Familial Systemic Lupus Erythematosus in Finland

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ABSTRACT. ***Objective.*** To perform a cross sectional nation-wide clinical study of familial systemic lupus erythematosus (SLE) in Finland.

Methods. We sought to identify all Finnish families in which at least 2 members satisfied the classification criteria for SLE. About 1200 patients with SLE (80–85% of all patients attending Finnish hospitals) were contacted. Personal and/or phone interviews and examination of medical records were used to verify the diagnoses. A comparison of clinical characteristics was made between familial cases of SLE and matched sporadic controls.

Results. We identified 53 multiplex families with 113 SLE patients. Forty-six families had 2 affected members and 7 families had 3 affected members. There were 3 pairs of monozygotic female twins and one pair of dizygotic twins of the opposite sex concordant for SLE. Eleven (9.7%) of the 113 familial cases of SLE were male. No differences were found in the clinical presentation of SLE between familial and sporadic cases (sex, age at onset, major clinical manifestations, and common laboratory tests). The incidence of familial SLE was ~4–5%.

Conclusion. Our study shows that familial and sporadic SLE are not different disease entities; this means that we can extrapolate the results of future genetic analyses in multiplex SLE families to all patients with SLE. (J Rheumatol 2001;28:758-60)

Key Indexing Terms:
SYSTEMIC LUPUS ERYTHEMATOSUS FAMILIAL CLINICAL FEATURES

Studies on familial systemic lupus erythematosus (SLE) have been case reports, small series of multiplex families, or studies from a defined lupus clinic or area of a country[1-4]. There are essentially no studies where multiplex SLE families from a defined population have been identified and characterized. Our aim was to identify all multiplex SLE families in Finland and to perform a clinical study of familial SLE as a basis for a nation-wide genetic mapping project. The specific questions of this study were as follows. What are the familial relationships of affected members in multiplex SLE families? Is familial SLE clinically different from sporadic disease, and are there differences in clinical presentations within familial cases?

MATERIALS AND METHODS

The first recruitment phase was started in March 1995. All patients with a clinical diagnosis of SLE who had attended the University Hospitals of Helsinki and Kuopio between January 1992 and March 1995 were identified from the corresponding hospital registries and contacted personally or by mail. All patients with SLE registered in the Lupus Foundation of Finland were contacted by mail, and advertisements about our study were published in patient information bulletins.

The second recruitment phase was started in the fall of 1996. SLE patients attending the central hospitals and 4 other major hospitals in Finland (21 hospitals altogether) between 1993 and 1996 were contacted by mail. Practically all patients with SLE in our country are seen by a rheumatologist in public hospitals, and we calculated that at least 1200 patients (80–85% of all patients) were contacted in the different recruitement phases of the study.

Patients who stated that they had another family member with SLE or a similar disease form the basis of this study. These subjects were interviewed by the responsible rheumatologist either personally or by telephone, and the medical records from different hospitals were examined after obtaining permission from the Ministry of Health. Clinical data gathered for this study were the 11 criteria for the classification of SLE, the date of the first symptom clearly attributable to SLE, a history of venous thrombosis verified by phlebography or ultrasound, and cerebral arterial thrombosis verified by clinical examination and/or by brain computerized tomography or magnetic resonance imaging.

Multiplex SLE families were defined as families where at least 2 members satisfied at least 4 of the criteria for the classification of SLE[5]. The controls (sporadic cases) were consecutive patients with SLE who did not have a family history of SLE.

For comparison of clinical characteristics between familial and sporadic SLE, sporadic cases were listed in alphabethical order. From this list, the first sex-matched patient matching for age (± 2 years in women and ± 4 years in men) and the duration of SLE symptoms (± 4.5 years in women, ± 11 years in men) was chosen as a control case for each familial case. Cases and controls were comparable; the mean ages at onset of SLE symptoms was 30.7 vs 30.5 years and at the time of clinical diagnoses 34.9 vs 34.3 years, respectively.

The chi-square test and, when appropriate, Fisher's exact test were used to compare the difference in clinical characteristics between familial and sporadic cases of SLE. The Bonferroni correction was used for multiple comparisons.

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RESULTS

We identified 53 multiplex SLE families. There were 46 families with 2 affected members (Table 1). There were 3 sets of female monozygotic twins and one set of dizygotic twins of the opposite sex concordant for SLE. In 7 families, 3 members were affected (Table 2).

One-hundred thirteen members from 53 families were classified as familial cases of SLE. Eleven (9.7%) of the 113 affected persons were male. When multiple comparisons were taken into account, no statistical differences in clinical manifestations and laboratory findings between familial and sporadic cases of SLE were found (Table 3). The mean number of American Rheumatism Association (ARA) criteria fulfilled by familial cases was 5.2 (range 4–9) and by sporadic cases 5.4 (range 4–9).

There were no statistical differences in clinical characteristics between men with familial SLE compared with matched control male patients with SLE or in those SLE patients who were close relatives (34 affected siblings and 20 cases of parent-offspring combinations) compared with those familial SLE patients who were more distant relatives (32 affected).

The mean age at onset of SLE in familial cases was 30.7 years (range 1–66) and in sex and age matched sporadic controls 29.0 years (range 7–59).

Table 1. Familial cases of SLE in families with 2 members affected.

Relationship	No. of Families
Sister/sister	14
Sister/brother	3
Mother/daughter	8
Father/daughter	2
Female identical twins	2
Female/male twins	1
Aunt/nephew	2
Aunt/niece	5
Female cousins	3
Distant relatives	6
Total	46

Table 2. Familial cases of SLE in families with 3 members affected.

Relationship	No. of Families	No. of Individuals
Daughter/mother/aunt	2	6
Daughter/father/aunt	1	3
Identical sisters/nephew	1	3
Mother/daughter/son	1	3
Son/mother/mother's female cousin	1	3
3 distant relatives	1	3
Total	7	21

Table 3. Comparison of clinical characteristics between familial and matched sporadic cases of SLE.

Clinical Characteristics	Familial SLE n = 113 (%)	Sporadic SLE n = 113 (%)	Difference, p*
Butterfly rash	52/113 (46)	57/113 (50)	NS
Discoid rash	6/113 (5)	13/113 (12)	NS
Photosensitivity	78/113 (69)	72/113 (64)	NS
Mouth ulcers	19/111 (17)	13/113 (12)	NS
Arthritis	89/113 (79)	99/113 (88)	NS
Pleuritis	17/113 (16)	28/113 (25)	NS
Pericarditis	11/113 (10)	22/113 (20)	0.036
Nephritis	30/113 (27)	33/113 (29)	NS
Convulsions	10/113 (9)	4/113 (4)	NS
Psychosis	2/113 (2)	3/113 (3)	NS
AIHA	4/107 (4)	4/109 (4)	NS
Leukopenia	78/110 (71)	74/110 (67)	NS
Thrombocytopenia	17/108 (16)	26/109 (24)	NS
DNA antibodies	67/96 (70)	93/112 (83)	0.024
FP-STS	7/42 (17)	12/48 (25)	NS
Antinuclear antibodies	109/111 (98)	110/112 (98)	NS
Deep venous thrombosis	15/113 (13)	8/113 (7)	NS
Stroke or TIA	9/113 (8)	2/113 (2)	0.034

* p values < 0.05 are shown; Bonferroni correction for multiple comparisons yielded a significance level of 0.0028.
AIHA: autoimmune hemolytic anemia; FP-STS: false positive standard test for syphilis; TIA: transient ischemic attack.

DISCUSSION

In a nation-wide study, we used several sources of recruitment and consider that practically all multiplex SLE families in Finland were identified and clinically characterized. We found 46 families with 2 affected members and 7 families with 3 affected members. We found no families with more than 3 members with SLE. This reflects both the low prevalence of SLE in the general population and the presumably low penetrance of SLE susceptibility genes.

Large families with many cases of SLE appear to be rare. Brunjes, *et al*[1] described a family with 4 sisters. Sestak, *et al*[6] described a large pedigree with 8 female SLE patients and aggregation of other autoimmune features in several blood relatives, especially in women.

We found no significant differences in the clinical presentation between familial and sporadic cases of SLE or between those SLE patients who were close relatives compared to more distant relatives. These findings correspond well with other studies[4,7] and suggest that familial SLE is not a different disease entity from non-familial SLE.

It has been reported that relatives of male SLE probands and probands whose disease started at young age (< 30 years) have a higher risk of SLE than relatives of female or older probands[2,3]. These findings are not supported by our study. We did not find that familial SLE would be a predominantly male disease and the mean age at onset of SLE in familial cases was even higher than in sporadic controls.

Our study shows that familial and sporadic SLE are not different disease entities, and this means that we can extrapolate the results of future genetic analyses in multiplex SLE families to all patients with SLE. Family studies form the

basis for further assessment of genetic contributions to SLE, which may be easier in simplified and isolated populations, such as the Finnish population, than in diverse continental populations.

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