Original research

Clinical and epidemiological characterization of patients with lupus nephropathy in Santander, Colombia: the importance of the renal biopsy

Caracterización clínica de pacientes con nefropatía lúpica en Santander, la importancia de la biopsia renal

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Abstract

Introduction: Systemic Lupus Erythematosus (SLE) has different clinical manifestations, being very relevant lupus nephropathy (LN) because is associated with progression to advanced chronic kidney disease (CKD) and mortality.

Objective: Determination of the clinical and epidemiological characteristics of the LN in Santander.

Methods: A descriptive observational study of a series of cases in patients with LN diagnosis, evaluated between January 2017 and 2018 for the first time in a nephroprotection consultation. Qualitative and quantitative variables are defined according to the inclusion and exclusion criteria. Electronic medical records were reviewed, and data analysis was performed through SPSS®.

Results: 14 patients (85% women) were studied. The average age of diagnosis of LN was 36 years, mostly with stages of CKD 1 and 2 (72%) with proteinuria A3 (85%). Renal biopsy was performed in the 64%, with a conclusive result in the 50%, being the histopathological grade IV of LN the most common. The most frequent maintenance therapy was corticosteroid alone (35.7%), followed by the combination of corticosteroid and mycophenolate (28.5%).

Conclusion: LN predominates in young women, and presenting in early stages of CKD, with high degrees of proteinuria, so a thorough evaluation should be performed in search of LN in all patients with SLE through early nephrological screening and monitoring programs. The histopathological grade IV found is like that reported in Latin America. There are administrative and technical difficulties in the performance of renal biopsies, emphasis should be placed on the realization of this procedure because it takes a primary role in defining the treatment.

Key words: Colombia, Lupus Erythematosus Systemic, Lupus Nephropathy, Biopsy, proteinuria, chronic kidney insufficiency.

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Resumen

Introducción: el lupus eritematoso sistémico (LES) presenta diferentes manifestaciones clínicas, una de estas es la nefropatía lúpica (NL), que se asocia con progresión a enfermedad renal crónica (ERC) avanzada y mortalidad.

Objetivo: determinación de las características clínicas y epidemiológicas de la NLen Santander.

Métodos: estudio observacional descriptivo tipo serie de casos en pacientes con NL evaluados por primera vez, entre enero de 2017 a enero 2018, en consulta de nefroprevención. Según criterios de inclusión y exclusión se definieron variables cualitativas y cuantitativas. Se revisaron historias clínicas y el análisis de datos se realizó por medio de SPSS®.

Resultados: se estudiaron 14 pacientes (85 % mujeres), la edad promedio de diagnóstico de NL fue de 36 años, con ERC 1 y 2 (72 %) y con proteinuria A3 (85 %). Se obtuvo biopsia renal en 64 %, con resultado concluyente en el 50 %, la clase histopatológica IV de NL fue la más común. La terapia de mantenimiento más frecuente fue corticoide en monoterapia (36 %), seguido de la combinación de corticoide y micofenolato (29 %).

Conclusión: la NL predomina en mujeres jóvenes, en estadios tempranos de ERC con altos grados de proteinuria, por lo que se debe realizar una evaluación minuciosa en búsqueda de NL a todos los pacientes con LES, mediante programas de detección y seguimiento nefrológico temprano. El grado histopatológico IV fue el más frecuente, similar a lo reportado en Latinoamérica. Existen dificultades administrativas y técnicas en la toma de biopsias renales, se debe hacer énfasis en la necesidad de su realización, por su primordial importancia para definir el tratamiento.

Palabras clave: Colombia, lupus eritematoso sistémico, nefropatía, lúpica, biopsia, proteinuria, insuficiencia renal crónica.

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Introduction

Systemic lupus erythematosus (SLE) is a complex chronic and multisystem autoimmune disease that predominates in women, with diverse clinical manifestations. It has a worldwide incidence rate between 1 and 10 per 100,000 inhabitants per year and a prevalence of 20 to 70 per 100,000 inhabitants, contributing to a significant decrease in quality of life and a lower life expectancy in the affected population.[1] In Colombia, the data are limited, however, it has been described a prevalence of 8.77/100,000 inhabitants, with a female:male ratio of 8: 1, in individuals aged between 45 and 49 years.[2]

The characterization of lupus nephropathy is important in patients with SLE, since it is undoubtedly the main predictor of poor prognosis.[3] The clinical manifestations of LN can be subtle, with abnormalities detected mainly in the urinalysis with predominant findings of proteinuria, hematuria, tubular alterations and renal failure.[4] According to the Latin American Group for the Study of Lupus (GLADEL, *Grupo Latinoamericano de Estudio del Lupus*) cohort, LN.is present in 52 % of patients with SLE in Latin America,[5] and in Colombia it has been described that up to 55 % develop renal involvement.[6]

In Santander, Colombia, there are no data describing the behavior of LN in our population. It was sought to collect, for the first time, the clinical and epidemiological characteristics of this population upon admission to a nephroprotection program and characterize the most used treatments, with the purpose of knowing our population and establishing strategies for its evaluation and management.

Methodology

A descriptive observational study of a series of cases was conducted in 14 patients diagnosed with lupus nephropathy, assessed for the first time in the outpatient nephrology consultation of the FME PREVER program of FRESENIUS in Bucaramanga, Santander, from January 2017 to January 2018. The following inclusion criteria were defined: cases of patients over 18 years of age with a diagnosis of lupus nephropathy with CKD in stages 1 to 5, and patients on renal replacement therapy were excluded.

Data collection was carried out through the review of electronic medical records, in a previously designed format. The variables that were taken into account were: sociodemographic variables, age of diagnosis of SLE and LN, clinical manifestations at the time of diagnosis, comorbidities, glomerular filtration rate by CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration), stages of CKD, proteinuria, blood pressure, body mass index, renal biopsy, histopathological result and treatment schemes.

The data analysis was performed with descriptive statistics, with the calculation of measures of central tendency and calculations of frequency, by means of the SPSS® software. The study was approved by the ethics and research committee of the Autonomous University of Bucaramanga (*Universidad Autónoma de Bucaramanga*).

Results

14 patients with a diagnosis of LN were studied. The sociodemographic variables are described in Table 1. As associated comorbidities, the patients presented: hypothyroidism (28.6%), essential arterial hypertension (21.4%), secondary arterial hypertension (21.4%), type 2 diabetes mellitus (14.3%),

Table 1. Sociodemographic variables.

Variables	Results
Age (years)	38± 17 (n: 14)
Sex (female %)	85 % (n: 12)
Race (percentage) - Mestizo - Afro-Latin American - Other	 93 % (n:13) 7 % (n:1) 0%
Age of diagnosis of SLE-years	32 ± 15.6
Age of diagnosis of LN -years	36 ± 1

deep vein thrombosis 14.3% (n:2), rheumatoid arthritis 7.1% (n:1) and finally, there was a patient with antiphospholipid antibody syndrome (7.1%). The clinical criteria for the diagnosis of SLE, according to SLICC 2012 in order of frequency were: synovitis or arthritis (78.6%), acute cutaneous lupus (35.7%), oral ulcers (21.4%), pleurisy (21.4%), pericarditis (14.3%), alopecia (14.3%) leukopenia (14.3%), thrombocytopenia (14.3%), seizures (7%), and hemolytic anemia (7%).

As for the clinical variables, it was found an average SBP of 118 ±2.7 mmHg and DBP of 71 ± 9.9 mmHg; BMI: 24.51 ± 4.4 kg/m^2; 35.7% of patients had an adequate weight, 35.7% overweight, and 21.4% obesity grade I. Table 2 describes the laboratory variables that were evaluated in the study. Of the 14 patients, 9 (64%) had a renal biopsy report, and 2 of the results were inconclusive, one case because not enough glomeruli were obtained for the study and another because immunohistochemistry tests were not carried out. The reasons why 5 patients did not have a renal biopsy were: one patient with contraindication due to anticoagulation, another patient did not want to undergo the procedure and 3 patients were waiting for administrative procedures.

The degrees of lupus nephropathy are recorded in Figure 1, with LN class IV being the most frequent. Finally, maintenance therapy regimens are recorded in Figure 2, where corticosteroid monotherapy corresponds to 36%, followed by the combination of corticosteroids with mycophenolate (29%), which are the most used treatment schemes.

Table 2. Clinical and laboratory variables.

Variables	Results
Creatinine - mg/dl	1.09 ± 0.5
BUN – mg/dl	18.9 ± 9.9
Hemoglobin -gr/ dl	12.06 ± 1.5
Proteinuria - mg	1575 ± 1171.2
TFG CKD EPI – ml/min	84.41± 38.9
CKD stage according to GFR	
- I	36 % (n:5)
- II	36 % (n:5)
- IIIa	7 % (n:1)
- IIIb	14 % (n:2)
- IV	7 % (n:1)
- V	
CKD stage according to proteinuria	
- A1	7.1 % (n: 1)
- A2	7.1 % (n:1)
- A3	85.7 % (n:12)

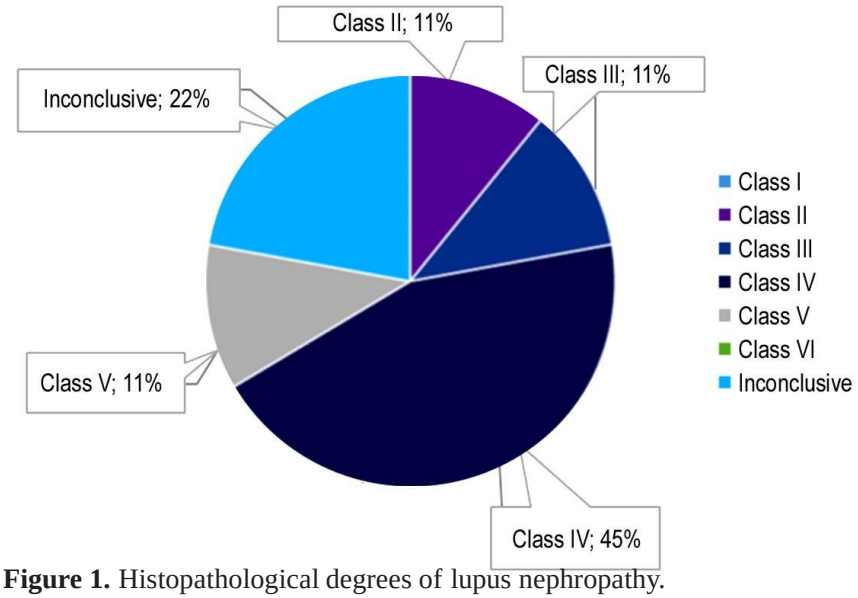

Figure 1. Histopathological degrees of lupus nephropathy.

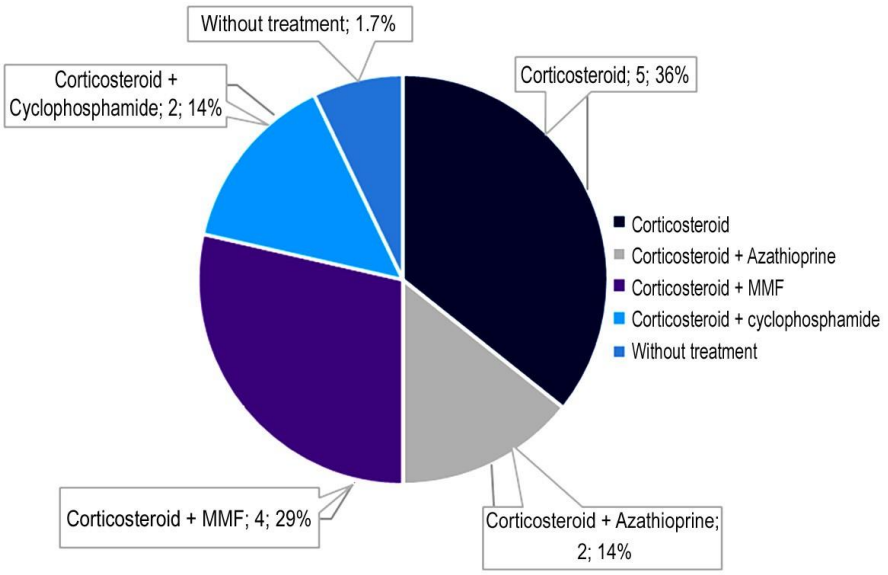

Figure 2. Combined treatment schemes.

Discussion

14 cases of patients with LN are described, of them, 85% were of female gender, which is consistent with what was described in the GLADEL cohort, in which they report that 89.9% of the patients were women.[5] Globally, a multicenter study conducted by Hanly J, et al., in which 1827 patients with SLE were studied, reported that LN affects up to 40% and that 4.3% of these patients were associated with end-stage CKD.[3] In our case series only one patient was in stage V of CKD, which corresponded to 7.1% of the patients, this connotes a similar finding given the difference in the number of patients.

The average age of diagnosis that we found for both SLE (32 years) and LN (36 years) is similar to the results described in the GLADEL[5] cohort (30 years), which indicates that this is a disease that predominates in a productive age also in our population and that can generate impact on a personal, social, family and economic level, by affecting the quality of life of women of childbearing age, in some cases heads of households and in full stage of labor productivity.

As for the diagnostic clinical criteria for SLE, in our case series it was shown that arthritis occupies the first place (78.6%), followed by acute cutaneous lupus (35.7%), and In the third place oral ulcers (21,4%), pleurisy (21.4%) and pericarditis (14.3%). These findings are partially comparable to those of Anaya et al., who found that the clinical and immunological characteristics that occur most frequently associated with LN in Colombian patients are pleurisy in 20% ($p < 0.0005$) and positive anti-DNA in 66% ($p < 0.0003$),[7] unfortunately, we did not have complete immunological data in our study, since the results were reported by different laboratories in different units, which prevented an adequate record thereof.

High blood pressure as a frequent comorbidity (44.8%) in our case series is similar with a study conducted at the San Pedro Claver Clinic in Bogotá, Colombia, where it was found a prevalence of 45% of HBP associated with LN,[8] however, in the GLADEL[5] cohort the percentage of patients with SLE and HBP was lower (26%).

Among the manifestations of LN presented by our patients, the predominant finding was proteinuria,

whose average values were 1,575 mg ± 1171.2 mg, most of them classified according to the level of proteinuria in stage A3, taking into account that the majority of our patients were in stages I and II (36%) of CKD. The opposite with the results obtained in the study by Arroyo, et al.,[9] in which 100% of patients with A3 proteinuria were in stage IV. Considering that patients with early stages of CKD present high degrees of proteinuria, early suspicion of LN is required in patients with preserved renal function, for this reason strict monitoring of renal parameters is necessary in patients with SLE, in order to prevent deterioration to advanced stages of CKD and the development of associated complications. The control and adequate approach of these patients with an early referral to nephrology will allow an improvement in their quality of life, as proposed by Aroca, et al.,[10] through the implementation of a management model of lupus nephritis developed and based on case management and integrated by service networks.

The most frequent histopathological class found in our study was class IV, data consistent with that reflected in the literature published by Arroyo et al., in a study of the Colombian Caribbean with a 62.5% predominance of the class IV.[9] Worldwide it is found that LN class IV is the most frequent, which shows the importance of establishing this diagnosis in order to be able to provide a more specific treatment.[11-12]

Five of the patients belonging to our case series did not have a renal biopsy report, due to related clinical conditions or to administrative difficulties in its authorization. In addition, in two of the patients there were technical inconveniences with the reports, due to the insufficient glomeruli samples and the lack of immunofluorescence analysis. It is essential to perform a renal biopsy in patients with suspected LN in order to establish the most appropriate treatment according to the histopathological class. Since according to the reviewed literature, histopathological classes I and II only require specific management if they are associated with significant proteinuria; and for classes III, IV and V the combination of glucocorticoids (GC) with mycophenolate mofetil (MMF) or azathioprine (AZA) is recommended.[13,14] In our case series it was found that the combined therapy most frequently used was GC and MMF (29%), it should be noted that if we had a renal biopsy in 100% of the cases, the number of patients who would benefit from this therapy would be expanded, given the high prevalence of class IV lupus nephropathy according to the findings in Colombia and in the world.

It is important to mention that 36% of the patients were in monotherapy with low-dose GC, which corresponded to patients who did not have renal biopsy. This clinical management was empirically oriented by the presence of proteinuria, however, the importance of the biopsy in this context shows us how we could go more in accordance with the KDIGO guidelines[15-16] for maintenance treatment in LN which recommend the progressive decrease of GC until low doses are achieved, along with immunosuppressive therapy in order to avoid long-term adverse effects; always taking into account that a rapid decrease or very low doses of GC can trigger a crisis of LN, which is why the management of patients must be individualized to maintain a stable and lasting renal function.

In addition, the Latin American clinical practice guidelines for the management of systemic lupus erythematosus, whose data were based on the study of the GLADEL cohort, recommend the preference of the use of MMF over CYC because it is more effective in Afro-descendants and Hispanics, in addition to having a better security profile.[17,18] In our case series we have managed to follow this recommendation, which is reflected in the use of immunomodulators that MMF uses in combination with GC, since our cases were mestizos (93%) and Afro-descendants (7%). However, the use of AZA and CYC was established due to the lack of delivery of MMF to patients, given the difficulty in administrative procedures with their healthcare provider, or because the management was initiated empirically prior to the nephrology consultation with an adequate response.

In our case series, only 23% of patients received antimalarial management, this differs from the recommendations made by Pons-Estel et al.,[19] in a study where the ethnicity and the protective effect of the use of antimalarials in LN were evaluated in

patients of the GLADEL cohort, which found that mestizo patients with high blood pressure who did not use antimalarials have an increased risk of developing kidney disease (OR 2.26, 95% CI 1.38, 3.70), reason by which the use of antimalarials is considered as a protective factor (OR 0.39, 95% CI 0.26; 0.58). The fact that 77% of patients did not take the antimalarial agent was due to the difficulty in its administration in 80% of the cases since there were problems in obtaining the medication and in the other 20% due to a lack of formulation of the drug. This shows the importance of carrying out joint and team management with the healthcare providers, rheumatology and internal medicine, stressing the importance of adding antimalarials to LN therapy, given the benefits that they represent.

There was a limitation when evaluating the induction treatment schemes in our study, since the patients had only a record of maintenance therapy, which was established by the hospital service of rheumatology or internal medicine, with schemes based on GC for the treatment of extrarenal manifestations.

Within the limitations of the study, it was also found that patients were previously evaluated in different healthcare centers, and it was not possible to have the medical records making difficult to collect the information. In addition, there was underreporting of immunological markers in the clinical records, with report of heterogeneous results, which made difficult to have a comparative analysis of these markers. The visits spaced due to difficulties in the transfer of patients or in the authorization by their healthcare provider make it difficult a more homogeneous management according to the guidelines and recommendations, including barriers to access specific diagnostic methods such as renal biopsy.

Conclusions

In the analyzed population, predominantly mestizo, lupus nephropathy is a manifestation that debuts mainly in women, from early stages of CKD with high degrees of proteinuria. Our findings are similar to those yielded in other world studies where LN class IV is the most frequent manifestation. As for the treatment schemes, it should be emphasized that a greater use of antimalarials should be implemented in our Hispanic patients and when facing the choice of induction and maintenance treatments, renal biopsy is of great importance. However, there are technical and administrative difficulties to take it, which imply an interdisciplinary management with the different specialties and with the healthcare providers in our country to get easy access to this important diagnostic tool.

This case series offers an approximation of both the clinical and epidemiological characteristics of the LN in Santander, which may be the beginning for the creation of more studies with a larger population, in order to encourage the active search of patients with LN in early stages of CKD and refer them to nephroprotection programs, achieving interdisciplinary management with rheumatology, internal medicine and dermatology; obtaining an optimal approach for these patients in order to improve treatment opportunities and their prognosis.

Conflict of interest

None.

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Ethical responsibilities

Protection of people and animals

The authors declare that no experiments were performed on human beings or animals for this research.

Data confidentiality

The authors declare that they have followed the protocols of their workplace on the publication of patient data.

Right to privacy and informed consent

The authors declare that patient data do not appear in this article.

Contribution of the authors

Mariana Torres Bustamante: study design, data collection, analysis and final writing of results, tables, graphs, discussion and conclusions.

Daniela Palomino: Contribution: study design, data collection, writing of the introduction, discussion and conclusions

Sergio Núñez: contribution, study design, data collection, writing of introduction and conclusions.

Ana María Celis: study design, data collection, and writing of the introduction.

Astrid Hernández: study approach, study design, review of results and correction of the manuscript.

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