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ORIGINAL ARTICLE

Age of onset influences on clinical and laboratory profile of patients with systemic lupus erythematosus

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Abstract The present study aims to evaluate differences in clinical and laboratory manifestations and medication use in the different ages of disease onset in patients with systemic lupus erythematosus (SLE). This cross-sectional study consisted of 598 SLE patients (550 female and 48 male), who attended the Rheumatology Clinic of the Hospital de Clínicas de Porto Alegre between 2003 and 2015. Demographic, clinical and laboratory data were collected. The patients were classified into three groups according to their ages at disease diagnosis. Mean age of diagnosis was 33.6 ± 14.3 years, and the median (25th–75th percentile) disease duration was 13 (7–20) years. Among the patients studied, 419 (70%) were adult-onset (aSLE), 90 (14.8%) were late-onset (lSLE) and 89 (14.8%) were childhood-onset (cSLE). The female to male ratio was higher in aSLE (18:1) compared to the other groups ($p = 0.001$). Arthritis was predominantly found in aSLE (78.5%) when compared with lSLE (57.7%) ($p < 0.001$). Nephritis was more common in cSLE (60.6%) than in lSLE (26.6%) ($p < 0.001$). Median (25th–75th percentile) of SLE disease activity index (SLEDAI) was higher in the cSLE group [2 (0–5)] when compared to the lSLE group [0 (0–4)] ($p = 0.045$). Childhood-onset SLE showed a more severe disease due to the higher incidence of nephritis and needed a more aggressive treatment with immunosuppressive drugs.

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Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease that involves many organs and systems. The etiology and pathogenesis of SLE remain poorly understood. Many observations suggest a role of genetic, immunologic, hormonal and environmental factors [1]. SLE displays wide spectrum of clinical and laboratory manifestations, showing a variable clinical course, prognosis and treatment response. Usually, the first manifestation of SLE occurs around the age of 16 to 55 years old, being more prevalent among women at childbearing age, but can affect individuals of any age [2, 3], typically in a 9:1 female to male ratio [4].

Population studies are trying to determine whether age of diagnosis is associated with specific disease phenotypes or not [5, 6]. Previous studies demonstrated heterogeneous clinical presentation, medication use and disease severity among different ages of onset groups. Late-onset SLE (lSLE) displays more insidious clinical course, lower rates of disease activity, less impairment of organs and systems, with lower prevalence of nephritis, and involvement of the central nervous system than the remaining groups [7, 8]. On the other hand, studies have shown that a childhood-onset (cSLE) group may have more severe disease and presents greater prevalence of clinical, immunological and serological abnormalities than other two groups [9, 10]. Even so, the influence of age at disease onset on the clinical presentation and prognosis remains not well recognized. The conclusions withdrawn from the published studies are limited by the small sample sizes, the different cutoff ages for the late- and childhood-onset and the heterogeneity of the patients [11, 12]. Studies evaluating the

Brazilian population are scarce [13–19], and they are necessary due to the high racial miscegenation in this population. This study aims to evaluate differences in clinical and laboratory manifestations and medication use in each SLE patient group according to the age of onset.

Materials and methods

Study population

This cross-sectional study consisted of 598 patients with SLE who attended the Rheumatology Clinic of the Hospital de Clínicas de Porto Alegre (HCPA) between 2003 and 2015, which is a tertiary care center which receives patients from the entire state of Rio Grande do Sul. All patients fulfilled the American College of Rheumatology (ACR) revised criteria for the classification of SLE [20, 21].

Interview during medical consultation and medical chart review were used to collect demographic, clinical and laboratory data, as well as treatment information. The study protocol was approved by the Ethics Committee of Hospital de Clínicas de Porto Alegre, and an informed consent form was obtained from all participants.

Ethnicity was defined as European-derived and non-European-derived patients. This classification was based on physical appearance, as judged by the researcher at the time of blood collection, and data about the ethnicity of parents/grandparents reported by the participants. These classification criteria that are used in Brazil are well documented and have been assessed by our group in previous studies [22]. Also, a recent study assessing individual inter-ethnic admixture and population substructure using a panel of 48-insertion–deletion ancestry informative markers validated this classification in European-derived individuals from our geographic region [23].

The patients were divided into three groups for the analysis according to the age at diagnosis. The date of symptom onset would be more appropriate to define the onset of the disease; however, for convenience, we chose the date of diagnosis, as this date is more reliable, and our work obtained the information retrospectively through database. Childhood-onset SLE was composed by those with diagnosis until 18 years old, adult-onset (aSLE) was composed by those with diagnosis between 18 and 50 years old and lSLE group had the patients with diagnosis after 50 years old. The selection of the groups' cutoff age is arbitrary, and the cutoff point we have chosen is the most widely used [2, 5, 14, 24–26].

Clinical and laboratory variables

The patients were evaluated during recruitment period using a standardized questionnaire for variables: age, gender, age at diagnosis, smoking status, other autoimmune diseases, body mass index (BMI) and treatment performed. Clinical manifestations of SLE included the presence of photosensitivity, malar rash, discoid rash, oral or nasal ulcers, arthritis, serositis (pleuritis or pericarditis), nephritis and neurological disease, defined as seizures or psychosis. All patients were submitted to the same laboratory evaluation which included the presence of hematological disorders (hemolytic anemia, leukopenia, lymphopenia or thrombocytopenia) and positive antinuclear antibody (ANA) (titer > 1:80) or other autoantibodies such as anti-dsDNA, anti-Sm, anti-RNP, anti-Ro/SSA, anti-La/SSB, anticardiolipin, lupus anticoagulant and false positive VDRL. It used indirect immunofluorescence to detect anti-dsDNA and ANA, chemiluminescence to detect anticardiolipin, coagulometry to detect lupus anticoagulant and agglutination to detect autoantibodies to extractable nuclear antigens (anti-ENA). All patients were also evaluated in regard to secondary antiphospholipid syndrome and secondary Sjögren's syndrome. The presence of sicca symptoms and thrombosis was actively searched in each appointment. Further evaluation by an ophthalmologist and otorhinolaryngologist was performed when dry symptoms were present. Doppler ultrasound was ordered when the presence of thrombus was suspected and the obstetric history was taken for all women in the study. The diagnosis was made according to the classification criteria for both diseases [27–30]. The SLE disease activity index (SLEDAI) and the systemic lupus international collaborating clinic (SLICC) damage index were applied to each patient as a measurement of disease activity and cumulative damage, respectively [31–34]. SLEDAI ≥1 was used to define active disease. It analysed any medication used in the course of disease like antimalarials (chloroquine or hydroxychloroquine), azathioprine, methotrexate, mycophenolate mofetil, cyclophosphamide, cyclosporine and rituximab. The usage of glucocorticoids was divided into oral glucocorticoid (<1 mg/Kg/day), immunosuppressive dose (≥1 mg/Kg/day) and pulse therapy with methylprednisolone (1000 mg/day, intravenous). All medications were reviewed in every medical appointment to secure adherence to the treatment; however, we do not have an estimate of non-adherent patients.

Statistical analysis

A descriptive analysis of data through calculation of mean and standard deviation (SD) for quantitative variables was performed while the frequency and percentage were calculated for categorical variables. The median and interquartile range were calculated to quantitative variables with asymmetrical distribution. We used the chi-square test with adjusted, standardized residual or Fisher's exact test to compare qualitative variables. Kruskal-Wallis was performed to compare quantitative variables with asymmetrical distribution, assessed by

Shapiro-Wilk test. The odd ratio and 95% confidence interval were also calculated. Data were analysed with SPSS software version 18.0, and a two-tailed value of $p < 0.05$ was taken to indicate statistical significance.

Results

Our study consisted of 598 patients consecutively included in our database from 2003 to 2015. The majority of the patients were women (91.9%), European-derived (73.2%); the mean age of diagnosis was 33.6 ± 14.3 years, and the median (25th–75th percentile) time of disease was 13 (7–20). The female to male rate of our population was 14:1. The main clinical manifestations found were arthritis (74.5%), hematologic disorders (74.5%), photosensitivity (71.7%), malar rash (56.3%) and nephritis (40.9%). ANA was positive in 99.2% of the patients. The most prevalent autoantibodies were anti-dsDNA (44.8%), anti-Ro/SSA (37.4%) and anti-RNP (28.7%) (Table 1).

Secondary Sjögren's syndrome was present in 50 (8.3%) patients, and secondary antiphospholipid syndrome was present in 40 (6.6%) patients of our whole group (Table 1). No difference among the groups was found (Table 2).

The history of SLE in the family was evaluated, and it was considered positive if any first-degree relative had the same diagnosis. The studied population presents 81 (13.6%) patients with a positive history of SLE in the family, but there was no difference among the groups (Table 2).

Of the patients included in this study, 419 (70%) had aSLE, 90 (14.8%) had lSLE and 89 (14.8%) had cSLE. We found a significant difference in gender distribution. There was higher female to male rate in the group of aSLE, when compared with the other groups (18:1 vs. 6.4:1 and 5.4:1 for cSLE and lSLE, respectively, $p < 0.001$).

The aSLE presents more arthritis than lSLE (78.5 vs. 57.7%, respectively, $p < 0.001$), while the cSLE presents more nephritis (60.6 vs. 26.6% for lSLE, $p < 0.001$) and malar rash (71.9 vs. 43.3% for lSLE). There were no differences in discoid rash, photosensitivity, oral or nasal ulcers, serositis and neurological disease among the groups (Table 2).

Regarding the laboratorial aspects, no differences were observed in the hematologic criteria (hemolytic anemia, leucopenia, lymphopenia and thrombocytopenia). The autoantibody panel (anti-Sm, anticardiolipin, lupus anticoagulant, ANA, anti-Ro/SSA, anti-La/SSB and anti-RNP) showed no difference among the groups, except that anti-dsDNA was more prevalent in cSLE, which also accompanies the increased prevalence of nephritis in this group (Table 2).

In order to identify different degrees of activity and chronicity in the three groups, we evaluated their SLEDAI and SLICC damage index, respectively. We found that cSLE has a higher median (25th–75th percentile) of SLEDAI at diagnosis when compared to lSLE [2 (0–5) vs. 0 (0–4), respectively, $p = 0.045$]. SLICC damage index on the other hand did not show difference among the groups (Table 2).

Analysis of medication use in treatment and maintenance of SLE was performed. The medications most commonly used in the treatment of SLE were antimalarials (94.8%), oral corticosteroids (Cs) (90.4%) and immunosuppressive dose of Cs (66.2%). We observed that the cSLE group had higher rates of use compared to the lSLE group, of the following drugs: oral Cs (98.8 vs. 83.3%, $p = 0.01$), immunosuppressive doses of Cs (83.1 vs. 46.6%, $p = 0.002$), pulse methylprednisolone (47.1 vs. 15.5%, $p < 0.001$), cyclophosphamide (47.1 vs. 12.2%, $p < 0.001$), azathioprine (65.1 vs. 31.1%, $p = 0.001$) and mycophenolate mofetil (16.8 vs. 2.2%, $p < 0.001$). No significant differences in relation to other medications were observed among groups (Table 3).

Table 1 Demographic, clinical and immunological characteristics of a cohort of patients with SLE

Patient's features	Whole ($n = 598$)
European-derived	438 (73.2)
Female	550 (91.9)
Age at diagnosis (years ± SD)	33.6 (14.3)
Disease duration[a]	13 (7–20)
Malar rash	337 (56.3)
Discoid rash	71 (11.8)
Photosensitivity	429 (71.7)
Oral ulcers	216 (36.1)
Arthritis	446 (74.5)
Serositis	152 (25.4)
Nephritis	245 (40.9)
Neurologic disorders	72 (12)
Hematologic disorders	446 (74.5)
Immunologic disorder	401 (67.0)
Anti-dsDNA	268 (44.8)
Anti-Sm	118 (19.7)
Anticardiolipin	153 (25.5)
Lupic anticoagulant	51 (8.5)
Anti-Ro/SSA	224 (37.4)
Anti-La/SSB	69 (11.5)
Anti-RNP	172 (28.7)
SLEDAI[a]	2 (0–4)
SLICC[a]	1 (0–2)
Sjögren syndrome	50 (8.3)
Antiphospholipid syndrome	40 (6.6)
Family history of SLE	81 (13.6)

All data were expressed as absolute value (percentage), unless otherwise indicated

SD standard deviation, *SLEDAI* systemic lupus erythematosus disease activity index, *SLICC* systemic lupus international collaborating clinics

[a] Median, 25th–75th percentile

Table 2 Characteristics of a cohort of patients with SLE according to age at onset

Patient's features	cSLE (n = 89)	aSLE (n = 419)	lSLE (n = 90)	p value
European-derived	75 (84.2)	298 (71.1)	65 (72.2)	0.06
Female	77 (86.5)[c]	397 (94.7)[b]	76 (84.4)[c]	<0.01
Age at diagnosis (years ± SD)	14.5 (3.5)	32.3 (8.6)	58.1 (6.9)	
Disease duration[a]	16 (10.5–23)	14 (7–21)	8 (5.7–14)	
Malar rash	64 (71.9)[b]	234 (55.8)	39 (43.3)[c]	<0.01
Discoid rash	9 (10.1)	52 (12.4)	10 (11.1)	0.81
Photosensitivity	63 (70.7)	308 (73.5)	58 (64.4)	0.20
Oral ulcers	36 (40.4)	151 (36)	29 (32.2)	0.48
Arthritis	65 (73.0)	329 (78.5)[b]	52 (57.7)[c]	<0.01
Serositis	25 (28.0)	111 (26.4)	16 (17.7)	0.17
Nephritis	54 (60.6)[b]	167 (39.8)	24 (26.6)[c]	<0.01
Neurologic disorders	15 (16.8)	47 (11.2)	10 (11.1)	0.30
Hematologic disorders	67 (75.2)	306 (73.0)	73 (81.1)	0.27
Hemolytic anemia	21 (23.5)	103 (24.5)	24 (26.6)	0.89
Leuko/lymphopenia	53 (59.5)	231 (55.1)	49 (54.4)	0.66
Thrombocytopenia	21 (23.5)	80 (19)	23 (25.5)	0.29
Immunologic disorder	70 (78.6)	270 (64.4)	61 (67.7)	0.20
Anti-dsDNA	55 (61.7)[b]	180 (42.9)	33 (36.6)	<0.01
Anti-Sm	19 (21.3)	84 (20)	15 (16.6)	0.61
Anticardiolipin	28 (31.4)	101 (24.1)	24 (26.6)	0.38
Lupic anticoagulant	11 (12.3)	32 (7.6)	8 (8.8)	0.35
Anti-Ro/SSA	27 (30.3)	168 (40)	29 (32.2)	0.13
Anti-La/SSB	8 (8.9)	51 (12.1)	10 (11.1)	0.75
Anti-RNP	25 (28)	127 (30.3)	20 (22.2)	0.23
Sjögren syndrome	5 (5.6)	35 (8.3)	10 (11.1)	0.33
Antiphospholipid syndrome	6 (6.7)	28 (6.6)	6 (6.6)	0.98
SLEDAI[a]	2 (0–5)[b]	2 (0–4)	0 (0–4)[c]	0.04
SLICC[a]	1 (0–2)	0.4 (0–2)	1 (0–1.75)	0.63
Family history of SLE	11 (12.3)	62 (14.7)	8 (8.8)	0.46

All data were expressed as absolute value (percentage), unless otherwise indicated. Chi-square or Fisher's exact test with adjusted, standardized residual to compare qualitative variables. Kruskal-Wallis to compare quantitative variables with asymmetrical distribution

SD standard deviation, *SLEDAI* systemic lupus erythematosus disease activity index, *SLICC* systemic lupus international collaborating clinics

[a] Median, 25th–75th percentile)

[b] Shows a positive association

[c] Shows a negative association

Discussion

The percentage of patients in each group was similar to most of the studies, with most individuals having diagnosis of SLE in adulthood [24, 35–38]. We found a higher prevalence of lSLE in comparison to another Brazilian cohort and to a Latin American cohort (Grupo Latino Americano De Estudio del Lupus) (14.8 vs. 3.9 and 6.9%, respectively) [13, 39]. It can be due to the fact that the population in southern Brazil is older than the general population in Brazil and Latin America. In our study, we found a reduction in the rate female to male in the youth group (6:1) and late-onset group (5:1) compared to the adult (18:1). These data are consistent with the literature [24, 25, 36, 40–42]. One hypothesis to explain this finding is the role of estrogen in the pathogenesis of SLE [2, 4, 43–45]. We found a higher prevalence of European-derived ethnicity in the three groups, but this relationship was more important in the cSLE group (8:1); this may reflect the small number of non-European-derived in our population or the result of genetic miscegenation.

The cSLE group had a higher frequency of nephritis and anti-dsDNA positivity, thus reflecting greater disease activity at diagnosis, measured by SLEDAI. Although renal involvement is common in all age groups, nephritis has been shown to

Table 3 Medication usage of a cohort of patients with SLE according to age at onset

Medication	Whole (n = 598)	cSLE (n = 89)	aSLE (n = 419)	lSLE (n = 90)	p value
Oral corticosteroid	541 (90.4)	88 (98.8)[a]	378 (90.2)	75 (83.3)[b]	<0.01
Immunosuppressive dose of Cs	396 (66.2)	74 (83.1)[a]	280 (66.8)	42 (46.6)[b]	<0.01
Pulse methylprednisolone	173 (28.9)	42 (47.1)[a]	117 (27.9)	14 (15.5)[b]	<0.01
Cyclophosphamide	175 (29.2)	42 (47.1)[a]	122 (29.1)	11 (12.2)[b]	<0.01
Methotrexate	107 (17.8)	11 (12.3)	78 (18.6)	18 (20)	0.35
Azatioprine	270 (45.1)	58 (65.1)[a]	184 (43.9)	28 (31.1)[b]	<0.01
Antimalarials	567 (94.8)	81 (91)	402 (95.9)	84 (93.3)	0.19
Mycophenolate mofetil	46 (7.6)	15 (16.8)[a]	29 (6.9)	2 (2.2)[b]	<0.01
Cyclosporin	7 (1.1)	0 (0.0)	7 (1.6)	0 (0.0)	0.42
Rituximab	8 (1.3)	2 (2.2)	5 (1.1)	1 (1.1)	0.66

All data were expressed as absolute value (percentage). Chi-square test with adjusted, standardized residual. Fisher's exact test to compare qualitative variables

[a] Shows a positive association

[b] Shows a negative association

be more prevalent and more severe in pediatric patients [7, 39, 46], necessitating even more aggressive treatment and resulting in worse prognosis [15]. In this study, a higher prevalence of hematologic involvement was not observed in cSLE; however, previous meta-analysis found increased presence of thrombocytopenia and autoimmune hemolytic anemia in this group [46]. In the inception cohort made by the Grupo Latino de Estudio de Lupus (GLADEL), there was a higher prevalence of malar rash, fever, oral ulcers, thrombocytopenia, hemolytic anemia and some neurological manifestations in this group of patients [47]. This data disagreement with GLADEL could be due to the ethnical difference between this big Latin American cohort and our cohort, since the former cohort is made by 40.9% of Caucasians while ours is made by 73.2% of European-derived patients.

In the lSLE group, the prevalence of Sjögren's syndrome had a tendency to be higher in the other groups, yet there was no statistical significance, probably on account of the small number of patients in each group. This data has already been verified in other studies [4, 24, 39, 48–50]. Many studies find high prevalence of sicca symptoms in lSLE [44]. However, the high prevalence of anti-Ro/SSA antibodies is not found in this subgroup of patients, despite being often found in Sjögren's syndrome [51]. Other classic findings of the syndrome (palpable purpura, swelling of parotid and rheumatoid factor) are not more frequent in lSLE. So prevalence of sicca symptoms in lSLE could be due primarily to glandular senescence [44]. There are conflicting data regarding the association of anti-Ro/SSA, anti-La/SSB and rheumatoid factor with the late-onset group [5, 25, 49, 52]. Our data showed no association.

Another finding that shows disagreement in the literature was serositis [3, 14, 53, 54], which in our population was not associated with the late-onset group. Some series of cases showed a higher prevalence of anemia in the late-onset group, but included all types of anemia, not just hemolytic anemia [40]; we have not found this association.

In the lSLE group, we found a lower prevalence of malar rash and nephritis when compared to the cSLE group and a lower prevalence of arthritis when compared to the aSLE. We also found a lower use of oral Cs, immunosuppressive dose of glucocorticoids, pulse of methylprednisolone, cyclophosphamide, azathioprine and mycophenolate mofetil when compared to cSLE. GLADEL found a lower prevalence of malar rash, photosensitivity and renal involvement in the late-onset group, while interstitial lung disease, pleural effusion and sicca symptoms were more frequent. They also found higher chances of ocular, pulmonary and cardiovascular involvement and lower chances of cutaneous involvement and cyclophosphamide use and lower number of cumulative criteria for SLE [39].

Antiphospholipid syndrome was not related to a specific group, present in 6.6% of whole patients. The antiphospholipid antibodies have a key role in the development of thromboembolic disease. One study showed that these antibodies were detected in 100% of patients who died due to acute myocardial infarction or stroke in a group of patients with aSLE and in 50% of patients with lSLE [24]. Our study did not evaluate the causes of death of our population.

Some studies show a higher prevalence of positive family history of autoimmune diseases in cSLE. Shorter exposure to triggering environmental factors may suggest that genetic factors are more strongly implicated in the pathogenesis of SLE in this age group [38, 55, 56]. In our study, the rate of patients with positive family history of SLE was similar in the three groups, not in agreement with literature data.

The chronicity score was similar among groups. The fact that the SLICC does not demonstrate a difference among age groups may show greater chronic involvement of cSLE, since it is expected that older patients have more features that increase the frequency with age, such as cardiovascular disease [57]. In addition, the SLICC damage index does not include forms of damage that are unique to pediatric patients, such as growth retardation and pubertal delay, which may cause damages such as short stature and premature osteoporosis [56]. Thus, we can judge that scores of chronicity may be underestimated in the youth group.

The treatment of SLE is similar for pediatric, adult and elderly patients, but most studies include only adult patients [58]. The treatment for SLE has changed during our study period. We now use frequently mycophenolate mofetil, rituximab and belimumab; nevertheless, these new drugs are still not available in the Brazilian public system, restricting its use for the majority of our population. We found high rates of immunosuppressive use in the cSLE group, which reflects the greater severity of disease in this age group. The lSLE usually requires a less aggressive treatment. The usage of antimalarials was high in our population (94.8%) and did not show any statistical difference among the groups. Antimalarials must be used as a base therapy for most of the patients with SLE, as it increases the life expectancy and decreases flares and thrombotic events, in addition to being considered very safe [59].

In conclusion, our findings corroborate literature data, showing a more aggressive presentation of SLE in childhood, requiring the use of high doses of glucocorticoids and immunosuppressive drugs. The present study found clinical significant differences among the groups. The cSLE group was more aggressive while lSLE was milder.

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Compliance with ethical standards

Disclosures None.

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