*Inmunología*
Vol. 23 / Núm 3/ Julio-Septiembre 2004: 278-283

# Silent lupus nephritis

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## *NEFROPATÍA SILENTE EN LUPUS ERITEMATOSO SISTÉMICO*

RESUMEN

La nefropatía lúpica (NL) incrementa la morbilidad y mortalidad asociada al lupus eritematoso sistémico (LES) pero el compromiso renal se expresa clínicamente, sólo en unas dos terceras partes de los pacientes. Un alto porcentaje de pacientes con LES pueden tener alteraciones morfológicas renales sin manifestaciones clínicas. Esta condición ha sido llamada nefropatía lúpica silente (NLS) y sólo puede ser confirmada por biopsia renal. Recientemente, nosotros detallamos las características inmunoclínicas y patológicas de la NLS en 41 de 42 pacientes con LES sin manifestaciones clínicas renales. La información colectada en este estudio y la obtenida de la búsqueda bibliográfica realizada, conforman la base de este artículo de revisión en el que se analizan las características patogénicas, inmunoclínicas, histopatológicas, de evolución y de pronóstico de esta patología.

Independientemente de las controversias relativas al diagnóstico, pronóstico y tratamiento de la NLS, nosotros creemos que se requiere de un diagnóstico histológico preciso para el seguimiento y tratamiento adecuado de la lesión glomerular en NL, incluyendo aquellos pacientes con NLS. Se requieren además estudios prospectivos para la búsqueda de marcadores confiables inmunopatológicos con el fin de precisar no sólo los patrones posibles de progresión de la NLS sino su respuesta a protocolos terapéuticos razonables.

PALABRAS CLAVE: Lupus eritematoso sistémico / Nefritis lúpica / Nefropatía lúpica.

ABSTRACT

Lupus Nephritis (LN) increases the morbidity and mortality associated with Systemic Lupus Erythematosus (SLE) but renal clinical involvement is only expressed in about two-third of the patients. A much higher percentage would have morphologic evidences of renal disease without clinical manifestations. This condition has been referred as Silent Lupus Nephritis (SLN) and may only be confirmed if renal biopsy is performed systematically. Recently, we further detailed the immunoclinical and pathological characteristics of SLN in 41 out of 42 patients that were SLE bearers of SLN. The data recorded from this study and the information obtained from the bibliography, conform the basis of this review where the characteristics in pathogenesis, immunoclinical, histopathological, evolution and prognosis are considered.

Irrespectively of the controversies regarding diagnosis, prognosis and treatment in SLN, we believe that a precise histological diagnosis is required for a rational management and follow-up of the glomerular lesion in LN, including those present in SLN patients. Prospective studies are required to further seek for eventual immunopathological markers to assess not only the possible patterns of SLN progression but its response to comprehensive therapeutic protocols.

KEY WORDS: Lupus nephritis / Silent lupus nephritis / Systemic lupus erythematosus.

**TABLE I.** Diagnostic criteria for silent lupus nephritis

| Patient | Criteria | Ref |
|---|---|---|
| SLE diagnosis | 4 or more criteria of the American College of Rheumatology for SLE | 35 |
| Absence of renal clinical manifestations | Normal plasma creatinine: 0.6 to 1.4 mg/dl<br>Normal creatinine clearance: 70 to 120 ml/min/square meter of body surface<br>Absence of clinical proteinuria : ≤ 300 mg/day in 24 hours urine collection<br>Normal urinary sediment:<br>Leucocytes: 1-5 per X 40 power field<br>Erythrocytes: 1-5 per X 40 power field<br>Casts: absent | 24 |
| Glomerular lesions in renal biopsy | Patients with class II, III, IV, V or VI of the WHO classification of glomerulonephritis in SLE | 42 |

## INTRODUCTION

Lupus Nephritis (LN) is one of the most frequent and serious complications of Systemic Lupus Erythematosus (SLE). The renal manifestations of SLE are highly pleomorphic with respect to their clinical and morphologic expressions[1-4]. Clinical involvement is expressed in about two-third of patients[5-11], but several studies published since the 1970´s proved that a much higher percentage would have morphologic evidences of renal disease without clinical manifestations[12-17]. This condition has been referred as Silent Lupus Nephritis (SLN) and may only be diagnosed if renal biopsy is performed systematically[13-16,17-23] (Table I).

Recently, we investigated and detailed the immunoclinical and pathological characteristics of SLN in 41 out of 42 patients with SLE without renal clinical manifestations[24]. The data recorded from this study and the information obtained from the bibliography related with this subject conform the basis of this review.

## PATHOGENESIS

The presence of possible pathogenic autoantibodies capable of structuring complement activating immune complexes in SLN patients allows us to emphasise their possible participation in the induction of early silent glomerular lesions. Among them, cationic anti-ds DNA antibodies, which are able to interact with heparin sulphate heavily present in the glomerular basement membrane, would facilitate the deposition and/or the *in situ* formation of immune complexes and the local activation of the complement cascade[25,26]. A large body of work suggests that anti-DNA antibodies play a determinant role in the pathogenesis of lupus nephritis, although autoantibodies with other specificities may also participate[27]. Some experiments have shown that nephritogenic lupus antibodies bind directly to glomerular endothelial or mesangial cells to initiate nephritis, whereas other investigators have observed that some anti-DNA, anti-histone and anti-nucleosome antibodies bind to nucleosomes previously localised within the glomeruli[28]. In Lupus prone mice, engineered so they lack T cells or specific cytokines, limited disease may be found despite a great deal of autoantibodies deposition; these findings suggest that T cell participate in the initiation of glomerulonephritis[29]. B cells have a role in the generation of antibody forming cells and are important as antigen-presenting cells for CD4+ T cells. They also participate in the activation of autoreactive T cells and promote the secretion of a variety of cytokines and chemokines following sustained renal disease[30].

In this context, it is also pertinent to mention that recently Arbuckle et al.[31] examining sera stored for over 10 years have reported the detection of anti-ds DNA antibodies many years before the clinical onset of overt SLE. Furthermore, we have previously reported employing a cluster analysis approach, that the absence of antibodies against extractable nuclear antigens (anti-ENA) increased eleven fold the odd ratio to develop SLE nephritis[32]. In the SLN study, we found the same trend although the differences between the two groups of SLE patients did not reach statistical significance.

## IMMUNOCLINICAL CHARACTERISTICS

In our study we concluded that patients fulfilling the defined criteria for SLN (Table I) showed universal prevalence of histopathological changes associated to significantly elevated levels of ANA, anti-ds DNA and CIC along with diminished CH50, C4 and C3 serum levels. These data suggested that SLN may represent an early stage in the

TABLE II. Silent lupus nephritis: WHO classes reported in 204 patients from the reviewed literature (1975-2003)

| Authors | Ref. | Total R. B* | WHO Class I | II | III | IV | V | VI |
|---|---|---|---|---|---|---|---|---|
| Cruchaud et al. 1975 | 12 | 6 | 0 | 5 | 0 | 1 | 0 | 0 |
| Eiser et al. 1979 | 13 | 13 | 3 | 4 | 3 | 3 | 0 | 0 |
| Hollcraft et al. 1976 | 14 | 10 | 0 | 0 | 0 | 10 | 0 | 0 |
| Mahajan et al. 1977 | 15 | 15 | 0 | 3 | 12 | 0 | 0 | 0 |
| Bennet et al. 1982 | 17 | 20 | 3 | 4 | 9 | 3 | 0 | 1 |
| Cavallo et al. | 18 | 8 | 0 | 4 | 0 | 4 | 0 | 0 |
| Font et al. 1987 | 19 | 15 | 6 | 7 | 2 | 0 | 0 | 0 |
| González et al. 1996 | 20 | 20 | 9 | 6 | 0 | 3 | 2 | 0 |
| Miyata 1993 | 22 | 16 | 0 | 16 | 0 | 0 | 0 | 0 |
| Woolf et al. 1979 | 23 | 8 | 0 | 2 | 2 | 4 | 0 | 0 |
| Zabaleta et al. 2003 | 24 | 42 | 1 | 26 | 4 | 5 | 6 | 0 |
| Roujeau et al. 1984 | 43 | 7 | 5 | 0 | 0 | 2 | 0 | 0 |
| Stamenkovic et al. 1986 | 59 | 24 | 11 | 7 | 0 | 5 | 1 | 0 |
| Total | | 204 | 38 | 84 | 32 | 40 | 9 | 1 |

*R.B: Renal biopsies.*

natural history of LN. A large study performed in a single centre by Font et al.[33], has shown cluster associations between certain clinical, haematological, and immunological features in SLE, reflecting specific patterns of disease expression. However, we do not know yet if specific markers could predict early in the course of the disease what cases may progress to more severe forms of LN and advanced renal failure. In addition, the question remains as to which patients should be treated in the early phase of the disease with potentially harmful drugs such as Cyclophosphamide.

Nevertheless, our results offer new and solid evidences in favour of the rationale of performing renal biopsy in patients with SLE; moreover, this procedure may provide valuable information about the class, severity, activity and chronicity index of renal compromise when SLN is present, which cannot be predicted on the basis of only extra renal clinical manifestations.

In our series, SLN was present in 97.6% of the patients with absence of clinical manifestations. This is coincident with previous studies, which have clearly shown that lesions of varying severity may occur in almost all SLE patients without clinical findings of renal involvement (Table II)[13-16,17-23].

Traditionally, only 25 to 50% of unselected patients with SLE have abnormalities in the urine or in renal function early in their course, although up to 60% of adults and 80% of children may later develop overt renal abnormalities[34]. It is also important to stress that renal lesions were found in our SLN, indistinct of time of evolution from apparent onset, age of the patient, gender or degree of extrarrenal clinical activity of the disease as measured by the SLEDAI scale.

## HISTOPATHOLOGICAL CHARACTERISTICS

The histological data that emerged from our study deserve some comments. WHO Class II was present in 64% of patients with SLN while the prevalence of class IV was observed in only 7.7% of the cases. WHO class II and less frequently class V may be found in early stages of the disease, before overt extrarrenal manifestations of SLE and serologic markers are detectable and months or years before the American College of Rheumatology criteria for SLE diagnosis are fulfilled[15,35,36]. These findings and those encountered in our investigation tend to confirm the idea that SLE is in fact a polymorphic clinical syndrome with a wide range of immunoclinical expressions even in the early course of the disease. At these early stages the manifestations may go from high levels of anti-ds DNA antibodies detected prior to clinical diagnosis to tissue damage, i.e. Overt Lupus Nephropathy (OLN) with WHO classes II or V without extrarrenal manifestations of SLE and absence of serologic markers. On the other hand, as in previously published series[1-11,37-41] WHO Class IV was the most prevalent histological form (51%) found in the group of SLE patients with OLN, while WHO class II was only found in 14% of these cases.

More recently, a new consensus was reached to formulate a revised classification of LN[42]. This new proposal recognised

Class I (from WHO LN histopathological classification) as the earliest SLE renal abnormality. Class I is characterised by normal glomeruli (light microscopy) and mesangial immune deposits detected by immunofluorescence (IF). Class II shows purely mesangial hypercellularity of any degree or mesangial matrix expansion by light microscopy with immune deposits as demonstrated by IF. Moreover, a few isolated subepithelial or subendothelial deposits may be visible by IF but not by light microscopy. We anticipate that the vast majority of SLN patients would show changes compatible with class I or II of this new guideline. In previous reports immunodeposits detected by IF or transmission electron microscopy without renal histological lesions and clinical abnormalities have been described in patients with SLE and discoid lupus[12,18,43].

## EVOLUTION

Although genetic and environmental factors that influence the evolution of the disease have been identified, the reason why some patients have mild renal lesions and others have fulminant or rapidly evolving renal injury remains a mystery[44]. Several prognostic indexes have been published but we still do not have definite clinical or histological predictors with high specificity and sensitivity of the natural history of LN[4,40,45-48]. The determination of urinary albumin excretion is considered by some authors as an important tool in the early detection of renal involvement in SLE[49-51]. Regarding SLN, we also do not know the prognostic significance of renal changes, a matter that also remains controversial[20,52].

## CLINICAL AND PROGNOSTIC SIGNIFICANCE

The clinical and prognostic significance of SLN has been a matter of debate. Some authors, based upon retrospective studies, consider that end stage renal failure is rare in this variety of LN, regardless of the histopathological renal lesion and that the patient's survival depends on non-renal causes[1,10,19,20,53,54]. According to this viewpoint, renal biopsy is useless in SLE patients without clinical renal manifestations. Other authors however, have reported that diffuse proliferative glomerulonephritis and other histological changes are related with a poor outcome[15,18,21,23,52,55-61]. Besides, we know that LN is not a static entity and it has a high capacity of transformation from one histological class to another[1,16,61-66].

## CONCLUSIONS

Irrespective of the controversies regarding diagnosis, prognosis and therapy in SLN, we believe that renal biopsy should be included in the initial work-up of patients fulfilling the diagnosis of SLE even in the absence of renal findings. Furthermore, since a precise histological diagnosis is needed for a rational management and also to monitor the response of the glomerular lesion, follow-up renal biopsy would be required.

LN increases the morbidity and mortality associated with SLE but renal survival has improved since the Cyclophosphamide in pulses was introduced as a therapeutic resource in the 1980´s[67]. New successful and safe therapeutic approaches are continuously considered for the treatment of SLE patients[68, 69]. Prospective studies are required to further seek for eventual immunopathological markers to assess not only the possible patterns of SLN progression but also its response to comprehensive therapeutic protocols.

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