Clinical features and race-specific incidence/ prevalence rates of systemic lupus erythematosus in a geographically complete cohort of patients

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Abstract

***Objectives*—To assess race-specific incidence and prevalence rates for systemic lupus erythematosus (SLE) using 1991 National Census data and to ascertain the frequency of clinical/laboratory features of a geographically complete cohort of patients with SLE.**

***Methods*—Multiple methods of retrieval were used to ascertain SLE patients including screening request cards for immunology investigations. Patients were classified according to the revised ARA criteria. Multiple logistic regression analysis was used to study the effects of age at diagnosis on the frequency of clinical/laboratory SLE features.**

***Results*—The overall one year period prevalence rate for SLE was 24·7 (age adjusted, 95% CI: 20·7–28·8)/100 000. Highest rates were seen in Afro-Caribbeans (207 (111–302)/100 000), followed by Asians (48·8 (10·5–87·1)/100 000), and then Whites (20·3 (16·6–24·0)/100 000). The mean age at diagnosis of SLE was 40·9 years (range: 11–83) with a mean interval between first definite SLE symptom and diagnosis of 61 months (0–518). In 85% of patients the first definite lupus feature was musculoskeletal and/or cutaneous. In this SLE cohort renal disease (22%) was observed less commonly than in previous studies and the 'classic' butterfly rash was present in only 30% of patients. Malar rash, thrombocytopaenia, positive anti-dsDNA antibodies, hypocomplementaemia (C4), and positive IgG anticardiolipin antibodies were all seen less commonly with increasing age at diagnosis.**

***Conclusions*—A closer estimate of the true frequency of clinical/laboratory SLE manifestations is likely from this geographically complete cohort of patients compared with studies that may be skewed by referral patterns.**

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Previously published data concerning the epidemiology of systemic lupus erythematosus (SLE) in Nottingham, United Kingdom, from 1989–90[1] were analysed using estimated population figures based on the 1981 census. Recent data from the 1991 National Census now enables calculation of race-specific incidence and prevalence rates because the 1981 Census did not provide accurate information on ethnic background.

Many studies have reported the frequency of clinical features of SLE[2–5] but are often not representative of the actual spectrum of SLE because the cohort originated from tertiary referral centres. Such cohorts will contain a bias because they have usually arisen from centres with a particular speciality interest, for example, rheumatology or nephrology, and consequently may contain a more severe spectrum of SLE. To obtain an accurate frequency of manifestations, it is necessary to examine all patients with SLE that have been ascertained from a defined geographical area.[6 7] We have therefore defined the clinical, haematological, biochemical, and immunological characteristics of a geographically complete cohort of patients with SLE living in Nottingham. As the incidence of SLE in Nottingham is highest in females aged 40–49 and 50–59 years,[1] the effects of age at diagnosis on the frequency of clinical and laboratory SLE manifestations could also be studied.

Materials and methods

The study was approved by the local Ethics Committee. The study area was that of the Nottingham Health District, which is served by two main hospitals, the Queen's Medical Centre (QMC) and the City Hospital. An attempt was made to ascertain all patients with SLE residing in this area during the period 1 May 1989 to 30 April 1990.

STUDY AREA

The defined area approximates to the metropolitan community of Greater Nottingham, which consists of the districts of Nottingham, Broxtowe, Gedling, Rushcliffe, and the Hucknall wards of Ashfield.[1] Based on the 1991 census the population of the area was 601 693, with 14 276 Afro-Caribbeans, 16 323 Asians, and 1661 Chinese.[8] The age distribution and male:female ratio of the local population accords with that of the United Kingdom.[8] All the major social classes are represented with a similar distribution to the whole of England and Wales and the main industries in the area include mining, quarrying, and the manufacture of textiles,

chemicals, and tobacco.[9] The vast majority of patients are seen through the National Health Service, but patients with SLE seen privately were also ascertained by the methods outlined below.

ASCERTAINMENT OF PATIENTS

Six principal methods of ascertainment were used, the details of which have been published previously[1]:

1) Notification by physicians working at the two main Nottingham hospitals.
2) A register of patients with connective tissue disease collated in the immunology department.
3) Screening of immunology investigation request cards, with follow up of patients with positive anti-nuclear antibodies (ANA, titre $\geq$ 1:25) or antibodies to dsDNA and/or with clinical details on the card relevant to a diagnosis of SLE.
4) The Nottingham renal unit computer.
5) The inpatient medical records computer.
6) Screening of acute psychiatric and psychogeriatric inpatient admissions.[10]

Patients with definite or possible SLE from any of these sources and who resided in the study area were then contacted and invited to attend the hospital to see one of the investigators (NH).

PATIENT INTERVIEW

At interview, the diagnosis of SLE was confirmed or refuted based on the principals of Fries and Holman,[11] on the evidence of multisystem disease, immunological abnormalities (for example, positive ANA $\pm$ antibodies to dsDNA) and in the absence of a better diagnosis. The disease was then classified using the revised ARA criteria[12]; only patients satisfying four or more criteria were included in the study. Other information directly relating to SLE was sought at this time, including age at first symptom and diagnosis, and a history of the following SLE manifestations: malar rash; discoid rash; photosensitivity; oral ulcers; non-erosive arthritis; pleuritis; pericarditis; persistent proteinuria greater than 0·5 g per day or greater than 3+ on stick testing if quantitation not performed; seizures; psychosis; haemolytic anaemia; leucopaenia; lymphopaenia; thrombocytopaenia; anti-dsDNA antibodies; anti-Sm antibodies; anti-nuclear antibodies (all of the above were defined according to the ARA guidelines[12]). The presence of cellular casts was not ascertained and therefore this criterion was not included in the analysis. In addition the following features were ascertained with the assistance (where applicable) of a current blood test: Raynaud's phenomenon; Sicca syndrome, with an abnormal Schirmer's test; anti-RNP antibodies; anti-Ro antibodies; anti-La antibodies; positive rheumatoid factor; positive Lupus anticoagulant; hypocomplementaemia for C3 and C4; raised C3 degradation products; and positive anticardiolipin antibodies (IgG and/or IgM). To facilitate the recording of these disease features each patient was interviewed with their case records.

SOCIOECONOMIC STATUS

Three measures were used:

1) The occupation of the economically active person in the household of the patient was graded into five groups[13]: professional or managerial; intermediate; skilled manual or non-manual; semi-skilled manual; or unskilled manual. Certain individuals such as students could not be graded into these recognised groupings and therefore were not included.
2) Based on area of residence, an index of multiple disadvantage is available for Nottinghamshire.[14] This is calculated from indicators of low income, unemployment, lack of skills, poor housing, poor health and family/educational problems. There are four levels of disadvantage, below average, moderate, serious, and extreme.
3) Residence status for each patient was assessed (that is, whether or not they owned their home, were a council tenant, or rented accommodation from a landlord).

LABORATORY METHODS

Anti-nuclear antibodies Sera were screened at a 1:10 dilution on a rat liver substrate by indirect immunofluorescence using polyvalent anti-human Ig. Positive sera were then titred using monovalent anti-sera to IgG and IgM.

Anti-dsDNA antibodies Two methods were used which involved: a) *Crithidia lucilliae* substrate by an indirect immunofluorescence; and b) an ELISA procedure (Diamedix Corporation, Florida).

Antibodies to extractable nuclear antigens These were identified by counter-current electrophoresis using rabbit thymus extract and human spleen extract on agarose gel, antibodies were specified using appropriate reference sera characterised from CDC standards (Centres for Disease Control, Atlanta, USA).

Rheumatoid factor Using the Rose-Waaler assay, with a titre $\geq$ 1:16 considered positive.

Plasma C3 degradation products (C3dg) This was performed using double-decker rocket immuno-electrophoresis through anti-C3c and anti-C3d (Dako).

Anti-Cardiolipin antibodies These were identified by an ELISA method as described by Gharavi *et al*,[15] and validated against international workshop standards obtained from the Rayne Institute, St Thomas's Hospital, London.

Lupus anticoagulant Detected by measuring the effect of patients' plasma on the kaolin clotting time of normal plasma.[16]

Plasma C3 and C4 complement levels Assayed by fluid phase turbidimetry.

STATISTICS

All data were stored on a mainframe computer and analyses were performed using SPSS-X3

Table 1 Race- and age-specific one year period prevalence rates for SLE

Age group	White		Asian		Afro-Caribbean		Chinese	
	No	Rate (/100 000)	No	Rate (/100 000)	No	Rate (/100 000)	No	Rate (/100 000)
0–9	0	–	0	–	0	0	0	–
10–19	1	1·5	1	29·0	0	–	1	358·4
20–29	14	15·2	0	–	4	128·0	0	–
30–39	18	22·9	3	112·6	3	159·7	1	304·9
40–49	30	38·9	1	59·0	7	767·5	0	–
50–59	24	39·3	2	159·5	6	382·2	0	–
60–69	23	38·1	0	–	1	100·4	0	–
70–79	4	9·8	0	–	0	–	0	–
≥80	3	1·4	0	–	0	–	0	–
ALL	117	20·5	7	42·9	21	147·1	2	120·4
Age S	117	20·3 (16·6–24·0)	7	48·8 (10·5–87·1)	21	207·0 (111–302)	2	92·9 (0–222)

ALL = Crude rate. Age S = Age standardised to a European population.

(Statistical Package for the Social Sciences) software. Age-standardised incidence and prevalence rates have been calculated based on a European population as a standard.[17]

Investigation of the relationship between individual clinical and immunological manifestations with age was performed using multivariate logistic regression by the method of maximum likelihood estimation. Each manifestation, coded dichotomously as present or absent for each patient, was used as the dependent variable in the regression model. Independent variables for each manifestation included: age at time of diagnosis of SLE (continuous variable); racial group (divided into White or non-White); sex; and length of follow up (in months). Preliminary logistic regression analyses found significant individual associations between each of four treatments with age: hydroxychloroquine; prednisolone; azathioprine; and cyclophosphamide. Thus each of these treatments was used in the regression model. All analysis was performed on Egret statistical software[18] and p values, odds ratios, and 95% confidence intervals derived. For each model, linearity of data was confirmed by using the quadratic function of age at diagnosis in the 'likelihood ratio test'.

Results

DEMOGRAPHIC FEATURES

A total of 147 patients were resident in the study area on 30 April 1990. Of these patients, 117 (80%) were White, 21 (14%) were Afro-Caribbean, 7 (5%) were Asian, and 2 (1%) were Chinese/Oriental. There were 136 females and 11 males. The mean age at disease onset, defined as the date of the first unequivocal SLE manifestation was 35·1 years (range: 11–75) overall, 34·6 (11–75) years for females, and 41·6 (18–68) years for males. The mean age at diagnosis of SLE was 40·9 years (11–83) overall, 40·4 years (11–83) for females, and 47·4 (21–70) for males. The mean interval between first symptom and diagnosis was 61 months (0–518).

Table 2 Race- and age-specific annual incidence rates for SLE

Age group	White		Asian		Afro-Caribbean	
	No	Rate (/100 000)	No	Rate (/100 000)	No	Rate (/100 000)
0–9	0	–	0	–	0	–
10–19	0	–	1	29·0	0	–
20–29	3	3·3	0	–	0	–
30–39	2	2·6	0	–	0	–
40–49	4	5·2	0	–	1	109·6
50–59	6	9·8	0	–	2	127·4
60–69	3	5·0	0	–	0	–
70–79	1	2·5	0	–	0	–
>80	0	–	0	–	0	–
ALL	19	3·3	1	6·1	3	21·0
Age S	19	3·4 (1·8–4·9)	1	4·1 (0–12·0)	3	31·9 (0–69·8)

ALL = Crude rate. Age S = Age standardised to a European population.

PREVALENCE

The overall age-standardised one year period prevalence rate for SLE was 24·7 (20·7–28·8; 95% confidence interval), 45·3 (37·6–53·0)/100 000 for females, and 3·7 (1·5–5·9)/100 000 for males (female:male ratio 12:1). Crude age- and race-specific one year period prevalence rates together with total number of cases are shown in table 1. Notably there were no male Afro-Caribbean patients with SLE. The highest age-specific prevalence rate was 1·3% and was seen in Afro-Caribbean females aged 40–49.

INCIDENCE

The overall age-standardised annual incidence rate was 4·0 (2·4–5·7)/100 000, 6·5 (3·6–9·5)/100 000 for females and 1·5 (0–2·9)/100 000 for males). Numbers of incident cases and crude age- and race-specific incidence rates are shown in table 2.

RACE-SPECIFIC RATES

The annual incidence rates and one year period prevalence rates were applied to a standard European population and these age-standardised rates are shown in tables 1, 2.

SOCIOECONOMIC STATUS

Indices of socioeconomic status varied between racial group: 50% of Asians and 57% of Afro-Caribbeans lived in areas of moderate to severe disadvantage compared with 34% of Whites. By occupation, 28·6% of Whites and Asians were Professional/Managerial or intermediate compared with 14·3% of Afro-Caribbeans. All Asian patients owned their houses, however, only 76% Whites and 67% Afro-Caribbeans were owner-occupiers. Indices of socioeconomic status are not available for healthy persons by different ethnic group but we have previously shown that occupational status and disadvantage score were similar for the SLE population and the total population in the study area.[1]

Table 3 First definite manifestations of SLE in the 147 patients resident in the study area

System	No	%	Manifestation	No
Musculoskeletal	92	63	Arthritis/arthralgia	92
Cutaneous	44	30	Malar rash	16
			Discoid rash	6
			Photosensitivity	34
Musculoskeletal and cutaneous	11	7		
Mucosal surface	23	16	Oral/nasopharyngeal ulcers	23
Haematological	9	6	Leucopaenia	3
			Lymphopaenia	5
			Thrombocytopaenia	3
Serositis	6	4	Pleurisy	6
Neuro-psychiatric	3	2	Seizures	3
Renal	1	1	Nephrotic syndrome	1

FIRST DEFINITE LUPUS FEATURES

The first definite lupus feature in each patient is shown in table 3 and as some patients synchronously developed symptoms related to more than one organ system, more than 147 features are represented in the columns. For 85% of patients the first definite lupus feature was either musculoskeletal or cutaneous.

CUMULATIVE FREQUENCIES OF LUPUS CLINICAL FEATURES AND LABORATORY FINDINGS

The cumulative disease manifestations are shown in table 4 and 5, and are compared with previous series.[3 5 6 19] Important differences are the lower frequency of renal disease, malar/discoid rash, leucopaenia and thrombocytopaenia. In comparison with the study by Worral *et al*, these authors chose to use a total white cell count of less than $4{\cdot}5 \times 10^9$/L and a platelet count of less than 150 000/mm^3 as being significant, which differ from the conventional values in the ARA criteria. A higher frequency of Raynaud's phenomenon in this study was also observed. Only 54% of SLE patients had anti-dsDNA antibodies by *Crithidia lucilliae* and/or ELISA, and anti-Sm antibodies were infrequent (3%).

Table 4 Cumulative percentage frequencies of SLE manifestations in the two patient cohorts compared with other studies

Feature	Study area cohort (N = 147)	Worrall et al (1990)	Nived et al (1985)	Lee et al (1977)
Geographically complete	Yes	No	Yes	No
Female	93	96	88	85
White	82	63	N/A	96
Afro-Caribbean	12	21	N/A	1
Malar rash	30	90	43	36
Discoid rash	10		23	8
Photosensitivity	51	48	54	50
Naso-pharyngeal ulcers	37	36	14	29
Arthritis	91	94	97	62
Pleurisy	27	57	54	31
Pericarditis	10			25
Proteinuria (>0·5 g/day)	22	29	34	74
Seizures	7	9	9	7
Psychosis	2	3		16
Lymphopaenia	80	82	N/A	N/A
Leucopaenia	29	56	N/A	42
Thrombocytopaenia	6	21	N/A	16
Haemolytic anaemia	4	2	N/A	14
Sjögren's syndrome	19	22	18	N/A
Raynaud's phenomenon	65	N/A	40	46

Table 5 Percentage cumulative frequency of immunological features of SLE in the 147 patients compared with other studies

Feature	Study area cohort (n = 147)	Worrall et al (1990)	Jonsson et al (1988)
Geographically complete	Yes	No	Yes
ANA	97	99	100
Anti-dsDNA	54	55	73
Anti-Sm	3	7	12
Anti-RNP	22	19	24
Anti-Ro	30	39	44
Anti-Ro and La	11	13	18
+ve rheumatoid factor	41	27	10
Low C3	32	N/A	N/A
Low C4	37	N/A	N/A
Raised C3dg	69	N/A	N/A
Positive lupus anticoagulant	13	19	N/A
IgG anti-cardiolipin abs	25	38	43
IgM anti-cardiolipin abs	30		

Table 6 The effect of age at diagnosis on the frequency of selected clinical and immunological abnormalities

Clinical feature	Adjusted OR	95% CI
Malar rash	0·96	0·93–0·98
Discoid rash	0·98	0·95–1·02
Photosensitivity	0·98	0·96–1·00
Oral ulcers	0·99	0·96–1·01
Arthritis	1·00	0·96–1·04
Proteinuria	1·00	0·97–1·04
Thrombocytopaenia	0·95	0·90–0·99
Anti-dsDNA antibodies	0·96	0·94–0·99
Anti-Ro antibodies	0·97	0·94–1·00
Low C3	0·97	0·95–1·00
Low C4	0·97	0·94–0·99
IgG anti-Cardiolipin abs	0·96	0·93–0·98
IgM anti-Cardiolipin abs	0·99	0·97–1·02

OR = Odds ratios. These indicate annual incremental/decremental changes in the risk of having each clinical/laboratory manifestation. A significant association at the 5% level is indicated by 95% CIs that do not include the value 1·0.

THE EFFECT OF INCREASING AGE AT DIAGNOSIS ON THE FREQUENCY OF CLINICAL AND LABORATORY MANIFESTATIONS

Adjusted odds ratios (OR) and 95% confidence intervals (CI) for the association or selected manifestations and age is shown in table 6. The ORs indicate annual incremental/decremental changes in the risk of having each clinical/laboratory manifestation. For example, the risk of a patient diagnosed as having SLE at age 45 years of getting a malar rash (OR = 0·96) would be decreased by 4% compared with a patient diagnosed at 44 years old. A significant association at the 5% level is indicated by 95% CIs that do not include the value 1·0. Malar rash, thrombocytopaenia, hypocomplementaemia (for C4, but not C3), antibodies to dsDNA, and IgG anticardiolipin antibodies were less common with increasing age at diagnosis. No differences were observed for the other manifestations tested including: discoid rash; proteinuria, Raynaud's phenomenon; pleurisy; and pericarditis.

Discussion

We have noted marked variation in the frequencies of SLE amongst differing racial groups, and the increased prevalence of SLE in Asians compared with White groups has also been recorded in Leicester,[20] a city 25 miles south of the study area, and in Birmingham, 60 miles south-west of Nottingham.[21] In the Birmingham study, SLE was most common amongst Afro-Caribbeans which agrees with the Nottingham findings.[21] Although prevalence rates are similar in all three cities, annual incidence rates are higher in Nottingham (females: 6·5/100 000) compared with Birmingham (females: 2·3/100 000). This may reflect a genuine difference in SLE frequency or differences in case ascertainment. However, it is notable that both these incidence rates are still lower than those observed in

several cities within the USA.[22] Indices of socio-economic status do show differences between Whites and Afro-Caribbeans, but whether environmental factors or differences in health care utilisation, rather than host factors, explain the higher prevalence of SLE in Afro-Caribbeans awaits further investigation.

The validity of studies like this critically depend on having a complete cohort of patients living in a defined area which leads to an accurate reflection of the clinical features of SLE. Reliable estimates of frequencies of SLE clinical manifestations will also depend on the follow up period of each individual. For example, the clinical features of a patient with SLE diagnosed 20 years previously is more likely to be complete compared with a recently diagnosed patient. The mean duration of disease from first symptom to time of analysis in this study was 135 months, with a range of 2–560 months.

The frequency of individual clinical manifestations of SLE in this study can be compared to other series which have also analysed a complete geographical cohort. In two Swedish studies of the same population that were geographically complete,[6 19] the occurrence of many lupus features was similar. There was however, a lower frequency of both nephritis and serositis in Nottingham contrasting with mouth ulcers and Raynaud's phenomenon which were more commonly observed in our study. When comparing populations of different genetic stock it would be surprising if differences were not observed; the frequency of both mouth ulcers and serositis in this study is similar to that seen in Leicester, United Kingdom.[21] The frequency of clinical features in this complete cohort contrast with those depicted in medical textbooks. For example, the facial butterfly rash, classically associated with SLE, occurs in just 30% of patients. Stark contrasts can be drawn between the clinical features of a geographically defined SLE cohort and one collected from an organ based specialist unit; for example, renal involvement was noted in only 22% of patients in this study contrasting with Lee *et al*[3] who recorded nephritis in 74% of cases. The frequency of seizures (7%) and psychosis (2%) was low compared to both older (14%)[2] and more recent studies (13%).[23]

The frequency of antibodies to dsDNA (54%, using a *Crithidia Lucilliae* and ELISA assay) accords well with other studies.[5 6] Several patients had negative results using a *Crithidia* assay, but positive using a commercially available dsDNA ELISA assay confirming the reduced sensitivity of the *Crithidia Lucilliae* assay. This is likely to contribute to the lower frequency of anti-dsDNA antibodies (28%) in some previous studies in which these antibodies were detected only by the *Crithidia* assay.[23]

In Nottingham, the highest incidence of SLE is seen in the 40–59 year age group[1] and malar rash, thrombocytopaenia, hypocomplementaemia (C4), antibodies to dsDNA, and IgG anti-cardiolipin antibodies have been shown to be less common with increasing age at diagnosis. No relationship with frequency of renal disease was identified but this may be because of the low total number of SLE patients with proteinuria. Multivariate logistic regression analysis permits control of potential confounding factors allowing age at diagnosis to be a continuous variable, rather than forming arbitrary division. The manifestations that vary with age at diagnosis accord well with the findings of Ward and Studenski,[24] who used a similar analytical approach. Our study did not specifically address severity of disease but a relationship between antibodies to dsDNA and hypocomplementaemia with clinical exacerbations in SLE is well established.[25 26] It is therefore reasonable to imply that SLE presenting at an older age may be a milder disease contrasting with the sick young SLE patient with a butterfly rash.

In summary, this is the first study in the UK to present frequencies of SLE clinical manifestations in a complete cohort of patients living in a geographically defined area. Serious manifestations of SLE such as renal disease and particularly seizures and psychosis are not common.

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Addendum

There was en error in our previous publication.[1] Table 5 should read as follows:

Ethnic	*SLE patients* (%)*	*Total population in study area (%)*
Caucasian	79·6	95·9
Afro-Caribbean	14·3	2·1
Asian	4·8	2·0

*A further two patients with SLE were Chinese-Oriental.

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