Expression of systemic lupus erythematosus in various ethnic Jewish Israeli groups

A J Wysenbeek, L Leibovici, A Weinberger, D Guedj

Abstract

Objectives—To assess the expression of systemic lupus erythematosus (SLE) in Jewish Israeli patients according to ethnic origin.

Methods—Eighty four patients with SLE were divided into groups according to origin and compared for history, physical examination, and laboratory variables.

Results—Patients of Sephardic origin had more serious disease manifestations than Ashkenazi patients in 60 of the 76 variables examined. They had significantly worse muscle pain, alopecia, and cutaneous vasculitis, higher antibodies to DNA and erythrocyte sedimentation rate, and significantly lower complement and leucocytes. Sephardic patients were divided into subgroups according to country: Mediterranean area, Iran-Iraq-India, and Yemen. All three subgroups had more serious disease manifestations than the Ashkenazi group, and the Yemenite patients had the most serious manifestations among the Sephardic subgroups. The Sephardic patients had a significantly lower education level, but only origin, and not education level or age, was significantly related to disease manifestations on multivariate analysis.

Conclusion—More serious manifestations of SLE are found among Jewish patients of Sephardic origin, but these are not related to level of education or age.

(*Ann Rheum Dis* 1993; 52: 268–271)

Ethnic origin is one of the factors that may modulate the prevalence and expression of systemic lupus erythematosus (SLE). It was noted that SLE is more common among black and oriental subjects than white subjects.^{1 2} Several publications consider this question, and most of them report incidence, prevalence, and mortality due to SLE among various ethnic groups.³ Relatively little is known, however, about the expression of the disease in patients of different origin.

To consider this question we investigated disease expression in a group of Israeli patients with SLE of Ashkenazi and Sephardic origin.

Patients and methods

Data on patients with SLE followed up at the Beilinson Medical Center and diagnosed according to the 1982 American Rheumatism

Association (ARA) criteria for SLE⁴ were evaluated. Information gathered at each visit—patient's history and physical examination—was entered prospectively into a computerised database. Data were immediately converted by the examining doctor into 25 history and 29 physical examination variables, all on a scale of 0–3 (none, mild, moderate, severe). Patients were assessed by one of three doctors of the rheumatology unit.

RELATION BETWEEN ETHNIC ORIGIN AND DISEASE MANIFESTATIONS

Patients were divided into two groups according to their Ashkenazi or non-Ashkenazi (Sephardic) origin. Patients of mixed Ashkenazi-Sephardic origin and patients of Arabic origin were not included. The Sephardic group was subdivided into those from the Mediterranean area, Iran-Iraq-India, and Yemen. Patients of mixed Sephardic origin were not included in this subdivision. Groups were compared for the various disease variables. For each patient the maximum observed value for variables was recorded, and group medians were compared for each variable.

STATISTICAL EVALUATION

Group interval and ordinal data were compared by Wilcoxon's rank sum test and analysis of variance with paired *t* test. Nominal data were compared by the χ^2 test. Multiple linear regression analysis was used to investigate the relation between variables. Significance was not adjusted for multiple comparisons. Data are presented as mean (standard error of the mean).

Results

Of the 90 patients with SLE followed up at our centre, three of mixed Ashkenazi-Sephardic origin and three of Arabic origin were withdrawn from the study. The remaining 84 patients included 39 (46%) of Ashkenazi origin and 45 (54%) of Sephardic origin (table 1). Sex distribution was similar in both groups (5/39 *v* 3/45 men, *p*=0.5). The Ashkenazi group was older (46.9 (2.6) *v* 40.9 (2.2) years, *p*=0.09) and had a significantly higher level of education (13.0 (0.5) *v* 9.9 (0.6) years of schooling, *p*<0.001). The Ashkenazi patients were seen 8.5 (1.0) times during 654 (68) days compared with 8.6 (0.6) times during 746 (47) days for the Sephardic patients (*p*=0.5 for

The Rheumatology Unit, Beilinson Medical Center, Petah Tiqva, Sackler Faculty of Medicine, University of Tel Aviv, Israel
A J Wysenbeek
D Guedj

Department of Medicine B, Beilinson Medical Center, Petah Tiqva, Sackler Faculty of Medicine, University of Tel Aviv, Israel
L Leibovici
A Weinberger

Correspondence to: Dr Arjeh J Wysenbeek, Head Rheumatology Unit, Beilinson Medical Center, Petah Tiqva, Israel 49100.

Accepted for publication 9 December 1992

times, $p=0.8$ for days). Repeat assessment was conducted for 36/39 Ashkenazi patients and 42/45 Sephardic patients.

RELATION BETWEEN ETHNIC ORIGIN AND DISEASE MANIFESTATIONS

The Sephardic group had more serious disease manifestations for 60/76 (79%) clinical and laboratory variables examined. These were significant for alopecia and muscle tenderness by both patient history and physical examination, and for cutaneous vasculitis, antibodies to DNA, C3 complement, erythrocyte sedimentation rate, and white blood cell count. Only pericarditis had a significantly higher value in the Ashkenazi group (table 2).

The Sephardic group had higher creatinine concentrations (117.6 (15.9) *v* 93.7 (5.3) $\mu\text{mol/l}$, $p=0.4$) and higher prevalence of renal disease (35.6% *v* 28.2%, $p=0.6$). Central nervous system manifestations of psychosis, convulsions, or organic brain symptoms were monitored in 14 (31%) of Sephardic patients and 15 (38%) of Ashkenazi patients ($p=0.6$). In the Sephardic group 28 (62%) had rash and eight (18%) discoid rash compared with 21 (54%) and five (13%) respectively in the

Ashkenazi group. Prevalence of arthritis was 62% (Sephardic) compared with 51% (Ashkenazi) and of Raynaud's phenomenon 16% (Sephardic) compared with 10% (Ashkenazi). (All clinical variables presented are according to the doctor's examination.) Peak prednisone dose in the Ashkenazi and Sephardic groups was 24.7 (4.4) and 32.4 (3.5) mg/day respectively ($p=0.17$). When the Sephardic patients were divided into subgroups each of the three subgroups had worse disease manifestations than the Ashkenazi group; among the subgroups, the Yemenite patients had significantly worse disease manifestations (table 3).

INFLUENCE OF EDUCATION AND AGE

Ashkenazi patients as a group had a significantly higher level of education. To evaluate the contribution of education to the differences between the groups we divided the Ashkenazi and Sephardic patients according to years of schooling (less than 12, 12, and more than 12 years). The Ashkenazi group had more patients in the highest education group (>12 years) and the Sephardic had more in the lowest education group (<12 years). To equalise education level among the groups, patients were matched for schooling, such that not all patients were entered into the highest and lowest education groups (table 4). As shown, the clinical variables were equal in the three Ashkenazi education subgroups, whereas there was a trend towards milder disease in the Sephardic patients with the higher education. As for laboratory variables, the Ashkenazi patients with higher education had more serious disease manifestations, whereas recordings tended to be similar in the three Sephardic education subgroups. The influence of education and age was further evaluated by multiple linear regression (table 5). Results indicated that origin had the strongest influence on the various equations, while the influence of education and age was relatively minor. Education level in the Sephardic subgroups was 9.1, 10.2, and 9.7 years for the patients from the Mediterranean area, Iran-Iraq-India, and Yemen groups respectively ($p=0.8$). Respective mean ages were 39.4, 41.8, and 40.6 years ($p=0.9$). Thus there was no difference in level of education or age between the Yemenite group which had the most serious disease manifestations and the other two Sephardic subgroups.

Discussion

We compared clinical and laboratory disease variables between Ashkenazi and Sephardic Israeli patients with SLE. Sephardic patients were found to have more serious disease manifestations for most of the variables examined; they had significantly more muscle pain, alopecia, and cutaneous vasculitis, higher antibodies to DNA and sedimentation rate, and lower complement and leucocyte count.

When the Sephardic patients were subdivided by country of origin the Yemenite

Table 1 Origin of patient group

Origin	No	%
Ashkenazi	39	46
Sephardic	45	54
Mediterranean	11	13
Iran-Iraq-India	23	27
Yemen	8	10
Mixed Sephardic	3	4

Table 2 Disease manifestations according to the doctor's examination and laboratory tests. Results are given as mean (SEM). Prevalence of positive or pathological recordings is shown in square brackets

	Ashkenazi (n=39)	Sephardic (n=45)	p Value*
Muscle pain†	0.38 (0.12) [23]	1.00 (0.16) [53]	0.003
Alopecia†	0.79 (0.17) [44]	1.33 (0.16) [71]	0.017
Cutaneous vasculitis†	0.13 (0.08) [8]	0.60 (0.16) [27]	0.019
Pericarditis†	0.23 (0.11) [10]	0.00 (0.00) [0]	0.028
WBC‡ ($\times 10^9/\text{l}$)	5.41 (0.32) [21]	4.34 (0.23) [47]	0.005
C3 (mg/l)	794 (56)	614 (45)	0.02
Anti-DNA§	26.7 (4.0) [47]	42.1 (5.0) [61]	0.04
ESR§ (mm/h)	64.1 (5.4)	78.8 (5.0)	0.04

*Wilcoxon's rank sum test.

†Scale of 0–3 (none, mild, moderate, severe).

‡Percentage of patients with WBC $<4 \times 10^9/\text{l}$ is shown in square brackets.

§WBC=white blood cells; ESR=erythrocyte sedimentation rate.

¶Farr method. Range 0–100%. Percentage of patients >20% is shown in square brackets.

Table 3 Disease manifestations in the Sephardic subgroups. Patients of mixed Sephardic origin were not included. Values are given as mean (SEM)

	Iran-Iraq-India (n=23)	Mediterranean (n=11)	Yemen (n=8)	p Value*
Muscle pain†	0.87 (0.22)	1.00 (0.36)	1.50 (0.38)	0.35
Alopecia†	0.87 (0.19)	1.36 (0.34)	2.12 (0.23)¶	0.008
Cutaneous vasculitis†	0.22 (0.12)	0.82 (0.35)	1.37 (0.53)¶	0.017
WBC‡ ($\times 10^9/\text{l}$)	4.35 (0.33)	5.10 (0.47)	3.07 (0.28)¶	0.018
C3 (mg/l)	671 (67.5)	680 (101)	414 (49.0)¶	0.06
Anti-DNA§	36.9 (6.88)	36.8 (8.42)	58.2 (13.7)	0.26
ESR‡ (mm/h)	67.1 (6.06)	89.3 (11.0)	90.7 (11.8)	0.08

*Analysis of variance.

†Scale of 0–3 (none, mild, moderate, severe).

‡WBC=white blood cells; ESR=erythrocyte sedimentation rate.

§Farr method. Range 0–100%. Normal <20%.

¶Yemenite *v* Iran-Iraq-India, $p<0.05$.

¶Yemenite *v* Mediterranean, $p<0.05$.

Table 4 Comparison of Ashkenazi and Sephardic patients according to equal levels of education

	Schooling					
	<12 Years		12 Years		>12 Years	
	Askh.* (n=9)	Seph.* (n=9)	Askh. (n=12)	Seph. (n=15)	Askh. (n=7)	Seph. (n=7)
Muscle pain†	0.56	1.11	0.25	0.93	0.57	0.43
Alopecia†	0.78	1.67	0.50	1.47	0.85	0.57
Cutaneous vasculitis†	0.22	1.33	0.17	0.67	0.14	0.00
WBC* (×10 ⁹ /l)	5.61	4.10	5.55	4.05	3.94	5.26
C3 (mg/l)	1040	610	730	440	680	760
Anti-DNA‡	18	38	28	48	40	40
ESR* (mm/h)	63	82	81	80	44	84

*Askh.=Ashkenazi; Seph.=Sephardic; WBC=white blood cells; ESR=erythrocyte sedimentation rate.
†Scale of 0–3 (none, mild, moderate, severe).
‡Farr method. Range 0–100%. Normal <20%.

Table 5 Multiple linear regression analysis of combined effect of age, education and origin on dependent clinical variables

	Muscle pain		Alopecia		C3		Anti-DNA		ESR	
	Coef	p	Coef	p	Coef	p	Coef	p	Coef	p
Intercept	1.01	0.06	1.46	0.02	76.7	0.0001	54.0	0.002	76.7	0.003
Age	0.01	0.15	-0.00	0.87	0.18	0.49	-0.42	0.08	0.19	0.48
Education	-0.04	0.19	-0.01	0.78	-2.37	0.04	0.59	0.57	-0.46	0.70
Origin	-0.55	0.02	-0.42	0.14	25.3	0.004	-15.8	0.04	-15.3	0.08

group had the most disease manifestations. These results should be interpreted with caution, however, in view of the relatively small number of Yemenite patients examined. In addition, the leucopenia in the Yemenite patients might not necessarily have been related to SLE because healthy Yemenite Jews generally have low leucocyte counts,⁵ possibly as a result of the African genetic contribution to the Yemenite population.⁶ Studies on larger groups of Yemenite patients are needed to confirm our findings.

The Sephardic patients had a significantly lower level of education than the Ashkenazi patients. It has been shown that formal education level is an important factor in clinical status in patients with rheumatoid arthritis—that is, patients with little education had more disease manifestations as assessed by both clinical and laboratory markers.⁷ Recent studies indicate that this factor is more apparent in male patients with rheumatoid arthritis,⁸ and that occupation and income are also important.⁹

In another study socioeconomic status, which correlates with education level, was shown to be related to prognosis in patients with SLE: private patients with SLE of higher socioeconomic status had a better survival rate.¹⁰ The influence of socioeconomic status was also different between publicly funded patients with SLE and private patients.¹¹ Other studies have reported significant and independent effects of economic status and race on survival in SLE,¹² or no significant relation between socioeconomic status and outcome.¹³ Recently, Callahan and Pincus reported that clinical status was poorer in patients with SLE with low education level.¹⁴

We showed that most of the differences between the Ashkenazi and Sephardic patient groups persisted when patients were divided according to equal education level, except that

Sephardic patients with a higher education had relatively milder disease. The Yemenite patient group, which had the most severe disease indices, did not differ from the other Sephardic groups in education or age. Multivariate analysis indicated that origin is the cardinal factor in the clinical differences between our patients. Thus although education and age have some importance in the expression of SLE, their contribution seems to be relatively minor.

The higher severity of disease in the Sephardic patients could theoretically have been due to the fact that well educated Ashkenazi patients, possibly those with mild disease, may present earlier or get referrals more easily. Yet, when patients with equal education level were compared the Sephardic patients still had more severe disease expression. Thus this factor does not seem to constitute a significant bias in our study.

Hochberg investigated and extensively reviewed the epidemiology of SLE.³ Black patients in the United States had about a threefold higher incidence of SLE than white patients.^{15 16} He also discussed the effects of race on morbidity rates, and black subjects in the United States again had about a threefold prevalence of SLE in comparison with white subjects.^{15 17 18} These differences in incidence and prevalence were manifest for both men and women. Systemic lupus erythematosus was more prevalent among oriental than white subjects in Hawaii^{19 20} and New Zealand,²¹ and more prevalent among Asian than white subjects in England.²² Also, the mortality of black subjects with SLE was significantly higher than that for white subjects for both men and women.^{12 15 23–26}

Less is known about expression of the disease in the various races. Fessel compared data of white and black patients with SLE in San Francisco according to diagnostic criteria.¹⁷ As mentioned, the disease was more prevalent among black patients, who also had more haematological abnormalities and serositis, whereas non-black patients had more malar rash and convulsions/psychosis. Ginzler *et al* noted that black patients with SLE developed more severe renal, haematological, and central nervous system disease over a shorter period of time.¹¹ When data were corrected for socioeconomic status, race did not significantly influence survival. Ward and Studenski compared black subjects with white subjects according to the revised ARA criteria²⁷ and found that black subjects had a higher incidence of antibodies to Sm and RNP, more discoid rash and proteinuria, and, less commonly, photosensitivity. Samanta *et al* compared Asian patients and white patients with SLE in Britain.²² Asian patients had more renal disease, neuropsychiatric features, myalgic symptoms, and higher antinuclear antibodies and extractable nuclear antigens.

From the above data a trend can be seen of higher incidence and prevalence of disease, higher mortality, and more severe disease expression in the non-white races. This is in accordance with our observation of a more

severe disease expression among Sephardic Israeli patients with SLE. The explanation for this difference is unclear, but several suggestions can be made. Systemic lupus erythematosus is known to be related to female sex hormones.²⁸ Japanese and Bantu girls and young women were found to have a higher level of 17 β -oestradiol than white women.²⁹ Thus hormonal differences might explain the difference between races for the prevalence and expression of SLE.

Genetic heterogeneity might be another explanation. HLA-DR2, DR3, and DQw1 as well as the complement components located in the HLA system have been reported in association with SLE.³ Thus genetic differences between patient subgroups could be the basis for the clinical differences. Genetic markers were investigated in various Jewish populations,³⁰ and Ashkenazi, North African, and Iraqi Jewish populations were found to be consistently close in genetic constitution and distant from Yemenite Jews, Arabs, and non-Jewish German and Russian populations. This may be understood in accordance with our observation of more severe disease expression among our Yemenite patients. However, the above mentioned HLA-DR and complement alleles were not examined in this study.

In conclusion, our study shows differences between Israeli Jewish lupus patients of various ethnic origins. These findings may have implications on SLE research. Owing to the apparent difference between lupus patients of various origins, research in such patients should be stratified accordingly. Future studies should highlight prevalence and mortality among Jewish SLE patients, and further investigation of the HLA phenotypes of these groups may help to explain our findings and contribute towards better understanding of the pathogenesis of SLE.

We thank Mrs Mantsur Ilana for her secretarial assistance.

- 1 Schur P H. Clinical features of systemic lupus erythematosus. In: Kelley W N, Harris E D Jr, Ruddy S, Sledge C B, eds. *Textbook of rheumatology*. 3rd ed. Philadelphia: Saunders, 1989: 1101-29.
- 2 Rothfield N F. Systemic lupus erythematosus: Clinical aspects and treatment. In: McCarty D J, ed. *Arthritis and allied conditions*. 10th ed. Philadelphia: Lea and Febiger, 1985: 911-35.
- 3 Hochberg M C. Systemic lupus erythematosus. *Rheum Dis Clin North Am* 1990; **16**: 617-39.
- 4 Tan E M, Cohen A S, Fries J F, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 1271-7.
- 5 Schonfeld Y, Weinberger A, Avishar R, et al. Familial leukopenia among Yemenite Jews. *Isr J Med Sci* 1978; **14**: 1271-4.
- 6 Shaper A G, Lewis P. Genetic neutropenia in people of African origin. *Lancet* 1971; **ii**: 1021-3.
- 7 Callahan L F, Pincus T. Formal education level as a significant marker of clinical status in rheumatoid arthritis. *Arthritis Rheum* 1988; **31**: 1346-57.
- 8 Leigh J P, Fries J F. Education level and rheumatoid arthritis: evidence from five data centers. *J Rheumatol* 1991; **18**: 24-34.
- 9 Leigh J P, Fries J F. Occupation, income, and education as independent covariates of arthritis in four national probability samples. *Arthritis Rheum* 1991; **34**: 984-95.
- 10 Wallace D J, Podell T, Weiner J, Klinenberg J R, Forouzesh S, Dubois E L. Systemic lupus erythematosus—survival patterns. Experience with 609 patients. *JAMA* 1981; **245**: 934-8.
- 11 Ginzler E M, Diamond H S, Weiner M, et al. A multicenter study of outcome in systemic lupus erythematosus. *Arthritis Rheum* 1982; **25**: 601-11.
- 12 Studenski S, Allen N B, Caldwell D S, Rice J R, Polisson R P. Survival in systemic lupus erythematosus. A multivariate analysis of demographic factors. *Arthritis Rheum* 1987; **30**: 1326-32.
- 13 Esdale J M, Sampalis J S, Lacaille D, Danoff D. The relationship of socioeconomic status to subsequent health status in systemic lupus erythematosus. *Arthritis Rheum* 1988; **31**: 423-7.
- 14 Callahan L F, Pincus T. Associations between clinical status questionnaire scores and formal education level in persons with systemic lupus erythematosus. *Arthritis Rheum* 1990; **33**: 407-11.
- 15 Siegel M, Lee S L. The epidemiology of systemic lupus erythematosus. *Semin Arthritis Rheum* 1973; **3**: 1-54.
- 16 Hochberg M C. The incidence of systemic lupus erythematosus in Baltimore, Maryland, 1970-1977. *Arthritis Rheum* 1985; **28**: 80-6.
- 17 Fessel W J. Systemic lupus erythematosus in the community. *Arch Intern Med* 1974; **134**: 1027-35.
- 18 Michet C J, McKenna C H, Elveback L R, Kaslow R A, Kurland L T. Epidemiology of systemic lupus erythematosus and other connective tissue disease in Rochester, Minnesota, 1950 through 1979. *Mayo Clin Proc* 1985; **60**: 105-13.
- 19 Serdula M K, Rhoads G G. Frequency of systemic lupus erythematosus in different ethnic groups in Hawaii. *Arthritis Rheum* 1979; **22**: 328-33.
- 20 Catalano M A, Hoffmeier M. Frequency of systemic lupus erythematosus (SLE) among the ethnic groups of Hawaii. *Arthritis Rheum* 1989; **32**(suppl 4):S30.
- 21 Hart H H, Grigor R R, Caughey D E. Ethnic difference in the prevalence of systemic lupus erythematosus. *Ann Rheum Dis* 1983; **42**: 529-32.
- 22 Samanta A, Feehally J, Roy S, Nichol F E, Sheldon P J, Walls J. High prevalence of systemic disease and mortality in Asian subjects with systemic lupus erythematosus. *Ann Rheum Dis* 1991; **50**: 490-2.
- 23 Kaslow R A, Masi A T. Age, sex, and race effects on mortality from systemic lupus erythematosus in the United States. *Arthritis Rheum* 1978; **21**: 473-9.
- 24 Gordon M F, Stolley P D, Schinnar R. Trends in recent systemic lupus erythematosus mortality rates. *Arthritis Rheum* 1981; **24**: 762-9.
- 25 Lopez-Acuna D, Hochberg M C, Gittelsohn A M. Mortality from discoid and systemic lupus erythematosus in the United States, 1968-1978. *Arthritis Rheum* 1982; **25**(suppl):S80.
- 26 Reveille J D, Bartolucci A, Alarcon G S. Prognosis in systemic lupus erythematosus. Negative impact of increasing age at onset, black race, and thrombocytopenia, as well as causes of death. *Arthritis Rheum* 1990; **33**: 37-48.
- 27 Ward M M, Studenski S. Clinical manifestations of systemic lupus erythematosus. Identification of racial and socioeconomic influences. *Arch Intern Med* 1990; **150**: 849-53.
- 28 Lahita R G, Bradlow L, Fishman J, Kunkel H G. Estrogen metabolism in systemic lupus erythematosus: Patients and family members. *Arthritis Rheum* 1982; **25**: 843-46.
- 29 Hill P, Wynder E L, Helman P, Hickman R, Rona G, Kuno K. Plasma hormone levels in different ethnic populations of women. *Cancer Res* 1976; **36**: 2297-301.
- 30 Karlin S, Kenett R, Bonne-Tamir B. Analysis of biochemical genetic data on Jewish populations: II. Results and interpretations of heterogeneity indices and distance measures with respect to standards. *Am J Hum Genet* 1979; **31**: 341-65.