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Review

Symptomatic polyautoimmunity at diagnosis of 1463 childhood-onset lupus: A Brazilian multicenter study

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ABSTRACT

Objective: To evaluate symptomatic polyautoimmunity (PA) at childhood-onset systemic lupus erythematosus (cSLE) diagnosis, and its association with demographic data, disease activity, clinical manifestations and laboratorial abnormalities in a large Brazilian cSLE population.

Methods: A multicenter retrospective study was performed in 1463 cSLE(ACR criteria) patients from 27 Pediatric Rheumatology services. Symptomatic PA was defined according to the presence of more than one concomitant autoimmune disease(AD) and symptomatic multiple autoimmune syndrome(MAS) was defined as three or more AD. An investigator meeting was held to define the protocol. Demographic data, SLICC classification criteria and SLEDAI-2K were evaluated.

Results: At cSLE diagnosis symptomatic PA was observed in 144/1463(9.8%) and symptomatic MAS occurred in solely 10/1463(0.7%). In the former group the more frequently observed associated AD were Hashimoto thyroiditis $n = 42/144(29\%)$, antiphospholipid syndrome $n = 42/144(29\%)$, autoimmune hepatitis $n = 26/144(18\%)$ and type 1 diabetes mellitus $n = 23/144(15.9\%)$. Further comparisons between cSLE patients with and without PA showed a higher median age($p = 0.016$) and lower mean SLICC criteria ($p = 0.039$) in those with PA. Additionally, these cSLE patients had less renal involvement(35% vs. 44%, $p = 0.038$) and red blood cell cast(6% vs. 12%, $p = 0.042$) and more antiphospholipid antibodies(29% vs. 15%, $p < 0.0001$).

Conclusions: Approximately 10% of cSLE had symptomatic PA at diagnosis, particularly endocrine autoimmune disorders and antiphospholipid syndrome. Lupus was characterized by a mild disease onset and MAS was infrequently evidenced. Further studies are necessary to determine if this subgroup of cSLE patients have a distinct genetic background with a less severe disease and a better long-term outcome.

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1. Introduction

Childhood-onset systemic lupus erythematosus (cSLE) is a chronic autoimmune illness with a broad clinical and laboratory spectrum, which may involve any organs and systems [1–6]. One hallmark of the cSLE is that autoantibodies are directed against several cellular antigens and with possibility of concomitant multiple organ-specific autoimmune diseases (AD) [1, 7, 8].

Polyautoimmunity (PA), which is defined according to the presence of more than one AD in each patient [9–11], has been described in up to 41% of adult SLE [9]. However, to our knowledge the prevalence of PA in cSLE in a large series has not been studied and the report of this very rare association is restricted to only a few case series [7, 12].

Therefore, the objective of this multicenter cohort study was to evaluate symptomatic PA at cSLE diagnosis and the possible association with demographic data, disease activity, clinical manifestations and laboratorial abnormalities in a large Brazilian cSLE population.

2. Methods

2.1. Study design and patients

This is a retrospective multicenter observational cohort study including 1697 consecutive patients followed in 27 Pediatric Rheumatology tertiary referral services in Brazil. Two hundred thirty-four cSLE patients were excluded due to: incomplete medical charts ($n = 135$) and undifferentiated connective tissue disorder with 3 or fewer American College of Rheumatology (ACR) criteria ($n = 99$). The remaining 1463 cSLE patients comprised the study group and all of them fulfilled the ACR criteria [13], with disease onset before 18 years of age [5]. All Ethics Committees of all participating centers in Brazil approved this study, after the approval of the coordinating center.

An investigator meeting was held for this study in Brasilia, at the Brazilian Congress of Rheumatology in 2016, to refine a previous protocol including definitions of clinical and disease activity parameters. One investigator with Brazilian Board Pediatric Rheumatology Certifying Examination supervised data collection in each center. Discrepancies were sorted out by one or more rounds of queries for accuracy. Data was collected between September 2016 and May 2017.

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

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

Demographic data included age at cSLE diagnosis and gender. Ethnics groups were classified in: Caucasian (patients with white European ancestors), Afro-Latin Americans (patients with at least one African ancestor), Asian (patients with at least one Asian ancestor) and other/unknown [6]. Definitions of clinical and immunologic criteria were used according to Systemic Lupus International Collaborating Clinics Classification Criteria for Systemic Lupus Erythematosus (SLICC) [14]. SLE Disease Activity Index 2000 (SLEDAI-2K) was used to assess disease activity [15].

Laboratory assessment included retrospective analysis of complete blood cell count, urinalysis and 24-h urine protein excretion or urine protein/creatinine ratio. Complement levels (CH50, C3 and C4) were assessed by immunodiffusion, turbidimetric immunoassay or immunonephelometry. Antinuclear antibodies (ANA) were tested by indirect immunofluorescence. Anti-double-stranded DNA (anti-dsDNA) were evaluated by indirect immunofluorescence or Enzyme Linked Immuno Sorbent Assay (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. All of them were carried out at each center. The cut-off values from the kit manufacturer were used to define abnormal values. Lupus anticoagulant was detected according to the guidelines of the International Society on Thrombosis and Hemostasis [16].

2.3. Polyautoimmunity diagnosis

Symptomatic PA was defined according to the presence of more than one AD in each patient. Symptomatic multiple autoimmune syndrome (MAS) was defined as three or more AD [9]. The following symptomatic AD were carefully assessed in all patient's chart: antiphospholipid syndrome [17, 18], autoimmune gastritis [19], autoimmune hepatitis [20–23], autoimmune sclerosing cholangitis [23, 24], autoimmune vitiligo [25], celiac disease [26], Hashimoto thyroiditis [27], Sjögren syndrome [28], type 1 diabetes mellitus (T1DM) [29] and myasthenia gravis [30].

Antiphospholipid syndrome was diagnosed according to the preliminary criteria for the classification of pediatric antiphospholipid syndrome [17, 18]. Autoimmune gastritis was defined by clinical manifestations (megaloblastic anemia secondary to vitamin B12 and iron deficiency, and diarrhea) associated with gastric atrophy confirmed by histology, positive parietal cell autoantibody and anti-intrinsic factor positivity [19]. Autoimmune hepatitis was defined as a progressive chronic hepatitis of unknown origin, with elevated transaminase levels, hypergammaglobulinemia, serum autoantibodies and histological characteristics [20–23]. Autoimmune sclerosing cholangitis was diagnosed according to clinical/biochemical features of cholestasis, presence of antimitochondrial antibody, and histological or cholangiographic findings [23, 24]. Autoimmune vitiligo was characterized by destruction of skin melano-cytes, hypopigmented and asymptomatic macules with demarcated margins and association with AD [25].

Celiac disease was defined by at least four of the following: clinical manifestations (such as chronic diarrhea, stunting and/or iron deficiency anemia), positivity for immunoglobulin A class anti-endomysial antibody, HLA-DQ2 or DQ8 genotype, small intestine biopsy compatible with celiac enteropathy, and response to gluten-free diet [26].

Hashimoto's thyroiditis was defined as clinical manifestations (such as goiter, increasingly fatigue, sluggish, dry skin, constipation, and/or hoarse voice) associated with reduced free thyroxine (T4) and elevated TSH levels [27]. The presence of at least one antithyroid antibody [antithyroid peroxidase antibody, anti-thyroglobulin antibody or antithyroid stimulating hormone receptor antibody] was required to characterize Hashimoto's thyroiditis [7].

Sjögren's syndrome was established according to the American-European Consensus Group [28]. T1DM was diagnosed by polyuria, polydipsia and unexplained weight loss, and increased plasma glucose ≥ 200 mg/dL at any time of day or fasting glucose ≥ 126 mg/dL [29], and without glucocorticosteroid use. Myastenia gravis was diagnosed according to ACR nomenclature and case definitions for neuropsychiatric lupus syndromes [30].

2.3.1. Statistical analysis

The results for the continuous variables were presented by median (minimum and maximum value) or mean ± standard deviation (SD), and for categorical variables presented as frequency (percentage). The scores that had normal and abnormal distributions were compared by Student's *t*-test and Mann-Whitney test, respectively. The differences of categorical variables were calculated by Fisher's exact test or Pearson chi-square test, as appropriated. The adopted significance levels in all analyses were set at 5%.

3. Results

Symptomatic PA was observed in 144/1463 (9.8%) at cSLE diagnosis. The following symptomatic AD were observed in cSLE patients at diagnosis: Hashimoto thyroiditis $n = 42/144$ (29%), antiphospholipid syndrome $n = 42/144$ (29%), autoimmune hepatitis $n = 26/144$

Table 1
Demographic data and disease activity score in 1463 childhood-onset systemic lupus erythematosus (cSLE) patients according to the presence of symptomatic polyautoimmunity (PA) at diagnosis.

Variables	With PA (n = 144)	Without PA (n = 1319)	p
Demographic data			
Age at cSLE diagnosis, years, n = 1463	13 (0.3–18)	12 (0.4–18)	0.016
Male gender, n = 222	19 (13)	203 (15)	0.486
Ethnic groups, n = 1448			0.461
Caucasian	65 (46)	671 (51)	–
Afro-Latin American	61 (44)	432 (33)	–
Asian	1 (0.7)	6 (0.5)	–
Other/unknown	13 (9)	199 (15)	–
Disease activity score at diagnosis, n = 1400			
SLEDAI-2 K, n = 1400	13 (1–48)	14 (1–63)	0.139
SLEDAI-2 K ≥ 8, n = 1400	111 (80)	1079 (85)	0.114

Results are presented in n (%) and median (range), SLEDAI-2K - Systemic Lupus Erythematosus Disease Activity Index 2000.

(18%), T1DM n = 23/144 (15.9%), autoimmune vitiligo n = 4/144 (2.8%), celiac disease n = 3/144 (2%), Sjögren syndrome n = 1/144 (0.7%), autoimmune gastritis n = 1/144 (0.7%), primary sclerosing cholangitis n = 1/144 (0.7%) and myasthenia gravis n = 1/144 (0.7%).

Symptomatic MAS was observed in 10/1463 (0.7%) patients, particularly T1DM and autoimmune hepatitis diseases in 6/10 patients.

Table 1 shows demographic data and disease activity score in 1463 cSLE patients according to the presence of symptomatic PA at diagnosis. The median age at cSLE diagnosis was higher in cSLE patients with PA compared to those without this condition [13 (0.3–18) vs. 12 (0.4–18) years, p = 0.016]. No differences were evidenced between gender, ethnicity and SLEDAI-2 K score between the two groups ($p > 0.05$, Table 1).

Table 2 illustrates clinical and immunological definitions of SLICC in 1463 cSLE patients according to the presence of symptomatic PA at diagnosis. The median of SLICC criteria was lower in cSLE patients with PA compared to those without [6 (4–11) vs. 6 (4–13), p = 0.039]. Frequencies of renal involvement (35% vs. 44%, p = 0.038) and red blood cell cast (6% vs. 12%, p = 0.042) were reduced in the former group, whereas antiphospholipid antibodies were higher in cSLE with PA (29% vs. 15%, $p < 0.0001$). No differences were evidenced in the other clinical manifestations and laboratorial tests in the two groups ($p < 0.05$, Table 2).

Table 2
Clinical and immunological definitions of Systemic Lupus International Collaborating Clinics Classification Criteria (SLICC) in 1463 childhood-onset systemic lupus erythematosus (cSLE) patients according to the presence of symptomatic polyautoimmunity (PA) at diagnosis.

Variables	With PA (n = 144)	Without PA (n = 1319)	p
Number of SLICC criteria (0–17), n = 1463	6 (4–11)	6 (4–13)	0.039
1. Acute cutaneous lupus	92 (64)	849 (64)	0.909
Malar rash	79 (55)	699 (53)	0.670
Bullous lupus	4 (3)	22 (2)	0.315
Toxic epidermal necrolysis	1 (0.7)	1 (0.1)	1.000
Maculopapular lupus rash	8 (6)	65 (5)	0.743
Photosensitive lupus rash	64 (44)	605 (46)	0.745
Subacute cutaneous lupus	3 (2)	30 (2)	1.000
2. Chronic cutaneous lupus	7 (5)	84 (6)	0.477
Discoid rash	6 (4)	69 (5)	0.582
Hypertrophic (verrucous) lupus	1 (0.7)	1 (0.1)	1.000
Lupus panniculitis	0 (0)	7 (0.5)	1.000
Mucosal lupus	0 (0)	1 (0.1)	1.000
Lupus erythematosus tumidus	0 (0)	2 (0.2)	1.000
Chillblains lupus	0 (0)	1 (0.1)	1.000
Overlap	0 (0)	5 (0.4)	1.000
3. Oral ulcers	50 (35)	453 (34)	0.928
Palate	22 (15)	170 (13)	0.422
Buccal	35 (24)	329 (25)	0.867
Tongue	5 (3)	25 (2)	0.209
Nasal	1 (0,7)	16 (1)	1.000
4. Nonscarring alopecia	38 (26)	276 (21)	0.129
5. Synovitis	104 (72)	920 (70)	0.539
6. Serositis	37 (26)	383 (29)	0.400
Pleuritis	22 (15)	238 (18)	0.410
Pericarditis	25 (17)	258 (20)	0.526
7. Renal	50 (35)	577 (44)	0.038
Proteinuria > 0.5 g/day	49 (34)	526 (40)	0,172
Red blood cells casts	9 (6)	157 (12)	0.042
8. Neurologic	17 (12)	151 (11)	0.898
9. Hemolytic anemia	36 (25)	281 (21)	0.307
10.Leukopenia or lymphopenia	66 (46)	555 (42)	0.387
11.Thrombocytopenia	26 (18)	248 (19)	0.827
Immunological criteria			
12. Antinuclear antibody	140 (97)	1240 (94)	0.114
13. Anti-dsDNA antibody	94 (65)	807 (61)	0.337
14. Anti-Sm antibody	38 (26)	306 (23)	0.391
15. Antiphospholipid antibody	42 (29)	201 (15)	< 0.0001
16. Low complement (C3, C4 or CH50)	68 (47)	615 (47)	0.892
17. Isolated direct Coombs test	9 (6)	83 (6)	0.984

Results are presented in n (%) and median (range).

4. Discussion

Our large Brazilian multicenter study demonstrated that almost 10% of cSLE had symptomatic PA at diagnosis, particularly endocrine autoimmune disorders and antiphospholipid syndrome. Patients with PA were older and had mild disease onset, and MAS was rarely observed.

The advantage of the study was the large sample size of the cSLE population followed at 27 Brazilian University Services, including centers of all regions of our country. Other relevant point was the use of a standardized database to minimize bias. The main weakness observed herein was the retrospective design, inclusion of only symptomatic PA which may have underestimated subclinical PA, and the lack of familiar history of autoimmunity.

The cSLE pathophysiology consists of an exacerbated response of B cells and T cells, loss of tolerance to autoantigens and the possibility of multiple organ-specific autoantibodies and PA [7, 31, 32]. The concomitance of one or several AD in cSLE patients observed herein corroborates with the hypothesis that these diseases may share the same underlying mechanism [9]. In fact, a lower frequency of nephritis was observed in this subgroup of patients suggesting a distinct phenotype with milder cSLE, contrasting with almost 50% nephritis in overall cSLE at disease onset [6, 33].

We further confirmed and extended previous observation of approximately 2–3% associated antiphospholipid syndrome at cSLE presentation [6, 33]. We further demonstrated that this frequency was comparable to symptomatic autoimmune thyroid disease, particularly Hashimoto's thryroiditis that was reported during follow-up in 5% of cSLE [7] and was not described at disease onset in a French study [33].

The occurrence of association of lupus and autoimmune hepatitis was reported from 1% to 10% of cSLE and adult SLE populations during follow-up [23, 34] and 0.4% at disease diagnosis [20], a frequency comparable to the one observed herein (1.7%). T1DM was also an uncommon autoimmune endocrine disorder (1.4%) and not related to glucocorticosteroid therapy [35].

MAS in adults had a distinct overlap profile compared to children with SLE. In adults the most frequent associated autoimmune disorders with SLE were Sjögren syndrome and rheumatoid arthritis [9], whereas in children and adolescents we observed more often T1DM and autoimmune hepatitis diseases.

In conclusion, 10% of cSLE had symptomatic PA at diagnosis with

mild disease onset and particularly associated with endocrine autoimmune disorders and antiphospholipid syndrome. Further studies are necessary to determine if this subgroup of cSLE patients have a distinct genetic background with a less severe disease and a better long-term outcome.

Disclosure statement

The authors have declared no conflicts of interest.

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