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ORIGINAL ARTICLE

Disease presentation of 1312 childhood-onset systemic lupus erythematosus: influence of ethnicity

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Abstract

Objective To evaluate the influence of ethnicity in presentation of childhood-onset systemic lupus erythematosus (cSLE) patients.

Methods This multicenter study included cSLE patients (American College of Rheumatology criteria) followed in 27 Pediatric Rheumatology services of Brazil. Ethnicities were classified in four groups according to the parents' and all four grandparents' self-reported ethnicity. The statistical analysis was performed using the Bonferroni's correction ($p < 0.0027$).

Results According to ethnic groups, 1537 cSLE patients were classified in Caucasian ($n = 786$), African-Latin American ($n = 526$), Asian ($n = 8$), and others/unknown ($n = 217$). Comparisons between 1312 African-Latin American and Caucasian revealed similar median age at cSLE diagnosis [12.2(2.6–18) vs. 12.1(0.3–18) years, $p = 0.234$], time interval to diagnosis [0.25(0–12) vs. 0.3(0–10) years, $p = 0.034$], and SLEDAI-2K score [14(0–55) vs. 14(0–63), $p = 0.781$] in both groups. The mean number of diagnostic criteria according to SLICC (6.47 ± 1.911 vs. 5.81 ± 1.631, $p < 0.0001$) and frequencies of maculopapular lupus rash (8% vs. 3%, $p < 0.0001$), palate oral ulcers (17% vs. 11%, $p = 0.001$), tongue oral ulcers (4% vs. 1%, $p = 0.001$), and nonscarring alopecia (29% vs. 16%, $p < 0.0001$) were significantly higher in African-Latin American, whereas malar rash (45% vs. 58%, $p < 0.0001$) was more frequent in Caucasian. The presence of anti-phospholipid antibody (23% vs. 12%, $p < 0.0001$), low complement levels (58% vs. 41%, $p < 0.0001$), and isolated direct Coombs test (10% vs. 5%, $p = 0.001$) was also significantly higher in the former group.

Conclusions Our study demonstrated that disease presentation severity of African-Latin American cSLE patients is comparable with Caucasian. Mucocutaneous manifestations and autoantibodies profile were the only distinctive features of the former group. The unique mixed background of Brazilian patients probably minimized race diversity spectrum of these patients.

Key Points
- *Our study demonstrated that disease presentation severity of African-Latin American cSLE patients is comparable with Caucasian.*
- *Mucocutaneous manifestations and autoantibodies profile were the only distinctive features of African-Latin American cSLE patients.*
- *African-Latin American cSLE patients had more often anti-phospholipid antibodies and hypocomplementemia.*
- *The unique mixed background of Brazilian patients probably minimized race diversity spectrum of these patients.*

Keywords Anti-phospholipid antibody · Childhood-onset systemic lupus erythematosus · Ethnicity · Race

Introduction

Childhood-onset systemic lupus erythematosus (cSLE) is a rare autoimmune systemic disease characterized by the loss of immunological tolerance to several autoantigens and formation of immune complexes that are deposited in tissues and

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organs with consequent inflammation [1–3]. The clinical findings at presentation in cSLE are extremely variable according to the organ or tissue involved [4].

Ethnicity, particularly in African-American, Hispanic, and Asian, has been reported to be a predisposing factor and prognostic factor in adults SLE [5]. In addition, there are differences between demographic data, clinical manifestations, and laboratory abnormalities in cSLE patients according to ethnicity around the world, based on case series or case reports [6–12]. In North America, Latin American, and Europe, cSLE is more common and more severe in African ancestry compared with Caucasian [6–12].

Severe disease presentation with highly active multiorgan disease at diagnosis was reported in cSLE patients in South Africa [7]. However, to our knowledge, the influence of ethnic background in pediatric lupus presentation was not evaluated in a large population of Latin American country.

Therefore, the objective of the present study was to assess demographic data, clinical manifestations, laboratory abnormalities, and disease activity score in cSLE patients according to ethnic groups at diagnosis.

Methods

This is a retrospective multicenter cohort study including 1697 patients followed in 27 Brazilian Pediatric Rheumatology centres. One hundred sixty cSLE patients were excluded due to incomplete medical charts ($n = 61$) and less than 3 American College of Rheumatology (ACR) criteria ($n = 99$) [13]. The remaining 1537 cSLE patients fulfilled the ACR criteria, with disease onset before the age of 18 [14]. This study was approved by all Ethics Committees of participating services.

An investigator meeting was taken place to define clinical, laboratorial, and disease activity parameters, as previously reported [4, 15, 16]. Ethnic groups of cSLE patients were defined according to the self-reported ethnicity of parents and all four grandparents [4, 12, 17–19]. cSLE patients were classified in four groups: Caucasian (patient with all white European ancestors), African-Latin American (patient with at least one African ancestor), Asian (patient with at least one Asian ancestor), and others/unknown (patient who did not fulfilled the aforementioned groups) [4, 12, 17]. Data was collected between September 2016 and May 2017.

Demographic data included age at diagnosis, time interval to diagnosis (interval between first signs/symptoms to cSLE diagnosis), and gender. Definitions of clinical and immunologic criteria were used based on Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus (SLICC) [20]: hemolytic anemia defined as anemia, reticulocytosis and direct Coombs test; leukopenia as $< 4000/mm^3$ at least once in the absence of other known causes such as Felty's drugs and portal hypertension, lymphopenia as $< 1000/mm^3$ at least once in the absence of other known causes such as corticosteroids, drugs, and infection; thrombocytopenia as $< 100{,}000/mm^3$ at least once in the absence of other known causes such as drugs, portal hypertension, and thrombotic thrombocytopenic purpura; and low complement as low C3, C4, and/or CH50.

SLE Disease Activity Index 2000 (SLEDAI-2 K) was used to score disease activity [21]. Lupus nephritis histopathology at diagnosis was analyzed according to International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification [22].

Statistical analysis The sample size provided power of 80% to find differences from 3.9 to 5.0% in the frequencies of clinical manifestations and immunological abnormalities among the African-Latin Americans and Caucasians groups (Graphpad StatMate 1.01, GraphPad Software, Inc., CA, USA). The Statistical Package for the Social Sciences version 13.0 was used. Data were presented in numbers (percentages) for categorical variables, and differences between groups were assessed by Pearson chi-square or Fisher's exact test, as indicated. Data were shown in median (minimum to maximum value) or mean ± standard deviation

Table 1 Demographic data and disease activity score in 1.312 childhood-onset systemic lupus erythematosus (cSLE) patients according to ethnicity at diagnosis

Variables	African-Latin Americans ($n = 526$)	Caucasians ($n = 786$)	p
Demographic data			
Age at cSLE diagnosis, years, $n = 1.311$	12.2 (2.6–18)	12.1 (0.3–18)	0.234
Time interval to diagnosis*, years, $n = 1.287$	0.25 (0–12)	0.3 (0–10)	0.034
Male gender, $n = 1.312$	87 (16.5)	126 (16)	0.806
Disease activity score at diagnosis			
SLEDAI-2 K, $n = 1.254$	14 (0–55)	14 (0–63)	0.781

Results are presented in n (%) and median (range); *interval between first signs/symptoms to cSLE diagnosis; *SLEDAI-2K*, Systemic Lupus Erythematosus Disease Activity Index 2000; p value according to Bonferroni correction for multiple comparisons ($p < 0.0027$)

Table 2 Clinical and immunological features of Systemic Lupus International Collaborating Clinics Classification Criteria (SLICC) definitions in 1.312 childhood-onset systemic lupus erythematosus (cSLE) patients according to ethnicity at diagnosis

Variables	African-Latin Americans ($n = 526$)	Caucasians ($n = 786$)	p
Number of SLICC criteria (4–17)	6.47 ± 1.911	5.81 ± 1.631	*< 0.0001**
Clinical criteria			
1. Acute cutaneous lupus	312 (59)	534 (68)	*0.001**
Malar rash	237 (45)	458 (58)	*< 0.0001**
Bullous lupus	15 (3)	12 (1)	0.098
Toxic epidermal necrolysis	1 (0,2)	1 (0,1)	1.000
Maculopapular lupus rash	45 (8)	26 (3)	*< 0.0001**
Photosensitive lupus rash	217 (41)	374 (48)	0.024
Subacute cutaneous lupus	17 (3)	14 (2)	0.09
2. Chronic cutaneous lupus	42 (8)	39 (5)	0.026
Discoid rash	39 (7)	31 (4)	0.006
Hypertrophic (verrucous) lupus	0 (0)	2 (0.3)	0.519
Lupus panniculitis	1 (0.2)	7 (0.9)	0.155
Mucosal lupus	1 (0.2)	1 (0.1)	1.000
Lupus erythematosus tumidus	1 (0.2)	2 (0.3)	1.000
Chillblains lupus	0 (0)	1 (0,1)	1.000
Overlap	3 (0.6)	1 (0.1)	0.308
3. Oral ulcers	186 (35)	245 (31)	0.113
Palate	91 (17)	86 (11)	*0.001**
Buccal	129 (24)	185 (23)	0.681
Tongue	20 (4)	9 (1)	*0.001**
Nasal	9 (2)	4 (0,5)	0.031
4. Nonscarring alopecia	155 (29)	130 (16)	*< 0.0001**
5. Synovitis	359 (68)	539 (69)	0.901
6. Serositis	153 (29)	200 (25)	0.145
Pleuritis	103 (20)	130 (16)	0.158
Pericarditis	110 (21)	141 (18)	0.180
7. Renal	206 (39)	330 (42)	0.308
Proteinuria > 500 mg/day	199 (38)	305 (39)	0.723
Red blood cells casts	55 (10)	89 (11)	0.623
8. Neuropsychiatric	65 (12)	79 (10)	0.190
9. Hemolytic anemia	132 (25)	149 (19)	0.008
10.Leukopenia or lymphopenia	228 (43)	321 (41)	0.367
11.Thrombocytopenia	117 (22)	131 (17)	0.011
Immunological criteria			
12. Anti-nuclear antibody	495 (94)	730 (93)	0.380
13. Anti-dsDNA antibody	309 (59)	471 (60)	0.670
14. Anti-Sm antibody	139 (26)	164 (21)	0.019
15. Anti-phospholipid antibody	123 (23)	94 (12)	*< 0.0001**
16. Low complement (C3/C4/CH50)	307 (58)	324 (41)	*< 0.0001**
17. Isolated direct Coombs test	52 (10)	39 (5)	*0.001**

Results are presented in n (%) and mean ± standard deviation; *p value according to Bonferroni correction for multiple comparisons ($p < 0.0027$).
The italicized data indicate p<0.05

for continuous variables, and further comparisons between groups were conducted using Mann-Whitney test or Student's t test, accordingly. p values less than 0.05 were considered significant. Holm-Bonferroni correction for multiple comparisons was carried-out adjusting the significance level for p values less than 0.0027.

Table 3 International Society of Nephrology/Renal Pathology Society (ISN/RPS) classification of lupus nephritis (LN) in 1312 childhood-onset systemic lupus erythematosus (cSLE) patients according to ethnicity at diagnosis

Variables	African-Latin Americans ($n = 526$)	Caucasians ($n = 786$)	p
Renal biopsy at diagnosis, number	61/526 (12)	82/786 (10)	0.527
Minimal mesangial LN (class I)	7/61 (12)	3/82 (4)	0.098
Mesangial proliferative LN (class II)	5/61 (8)	19/82 (23)	0.023
Focal LN (class III)	8/61 (13)	11/82 (14)	1.000
Diffuse LN (class IV)	33/61 (54)	33/82 (40)	0.090
Membranous LN (class V)	8/61 (13)	15/82 (18)	0.493
Advanced sclerotic LN (class VI)	0/61 (0)	1/82 (1)	1.000

Results are presented in n (%); *p value according to Bonferroni correction for multiple comparisons ($p < 0.0027$)

Results

All of 1537 cSLE patients fulfilled both ACR and SLICC criteria (four criteria, including at least one immunologic criterion and one clinical criterion). None of them fulfilled the isolated biopsy-proven nephritis compatible with SLE and anti-nuclear antibody or anti-dsDNA antibody.

According to ethnic groups, 1537 cSLE patients were classified in Caucasian ($n = 786$), African-Latin American ($n = 526$), others/unknown ($n = 217$), and Asians ($n = 8$).

Comparisons between African-Latin Americans ($n = 526$) and Caucasians ($n = 786$) revealed similar median age at cSLE diagnosis [12.2 (2.6–18) vs. 12.1 (0.3–18) years, $p = 0.234$], time interval to diagnosis [0.25 (0–12) vs. 0.3 (0–10) years, $p = 0.034$], and SLEDAI-2K score [14 (0–55) vs. 14 (0–63), $p = 0.781$] in both groups. The frequency of male gender was alike in both groups (16.5% vs. 16%, $p = 0.806$) (Table 1).

The mean number of diagnostic criteria according to SLICC (6.47 ± 1.911 vs. 5.81 ± 1.631, $p < 0.0001$) was significantly higher in African-Latin American compared with Caucasian (Table 2).

The frequencies of maculopapular lupus rash (8% vs. 3%, $p < 0.0001$), palate oral ulcers (17% vs. 11%, $p = 0.001$), tongue oral ulcers (4% vs. 1%, $p = 0.001$), and nonscarring alopecia (29% vs. 16%, $p < 0.0001$) were significantly higher in African-Latin American compared with Caucasian. The presence of anti-phospholipid antibody (23% vs. 12%, $p < 0.0001$), low complement levels (C3, C4, and/or CH50) (58% vs. 41%, $p < 0.0001$), and isolated direct Coombs test (10% vs. 5%, $p = 0.001$) was also significantly higher in the former group (Table 2).

In contrast, the frequencies of acute cutaneous lupus (59% vs. 68%, $p = 0.001$) and malar rash (45% vs. 58%, $p < 0.0001$) were significantly reduced in African-Latin American than Caucasian.

Renal histopathology at diagnosis was evaluated in 143/1312 (11%). Table 3 shown ISN/RPS classification of lupus nephritis in these 1312 cSLE patients according to ethnicity at diagnosis.

Discussion

Our study demonstrated that childhood lupus disease presentation severity of African-Latin American cSLE patients is comparable with Caucasian, with a higher frequency of mucocutaneous manifestations and autoantibodies in the former group.

The strengths of the present study were the large sample size of the cSLE population followed at 27 Brazilian Pediatric Rheumatology Services and the use of standardized database to reduce bias. The main weakness observed herein was the retrospective design with possible missing data. In addition, SLE susceptibility genes were not assessed herein and therefore the influence of specific alleles in ethnic disparity was not evaluated [23].

The definition of ethnicity including ancestry was relevant to homogenize ethnic groups in the present study, as also reported by other groups [4, 12, 17]. Patient self-designation of ethnicity is probably less accurate since may not outweigh the role of social group identity [24].

Our study demonstrated that disease presentation severity in African-Latin American cSLE patients was comparable with Caucasian. Both groups had a multisystemic disease with similar frequencies of nephritis and anti-dsDNA antibodies. The unique feature of the African-Latin American cSLE patients at presentation was a higher frequency of mucocutaneous manifestation, which may account for the reduced time interval to diagnosis, although not statistically significant.

In addition, renal pathological patterns at diagnosis were comparable in African-Latin American and Caucasian cSLE patients. These findings contrast with a study in adults that evidenced that glomerular pathology was more severe at presentation in African descendant compared with Caucasian patients with severe lupus nephritis [25].

Differences between autoantibodies and laboratory abnormalities have been reported in cSLE patients according to race/ethnicity [8, 11, 12]. We confirmed herein that African-

Latin American cSLE patients had more often antiphospholipid antibodies and hypocomplementemia. In addition, we identified that these patients have more frequently isolated direct Coombs test.

Age at diagnosis was similar in African-Latin American and Caucasian in the present study contrasting to the reported younger at cSLE diagnosis for African descendant compared with Caucasians in a Canadian study [9].

In conclusion, our study demonstrated that disease presentation severity of African-Latin American cSLE patients is comparable with Caucasian. Mucocutaneous manifestations and autoantibodies profile were the only distinctive features of the former group. The unique mixed background of Brazilian patients probably minimized race diversity spectrum of these patients.

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Compliance with ethical standards

Disclosures None.

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