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ARTÍCULO ORIGINAL

Clinical and immunological factors associated with lupus nephritis in patients from northwestern Colombia

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A cross-sectional and multicenter study was undertaken to analyze the clinical and immunological characteristics at diagnosis associated with nephritis in northwestern Colombian patients with systemic lupus erythematosus (SLE). Thirty nine patients with lupus nephritis were included and were compared to 100 SLE patients without nephritis. A multivariate analysis was performed. The patients who developed nephritis had a higher frequency of oral ulcers (41% vs. 21%, OR=3.1, 95%CI: 1.3-7.5 *p*= 0.01) and malar erythema (77% vs. 45%, OR=4.4, 95%CI: 1.8-10.8 *p*=0.001). Lupus nephritis was observed in 77% of cases during the first year of the disease. The frequency of anti-DNA antibodies was higher in patients with nephritis, however, differences were not statistically significant (83% vs 64%, OR=2.6, 95%CI: 1.03-6.41, *p*=0.06). The presence of other autoantibodies (anti-Ro, anti-La, anti-RNP, anti-Sm and anticardiolipin) at diagnosis was similar in both groups. This autoantibody profile remained unchanged throughout the evolution of the disease. Patients with lupus nephritis had a higher prevalence of arterial hypertension (60% vs 10%, OR=13.7, 95%IC: 5-37, *p*=0.00001) and hyperlipidemia (30% vs 7%, OR=8.1, 95%IC: 2.5-27, *p*=0.0006) at onset. Finally, patients with lupus nephritis required more hospitalizations (>1) over the course of disease (89% vs 60%, OR=7.8, 95%CI: 2.1–29, *p*=0.002). In conclusion, lupus nephritis appears early during the course of SLE. Malar erythema, oral ulcers, hypertension and hyperlipidemia at onset of disease are associated factors. Lupus nephritis is a major risk factor leading to repeated hospitalizations. This study may help to assist in public health policies in our population in order to improve patient outcomes while simultaneously reducing disease costs.

Key words: systemic lupus erythematosus, lupus nephritis, risk factors, autoantibodies, hypertension, hyperlipidemia, Colombia.

Factores clínicos y epidemiológicos asociados con nefritis lúpica en pacientes del noroccidente colombiano

Este estudio transversal y multicéntrico investigó las características clínicas e inmunológicas asociadas con la nefritis lúpica en pacientes colombianos de Medellín. Se incluyeron treinta y nueve pacientes con nefritis lúpica y se compararon sus características con las de 100 pacientes con lupus eritematoso sistémico (LES) sin compromiso renal. Se realizó un análisis multivariado para evaluar los factores asociados con la nefritis lúpica. Los pacientes que desarrollaron nefritis presentaron, al inicio, más úlceras orales (41% vs. 21%, OR=3,1, IC95%: 1,3-7,5, *p*=0,01) y eritema malar (77% vs. 45%, OR=4,4, IC95%: 1,8-10,8, *p*=0,001) que aquellos pacientes sin nefropatía. La nefritis lúpica se observó en 77% de los casos durante el primer año de evolución del LES. La frecuencia de anticuerpos anti-ADN fue mayor en los pacientes con nefritis; sin embargo, las diferencias no fueron significativas (83% vs. 64%, OR=2,57, IC95%:1,03-6,41, *p*=0,06). La presencia de otros anticuerpos (anti-Ro, anti-La, anti-RNP, anti-Sm y anticardiolipina) en el momento del diagnóstico fue similar en ambos grupos. El perfil de los autoanticuerpos

permaneció sin modificación significativa durante el curso del LES. Los pacientes con nefritis lúpica presentaron una mayor prevalencia de hipertensión arterial (60% vs 10%, OR=13,7, IC95%: 5-37, *p*=0,00001) y dislipidemia (30% vs 7%, OR=8,1, IC95%: 2,5-27, *p*=0,0006) al inicio de la enfermedad que aquellos pacientes sin nefropatía. Los pacientes con nefritis lúpica requirieron más hospitalizaciones (>1) durante el curso de la enfermedad (89% vs 60%, OR=7,8, IC95%: 2,1-29, *p*=0,002). En conclusión, la nefritis lúpica se presenta tempranamente en el LES. El eritema malar, las úlceras orales, la hipertensión arterial y la dislipidemia son factores asociados. A su vez, la nefritis lúpica es un factor de riesgo de hospitalizaciones repetidas. Este estudio puede ser útil en la toma de decisiones de políticas de salud para beneficio de los pacientes y reducción de costos.

Palabras clave: lupus eritematoso sistémico, nefritis lúpica, factores de riesgo, autoanticuerpos, hipertensión arterial, dislipidemia, Colombia.

Systemic lupus erythematosus (SLE) is an autoimmune systemic disease characterized by a loss of immunologic tolerance to a multitude of self-antigens that may produce variable clinical manifestations. The clinical course is characterized by periods of remissions and acute or chronic relapses. The reported prevalence of SLE is 40-50 cases per 100,000 persons. Women in child-bearing age, in particular African-Americans, African-Caribbeans, Hispanic-Americans and Asians, are at higher risk (1,2). The diverse manifestations of SLE include the involvement of skin, joints, nervous system, renal, and hematological systems (3).

Lupus nephritis is one of the most serious complications of SLE being the major predictor of poor prognosis (2,3). The mortality is greater in patients with lupus nephritis than in those without renal damage (4). Among those patients with lupus nephritis, near 70% develop renal insufficiency (2).

Diverse clinical manifestations have been associated with lupus nephritis, the most frequently being malar erythema, pericarditis and arterial hypertension (5). The main laboratory associated abnormalities reported are anemia and low levels of serum complement. High titers of antibodies anti-dsDNA have also been associated with lupus nephritis activity (2). However, clinical manifestations of SLE vary according to ethnicity and geography (2). In this study we analyzed the clinical and immunological characteristics of patients with lupus nephritis from Medellin, northwestern Colombia.

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Patients and methods

Study population

This was a cross-sectional and multicenter study done during the period of January to June 2002. We included patients with lupus nephritis being treated at rheumatology units in the Clínica Universitaria Bolivariana, Corporación para Investigaciones Biológicas (CIB), Hospital Pablo Tobón Uribe, and Congregación Mariana, in Medellín. All patients met at least four of the classification criteria for SLE (6). In addition, patients with SLE without nephritis were also included. Patients without a complete medical record or those who did not meet SLE diagnosis criteria were excluded. From an ethical point of view, the study complied with Resolution No. 008430, 1993, issued by the Ministry of Health of the Republic of Colombia, and was classified as minimal risk research. The CIB Ethics Committee approved the study.

Clinical variables

Information on patient demographics and cumulative clinical and laboratory manifestations over the course of disease were obtained either by verification during discussion with the patient or by chart review, and were collected in a standard data collection form created for that purpose. Demographic, clinical and laboratory variables were included in the collection form. A guide for the data collection form was made to guarantee its reproducibility (k>0.6). Each clinical and

laboratory variable was registered as "present" or "absent" for each specific patient at the moment of diagnosis and then at any time during the course of the disease.

The clinical and laboratory variables associated with SLE, including each feature of the revised ACR criteria (6), were evaluated and defined as follows: 1) arthritis: non-erosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling or effusion; 2) malar rash; 3) photosensitivity; 4) alopecia; 5) discoid lupus; 6) Raynaud's phenomenon; 7) renal involvement: a renal biopsy result demonstrating World Health Organization (WHO) class II-V histopathology, active urinary sediment or proteinuria >500 mg/24 h. Nephrotic syndrome was defined as more than 3.5 g/day of proteinuria, hypoalbuminemia (less than 2.8 g/dl), hyperlipidemia and edema. Lupus nephritis was defined as present or absent according to the abnormalities of the previous tests; 8) neurologic involvement, as evidenced by seizures without any other definable cause, or psychosis lacking any other definable cause, or other conditions such as peripheral neuropathy, stroke, transverse myelitis, chorea, or other central nervous system lesions directly attributable to SLE in the absence of other causes; 9) pleuritis: pleural rub and/or effusion and/or typical pleuritic pain; 10) pericarditis: documented by electrocardiogram, rub, or evidence of pericardial effusion; 11) autoimmune hemolytic anemia, with an hematocrit count <35%, reticulocyte count >4%, and positive Coombs test; 12) leukopenia, white cells <4,000/mm^3; 13) thrombocytopenia, platelets <100,000/mm^3; 14) arterial or venous thrombosis diagnosed on clinical grounds and confirmed by appropriate tests.

Comorbidity at the moment of the first evaluation was also recorded, and included the presence or absence of arterial hypertension (blood pressure levels >140/90); diabetes mellitus (fasting glycemia $\geq$126 mg/dl in two occasions); coronary disease (history of myocardial infarction, stable or unstable angina), hyperlipidemia (LDL cholesterol >130 mg/dl and triglycerides >150 mg/dl); hypothyroidism (TSH >5 mU/L). The number of hospitalizations during the course of the disease was also registered.

Severity of disease

Disease severity and organ damage was evaluated using the systemic lupus international collaborating clinics (SLICC) damage index (SDI) (7).

Autoantibodies

Antinuclear antibodies (ANA) were determined by indirect immunofluorescence using HEp-2 cells as substrate, and anti-dsDNA antibodies were determined by indirect immunofluorescence with *Crithidia luciliae* as substrate, and by ELISA. Precipitating antibodies to extractable nuclear antigens, including Sm, U1-RNP, Ro/SSA, La/SSB, as well as anticardiolipin antibodies were detected by ELISA using diverse commercial kits.

Statistical analysis

Descriptive statistical data was computed. For the normal variables, mean and standard deviations (SD) are reported, and for the non-normal variables, medians and interquartile ranges (IQR) are reported. The test for normality was that of Kosmogrorov-Smirnov. The odd ratios (OR) are reported with 95% confidence intervals. A level of 1% of significance was established. The Bonferroni correction was done for multiple comparisons. A multivariable analysis was done and adjusted by age and time of duration of the disease through the estimation of OR using non conditional logistic regression. The analysis was performed using the SPSS software (8).

Results

Thirty nine patients with lupus nephritis were included in the study and were compared to 100 SLE patients without nephritis. The main clinical characteristics present in patients are shown in Table 1. The clinical manifestations at diagnosis were similar in both groups (Table 1). However, the multivariable analysis disclosed that patients who developed nephritis had a higher frequency of oral ulcers and malar erythema (Table 2). Lupus nephritis was observed within the first year following diagnosis in 30 (77%) cases. There were 6 (15%) cases of nephritis during the second year, 2 (5%) during the third year and one case (3%) at the fifth year of the disease. Fifteen lupus nephritis patients (38%) presented nephrotic syndrome;

Table 1. General characteristics of northwestern Colombian patients with SLE.

Characteristic	Nephritis n=39	Without nephritis n=100
Age, years (mean ± SD)	33 ± 14	33 ± 10
Gender, male: female	5:34	5:95
SLICC (median, IQR)	0 (0 - 5)	1 (0 - 5)
Duration of disease, years (mean ± SD)	3.9 ± 4.7	3.6 ± 4.3
Photosensitivity*	69	61
Oral ulcers*	41**	21
Malar erythema*	77**	45
Discoid lupus*	15	10
Serositis*	20	7
Neurologic involvement*	26	21
Arthritis*	72	77
Hemolytic anemia*	3	5
Leucopenia*	47	30
Thrombocytopenia*	21	19

SD: standard deviation, IQR: interquartile ranges.
* Clinical characteristics are reported in frequencies and at onset of disease.
** See Table 2.

proteinuria was present in 36 patients (92%). A renal biopsy was performed in 25 (64%) patients, with the corresponding reports indicating WHO grades III and IV in 20 cases (80%).

The frequencies of anti-DNA antibodies at onset were higher in patients who developed lupus nephritis (83%) as compared to patients who did not (64%), however, these differences were not statistically significant (OR=2.57, 95%CI: 1.03-6.41, *p*=0.06). The presence of ANA (97% vs. 94%), anti-Sm (37% vs 42%), anti-RNP (42% vs. 44%), anti-Ro (38% vs 47%), anti-La (32% vs. 31%), IgG anticardiolipin (44% vs. 39%), IgM anticardiolipin (33% vs. 34%), and lupus anticoagulant (13% vs. 19%) at diagnosis was similar in both groups. This autoantibody profile remained unchanged throughout the evolution of the disease.

At diagnosis and over the course of SLE, patients with nephritis as well as those without it had a similar proportion of abnormalities in other organs. Although the frequencies of cardiopulmonary (41% vs. 20%) and vascular manifestations (15% vs. 6%) were higher in patients with lupus nephritis as compared to patients without nephritis, these differences were not statistically significant in the multivariate analysis. Conversely, SLE patients with nephritis had a higher prevalence of arterial hypertension and hyperlipidemia when compared to patients without nephritis (Table 2). Finally, patients with nephritis required more hospitalizations (>1) than patients without nephritis (89% vs. 60%, OR=7.8, 95%CI: 2.1 - 29, *p*=0.002).

Discussion

In this study we observed that lupus nephritis appears early during the course of SLE. Malar rash, oral ulcers, hypertension and hyperlipidemia at onset of disease were found to be important associated factors. In addition, we observed that lupus nephritis is a major risk factor leading to repeated hospitalizations.

Although this study was not designed to evaluate the prevalence of lupus nephritis, previous reports from Medellín have shown that nephritis is found frequently (up to 53%) among SLE patients (9,10). Our results confirm previous studies showing that lupus nephritis in northwestern Colombian patients occurs early during the course of SLE (11,12).

Although the presence of ANA and anti-dsDNA antibodies are useful markers for the diagnosis of SLE, controversy exists about their value as an indicator of disease activity or as predictor of lupus nephritis (2,13). The relatively small numbers of

Table 2. Risk factors associated with lupus nephritis in northwestern Colombian patients (multivariate analysis).

	Nephritis n=39 (%)	Without nephritis n=100 (%)	OR	95% CI	*p*
Malar erythema	77	45	4.4	1.8 - 10.8	0.001
Oral ulcers	41	21	3.1	1.3 - 7.5	0.01
Hypertension	60	10	13.7	5 - 37	0.00001
Hyperlipidemia	30	7	8.1	2.5 - 27	0.0006

lupus nephritis patients in this study may explain the observed lack of association between anti-dsDNA antibodies and nephritis. Nevertheless, its prevalence was higher among lupus nephritis patients than those SLE patients without renal involvement. In a previous series of patients with lupus nephritis from Medellín, Pinto *et al.* observed that anti-Ro and anti-La antibodies were less frequent in lupus nephritis patients than in SLE patients without nephritis (14), suggesting a protective role for these antibodies. It should be emphasized that the presence of serum autoantibodies does not, by itself, correlate with the severity of the renal lesion. Patients with low levels of circulating autoantibodies have been observed to develop severe nephritis, and the corollary is that individuals with circulating autoantibodies have been reported to have mild or absence of disease (2,15-17). These observations indicate that qualitative/structural features of antibodies, rather than the magnitude of the immunoglobulin excess in the serum, are important in the immunopathogenesis of lupus nephritis.

In our study, the titers of autoantibodies were not considered (see methods section), thus we were unable to examine the influence of their levels on clinical variables including lupus nephritis. Other studies have found that patients with lupus nephritis had significantly higher levels of anti-dsDNA antibodies than patients with no renal disease (18,19). Anti-dsDNA antibodies may be present in SLE patients sera much earlier than previously suspected. Arbuckle *et al.* observed that SLE patients with a significant rise in anti-dsDNA antibodies at diagnosis were more likely to have renal disease than those who did not (20).

As mentioned earlier, not all antibodies can be equally pathogenic: some cause severe nephritis while others do not. The pathogenic, more specifically “nephritogenic”, autoantibodies have been characterized as being predominantly immunoglobulin G in isotype, cationic in charge, highly cross-reactive, and having features unique to their antigen-binding region that predisposes them to bind both intracellular and extracellular antigens (21-23).

Antiphospholipid antibodies have also been suggested to predict lupus nephritis (24). However, others have observed a lack of association between these antibodies and histological activity, chronicity of lupus nephritis or proteinuria (25). In our study, we did not find such antibodies to be associated with lupus nephritis. Alternatively, some studies have suggested a protective effect of rheumatoid factor as well as anti-La/SS-B antibodies in the development of lupus nephritis (3,5,13,26,27).

Some clinical characteristics have been associated with lupus nephritis, including malar erythema, pericarditis and arterial hypertension (5). The present study showed similar findings, 77% of the patients with lupus nephritis had malar erythema and 60% had hypertension at diagnosis, indicating that these manifestations are associated with renal involvement in northwestern Colombian patients with SLE. Previous reports have shown that hypertension and hyperlipidaemia are also associated with renal outcome and mortality in patients with a long-term outcome of lupus nephritis (24,28). Aggressive treatment of hypertension and hyperlipidaemia is therefore essential in early lupus nephritis in order to prevent further deterioration of renal function as the disease progresses (29).

Although morbidity and mortality from cardio-vascular and cerebrovascular diseases are common among women with SLE, in a multivariate analysis, Ward (30) found that risks for these outcomes were not greater among women with end-stage renal disease (ESRD) caused by lupus nephritis than among other women without diabetes with ESRD. Alternatively, the presence of anti-Ro antibodies has been associated with a greater potential for progressing to ESRD (31). Among the Hopkins Lupus Cohort, SLE patients with low C3 or thrombocytopenia were at greater risk to develop later lupus nephritis (32). Petri has highlighted that some of the predictors of later lupus nephritis might actually represent subclinical renal disease. For example, SLE patients who are anemic or hypertensive are more likely to later develop lupus nephritis (32).

As stated earlier, clinical manifestations of SLE may vary according to ethnicity. Recently,

Seligman *et al.* (33), in a retrospective analysis, found that male non-European Americans (including Mexicans and Hispanics), and patients who were younger than 33 years at SLE diagnosis were more likely to develop nephritis. British studies (34) suggest that patients of Afro-Caribbean and Asian origin living in the United Kingdom develop a more severe disease, including renal manifestations, than whites do. Similarly, a French study (5) reported a higher rate of renal complications for non-French nonwhite patients, particularly those of West Indian and Asian descent. In the 1980s, one of the largest North American studies (35) found that more Asian Americans had lupus nephritis than did European Americans (67% vs. 22%), but failed to find significant differences for Hispanic Americans and African Americans. More recently, the LUMINA study group observed that in African-American and Hispanic (Mexican or Central American) ethnicities, anti-dsDNA and anti-RNP antibodies were significant predictors of the occurrence of lupus nephritis (36).

It is well known than hospitalizations among SLE patients is much more frequent than among the general population (37), and that active disease is one of the main causes of hospitalization among those patients (38). Our study adds further evidence indicating that lupus nephritis represents a significantly higher risk for hospital requirements among patients with SLE.

The design of the current study and the nature of settings (third level hospitals) did not allow for uniform data collection and may have affected the classification of patients in terms of nephritis, for example, due to differences in access to care and resultant delays in the diagnosis of lupus or its complications. Other limitations of our study include the relatively small number of men. We also lacked information that might have influenced the risk of nephritis, including genetic and socioeconomic factors (36,39). Longitudinal studies are warranted to assess the prediction of lupus nephritis on quality of life and mortality. Finally, the current SLICC damage index was found to be inaccurate to discriminate the severity of SLE according to the presence of lupus nephritis (Table 1).

In brief, we have evaluated the clinical and immunological factors associated with lupus nephritis in northwestern Colombian patients. We hope that this study will serve to adopt public health policies aimed at improving patient outcome while simultaneously reducing disease costs. Our study stresses the need to further investigate the different factors associated with SLE in Colombians before extrapolating the results obtained to other populations (40).

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