still unknown. Associations between aPL positivity and hematologic or immunologic parameters of SLE activity have been described (5, 11) but the existence of an association between aPL and the renal histological markers of disease activity remains controversial.

The prevalence of aPL found in our patients with LN was 40.2%; this data is similar to that described in other studies (1, 6, 7, 12, 13) while it seems to be higher in the pediatric population (67%) (5). A higher prevalence of aPL in LN compared to other renal diseases has been described (2), but there are few data regarding an association between aPL and the different WHO classes in lupus nephritis.

In our study we did not observe a higher prevalence of aPL in any WHO class. Pasquali *et al.* (14) did not find a clear association between aPL and the different WHO classes. However, a higher frequency was found in patients with pure membranous LN compared to those with membranous LN and proliferation.

In contrast to this report, one study including 88 SLE patients showed that aCL correlated with thrombosis, thrombocytopenia, neuropsychiatric features and class V lupus nephritis, and the authors hypothesized that this might explain the higher incidence of renal vein thrombosis in patients with membranous LN (15). Some authors (13) found an association between the presence of IgG aCL and intra-glomerular thrombi and speculated that aPL may contribute to the pathogenesis of nephritis, but did not find an association between aPL and renal morphology defined by the WHO classification or long term renal function. In our series, thrombotic microangiopathy was found only in one patient who had class IV LN. Therefore, in our study the presence of thrombi is not associated with other active or chronical lesions in renal biopsy.

Perdiguero *et al*. (7) in a study of 23 patients found that class IV LN was the most common in both aPL positive and aPL negative patients (60.8%). The histological pattern was similar between aPL positive and negative aPL patients, with no differences in the evolution of renal function and no relation between the presence of aPL and ANA, anti dsDNA, ESR, immunoglobulin and complement level.

We did not find any association between the presence of aPL and the activity or chronicity scores. Furthermore, the presence of aPL in our series was not associated with intravascular thrombi as only one patient showed this finding in the biopsy. Studies on repeated renal biopsies in the same patient have shown that glomerular thrombi (one of the activity markers) in the initial biopsy strongly predicted evolution toward glomerular sclerosis. Other typical markers of histological activity such as necrosis or crescents were not similarly predictive (2). In a study on 51 patients, an association between aCL and pathological markers of disease activity has been found and the presence of aPL is described as a significant predictor of the course of LN (6). The difference with our results might be due to the lack of standardiza-

tion to measure aPL, the fluctuation of aPL or the subjective interpretation of biopsies among different pathologists.

In our study we did not find any positive or negative association between the presence of heavy proteinuria and the presence of aPL. Perez-Vazquez *et al.* (16), in an attempt to ascertain whether the negative association between nephrotic syndrome and serum aPL found in a previous study on 667 patients was due to urinary loss of aPL, investigated the presence of aPL in the urine of 6 SLE patients who had elevated serum aPL levels and developed nephrotic syndrome. They found urinary excretion of IgG but no IgM aPL. There was an apparent correlation between serum and urine IgG aPL levels, but not between urinary IgG aPL and total proteinuria. Several factors (such as decreased synthesis, increased catabolic rate or the effect of immunosuppressive treatment) may influence the serum levels of immunoglobulin in patients with nephrotic syndrome.

In summary, the prevalence of aPL in our series of patients with LN was 40.2%. We did not find any significant association between the presence of serum aPL and the different WHO classes or the presence of thrombotic microangiopathy. The presence of aPL at the time of biopsy does not seem to be related to histological activity or chronicity of LN or to proteinuria.

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