Juvenile, adult and late-onset systemic lupus erythematosus: A long-term follow-up study from a geographic and ethnically homogeneous population

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Abstract

Objectives

This paper aims to identify clinical and serological differences, damage accrual and mortality, in juvenile, adult and late-onset SLE.

Methods

We conducted our study with patients fulfilling SLE classification criteria taken from the Hospital Gregorio Marañon Autoimmune Systemic Rheumatic Diseases' Registry (1986 to 2012). Clinical characteristics, laboratory data and therapies used during the course of the disease were analysed with patients divided into 3 groups: juvenile-onset (≤18 years), adult-onset (19–50) and late onset (>50 years).

Results

Four hundred and forty-five patients were included. Renal disease and cutaneous manifestations were more frequent in the juvenile-onset group at disease onset. During follow-up, juvenile-onset group presented a higher incidence of renal disease, malar rash, Raynaud's phenomenon, cutaneous vasculitis, and neuropsychiatric manifestations than the other two groups. Arthritis and lymphopoenia were more frequent in the adult-onset group. Arterial hypertension and neoplasm were more frequent in the late-onset group. Low serum complement, anti-dsDNA, anti-U1RNP and anti-Sm antibodies were more common in the juvenile-onset group. Patients with late-onset SLE had more damage accrual. Thirty-seven patients (8.3%) died during the study. All-cause mortality was significantly higher in the late-onset group. Age at disease onset >50 years was an independent risk factor for damage accrual (OR, 2.2; 95%CI, 1.1–4.6; p=0.029) and mortality (OR, 2.6; 95%CI, 1.1–6.3; p=0.03).

Conclusion

We found significant differences in clinical and serological profiles between juvenile, adult and late-onset SLE. The most significant of which was a higher prevalence of neuropsychiatric and renal complications as well as different autoantibody signatures for the juvenile-onset group.

Key words

systemic lupus erythematosus, age of onset, clinical profile, immunological profile, damage accrual, mortality

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Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune disease with a wide range of clinical manifestations. Symptoms can appear during childhood, adulthood or late in life and may vary depending on the age at onset (1). Several authors have shown that the expression and severity of the disease are related to age of onset (2-17). Independent comparative studies (6, 7, 10) support the hypothesis that SLE in children is more active than SLE in adult patients, with a higher frequency of renal involvement, neuropsychiatric manifestations and anti-dsDNA. In addition, the disease progresses with a more rapid damage accrual in children. Other authors report inconsistent results between cohorts (11, 13, 15), suggesting that late-onset SLE patients may have more damage accrual but similar clinical profiles when compared to younger patients. These discordant results may be due to genetic and environmental differences in the studied populations. As previously shown in cohorts such as LUMINA (Lupus in Minorities: Nature *versus* Nurture) (17-19), GLADEL (Grupo Latinoamericano de estudio del Lupus) (20) and others (21-23), there is a great variability in clinical manifestations and disease severity between different ethnic groups. Therefore, data from an ethnically homogeous group may be able to elucidate more clearly disease manifestation. Previously (7), we showed that juvenile- and adult-onset lupus were clinically and immunologically different. In the present study, we aimed to identify clinical and serological differences in juvenile-, adult-onset and late-onset SLE. This study was carried out within a large, ethnically homogenous group which is, to the best of our knowledge, one of the largest monocentre cohorts described.

Methods

All patients fulfilling at least 4 of the American College of Rheumatology (ACR) classification criteria for SLE (24) between 1986 and 2012 were included in the "Autoimmune Systemic Rheumatic Diseases Registry" of the Hospital General Universitario Gregorio Marañon Rheumatology Department, a registry of 2406 patients diagnosed with autoimmune rheumatic diseases. Our register comprises data gathered on a large number of patients of a similar ethnic, geographic and socioeconomic background who underwent common treatment protocols. One of the main purposes of the registry is to determine the frequency of SLE manifestations and their relationship with the main autoantibodies in our environment, with particular attention to manifestations at disease onset, cardiovascular and infectious complications, malignancies and adverse effects of the different treatments used.

For this study, we included patients from the registry who fulfilled the following criteria: SLE diagnosis (24), Caucasian race and having had at least 10-years of disease duration prior to 2012, the end of the study period.

Data were collected prospectively from 1986 to 2012 including patient demographics, clinical symptoms, co-morbidities, cardiovascular risk factors, serological laboratory data and management characteristics of the patients according to a pre-defined protocol at onset and during the course of the disease. The clinical protocol remained the same throughout the whole observation period. All patients underwent a clinical assessment every 4 months as inpatients or outpatients. Institutional Review Board approval was obtained before the study began.

The clinical variables recorded were as follows:

1. characteristics at disease onset (first SLE-related symptoms or signs presented at diagnosis or during the first year of the disease);
2. characteristics during the course of the disease (data still present or appearance after 1 year of the disease);
3. systemic autoimmune diseases in first- and second-degree relatives including SLE, rheumatoid arthritis, systemic sclerosis, polymyositis, Sjögren's syndrome and primary antiphospholipid syndrome;
4. cumulative manifestations and therapies during the course of the disease (NSAIDs, antimalarials, steroids, immunosuppressive therapy and anticoagulants).

Patients were considered to have had a SLE manifestation when symptoms or signs defined by classification (24), damage criteria of SLE (25, 26) or activity criteria (27, 28) or text-book definitions (29, 30) appeared. Antiphospholipid syndrome (APS) was defined by the Sydney criteria (31) and Sjögren's syndrome was considered present as defined by European criteria (32).

An infection that requires hospitalisation was defined as severe. No specific protocol was used to rule out neoplasm in every patient, screening for specific malignancies was applied based on current recommendations at that time.

Complete blood count, biochemistry with liver and kidney profile, urine sediment, complement and immunoglobulin levels and anti-double-stranded deoxyribonucleic acid (dsDNA) were performed at each visit. Serum samples were tested, at least twice, for the presence of other autoantibodies at disease onset or during evolution. If tests resulted both positive or both negative, a third test was performed only in the event of new disease symptoms.

Non-organ-specific autoantibodies were investigated using indirect immunofluorescence (titers >1:80), which was performed according to standard procedures on cryostat sections of rat tissues (kidney, liver, and stomach) and in cultured HEp-2 cells (Mardx Diagnostics, Carlsbad, CA, USA) using a fluorescein-conjugated from rabbit to human (DAKO, Copenhagen, Denmark). Titers of antibodies to dsDNA were measured using radioimmunoassay (Anti-dsDNA kit IM77, Kodak Clinical Diagnostics Ltd, Amersham, UK); levels higher than 20 IU/ml indicated a positive result. Rheumatoid factor (>20 iu/ml) was measured using nephelometry (Beckman, Fullerton, CA, USA).

Sera were also studied for anti-dsDNA, anticardiolipin, anti-nRNP, anti-Sm, anti-Ro/SS-A, and anti-La/SS-B antibodies by enzyme-linked immunosorbent assay (ELISA). The inter-test variability determined between local laboratories during the study period was <5%. The ELISA methods could simultaneously detect IgG, IgM, and IgA (Rheuma ELISA TM System, Whittaker Bioproducts, Walkersville Maryland, USA) or IgG only (EIA gen Combi 4 kit, IFCI Clonesystems SpA, Casalecchio Di Reno, Bologna, Italy). Sera were diluted at 1:100. The optical density (OD) values were the arithmetic means of the OD 450 nm values obtained for each sample tested in duplicate. The cut-off was defined as a mean value of 90 normal controls plus a 3-fold standard deviation. The average intra- and inter-plate coefficients of variation were less than 5%.

Index organ damage was scored using the Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index (SDI) (25, 26). The last index scored was used for this analysis.

Patients were divided into 3 groups in line with age boundaries previously used (7, 8, 10): juvenile onset (≤18 years); adult onset (19–50 years); and late onset (>50 years).

Statistical analysis

Data were analysed using SPSS software, version 19 (SPSS, Chicago, IL, USA). Results were expressed as mean±SD for continuous variables and as frequencies (percentages) for binary and categorical variables. Clinical and laboratory findings from the 3 groups were compared using the chi-square test and a 1-way analysis of variance was applied for normally distributed quantitative variables; otherwise, the Kruskal-Wallis test was used. Damage accrual was defined as an SDI ≥1 and reported as a percentage and mean±SD value. The association between variables at diagnosis and during the disease course with accrual damage or mortality were assessed using bivariate analysis. The strongest independent predictor variables were identified by logistic regression analysis, using variables derived from bivariate analysis. The best-fit model was determined using the Enter method.

Results

Demographic features and clinical features at disease onset

A total of 501 SLE patients were recruited from 1986 to 2012, but only 445 (89%) completed more than 10 years of disease duration by 2012 (Table I shows classical ACR manifestations and other frequent disease features). The ratio of female to male patients differed significantly between the 3 groups (juvenile-onset, 6.1:1; adult-onset, 8.9:1; and late-onset, 3.5:1). Differences in family history of autoimmune diseases did not reach statistical significance between groups, although a higher frequency was observed in the juvenile-onset group than in the adult-onset and late-onset groups (16.3%, 10.5%, and 5.2%, respectively, $p>0.05$). Mean disease duration was significantly longer in the juvenile-onset group than in the late-onset group. Renal disease and cutaneous manifestations were more frequent in the juvenile-onset group at disease onset (17.4%, $p=0.023$ and 39.1%, $p<0.001$, respectively).

Clinical and laboratory features during follow-up

There were no significant differences in the number of patient visits or testing carried out on each study group (data not shown). Sjögren's syndrome tended to be more frequent in the late-onset group but differences were not statistically significant (0%; 4.3% and 5.2%, $p>0.05$).

During the follow-up (Table I), the juvenile-onset group continued to have a higher frequency of renal disease (63%, $p<0.001$). A total of 126 renal biopsies were performed at disease onset or during evolution based on clinical criteria, 9 biopsies were inconclusive, histological nephritis subtypes using World Health Organisation (WHO) classification (33) are described in Table 2. Malar rash (52.2%, $p<0.001$), Raynaud's phenomenon (42.2%, $p=0.008$), cutaneous vasculitis (32.6%, $p=0.006$), and neuropsychiatric manifestations (40.2%, $p=0.044$) were more common in the juvenile-onset group than in the other two groups. Arthritis and lymphopoenia were more frequent in the adult-onset group than in the other groups (92%, $p=0.031$ and 51.4%, $p=0.005$, respectively). Arterial hypertension and malignancy were more frequent in the late-onset group (40.3%, $p=0.48$ and 11.7%, $p=0.01$, respectively). The most common malignancy seen was uterine cervical cancer

Table I. Demographic and clinical characteristics of SLE patients with juvenile, adult or late-onset disease.

	Juvenile Onset (≤18 years) (n=92)	Adult Onset (19-50 years) (n=276)	Late Onset (>50 years) (n=77)	*p*-value
Sex, female (%)	79 (85.8)	248 (89.8)	60 (77.9)	0.021
Age, years, mean (range)	12.9 (7-18)	31.9 (19-50)	61.2 (51-86)	<0.001
Disease duration, mean±SD	13.2 ± 8.8	12.6 ± 8.6	10.0 ± 7.5	0.028
At disease onset				
Renal manifestations (%)	16 (17.4)	23 (8.3)	5 (6.5)	0.023
Cutaneous manifestations (%)	36 (39.1)	93 (33.7)	8 (10.4)	<0.001
During evolution of disease				
Malar rash (%)	48 (52.2)	130 (47.1)	17 (22.1)	<0.001
Discoid rash (%)	17 (18.5)	44 (15.9)	7 (9.1)	0.212
Photosensitivity (%)	40 (43.5)	147 (53.3)	31 (40.3)	0.065
Oral ulcers (%)	41 (44.6)	128 (46.4)	31 (40.3)	0.632
Arthritis (%)	78 (84.8)	254 (92.0)	64 (83.1)	0.031
Serositis (%)	26 (28.3)	88 (31.9)	27 (35.1)	0.635
Renal disorder (%)	58 (63.0)	124 (44.9)	22 (28.6)	<0.001
Neuropsychiatric manifestations (%)	37 (40.2)	75 (27.2)	20 (26.0)	0.044
Raynaud's phenomenon (%)	39 (42.4)	82 (29.7)	16 (20.8)	0.008
Antiphospholipid syndrome (%)	11 (12.0)	59 (21.4)	14 (18.2)	0.133
Cutaneous vasculitis (%)	30 (32.6)	56 (20.3)	10 (13.0)	0.006
Hypertension (%)	35 (38.0)	77 (27.9)	31 (40.3)	0.048
Neoplasm (%)	2 (2.20)	13 (4.7)	9 (11.7)	0.017
Damage accrual, SDI ≥1 (%)	63 (68.5)	176 (63.8)	61 (79.2)	0.037
SDI, mean±SD	1.86 ± 2.2	1.67 ± 2.0	2.47 ± 2.5	0.019
Mortality (%)	7 (7.6)	17 (6.2)	13 (16.9)	0.009

SLE: systemic lupus erythematosus; SDI: Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index.

Table II. Laboratory tests characteristics of SLE patients with juvenile, adult or late-onset disease.

	Tested	Juvenile Onset (≤18 years) (n=92) n (%)	Adult Onset (19-50 years) (n=276) n (%)	Late Onset (>50 years) (n=77) n (%)	*p*-value
Renal Biopsy (WHO classification)	126	46 (36.5)	67 (53.2)	13 (10.3)	<0.001
Class I	6	2 (4.3)	4 (6)	0 (0)	N/A
Class II	9	4 (8.7)	4 (6)	1 (7.7)	N/A
Class III	15	9 (19.6)	5 (7.4)	1 (7.7)	N/A
Class IV	61	24 (52.2)	33 (49.2)	4 (30.8)	0.387
Class V	26	6 (13)	16 (23.9)	4 (30.8)	0.239
Anaemia	445	57 (62)	156 (56.5)	38 (49.4)	0.258
Leucopoenia	445	51 (55.4)	142 (51.4)	30 (39)	0.079
Lymphopoenia	445	27 (29.3)	134 (48.6)	31 (40.3)	0.005
Thrombocytopoenia	445	22 (23.9)	62 (22.5)	13 (16.9)	0.496
Low serum complement	432	80 (87)	220 (81.2)	40 (58)	<0.001
Increased immunoglobulin	445	38 (56.2)	155 (56.2)	37 (48.1)	0.037
ANA	445	92 (100)	269 (97.5)	71 (92.2)	N/A
Anti-dsDNA	431	75 (82.4)	198 (72.8)	37 (54.4)	<0.001
Anticardiolipin	347	35 (49.3)	127 (55.7)	29 (60.4)	0.461
Lupus anticoagulant	134	14 (46.7)	32 (34.8)	4 (33.3)	0.483
Rheumatoid factor	418	27 (30.7)	100 (38.6)	34 (47.9)	0.086
ELISA anti-U1RNP	412	41 (46.1)	84 (32.4)	19 (29.7)	0.042
ELISA anti-Sm	412	23 (25.8)	42 (16.2)	7 (10.9)	0.039
ELISA anti-SSA/Ro	421	29 (32.6)	110 (41.8)	27 (39.1)	0.304
ELISA anti-SSB/La	421	12 (13.5)	44 (16.7)	16 (23.2)	0.266

SLE: systemic lupus erythematosus; WHO: World Health Organisation; N/A: not applicable; ANA: anti-nuclear antibodies; dsDNA: double strand DNA; ELISA: enzyme-linked immunosorbent assay.

followed by nephro-urological, lymphoma, breast and skin cancer (8, 3, 3, 2 and 2 cases, respectively) we also observed 6 isolated cases of other solid neoplasms.

No significant differences were found between the three groups when examining secondary antiphospholipid syndrome and severe infections ($p>0.05$). Treatments administered were similar in the three groups, both, used standard drugs (*i.e.* NSAIDs, antimalarials, glucocorticoids, immunosuppressive and anticoagulant agents) and dosages; cumulative doses were not collected in the registry.

Low serum complement (87%, $p<0.001$), anti-dsDNA (82.4%, $p<0.001$), anti-U1RNP (46.1%, $p=0.042$) and anti-Sm antibodies (25.8%, $p=0.039$) were more common in the juvenile-onset group. Table II provides a complete summary of complementary tests. Increased immunoglobulin levels were less common in the late-onset than in juvenile-onset SLE patients (48.1%, $p=0.037$).

Disease damage accrual and mortality

The mean SDI score at the end of the follow-up period was 2 (SD 2.23) in the total group. Three hundred patients (67.4%) had a SDI ≥1. Based on the mean SDI scores, patients with late-onset SLE had more damage than patients in the other 2 groups (2.47, $p=0.019$) (Table I). Thirty-seven patients (8.3%) died during the study. Main causes of death were cardiovascular disease and infections. All-cause mortality was significantly higher in the late-onset group than in the juvenile- and adult-onset groups (16.9%, 7.6% and 6.2% respectively, $p=0.009$) (Table I).

When the whole cohort was examined based on the presence of damage accrual, a significant association was found for hypertension, Raynaud's phenomenon, fever, cutaneous vasculitis, antiphospholipid syndrome, anaemia, thrombocytopenia, age at disease onset >50 years, male sex, and anti-dsDNA at the univariant analysis (Table III). A longer disease course and the presence of anti-SSA/Ro and anti-SSB/La were related to a lower frequency of damage accrual (Table III). Neither medication

nor other co-morbidities were identified as predictors of SLE outcome. A multivariate logistic regression model revealed hypertension (OR, 4.7; 95%CI 2.6–8.6; $p<0.001$), cutaneous vasculitis (OR, 3; 95%CI 1.6–5.9; $p=0.001$), thrombocytopoenia (OR, 2.3; 95%CI 1.2–4.4; $p=0.01$), Raynaud's phenomenon (OR, 2; 95%CI 1.2–3.5; $p<0.009$), and age at disease onset >50 years (OR, 2.2; 95%CI 1.1–4.6; $p<0.029$) to be independent risk factors for damage accrual.

Univariant analysis revealed a higher probability of mortality for male and patients with age at disease onset >50 years, SDI≥1, anticardiolipin IgG, neoplasm, antiphospholipid syndrome, serositis and neuropsychiatric, haematologic, hypertension, pulmonary and musculoskeletal manifestations (Table IV). The multivariate analysis revealed the independent predictors of mortality to be musculoskeletal manifestations (OR, 2.4; 95%CI 1.1–5.4; $p=0.03$), damage accrual (OR, 12; 95%CI 1.6–92; $p=0.01$) and age at onset >50 years (OR, 2.6; 95%CI 1.1–6.3; $p=0.03$).

In the multivariate analysis no disease manifestations at onset were found to be an independent risk factor for damage accrual nor mortality.

A sub-analysis (data not shown) of damage accrual based on year of disease onset (dividing by periods of 5 years) demonstrated that patients enrolled in the registry before 1996 had a higher SDI ($p<0.001$) that patients enrolled after 1996. No significant differences were observed regarding mortality.

Table III. Univariant and multivariant analysis of clinical and laboratory features related to damage accrual.

	SDI=0 (%)	SDI≥1 (%)	OR (95%CI)	*p*-value
Age at onset (>50 years)*	11.0	20.4	2.1 (1.1-3.7)	0.010
Male sex	8.3	15.3	2.0 (1.0-3.9)	0.040
Disease duration, mean±SD	13.8 ± 8.9	9.2 ± 6.5	0.93 (0.9-0.95)	<0.001
Features during disease evolution				
Hypertension*	11.7	42.0	5.4 (3.1-9.5)	<0.001
Raynaud's phenomenon*	21.4	35.3	2.0 (1.3-3.2)	0.003
Fever	26.9	39.7	1.8 (1.1-2.7)	0.009
Cutaneous vasculitis*	10.3	27.0	3.2 (1.8-5.8)	<0.001
Anemia	44.8	62.0	2.0 (1.3-3.0)	0.001
Antiphospholipid syndrome	7.6	24.3	3.9 (2.0-7.6)	<0.001
Thrombocytopoenia*	14.5	25.3	2.0 (1.1-3.4)	0.010
ELISA anti-SSA/Ro	50.7	34.0	0.5 (0.3-0.8)	0.001
ELISA anti-SSB/La	26.5	12.6	0.4 (0.2-0.7)	0.001
Anti-dsDNA	62.9	76.4	1.9 (1.2-2.9)	0.004

SDI: Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index; dsDNA: double strand DNA; ELISA: enzyme-linked immunosorbent assay. *Independent risk factors for damage accrual in the multivariant analysis, OR and 95%CI are shown in the results section.

Table IV. Univariant and multivariant analysis of clinical and laboratory features related to mortality.

	Dead (%)	Alive (%)	OR (95%CI)	*p*-value
Serositis	48	30	2.2 (1.1-4.3)	0.022
Neuropsychiatric manifestations	46	28	2.1 (1.1-4.3)	0.024
Haematologic disorder	94	79	4.6 (1.1-19.8)	0.030
Hypertension	51	30	2.4 (1.2-4.7)	0.009
Pulmonary manifestations	56	34	2.5 (1.2-5.0)	0.005
Musculoskeletal manifestations*	43	19	3.1 (1.5-6.2)	0.001
Neoplasms	16	4	4.1 (1.5-11.3)	0.002
Antiphospholipid syndrome	35	17	2.6 (1.3-5.4)	0.008
Anticardiolipin IgG	65	45	2.1 (1.0-4.4)	0.043
Age at onset (>50 years)*	35	16	2.9 (1.4-6.0)	0.003
Male sex	27	12	2.7 (1.2-6.0)	0.008
SDI≥1*	97.3	65	19.4 (2.6-143.1)	10.004

SDI: Systemic Lupus International Collaborative Clinics/American College of Rheumatology Damage Index. *Independent risk factors for mortality in the multivariant analysis, OR and 95%CI are shown in the results section.

Discussion

In an effort to try to identify clinical and serological characteristics which may be associated with juvenile, adult and late onset SLE, we conducted a study of 445 SLE patients over a 25-year period and found significant clinical and immunological features which may be characteristic of each group. Juvenile-, adult- and late-onset SLE groups have been previously compared in the literature (2-17) in attempts to identify the main clinical and immunological features that characterise each age group. Contradictory findings may be due to different age cut-off parameters or possibly comparing separately juvenile-onset (6, 7, 10, 12, 14, 17, 34-40) and late-onset (2-5, 11, 13, 15, 41-43) SLE with the remaining SLE patients; as well as variability in clinical manifestations between different ethnic groups (2-8, 44, 45). A mono-ethnic study of this nature should be able to lend support or otherwise to known disease characteristics.

Our study brought up many results, we will attempt to describe these results in terms of relative clinical significance. We found a significantly higher incidence of renal (both at disease onset and during follow-up) and neuropsychiatric complications in juvenile-onset SLE. Additionally, malar rash, mucocutaneous involvement, renal involvement and increased anti-dsDNA were found to be more common in juvenile-onset SLE than in adult or late onset. This is consistent with two large meta-analyses by Livingston *et al*. (12) which directly compared childhood-onset with adult-onset patients to determine differences in clinical manifestations, auto-antibody profiles and damage accrual (38). Our study lends support to the hypothesis that SLE is more active in children. On the other hand, our results were at variance with the Livingston *et al*. studies which indicated a higher frequency of thrombo-

cytopenia, haemolytic anaemia, fever, lymphadenopathy, anticardiolipin antibodies and less rheumatoid factor in the juvenile-onset group. We also found a greater frequency of anti-U1RNP and anti-Sm antibodies in juvenile-onset compared to later-onset groups.

In line with previous studies (3, 5, 9), we found arthritis and lymphopoenia to be more frequent in patients experiencing disease onset between 18 and 50.

Perhaps also of primary clinical significance, we found that, at onset, the clinical profile of the late-onset group revealed a lower frequency of cutaneous manifestations. Similar results were published for Spanish (46), Brazilian (3), and Chinese (47) populations. Since skin manifestations play a key role (6) in diagnosis, this may lead to potential mis-diagnosis or diagnostic delay (9). As previously reported (4, 48), we found late-onset lupus to be an independent predictor of damage accrual and mortality. The higher prevalence of co-morbid conditions and greater SDI index score in the late onset group can be attributed to ageing and greater exposure to traditional cardiovascular risk factors (3, 4, 11, 43). Many authors (42, 46, 47) argue that late-onset SLE is a milder variant of the disease, probably due to immunosenescence, whereas this was not confirmed in our results or results from other populations that showed greater SDI organ damage and mortality rates (3, 4, 49). Disease duration, on the other hand, was not an independent risk factor for damage accrual and mortality in our study, which differ to findings by Stoll *et al*. (50). The inverse association between disease duration and damage accrual that contradicts previous reports could be explained by the shorter disease duration observed in the late onset group, the same group that showed a higher SDI compared against the other two groups.

Associating certain disease manifestations, auto-antibody profile and other serological phenomena to different SLE age of onset populations may enable us to better understand disease behavior and its subsequent treatment. Research has been done previously but results remain disparate probably owing to the diversity of the studied populations. For example, Hispanics with a strong Amerindian background seem to have more aggressive SLE manifestations than observed in Spaniards (3, 39). Additionally, the frequency of clinical manifestations and auto-antibodies differed significantly among ethnicities (18, 20, 51-53). The strength of our study is that specific disease characteristics and immunology can be better observed through an ethnically homogeneous patient group. Some limitations, however, should be noted. A fundamental potential weakness of all observational studies is that some findings could be due to confounding or bias effects. We were not able to determine disease activity, cumulative doses or clinical response to treatment due to registry limitations. Also, the the fact that most patients were recruited before 2000 suggests that these patients were not exposed to current standards of treatment and this may have affected the development of organ damage. A sample selection bias is expected, since patients are from a single tertiary centre. As patients were evaluated by different physicians, an interobserver variability in the patients' management may be expected, however, the data collection process was strictly standardised among the staff members during the whole study period.

Conclusion

In summary, we found significant differences in clinical and serological profiles between juvenile, adult and late-onset SLE. Juvenile-onset patients showed a higher frequency of renal and neuropsychiatric manifestations and more frequently developed anti-dsDNA, anti-U1RNP and anti-Sm antibodies. Adult patients developed arthritis and lymphopoenia more frequently. Late-onset patient had significantly fewer cutaneous manifestations, higher damage accrual and mortality.

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References

1. AMADOR-PATARROYO MJ, RODRIGUEZ-RODRIGUEZ A, MONTOYA-ORTIZ G: How does age at onset influence the outcome of autoimmune diseases? *Autoimmune Dis* 2012; 2012: 2517-30.
2. ACHOUR A, MANKAI A, THABET Y *et al*.: Systemic lupus erythematosus in the elderly. *Rheumatol Int* 2012; 32: 1225-9.
3. APPENZELLER S, PEREIRA DA, COSTALLAT LT: Greater accrual damage in late-onset systemic lupus erythematosus: a long-term follow-up study. *Lupus* 2008; 17: 1023-8.
4. BERTOLI AM, ALARCON GS, CALVO-ALEN J *et al*.: Systemic lupus erythematosus in a multiethnic US cohort. XXXIII. Clinical [corrected] features, course, and outcome in patients with late-onset disease. *Arthritis Rheum* 2006; 54: 1580-7.
5. BODDAERT J, HUONG DL, AMOURA Z, WECHSLER B, GODEAU P, PIETTE JC: Late-onset systemic lupus erythematosus: a personal series of 47 patients and pooled analysis of 714 cases in the literature. *Medicine* (Baltimore) 2004; 83: 348-59.
6. BRUNNER HI, GLADMAN DD, IBANEZ D, UROWITZ MD, SILVERMAN ED: Difference in disease features between childhood-onset and adult-onset systemic lupus erythematosus. *Arthritis Rheum* 2008; 58: 556-62.
7. CARRENO L, LOPEZ-LONGO FJ, MONTEAGUDO I *et al*.: Immunological and clinical differences between juvenile and adult onset of systemic lupus erythematosus. *Lupus* 1999; 8: 287-92.
8. COSTALLAT LT, COIMBRA AM: Systemic lupus erythematosus: clinical and laboratory aspects related to age at disease onset. *Clin Exp Rheumatol* 1994; 12: 603-7.
9. FONT J, PALLARES L, CERVERA R *et al*.: Systemic lupus erythematosus in the elderly: clinical and immunological characteristics. *Ann Rheum Dis* 1991; 50: 702-5.
10. HOFFMAN IE, LAUWERYS BR, DE KEYSER F *et al*.: Juvenile-onset systemic lupus erythematosus: different clinical and serological pattern than adult-onset systemic lupus erythematosus. *Ann Rheum Dis* 2009; 68: 412-5.
11. LALANI S, POPE J, DE LEON F, PESCHKEN C, MEMBERS OF CA NFOL: Clinical features and prognosis of late-onset systemic lupus erythematosus: results from the 1000 faces of lupus study. *J Rheumatol* 2010; 37: 38-44.
12. LIVINGSTON B, BONNER A, POPE J: Differences in clinical manifestations between childhood-onset lupus and adult-onset lupus: a meta-analysis. *Lupus* 2011; 20: 1345-55.
13. PADOVAN M, GOVONI M, CASTELLINO G, RIZZO N, FOTINIDI M, TROTTA F: Late onset systemic lupus erythematosus: no substantial differences using different cut-off ages. *Rheumatol Int* 2007; 27: 735-41.
14. RAMIREZ GOMEZ LA, URIBE URIBE O, OSIO URIBE O *et al*.: Childhood systemic lupus erythematosus in Latin America. The GLADEL experience in 230 children. *Lupus* 2008; 17: 596-604.
15. SAYARLIOGLU M, CEFLE A, KAMALI S *et al*.: Characteristics of patients with late onset systemic lupus erythematosus in Turkey. *Int J Clin Pract* 2005; 59: 183-7.

16. TUCKER LB, MENON S, SCHALLER JG, ISENBERG DA: Adult- and childhood-onset systemic lupus erythematosus: a comparison of onset, clinical features, serology, and outcome. *Br J Rheumatol* 1995; 34: 866-72.
17. TUCKER LB, URIBE AG, FERNANDEZ M *et al*.: Adolescent onset of lupus results in more aggressive disease and worse outcomes: results of a nested matched case-control study within LUMINA, a multiethnic US cohort (LUMINA LVII). *Lupus* 2008; 17: 314-22.
18. CALVO-ALEN J, VILA LM, REVEILLE JD, ALARCON GS: Effect of ethnicity on disease activity in systemic lupus erythematosus. *J Rheumatol* 2005; 32: 962-3; author reply 3.
19. URIBE AG, MCGWIN G, JR., REVEILLE JD, ALARCON GS: What have we learned from a 10-year experience with the LUMINA (Lupus in Minorities; Nature vs. nurture) cohort? Where are we heading? *Autoimmun Rev* 2004; 3: 321-9.
20. PONS-ESTEL BA, CATOGGIO LJ, CARDIEL MH *et al*.: The GLADEL multinational Latin American prospective inception cohort of 1,214 patients with systemic lupus erythematosus: ethnic and disease heterogeneity among "Hispanics". *Medicine* (Baltimore) 2004; 83: 1-17.
21. ALARCON GS, MCGWIN G, JR., PETRI M *et al*.: Baseline characteristics of a multiethnic lupus cohort: PROFILE. *Lupus* 2002; 11: 95-101.
22. COOPER GS, PARKS CG, TREADWELL EL *et al*.: Differences by race, sex and age in the clinical and immunologic features of recently diagnosed systemic lupus erythematosus patients in the southeastern United States. *Lupus* 2002; 11: 161-7.
23. PETRI M: Lupus in Baltimore: evidence-based 'clinical pearls' from the Hopkins Lupus Cohort. *Lupus* 2005; 14: 970-3.
24. HOCHBERG MC: Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. *Arthritis Rheum* 1997; 40: 1725.
25. GLADMAN D, GINZLER E, GOLDSMITH C *et al*.: The development and initial validation of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology damage index for systemic lupus erythematosus. *Arthritis Rheum* 1996; 39: 363-9.
26. GLADMAN DD, GOLDSMITH CH, UROWITZ MB *et al*.: The Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index for Systemic Lupus Erythematosus International Comparison. *J Rheumatol* 2000; 27: 373-6.
27. HAWKER G, GABRIEL S, BOMBARDIER C, GOLDSMITH C, CARON D, GLADMAN D: A reliability study of SLEDAI: a disease activity index for systemic lupus erythematosus. *J Rheumatol* 1993; 20: 657-60.
28. YEE CS, FAREWELL V, ISENBERG DA *et al*.: Revised British Isles Lupus Assessment Group 2004 index: a reliable tool for assessment of systemic lupus erythematosus activity. *Arthritis Rheum* 2006; 54: 3300-5.
29. KHAMASHTA M: [Systemic lupus erythematosis]. 3rd Spanish ed. Barcelona: Caduceo Multimedia 2009. 568 p.
30. EDWORTHY S: Clinical manifestations of systemic lupus erythematosus. *In*: HARRIS ED JR BR, FIRESTEIN GS, GENOVESE MC, SERGENT JS, RUDDY S, SLEDGE CB (Eds.) *Kelley's Textbook of Rheumatology. II*. 7th ed. Philadelphia: Elsevier Saunders; 2005. p. 1201-24.
31. MIYAKIS S, LOCKSHIN MD, ATSUMI T *et al*.: International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). *J Thromb Haemost* 2006; 4: 295-306.
32. VITALI C, BOMBARDIERI S, JONSSON R *et al*.: Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. *Ann Rheum Dis* 2002; 61: 554-8.
33. CHURG J: Renal Disease: Classification and Atlas of Glomerular Disease. Tokio: Igaku-Shoin; 1982.
34. FONT J, CERVERA R, ESPINOSA G *et al*.: Systemic lupus erythematosus (SLE) in childhood: analysis of clinical and immunological findings in 34 patients and comparison with SLE characteristics in adults. *Ann Rheum Dis* 1998; 57: 456-9.
35. HERSH AO, TRUPIN L, YAZDANY J *et al*.: Childhood-onset disease as a predictor of mortality in an adult cohort of patients with systemic lupus erythematosus. *Arthritis Care Res* (Hoboken) 2010; 62: 1152-9.
36. HERSH AO, VON SCHEVEN E, YAZDANY J *et al*.: Differences in long-term disease activity and treatment of adult patients with childhood- and adult-onset systemic lupus erythematosus. *Arthritis Rheum* 2009; 61: 13-20.
37. LENG RX, ZHU QQ, PAN HF, FENG JB, TAO JH, YE DQ: Juvenile and adult-onset systemic lupus erythematosus: an ethnicity-based comparison. *Rheumatol Int* 2011; 31: 699-700.
38. LIVINGSTON B, BONNER A, POPE J: Differences in autoantibody profiles and disease activity and damage scores between childhood- and adult-onset systemic lupus erythematosus: a meta-analysis. *Semin Arthritis Rheum* 2012; 42: 271-80.
39. LOPEZ P, MOZO L, GUTIERREZ C, SUAREZ A: Epidemiology of systemic lupus erythematosus in a northern Spanish population: gender and age influence on immunological features. *Lupus* 2003; 12: 860-5.
40. SILVA CA, AVCIN T, BRUNNER HI: Taxonomy for systemic lupus erythematosus with onset before adulthood. *Arthritis Care Res* (Hoboken) 2012; 64: 1787-93.
41. KOH ET, BOEY ML: Late onset lupus: a clinical and immunological study in a predominantly Chinese population. *J Rheumatol* 1994; 21: 1463-7.
42. PU SJ, LUO SF, WU YJ, CHENG HS, HO HH: The clinical features and prognosis of lupus with disease onset at age 65 and older. *Lupus* 2000; 9: 96-100.
43. TOMIC-LUCIC A, PETROVIC R, RADAK-PEROVIC M *et al*.: Late-onset systemic lupus erythematosus: clinical features, course, and prognosis. *Clin Rheumatol* 2013; 32: 1053-8.
44. AL HAMZI H, ALHAYMOUNI B, AL SHAIKH A, AL-MAYOUF SM: Outcome of adult Saudi patients with childhood-onset systemic lupus erythematosus. *Clin Exp Rheumatol* 2014; 32: 984-8.
45. LUKIC A, LUKIC IK, MALCIC I *et al*.: Childhood-onset systemic lupus erythematosus in Croatia: demographic, clinical and laboratory features, and factors influencing time to diagnosis. *Clin Exp Rheumatol* 2013; 31: 803-12.
46. FORMIGA F, MOGA I, PAC M, MITJAVILA F, RIVERA A, PUJOL R: Mild presentation of systemic lupus erythematosus in elderly patients assessed by SLEDAI. SLE Disease Activity Index. *Lupus* 1999; 8: 462-5.
47. HO CT, MOK CC, LAU CS, WONG RW: Late onset systemic lupus erythematosus in southern Chinese. *Ann Rheum Dis* 1998; 57: 437-40.
48. REVEILLE JD, BARTOLUCCI A, ALARCON GS: 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.
49. MAK SK, LAM EK, WONG AK: Clinical profile of patients with late-onset SLE: not a benign subgroup. *Lupus* 1998; 7: 23-8.
50. STOLL T, SUTCLIFFE N, MACH J, KLAGHOFER R, ISENBERG DA: Analysis of the relationship between disease activity and damage in patients with systemic lupus erythematosus--a 5-yr prospective study. *Rheumatology* (Oxford) 2004; 43: 1039-44.
51. JURENCAK R, FRITZLER M, TYRRELL P, HIRAKI L, BENSELER S, SILVERMAN E: Autoantibodies in pediatric systemic lupus erythematosus: ethnic grouping, cluster analysis, and clinical correlations. *J Rheumatol* 2009; 36: 416-21.
52. LEVY DM, PESCHKEN CA, TUCKER LB *et al*.: Influence of ethnicity on childhood-onset systemic lupus erythematosus: results from a multiethnic multicenter Canadian cohort. *Arthritis Care Res* (Hoboken) 2013; 65: 152-60.
53. PESCHKEN CA, KATZ SJ, SILVERMAN E *et al*.: The 1000 Canadian faces of lupus: determinants of disease outcome in a large multiethnic cohort. *J Rheumatol* 2009; 36: 1200-8.