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Systemic lupus erythematosus in Europe at the change of the millennium: Lessons from the "Euro-Lupus Project"

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On behalf of the members of the "European Working Party on Systemic Lupus Erythematosus" [1]

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Abstract

The "Euro-Lupus Cohort" is composed by 1000 patients with systemic lupus erythematosus (SLE) that have been followed prospectively since 1991. These patients have been gathered by a European consortium—the "Euro-Lupus Project Group". This consortium was originated as part of the network promoted by the "European Working Party on SLE", a working group created in 1990 in order to promote research in Europe on the different problems related to this disease. The "Euro-Lupus Cohort" provides an updated information on the SLE morbidity and mortality characteristics in the present decade as well as defines several clinical and immunological prognostic factors.

Keywords: Epidemiology; Morbidity; Mortality; Prognostic factors; Systemic lupus erythematosus

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Contents

1. Introduction . . . 181
2. Objectives of the "Euro-Lupus Project". . . . 181
3. General characteristics of the "Euro-Lupus Cohort" . . . 181
4. Patterns of disease expression in specific SLE subsets . . . 182
4.1. Childhood onset SLE . . . 182
4.2. Older onset SLE . . . 182
4.3. SLE in males . . . 182
4.4. SLE with high titer of anti-dsDNA antibodies. . . . 183
4.5. SLE with anti-ENA antibodies . . . 183
4.6. SLE with rheumatoid factor . . . 183
4.7. SLE with antiphospholipid antibodies . . . 183
5. Morbidity and mortality during the follow-up . . . 183
Take-home messages. . . . 186
References . . . 186

1. Introduction

Systemic lupus erythematosus (SLE) is the most diverse of the autoimmune diseases because it may affect any organ of the body and display a broad spectrum of clinical and immunological manifestations. One question that arises is whether the age at onset of the disease, the sex, or the autoantibody pattern, among other factors, can modify the disease expression and define some specific SLE subsets. Several investigators have addressed this problem with controversial results. This is probably due to the small number of patients that have been analyzed, the disparity in selection criteria for patient inclusion, or the definition of the variables.

On the other hand, in recent years, both SLE morbidity and mortality have been modified due to a number of possible reasons, including a better knowledge of its pathogenetic mechanisms and prognostic factors as well as the use of immunosuppressive regimes. It has been suggested that the spectrum of clinical manifestations as well as the causes of death are different depending on the time of evolution of the disease. Furthermore, it has been postulated that SLE tends to enter into remission in many patients after a long time of evolution.

In an attempt to clarify the long-term evolution of patients with SLE in Europe, the "Euro-Lupus Project" was started in 1991. The "Euro-Lupus" cohort was composed by 1000 patients with SLE that were gathered by a consortium that included more than 40 investigators from seven European countries. This consortium was originated as part of the network promoted by the "European Working Party on SLE" [1].

2. Objectives of the "Euro-Lupus Project"

The "Euro-Lupus Project" started with a multicenter, consecutive and prospective design. In order to gather a sizeable series of patients, twelve tertiary referral university centers agreed to take part in the study. The final cohort included 1000 unselected patients that were prospectively followed during 10 years. The objectives of the project were: i) to determine the incidence of the different clinical manifestations at the onset of the disease and during the follow-up; ii) to analyze the biological and immunological features of these patients and the relationship with their clinical manifestations in order to clearly define different subsets of the disease; iii) to determine the natural history, severity and response to treatment of these SLE subsets; iv) to evaluate the morbidity of the different SLE subsets (including the complications induced by the different treatment regimens of this condition); and v) to establish the mortality rate and the main causes of death in the European population.

3. General characteristics of the "Euro-Lupus Cohort"

The general characteristics of this cohort at the beginning of the study were published in 1993 [2].

Although SLE is being recognized with increasing frequency in medical practice, the diversity of its clinical and laboratory features at presentation makes precise diagnosis a real challenge for the clinician and this has been reflected in the "Euro-LupusProject". In this cohort, less than a half of the patients presented the typical SLE malar rash at the onset of the disease. On the contrary, a great proportion of patients presented nonspecific symptoms, such as arthritis and fever. This was reflected in the delay in establishing the final diagnosis of SLE. We have found that mean age at the onset of symptoms was 29 years and at the fulfillment of 4 or more of the American College of Rheumatology (ACR) criteria for the classification of SLE was 31 years. Therefore, the mean time between the first manifestations and the final classification of SLE was 2 years.

4. Patterns of disease expression in specific SLE subsets

An important question that has been raised by several authors is whether the age at onset of the disease, the gender, or the autoantibody pattern, among other factors, can modify the disease expression and define some specific SLE subsets.

4.1. Childhood onset SLE

In the "Euro-Lupus" cohort, 76 out of the 1000 patients with SLE (8%) developed the disease before the age of 14. Female/male ratio (7/1) was not as pronounced as in the general SLE population (10/1). In addition, the clinical and immunological pattern of SLE in childhood patients slightly differs from the disease in the rest of the SLE patients. It is of note that childhood onset patients more often showed severe organ involvement as a presenting manifestation, nephropathy being a prominent feature. Other major complaints, such as neurologic involvement, thrombocytopenia, and hemolytic anemia, were also common as initial features in the childhood onset group. However, during the evolution, the disease pattern was quite similar in childhood onset and adult patients.

Interestingly, the initial diagnosis in the childhood onset group was delayed, presumably because doctors are reluctant to diagnose SLE in childhood patients and because the most typical signs and symptoms are more uncommon. This is reflected in this cohort with a mean 5 year delay in establishing the diagnosis of SLE in the childhood onset group.

4.2. Older onset SLE

Although SLE has traditionally been considered a disease of young women, several reports have described SLE in elderly populations. In the "Euro-Lupus" cohort, 90 patients (9%) developed the disease after the age of 50. Although some authors have found no differences in the female/male ratio related with aging, our observations suggest that female predominance is not so pronounced in the elderly onset group (5/1). The clinical expression of SLE in elderly patients differs in several aspects from the disease in young adults. The most common manifestations in the older-onset patients are themselves interesting, and several authors have pointed out that the clinical picture resemble best the patients with drug-induced SLE, primary Sjögren's syndrome, or polymyalgia rheumatica. Thus, in this cohort, typical SLE manifestations, such as malar rash, photosensitivity, arthritis or nephropathy, were less common than in the younger patients. In contrast, sicca syndrome was very frequently found.

Although the explanation for this apparent age-related variability in the expression of the disease is still unclear, demographic factors and differences in genetic predisposition or responsiveness of an aging immune system may be implicated. It has been speculated that older and younger patients may have different genetic determinants of disease and respond to different triggering mechanisms. Alternatively, the less exuberant expression of SLE both clinically and immunologically in older patients may reflect senescence of the immune system.

4.3. SLE in males

In the "Euro-Lupus Cohort", 92 out of the 1000 (9%) patients with SLE were men. Overall experience with male SLE patients is not extensive and the precise frequency of clinical and serological features

differs from study to study. In this project, we analyzed the clinical expression and immunological features of SLE in men and women both at disease onset and during the follow-up period. This enabled us to note several interesting clinical differences. Firstly, we found a higher prevalence of serositis in our male patients as a presenting manifestation. On the contrary, arthritis tended to occur less commonly in these patients, although the difference did not reach statistical significance. This atypical presentation is of paramount importance because it can lead to a delay in establishing the correct diagnosis. Secondly, when we analyzed the clinical manifestations during the evolution, we found a lower prevalence of arthritis in the male group. The prevalence of nephropathy, neurological involvement, thrombocytopenia, vasculitis and serositis was similar in both groups. In addition, no significant immunological differences were found between men and women.

4.4. SLE with high titer of anti-dsDNA antibodies

High titer of anti-dsDNA has been considered to be the best marker of disease activity in SLE. We have also found that they were associated with a higher prevalence of nephropathy, hemolytic anemia, and fever. On the contrary, patients with high titer of these antibodies have a lower prevalence of thrombosis and sicca syndrome.

4.5. SLE with anti-ENA antibodies

Anti-Ro (SSA) antibodies, often accompanied by anti-La (SSB), is found in SLE with a prevalence varying between 20% and 30%. The former have been found to be associated with a higher prevalence of subacute cutaneous lesions and sicca syndrome, but with a lower prevalence of thrombocytopenia. Anti-La (SSB) have been found associated with malar rash, subacute cutaneous lesions, photosensitivity, arthritis, serositis, and thrombosis. The prevalence of anti-U1-snRNP was 13%. Patients with these antibodies had a higher incidence of Raynaud's phenomenon, myositis, and lymphadenopathy. Anti-Sm antibodies occurred in 10% of patients and was more prevalent in those with oral ulcers and myositis, but less in those with sicca syndrome.

4.6. SLE with rheumatoid factor

The presence of rheumatoid factor has been found in 18% of the patients. Interestingly, these patients have a higher prevalence of sicca syndrome, but a lower prevalence of nephropathy.

4.7. SLE with antiphospholipid antibodies

In this cohort, positive levels of antiphospholipid antibodies were strongly associated with thrombosis, spontaneous fetal losses, and thrombocytopenia. This reinforces previous findings stressing such an association. We also found a significant association between the presence of IgM aCL and hemolytic anemia. This association has been rarely reported and has been suggested that the antiphospholipid antibodies may react with the cell wall of either erythrocytes or platelets and can cause their destruction either by complement or by receptor mediated entrapment by reticuloendothelial system. Possibly, IgM aCL would best cause spleen clearance of erythrocytes and their complement mediated damage could hence be entertained. Although the real mechanism of action of antiphospholipid antibodies is still unclear, the presence of these antibodies should be considered a risk factor for thrombosis, spontaneous fetal loss, and thrombocytopenia in patients with SLE.

5. Morbidity and mortality during the follow-up

The natural history of SLE is characterized by episodes of relapses or flares, interchanging with remissions, and the outcome is highly variable ranging from permanent remission to death. However, both morbidity and mortality have been modified in recent years due to a number of possible reasons, including the more conservative use of corticosteroids and of modified immunosuppressive regimens. Additionally, a better knowledge of the prognostic factors for morbidity and mortality can improve the management of these patients. In an attempt to clarify the evolution of patients with SLE in the present decade, the "Euro-Lupus Cohort" has been followed prospectively by the same physicians during the ensuing 10 years. The aims of this longitudinal part of the study were to assess the frequency and characteristics of the

Table 1
Clinical manifestations related to SLE in the "Euro-Lupus" cohort during the 10-year prospective study (1990–2000)

SLE manifestations	1990–2000 ($n=1000$) No. (%)	1990–1995 ($n=1000$) No. (%)	1995–2000 ($n=840$)[a] No. (%)	p[b]
Malar rash	311 (31.1)	264 (26.4)	144 (17.1)	<0.001
Discoid lesions	78 (7.8)	54 (5.4)	50 (5.9)	
Subacute cutaneous lesions	67 (6.7)	46 (4.6)	21 (2.5)	0.023
Photosensitivity	229 (22.9)	187 (18.7)	112 (13.3)	0.002
Oral ulcers	125 (12.5)	89 (8.9)	61 (7.3)	
Arthritis	481 (48.1)	413 (41.3)	240 (28.6)	<0.001
Serositis	160 (16)	129 (12.9)	52 (6.2)	<0.001
Nephropathy	279 (27.9)	222 (22.2)	57 (6.8)	<0.001
Neurologic involvement	194 (19.4)	136 (13.6)	97 (11.5)	
Thrombocytopenia	134 (13.4)	95 (9.5)	76 (9.0)	
Hemolytic anemia	48 (4.8)	33 (3.3)	24 (2.9)	
Fever	166 (16.6)	139 (13.9)	62 (7.4)	<0.001
Raynaud phenomenon	163 (16.3)	132 (13.2)	74 (8.9)	0.003
Livedo reticularis	70 (7.0)	55 (5.5)	30 (3.6)	
Thrombosis	92 (9.2)	72 (7.2)	41 (4.9)	0.049
Myositis	43 (4.3)	40 (4)	11 (1.3)	<0.001

[a] Number of patients that continued in the study in 1995.
[b] All p values are a comparison between the frequencies in the 1990–1995 and in the 1995–2000 periods.

main causes of morbidity and mortality during this period (1991–2000), as well as to know the prognostic significance for morbidity and mortality of the main immunological parameters used in the clinical practice [3,4].

The frequencies of the main clinical manifestations related to SLE that appeared during the 10 years of the prospective study in the present European cohort (Table 1) are slightly lower than those reported in several large series from America [5,6] and Asia [7] that have been published in the last decade (Table 2). In this European cohort, active nephropathy was diagnosed in 27.9% of the patients during the prospective study [4], while the frequencies in other studies ranges between 40.2% in an American series [6] and 74% in an Asian series [7]. These lower frequencies of SLE clinical manifestations could be due to genetic or environmental differences between Europeans and Americans or Asians but could also reflect the effect of medical care during the study because of the prospective nature of the "Euro-Lupus Project". Furthermore, we have found a lower frequency of most SLE

Table 2
Comparison of the main clinical manifestations related to SLE in several large series reported during the last decade

Authors	Petri et al. [5]	Wang et al. [7]	Alarcón et al. [6]	Present cohort
No. of patients	574	539	555	1000
Geographical area	America	Asia	America	Europe
Malar rash	331 (57.7)	410 (76.1)	322 (58)	311 (31.1)
Discoid lesions	162 (28.2)	30 (5.6)	107 (19.3)	78 (7.8)
Photosensitivity	335 (58.4)	222 (41.2)	334 (60.2)	229 (22.9)
Oral ulcers	219 (38.2)	185 (34.3)	293 (52.8)	125 (12.5)
Arthritis	NR	272 (50.5)	489 (88.1)	481 (48.1)
Nephropathy	319 (55.6)	399 (74)	223 (40.2)	279 (27.9)
Neurologic involvement	NR	123 (22.8)	67 (12.1)	194 (19.4)
Thrombocytopenia	NR	161 (29.9)	NR	134 (13.4)
Hemolytic anemia	NR	102 (18.9)	NR	48 (4.8)

NR: Not reported.

manifestations during the last 5 years of this prospective study (1995–2000) [4], compared with the cumulative clinical manifestations during the initial 5 years of the study (1990–1995) [3]. For instance, the frequency of active lupus nephropathy during the last 5 years was 6.8% [4] while we had previously found a cumulative prevalence of 22.2% during the initial 5 years of the study [3]. These lower frequencies in the last 5 years probably reflect the effect of therapy and of medical care during the study, but also can be due to a less severe activity of the disease after a long time of evolution.

Previously published studies have addressed the problem of assessing prognostic factors for morbidity and mortality, as well as survival probabilities, by means of retrospective analyses of the clinical manifestations from the onset or from the diagnosis of the disease until the time of the study. However, we designed the present project in a prospective fashion in order to predict the risk for the development of an event according to the presence or absence of the immunological marker in a given moment, irrespective of the time from the onset or from the diagnosis of the disease. The "Euro-Lupus project" has the additional value of giving the estimated relative risk for each event in a 5-year period of time. Among the different immunological markers, the assessment of the value of anti-dsDNA antibodies for predicting the development of nephritis (RR = 1.79) and hemolytic anemia (RR = 2.49) and of aCL and LA for prediciting the development of the clinical manifestations of the antiphospholipid syndrome (thrombosis, fetal losses and thrombocytopenia) (RR = 1.2–1.53) is of paramount importance due to the potential severity of these SLE manifestations.

Over the past 50 years, there has been significant improvement in the survival of patients with SLE. Whereas earlier studies in the 1950s reported a survival rate of less than 50% at 5 years, more recent studies indicated that over 93% of patients with SLE survive for 5 years and 85% survive for 10 years. In our European cohort, we have found a 92% survival after 10 years from the time of entry into the study [4]. These improved survival rates may be related to the advanced medical therapy in general (antihypertensive agents, availability of renal dialysis, transplantation and antibiotics), along with a better understanding of the pathogenesis of the disease, earlier diagnosis and inclusion of milder cases in recent studies, but it may also be caused by the more intensive forms of treatment such as the use of cytotoxic drugs, immunosuppressive drugs and high-dose prednisolone. Furthermore, the slightly higher survival in this European cohort when compared with the American series may be also due to predominance of Caucasian patients in the present cohort (97.1%); it is known that race influences outcome in SLE and Blacks and Hispanic Americans of mestizo or native Indian origin have a poorer outcome.

Table 3
Causes of death in the "Euro-Lupus" cohort during the 10-year prospective study (1990–2000)

Causes of death	1990–2000 (Total = 68)	1990–1995 (Total = 45)	1995–2000 (Total = 23)
	No. (%)	No. (%)	No. (%)
Active SLE	18 (26.5)	13 (28.9)	5 (21.7)
Multi-system	5 (7.4)	4 (8.9)	1 (4.3)
Renal	6 (8.8)	4 (8.9)	2 (8.7)
Cardio-pulmonary	3 (4.4)	3 (6.7)	0 (0)
Hematologic	1 (1.5)	1 (2.2)	0 (0)
Neurologic	3 (4.4)	1 (2.2)	2 (8.7)
Infections	17 (25)	13 (28.9)[a]	4 (17.4)[b]
Bacterial sepsis	15 (22.1)	11 (24.4)	4 (17.4)
Pulmonary	6 (8.8)	4 (8.9)	2 (8.7)
Abdominal	5 (7.4)	4 (8.9)	1 (4.3)
Urinary	4 (5.9)	3 (6.7)	1 (4.3)
Fungal	1 (1.5)	1 (2.2)	0
Viral	1 (1.5)	1 (2.2)	0
Thromboses	18 (26.5)	12 (26.7)	6 (26.1)
Cerebral	8 (11.8)	5 (11.1)	3 (13)
Pulmonary	4 (5.9)	3 (6.7)	1 (4.3)
Coronary	5 (7.4)	3 (6.7)	2 (8.7)
Other	1 (1.5)	1 (2.2)	0 (0)
Malignancies	4 (5.9)	3 (6.7)	1 (4.3)
Breast	1 (1.5)	1 (2.2)	0 (0)
Lung	2 (2.9)	1 (2.2)	0 (0)
Lymphoma	1 (1.5)	1 (2.2)	0 (0)
Gastric bleeding	2 (2.9)	2 (4.4)[c]	0 (0)
Obstetric	1 (1.5)	1 (2.2)	0 (0)
Suicide	1 (1.5)	1 (2.2)	0 (0)
Surgical	1 (1.5)	1 (2.2)	0 (0)
Accident	1 (1.5)	0 (0)	1 (4.3)
Unknown	14 (20.6)	7 (15.6)	7 (30.4)

[a] In 6 patients, the cause of death was attributed to infection plus other factors (active SLE in 5 and thrombosis in 1).
[b] In 1 patient, the cause of death was attributed to infections plus active SLE.
[c] In 2 patients, the cause of death was attributed to gastric bleeding plus other factors (active SLE in 1 and infection in 1).

The improved survival of patients with SLE has been associated with an alteration in the patterns of mortality. We have found a similar percentage of active SLE (26.5%), thromboses (26.5%) and infections (25%) as the main causes of death in the total 10-year observational period. However, it is important to stress that when the causes of death during the initial 5 years of follow-up were compared with those during the ensuing 5 years, active SLE and infections (28.9%, each) appeared to be the most common causes during the initial 5 years [3], while thromboses (26.1%) became the most common cause of death during the last 5 years [4] (Table 3).

Take-home messages

- The "Euro-Lupus Project" gives updated information on the SLE morbidity and mortality characteristics in the last decade of the twentieth century.
- The age at onset of the disease, the gender, and the autoantibody pattern, among other factors, modify the disease expression and define some specific SLE subsets.
- Most of the SLE inflammatory manifestations are less common after a long-term evolution of the disease, thus probably reflecting the effect of therapy as well as the progressive remission of the disease in many patients.
- A more prominent role of thrombotic events is becoming evident affecting both morbidity and mortality in SLE.

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Polymorphisms in the tyrosine kinase 2 and interferon regulatory factor 5 genes are associated with systemic lupus erythematosus.

Systemic lupus erythematosus (SLE) is a complex systemic autoimmune disease caused by both genetic and environmental factors. Increased production of type I interferon (IFN) and expression of IFN-inducible genes is commonly observed in SLE and may be pivotal in the molecular pathogenesis of the disease. Sigurdsson S. et al. (Am J Hum Genet 2005; 76:528-37), analyzed 44 single-nucleotide polymorphisms (SNPs) in 13 genes from the type I IFN pathway in 679 Swedish, Finnish, and Icelandic patients with SLE, in 798 unaffected family members, and in 438 unrelated control individuals for joint linkage and association with SLE. In two of the genes, the tyrosine kinase 2 (TYK2) and IFN regulatory factor 5 (IRF5) genes, the authors identified SNPs that displayed strong signals in joint analysis of linkage and association (unadjusted $p < 10^{-7}$) with SLE. TYK2 binds to the type I IFN receptor complex and IRF5 is a regulator of type I IFN gene expression. Thus, these results support a disease mechanism in SLE that involves key components of the type I IFN system.