Lupus (2017) 26, 996–1001
journals.sagepub.com/home/lup

CONCISE REPORT

Outcomes of 847 childhood-onset systemic lupus erythematosus patients in three age groups

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Objective: The objective of this study was to assess outcomes of childhood systemic lupus erythematosus (cSLE) in three different age groups evaluated at last visit: group A early-onset disease (<6 years), group B school age (≥6 and <12 years) and group C adolescent (≥12 and <18 years). **Methods:** An observational cohort study was performed in ten pediatric rheumatology centers, including 847 cSLE patients. **Results:** Group A had 39 (4%), B 395 (47%) and C 413 (49%). Median disease duration was significantly higher in group A compared to groups B and C (8.3 (0.1–23.4) vs 6.2 (0–17) vs 3.3 (0–14.6) years, $p < 0.0001$). The median Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SLICC/ACR-DI) (0 (0–9) vs 0 (0–6) vs 0 (0–7), $p = 0.065$) was comparable in the three groups. Further analysis of organ/system damage revealed that frequencies of neuropsychiatric (21% vs 10% vs 7%, $p = 0.007$), skin (10% vs 1% vs 3%, $p = 0.002$) and peripheral vascular involvements (5% vs 3% vs 0.3%, $p = 0.008$) were more often observed in group A compared to groups B and C. Frequencies of severe cumulative lupus manifestations such as nephritis, thrombocytopenia, and autoimmune hemolytic anemia were similar in all groups ($p > 0.05$). Mortality rate was significantly higher in group A compared to groups B and C (15% vs 10% vs 6%, $p = 0.028$). Out of 69 deaths, 33/69 (48%) occurred within the first two years after diagnosis. Infections accounted for 54/69 (78%) of the deaths and 38/54 (70%) had concomitant disease activity. **Conclusions:** This large multicenter study provided evidence that early-onset cSLE group had distinct outcomes. This group was characterized by higher mortality rate and neuropsychiatric/vascular/skin organ damage in spite of comparable frequencies of severe cumulative lupus manifestations. We also identified that overall death in cSLE patients was an early event mainly attributed to infection associated with disease activity. *Lupus* (2017) **26,** 996–1001.

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Received 23 June 2016; accepted 3 January 2017

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10.1177/0961203317690616

Key words: Childhood-onset systemic lupus erythematosus; nephritis; outcome; death; mortality and cumulative damage

Introduction

Early childhood-onset SLE (cSLE) is a rare autoimmune disease that may lead to significant morbidity and mortality.[1–3] Recently, a large Brazilian multicenter study reported distinct clinical and laboratory profiles at cSLE diagnosis.[1]

Another recent large study comparing cSLE with adult-onset SLE revealed a more aggressive and worse outcome in the former group.[4] However, analysis of age-related differences regarding outcomes focused on pediatric patients and, in particular, assessing early-onset cSLE patients (<6 years) has been limited to very small sample sizes, precluding a definitive conclusion about the findings.[4–9]

Thus, the aim of this large multicenter study was to evaluate demographic data, cumulative clinical and laboratory features, disease accrual damage, and mortality rate in three different age groups of cSLE assessed at last visit: group A—early-onset disease (<6 years at diagnosis): group B—school age (≥6 and <12 years); and group C—adolescent (≥12 and <18 years).

Patients and methods

A retrospective multicenter cohort study included 1017 consecutive cSLE patients followed at ten pediatric rheumatology centers in São Paulo state, Brazil. The charts were reviewed from 2012-2014. One hundred and seventy patients were excluded, due to the reasons previously reported.[1] The remaining 847 cSLE patients comprised the study group, and all patients fulfilled the American College of Rheumatology (ACR) criteria,[10] with disease onset before 18 years of age.[3]

All investigators were trained in terms of protocol definitions of clinical parameters, disease activity, and damage scores.[1] Patient's medical charts were meticulously reviewed according to a comprehensive standardized protocol for demographic data, cumulative clinical features, laboratory findings, treatments, and outcomes of cSLE evaluated at last visit.

Demographic data, cumulative clinical and laboratory features, disease activity/damage, and deaths in cSLE patients

Age at cSLE diagnosis, disease duration, and gender were evaluated. Ethnic groups were divided into four categories: White (patients with white European ancestors), African–Latin Americans (patients born in Latin America with at least one African ancestor), Asian (patients with Asian ancestors), and other/unknown.[1]

Descriptors and definitions of SLE Disease Activity Index 2000 (SLEDAI-2K) were used to score disease activity during the last visit,[11] and custom definitions as previously described.[1] Neuropsychiatric lupus comprised 19 syndromes according to ACR classification criteria.[12] Antiphospholipid syndrome (APS) was diagnosed according to the current criteria for the classification of pediatric APS.[13]

Cumulative damage at the last visit was scored using the Systemic Lupus International Collaborating Clinics/ACR-Damage Index (SLICC-ACR/DI).[14] Cumulative treatment data (prednisone, intravenous methylprednisolone, chloroquine diphosphate, hydroxychloroquine sulfate, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, intravenous cyclophosphamide, intravenous immunoglobulin, rituximab, and plasmapheresis) were also recorded.

Statistical analysis

Statistical analyses were carried out according to Statistical Package for the Social Sciences, version 13.0. Results were presented as a number (frequency) for categorical variables and median (range) or mean ± standard deviation (SD) for continuous variables. Categorical variables were first compared by Pearson χ^2 test, which necessitates that at least 80% of the cells have an expected frequency of ≥ 5 and no cell must have an expected frequency of < 1. If the subgroup analysis included less than 300 subjects and the criteria for Pearson χ^2 test was not met, then the Fisher–Freeman–Halton exact test was used. The Kruskal–Wallis test was used to compare continuous variables with non-normal distribution involving the three age groups (non-parametric one-way analysis of variance (ANOVA)), followed by a post-hoc

analysis using Dunn's multiple comparison test to determine where the difference had occurred between the three groups' outcomes. The significance level in all analyses was set at 5%.

Results

Patients were classified into three age groups: A 39 (4%), B 395 (47%), and C 413 (49%). Comparison of demographic data, cumulative clinical manifestations, and disease activity/damage scores at the last visit in 847 cSLE patients in three age groups are illustrated in Table 1. The median of disease duration was significantly higher in group A compared to groups B and C (8.3 (0.1–23.4) vs 6.2 (0–17) vs 3.3 (0–14.6) years, $p < 0.0001$), with similar frequencies of male gender (20% vs 16% vs 12%, p=0.155) (Table 1).

Groups had distinct patterns of cumulative characteristics. In group A, frequencies of cumulative fever (82% vs 76% vs 61%, $p < 0.0001$), overall reticuloendothelial manifestations (54% vs 48% vs 32%, $p < 0.0001$), and pericarditis (41% vs 28% vs 22%, $p = 0.011$) were significantly higher compared to groups B and C (Table 1). Regarding therapy, cyclosporine use was also more often observed in group A (24% vs 11% vs 8%, $p = 0.007$) (Table 2).

Mortality rate was significantly higher in group A compared to groups B and C (15% vs 10% vs 6%, $p = 0.028$). The median disease duration between cSLE diagnosis and death were similar in the three age groups (2.9 (0.3–12.8) vs 3.6 (0.17–12) vs 1.46 (0.6–15.3), $p = 0.068$) (Table 1). Of 69 deaths overall, 33/69 (48%) occurred during the first two years after diagnosis and 8/33 (24%) in the first month after diagnosis. Infections accounted for 54/69 (78%) of overall deaths, with 38/54 (70%) having presented concomitant disease activity. Other causes of death were nephritis (acute kidney injury or chronic renal disease) in six (9%) cSLE patients, alveolar hemorrhage in three (4%), massive intracranial bleeding in one (1.4%), multiple thrombosis due to catastrophic APS in one (1.4%), B-cell lymphoma in one (1.4%), and unknown etiologies in three (4%).

SLICC/ACR-DI score ≥ 1 was observed in 249/764 (33%) patients, with a similar frequency in all groups (39% vs 36% vs 29%, $p = 0.070$). Likewise, the median SLICC/ACR-DI (0 (0–9) vs 0 (0–6) vs 0 (0–7), $p = 0.065$) was low and comparable in the three age groups (Table 1). Further analysis of organ damage domain revealed that frequencies of neuropsychiatric (21% vs 10% vs 7%, $p = 0.007$), skin (10% vs 1% vs 3%, $p = 0.002$), and peripheral vascular damage (5% vs 3% vs 0.3%, $p = 0.008$) were more often observed in group A compared to groups B and C. The frequencies of renal (8% vs 7% vs 8%, $p = 0.912$) and musculoskeletal damage (10% vs 10% vs 10%, $p = 0.989$) were similar in all groups.

Group B had higher frequencies of cumulative central nervous system involvements (46% vs 58% vs 41%, $p < 0.0001$) compared to groups A and C (Table 1). The median of prednisone cumulative dose was significantly higher in group B versus groups A and C (20.6 (1.6–74.5) vs 21.7 (0.6–103.9) vs 17.6 (0.1–105.5) gm, $p = 0.015$) (Table 2). Ocular damage was observed more often in group B compared to groups A and C (10% vs 13% vs 7%, $p = 0.017$) (Table 1).

Group C had no distinct characteristics compared to groups A and B (Tables 1 and 2).

Discussion

We identified that cumulative clinical manifestations and disease damage of cSLE patients varied considerably according to patient's age at disease diagnosis, with distinct cumulative features particularly in the early-onset cSLE group. We also observed that death in cSLE patients was an early outcome mainly attributed to infections associated with disease activity.

With regard to the early-onset cSLE group, we confirmed a previous observation of higher frequency of deaths and identified that infection associated with disease activity was the main cause responsible for this outcome in this group of patients.[9] The reported disease severity related to male gender[6] did not seem to contribute to a higher frequency of death in the early-onset cSLE, since the male distribution was alike in the three age groups analyzed. The predominant cumulative clinical features in this age group was fever and reticuloendothelial manifestations, findings also reported in Chinese patients of the same age group.[5]

One third of our cSLE patients had at least one organ/system damaged, with a comparable frequency in the three age groups, in spite of distinct disease duration. This frequency of damage was similar to the one observed in an international study including 39 countries.[15] The predominance of neuropsychiatric damage in the early-onset cSLE is worrisome, since it may affect health-related quality of life and may induce learning disabilities.

Table 1 Demographic data, cumulative clinical manifestations, disease activity/damage scores at last visit, and deaths in 847 childhood-onset systemic lupus erythematosus (cSLE) patients according to age groups at diagnosis

Variables	*Group A (<6 yrs)* n = *39*	*Group B (≥6 <12 yrs)* n = *395*	*Group C (≥12 <18 yrs)* n = *413*	p
Demographic data				
Age at cSLE diagnosis, years, $n=847$	4.25 (0.25–5.9)	10 (6–11.9)	13.8 (12–17.8)	**<0.0001**[a]
Disease duration, years, $n=842$	8.3 (0.1–23.4)	6.2 (0–17)	3.3 (0–14.6)	**<0.0001**[a]
Male gender, $n=847$	8/39 (20)	63/395 (16)	50/413 (12)	0.155
Ethnic groups, $n=825$				NA
White	28/37 (76)	278/383 (73)	282/405 (70)	–
African–Latin American	9/37 (24)	101/383 (26)	115/405 (28)	–
Asian	0/37 (0)	2/383 (0.5)	2/405 (0.5)	–
Other/unknown	0/37 (0)	2/383 (0.5)	6/405 (1.5)	–
Cumulative clinical manifestations				
Fever, $n=843$	32/39 (82)	298/394 (76)	251/410 (61)	**<0.0001**
Reticuloendothelial manifestations, $n=844$	21/39 (54)	187/393 (48)	130/412 (32)	**<0.0001**
Mucocutaneous involvement, $n=846$	38/39 (97)	365/395 (92)	381/412 (92)	0.505
Musculoskeletal involvement, $n=847$	32/39 (82)	300/395 (76)	319/413 (77)	0.667
Serositis, $n=841$	19/39 (49)	143/392 (36)	131/410 (32)	0.071
Pericarditis, $n=841$	16/39 (41)	110/392 (28)	90/410 (22)	**0.011**
Nephritis, $n=842$	25/39 (64)	275/393 (70)	254/410 (62)	0.055
Neuropsychiatric involvement, $n=844$	18/39 (46)	229/395 (58)	173/410 (42)	**<0.0001**
Autoimmune hemolytic anemia, $n=837$	12/39 (31)	110/389 (28)	87/409 (21)	0.051
Thrombocytopenia, $<100{,}000/mm^3$, $n=838$	10/39 (26)	93/390 (24)	82/409 (20)	0.372
Current disease activity score at last visit				
SLEDAI-2K, $n=839$	6 (0–30)	4 (0–45)	4 (0–35)	0.615
SLEDAI-2K ≥ 8, $n=839$	16/39 (41)	96/390 (25)	86/410 (21)	**0.015**
Disease damage score at last visit				
SLICC/ACR-DI, $n=764$	0 (0–9)	0 (0–6)	0 (0–7)	0.065
SLICC/ACR-DI ≥ 1, $n=764$	15/38 (39)	130/362 (36)	104/364 (29)	0.070
Neuropsychiatric	8/38 (21)	36/362 (10)	24/364 (7)	**0.007**
Skin	4/38 (10)	5/362 (1)	10/364 (3)	**0.002**
Peripheral vascular	2/38 (5)	10/362 (3)	1/364 (0.3)	**0.008**
Ocular	4/38 (10)	48/362 (13)	25/364 (7)	**0.017**
Renal	3/38 (8)	25/362 (7)	28/364 (8)	0.912
Musculoskeletal	4/38 (10)	38/362 (10)	37/364 (10)	0.989
Cardiovascular	2/38 (5)	6/362 (2)	5/364 (1)	0.210
Deaths, $n=69/841$	6/39 (15)	39/393 (10)	24/409 (6)	0.028
Disease duration between cSLE diagnosis and death, years	2.9 (0.3–12.8)	3.6 (0.17–12)	1.46 (0.6–15.3)	0.068
Infections, $n=54/69$	5/6 (83)	29/39 (74)	20/24 (83)	NA
Infections associated with disease activity, $n=38/54$	3/5 (60)	20/29 (69)	15/20 (75)	NA

Results are presented in n(%) and median (range).
APS: antiphospholipid syndrome; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; NA: not applicable to assess Pearson χ^2 test.
[a]Post-hoc analysis by Dunn's multiple comparison test showed significant difference between all age groups ($p<0.001$).

In contrast to the early-onset cSLE group, the prepubertal patients had a low frequency of cumulative neuropsychiatric damage. The higher frequency of glucocorticoid use in these patients suggested that central nervous system lesions were probably responsive to this therapy, and the latter may explain the ocular damage observed in this transitional group.[16] Other studies, however, have not evidenced a distinct pattern of manifestations in this transition stage group.[5,6]

In spite of a report of an increased prevalence of musculoskeletal manifestations in Italian cSLE adolescents,[6] a unique characteristic in this age group was not observed here.

One of the advantages of the present study was the standardized protocol,[1,17–20] with established clinical parameters evaluated during the disease course, and disease activity/damage definitions for quantitative scores. Additionally, a representative large sample of cSLE patients was assessed, with a substantial inclusion of the death figures and accrued damage in the less frequent age group.[5–7,9] Nevertheless, the main limitation of our study was the missing data of some variables due to the

Table 2 Cumulative treatments at last visit in 847 childhood-onset systemic lupus erythematosus (cSLE) patients according to age groups at diagnosis

Cumulative treatments variables	*Group A (<6 yrs)* n = *39*	*Group B (≥6 <12 yrs)* n = *395*	*Group C (≥12 <18 yrs)* n = *413*	p
Nonsteroidal anti-inflammatory, $n = 840$	13/38 (34)	118/393 (30)	101/409 (25)	0.156
Prednisone, $n = 838$	38/38 (100)	384/390 (98)	403/410 (98)	0.717
Cumulative dose, gm, $n = 711$	20.6 (1.6–74.5)	21.7 (0.6–103.9)	17.6 (0.1–105.5)	0.015[a]
Intravenous methylprednisolone, $n = 839$	26/38 (68)	279/394 (71)	275/407 (68)	0.607
Cumulative dose, gm, $n = 473$	9 (1.4–78.6)	8.7 (0.2–138.5)	9 (0.5–111.7)	0.920
Total glucocorticoid dose, gm, $n = 689$	24.7 (1.6–111.6)	28.3 (0.5–205.5)	25.8 (0–2717)	0.687
Antimalarial drugs, $n = 842$	31/38 (82)	325/393 (82)	344/411 (83)	0.899
Immunosuppressive agents, $n = 843$	31/38 (81)	333/393 (85)	350/412 (85)	0.858
Azathioprine, $n = 839$	22/38 (58)	226/392 (58)	264/409 (64)	0.125
Cyclosporine, $n = 837$	9/38 (24)	43/390 (11)	22/409 (8)	0.007
Methotrexate, $n = 837$	10/38 (26)	100/389 (26)	80/410 (19)	0.097
Mycophenolate mofetil, $n = 835$	9/37 (24)	92/389 (23)	74/409 (18)	0.137
Intravenous cyclophosphamide, $n = 842$	17/38 (45)	186/393 (47)	149/411 (36)	0.006
Cumulative dose, gm, $n = 309$	6.8 (0.3–32)	7.8 (0.4–93)	6.4 (0.5–47)	0.373

Results are presented in *n*(%) and median (range).
ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; NA: not applicable to assess Pearson χ^2 test.
[a]Post-hoc analysis by Dunn's multiple comparison test showed significant differences between cumulative dose of prednisone between groups B vs C ($p < 0.05$).

retrospective study design. SLEDAI over time was also not assessed. Therefore, a further inception cohort study evaluating outcomes in a large Latin America cSLE population will be necessary.

In conclusion, this large multicenter study provided evidence that the early-onset cSLE group had distinct cumulative clinical features and outcomes. This group was characterized by higher mortality rate and neuropsychiatric/vascular/skin organ damage. We also identified that overall death in cSLE patients was an early outcome mainly attributed to infections associated with disease activity.

Acknowledgement

Our gratitude goes to Ulysses Doria-Filho for the statistical analysis.

Declaration of conflicting interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 301805/2013-0 to RMRP, 303752/2015-7 to MTT, 301479/2015-1 to CSM, 305068/2014-8 to EB and 303422/2015-7 to CAS), Federico Foundation (to EB, RMRP and CAS) and by Núcleo de Apoio à Pesquisa "Saúde da Criança e do Adolescente" da USP (NAP-CriAd) to CAS.

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