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PEDIATRIC LUPUS

Characteristics of 1555 childhood-onset lupus in three groups based on distinct time intervals to disease diagnosis: a Brazilian multicenter study

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Objective: The objective of this study was to compare demographic data, clinical/laboratorial features and disease activity at diagnosis in three different groups with distinct time intervals between onset of signs/symptoms and disease diagnosis. **Methods:** A multicenter study was performed in 1555 childhood-onset systemic lupus erythematosus (American College of Rheumatology criteria) patients from 27 pediatric rheumatology services. Patients were divided into three childhood-onset systemic lupus erythematosus groups: A: short time interval to diagnosis (<1 month); B: intermediate time interval (≥1 and <3 months); and C: long time interval (≥3 months). An investigator meeting was held to define the protocol. Demographic data, SLICC classification criteria and SLEDAI-2 K were evaluated. **Results:** The number of patients in each group was: A = 60 (4%); B = 522 (33.5%); and C = 973 (62.5%). The median age at diagnosis (11.1 (4.2–17) vs. 12 (1.9–17.7) vs. 12.5 (3–18) years, $P = 0.025$) was significantly lower in group A compared with groups B and C. The median number of diagnostic criteria according to SLICC (7 (4–12) vs. 6 (4–13) vs. 6 (4–12), $P < 0.0001$) and SLEDAI-2 K (18 (6–57) vs. 16 (2–63) vs. 13 (1–49), $P < 0.0001$) were significantly higher in group A than the other two groups. The frequency of oral ulcers in the palate (25% vs. 15% vs. 11%, $P = 0.003$), pleuritis (25% vs. 24% vs. 14%, $P < 0.0001$), nephritis (52% vs. 47% vs. 40%, $P = 0.009$), neuropsychiatric manifestations (22% vs. 13% vs. 10%, $P = 0.008$), thrombocytopenia (32% vs. 18% vs. 19%, $P = 0.037$), leucopenia/lymphopenia (65% vs. 46% vs. 40%, $P < 0.0001$) and anti-dsDNA antibodies (79% vs. 66% vs. 61%, $P = 0.01$) were significantly higher in group A compared with the other groups. In contrast, group C had a less severe disease characterized by higher frequencies of synovitis (61% vs. 66% vs. 71%, $P = 0.032$) and lower frequencies of serositis (37% vs. 33% vs. 25%, $P = 0.002$), proteinuria >500 mg/day (48% vs. 45% vs. 36%, $P = 0.002$) and low complement levels (81% vs. 81% vs. 71%, $P < 0.0001$) compared with groups A or B. **Conclusions:** Our large Brazilian multicenter study demonstrated that for most childhood-onset systemic lupus erythematosus

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patients, diagnosis is delayed probably due to mild disease onset. Conversely, the minority has a very short time interval to diagnosis and a presentation with a more severe and active multisystemic condition. *Lupus* (2018) **27,** 1712–1717.

Key words: Childhood-onset systemic lupus erythematosus; diagnosis; disease damage and disease activity

Introduction

Childhood-onset systemic lupus erythematosus (cSLE) is a multisystemic autoimmune and inflammatory disease that may involve any organ and system.[1–7]

We recently reported distinct clinical and laboratory features in early-onset and adolescent groups at cSLE diagnosis in a cohort of the Sao Paulo state Brazilian Childhood-onset Systemic Lupus Erythematosus (BRAC-SLE) registry group.[8]

The constellation of characteristic signs, symptoms and laboratory findings may occur serially or simultaneously during any interval of time in cSLE patients. Several reports suggest that cSLE onset is characterized by a more active disease and abrupt presentation than adult SLE populations.[9–11] However, it is unknown if distinct time intervals are related to different disease phenotypes and severity in the cSLE population. Definition of this parameter is critical to improve awareness among pediatricians, because it was demonstrated that the identification of signs and symptoms at disease presentation was the relevant factor influencing early referral.[12]

Therefore, the objective of the present multicenter study in Brazil was to compare demographic data, clinical and laboratorial parameters and disease activity score at diagnosis in three different groups with distinct time intervals between the onset of signs/symptoms and cSLE diagnosis.

Methods

Study design and patients

This is a retrospective multicenter cohort study including 1697 consecutive patients followed in 27 pediatric rheumatology tertiary referral services in Brazil. One hundred and forty-two cSLE patients were excluded due to incomplete medical charts ($n=43$) and undifferentiated connective tissue disorders with three or fewer American College of Rheumatology (ACR) criteria ($n=99$). The remaining 1555 cSLE patients comprised the study group. All 1555 cSLE patients fulfilled the ACR criteria,[13] with disease onset before 18 years of age.[1] These cSLE patients were located in five regions of Brazil: north ($n=34$); northeast ($n=259$); central-west ($n=124$); southeast ($n=1075$) and south ($n=63$). This study was approved by all ethics committees of each participating university hospital in Brazil.

An investigator meeting was held for this study in Brasilia, at the time of the Brazilian Congress of Rheumatology in 2016, to refine a previous protocol including definitions of clinical and disease activity parameters.[8] One investigator with the Brazilian board pediatric rheumatology certifying examination supervised data collection in each center. Discrepancies were sorted out by one or more rounds of queries to check accuracy. Data were collected between September 2016 and May 2017.

Patients' medical charts were carefully reviewed according to an extensive standardized protocol for demographic data, clinical features, laboratory findings and therapeutic data at cSLE diagnosis.

Patients were divided into three cSLE groups: A: short time interval to diagnosis (<1 month); B: intermediate time interval (≥1 and <3 months); and C: long time interval (≥3 months).

Demographic data, clinical and laboratory assessment and disease activity at cSLE diagnosis

Demographic data included age at cSLE diagnosis and gender. Ethnic groups were classified into: white (patients with white European ancestors); African-Latin American (patients with at least one African ancestor); Asian (patients with Asian ancestors); and other/unknown.[8] Definitions of clinical and immunological criteria were used according to Systemic Lupus International Collaborating Clinics (SLICC) classification criteria for systemic lupus erythematosus.[14]

Laboratory assessment included retrospective analysis of complete blood cell count, serum urea and creatinine, urinalysis and 24-hour urine protein excretion or urine protein/creatinine ratio. Complement levels (CH50, C3 and C4) were assessed by immunodiffusion, turbidimetric immunoassay or immunonephelometry. Antinuclear antibodies were tested by

indirect immunofluorescence; anti-dsDNA by indirect immunofluorescence or ELISA; anti-Sm by passive hemagglutination or ELISA; anticardiolipin IgG and IgM by ELISA; and anti-β glycoprotein I IgG and IgM autoantibodies by ELISA were carried out at each center. The cut-off values from the kit manufacturer were used to define abnormal. Lupus anticoagulant was detected according to the guidelines of the International Society on Thrombosis and Hemostasis.

The Systemic Lupus Erythematosis Disease Activity Index 2000 (SLEDAI-2 K) was used to score disease activity.[14,15]

Statistical analysis

The sample size provided power of 80% to find differences from 14.4% to 18.0% in the frequencies of moderate/severe manifestations (as neuropsychiatric and nephritis) among the three groups (Graphpad StatMate 1.01; GraphPad Software, Inc., CA, USA). All statistical analyses were carried out with the statistical package for the social sciences, version 13.0. Results were presented as an absolute number and frequency for categorical variables, and median (range) or mean ± standard deviation for continuous variables. To evaluate the number and frequency, categorical variable comparisons were first assessed by the Pearson chi-square test which requires that at least 80% of the cells must have an expected frequency of five or more and no cell must have an expected frequency of less than one, followed by a post-hoc analysis by 2×2 chi-square test to determine where the difference occurred between the groups. The Kruskal–Wallis test was used to compare medians of continuous variables with non-normal distribution involving three cSLE groups (non-parametric one-way analysis of variance; ANOVA), followed by a post-hoc analysis by Dunn's multiple comparison test to determine where the difference occurred between the groups. The adopted significance level in all analysis was set at 5%.

Results

The most frequent first signs and symptoms at disease presentation reported in 1555 cSLE patients were: fever (26%), arthritis (26%), malar rash (8%), arthralgia (7%), edema (4%), oral ulcers (2%), adenomegaly (2%), seizure (1.5%) and abnormal urinalyses (1.5%).

Patients were divided into three age groups: A = 60 (4%); B = 522 (33.5%); and C = 973 (62.5%). In group C, the range of time interval between the onset of signs/symptoms and disease diagnosis varied from 3 months to 12 years (median 6 months). The longest time interval to diagnosis was observed in a patient with idiopathic thrombocytopenia purpura that preceded the cSLE diagnosis by 12 years.

The median age at diagnosis (11.1 (4.2–17) vs. 12 (1.9–17.7) vs. 12.5 (3–18) years, $P = 0.025$) was significantly lower in group A compared with groups B and C (Table 1). The median of the SLEDAI-2 K

Table 1 Demographic data and disease activity score in 1555 childhood-onset systemic lupus erythematosus (cSLE) patients according to interval between first signs/symptoms to cSLE diagnosis in months

Variables	*Group A (<1 m)* (n = *60*)	*Group B (≥1 <3 m)* (n = *522*)	*Group C (≥3 m)* (n = *973*)	P *value*
Demographic data				
Age at cSLE diagnosis, years, $n = 1554$	11.1 (4.2–17)	12 (1.9–17.7)	12.5 (3–18)	**0.025**[a]
Male gender, $n = 1555$	10 (17)	82 (16)	144 (15)	0.850
Ethnic groups, $n = 1539$				NA
White	28/60 (47)	264/517 (51)	494/962 (51)	–
African-Latin American	30/60 (50)	185/517 (36)	311/962 (32)	–
Asian	0/60 (0)	3/517 (0.6)	5/962 (0.5)	–
Other/unknown	2/60 (3)	65/517 (13)	152/962 (16)	–
Disease activity score at diagnosis				
SLEDAI-2 K, $n = 1475$	18 (6–57)	16 (2–63)	13 (1–49)[b]	**<0.0001**

Results are presented in *n* (%) and median (range).
SLEDAI-2 K: Systemic Lupus Erythematosus Disease Activity Index 2000; NA: not applicable to assess by Pearson chi-square test.
[a]Post-hoc analysis by Dunn's multiple comparison test showed significant difference between all age groups and SLEDAI-2 K at c-SLE diagnosis ($P < 0.05$).
[b]Post-hoc analysis by 2×2 chi-square test showed difference between groups B and C ($P < 0.05$).

score (18 (6–57) vs. 16 (2–63) vs. 13 (1–49), $P < 0.0001$) was significantly higher in group A than groups B and C (Table 1).

The median number of diagnostic criteria according to SLICC (7 (4–12) vs. 6 (4–13) vs. 6 (4–12), $P < 0.0001$) was significantly higher in group A than the other two groups (Table 2).

The frequency of oral ulcers in the palate (25% vs. 15% vs. 11%, $P = 0.003$), pleuritis (25% vs. 24% vs. 14%, $P < 0.0001$), nephritis (52% vs. 47% vs.

Table 2 Clinical and immunological definitions of Systemic Lupus International Collaborating Clinics Classification Criteria (SLICC) in 1555 childhood-onset systemic lupus erythematosus (cSLE) patients according to interval between first signs/symptoms to cSLE diagnosis in months

Variables	*Group A (<1 m)* n = *60*	*Group B (≥1 <3 m)* n = *522*	*Group C (≥3 m)* n = *973*	P *value*
Number of SLICC criteria (4–17), $n = 1555$	7 (4–12)	6 (4–13)	6 (4–12)	**<0.0001**[a]
Clinical criteria				
1. Acute cutaneous lupus, $n = 1555$	35 (58)	332 (64)	633 (65)	0.526
Malar rash, $n = 1555$	34 (57)	280 (54)	499 (51)	0.539
Bullous lupus, $n = 1555$	2 (3)	9 (2)	17 (2)	NA
Toxic epidermal necrolysis, $n = 1555$	1 (2)	0 (0)	1 (0.1)	NA
Maculopapular lupus rash, $n = 1555$	3 (5)	32 (6)	41 (4)	NA
Photosensitive lupus rash, $n = 1555$	26 (43)	229 (44)	432 (44)	0.972
Subacute cutaneous lupus, $n = 1555$	0 (0)	12 (2)	21 (2)	NA
2. Chronic cutaneous lupus, $n = 1555$	5 (8)	34 (6)	66 (7)	0.866
Discoid rash, $n = 1555$	5 (8)	26 (5)	56 (6)	NA
Hypertrophic (verrucous) lupus, $n = 1555$	0 (0)	1 (0.2)	1 (0.1)	NA
Lupus panniculitis, $n = 1555$	0 (0)	3 (0.6)	4 (0.4)	NA
Mucosal lupus, $n = 1555$	0 (0)	0 (0)	1 (0.1)	NA
Lupus erythematosus tumidus, $n = 1555$	0 (0)	1 (0.2)	1 (0.1)	NA
Chillblains lupus, $n = 1555$	0 (0)	0 (0)	1 (0.1)	NA
Overlap, $n = 1555$	0 (0)	3 (0.6)	2 (0.2)	NA
3. Oral ulcers, $n = 1555$	21 (35)	178 (34)	334 (34)	0.989
Palate, $n = 1554$	15 (25)[c]	77 (15)	110 (11)	**0.003**
Buccal, $n = 1555$	10 (17)	113 (22)	263 (27)[d]	**0.032**
Tongue, $n = 1555$	1 (2)	7 (2)	22 (2)	NA
Nasal, $n = 1555$	0 (0)	9 (2)	8 (0.8)	NA
4. Non-scarring alopecia, $n = 1555$	17 (28)	110 (21)	204 (21)	0.396
5. Synovitis, $n = 1555$	37 (61)	345 (66)	698 (71)[d]	**0.032**
6. Serositis, $n = 1555$	22 (37)	172 (33)	244 (25)[d]	**0.002**
Pleuritis, $n = 1555$	15 (25)[c]	123 (24)	137 (14)[d]	**<0.0001**
Pericarditis, $n = 1555$	15 (25)	113 (22)	178 (18)	0.171
7. Renal, $n = 1555$	31 (52)[c]	247 (47)	389 (40)[d]	**0.009**
Proteinuria >500 mg/day, $n = 1555$	29 (48)	233 (45)	350 (36)[d]	**0.002**
Red blood cell casts, $n = 1555$	6 (10)	61 (12)	109 (11)	0.911
8. Neuropsychiatric, $n = 1555$	13 (22)[c]	68 (13)	97 (10)	**0.008**
9. Hemolytic anemia, $n = 1555$	17 (28)	118 (23)	203 (21)	0.332
10. Leukopenia or lymphopenia, $n = 1555$	39 (65)[b,c]	240 (46)	386 (40)	**<0.0001**
11. Thrombocytopenia, $n = 1555$	19 (32)[b,c]	95 (18)	181 (19)	**0.037**
Immunological criteria				
12. Antinuclear antibody, $n = 1555$	58 (97)	499 (96)	938 (97)	NA
13. Anti-dsDNA antibody, $n = 1501$	44/56 (79)[c]	332/503 (66)	576/942 (61)	**0.01**
14. Anti-Sm antibody, $n = 1367$	21/55 (38)	149/452 (33)	301/860 (35)	0.639
15. Antiphospholipid antibody, $n = 1368$	20/54 (37)	129/461 (28)	278/853 (33)	0.146
16. Low complement (C3/C4/CH50), $n = 1342$	44/54 (81)	364/448 (81)	600/840 (71)[d]	**<0.0001**
17. Isolated direct Coombs test, $n = 928$	13/40 (32)	111/322 (34)	204/566 (36)	0.831

Results are presented in *n* (%) and median (range).
NA: not applicable to assess by Pearson chi-square test.
[a]Post-hoc analysis by Dunn's multiple comparison test showed significant difference between all age groups in the number of SLICC criteria at c-SLE diagnosis ($P < 0.05$).
[b]Post-hoc analysis by 2×2 chi-square test showed difference between groups A and B ($P < 0.05$).
[c]Post-hoc analysis by 2×2 chi-square test using Bonferroni correction showed difference between groups A and C ($P < 0.05$).
[d]Post-hoc analysis by 2×2 chi-square test showed difference between groups B and C ($P < 0.05$).

40%, $P = 0.009$), neuropsychiatric manifestations (22% vs. 13% vs. 10%, $P = 0.008$), thrombocytopenia (32% vs. 18% vs. 19%, $P = 0.037$), leucopenia/lymphopenia (65% vs. 46% vs. 40%, $P < 0.0001$) and anti-dsDNA antibodies (79% vs. 66% vs. 61%, $P = 0.01$) were significantly higher in group A than the other groups (Table 2).

In addition, the frequencies of oral ulcers (buccal) (17% vs. 22% vs. 27%, $P = 0.032$) and synovitis (61% vs. 66% vs. 71%, $P = 0.032$) were significantly higher in group C compared with groups A or B (Table 2). In contrast, the frequencies of serositis (37% vs. 33% vs. 25%, $P = 0.002$), proteinuria greater than 500 mg/day (48% vs. 45% vs. 36%, $P = 0.002$) and low complement (81% vs. 81% vs. 71%, $P < 0.0001$) were significantly lower in group C compared with groups A or B (Table 2).

Discussion

Our large Brazilian multicenter study demonstrated that cSLE diagnosis was delayed for most patients probably due to mild disease onset. Conversely, the minority had a very short time interval to diagnosis and a presentation with a more severe and active multisystemic condition.

The strong point of this study was the large sample size of the cSLE population followed at 27 Brazilian university services, distributed in all regions of the country. Another advantage was the use of a standardized database to minimize bias. The main weakness observed herein was the retrospective design; however, the low incidence of missing data due to investigator supervision in each center minimized this methodological limitation.

The time interval between cSLE onset and diagnosis is variable, ranging from days to years, resulting in acute, intermittent or chronic disease at presentation.[2,16,17] The longest time interval to diagnosis observed in the present study occurred in a patient with hematological complications, also reported in other studies.[18]

Importantly, our study was the first to demonstrate unequivocally that the majority of cSLE patients had a long time interval from the onset of signs and symptoms to diagnosis. Mild disease, characterized by synovitis and a low frequency of proteinuria, were distinct features of this group. These findings may account for the delay in cSLE diagnosis, because a variety of other differential diagnoses of acute, intermittent or chronic arthritis, such as metabolic, infectious, malignancy and other autoimmune and autoinflammatory diseases should be excluded.[5,6,19]

In fact, a longer referral to a pediatric rheumatologist was reported in a small group of cSLE patients, contrasting with juvenile idiopathic arthritis, Kawasaki disease and Henoch–Schönlein purpura patients who were referred more promptly to this specialist.[12]

A short time interval to diagnosis was rarely observed in the present study in cSLE patients. We demonstrate herein that these patients have multisystemic and severe presentations with neuropsychiatric, renal, serositis and hematological manifestations. In addition, the group with a short time interval to cSLE diagnosis had a high number of SLICC criteria, elevated anti-dsDNA autoantibodies and high disease activity score. This abrupt, aggressive and acute onset presentation may facilitate a prompt diagnosis by general pediatricians and subspecialists.

In conclusion, the minority of cSLE patients has a shorter time interval to diagnosis characterized by active disease and multisystemic severe presentation facilitating the early recognition of the disease. In contrast, the majority of cSLE patients has a long time interval to diagnosis, and the mild lupus manifestations seem to contribute to the diagnosis delay.

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