Systemic Lupus Erythematosus in Northwestern Spain
A 20-Year Epidemiologic Study

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Abstract: To further investigate the epidemiology of systemic lupus erythematosus (SLE) in southern Europe, we assessed the incidence, prevalence, clinical spectrum of the disease, flares, and survival of patients diagnosed with SLE in the Lugo region of northwestern Spain. Between January 1987 and December 2006, 150 Lugo residents were diagnosed as having SLE according to the 1982 American College of Rheumatology criteria for the classification of SLE. Women outnumbered men (127 [84.7%] vs. 23 [15.3%]). The mean age at the time of disease diagnosis was 46.1 ± 19.6 years. The mean follow-up from the time of disease diagnosis was 7.8 ± 4.5 years. The age- and sex-adjusted annual incidence rate over the 20-year study period was 3.6 (95% confidence interval [CI], 3.0–4.2) per 100,000 population aged 15 years and older. The overall annual incidence rate over the 20-year study period in women (5.9/100,000 population aged ≥15 yr; 95% CI, 4.9–7.0) was higher than in men (1.1/100,000 population aged ≥15 yr; 95% CI, 0.7–1.7) (p < 0.001). By December 31, 2006, the overall age-adjusted SLE prevalence in the Lugo region for patients who fulfilled at least 4 of 1982 American College of Rheumatology criteria was 17.5 per 100,000 population aged 15 years and older (95% CI, 12.6–24.1). Prevalence in women (29.2/100,000 population aged ≥15 yr; 95% CI, 20.0–40.7) was higher than in men (5.8/100,000 population aged ≥15 yr; 95% CI, 2.0–12.0).

The most frequent clinical manifestation was arthritis. As reported in population-based studies on SLE patients of European descent, renal disease was observed in only 27.3% of the patients. The rate of flares was 0.084/year. A younger age and the presence of nephritis at the time of disease diagnosis were associated with the development of flares during the follow-up of Lugo patients. Compared with the general population the probability of survival in patients with SLE was significantly reduced (p = 0.04).

In conclusion, the present study establishes a baseline estimate of the incidence and clinical spectrum of SLE in northwestern Spain. According to our results, the incidence of SLE in northwestern Spain is slightly higher than that reported in most European regions. Patients with SLE from northwestern Spain have a later average age onset and a lower frequency of nephritis than in the African-American population. However, our data show a reduced probability of survival in Spanish patients with SLE.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease with a wide spectrum of clinical manifestations. It was previously considered an uncommon condition. However, the development of several immunologic tests has allowed the description of many atypical or benign cases that otherwise might not be diagnosed. Furthermore, with the introduction since 1982 of a set of more sensitive criteria for SLE classification, more cases are detected than previously.[39]

The incidence of SLE varies according to the characteristics of each population, such as patients' age, sex, ethnicity, and the period of time studied. Epidemiologic studies suggest the occurrence of SLE differs among different countries, and even among different areas of the same country.[21,22,28] These differences are also observed among population groups of the same race living in different parts of the world, suggesting that besides genetic susceptibility, geographic and environmental factors are implicated in the development of this connective tissue disease.[12,21,22,28] Recent studies in Europe and the United States suggest an increase in the incidence and improvement of survival rates in SLE. These observations may explain an increase in the prevalence of SLE.[22,40] However, information on the epidemiology of SLE in southern Europe, and specifically in Spain, is limited. Only a few studies have assessed the clinical spectrum of SLE in Spanish individuals,[15,17,35] and data specifically addressing the incidence and prevalence of SLE in Spanish individuals are scarce.[27] Lopez et al[27] reported a prevalence of 34.12/100,000 and an incidence of 2.15/100,000 per year in the population of Asturias in northern Spain.

To further investigate the epidemiology of SLE, we assessed the incidence, prevalence, clinical spectrum, and survival of all patients diagnosed with SLE according to the 1982 American College of Rheumatology (ACR) classification criteria[39] at the single hospital for a well-defined population of northwestern Spain.

PATIENTS AND METHODS

We assessed the case records of all patients diagnosed with SLE at the department of medicine of the Hospital Xeral-Calde

of Lugo over the period 1987–2006. This hospital is the single referral center for a mixed rural and urban white population of almost a quarter million people. Hospital Xeral-Calde provides medical care to a very specific area of the interior of Galicia in northwestern Spain. Because of this, there are no other centers where SLE patients could present. This area has been geographically isolated from the rest of Galicia and the rest of Spain for many centuries. The population is relatively static, and no important migration has occurred in the area during the last 2 decades.[3,18] Epidemiologic studies on other rheumatic diseases in patients from this region have been reported elsewhere.[3,16,19,20]

As previously performed when we assessed the spectrum of scleroderma in the Lugo region,[3] for the present study we assessed the clinical records of all patients identified as having SLE using the administrative hospital registry. The hospital registry includes all patients attended in the hospital; it codifies diagnosis using International Classification of Diseases, 9th revision, Clinical Modification (ICD9-CM). To reduce the risk of underestimating the incidence of SLE, we also reviewed all records of patients classified as having other connective tissue diseases (ICD9-CM codes: 710.1–710.9). The vast majority of SLE patients (over 95%) were detected using the specific registry for SLE. A few others (<5%) were diagnosed with the search for all records of patients classified as having other connective tissue diseases.

Patients were classified as having SLE if they and fulfilled at least 4 of the American College of Rheumatology criteria (formerly called American Rheumatism Association) for the classification of SLE.[39]

The majority of patients were included in the registry because they fulfilled at least 4 of the ACR criteria for SLE. In these cases the date of diagnosis was the date they were diagnosed as having SLE at the hospital. In the few cases (<5%) in whom a diagnosis was retrospectively made by reviewing medical records, we considered the date of diagnosis as the date when they fulfilled at least 4 classification criteria for SLE.[39]

In most cases (83%) patients with SLE were diagnosed by rheumatologists or less commonly (17%) by nephrologists, dermatologists, or internal medicine staff members. However, once the diagnosis was made, the vast majority of patients were periodically followed at the rheumatology outpatient clinics of the hospital.

Rheumatologists used the same criteria for assessment of patients. Over the period of study, 6 rheumatologists assessed the patients; 1 of them, with a special interest in patients with connective tissue diseases (MAGG), was working at the hospital from the time the rheumatology unit was established until the end of the present study.

Patients were specifically asked for joint symptoms; history of puffy hands and feet; myalgia; weakness; history of thrombotic phenomena; dry mouth and dry eye symptoms; photosensitivity and skin rashes, especially after exposure to sunlight; Raynaud phenomenon; or any other symptoms of connective tissue diseases. A physical examination looking for clinical features of connective tissue diseases was conducted. Data were incorporated into the clinical history and then they were included in a database for further evaluation.

In all cases, a full blood cell count and biochemistry profile including antinuclear antibody (ANA) testing for connective tissue diseases was performed. Most patients were followed at the rheumatology outpatient clinic at least twice per year.

Disease flares were characterized by constitutional symptoms, musculoskeletal, mucocutaneous, neurologic, cardiovascular/respiratory, vasculitis, renal, and/or hematologic involvement associated with abnormal serologies (decreasing levels of C3 and C4 or positive/increased anti-double-stranded DNA titer).

Antibody Determination

Patients with a diagnosis of connective tissue disease were assessed for the presence of ANA by routine screening of indirect immunofluorescence (IIF) ANA testing over the period of study. ANA were detected using IIF with the commercially prepared HEp-2 cell line as substrate at the initial dilution of 1:80 using polyvalent secondary antibody. They were considered to be positive if results were positive at a dilution of 1:160 or greater. Antibodies to saline extractable nuclear antigen (SSA/Ro, SSB/La, RNP, and Sm) were detected by double immunodiffusion using reference sera of each known antibody specificity and/or ELISA kits. Anti-double-stranded DNA antibodies were initially measured by IIF using *Crithidia luciliae*, and then by ELISA in the last years of the study. Anticardiolipin antibodies were measured by ELISA. A positive test for lupus anticoagulant was defined as prolonged activated protrombin time, irreversible by dilution with normal plasma and a positive platelet neutralizing test.

Statistical Analysis

Continuous data were described as mean ± standard deviation (mean ± SD), median and range or interquartile range, and categorical variables as percentages. For continuous variables, mean values were compared using the Kruskall-Wallis test, because of lack of normality; percentages were compared using the chi-square test or the Fisher exact test, as needed.

The target population was census based. The population distribution was provided by the Instituto Nacional de Estadística (INE). In the Lugo region, population grouped by age and sex was estimated by exponential interpolation from census data. In Spain the censuses were surveyed every 10 years if the last digit of the year was 0. More recently, censuses have been performed in the years whose last digit is 1. The population between censuses is established by interpolation. The formula provided by the INE: $Pt = P0 (1+r)^t$, where Pt is the population to be calculated, P0 is the reference population, t is the lag of time to be extrapolated, and r is the growth rate of the population for this period.

Age-standardized incidence rates were calculated by the direct method using the European population as standard; the European standard was preferred to the world standard because it better represents a developed country's population. Rates were reported as cases per 100,000 population aged 15 years and older. They were calculated using the number of new cases observed divided by the estimated population aged 15 years and older. The age-adjusted incidence rate was calculated for 5-year periods to avoid random changes. A prevalent case was defined as any patient diagnosed with SLE resident in the Lugo region on December 31, 2006. Prevalence by December 2006 was estimated as number of prevalent cases of SLE divided by population living in Lugo by this date. We used Poisson distribution to estimate rates and confidence intervals (CIs). To test whether incidence rate increased with age or with calendar period, we used a nonparametric test for trend across ordered groups developed by Cuzick.[11]

All patients were followed at the same hospital where a diagnosis of SLE was made (Hospital Xeral-Calde, Lugo). When available (in most cases), specific information on time and cause of death was retrieved from patients' hospital medical records. For attributing cause of death, 2 clinicians (MDA and FMV) independently reviewed the clinical records of patients with SLE; discrepancies were resolved by consensus. If the patient was lost to follow-up and phone contact with the patient or his/her relatives was not possible, we consulted the National Death Index.

TABLE 1. Main Epidemiologic Features of Patients Diagnosed With SLE in Lugo, Spain, 1987–2006

Characteristic	
Total no. of patients	150
Women/men (no.)	127/23
Women (%)	84.7
Age, yr*	
At symptom onset	44.5 ± 19.2; 42 (28–59)
At time of disease diagnosis	46.1 ± 19.6; 43.5 (30–63.5)
Delay to diagnosis, yr†	0.5 (0.25–1)
Follow-up from disease diagnosis, yr*	7.8 ± 4.5; 7.6 (4.6–10.1)

Abbreviations: IQR = interquartile range.

*Mean ± SD; median (IQR).

†Delay to diagnosis from the onset of symptoms to the time of diagnosis of SLE. Median (IQR).

This is a national registry developed only for research purposes; it includes all deaths in Spanish people by linking with the official civil registry. In these cases, the cause of death was considered unknown. Log-rank test was used for comparing Kaplan-Meier curves.

Probability of survival from diagnosis date was estimated using the Kaplan-Meier method; patients alive at the end of the follow-up were considered as censored. Results are presented as probability of survival at 5, 10, and 15 years of follow-up. Statistical significance was defined as p ≤ 0.05. Calculations were performed with the statistical package Stata 10/SE (Stata Corporation, College Station, TX).

RESULTS

Main Epidemiologic Features of SLE Patients

Between January 1987 and December 2006, 150 Lugo residents were diagnosed as having SLE according to the 1982 ACR criteria for the classification of SLE.[39] The main epidemiologic features of these patients are summarized in Table 1. Women outnumbered men (127 [84.7%] vs. 23 [15.3%], respectively). The mean age at the time of disease diagnosis was 46.1 ± 19.6 years. The mean follow-up from the time of disease diagnosis was 7.8 ± 4.5 years (range, 0–20 yr).

Age- and Sex-Specific Annual Incidence Rates

Table 2 shows the age- and sex-specific rates of SLE. Based on the 1982 ACR criteria,[39] the age- and sex-adjusted annual incidence rate over the 20-year study period was 3.6 per 100,000 population aged 15 years and older (95% CI, 3.0–4.2). Using these criteria,[39] the overall annual incidence rate over the 20-year study period in women (5.9/100,000 population aged ≥15 yr; 95% CI, 4.9–7.0) was higher than in men (1.1/100,000 population aged ≥15 yr; 95% CI, 0.7–1.7) (p < 0.001).

In comparing incidence rates stratified by specific age groups, we observed that the incidence was higher in women than in men aged younger than 60 years. However in the older age groups (aged 60–69, 70–79, and ≥80 yr), no statistically significant differences in the annual incidence between women and men were observed (see Table 2). To further assess this issue we stratified all the patients in only 3 age groups (aged <45, 45–64, and >65 yr). Following this procedure, again we observed that the incidence was much higher in women than in men aged younger than 65 years (p < 0.001 for <45 and 45–64 age groups). In addition, when we established an age group encompassing all patients aged 65 years and older, we observed that the incidence was also significantly higher in women than in men (p = 0.02) (Table 3).

Using the group of patients aged 60–69 years as a reference because it was the largest population age group in Lugo, we found that the incidence was significantly increased in patients aged 20–29 years at the time of disease diagnosis (see Table 2). A marginally increased incidence was observed in the 30–39, 40–49, and 50–59 year-old age groups compared with the 60–69 year-old age group.

Age- and Sex-Specific Incidence Rates for 5-Year Time Periods

To establish whether there was a change in the incidence of SLE over the 20-year period of study, we assessed age- and sex-adjusted annual incidence rates per 100,000 population aged 15 years and older for 4 consecutive 5-year time periods from 1987 to 2006 (Table 4). Based on the 1982 ACR criteria,[39] the overall incidence rates were significantly higher in the period 1992–1996 and 1997–2001 than in the 1987–1991 period. However, due to a decrease in the incidence over the period 2002–2006 compared to the 1992–1996 and 1997–2001 periods, the trend in the incidence in women (p = 0.08) and the overall (total) trend in

TABLE 2. Age- and Sex-Specific Mean Annual Incidence Rates* (95% CI) of SLE per 100,000 People, by Age of Disease Diagnosis

Age Group (yr)	Men	Women	P†	Total	P‡
15–19	0.7 (0.0–3.7)	6.5 (3.0–12.4)	0.009	3.5 (1.7–6.4)	0.28
20–29	1.0 (0.2–2.9)	8.5 (5.5–12.4)	<0.001	4.8 (3.2–6.9)	0.02
30–39	0.6 (0.1–2.2)	8.0 (5.2–11.7)	<0.001	4.3 (2.8–6.2)	0.047
40–49	1.6 (0.5–3.8)	7.2 (4.4–11.1)	0.001	4.3 (2.8–6.3)	0.06
50–59	0.8 (0.1–2.8)	7.9 (4.9–12.1)	<0.001	4.4 (2.8–6.6)	0.049
60–69	1.3 (0.3–3.2)	3.1 (1.6–5.6)	0.13	2.2 (1.3–3.7)	Ref.§
70–79	1.7 (0.5–4.2)	4.3 (2.3–7.3)	0.09	3.1 (1.8–5.0)	0.38
≥80	1.4 (0.2–5.2)	1.1 (0.1–3.8)	1.00	1.2 (0.3–3.1)	0.34
Total	1.1 (0.7–1.7)	5.9 (4.9–7.0)	<0.001	3.6 (3.0–4.2)	

*Based on the 1982 American College of Rheumatology criteria for the classification of SLE.[39]

†P values for differences between men and women.

‡P values for differences between age groups.

§The 60–69 year age group was taken as reference because it was the largest population age group.

TABLE 3. Age- and Sex-Specific Mean Annual Incidence Rates* (95% CI) of SLE per 100,000 People, by Age of Disease Diagnosis

Age Group (yr)	Men	Women	P†	Total	P‡
<45	1.0 (0.4–1.8)	7.3 (5.6–9.2)	<0.001	4.1 (3.2–5.1)	0.08
45–64	1.1 (0.4–2.3)	5.7 (3.9–8.0)	<0.001	3.4 (2.4–4.6)	0.48
≥65	1.5 (0.6–2.9)	3.9 (2.5–5.7)	0.02	2.8 (2.0–3.9)	Ref.

*See Table 2.
†P values for differences between men and women.
‡P values for differences between age groups.

the incidence remained out of the range of significance (p = 0.11) (see Table 4).

Prevalence of SLE

By December 31, 2006, the overall age-adjusted SLE prevalence in the Lugo region for patients who fulfilled at least 4 of 1982 ACR classification criteria[39] was 17.5 per 100,000 population aged 15 years and older (95% CI, 12.6–24.1). Prevalence in women (29.2/100,000 population aged ≥15 yr; 95% CI, 20.0–40.7) was higher than in men (5.8/100,000 population aged ≥15 yr; 95% CI, 2.0–12.0) (Table 5).

Main Clinical Features of the Disease

The most frequent clinical manifestation was arthritis (68.7%), 39.3% had malar rash, and 42.7% photosensitivity. Serositis was observed in 26.7% of patients. Raynaud phenomenon was noted in 36.7%. Almost 20% had renal disease at the time of disease diagnosis, and 27.3% suffered renal disease over the course of the disease. A renal biopsy was performed in 26 patients. Based on the 1982 classification published under the auspices of the World Health Organization,[10,46] 11 of these 26 patients had class IV diffuse glomerulonephritis, 7 had class III focal lupus nephritis, 5 of the 26 encompassed definitions for class V membranous lupus nephritis, and 3 were classified as having mesangial proliferative class II lupus nephritis. Other clinical characteristics of this series of patients diagnosed with SLE are summarized in Table 6.

Laboratory Data of Patients With SLE

As shown in Table 6, 44.7% of patients had a leukocyte count lower than 4000/mm^3, 72.7% less than 1500 lymphocytes/mm^3, and 20% a platelet count less than 100,000/mm^3. Hemolytic anemia was noted in 8.7%.

At the time of disease diagnosis, 149 of 150 (99.3%) patients were ANA positive. Ninety-one (60.7%) were anti-DNA positive, and 25 (16.7%) were anti-Sm positive. Information related to other autoantibodies is summarized in Table 7.

Anticardiolipin antibodies were positive in 66 of 140 (47.1%) patients in whom they were tested. Lupus anticoagulant was positive in 13 (8.7%) patients. Rheumatoid factor was found in 33 (22%) patients.

Flares and Causes of Death in SLE

At the end of the study 57 of 150 (38%) patients had experienced flares of the diseases (median, 2; range, 1–7 flares). Most patients who had this complication suffered 1 (n = 28) or 2 (n = 16) flares. No sex differences were observed in the frequency of flares (women: 49 of 127 [38.6%]; men 8 of 23 [34.8%]; p = 0.73).

The rate of flares per year was 0.084 (95% CI, 0.070–0.101). The most common features at the time of flares were asthenia, fever, arthralgia or arthritis, skin and renal manifestations, hematologic cytopenia, and, less commonly, serositis.

Patients who had flares were younger at the time of SLE diagnosis (mean age at time of disease diagnosis ± SD in the group of patients with flares 40.6 ± 19.8 yr vs. 48.2 ± 19.0 yr in the subgroup of patients without flares; p = 0.01). This younger age in the subgroup of patients who experienced flares was still present when a correction for follow-up time (duration of follow-up) was performed. A logistic regression analysis showed the following significant data regarding flares: a) age at time of diagnosis: odds ratio (OR), 0.98; 95% CI, 0.96–1.00; p = 0.044; b) follow-time (per year): OR, 1.12; 95% CI, 1.05–1.19; p = 0.001. Patients who had nephritis at the time of disease diagnosis were younger and experienced flares (17 of 29 patients; 58.6%) more commonly than the remaining patients who did not have renal disease at the time of SLE diagnosis (40 of 121 patients; 33.1%); p = 0.01. In addition, a logistic regression analysis to establish the potential association of nephritis at the time of disease diagnosis with the development of flares in the

TABLE 4. Age- and Sex-Adjusted Incidence Rates* (95% CI) per 100,000 People Aged ≥15 Years for 5-Year Time Periods, by Year of Disease Diagnosis

Period	Men	P†	Women	P‡	Total	P§
1987–1991	0.4 (0.0–1.3)	Ref.	3.2 (1.9–4.5)	Ref.	1.9 (1.1–2.8)	Ref.
1992–1996	1.7 (0.6–2.9)	0.006	7.1 (4.7–9.5)	0.003	4.5 (3.2–5.8)	<0.001
1997–2001	1.1 (0.4–2.4)	0.02	9.6 (6.7–12.5)	<0.001	5.7 (4.4–7.3)	<0.001
2002–2006	0.7 (0.2–1.9)	0.22	2.3 (1.1–3.7)	1.00	1.6 (1.0–2.6)	0.87
Total	0.9 (0.6–1.4)		5.6 (4.6–6.5)		3.5 (3.0–4.1)	

*See Table 2.
†P for trend in men: 0.15.
‡P for trend in women: 0.08.
§P for the overall trend in both men and women (total): 0.11.

TABLE 5. Age-Adjusted Prevalence Rates (95% CI) per 100,000 People Aged ≥15 Years for SLE in Lugo, Spain, on December 31, 2006*

Men	5.8 (2.0–12.0)
Women	29.2 (20.0–40.7)
Total	17.5 (12.6–24.1)

*Prevalence of SLE diagnosed from 1987 onward.

follow-up adjusting for age at the time of diagnosis confirmed this association (OR, 2.49; 95% CI, 1.07–5.80; p = 0.035).

Causes of death in this cohort are summarized in Table 8. Cancer, infections, and cardiovascular complications (congestive heart failure and ischemic heart disease) were the most common causes of death.

Survival Analysis

Compared with that in the general population, the probability of survival in patients with SLE was significantly reduced (p = 0.04) (Figure 1). While the 5-year probability of survival in the general population was 97.4%, it was 94.1% in patients with SLE. The decreased probability of survival was also evident after that time: the 10-year and 15-year survival probabilities were 93.8% and 88.7% in the general population and 87.4% and 79.5% in patients with SLE, respectively.

Furthermore, the probability of survival was reduced in men. However, probably due to the sample size, the differences between men and women did not reach statistical significance.

TABLE 6. Main Clinical and Laboratory Features of Patients Diagnosed With SLE Between 1987 and 2006

Feature	No. (%)
Arthritis	103 (68.7)
Raynaud phenomenon	55 (36.7)
Malar rash	59 (39.3)
Photosensitivity	64 (42.7)
Discoid lesions	8 (5.3)
Oral ulcers	22 (14.7)
Cutaneous vasculitis	17 (11.3)
Livedo reticularis	5 (3.3)
Serositis	40 (26.7)
Interstitial lung disease	3 (2.0)
Lymphadenopathy	18 (12.0)
Secondary Sjögren syndrome	27 (18.0)
Renal disease*	41 (27.3)
Renal disease at time of disease diagnosis	29 (19.3)
Central nervous system disorder†	7 (4.7)
Myositis	5 (3.3)
Severe mononeuritis multiplex secondary to necrotizing vasculitis	2 (1.3)
Leukopenia (WBC <4000/mm³)	67 (44.7)
Lymphopenia (<1500/mm³)	109 (72.7)
Thrombocytopenia (platelet count <100,000/mm³)	30 (20.0)
Hemolytic anemia	13 (8.7)

*Persistent proteinuria >0.5 g/d or cellular casts.[39]
†Including seizures and psychosis.

TABLE 7. Antinuclear Antibodies in Patients With SLE

	No. (%)
ANA positive	149 (99.3)
Anti-DNA positive	91 (60.7)
Anti-Sm positive	25 (16.7)
Anti-RNP positive	29 (19.3)
Anti-SSA	43 (28.6)
Anti-SSB	22 (14.7)

Table 9 summarizes the 5-year, 10-year, and 15-year probability of survival after the diagnosis of SLE in the whole group of SLE patients and in SLE according to sex.

DISCUSSION

In the present study we describe epidemiologic data on SLE in a well-defined region of northwestern Spain, to our knowledge for first time.

Female Predominance of SLE

In most studies 90% or more of patients with SLE are women, and because of this, the incidence and prevalence rates for men are approximately 1/10th those in women.[4,34] SLE in Lugo was also more common in women. However, in northwestern Spain the frequency of females was 84.7%. This frequency was remarkably similar to that reported in the United Kingdom in the period 1990–1999 (83.9%).[37]

The women to men ratio in northwestern Spain was 5.5:1. This ratio is almost similar to that of 6.2:1 reported by Alarcón et al[2] in North American SLE patients who were descendants of Europeans, and slightly lower than that of 7.5:1 described by Alamanos et al[1] in Greece. An explanation for the lower frequency of women in the European populations compared to that observed in the African American population is still unknown. It is possible that genetic factors might account for such differences in the incidence and clinical expression of the disease.

Age of Onset

The mean age ± SD at the time of disease diagnosis in northwestern Spain and in the United Kingdom were also very

TABLE 8. Causes of Death in 19 Patients With SLE

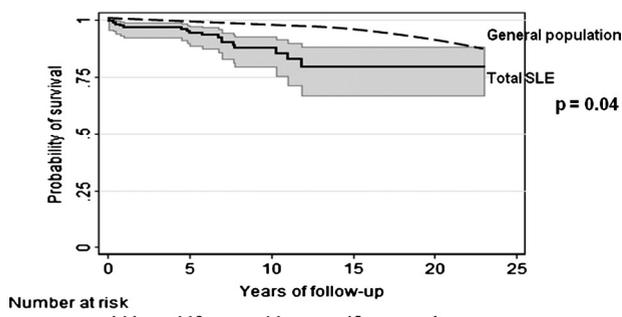| Cause	No. of Patients
Cancer	5
Breast	1
Lung	1
Pancreas	1
Lymphoma	1
Carcinomatosis of unknown primary site	1
Infection	4
Sepsis due to salmonella infection	2
Pneumonia due to cytomegalovirus	1
Peritonitis	1
Congestive heart failure and ischemic heart disease	4
Chronic renal insufficiency	2
Hepatic failure	1
Unknown*	3

*Death occurred out of the hospital.

FIGURE 1. Probability of survival from time of diagnosis to death for patients with SLE in Lugo, Spain (solid line) and 95% confidence band (gray area) compared to expected survival for the general population with the same age and sex composition (dashed line).

similar (46.1 ± 19.6 yr in northwestern Spain, and 47.3 ± 16.4 yr in the United Kingdom).[37] Classically SLE was considered a disease involving mainly reproductive-age women, in particular African American women.[34] In keeping with these observations, a progressive decline in the incidence of SLE in women seemed to exist in northwestern Spain when patients were stratified in 3 age groups (aged <45 yr, 45–64 yr, and ≥65 yr).

A series of studies has demonstrated that patterns in the incidence of SLE in European women are different from those observed in African Americans.[34] With respect to this, the peak incidence rate in northwestern Greece was found in the 30–49 year-old age group.[1] Also, in a large study from the United Kingdom based on the General Practice Research Database, the highest age-specific incidence rates were seen in individuals aged more than 40 years.[37] In the United Kingdom study, peak incidences occurred at age 50–54 years for women and age 70–74 years for men.[37] In line with these observations, an epidemiologic study conducted in southern Sweden showed that during the period 1987–1991, the median age at diagnosis of SLE was 47 years, and there was a high incidence rate in people aged 65–74 years.[38]

Explanations are unclear for the later average age of SLE onset and for differences in the expression of SLE in the European population of northwestern Spain compared to those found in the African-American population. However, differences in genetic predisposition or the decrease in the response of an aging immune system may be a factor influencing a later onset in our European population compared with that observed in African-American individuals. As pointed out by Cervera et al,[7] older patients may have different genetic determinants of disease, and therefore they may respond to different triggering mechanisms than younger patients.

Incidence and Prevalence of SLE

Incidence and prevalence rates of SLE in people of African or of Asian background are approximately 2–3 times higher than in white populations.[8,23,24,29,36] Table 10 shows incidence rates of SLE in white individuals from Europe[1,14,23–25,27] as well as in populations from other continents from several epidemiologic studies conducted over the last 2 decades.[9,13,31,42]

A comparative analysis shows that the mean annual incidence rate in the Lugo region of northwestern Spain in the period 1987–2006 was similar to that reported in Nottingham, United Kingdom, in the period 1989–1990.[23] However, it seems to be higher than that found in the Scandinavian population.[14,25] More importantly, based on the 1982 ACR classification criteria, the mean incidence rate of SLE in Lugo in the period 1987–2006 (3.5/100,000 people aged ≥15 yr) was higher than that noted in

Greece in the period 1982–2001 (1.9/100,000 individuals)[1] and in the neighboring region of Asturias (northern Spain) in the period 1998–2002 (2.15/100,000 individuals).[27] The reasons for this higher incidence of SLE in Lugo compared with those observed in other parts of Europe, and specifically in southern Europe, are unknown. However, it is possible that unknown environmental factors might influence the fluctuations in the incidence of SLE.

Changes in the incidence of SLE have been reported in several studies. Uramoto et al[40] described an increase in the incidence in Olmsted County, MN, when they assessed the age- and sex-adjusted incidence rate in the periods 1950–1979 and 1980–1992. They found very different incidence rates (1.5 and 5.6 per 100,000 people, respectively). Similar increases in incidence rates were seen in a Danish study that encompassed the periods 1980–1984, 1985–1989, and 1990–1994.[44] Based on the 1982 ACR classification criteria, these authors noted an increase in the incidence from 1.0/100,000 to 3.6/100,000 people during the study period 1980–1994.[44] This increase may be explained by a more accurate ascertainment of cases leading to early diagnosis of milder cases. However, this is in contradiction to the decline observed in northwestern Spain in the period 2002–2006 compared with the rates noted in the periods 1992–1996 and 1997–2001.

Early diagnosis and improved survival due to the use of more effective therapies may account for an increased prevalence of SLE in the last decades. Differences in the definitions used for inclusion may also explain differences in the prevalence among different studies. Prevalence of SLE is higher in North American series than in European population-based studies. Using the number of adults in California and Pennsylvania who were hospitalized in 2000 and had SLE among their discharge diagnoses, Chakravarty et al[8] reported that the estimated overall age-, sex-, and race/ethnicity-adjusted prevalence per 100,000 people aged 18 years and older in 2000 was 107.6 (95% CI, 106.1–109.2) in California and 149.5 (95% CI, 146.9–152.2) in Pennsylvania. Additional data on prevalence of SLE in the last 2 decades in different parts of the world are shown in Table 10. Using the 1982 ACR classification criteria, the overall sex-adjusted prevalence rate for SLE in northwestern Spain on December 31, 2006, was 17.5 per 100,000 people aged 15 years and older (95% CI, 12.6–24.1). Prevalence of SLE in northwestern Spain was 5 times as high in women as in men. The prevalence was similar to that found in the United Kingdom[23,24] and in white individuals from Manitoba, Canada (20.6/100,000 people), but lower than that observed among North American Indians from this Canadian region (42.3/100,000 people).[32]

SLE and Clinical Features

In the current series the most common clinical manifestation was arthritis. It was also the most common feature in a series of 94 Danish patients aged 15 years old and older who met at least 4 of the revised ACR classification criteria for SLE.[26]

The frequency of renal disease is at least twice as common in Asian and Hispanic individuals compared with that observed

TABLE 9. Survival Analysis (95% CI) in Patients With SLE

| | Probability of Survival | | |
	5-Year	10-Year	15-Year
Women	94.6 (88.2–97.5)	89.2 (80.5–94.1)	80.0 (65.4–88.9)
Men	91.3 (69.5–97.8)	78.3 (50.9–91.5)	—
Total	94.1 (88.4–97.0)	87.4 (79.4–92.5)	79.5 (66.7–87.8)

TABLE 10. Incidence and Prevalence of SLE by Location, Present and Previous Reports*

Location (ref.)	Age (yr)	Study Period	Incidence/10^5	Prevalence/10^5
Taiwan[9]	All	2000–2007	8.1	67.4
Natal, Brazil[42]	≥15	2000	8.7	NA
Northern Norway[14]	≥16	1996–2006	3.0	64.1†
Funen County, Denmark[25]	All	1995–2003	1.04	28.3
Wisconsin, United States[31]	All	1991–2001	5.1	78.5
Martinique (Afro-Caribbean)[13]	All	1990–1999	4.7	64.2
United Kingdom				
Birmingham[24]	≥18	1991	2.5	20.7
Nottingham[23]	All	1989–90	3.4	20.3
Asturias, northern Spain[27]	All	1988–2002	2.15	34.1
Lugo, northwestern Spain (PR)‡	≥15	1987–2006	3.5	17.5
Southern Greece[1]	All	1982–2001	1.9	38.1

Abbreviations: NA = not available, PR = present report.
*Including men and women.
†Crude rates.
‡Prevalence of SLE patients diagnosed from 1987 onward.

in the European population.[2,5,33,45] With respect to this, Alarcón et al[2] showed statistically significant differences in the frequency of renal disease among European descendents (22.7%) compared with that observed in other North American ethnic groups (Hispanic, 59% and African Americans, 54.4%). In northwestern Spain, renal disease was observed in only 27.3% of patients. In keeping with our findings, Cervera et al[7] described the presence of nephropathy in 279 of 1000 (27.9%) patients from the Euro-Lupus cohort during a 10-year prospective study (1990–2000). A lower frequency of renal disease (15.2%) was reported in northwestern Greece in the period 1982–2001.[1] Therefore, our data confirmed that lupus nephritis is less prevalent in SLE patients of European descent than in African American patients.[4]

ANA Results

In our series the frequency of anti-DNA-positive patients was slightly lower (60.7%) than in the Euro-Lupus cohort (78%).[5,6] In contrast, the frequency of anti-Sm-positive patients in northwestern Spain was slightly higher (16.7%) than in the Euro-Lupus cohort (10%).[5,6] Frequency of anti-SSA and anti-SSB in northwestern Spain (28.6% and 14.7%, respectively) did not differ much from that noted in the Euro-Lupus cohort (25% and 19%, respectively).[5,6]

SLE and Flares

The frequency of flares (almost 40%) and the rate of flares (0.084/yr) in northwestern Spain was similar to that reported in Greece (43% flares and an annual rate of flare of 0.07 after 10-yr follow-up).[43] However, the rate of annual flare in northwestern Spain was lower than that reported in most series, which generally report ranges between 0.2 and 2.18 per year.[26] A younger age at the time of disease diagnosis and the presence of nephritis were associated with the development of flares in the follow-up of our patients.

SLE and Mortality

Although survival in patients with SLE has improved in recent years,[38,41] it remains reduced compared to survival in age- and sex-matched populations.[30,38] The probability of survival of SLE patients from northwestern Spain was significantly reduced

compared with the general population. In Lugo, cancer and infectious and cardiovascular complications were the leading causes of death among patients with SLE. With improvement in survival due to better management of the lupus nephritis and the infectious complications, we expect that cardiovascular diseases will become the major cause of patient mortality on longer follow-up.

In conclusion, despite the retrospective nature of the current study, we have established a baseline estimate of the incidence and clinical spectrum of SLE in northwestern Spain. Our results confirm that the incidence of SLE in northwestern Spain is slightly higher than that reported in most European regions. As observed in previous population-based studies, it is also higher in women than in men. Patients with SLE from northwestern Spain have a later average age of onset and a lower frequency of nephritis than patients in the African-American population. However, in northwestern Spain, SLE patients have a lower survival than the general population.

REFERENCES

1. Alamanos Y, Voulgari PV, Siozos C, Katsimpri P, Tsintzos S, Dimou G, Politi EN, Rapti A, Laina G, Drosos AA. Epidemiology of systemic lupus erythematosus in northwest Greece 1982–2001. *J Rheumatol.* 2003;30:731–735.

2. Alarcón GS, McGwin G Jr, Petri M, Reveille JD, Ramsey-Goldman R, Kimberly RP; PROFILE Study Group. Baseline characteristics of a multiethnic lupus cohort: PROFILE. *Lupus.* 2002;11:95–101.

3. Arias-Nuñez MC, Llorca J, Vazquez-Rodriguez TR, Gomez-Acebo I, Miranda-Filloy JA, Martin J, Gonzalez-Juanatey C, Gonzalez-Gay MA. Systemic sclerosis in northwestern Spain: a 19-year epidemiologic study. *Medicine (Baltimore).* 2008;87:272–280.

4. Borchers AT, Naguwa SM, Shoenfeld Y, Gershwin ME. The geoepidemiology of systemic lupus erythematosus. *Autoimmun Rev.* 2010;9:A277–A287.

5. Cervera R, Abarca-Costalago M, Abramovicz D, Allegri F, Annunziata P, Aydintug AO, Bacarelli MR, Bellisai F, Bernardino I,

Biernat-Kaluza E, Blockmans D, Boki K, Bracci L, Campanella V, Camps MT, Carcassi C, Cattaneo R, Cauli A, Cervera R, Chwalinska-Sadowska H, Contu L, Cosyns JP, Danieli MG, DCruz D, Depresseux G, Direskeneli H, Domenèch I, Espinosa G, Fernández-Nebro A, Ferrara GB, Font J, Frutos MA, Galeazzi M, García-Carrasco M, García Iglesias MF, García-Tobaruela A, George J, Gil A, González-Santos P, Grana M, Gül A, Haga HJ, de Haro-Liger M, Houssiau F, Hughes GR, Ingelmo M, Jedryka-Góral A, Khamashta MA, Lavilla P, Levi Y, López-Dulpa M, López-Soto A, Maldykowa H, Marcolongo R, Mathieu A, Morozzi G, Nicolopoulou N, Papasteriades C, Passiu G, Perelló I, Petera P, Petrovic R, Piette JC, Pintado V, de Pita O, Popovic R, Pucci G, Puddu P, de Ramón E, Ramos-Casals M, Rodríguez-Andreu J, Ruiz-Irastorza G, Sanchez-Lora J, Sanna G, Scorza R, Sebastiani GD, Sherer Y, Shoenfeld Y, Simpatico A, Sinico RA, Smolen J, Tincani A, Tokgöz G, Urbano-Márquez A, Vasconcelos C, Vázquez JJ, Veronesi J, Vianna J, Vivancos J; European Working Party on Systemic Lupus Erythematosus. Systemic lupus erythematosus in Europe at the change of the millennium: lessons from the "Euro-Lupus Project." *Autoimmun Rev*. 2006;5:180–186.

6. Cervera R, Khamashta MA, Font J, Sebastiani GD, Gil A, Lavilla P, Doménech I, Aydintug AO, Jedryka-Góral A, de Ramón E, Galeazzi M, Haga H-J, Mathieu A, Houssiau F, Ingelmo M, Hughes GRV; The European Working Party on Systemic Lupus Erythematosus. Systemic lupus erythematosus: clinical and immunologic patterns of disease expression in a cohort of 1,000 patients. The European Working Party on Systemic Lupus Erythematosus. *Medicine (Baltimore)*. 1993;72:113–124.

7. Cervera R, Khamashta MA, Hughes GRV. The Euro-Lupus project: epidemiology of systemic lupus erythematosus in Europe. *Lupus*. 2009;18:869–874.

8. Chakravarty EF, Bush TM, Manzi S, Clarke AE, Ward MM. Prevalence of adult systemic lupus erythematosus in California and Pennsylvania in 2000: estimates obtained using hospitalization data. *Arthritis Rheum*. 2007;56:2092–2094.

9. Chiu YM, Lai CH. Nationwide population-based epidemiologic study of systemic lupus erythematosus in Taiwan. *Lupus*. 2010;19:1250–1255.

10. Churg J, Sobin LH. *Renal Disease: Classification and Atlas of Glomerular Disease*. Tokyo: Igaku-Shoin; 1982.

11. Cuzick J. A Wilcoxon-type test for trend. *Stat Med*. 1985;4:87–90.

12. Danchenko N, Satia JA, Anthony MS. Epidemiology of systemic lupus erythematosus: a comparison of worldwide disease burden. *Lupus*. 2006;15:308–318.

13. Deligny C, Thomas L, Dubreuil F, Theodose C, Garsaud AM, Numeric P, Ranlin A, Jean-Baptiste G, Arfi S. Lupus systemique en Martinique: enquete epidemiologique ([Systemic lupus erythematosus in Martinique: an epidemiologic study]). *Rev Med Interne*. 2002;23:21–29.

14. Eilertsen GO, Becker-Merok A, Nossent JC. The influence of the 1997 updated classification criteria for systemic lupus erythematosus: epidemiology, disease presentation, and patient management. *J Rheumatol*. 2009;36:552–559.

15. Font J, Cervera R, Ramos-Casals M, Garcia-Carrasco M, Sents J, Herrero C, del Olmo JA, Darnell A, Ingelmo M. Clusters of clinical and immunologic features in systemic lupus erythematosus: analysis of 600 patients from a single center. *Semin Arthritis Rheum*. 2004;33:217–230.

16. Garcia-Porrua C, Gonzalez-Gay MA, Vazquez-Caruncho M, Lopez-Lazaro L, Lueiro M, Fernandez ML, Alvarez-Ferreira J, Pujol RM. Erythema nodosum: etiologic and predictive factors in a defined population. *Arthritis Rheum*. 2000;43:584–592.

17. Gomez J, Suarez A, Lopez P, Mozo L, Diaz JB, Gutierrez C. Systemic lupus erythematosus in Asturias, Spain: clinical and serologic features. *Medicine (Baltimore)*. 2006;85:157–168.

18. Gonzalez-Gay MA. Giant cell arteritis and polymyalgia rheumatica: two different but often overlapping conditions. *Semin Arthritis Rheum*. 2004;33:289–293.

19. Gonzalez-Gay MA, Garcia-Porrua C, Guerrero J, Rodriguez-Ledo P, Llorca J. The epidemiology of the primary systemic vasculitides in northwest Spain: implications of the Chapel Hill Consensus Conference definitions. *Arthritis Rheum*. 2003;49:388–393.

20. Gonzalez-Gay MA, Miranda-Filloy JA, Lopez-Diaz MJ, Perez-Alvarez R, Gonzalez-Juanatey C, Sanchez-Andrade A, Martin J, Llorca J. Giant cell arteritis in northwestern Spain: a 25-year epidemiologic study. *Medicine (Baltimore)*. 2007;86:61–68.

21. Hart HH, Grigor RR, Caughey DE. Ethnic differences in the prevalence of systemic lupus erythematosus. *Ann Rheum Dis*. 1983;42:529–532.

22. Hopkinson N. Epidemiology of systemic lupus erythematosus. *Ann Rheum Dis*. 1992;51:1292–1294.

23. Hopkinson ND, Doherty M, Powell RJ. The prevalence and incidence of systemic lupus erythematosus in Nottingham, UK, 1989–1990. *Br J Rheumatol*. 1993;32:110–115.

24. Johnson AE, Gordon C, Palmer RG, Bacon PA. The prevalence and incidence of systemic lupus erythematosus in Birmingham, England. Relationship to ethnicity and country of birth. *Arthritis Rheum*. 1995;38:551–558.

25. Laustrup H, Voss A, Green A, Junker P. Occurrence of systemic lupus erythematosus in a Danish community: an 8-year prospective study. *Scand J Rheumatol*. 2009;38:128–132.

26. Laustrup H, Voss A, Green A, Junker P. SLE disease patterns in a Danish population-based lupus cohort: an 8-year prospective study. *Lupus*. 2010;19:239–246.

27. Lopez P, Mozo L, Gutierrez C, Suarez A. Epidemiology of systemic lupus erythematosus in a northern Spanish population: gender and age influence on immunological features. *Lupus*. 2003;12:860–865.

28. Manzi S. Epidemiology of systemic lupus erythematosus. *Am J Manag Care*. 2001;7(Suppl 16):S474–S479.

29. McCarty DJ, Manzi S, Medsger TA Jr, Ramsey-Goldman R, LaPorte RE, Kwoh CK. Incidence of systemic lupus erythematosus. Race and gender differences. *Arthritis Rheum*. 1995;38:1260–1270.

30. Mok CC, To CH, Ho LY, Yu KL. Incidence and mortality of systemic lupus erythematosus in a southern Chinese population, 2000–2006. *J Rheumatol*. 2008;35:1978–1982.

31. Naleway AL, Davis ME, Greenlee RT, Wilson DA, McCarty DJ. Epidemiology of systemic lupus erythematosus in rural Wisconsin. *Lupus*. 2005;14:862–866.

32. Peschken CA, Esdaile JM. Systemic lupus erythematosus in North American Indians: a population based study. *J Rheumatol*. 2000;27:1884–1891.

33. Petri M. The effect of race on the presentation and course of SLE in the United States [abstract]. *Arthritis Rheum*. 1997;40:S162.

34. Pons-Estel GJ, Alarcon GS, Scofield L, Reinlib L, Cooper GS. Understanding the epidemiology and progression of systemic lupus erythematosus. *Semin Arthritis Rheum*. 2010;39:257–268.

35. Ramal LM, Lopez-Nevot MA, Sabio JM, Jaimez L, Paco L, Sanchez J, de Ramon E, Fernandez-Nebro A, Ortego N, Ruiz-Cantero A, Rivera F, Martin J, Jimenez-Alonso J; Grupo Lupus Virgen de las Nieves. Systemic lupus erythematosus in southern Spain: a comparative clinical and genetic study between caucasian and gypsy patients. *Lupus*. 2004;13:934–940.

36. Samanta A, Feehally J, Roy S, Nichol FE, Sheldon PJ, Walls J. High prevalence of systemic disease and mortality in Asian subjects with systemic lupus erythematosus. *Ann Rheum Dis*. 1991;50:490–492.

37. Somers EC, Thomas SL, Smeeth L, Schoonen WM, Hall AJ. Incidence of systemic lupus erythematosus in the United Kingdom, 1990–1999. *Arthritis Rheum*. 2007;57:612–618.

38. Stahl-Hallengren C, Jonsen A, Nived O, Sturfelt G. Incidence studies of systemic lupus erythematosus in southern Sweden: increasing age, decreasing frequency of renal manifestations and good prognosis. *J Rheumatol*. 2000;27:685–691.

39. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, Schaller JG, Talal N, Winchester RJ. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum*. 1982;25:1271–1277.

40. Uramoto KM, Michet CJ Jr, Thumboo J, Sunku J, O'Fallon WM, Gabriel SE. Trends in the incidence and mortality of systemic lupus erythematosus, 1950–1992. *Arthritis Rheum*. 1999;42:46–50.

41. Urowitz MB, Gladman DD, Tom BD, Ibanez D, Farewell VT. Changing patterns in mortality and disease outcomes for patients with systemic lupus erythematosus. *J Rheumatol*. 2008;35:2152–2158.

42. Vilar MJ, Sato EI. Estimating the incidence of systemic lupus erythematosus in a tropical region (Natal, Brazil). *Lupus*. 2002;11:528–532.

43. Vlachoyiannopoulos PG, Karassa FB, Karakostas KX, Drosos AA, Moutsopoulos HM. Systemic lupus erythematosus in Greece. Clinical features, evolution and outcome: a descriptive analysis of 292 patients. *Lupus*. 1993;2:303–312.

44. Voss A, Green A, Junker P. Systemic lupus erythematosus in Denmark: clinical and epidemiological characterization of a county-based cohort. *Scand J Rheumatol*. 1998;27:98–105.

45. Wang F, Wang CL, Tan CT, Manivasagar M. Systemic lupus erythematosus in Malaysia: a study of 539 patients and comparison of prevalence and disease expression in different racial and gender groups. *Lupus*. 1997;6:248–253.

46. Weening JJ, D'Agati VD, Schwartz MM, Seshan SV, Alpers CE, Appel GB, Balow JE, Bruijn JA, Cook T, Ferrario F, Fogo AB, Ginzler EM, Hebert L, Hill G, Hill P, Jennette JC, Kong NC, Lesavre P, Lockshin M, Looi LM, Makino H, Moura LA, Nagata M. The classification of glomerulonephritis in systemic lupus erythematosus revisited. *J Am Soc Nephrol*. 2004;15:241–250.