

General characteristics and familial aggregation in patients with systemic lupus erythematosus

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease characterized by the production of autoantibodies, which deposit within tissues and fix complement leading to systemic inflammation (1). Is a heterogeneous disease with a continuum of disease activity. Some patients can have predominant skin and joint involvement, whereas others can present with organ-threatening diseases such as nephritis, cardiac involvement or even neurologic manifestations. Relatives of patients with SLE appear to be at higher risk of SLE and other autoimmune diseases, but estimates of individual familial risks are largely unavailable or unreliable (2,3).

Keywords: systemic lupus disease, familial aggregation, siblings, autoimmune disorders

INTRODUCTION

Systemic lupus erythematosus is an autoimmune disease in which a person's immune system attacks various organs or cells of the body, causing damage and dysfunction. SLE is called a multisystem disease because it can affect many different tissues and organs in the body. Some patients with SLE have very mild disease, which can be treated with simple medications, whereas others can have serious, life-threatening complications. Lupus is more common in women than men, and for reasons that are not precisely understood, its peak incidence is after puberty (4).

The best evidence that SLE is genetically determined is from studies of familial aggregation (an increased frequency of persons with SLE in the same family) (5). For example, an identical twin of a patient with SLE has a 25% to 50% chance of developing the disease, but the risk is 10 times less if the affected twin was nonidentical (risk 2% to 5%). Still,

the latter risk is much greater than that in the general population. First degree relatives with a family history of SLE have a 6-fold higher risk of developing SLE and a 4-fold higher risk of developing a non-SLE autoimmune disease. (20% to 25%) or have a positive ANA (30%) (6). Population-based studies have shown that susceptibility to SLE, similar to other autoimmune disease in humans, is linked to particular class II genes of the major histocompatibility complex (HLA) in humans (HLA DR2 and HLA Dr3 increase relative risk 2 to 3 times), which may allow more efficient presentation of self antigens to self reactive T and B cells. In addition, early complement component (C1q, C2, C4) deficiencies increase the risk 5 to 10 times (7). In summary, SLE is polygenetic which helps explain its varied disease manifestations. The genetic risk loci vary between patients with different clinical and serological manifestations and may differ between ethnic groups (8).

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OBJECTIVE

The aims of the present work were to describe the characteristics of a representative sample of adult patients with SLE (2012 ACR/SLICC revised criteria for diagnosis of SLE) (9), to determine SLE status using (SLEDAI-2K) (10) and to determine whether there is familial aggregation of systemic SLE and/or other autoimmune diseases (AID) in SLE patients and to identify clinical differences between patients with and those without familial autoimmunity.

METHOD

A total of 225 SLE patients were included. We realized a cross-sectional study by enrolling those patients with SLE admitted in our hospital between January 2015 and August 2018. We interviewed 225 SLE patients to ascertain whether they had relatives with SLE and/or other autoimmune diseases.

We studied consecutive lupus pro-bands satisfying the 2012 SLICC Classification Criteria in a hospital-based, probing for 3 generation pedigree charting, clinical and investigational parameters.

We analysed the data applying Student's t-test, Chi-Square Test, ANOVA, and Pearson's correlation.

RESULTS

Multiple variables per patient were collected. Variables were divided into several groups:

1. Demographic data: age, gender and geographic region.
2. The major manifestations of the disease.
3. Coexistence of antiphospholipid syndrome, as defined by the Sydney classification criteria.
4. SLE status, using the activity index SLEDAI-2K. Laboratory findings, imaging or pathological studies.
5. Any treatments undergone and the reason for discontinuation, if applicable.
6. Family history and any link to the siblings.
7. The incidence of AID of the relatives of a SLE and non-SLE group.

The study included 225 SLE patients of whom 215 (95.55%) were women and 10 (4.44%) were men with a mean age 44.6 years and the mean disease duration was 6.5 years (Fig. 1).

Of the 215 women who participated in this study, 95 (44.1%) had primary education and 120 (55.8%) had mid-level education or higher (Fig. 2). As for

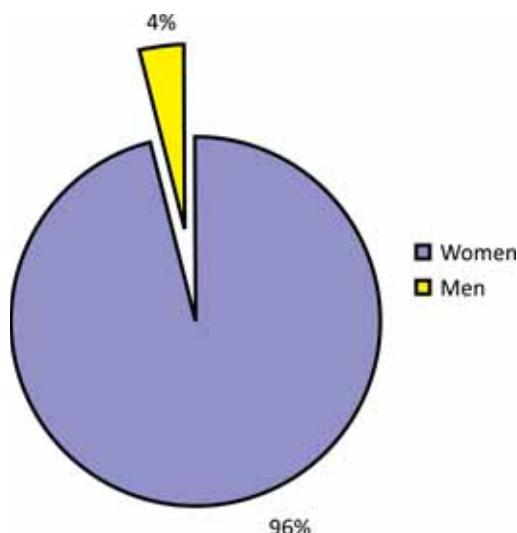


FIGURE 1. Gender distribution of SLE patients

marital status, 67.4% lived with a partner and 32.6% lived alone or with children and families.

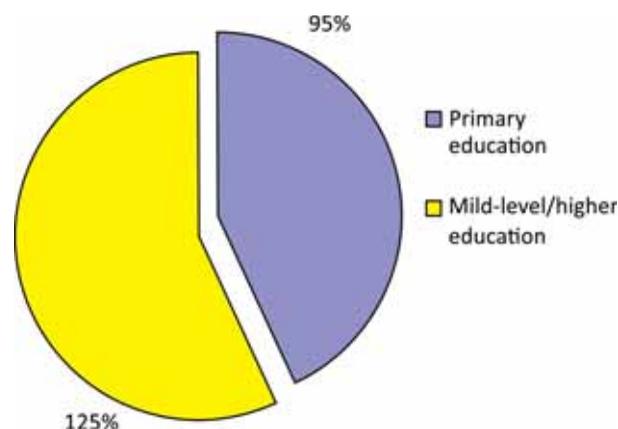


FIGURE 2. Patient education (n=225)

The distribution of rural versus urban patients by geographic region was described. The number of patients from urban areas was higher than that the number of patients from rural areas, respectively 64% versus 35% (Fig. 3).

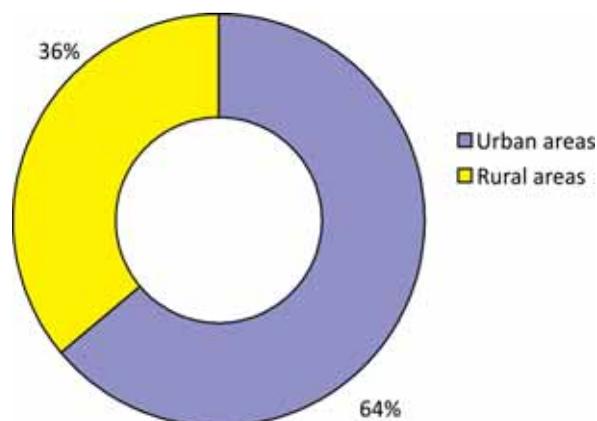


FIGURE 3. Geographic region

We also analysed all the manifestations in LES patients. Joint involvement was the most frequent clinical manifestation in patients (96.44%), followed by mucocutaneous manifestation which occurs in 88% of patients.

The major hematological manifestations of SLE patients are anemia which appear in 92 (40.88%) patients, leukopenia founded in 53 (23.55%) patients, lymphopenia in 68 (30.22%) patients and thrombocytopenia which occur in 26 (11.55%) patients (Fig. 4).

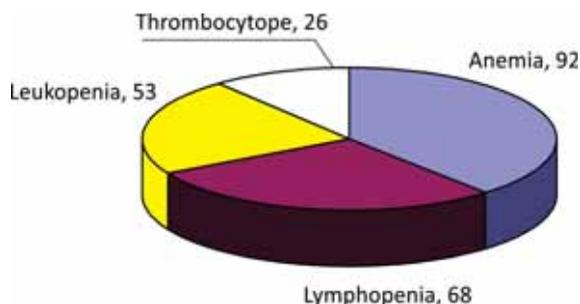


FIGURE 4. The hematological manifestations of SLE patients (n = 225)

Regarding immunological manifestations, anti-nuclear antibodies (ANA) were found in only 143 patients (probably they were not been performed in all the patients), anti-dsDNA antibodies, which are incredibly specific for SLE, were determined in 177 patients, anti-Sm in 24 patients, anti-Ro (SSA) in 76 patients and anti-La (SSB) in 24 patients. Also, hypocomplementemia was observed in 114 (50.6%) patients with SLE (Fig. 5).

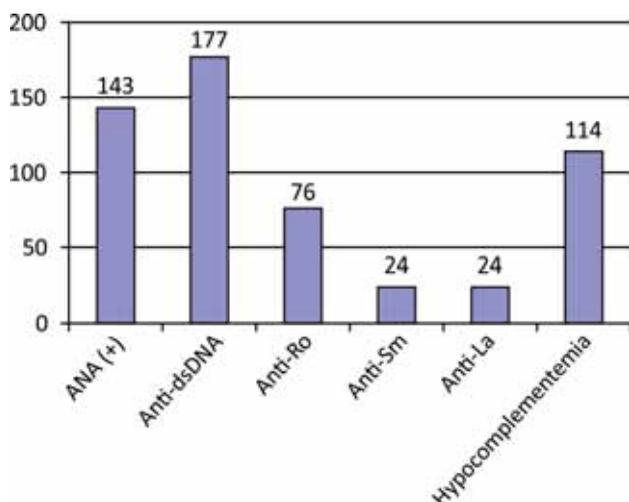


FIGURE 5. Immunological findings in SLE patients

Organ involvements are frequently observed in SLE patients. In our study, this has been noticed as well. The most common manifestation

was renal involvement in 69 patients, followed close behind by lupus serositis in 51 patients. Neurological manifestations were observed in 29 patients and 4 cases of psychiatric symptoms were reported. Cardiovascular manifestations have been noted in 9 patients and pulmonary involvement in 4 patients (Fig. 6).

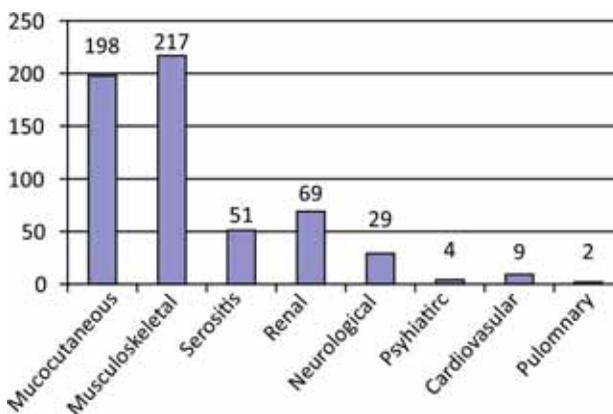


FIGURE 6. Organ involvement in SLE patients

The antiphospholipid syndrome (APS) is one of the most encountered autoimmunity in SLE patients and these two pathogenesis seem to intricate (11). The APS diagnosis was sustained according to the 2006 Sydney APS’s criteria (12). We observed 36 SLE patients with secondary APS, mostly with both IgM and IgG of anticardiolipin antibodies (aCL) positive. Only 28 patients were using oral anticoagulants for the APS.

A particular challenge in patients with lupus has been distinguishing mild, moderate, and severe flares and distinguishing them from ongoing, persistent disease. So, the evaluation of disease activity was performed by SLEDAI-2K. In the present study, the disease was very active (SLEDAI > 11) in 10 (4.4%) of participants, mild to moderate activity (SLEDAI = 1-10) in 206 (91.5%), and inactivity (SLEDAI = 0) in 8 (3.5%) (Table 1).

TABLE 1. Disease activity in SLE patients

	Status	Sledai score	n	%
Status	Inactive	0	8	3.5
	Mild to moderate	1-10	206	91.5
	Intense	≥11	10	4.4
Total			225	100

Regarding the treatment, 146 patients were treated only with hydroxychloroquine (HCQ), 14 patients only with azathioprine (AZA) and 46 patients concomitant treatment with HCQ and other immunosuppressive drug like azathioprine, mycopheno-

late mofetil, methotrexate or cyclophosphamide. Patients who had renal involvement in the past have been treated with cyclophosphamide (CFM), actually only 2 patients are still taking CFM. Mycophenolate mofetil (MMF) was used in 7 patients for refractory and relapsing lupus nephritis or other SLE organ manifestations. 6 patients were receiving monotherapy with methotrexate (MTX) for skin disease, arthritis, and other non-life-threatening forms of disease that have not responded to HCQ or low doses of prednisone (Table 2).

TABLE 2. Treatments in SLE patients

Prescription medication	Number of Patients
HCQ	16
AZA	14
MMF	7
CFM	2
MTX	6
Combination therapy (HCQ+AZA/MMF/MTX/CFM)	46
Systemic corticosteroid	
No use	77
Low dose (0-10)	66
Medium dose (10-20)	71
High dose (>20)	9

Steroid therapy was used in 146 (64.88%) patients, 71 of them using medium dose and 66 patients using low dose of glucocorticoids (Table 8).

Many studies have extensively evaluated family aggregation in rheumatic autoimmune disease (13-16). A study which have investigated familial autoimmunity in five major autoimmune diseases, namely, rheumatoid arthritis, systemic lupus erythematosus, autoimmune thyroid disease, multiple sclerosis and type 1 diabetes mellitus founded that aggregation of autoimmune thyroid disease, followed by systemic lupus erythematosus and rheumatoid arthritis, was the most encountered (17).

Regarding our study, we identified 72 (32%) first-, second-, or third-degree relatives with autoim-

mune diseases (AID). So, the prevalence of AID in this group is estimated as 32%. Among the relatives, there were 20 with SLE, 19 with rheumatoid arthritis (RA), 22 with autoimmune thyroiditis (AIT), 2 with ankylosing spondylitis (AS), 7 with type 1 diabetes mellitus and 2 with polymyositis (PM). Six SLE patients had 2 or more relatives with an autoimmune disease. AID including lupus was seen commonly in 1st degree (33 relatives) followed by 2nd degree relatives (27 relatives) (Table 3).

SLE patients who have relatives with SLE have multiple organ manifestations, including renal and neurological manifestations. However, patients with more severe disease tend to have 1st-degree relatives with SLE. These first-degree relatives (n=9) with SLE have mucocutaneous, musculoskeletal, immunological and renal manifestations. Two aunts have cardiovascular manifestations and one cousin have psychiatric manifestation.

Our SLE patients were compared with a control group – 225 consecutive hospital inpatients with no SLE disease from similar geographical areas included as controls. They were admitted to our hospital for other conditions. The mean age was 47.2 years, with 64.8% women and 35,1% men (Table 10). Compared to SLE cohort, we identified 54 (24%) first- and second-degree relatives with AID. 10 relatives were with SLE, 18 with RA, 10 with AIT, 6 with AS, 8 with type 1 diabetes mellitus and 2 with polymyositis (Fig. 7).

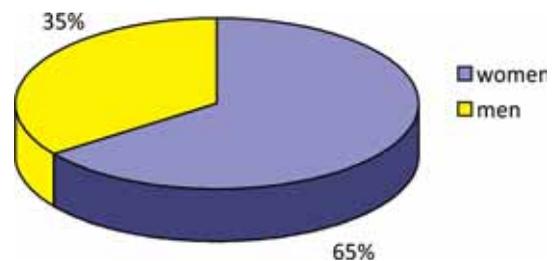


FIGURE 7. Gender distribution of non-SLE patients

The risk of AID in non-SLE group from this study is 24%. So, the the risk ratio is $RR = 32\%/24\% = 1.33$,

TABLE 3. Autoimmune diseases in relatives of SLE patients according to familial degree

Disease in relatives	1 st -degree relatives			2 nd -degree relatives			3 rd -degree relatives (cousins)
	Parents	Offspring	Siblings	Grandparents	Uncles/aunts	Nephews/nieces	
SLE	3	4	2	4	3	1	3
RA	4	4	3	2	3	1	2
AIT	5	2	2	2	4	2	5
AS	1	0	1	0	0	0	0
Type 1 diabetes	1	0	1	2	0	2	1
PM	0	0	0	0	0	1	1

TABLE 4. Autoimmune diseases in relatives of non-SLE patients according to familial degree

Disease in relatives	1 st -degree relatives			2 nd -degree relatives		
	Parents	Offspring	Siblings	Grandparents	Uncles/aunts	Nephews/nieces
SLE	2	2	4	0	0	2
RA	5	3	4	2	2	2
AIT	6	0	2	1	0	1
AS	2	1	0	0	2	1
Type 1 diabetes	2	1	1	2	1	1
PM	0	0	1	1	0	0

meaning that SLE patients have 1.33 the risk of having relatives with SLE as non-SLE patients (a 100% increase in risk).

Regarding the odds ratio, this is $OR = 0.64/0.31 = 2.06$, that means that SLE patients have 2.06 times the odds of non-SLE patients (a 200% increase in odds) [95% confidence interval (CI) = 0.959, 4.589, $p = 0.059$].

We established 3 main groups from the SLE sample:

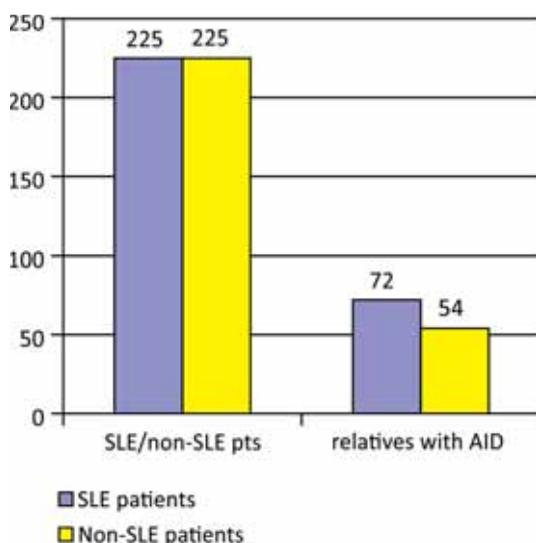
1) patients who had at least 1 first-, second-, or third-degree relative with any autoimmune disease (AIT, AS, diabetes mellitus, polymyositis) ($n=33$)

2) patients who had at least 1 first-, second-, or third-degree relative with SLE ($n=20$)

3) patients who had at least 1 first-, second-, or third-degree relative with RA ($n=19$).

Sex differences in familial risks are not apparent despite women with a female affective relative tending to have a higher relative risk.

We found more relatives with AID in SLE group, when comparing with non-SLE group. We also found familial aggregation for autoimmune disease in non-SLE group, respectively 54 relatives with AID (Fig. 8).

**FIGURE 8.** The incidence of AID of the relatives in both groups

There are several limitations to the present study. First, it was restricted to Romania, and different findings may occur in other populations and environments. Therefore, additional studies in other country are required to determine the generalizability of our findings. Second, we do not have detailed information on clinical findings, laboratory testing, and examinations for the SLE relatives.

DISCUSSION

A total of 225 SLE patients were studied of whom 215 (95.55%) were women and 10 (4.44%) were men with a mean age 44.6 years.

The clinical and immunological characteristics of our SLE patients are largely comparable to most major studies.

Main differences included prominent major organ damage and high pre-valence of anti-dsDNA and anti-Sm antibodies.

In the present study, the disease was very active (SLEDAI > 11) in 10 (4.4%) of participants, mild to moderate activity (SLEDAI = 1-10) in 206 (91.5%), and inactivity (SLEDAI = 0) in 8 (3.5%).

Regarding the treatment, 146 patients were treated with hydroxychloroquine (HCQ) in monotherapy and 14 patients with *azathioprine* (AZA). Mycophenolate mofetil (MMF) was used in 7 patients for refractory and relapsing lupus nephritis or other SLE organ manifestations. 6 patients were receiving methotrexate (MTX) for skin disease, arthritis, and other non-life-threatening forms of disease that have not responded to HCQ or low doses of prednisone.

The importance of familial autoimmunity has been shown in our study. We identified 72 first-, second-, or third-degree relatives with AID, which was seen commonly in 1st degree (33 relatives) followed by 2nd degree relatives (27 relatives). Among the relatives, there were 20 with SLE, 19 with rheumatoid arthritis, 22 with autoimmune thyroiditis, 2 with ankylosing spondylitis, 7 with type 1 diabetes mel-

litus and 2 with polymyositis. Six SLE patients had 2 or more relatives with an autoimmune disease.

Those patients with higher socioeconomic level were more likely to have familial autoimmunity.

Compared to controls, SLE patients have 1.33 the risk of having relatives with SLE as non-SLE patients with OR = 2.06 [95% confidence interval (CI) = 0.959, 4.589, p = 0.059].

In SLE there is familial aggregation of SLE, RA, and autoimmune disease in general. The individual risks of SLE and other autoimmune diseases were increased in families that included patients with SLE. The elevated rate of autoimmunity among blood relatives suggests a complex interaction of genetic contributing to disease.

CONCLUSIONS

The pathogenesis of SLE is multifactorial, including genetic and environmental factors. Genetic predisposition plays a crucial role in susceptibility.

Strong familial aggregation in SLE has been reported but, to the best of our knowledge, this is the

first population-based study investigating familial aggregation of SLE and coaggregation of other autoimmune diseases in relatives of people with SLE.

These data should be considered when counseling families with affected members.

The high rate of autoimmunity among both blood relatives and nonconsanguineous mates in this unusual pedigree suggests a complex interaction of genetic and environmental factors contributing to disease (7,18).

Given the clinical and etiologic heterogeneity of ADs, understanding the relationship of genotype to phenotype is an extremely important goal for research aimed at gene identification. Thus, further studies of familial autoimmunity will help in increasing the knowledge about the common mechanisms of autoimmunity (17).

Family history of SLE is associated with a clearly elevated risk of SLE and, to a much lesser degree, of RA, AIT and other AID.

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