Systemic Lupus Erythematosus in Lithuania: Demographical and Clinical Features in a County-based Cohort

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Objective. The aim of the study was to investigate the systemic lupus erythematosus (SLE) clinical symptoms as defined in ARC diagnostic criteria 1982, disease-related clinical features and co-morbidities in relation to disease duration.

Methods. The data for this study were retrieved from the Vilnius SLE register database developed in the end of 1999. The sample size for this cross-sectional study comprised 59 definite SLE cases and included the extended information about their demographical and clinical data, disease related clinical findings and co-morbidities. **Results**. Arthritis was the most common clinical manifestation with 88.1% of patients complaining of joint pain. Photosensitivity and malar rash was recorded in 71.2% and 62.7%, respectively. Kidney damage, oral ulcers and discoid rash were noted in 40.7% each, while CNS involvement and pleurisy were less common (22% each). The laboratory findings for haematological, immunological disorder and ANA test were confirmed as positive in 42.4%, 86.4% and 74.6% of cases, respectively. The mean of the cumulative count of diagnostic criteria was 5.9 (SD = 1.7) with the range between 4 and 10. The analyses of SLE clinical features showed no clinically important trend in developing more clinical symptoms over time, unlikely to co-morbidities demonstrating the trend to increase with time. These were angina pectoris, visual disturbances, acute and chronic pulmonary disease and allergies for medication and other allergens being significantly prevalent for those with a long-standing disease. In conclusion, SLE patients do not tend to develop more clinical features over time, but the occurrence of co-morbidities is significant.

Key words: systemic lypus erythe motosus, epidemiology, manifestations, co-morbiolites

INTRODUCTION

The traditional view of systemic lupus erythematosus (SLE) as of a rare and incurable disease has changed tremendously in the last four decades and the overall mortality rates have improved dramatically over this period of time. With improving prognosis and surveillance life threatening SLE features are not often prominent in the overall picture of the disease (1).

With the development of new treatment modalities and a new insight into the pathogenesis of the disease the understanding of SLE changes from an incurable and fatal disease to a slowly grumbling with irreversible organ damage. Moreover, the organ damage is not always related to immunological inflammatory mechanisms, but more likely to aging or co-morbidities or even adverse effects of the treatment. Thus, reporting about clinical findings in general and in relation to disease duration is still worth while, since it is always a challenge to distinguish these clinical findings from active SLE (2).

The aim of the study was to investigate the SLE clinical symptoms as defined in ARC diagnostic criteria 1982, disease-related clinical features and co-morbidities in relation to the disease duration periods.

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PATIENTS AND METHODS

The data for this study were retrieved from the SLE register database developed in the end of 1999 with the Bioethical Committee approval obtained a year later.

The *Vilnius SLE register* aims to measure the disease demographical, clinical, social and treatment aspects with respect to strictly defined and representative geographical area, the Vilnius City in particular. The crude demographical data about the SLE patients were retrieved from two sources. First, 14 Vilnius outpatient clinics were asked to report all SLE cases they had on the list with the indication of patients' surname and living place (A.L.). Second, the tertiary clinical center registration books were reviewed for the period January 1990 to the end of 1999 for SLE diagnosis (N. Ž.). Those named SLE patients were contacted by mail or telephone and asked to participate in a SLE register study and invited for the interview and examination to the Institute of Experimental and Clinical Medicine (N. Ž.). Only patients who fulfilled the ACR 1982 revised criteria for the classification of SLE (3) and were Vilnius residents at the time of interview were included in the study. An extended questionnaire containing demographical data, treatment-specific questions, clinical and recent laboratory data, SLE-related connective tissue disease features, co- morbidities and scales SLEDAI, SDI, HAQ, AIMS questions for depression and anxiety and SF-36 were filled out by investigator or patient when appropriate and the blood samples were taken for laboratory evaluation (4). When the verbal information was not sufficient the patient record books were reviewed in parallel. The data for every patient were entered into STATISTICA database and served for further analyses undertaken in this particular study. A short patient's recruitment scheme is presented in Figure.

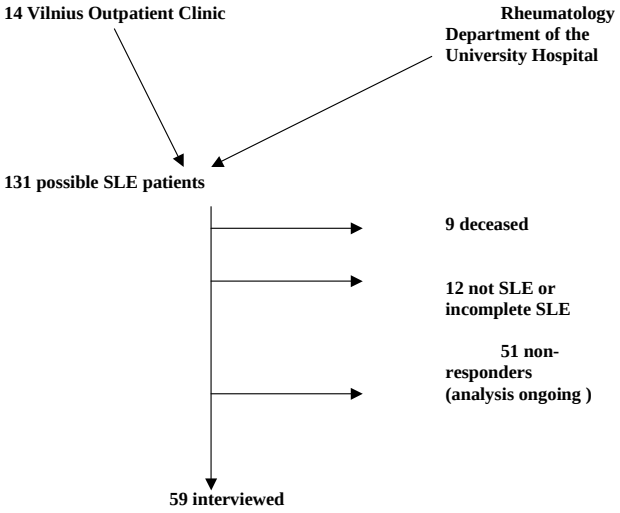

Figure. A short patients' recruitment scheme

The sample for this cross-sectional study comprised 59 definite SLE cases, and the demographical and clinical features and co-morbidities were retrieved for further analysis including crude demographical data, education level, employment, marital and social status, prevalence of rheumatic disease among relatives. The clinical variables were encountered as defined in the guidelines for SLE classification 1982 and dichotomized for being ever present or not present at all: malar rash, discoid rash, photosensitivity, mucous ulceration in the mouth and nasopharynx, non-erosive arthritis, pleurisy or/and pericarditis, kidney damage (proteinuria or cellular casts), CNS manifestations (convulsion, psychosis, stroke), haematological disorders (anaemia, leucopoenia, lymphopenia, thrombocytopenia), immunological disorders (LE cells or a-DNA positivity) and finally antinuclear antibodies (IIF, Hep-2 cells). In addition, other clinical findings attributed to connective tissue damage: alopecia, oesophageal dysmotility, thrombosis, skin ulcers, Reynauld phenomena, Jaccoud arthropathy, sicca symptoms in mouth or eyes, fever, fatigue, rash on the body, dizziness, trouble with thinking, headache and the following co-morbidities: angina pectoris, visual disturbances, hypertension, acute and chronic pulmonary disease, peptic ulcer, fractures including aseptic osteonecrosis, thyroid gland disease, diabetes mellitus, back pain, cancer, allergies for medications and other allergens were encountered. The clinical findings and co-morbidities were analysed if occurred with the onset of the disease or later. The whole setting was divided into three disease duration groups distinguishing between short-term disease (≤ 4 yr), average disease duration (4–10 yr), and long-term disease (>10 yr).

Statistical analysis

The F-ratio (ANOVA) was applied for cumulative criteria comparisons and Pearson chi-square method for proportions of clinical features in different disease duration groups. Since these analyses greatly depend on a normal distribution of variables used, analyses were also performed using ranks, without noting any important changes in results. The differences between the means or proportions were considered as significant at $p < 0.05$. The computations were performed using STATISTICA 6.0 software.

RESULTS

The demographic analysis of this population-based SLE setting revealed the middle-aged (45.4; SD = = 14.2) female (96.6%) dominating in the whole

Table 1. **Demographic and social characteristics of 59 SLE patients**

Demographic characteristics	(n = 59)
Age (SD) in years	45.4 (14.2)
Female	96.6%
Education in years	14.2 (2.6) m.
Rheumatic diseases in family	17.0%
Having job (< 65 years)	44.7%
Not married	32.2%
Without children	42.4%
Single in daily living	18.7%
Disease duration (SD) in years	11.1(11.2)
Prodromal period (SD) in years	3.4(5.3)

group of SLE patients (Table 1). Of them 44.7% were still working, though the employment rate in comparison with that before the disease lowered distinctly despite the high education level observed within the group. The duration of the disease varied widely (11.1; SD = 11.2) the same as the time period before the diagnosis (3.4; SD = 5.3). Rheumatic diseases were not prevalent among the patients' relatives and comprised only 17%. Analysis of the social aspects of the life revealed an evidently high proportion of patients without children (42.4%); 32.2% were never married and 18.7% were single in their daily living.

Disease manifestations

Arthritis was the most common clinical manifestation with 88.1% of patients complaining of joint tenderness or swollenness in the past or currently. Photosensitivity and malar rash were recorded in 71.2% and 62.7%, respectively. Kidney damage, oral ulcers and discoid rash were noted in 40.7% each while CNS involvement and pleurisity were less common (22% each). The serological findings for haematological, immunological disorder and ANA were positive in 42.4%, 86.4% and 74.6% of cases, respectively. The mean of the cumulative count of diagnostic criteria was 5.9 (SD = 1.7) with the range between 4 and 10 (Table 2).

Table 2. **Prevalence of SLE-related manifestations and co-morbidities in different disease duration cohorts in 59 Lithuanian patients**

	Disease duration cohorts			
	Total n = 59 n/%	≤ 4 years n = 22 n/%	4–10 years n = 14 n/%	>10 years n = 23 n/%
1	*2*	*3*	*4*	*5*
Sum of ACR criteria	5.9(SD = 1.7)	5.9(SD = 1.6)	5.4(SD = 1.4)	6.3(SD = 1.8)
ARC classification criteria manifestations				
Malar rash	37/62.7	12/20.3	8/13.6	17/28.8
Discoid rash	24/40.7	9/15.3	3.0/5.1	12/20.3
Photosensitivity	42/71.2	15/25.4	9/15.3	18/30.5
Oral ulcers	24/40.7	8/13.6	5/8.5	11/18.6
Pleurisies or/and pericarditis	13/22.0	4/6.8	3/5.1	6/10.2
Non erosive arthritis	52/88.1	19/32.2	13/22.0	20/34.0
Kidney damage	24/40.7	9/15.3	7/12.9	8/13.6
CNS manifestations	13/22.0	5/8.5	1/1.7	7/12.0
Hematological disorders	25/42.4			
Immunological disorders	51/86.4			
ANA	44/74.6			
Other clinical findings				
Alopecia	44/74.6	13/22.03	12/20.3	19/32.2
Esophageal dysmotility	16/27.1	3/5.1	3/5.1	10/17.0
Thrombosis	8/13.6	5/8.5	2/3.4	1/1.7
Skin ulcers	12/20.3	4/6.8	2/3.4	6/10.2
Reynauld phenomena	26/44.1	8/13.6	4/6.8	14/23.7
Jaccoud arthropathy	7/11.9	2/3.4	1/1.7	4/6.8
Sicca symptoms in eyes	25/42.4	6/10.2	5/8.5	14/23.8
Sicca symptoms in mouth	25/42.4	7/11.9	6/10.1	12/20.3

Table 2 (continue)

1	2	3	4	5
Fever	47/79.7	15/25.4	12/20.3	20/34.0
Fatigue	55/93.2	20/33.9	13/22.03	22/37.3
Rash on the body	32/54.2	11/18.6	8/13.6	13/22.0
Dizziness	29/49.2	11/18.6	5/8.5	13/22.0
Trouble with thinking	35/59.3	10/17.0	8/13.6	17/28.8
Headache	38/64.4	10/17.0	10/17.0	18/30.5
Co-morbidities				
Angina pectoris	23/39.0	4/6.8	6/10.2	13/22.0*
Visual disturbances	29/49.2	6/10.2	8/13.6	15/25.4*
Hypertension	18/30.5	6/10.2	3/5.1	9/15.3
Acute pulmonary disease	26/44.1	5/8.4	5/8.4	16/27.1*
Chronic pulmonary disease	14/23.7	2/3.4	2/3.4	10/17.0*
Peptic ulcer	4/6.8	1/1.7	1/1.7	2/3.4
Fractures	13/22.0	5/8.5	2/3.4	6/10.1
Thyroid gland disease	13/22.0	4/6.8	4/6.8	5/8.5
Back pain	34/57.6	10/17.0	9/15.3	15/25.4
Cancer	4/6.8	1/1.7	0/0	3/5.1
Allergy to medications	25//42.4	7/11.8	3/5.1	15/25.4*
Other allergies	15/25.4	2/3.4	3/5.1	10/17.0*

*Significant level <0.05 between different disease duration cohorts.

The following *SLE-related features* were common in the interviewed patients: alopecia (74.%), fever (79.7%), fatigue (93.2%), rash on the body (54.2%), trouble with thinking (59.3%), headache (64.4%). The sum of clinical criteria did not show any important increase over time. Analysis of SLE manifestations and SLE-related features showed no clinically important trend in developing more clinical symptoms over time, though there were a tendency to augmentation in almost all clinical features, except for kidney damage remaining stable over time and thrombosis, which was less frequent in a long-term disease than otherwise.

The co-morbidities as they are listed in Patients and Methods could be ranged as highly prevalent such as back pain (57.6%), visual disturbances (49.2%), acute pulmonary diseases (44.1%), allergy for medications (42.4%), angina pectoris (39.0%), hypertension (30.5%), other allergies (25.4%), chronic pulmonary disease (23.7%), and less prevalent such as fractures, thyroid gland disease, peptic ulcers, and cancer. Diabetes mellitus was not detected in the patients examined. Conversely to the other manifestations mentioned, several co-morbidities definitely tended to increase with time. These were angina pectoris (from 6.8% to 22.0%), visual disturbances (from 10.2% to 25.4%), acute (from 8.4% to 27.1%) and chronic pulmonary disease (from 3.4% to 17.0%), and allergies for medication (from 11.8% to 25.4%) and other allergens (from 3.4% to 17.0%) which increased significantly in patients with a long-standing disease.

DISCUSSION

Despite an essential decrease in the morbidity and mortality rates during the last decade, SLE is still considered as a fatal disease of unknown origin with a significant involvement of vital organs in most cases (5). It is universally accepted that patients dying early usually succumb to active lupus and infection, while patients who survive after 5 years of disease often die of end organ dysfunction or due to degenerative vascular disease (2). The data about SLE and related conditions are usually reported from the hospital-based or centre-based study samples. We believe that SLE seen in hospital is slightly distinct from that register-based if evaluated by its demographical features, activity and organ damage. The higher proportion of mild cases with lower activity and minor organ damage in better social conditions could be found in register-based study samples when compared to hospital patients. Consequently, the proportions of affected systems, positive laboratory data and definitely the surveillance if counted for hospital- or centre-based patients are different from that in population. To our knowledge, SLE studies to estimate the prevalence and clinical manifestations

in population-based samples or/and general practice diagnostic registers have been conducted in Scandinavian countries, Great Britain and the United States (6–10). Musculoskeletal manifestations, mainly arthritis, in our patients occurred as frequently as in patients reported from Sweden (6), Denmark (7), Great Britain (8) or the United States (10). We found 40.7% cases from the whole setting presenting with kidney involvement, and the reported figure is a bit lower than reported from the United States and similar to those from Danish and Swedish studies. On the contrary, the proportions of malar rash, discoid lupus, photosensitivity, oral or nasopharyngeal ulcers and cerebral disorders are higher in our study than in the mentioned studies. The proportion of serositis was also shown to be less prevalent in our patients. This could be due to recall biases of the patients or documentations lack at the time of interview, or in some cases it could be underdiagnosed or not documented at all. The overall higher cumulative criteria and proportions of other affected systems most probably reflect the specificity of this study when patients more seriously ill were more willing to participate in the study than those who where moderately ill. Moreover, the information obtained from a patient directly could overestimate the meaning of clinical manifestations, especially if they were not present at the moment, while the information collected from the treating physician or record book could underestimate or simply overlook clinically important data (11).

The clinical symptoms as defined in SLE classification criteria or related to connective tissue damage tended to increase, but did not reach clinical significance in any of domains. Possibly it could be due to the small study sample comprising a little number of examined patients, since a similar study conducted in Mexico with 210 patients yielded a direct relationship between disease duration and SLE-related ocular, renal, musculoskeletal, skin damage, and gonadal failure.

It is well known that SLE patients in our days survive longer and the treating physician often faces the problem of distinguishing between active lupus patients and those manifesting with symptoms apparently unrelated to acute immunological inflammation or even age-related co-morbidities. Our SLE register-based study showed that several conditions out of the whole range were particularly prone to increase in frequency with time. These were angina pectoris, visual disturbances, acute and chronic pulmonary disease as well as allergy for medication and other allergens. Though we called these conditions co-morbidities, it could be argued since the mechanisms for their initiation could be sought in a purely immunological dysfunction. This could be especially attributed to visual disturbances, hypertension, acute and chronic pulmonary disease and allergies. The phenomena of angina pectoris have been thoroughly investigated by Urowitz M (12) and Bruce IN (13), and it is now proved that SLE is a risk factor for developing angina pectoris even in young patients. Our study with increasing rates of angina pectoris occurrence in the late disease is in agreement with this statement.

Although our data did not confirm the increasing prevalence of SLE-related symptoms in time, the developing of arteriosclerosis and age-related symptoms were evident. In other words, our study showed that the disease usually progresses with the same symptoms as it starts, but with a significant supplement of clinical conditions over time. In conclusion, we cannot predic that the development of SLE-related features is meaningless over time, but the association with disease duration is stronger when analysing co-morbidities than SLE features.

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SISTEMINĖ RAUDONOJI VILKLIGĖ LIETUVOJE: DEMOGRAFINIAI IR KLINIKINIAI LIGOS POŽYMIAI BENDRUOMENĖJE

S a n t r a u k a

Tyrimo tikslas – ištirti sisteminei raudonajai vilkligei (SRV) būdingus požymius pagal ARA 1982 diagnozės nustatymo kriterijus, su liga susijusius kitus požymius ir lydinčias ligas. Duomenys apie ligonius buvo gauti iš SRV duomenų bazės, kurią sudarė 59 ištirti SRV ligoniai. Išanalizuoti šių ligonių demografiniai rodikliai, klinikiniai požymiai, taip pat lydinčios ligos apskritai ir pagal ligos trukmę: trumpai, vidutiniškai ir ilgai sergantys. Konstatuota, jog dažniausi simptomai yra artritas (88,1%), padidėjęs jautrumas saulei (71,2%) ir eriteminis veido bėrimas (62,7%). Inkstų pakenkimas, opos burnoje ir diskoidinis bėrimas pasitaikė 40,7%, o CNS pakenkimas ir pleuritas – 22%. Hematologiniai, imunologiniai pokyčiai ir teigiamas ANA testas nustatyti atitinkamai 42,4%, 86,4% ir 74,6% ligonių. Bendra SRV kriterijų suma sudarė 5,9 (SD = 1,7) ir svyravo tarp 4 ir 10. SRV pasireiškimo požymių dažnumas ir su liga susijusių požymių dažnumas ligos metu nedidėjo. Lyginant trumpai ir ilgai sergančiuosius, statistiškai patikimai dažnėjo lydinčios ligos: krūtinės angina (nuo 6,8% iki 22,0%), regėjimo sutrikimai (nuo 10,2% iki 25,4%), ūmios (nuo 8,4% iki 27,1%) ir lėtinės (nuo 3,4% iki 17,0%) plaučių ligos, alergija medikamentams (nuo 11,8% iki 25,4%) ir kitiems alergenams (nuo 3,4% iki 17,0%). Taigi ligos požymių sergant vilklige daugėja, tačiau statistiškai patikimas didėjimas gautas analizuojant lydinčias ligas, o ne vilkligės požymius.

Raktažodžiai: sisteminė raudonoji vilkligė, epidemiologija, klinikiniai požymiai, lydinčios ligos