

Lower Incidence of Severe Damage to Target Organs in Mexican Patients With Systemic Sclerosis and Diffuse Skin Affection

Jorge Rojas-Serrano,^a Helga Codina-Velásquez,^b Gabriel Medrano-Ramírez,^b J. Abraham Simón,^c Olga Vera-Lastra,^d and Janitzia Vázquez-Mellado^e

^aInstituto Nacional de Enfermedades Respiratorias, Universidad Nacional Autónoma de México, Facultad de Medicina, México

^bDepartamento de Reumatología, Hospital General de México, México

^cUnidad de Investigación Médica, UMAE, Mérida, México

^dHospital de Especialidades Antonio Fraga Mouret, Centro Médico Nacional La Raza, IMSS, México

^eUniversidad Nacional Autónoma de México, Facultad de Medicina, Departamento de Reumatología, Hospital General de México, México

Objective: To determine the cumulative incidence of severe organ involvement in Mexican patients with systemic sclerosis (SS) and diffuse scleroderma at 3 years from the onset of SS symptoms, and to compare it with the cumulative incidence observed in a cohort of white patients with SS.

Patients and method: Patients with SS and diffuse scleroderma were evaluated within the first 2 years from the onset of SS symptoms and were included. An estimation of the cumulative incidence of severe involvement to the skin, kidney, heart, lungs, and gastrointestinal track at 3 years from the onset of SS symptoms was carried out. This cumulative incidence was compared with that of white SS patients with diffuse scleroderma, using the one sample test for a binomial proportion.

Results: Sixty-three patients were included. The cumulative incidence of severe involvement to the skin was 3.17% (2/63) (95% CI, 0.04-11); kidney involvement in 4.17% (3/63) (95% CI, 0.99-13.29); heart involvement in 1.6% (1/63) (95% CI, 0.04-8.5); lung involvement in 11.11% (7/63) (95% CI, 4.5-21.5); and gastrointestinal involvement in 4.7% (3/63) (95% CI, 0.99-13.3). Mexican patients had a lower incidence of severe skin involvement ($P=.0001$), kidney involvement ($P=.03$), and heart involvement ($P=.03$) compared to white SS patients with diffuse scleroderma.

Conclusions: The cumulative incidence of severe organ involvement in SS Mexican patients with diffuse

scleroderma was determined. The incidence of severe skin, kidney, and heart involvement is lower than in white SS patients with diffuse scleroderma.

Keywords: Systemic sclerosis. Diffuse scleroderma. Ethnic differences in epidemiology. Clinical expression differences.

Menor incidencia de daño grave en órganos diana en pacientes mexicanos con esclerosis sistémica con afección cutánea difusa

Objetivo: Determinar la incidencia acumulada de daño grave en órganos diana en la esclerosis sistémica con afección cutánea difusa (ESD), en una cohorte de pacientes mexicanos a los 3 años desde el inicio de los síntomas de la enfermedad, y compararla con lo observado en una cohorte de pacientes blancos.

Pacientes y método: Se incluyó a los pacientes evaluados por primera vez en los primeros 2 años desde el inicio de los síntomas de la ESD. Se determinó la incidencia acumulada de daño grave en los siguientes órganos: piel, riñones, sistemas cardiovascular, pulmonar y gastrointestinal, y se comparó con lo observado en una cohorte donde el 94% de los pacientes son blancos, mediante la prueba de una muestra para una proporción binomial.

Resultados: Se encontró que 63 pacientes cumplían los criterios del estudio. La incidencia acumulada de daño grave en la piel fue del 3,17% (2/63) (intervalo de confianza [IC] del 95%, 0,04-11); daño renal del 4,17% (3/63) (IC del 95%, 0,99-13,29); daño cardiovascular del 1,6% (1/63) (IC del 95%, 0,04-8,5); daño pulmonar grave del 11,11% (7/63) (IC del 95%, 4,5-21,5), y daño gastrointestinal del 4,7% (3/63) (IC del 95%, 0,99-13,3). Al comparar los datos con los observados en pacientes blancos en el mismo período de evolución de la ESD, se

Correspondence: Dr. J. Rojas-Serrano.
Instituto Nacional de Enfermedades Respiratorias.
Calzada de Tlalpan 4502. Sección XVI. Tlalpan. 14080 México DF. México.
E-mail: jrojas@iner.gob.mx

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encontró una menor incidencia de daño grave en la piel ($p = 0,0001$), y daño renal ($p = 0,03$) y cardiovascular ($p = 0,03$).

Conclusiones: Se determinó la incidencia de daño grave en órganos diana en pacientes mexicanos con ESD a los 3 años desde el inicio de los síntomas. La incidencia de daño de piel, y daño renal y cardiovascular es menor que lo observado en pacientes de raza blanca.

Palabras clave: Esclerosis sistémica. Esclerodermia difusa. Diferencias étnicas en epidemiología. Diferencias en la expresión clínica.

Introduction

Systemic sclerosis with diffuse skin affection (DSS) is characterized by proximal scleroderma of the elbows and knees, as well as the affection of internal organs that can lead to the loss of their function.¹ Steen et al² described the cumulative incidence of severe damage to target organs in DSS in the Pittsburg cohort, in which 94% of the patients are white. They found that the largest cumulative incidence of severe damage to target organs appears in the first 3 years since the start of symptoms that can be attributed to DSS, and have described a cumulative incidence of kidney damage in this period of 13%, skin affection of 18%, cardiovascular system of 8%, gastrointestinal system of 4%, and severe lung damage of 8%.

On the other hand, differences in the clinical expression of the studied ethnic groups have been found: African-American patients have a greater frequency of inflammatory manifestations, pulmonary arterial hypertension, pleural effusion, myopathy, kidney failure, as well as lung fibrosis when comparing them to white patients.³⁻⁵ Differences in the clinical expression among different ethnic groups can be observed even in patients with the same autoantibody profile. Kuwana et al⁶ compared African-American, Japanese, and Choctaw native patients, all of them with antitopoisomerase I, in their clinical and serological characteristics. Once again, white patients had a lower frequency of pulmonary fibrosis and better survival rates than the rest of the ethnic groups. In our case (México City), the general impression of the physicians attending patients with DSS is that they have a lower incidence of severe renal damage (renal crisis). This study was undertaken with the objective of determining the cumulative incidence of severe damage to target organs in Mexican patients at 3 years since onset DSS symptoms, and to compare this cumulative incidence with that informed in another patient population,² in which 94% of the sample are white persons.

Patients and Method

The design of the study was that of a retrospective cohort. Information was obtained from the clinical files of the patients in the 2 hospital centers where the study was carried out (Hospital General de México and Centro Médico Nacional La Raza). The patients who were included had to fulfill the criteria for systemic sclerosis proposed by the ARA⁷ and presented a pattern of skin affection according to that published by LeRoy et al.⁸ Both hospital centers are in México City. The first provides medical care to an open population while the other provides for patients with social security. Patients who are attended are Mexican mestizo (descendant from native Americans and Europeans). In both centers, patients with DSS are evaluated in a standard manner at least once every 6 months and a determination of the modified Rodnan scale is performed in each visit and, in the case the patients so requires it, they undergo more frequent evaluations according to the criteria of the physician who is treating them. Laboratory testing, and the frequency with which they are done is decided according to the medical care necessities of the patient. A spirometry and a chest x-ray are performed once a year to every patient in both centers. Attending physicians are rheumatologists or internal medicine specialists who evaluate the patients in search of severe damage to target organs, according to the definitions proposed by Steen and Medsger, which are described later.⁸ In order to avoid a survivor's cohort, we only included patients whose first time visit occurred in the first 2 years since the onset of the DSS symptoms. Data collection: a physician blinded to the objectives of the study reviewed the files and collected the clinical and laboratory variables. In case of death, the cause was determined according to the file and an interview with the attending physician. In case the patient had severe damage to target organs, the time at which this had happened since the onset of symptoms attributed to DSS was recorded.

To define severe damage to target organs, the same operational definitions proposed by Steen et al² were employed:

1. Severe renal damage (renal crisis). It is defined as the presence of malignant hypertension and/or acute renal failure, and/or microangiopathic hemolytic anemia (MHA). Patients with recent-onset hypertension, without an increase in the serum concentrations of serum creatinine, or MHA are not classified as bearing severe renal damage, even if successfully treated with angiotensin converting enzyme inhibitors.
2. Severe cardiovascular damage. It is defined as the presence of cardiomyopathy with a reduced left ventricular ejection fraction and symptoms of congestive heart failure or symptomatic pericarditis with chest pain of heart failure due to the effusion, or an arrhythmia that is attributed

to cardiac damage by the DSS and that merits treatment. Patients with a non-symptomatic decrease in the ventricular ejection fraction, pericardial effusion, or asymptomatic arrhythmias do not fit into the severe cardiac damage classification. Problems not related to scleroderma and non-specific changes in the echocardiogram, electrocardiogram, as well as Holter monitoring are not considered as severe cardiac damage either.

3. Severe lung damage. It is defined as lung fibrosis demonstrated through chest x-ray and a forced vital capacity of <55% of that predicted. Pulmonary hypertension is not included in this definition.

4. Severe gastrointestinal damage. It is defined as the presence of deficient intestinal absorption syndrome or repeated episodes of intestinal obstruction, or severe gastrointestinal problems that require nutritional support. Diarrheal bouts that respond to antibiotics and do not lead to malnutrition, postprandial abdominal fullness and esophageal stenosis are not classified as severe damage to the target organ unless associated to a loss of 10% of body weight or hospital admissions.

5. Severe skin damage. A modified Rodnan score of >40 from a maximum 51.

Statistical Analysis

Categorical variables are described as frequencies and percentages, numerical variables as means, standard deviations (SD), and medians. The cumulative incidence of DSS severe damage to target organs at 3 years since the onset of DSS and its 95% confidence intervals (CI) were determined through an exact binomial method. This incidence was compared to that informed by Steen et al² in the same period since the onset of symptoms of DSS through the single-tailed binomial proportion of a sample hypothesis test. A *P* value less than .05 was considered significant. Analysis was performed with the STATA (9.2) software package.

Results

Of 200 patients with the diagnosis of scleroderma found at both centers, 63 had DSS and had been evaluated for the first time during the first 2 years since the onset of symptoms (Table 1). Of these, 61 (97%) were women, with a mean age at the onset of the symptoms of 35.6 (15) (median, 32) years. At the moment of first-time evaluation, they had a median of 12 months (interval, 3-24) since the start of symptoms. The median score of the modified Rodnan scale (parting from the highest score of each patient during all of the follow-up) was 15 (interval, 4-49). All of the patients who were included fulfilled the DSS classification criteria proposed by LeRoy et al.⁸ Ten (16%) patients received, at some point, cyclophosphamide

TABLE 1. Characteristics of the Study Cohort (n=63)^a

Variable	
Women	61 (97%)
Age at onset of symptoms, mean (SD), y	35.6 (15)
Mexican mestizo population	63 (100%)
Time from the onset of symptoms to the first evaluation, median (range), y	12 (3-24)
Positive antinuclear antibodies	63 (100%)
Classification criteria for systemic sclerosis (ARA, 1980)	
Major criteria	
Acrosclerosis	63 (100%)
Minor criteria	
Sclerodactilia	63 (100%)
Scarring on fingertips	54 (86%)
Basal lung fibrosis	35 (56%)
Rodnan scale score (from each patients highest score), median (range)	15 (4-49)

^aSD indicates standard deviation.

at a variable dose, both orally and as monthly iv bolus. The cumulative incidence of severe damage to target organs at 3 years since the onset of the scleroderma symptoms was as follows: skin, 3.17% (2/63) (95% CI, 0.04-11); renal crisis, 4.17% (3/63) (95% CI, 0.99-13.29); heart damage, 1.6% (1/63) (95% CI, 0.04-8.5); severe lung damage, 11.11% (7/63) (95% CI, 4.5-21.5); gastrointestinal damage, 4.7% (3/63) (95% CI, 0.99-13.3). During the evaluation period, 3 (5%) patients died. The causes of death were severe intestinal damage in 2 patients and a renal crisis in 1 patient.

When comparing the frequency of cumulative damage in the first 3 years since the onset of symptoms in our patients and data compared by Steen and Medsger, we found statistically significant differences in the frequency of severe skin, renal, and cardiovascular damage, with a reduced frequency in patients of Mexico City and, on the contrary, lung and gastrointestinal damage being more frequent in this group of patients, without reaching a statistically significant difference (Table 2).

Discussion

The results obtained in this study point to the fact that the frequency of severe skin, renal, and cardiovascular damage is lower in Mexican patients than in patients who are white, and to a higher incidence, without achieving statistical significance, of gastrointestinal and lung damage.

TABLE 2. Comparison of the Frequency of Cumulative Damage to Target Organ in the First 3 Years of the Disease Between Mexican Patients and the Pittsburg Cohort

Target Organ Damage (n=63)	Mexicans	Pittsburg (n=953)	P ^a
Skin	3.17%	18%	.001
Renal crisis	4.17%	13%	.03
Cardiovascular	1.6%	8%	.03
Gastrointestinal	6%	4%	.75
Lung	12%	8%	.87

^aValue of *P* was estimated through a single-tailed binomial proportion of a sample hypothesis test.

These results need to be analyzed from several perspectives, the first of which is the follow-up period in both cohorts, even if the study by Steen et al² followed the patients for enough time to estimate the cumulative incidence until 9 years after the onset of symptoms, that same paper proved that the highest degree of cumulative incidence of severe damage to the target organ occurs in the first 3 years since the onset of symptoms. In fact, it is additional evidence that supports the concept by which the “progressive” adjective was dropped from systemic sclerosis,⁷ because it is now known that progression of the disease is not linear and, occasionally, even untreated patients can show improvement.^{9,10} Therefore, comparing both cohorts only during the first 3 years since the onset of symptoms is a valid concept and concordant with what we know of the natural history of DSS.

Both cohorts have a clinical evaluation system that is very similar: laboratory tests are requested at the attending physicians discretion and patients are visited at least twice a year. In both cases, if the patient requires it, an additional appointment is programmed. On the other hand, the definitions of severe damage are clinically evident; all have severe manifestations and oblige the patients to search for medical help immediately, making this a factor that we do not consider to have influenced the results that were obtained. Steen et al² do not mention the treatment of their patients. In our cohort, 15% of patients received cyclophosphamide and it could be speculated that this drug could have modified the evolution and reduced the cumulative incidence of severe damage. The role of cyclophosphamide as a modifier of disease is controversial; in a recently published clinical trial¹¹ which compared the use of cyclophosphamide versus placebo on the effect of pulmonary function in DSS found a statistically significant difference in the forced vital capacity of the group receiving cyclophosphamide, but from the functional and clinical standpoint, this difference was insignificant.

With the objective of avoiding a survivors cohort and therefore of erroneously estimating the cumulative incidence of severe damage to target organs, we only

included patients who were evaluated for the first time within the first 2 years since the onset of DSS. When using these admission criteria, the total number of patients included in the study was reduced; however, we consider that the numbers we obtained this way better reflect the cumulative incidence of damage in DSS in Mexican patients.

There are important differences between the ethnic groups which were studied regarding the clinical expression of scleroderma: African-American patients have a larger frequency of diffuse scleroderma and inflammatory manifestations than whites.³⁻⁵ Differences have also been noted when comparing whites to other ethnic groups such as “Hispanics” (who in their majority are Mexican-Americans), as well as Japanese patients and those from Thailand,^{3,4,12} and in this case, whites also have a lesser frequency of diffuse skin disease and antitopoisomerase I antibodies, and a greater frequency of anticentromeric antibodies.¹³ Difference in the clinical expression of the disease can be observed even in patients with the same autoantibody. Kuwana et al⁶ compared African-American, Japanese, and Choctaw native patients, all of them bearing antitopoisomerase I, in their clinical and serological characteristics. Once again, the white patients had a lesser frequency of pulmonary fibrosis and better survival rates. This points to the notion that DSS is a disease in which the ethnic group the patient belongs to is a important influence on its clinical expression.

There are currently no environmental or sociocultural factors that have been identified as a potential explanation for these differences. Niert et al¹⁴ carried out a study to determine if the level of education, gender, disease duration, and its classification influenced the clinical manifestations. After adjusting the African-American and white patients with these variables, differences between the clinical manifestations of both ethnic groups persisted. It has been proposed that genetic factors can play a fundamental role in the clinical expression of the disease, Arnett et al¹⁵ described that the Choctaw natives of Oklahoma have a large prevalence of DSS, which stands in contrast to Choctaw natives of other states of the United States in which not a single case was found in spite of sharing HLA haplotypes. The experience with the Choctaw natives points to the likeliest scenario being the interaction of environmental and genetic factors as the determinants of the appearance of DSS and its clinical expression.

Our study has differences that are common to its retrospective design, in addition to a small number of patients. Another limitation of the study is that we only performed antinuclear antibodies to our patients, but an import number of them (50% of cases) did not have the specific pattern, this being the reason we did not include this data in the study. In spite of this we consider it adequately reflects the cumulative incidence of severe damage in target organs in this population.

In conclusion, we determined the cumulative incidence at 3 years since the onset of symptoms of DSS in a population of Mexican mestizo. The incidence of severe damage to target organs is different from what has been informed in white patients, which is lower in skin, kidneys, and the cardiovascular system, and with a lung and gastrointestinal incidence that is similar.

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