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Damage in Cuban patients with systemic lupus erythematosus. Relation with disease features

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ABSTRACT

Objective: To determine damage presence and predictors factors for its appearance in a cohort of Cuban patients with systemic lupus erythematosus (SLE).
Patients and methods: A retrospective cohort study included 80 patients presenting with SLE seen in Rheumatology Service of "Hermanos Ameijeiras" Clinical Surgical Hospital in Havana City, Cuba. Damage was assessed using The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (ACR) Damage Index (SLIC/ACR), a tool approved for damage measurement. Damage presence was related to initial disease features to diagnose this condition, to sociodemographic elements, to treatments used, and to the disease course time. Statistical analysis had two variants: the univariate and multivariate type using Chi2 and statistical significance was established in $P<.05$.
Results: We found that 39 patients (48.8%) had some degree of damage. More involved domains were the musculoskeletal (18.8%), neuropsychiatric, and skin, 16.3%, pulmonary and ocular, present in 15% of cases. In the multivariate analysis, damage was associated with the use of higher than 30 mg/day Prednisone doses for more of 4 weeks (OR=54.68, CI 95%=3.56-97.45, P=.001), presence of leukopenia (RO=18.73, CI 95%=2.74-62.23 m P=.004), and time course of disease (OR=1.02, CI 95%=1.00 2-1.09, P=.006).
Conclusions: Damage was practically present in half of the study patients, the most involved domain was the musculoskeletal, and use of higher than 30 mg prednisone doses were the factor most associated with the presence of damage.

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Daño en pacientes cubanos con lupus eritematoso sistémico. Relación con características de la enfermedad

RESUMEN

Objetivo: Determinar la presencia de daño y factores predictores de su aparición en una cohorte de pacientes cubanos con lupus eritematoso sistémico (LES).
Pacientes y método: Se realizó un estudio de cohorte retrospectivo que incluyó a 80 pacientes con LES atendidos en el Servicio de Reumatología del Hospital Hermanos Ameijeiras en la ciudad de La Habana, Cuba. El daño fue determinado aplicando el Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index. La presencia de daño se relacionó con las características iniciales de la enfermedad al diagnóstico, con elementos sociodemográficos, con los tratamientos utilizados y con el tiempo de evolución de la enfermedad. El análisis estadístico incluyó estudios univariante y multivariado, y se utilizó el test de Chi-cuadrado (la significación estadística se fijó en p = 0,05).
Resultados: Encontramos que 39 pacientes (48,8%) tenían algún grado de daño. Los dominios más afectados fueron el músculo esquelético (18,8%), el neuropsiquiátrico y la piel, ambos con un 16,3%. En el análisis multivariado el daño se asoció con la utilización de dosis de prednisona mayores de 30 mg diarios por más de cuatro semanas (OR = 54,68; IC 95%: 3,56-97,45; p = 0,001), presencia de leucopenia (OR = 18,73; IC 95%: 2,74-62,23; p = 0,004) y el tiempo mayor de evolución de la enfermedad (OR = 1,02; IC 95%:1,002-1,09; p = 0,006).
Conclusiones: El daño estuvo presente prácticamente en la mitad de los pacientes estudiados, el dominio más afectado fue el musculoesquelético y la utilización de dosis mayores a 30 mg de prednisona fue el factor más asociado con la presencia de daño.

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Introduction

Systemic lupus erythematosus (SLE) is a systemic, autoimmune disease of unknown etiology, with a variable course and prognosis, in which survival has significantly improved in recent years.

The analysis of several studies' survival rates[1-4] shows progressive improvement compared to the 1950s. However, morbidity due to the diverse manifestations of the disease during its progression and the effects of the treatment required to control them is still considerable. The concept of damage is used to define irreversible lesions caused by disease progression, treatment or associated diseases. The international rheumatology community has used a semiquantitative instrument with the object of measuring damage. The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index[5] has been proposed by an ACR approved panel of experts, universally applied, that measures the presence of irreversible manifestations, present for at least 6 months, in nine organs or systems.

Some sociodemographic, environmental and genetic factors have been recognized as elements which might influence the manifestations and damage in patients with SLE.[6-10] SLE has been seen to be more severe in African Americans, Asians and Hispanics than in patients of Caucasian descent.[11-16] One study by Calvo-Alén et al that compared patients from the north of Spain with Hispanics from Texas with Mexican ascendancy showed that the latter had a more severe disease and more cumulative damage.[17]

Damage, survival rates and the quality of life related to health levels are between the most useful indicators of disease; in addition, damage has been shown to be a predictor of mortality.[18-20]

Although the Cuban population is multiethnic, its origins are mainly Spanish and it constitutes a population with different ethnic characteristics from that of Spain and other Latin American populations in which admixture with the native population was higher. The objective of the study was to know the prevalence of damage in a group of Cuban patients with SLE and identify their predictor factors.

Patients and methods

This is a retrospective, observational study that included consecutive patients seen at the Rheumatology department of the Hospital Hermanos Ameijeiras in the city of Havana, Cuba, between the months of January and July of 2006 and who had, at least, four classification criteria for SLE[21] with a time since the onset of disease of at least a year and agreed to participate in the study. The scientific commission of the institution, a center of the Public Health Ministry approved the project.

Sociodemographic, gender, ethnic group, years of schooling, clinical and laboratory data at the moment of diagnosis was obtained from the patients' file, as well as time since the onset of disease, therapy employed and calculated cumulative damage using the SLICC/ACR instrument.[5] The existence of damage in the presence of at least one of the 39 domains of the index was considered (SLICC>0).

Statistical analysis

The association between the sociodemographic characteristics of the patients, their clinical and laboratory elements at the time of diagnosis and treatments used, with the existence of damage was studied. The statistical analysis was done on two tiers, univariate and multivariate. The former evaluated the presence of an association between each one of the variables and the presence of damage. Contingency tables and the Chi-squared test were used for qualitative variables. The second tier applied the multivariate logistical regression model with the variable of damage presence as response. Because of the great number of variables contemplated, only those having a statistically significant difference ($P<.05$) in the logistical regression were included with relation to the presence of damage in the univariate tier.

Results

Eighty patients diagnosed and attended at the Rheumatology department of the Hospital Hermanos Ameijeiras were studied, 76 were female (95%) and 4 male (5%). Mean age of the cases was 29±10 years and time since the onset of disease was 94.8 months (Table 1). Thirty-nine patients (48.8%) presented some type of damage. The table represents the association between the time since the onset of disease and the presence of damage: 1) less than 60 months since onset, damage present in 9 of 28 cases (32.1%); 2) between 61 and 120 months since onset, damage present in 13 of 27 cases (48.1%), and 3) over 120 months, damage in 17 of 25 cases (68%). Mean scores for cumulative damage was 0.61; 1.15, and 1.92 for the three groups, respectively.

Damage was present in all of the organs or systems evaluated by the SLICC/ACR, with the exception of gastrointestinal (Table 2). The index domains with the most affection were musculoskeletal, skin, neuro-psychiatric, pulmonary and ocular.

No association between sociodemographic variables (age, gender, color of the skin, occupation and schooling), present at the moment of diagnosis of disease, with the ulterior presence of damage was seen.

Table 3 expresses the association of clinical manifestations, of laboratory alterations and treatments employed with the appearance of damage. In the univariate analysis, there was an association between the presence of damage with the existence of discoid lesions ($P=.036$), psychosis ($P=.035$), vasculitis ($P=.007$) and leukopenia ($P=.035$). None of the other laboratory alterations was associated with damage. In the univariate analysis, the use of prednisone doses over 30 mg for more than 4 weeks ($P=.007$), pulse methylprednisolone ($P=.043$), cloroquine ($P=.038$) and pulse cyclophosphamide ($P=.022$) were associated to damage (Table 3).

In the multivariate analysis (Table 4) variables that were independently associated to the presence of damage were the use of prednisone at a dose over 30 mg for over 4 weeks, the presence of leucopenia at the beginning of the disease and a longer time since onset of SLE.

Discussion

This study has determined the presence of damage in a group of Cuban patients with SLE seen at a third level hospital, which tends

Table 1
Patient characteristics (n=80)

Age in years, mean (SD)	29.05 (±10.6)
Femle gender, n (%)	76 (95)
Skin color, n (%)	
White, n (%)	60 (75)
Non white, n (%)	20 (25)
Duration of disease in months, mean (SD)	94.8 (±63.5)
Patients with damage, n (%)	39 (48.8)
Time since onset and damage	
A) Less than 60 months	
1) Patients with damage, n (%)	9 (32.1)
2) Damage index, mean (SD)	0.61 (±1.29)
B) Between 61 and 120 months	
1) Patients with damage, n (%)	13 (48.1)
2) Mean damage index (SD)	1.15 (±1.56)
C) More than 120 months	
1) Patients with damage, n (%)	17 (68)
2) Damage index, mean (SD)	1.92 (± 1.91)

SD: standard deviation.

to patients from different parts of the country. The musculoskeletal system was the most affected and the use of prednisone over 30 mg a day for more than four weeks was the independent variable more strongly associated to the presence of damage.

Rates and patterns of damage distribution have been described in the literature and vary according to clinical, ethnic and sociodemographic factors.[22] The results obtained by our research, with a prevalence of damage of 48.8%, coincides with that communicated by other studies in other countries, where it oscillates between 40 and 70%.[23-28]

The musculoskeletal, neuro-psychiatric and ocular domains of the SLICC/ACR index are among the most compromised in several studies that analyze this.[24-26,29-31] Our results were similar, although skin affection was more frequent than ocular.

Skin damage, as reported in other studies, varies between 4 and 14%.[22,27,32,33] However in our geographical region, specifically Brazil, several groups have reported an elevated presence of skin damage, with a prevalence of 20 to 50%.[34-36]

In our patients, skin affection occupied second place. The higher frequency of skin damage in the Caribbean and in a country like Brazil (which, as in the case of Cuba has suffered more ethnic admixture than North America or Europe), may be considered to be under the influence of genetic factors. However, our results did not find evidence that suggested that the color of the skin was

associated with the presence of skin damage, making us consider that environmental factors influenced skin affection to a greater degree, because exposure to sunlight is more intense in the Caribbean than in other areas of the world. In other Latin American countries with different environmental and ethnic characteristics, the affection of other organs, not the skin, is more frequent. Cassano et al in Argentina found that the most affected systems in relation to damage were the kidneys, neuro psychiatric, cardiovascular and musculoskeletal.[37]

Ultraviolet radiation, in SLE patients, is known to induce the appearance of new skin lesions, exacerbate existing ones and even provoke disease flares and favor its progression.[38]

The presence of renal damage in studies varies from 13 to 23%[22,24,27,28] while in our study it only reached 2.5%. We consider that this low prevalence can be due, on one hand, to the relatively short time since the onset of disease and, on the other, to the systematic search for nephropathy that we performed and which led to early diagnosis and treatment of lupus nephritis. 20% of cases presented nephropathy, demonstrated by renal biopsy, in the form of a focal proliferative, diffuse proliferative or membranous nephropathy. All of them used pulse cyclophosphamide during prolonged periods of time, with a 6-month induction period and a two-year trimester maintenance period. This prolonged treatment scheme, although not exempt of complications, leads to prolonged remission and avoids the appearance of irreversible damage that leads to important deterioration of renal disease. We consider that this might have contributed to a low prevalence of renal damage.

The only unaffected domain in our study was the gastrointestinal one, which in other studies occupies approximately 7%.[22,27,29,30,32,33] However, studies performed in Brazil, with similar ethnic characteristics to the Cuban population, does not show gastrointestinal damage either.[35,36,39]

Table 2
Distribution of damage by domains

Domains	Frequency n (%)
Musculoskeletal	15 (18.8)
Skin	13 (16.3)
Neuropsychiatric	13 (16.3)
Pulmonary	12 (15)
Ocular	12 (15)
Cardiovascular	4 (5)
Peripheral vascular	4 (5)
Gonadal Insufficiency	3 (3.8)
Renal	2 (2.5)
Neoplasia	2 (2.5)
Diabetes	1 (1.3)
Gastrointestinal	0

Table 4
Damage predictive factors in the logistical regression analysis

Variables	OR (95% CI)	P
Use of prednisone over 30 mg	54.68 (3.56-97.45)	.001
Leukopenia	18.73 (2.74-62.23)	.004
Time since onset in months	1.02 (1.002-1.09)	.006

CI: confidence interval; OR: odds ratio.

Table 3
Association of the clinical characteristics, laboratory alterations and treatment used in the presence of damage

Clinical characteristics	All patients (n=80), n (%)		With damage (n=39), n (%)		No damage (n=41), n (%)		P
Rash	55	68.8	25	45.5	30	54.5	.382
Discoid lesions	24	30	16	66.7	8	33.3	.036
Arthritis	70	87.5	34	48.6	36	51.4	.933
Nephropathies	16	20	7	43.8	9	56.2	.567
Convulsions	3	3.8	2	66.7	1	33.3	.527
Psychosis	4	5	4	100	0		.035
Vasculitis	15	18.8	12	80	3	20	.007
Pericarditis	9	11.3	6	66.7	3	33.3	.254
Pleurisy	10	12.5	7	70	3	30	.151
Anemia	32	40.0	17	53.1	15	46.9	.523
Leukopenia	15	18.85	11	73.3	4	26.7	.035
Thrombocytopenia	5	6.3	3	60	2	40	.603
Elevated Anti-DNA	49	61.3	27	55.1	22	44.9	.120
Low C3	10	12.5	6	60	4	40	.459
Proteinuria > 0.5 g	16	20	7	43.8	9	56.2	.567
Elevated creatinine	1	1.3	1	100	0		.314
Prednisone > 30 mg daily	64	80	36	56.3	28	43.7	.007
Pulse methylprednisolone	30	37.5	19	63.3	11	36.7	.043
Cloroquine	46	57.5	27	58.7	19	41.3	.038
Azathioprine	41	51.2	24	58.5	17	41.5	.073
Cyclophosphamide	27	33.8	18	66.7	9	33.3	.022

DNA: deoxyribonucleic acid.

No association was seen between the sociodemographic characteristics (age, gender, skin color, occupation and schooling) and the presence of damage. Other studies[24-26,36] show that a greater age at diagnosis is a predictor of damage. In them, the mean age at the onset of disease varies from 36 to 40 years, while in the present group its 29 years. We believe that this lower age has an influence on the lower prevalence of comorbidity and a reduced development of damage.

Gender did not influence the appearance of damage, coinciding with several other studies.[25,26,36] Previous studies have been controversial regarding ethnicity (a variable related to socioeconomic conditions) in the appearance of disease. Some have shown that persons of African-Caribbean ancestry have an increased risk for it[16,28,40] and other, such as ours, have not found any influence.[22,36] It seems that it is necessary to clear the effects of ethnicity and socioeconomic factors on the development of damage.

The longer time since onset of disease in our study was one of the three variables which were independently associated to damage. We consider that a longer time since onset allows comorbidities to appear due to the disease itself or the influence of treatments during its progression. After 10 years since the disease onset, more than 50% of patients presented it, something corroborated by other researchers.[24,25,28] Its presence increases with time since onset, making it necessary to periodically asses follow up ion these patients because of the association of damage with increased mortality.[20,41]

Leukopenia at the onset of disease is another variable that was independently associated to the presence of damage. The development of damage increases 18 times in them; this finding has recently been shown in another study, associated to neuropsychiatric activity,[26] although we agree with other researchers,[42,43] that other studies are required to precise their influence in leading to irreversible alterations.

The use of prednisone at a dose over 30 mg a day for more than 4 weeks was the variable that, in most cases, was independently associated to the appearance of damage (54 times higher). Steroids remain among the main treatment choices in patients with SLE, but their contribution to damage has been considered important.[44] Our results coincide with those of other studies, which in the multivariate analysis have seen an association between the presence of damage and the use of steroids.[36,44,45]

One controversial result of this study was the relationship seen between the use of antimalarials and damage, when several other studies show that this intervention is protective.[46,47] This could be due to the increased prevalence of discoid lupus in our group (30%), an irreversible lesion that responds poorly to antimalarials. We consider that one of the limitations of the study is not to have considered the influence of disease activity with the presence of damage.

In conclusion, damage is present in almost 50% of patients studied and the musculoskeletal domain is the most affected. It is important to implement strategies that allow us to reduce their appearance, along with the rational use of steroids and the implementation of measures for the better prevention and control of comorbidity associated with a longer time since the onset of disease in these patients.

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