Epidemiology of Systemic Lupus Erythematosus in Northwest Greece 1982–2001

YANNIS ALAMANOS, PARASKEVI V. VOULGARI, CHRISTOS SIOZOS, PELAGIA KATSIMPRI, STYLIANOS TSINTZOS, GEORGIOS DIMOU, EUDOKIA N. POLITI, ANTONIA RAPTI, GIANNA LAINA, and ALEXANDROS A. DROSOS

ABSTRACT. ***Objective.*** To investigate the frequency, distribution, and mortality of systemic lupus erythematosus (SLE) in a defined area of northwest Greece.

Methods. Cases were recorded from 3 sources: inpatients and outpatients referred to the rheumatology clinic of the Ioannina University Hospital; inpatients and outpatients referred to the rheumatology clinic of Ioannina General Hospital; and patients referred to private rheumatologists practicing in the study area. All patients identified between January 1, 1982, and December 31, 2001, resident in the study area were included. Diagnosis was confirmed by the 1982 revised criteria of the American College of Rheumatology. Incidence and prevalence rates were calculated as number of cases per hundred thousand inhabitants. Population data were based on the 1981, 1991, and 2001 National Census.

Results. A total of 178 cases of SLE were diagnosed during the study period, giving a mean annual incidence rate of 1.9 cases/100,000 inhabitants (95% CI 1.49–2.31). The female/male ratio was 7.4. A significant variation of SLE rates among different districts of the study area was observed. Incidence rates were higher for the urban population. The peak of incidence was observed in the 30–49 age group for both sexes. There was a slight increase in the incidence of SLE during the study period. The 5 year survival rate was 96.8% and the 10 year survival rate was 90.3%.

Conclusion. We found a relatively low frequency of SLE in northwest Greece. Age at diagnosis was younger than expected. (J Rheumatol 2003;30:731–5)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS EPIDEMIOLOGY
INCIDENCE FREQUENCY SURVIVAL

Systemic lupus erythematosus (SLE) is a widespread disease affecting several organ systems. Epidemiological studies suggest the occurrence of SLE differs among different countries, and even among different areas of the same country[1]. Differences are also observed among population groups of the same race living in different parts of the world, suggesting that environmental factors are involved in the development of SLE. Ethnic and geographical factors also seem to influence the incidence and prevalence of the disease[1–3].

Studies in Europe and the United States suggest an increase of SLE incidence during the last decades, although survival rates have improved. These trends can lead to an increased prevalence of the disease[1,4]. Despite numerous studies on the occurrence of SLE from northern Europe and the United States, no studies on the epidemiology of the disease in southern Europe have been published. Investigation of the epidemiological characteristics of SLE in southern Europe and the Mediterranean countries would be of interest because of the possible effect of environmental and lifestyle factors on the frequency and severity of the disease.

We investigated the frequency, distribution, and mortality of SLE for the period 1982–2001 in an area of northwest Greece, with a total population of roughly 488,000 inhabitants according to the National Census of 2001. The study was carried out as part of the framework for the creation of a systematic recording system for autoimmune rheumatic diseases in this area.

MATERIALS AND METHODS

The study area included 6 districts of northwest Greece, 4 on the mainland and 2 in the islands. The total population of the area was 488,435 according to the National Census of 2001. Urban residents represented 36.5% of the total population, living in the capitals of the 6 districts. There are 2 rheumatology clinics in the area, both in Ioannina, the largest city of northwest Greece, with a medical school and a university hospital.

Cases were selected from 3 sources: (1) inpatients and outpatients referred to the rheumatology clinic of Ioannina University Hospital; (2) inpatients and outpatients referred to the rheumatology clinic of the Ioannina General Hospital; and (3) patients referred to private rheumatologists practicing in the study area (8 private rheumatologists). These 3 sources represent all

From the Department of Hygiene and Epidemiology and the Department of Internal Medicine, Medical School, University of Ioannina; and General Hospital of Ioannina, Ioannina, Greece.

Y. Alamanos, MD, Assistant Professor; S. Tsintzos, Medical Student, Department of Hygiene and Epidemiology; P.V. Voulgari, MD, Attending Rheumatologist; P. Katsimpri, MB, BS, Fellow in Rheumatology; A.A. Drosos, MD, FACR, Professor of Medicine/Rheumatology, Department of Internal Medicine; C. Siozos, MD, Consultant Rheumatologist, General Hospital of Ioannina; G. Dimou, MD, Private Practice Rheumatologist; E.N. Politi, MD, Private Practice Rheumatologist; A. Rapti, MD, Private Practice Rheumatologist; G. Laina, MD, Private Practice Rheumatologist.

Address reprint requests to Dr. A.A. Drosos, Department of Internal Medicine, Medical School, University of Ioannina, 451 10 Ioannina, Greece. E–mail: adrosos@cc.uoi.gr

Submitted May 8, 2002; revision accepted September 23, 2002.

points where patients diagnosed with SLE could be referred in the area. Patients were identified through medical records from the 2 hospitals and the private practices. All patients referred between January 1, 1982, and December 31, 2001, resident in the study area were included in the study. An incidence case was defined as any patient with SLE, diagnosed during the study period, resident in the study area for at least one year before the diagnosis. A prevalence case was defined as any patient with SLE who was a resident of the study area on December 31, 2001.

Diagnosis according to the American College of Rheumatology revised criteria[5] was confirmed by reviewing medical records. The term "renal disorder" includes proteinuria > 0.5 g/24 h or microscopic hematuria or the presence of cellular casts[5]. Incidence, prevalence, and mortality rates were calculated as the number of cases per hundred thousand inhabitants. Age adjusted rates were obtained by the direct method using the 2001 National Census of the Greek population. Survival rates were estimated using the Kaplan–Meier method. Population data were based on the 1981, 1991, and 2001 National Census.

RESULTS

A total of 178 cases of SLE among residents of the study area were diagnosed during the period January 1, 1982 to December 31, 2001. These cases represent a mean annual incidence rate of 1.90 cases/100,000 inhabitants (95% CI 1.49–2.31), with a female/male ratio of 7.4. The mean age at the time of diagnosis was 39.1 (SD 16.9, range 6–68) years for men and 38.8 (SD 18.4, range 2–81) years for women. Twenty–seven patients (15.2%) presented with renal disorder at the time of first diagnosis. Other major clinical and laboratory characteristics of the cohort are shown in Table 1.

Table 2 presents the age and sex-specific prevalence rates of SLE in the defined area by December 31, 2001. The total prevalence of SLE for women was 69.27 and for men 9.46 cases/100,000, and the total female/male ratio was 7.32.

Incidence rates of SLE varied among the 6 districts of the study area. The highest age adjusted rate observed in a district was 2.13, and the lowest was 1.45. The disease incidence was also higher among the urban population in all study districts (2.25 in the urban vs 1.68 in the rural population).

Age and sex-specific incidence rates for the period 1982–2001 are illustrated in Figure 1. The peak incidence rates were in the age group 30–49 for both sexes.

Table 3 shows the evolution of mean annual incidence rates (for 5-year periods) during the period studied. There is a slight increase of SLE incidence with time, and this is seen more clearly among women.

The 5–year and 10–year survival rates were 96.8% and 90.3%, respectively. A total of 12 deaths were identified among the 178 SLE patients during the study period. The standardized mortality ratio for this SLE cohort was 1.3 compared with the general population of the area. Two deaths were related to renal insufficiency and 2 to infection.

Table 1. Characteristics of SLE patients diagnosed during the period 1982–2001.

Total no. of patients	178
Female/male	157/21
Age at diagnosis, yrs, mean (± SD)	38.83 (18.02)
Men	39.14 (16.95)
Women	38.79 (18.36)
Disease duration, yrs, mean (± SD)	8.25 (5.45)
Photosensitivity, n (%)	91 (51.1)
Butterfly rash, n (%)	118 (66.3)
Arthritis, n (%)	89 (50)
Serositis, n (%)	20 (11.2)
Renal disorder at diagnosis, n (%)	27 (15.2)
Antinuclear antibodies, n (%)	153 (86)
Antibodies to double stranded DNA, n (%)	79 (44.4)
Anti-Smith antibodies, n (%)	19 (10.7)

DISCUSSION

Studies in North America and northern European countries have reported annual incidence rates of diagnosed SLE between 1.5 and 8 cases/100,000 inhabitants[1,4,6–9]. Our results suggest a relatively low incidence of SLE in the population of northwest Greece.

The sex ratio in the Greek population is comparable with the sex ratio found in other studies. The peak incidence rates occurred in the group aged 30–49 years, with a mean age at diagnosis of about 39 years. This finding suggests an early onset of the disease in our population. Although data from other epidemiological studies vary widely, most studies indicate a mean age at diagnosis between 45 and 55 years[1,4,8,10]. The prevalence of the disease is increasing with age and this is explained by the long survival.

We observed a slight increase in SLE incidence rates during the study period. Data from other studies concerning trends in disease incidence during the last decades are controversial. They suggest an increase in the occurrence of the disease in some countries, and a relatively constant or even decreasing incidence in other countries[4,7,8]. The increase may partly be artifactual, considering several factors such as better

Table 2. Point prevalence by age and sex of SLE cases residing in northwest Greece by December 31, 2001. Data are number of cases (n), age specific rates [cases per 100,000 inhabitants] (95% CI).

Age, yrs	Female	Male	Total	Female/Male Ratio
< 45	(77) 46.64 (42.86–50.42)	(10) 6.03 (5.01–7.05)	(87) 26.63 (24.60–28.69)	8.24
45–64	(52) 85.19 (83.88–86.50)	(7) 11.89 (10.22–13.56)	(59) 49.22 (47.93–50.51)	7.16
> 65	(41) 91.08 (90.01–92.15)	(6) 17.20 (15.69–18.71)	(47) 58.83 (57.10–60.56)	5.30
Total	(170) 69.27 (65.90–72.64)	(23) 9.46 (6.14–12.78)	(193) 39.51 (37.70–41.62)	7.32
Age adjusted	67.33 (64.36–71.50)	9.09 (5.77–12.41)	38.12 (36.31–39.93)	

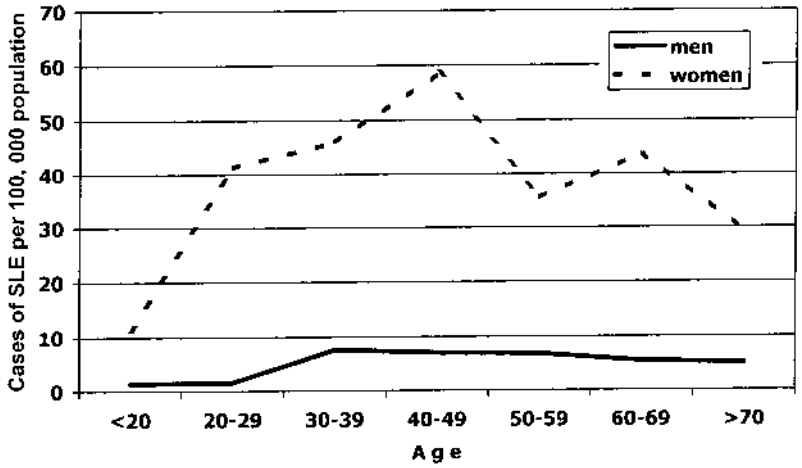

Figure 1. Age and sex-specific mean annual incidence rates of SLE per 100,000 inhabitants, 1982–2001.

Table 3. New cases of SLE per 5 years over the period 1982–2001. Data are mean annual incidence rates per 100,000 inhabitants (95% CI).

	1982–86	1987–91	1992–96	1997–2001	p*
Men	0.45 (0.39–0.51)	0.60 (0.55–0.65)	0.25 (0.20–0.30)	0.49 (0.45–0.53)	NS
Women	2.21 (1.62–2.80)	3.12 (2.57–3.67)	3.24 (2.72–3.76)	3.67 (3.16–4.18)	< 0.05
Total	1.37 (0.95–1.79)	1.88 (1.46–2.30)	1.79 (1.38–2.20)	2.10 (1.69–2.51)	< 0.05
Age adjusted	1.41 (0.99–1.83)	1.95 (1.04–2.72)	1.86 (1.45–2.27)	2.19 (1.78–2.60)	< 0.05

*According to chi-square — trends in proportion. NS: not statistically significant.

access to health services, better diagnosis, or increased physician awareness of SLE in recent years. In our study it is important that the study period begins in 1982, so diagnosis of SLE cases was based on the 1982 revised criteria practically for all cases identified.

We observed a significant variation of SLE occurrence among different districts, and between rural and urban areas. This finding could be attributed to real differences, but could also be partly related to a possible underestimation of the disease frequency, mainly in the rural areas. It is possible that some SLE cases remain undiagnosed in rural areas, where health services are less developed than in urban areas. This could be true mainly for mild cases, and for areas with moderate access to health services. Another cause for relative underestimation of incidence and prevalence rates in rural areas could be related to the data from the National Census. These data are thought to present a slight overestimation of the rural population in some areas of the country, because some people resident in urban areas move to their villages of origin on the day of the census. For these reasons we consider that differences for SLE rates between rural and urban areas and differences among districts of the area studied could be slightly overestimated.

We used several sources and procedures for case identification and recording, in order to reduce potential underestimation of SLE cases and avoid bias. It has been reported that by using multiple sources of retrieval the completeness of data collection is considerably increased[11]. However, it is still possible that a small number of SLE patients living in the study area could escape our recording system. These patients may never be referred to any public or private rheumatologist practicing in the study area, since they are systematically treated at a rheumatology center in Athens. However, these patients could represent only a very small percentage of SLE cases in the area we studied.

Although these methodological issues may put some limitations on the interpretation of the results, the findings suggest a relatively low frequency of SLE in the population studied. Several environmental and genetic factors could be related to this finding. Environmental factors possibly associated with the risk of SLE, such as oral contraceptive use, estrogen replacement therapy, and smoking, could in part explain these findings. These factors are infrequent among the rural female population living in the study area. On the other hand, exposure to ultraviolet light is considered a factor that probably increases occurrence of SLE. This exposure is higher in our population, compared with populations from northern Europe[12–17]. The paradox of high exposure to ultraviolet light but low SLE incidence could be explained by the presence of protective factors, such as dietary factors, in the population

studied. Dietary factors, and lipids in particular, have also been involved in the etiology of SLE, although the possible role of these factors remains uncertain. In the population studied, elements of the Mediterranean diet, such as olive oil consumption, could offer a protective effect[13].

A large number of drugs and an increasing number of environmental pollutants have been reported as factors increasing the risk of SLE[13,18]. It is probable that the population of northwest Greece generally presents a low level of exposure to environmental pollutants. In this study we did not exclude cases considered as drug related lupus, but these cases probably represent a small proportion of the total SLE cases recorded. Viral infections, and in particular retroviruses, have also been suggested and studied as possible risk factors for SLE. Their role remains uncertain[13,18]. In any case, we do not expect these types of infections to be widespread in our population.

The role of genetic factors in the occurrence of SLE is not clear, although there are considerable indications that development of the disease has an important genetic basis. Association studies suggest the existence of genetic effects by the alleles encoded in the HLA, deficiencies in the complement genes, and the low affinity variants of Fcγ receptors. Linkage studies have been performed indicating linkage to several chromosomal regions. Many of the identified chromosomal regions co–localize with loci implicated in other autoimmune diseases[12,13,19–21]. Our population could be considered a genetically homogeneous Caucasian population. There are no significant numbers of immigrants of Asian or African origin resident in the area. This could also be related to the low frequency observed. Studies from other countries suggest significant differences in SLE rates among different ethnic groups living in the same area, with a lower occurrence of the disease among whites[22–24].

Survival was higher among these patients with SLE in northwest Greece compared with survival rates observed in other studies. In studies from northern Europe and the United States concerning patients followed since 1980, survival at 5 years exceeded 90%. These estimates are generally higher than survival estimates from earlier studies, suggesting that short term survival of SLE has improved[4,8,25]. In this study, survival at 5 years was 97% and at 10 years, 90%. A possible explanation for this finding in our population, compared with survival rates reported from other studies, could be the relatively low mean age at diagnosis we observed. This finding could also be related to earlier diagnoses of SLE in the area. However, there is no evidence to support this explanation. A study by Swaak, *et al* suggests there is no significant difference between the age at diagnosis and the interval between the onset of symptoms and diagnosis[26]. On the other hand, age is an independent factor associated with survival. Another explanation could be related to increased recognition of milder disease, as well as to an increased proportion of less severe cases of SLE. Previous studies carried out in Greek patients with SLE suggest some peculiarities in their clinical and serological profile, in comparison to studies from other countries. It is also interesting that studies suggest milder disease and a low frequency of other autoimmune rheumatic conditions in southern Europe[27–30].

Our findings provide an epidemiological profile of SLE in northwest Greece characterized by a relatively low frequency of the disease, a sex ratio comparable with the ratio reported from other studies, a low age at diagnosis, and an improved prognosis. Significant variations among districts of the same major study area were observed. Further epidemiological investigation of SLE, as well as study of the epidemiology of other rheumatic diseases in the area, will offer a global perspective on the profile of these diseases in northwest Greece, in the context of the creation of a systematic recording system.

ACKNOWLEDGMENT

We thank Dr. D.N. Psychos and Dr. M. Tympanidou for kindly providing data on their patients. We also thank E. Horti and S. Voulgaris for secretarial assistance.

REFERENCES

1. Hopkinson N. Epidemiology of systemic lupus erythematosus. Ann Rheum Dis 1992;51:243–5.
2. Hart HH, Grigor RR, Caughey DE. Ethnic differences in the prevalence of systemic lupus erythematosus. Ann Rheum Dis 1983;42:529–32.
3. Manzi S. Epidemiology of systemic lupus erythematosus. Am J Manag Care 2001;7 Suppl 16:S474–9.
4. 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.
5. Tan EM, Cohen AS, Fries JF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271–7.
6. Hopkinson ND, Doherty M, Powell RJ. The prevalence and incidence of systemic lupus erythematosus in Nottingham, UK, 1989–1990. Br J Rheumatol 1993;32:110–5.
7. Gudmundsson S, Steinsson K. Systemic lupus erythematosus in Iceland 1975 through 1984. A nationwide epidemiological study in an unselected population. J Rheumatol 1990;17:1162–7.
8. Stahl–Hallengren C, Jonsen A, Nived O, Sturfeld G. Incidence studies of systemic lupus erythematosus in Southern Sweden: increasing age, decreasing frequency of renal manifestations and good prognosis. J Rheumatol 2000;27:685–91.
9. 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.
10. 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;38:1260–70.
11. Jonsson H, Nived O, Sturfelt G, Silman A. Estimating the incidence of systemic lupus erythematosus in a defined population using multiple sources of retrieval. Br J Rheumatol 1990;29:185–8.
12. McAlindon T. Update in the epidemiology of systemic lupus erythematosus: new spins on old ideas. Curr Opin Rheumatol 2000;12:104–12.
13. Hess EV, Farthey Y. Etiology, environmental relationships, epidemiology, and genetics of systemic lupus erythematosus. Curr Opin Rheumatol 1995;7:371–5.
14. Sanchez–Guerrero J, Karlson EW, Liang MH, Hunter DJ, Speizer

FE, Colditz GA. Past use of oral contraceptives and the risk of developing systemic lupus erythematosus. Arthritis Rheum 1997;40:804–8.
15. Sanchez–Guerrero J, Liang MH, Karlson EW, Hunter DJ, Colditz GA. Postmenopausal estrogen therapy and the risk of developing systemic lupus erythematosus. Ann Intern Med 1995;122:430–3.
16. Petzelbauer P, Binder M, Nikolakis P, Ortel B, Honigsmann H. Severe sun sensitivity and the presence of antinuclear antibodies in patients with polymorphous light eruption–like lesions. A form fruste of photosensitive lupus erythematosus? J Am Acad Dermatol 1992;26:68–74.
17. Zamansky GB. Sunlight–induced pathogenesis in systemic lupus erythematosus. J Invest Dermatol 1985;85:179–80.
18. Hess EV. Are there environmental forms of systemic autoimmune diseases? Environ Health Perspect 1999;107 Suppl 5:709–11.
19. Schur PH. Genetics of systemic lupus erythematosus. Lupus 1995;4:425–37.
20. Lindqvist AK, Alarcon–Riquelme ME. The genetics of systemic lupus erythematosus. Scand J Immunol 1999;50:562–71.
21. Ahmad YA, Bruce IN. Genetic epidemiology: systemic lupus erythematosus. Arthritis Res 2001;3:331–6.
22. 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;38:551–8.
23. Samanta A, Roy S, Feehally J, Symmons DP. The prevalence of diagnosed systemic lupus erythematosus in whites and Indian Asian immigrants in Leicester city, UK. Br J Rheumatol 1992;31:679–82.
24. Bae SC, Fraser P, Liang MH. The epidemiology of systemic lupus erythematosus in populations of African ancestry: a critical review of the "prevalence gradient hypothesis". Arthritis Rheum 1998;41:2091–9.
25. Trager J, Ward MM. Mortality and causes of death in systemic lupus erythematosus. Curr Opin Rheumatol 2001;13:345–51.
26. Swaak AJ, Nieuwenhuis EJ, Smeenk RJ. Changes in clinical features of patients with systemic lupus erythematosus followed prospectively over 2 decades. Rheumatol Int 1992;12:71–5.
27. Andonopoulos AP, Papasteriades CA, Drosos AA, Dimou GS, Moutsopoulos HM. HLA alloantigens in Greek patients with systemic lupus erythematosus. Clin Exp Rheumatol 1990;8:47–50.
28. Vlachoyiannopoulos PG, Karassa FB, Karakosta KX, Drosos AA, Moutsopoulos HM. Systemic lupus erythematosus in Greece. Clinical features, evolution and outcome: a descriptive analysis of 292 patients. Lupus 1993;2:303–12.
29. Drosos AA, Alamanos I, Voulgari PV, et al. Epidemiology of adult rheumatoid arthritis in northwest Greece 1987–95. J Rheumatol 1997;24:2129–33.
30. Drosos AA, Lanchbury JS, Panayi GS, Moutsopoulos HM. Rheumatoid arthritis in Greek and British patients. A comparative clinical, radiologic, and serologic study. Arthritis Rheum 1992;35:745–8.