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Chronic Spontaneous Urticaria: A Survey of 852 Cases of Childhood-Onset Systemic Lupus Erythematosus

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Key Words
Childhood-onset systemic lupus erythematosus · Chronic spontaneous urticaria · Organ involvement

Abstract
Background: Data regarding the prevalence of chronic spontaneous urticaria (CSU) in childhood-onset systemic lupus erythematosus (cSLE) patients and possible associated factors are limited to a few case reports. The objectives of this study were to assess CSU in a large cSLE population, in order to evaluate the demographic data, clinical manifestations, disease activity/damage, laboratory abnormalities and treatment. ***Methods:*** A retrospective multicenter cohort study (Brazilian cSLE group) was performed in 10 Pediatric Rheumatology services and included 852 cSLE patients. CSU was diagnosed according to the guidelines of the European Academy of Allergy and Clinical Immunology, the Global Allergy and Asthma European Network, the European Dermatology Forum and the World Allergy Organization. Patients with CSU (evaluated at urticaria diagnosis) and patients without CSU (evaluated at the last visit) were assessed for lupus clinical/laboratory features and treatment. ***Results:*** CSU was observed in 10/852 cSLE patients (1.17%). The median of cSLE duration at urticaria diagnosis was 0 (–3 to 5) years. Comparison of cSLE patients with and without CSU revealed a greater frequency of constitutional symptoms (40 vs. 8%, $p = 0.006$), reticuloendothelial system involvement (30 vs. 3%, $p = 0.003$), mucocutaneous (90 vs. 28%, $p < 0.0001$) and musculoskeletal manifestations (50 vs. 6%, $p < 0.0001$) and methylprednisolone pulse therapy use (60 vs. 9%, $p < 0.0001$) in the former group. The frequency of immunosuppressive treatment was lower in patients with CSU ($p = 0.018$). The median SLE Disease Activity Index 2000 (12 vs. 2, $p < 0.0001$) and erythrocyte sedimentation rate (40 vs. 19 mm/1st hour, $p = 0.024$), was higher in patients with CSU. ***Conclusions:*** To our knowledge, this is the first study with evidence that CSU may be linked to cSLE. We also demon-

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strated that this particular skin manifestation occurs predominantly at disease onset and is associated with lupus moderate/high disease activity without major organ involvement.

Introduction

Childhood-onset systemic lupus erythematosus (cSLE) is a rare autoimmune disorder that may affect multiple organs and systems [1, 2]. The mucocutaneous involvement has been reported in approximately 70% of these patients [1, 3, 4].

Indeed, a variety of cutaneous manifestations can be observed in lupus patients [1, 3, 4], including urticaria [5–8]. This skin involvement is defined by the sudden onset of wheals, angioedema or both. Wheals are characterized by evanescent lesions, with central swelling of variable size usually surrounded by a reflex erythema, and associated with an itching or burning sensation [9].

A previous study found that patients with chronic urticaria have a higher incidence of SLE in the adult population, but a systematic evaluation of disease parameters was not performed [5]. Few case reports have evaluated urticaria either in adult cSLE patients [6–8]. However, the prevalence of this manifestation in the pediatric lupus population and the possible associated factors have not been studied.

Therefore, the objective of this study was to assess chronic spontaneous urticaria (CSU) in a large cSLE population, and to evaluate demographic data, clinical manifestations, disease activity, cumulative disease damage, laboratory abnormalities and treatment.

Materials and Methods

Study Procedure and Patient Selection

This was a retrospective, multicenter cohort study (Brazilian cSLE group) including 1,017 cSLE patients followed in 10 Pediatric Rheumatology tertiary referral services in São Paulo State, Brazil. One hundred and sixty-five patients were excluded due to incomplete medical charts (n = 96), undifferentiated connective tissue disorder with ≤3 American College of Rheumatology (ACR) criteria (n = 43), isolated cutaneous lupus erythematosus (n = 11), neonatal lupus erythematosus (n = 8), drug-induced lupus (n = 5) and other autoimmune diseases (n = 2). None of the patients had urticaria vasculitis, hypocomplementemic urticaria vasculitis syndrome or malignancies. Therefore, the study group comprised 852 cSLE patients. All patients fulfilled the ACR lupus criteria [10], with disease onset before 18 years of age [11] and current age of ≤25 years. The Committee for Research Ethics of each center approved the study.

An investigator meeting was held for this study on the 29 September 2012 in São Paulo city to define the protocol and standardize clinical, laboratory and treatment parameters definition, disease activity and damage-tools scoring. Data collection training was conducted locally by investigators in each center and a unique database was built up (by M.P.L.F. and M.F.C.S.). Data discrepancy was sorted out by ≥1 rounds of queries for accuracy. Data were collected between November 2012 and October 2014.

Patient's medical charts were carefully reviewed according to an extensive standardized protocol for demographic data, clinical features, laboratory findings, therapeutic data, outcomes and CSU characteristics. Patients with CSU (evaluated at urticaria diagnosis) and patients without CSU (evaluated at the last visit) were divided in 2 groups and assessed for the clinical, laboratory and treatment features of lupus.

CSU was diagnosed according to the dermatology section of the guidelines of the European Academy of Allergy and Clinical Immunology, the EU-funded Network of Excellence, the Global Allergy and Asthma European Network, the European Dermatology Forum and the World Allergy Organization, and defined as the spontaneous appearance of at least one manifestation, i.e. a wheal and/or angioedema that lasted for ≥6 weeks, excluding inducible urticaria [9]. We evaluated the total urticaria duration (from onset of wheals to complete resolution), the time between urticaria onset and cSLE diagnosis, the distribution of wheals, the presence of angioedema, painful lesions, current allergies (rhinitis and asthma), a family history of atopic diseases and current infections. Eosinophilia (>500 eosinophils/mm^3) and elevated levels of serum IgE (>200 IU/ml) were also evaluated.

Demographic Data, Clinical Evaluation, Disease Activity and Damage and Therapies

Demographic data included gender, race, current age, age at cSLE onset and disease duration. SLE clinical manifestations were defined as: constitutional symptoms (fever and weight loss), involvement of the reticuloendothelial system (adenomegaly, hepatomegaly and splenomegaly), mucocutaneous lesions (malar or discoid rash, photosensitivity, nasal or oral ulcers, alopecia and cutaneous vasculitis, i.e. ulceration, periungueal infarction or splinter hemorrhage), musculoskeletal involvement (nonerosive arthritis and myositis), serositis (pleuritis and pericarditis), nephritis (proteinuria ≥0.5 g/24 h, the presence of cellular casts, persistent hematuria ≥5 red blood cells/high-power field and/or persistent leukocituria ≥5 leukocytes/high-power field), hematologic abnormalities, i.e. autoimmune hemolytic anemia, leukopenia (a white blood cell count <4,000/mm^3), lymphopenia (lymphocytes <1,500/mm^3) and thrombocytopenia (a platelet count <100,000/mm^3) on two or more occasions in the absence of drugs or infection. Neuropsychiatric lupus included 19 syndromes according to ACR classification criteria [12]. Hypothyroidism was defined as reduced free thyroxine (T_4) and elevated thyroid-stimulating hormone (TSH) levels, and subclinical hypothyroidism as elevated TSH associated with normal T_4. The presence of antithyroid antibodies, i.e. antithyroid peroxidase, antithyroglobulin and anti-TSH receptor antibody, and hypothyroidism was necessary for a diagnosis of autoimmune thyroiditis [13]. Antiphospholipid syndrome was diagnosed according to the presence of arterial and/or venous thrombosis and antiphospholipid antibodies [14].

High blood pressure was defined as systolic and/or diastolic blood pressures ≥95th percentile for gender, age and height on ≥3

Table 1. CSU characteristics in cSLE patients

Characteristics	Patient No.									
	1	2	3	4	5	6	7	8	9	10
Age at CSU onset, years	13.1	10.7	10.2	13.2	17.1	16.2	7.1	8.7	13.8	15.7
Disease duration until CSU, months	–36	0	–6	7	1	0	0	0	61	0
Total duration of CSU, days	65	60	272	270	140	240	720	140	44	760
Angioedema	yes	no	no	no	no	yes	no	no	no	yes
Allergic asthma	yes	no	no	no	no	no	no	no	yes	no
Allergic rhinitis	no	no	yes	no	no	yes	no	no	no	no
Autoimmune thyroiditis	yes	no	no	no	no	no	yes	no	no	no
Drug therapy	CE, AH	CE, AH	CE, AH, AM	CE, AH, AM	CE, AM	CE, AH, AM	CE, AM, Aza	CE, AM	CE, AM, Mtx	CE, AH, AM

AH = H1-antihistamines; AM = antimalarials; Aza = azathioprine; CE = corticosteroids; Mtx = methotrexate.

occasions [15]. Acute kidney injury was determined by a sudden increase in serum creatinine >2 mg/dl [16] or by modified RIFLE (risk, injury, failure, loss of kidney function and end-stage kidney disease) criteria [17]. Chronic renal disease was defined as structural or functional abnormalities of the kidney for ≥3 months (with or without a decreased glomerular filtration rate) or a glomerular filtration rate <60 ml/min/1.73 m^2 for ≥3 months [18].

Laboratorial assessment included the erythrocyte sedimentation rate, C-reactive protein, a complete blood cell count, serum urea and creatinine, urinalysis and 24-hour urine protein excretion. Complement levels (CH50, C3 and C4) and anti-double-stranded DNA autoantibodies were carried out at each of the centers involved and the cut off values were considered valid. SLE disease activity and cumulative damage were scored according to the SLE Disease Activity Index 2000 (SLEDAI-2K) [19], which may range from 0 to 105, and the Systemic Lupus International Collaborating Clinics/ACR-Damage Index [20], which may range from 0 to 47, respectively.

Current therapy (prednisone, intravenous methylprednisolone pulse, chloroquine diphosphate, hydroxychloroquine sulfate, methotrexate, azathioprine, cyclosporine, mycophenolate, intravenous cyclophosphamide, intravenous gammaglobulin and rituximab) was also recorded.

Statistical Analysis

Results are presented as number (%) for categorical variables and median (range) for continuous variables. Comparisons of categorical variables were assessed by the Fisher exact test. Continuous variables from cSLE patients with and without CSU were compared with the Mann-Whitney test. The significance levels of the independent variables were set at 5% ($p < 0.05$).

Results

CSU was observed in 10/852 cSLE patients (1.17%) with a median of total urticaria duration of 190 days (44–760 days). The median cSLE duration at urticaria diagnosis was 0 (–3 to 5) years and the age at urticaria onset was 13 (7–17) years. Isolated CSU was observed in 2 cSLE patients before lupus diagnosis, at diagnosis in 5 and after diagnosis in 3. Wheals were present in all of the 10 cSLE patients and angioedema was observed in 3. Wheal distribution was diffuse (trunk, upper/lower limbs and/or face) in 9 and in the lower limbs in 1. None of them had painful lesions, acute/chronic infections or helminthic parasitic infections. Current allergies were reported in 4/10 patients: rhinitis in 2 and asthma in 2. A family history of atopic diseases was observed in 3/10 patients. Eosinophilia was evident in 1/10 with no allergy spectrum. IgE was available in 5/10 cSLE patients and an elevated serum IgE level was observed in 1/5 cSLE patients without asthma or rhinitis. Moderate disease activity, at least (SLEDAI-2K ≥6), was observed in 100%. Medications used for CSU included H1-antihistamines and glucocorticoids for 2 patients who developed CSU before cSLE diagnosis. The other patients presenting with CSU at or after lupus diagnosis were treated with H1-antihistamines (60%), glucocorticoids (100%), antimalarials (80%) and immunosuppressive agents (20%). Table 1 shows CSU characteristics in cSLE patients.

Demographic data, clinical manifestations and disease activity/damage scores in 852 cSLE patients according to the presence of CSU are shown in table 2. The comparison of cSLE patients with and without CSU revealed greater frequency of constitutional symptoms (40 vs. 8%, $p = 0.006$), reticuloendothelial system involvement (30 vs. 3%, $p = 0.003$) and mucocutaneous (90 vs. 28%, $p < 0.0001$) and musculoskeletal manifestations (50 vs. 6%, $p < 0.0001$). The median SLEDAI-2K (12 vs. 2, $p < 0.0001$) was also significantly greater in patients with CSU. Disease damage (current Systemic Lupus International Col-

Table 2. Demographic data, clinical manifestations and disease activity/damage scores in 852 cSLE patients at CSU diagnosis compared to those without CSU (at last visit)

Variables	With CSU (n = 10)	Without CSU (n = 842)	p value
Demographic data			
Female gender (n = 852)	8/10 (80)	724/842 (86)	0.639
Caucasian (n = 830)	8/10 (80)	584/820 (71)	0.733
Age at cSLE onset, years (n = 846)	11.62 (7.1–17)	11.87 (0.25–17.83)	0.554
Clinical manifestations			
Constitutional features (n = 848)	4/10 (40)	64/838 (8)	0.006
Fever (n = 848)	2/10 (20)	47/838 (6)	0.109
Weight loss (n = 823)	3/10 (30)	27/813 (3)	0.004
Reticuloendothelial system involvement (n = 848)	3/10 (30)	23/838 (3)	0.003
Lymphadenopathy (n = 847)	2/10 (20)	11/837 (1)	0.009
Hepatomegaly (n = 848)	1/10 (10)	17/838 (2)	0.194
Splenomegaly (n = 848)	0/10 (0)	6/838 (1)	1.000
Mucocutaneous involvement (n = 850)	9/10 (90)	239/840 (28)	<0.0001
Malar rash (n = 847)	6/10 (60)	114/837 (14)	0.001
Discoid rash (n = 849)	0/10 (0)	12/839 (1)	1.000
Photosensitivity (n = 850)	8/10 (80)	107/840 (13)	<0.0001
Mucosal ulcers (n = 849)	1/10 (10)	35/839 (4)	0.353
Alopecia (n = 849)	4/10 (40)	63/839 (7)	0.005
Cutaneous vasculitis (n = 848)	4/10 (40)	52/838 (6)	0.003
Musculoskeletal involvement (n = 850)	5/10 (50)	52/840 (6)	<0.0001
Arthritis (n = 849)	4/10 (40)	47/839 (6)	0.002
Myositis (n = 849)	1/10 (10)	6/839 (1)	0.080
Serositis (n = 850)	0/10 (0)	13/840 (1)	1.000
Pleuritis (n = 848)	0/10 (0)	11/838 (1)	1.000
Pericarditis (n = 848)	0/10 (0)	11/838 (1)	1.000
Neuropsychiatric involvement (n = 850)	1/10 (10)	68/840 (8)	0.573
Central nervous system (n = 847)	1/10 (10)	67/837 (8)	0.569
Peripheral nervous system (n = 844)	0/10 (0)	4/834 (0)	1.000
Nephritis (n = 830)	3/10 (30)	165/820 (20)	0.432
Other			
Arterial hypertension (n = 842)	1/10 (10)	108/832 (13)	1.000
Acute renal failure (n = 841)	0/10 (0)	31/831 (4)	1.000
Chronic renal failure (n = 841)	0/10 (0)	25/831 (3)	1.000
Disease activity/damage			
SLEDAI-2K (n = 753)	12 (4–24)	2 (0–45)	<0.0001
SLICC/ACR-DI (n = 770)	0 (0–1)	0 (0–9)	0.740

Results are presented as n (%) or median (range). SLICC/ACR-DI = Systemic Lupus International Collaborating Clinics/ACR – Damage Index.

laborating Clinics/ACR-Damage Index value) was similar in the 2 groups (p = 0.740; table 2).

Laboratory characteristics and treatment of 852 cSLE according to the presence of CSU are illustrated in table 3. The median erythrocyte sedimentation rate (40 vs. 19 mm/1st hour, p = 0.024) and current prednisone dose in mg/day (30 vs. 11.2, p = 0.010) and in mg/kg/day (0.89 vs. 0.22, p < 0.0001) were significantly higher in patients with CSU than in without urticaria. The use of methylprednisolone pulse therapy (60 vs. 9%, p < 0.0001) was significantly greater in the former group. The frequency of immunosuppressive treatment was lower in patients with CSU (20 vs. 61%, p = 0.018; table 3).

Further analysis of associated diseases demonstrated that autoimmune thyroiditis was evident in 2/10 of CSU cSLE patients (20%) compared to 30/806 without CSU (4%, p = 0.055). No case of antiphospholipid syndrome was observed in the former group (0 vs. 5%, p = 1.0).

Table 3. Laboratory characteristics and treatment of 852 cSLE patients at CSU diagnosis compared to the patients without CSU (at the last visit)

Variables	With CSU (n = 10)	Without CSU (n = 842)	p value
Laboratory values			
ESR, mm/1st hour, (n = 709)	40 (15–95)	19 (1–135)	0.024
CRP, mg/dl (n = 551)	1.79 (0–14)	0.7 (0–404)	0.320
Autoimmune hemolytic anemia (n = 825)	0/10 (0)	26/815 (3)	1.000
Leukopenia <4,000/mm^3 (n = 788)	1/10 (10)	62/778 (8)	0.568
Lymphopenia <1,500/mm^3 (n = 788)	3/10 (30)	138/778 (18)	0.396
Thrombocytopenia, <150,000/mm^3 (n = 793)	0/10 (0)	37/783 (5)	1.000
Hematuria (n = 755)	3/10 (30)	133/745 (18)	0.398
Cilindruria (n = 746)	0/10 (0)	27/736 (4)	1.000
Proteinuria (n = 641)	1/10 (10)	149/631 (24)	0.466
Low C3, C4 and/or CH50 (n = 617)	5/8 (62)	271/609 (44)	0.477
Anti-double-stranded DNA (n = 718)	3/10 (30)	265/708 (37)	0.751
Treatment			
Nonsteroidal anti-inflammatory drugs (n = 840)	0/10 (0)	46/830 (5)	1.000
Glucocorticosteroids			
Prednisone (n = 842)	10/10 (100)	655/832 (79)	0.132
Current dose, mg/day (n = 665)	30 (1–60)	11.2 (1–90)	0.010
mg/kg/day (n = 644)	0.89 (0.35–1.2)	0.22 (0.02–10)	<0.0001
Methylprednisolone pulse therapy (n = 838)	6/10 (60)	71/828 (9)	<0.0001
Antimalarial drugs (n = 839)	8/10 (80)	558/829 (67)	0.513
Chloroquine diphosphate (n = 814)	2/10 (20)	129/804 (16)	0.667
Hydroxychloroquine sulfate (n = 816)	6/10 (60)	444/806 (55)	1.000
Immunosuppressive agents (n = 843)	2/10 (20)	505/833 (61)	0.018
Azathioprine (n = 840)	1/10 (10)	287/830 (35)	0.178
Cyclosporine (n = 843)	0/10 (0)	30/833 (4)	1.000
Methotrexate (n = 842)	1/10 (10)	70/832 (8)	0.588
Mycophenolate mofetil (n = 843)	0/10 (0)	117/833 (14)	0.373
Cyclophosphamide (n = 842)	0/10 (0)	45/832 (5)	1.000
Other			
Intravenous immunoglobulin (n = 842)	0/10 (0)	14/832 (2)	1.000
Rituximab (n = 841)	0/10 (0)	1/831 (0)	1.000

Results are presented as n (%) or median (range). CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

Discussion

To our knowledge, this is the first study with evidence that CSU may be linked to cSLE patients and associated with moderate/high disease activity.

The strength of this multicentric study was the large sample size of the cSLE population followed at 10 university services in São Paulo State, Brazil, as well as the use of a standardized database to minimize bias. The CSU definition was based on international consensus [9]. Diseases related to urticaria/angioedema were excluded, particularly urticaria vasculitis and hypocomplementemic urticaria vasculitis syndrome [21–23], since these abnormalities are associated with localized, nonblanching, painful lesions [23] which persist for >24 h and leave brownish residues when healed [22].

The main weakness of the study was the retrospective design with possible missing data. An evaluation of autoimmune markers associated with CSU, such as an autologous serum skin test or circulating functional autoantibodies (directed against IgE or high-affinity IgE receptor – FcεRI), was not performed [24–27], and an IgE measurement was not available for all patients with CSU. Cryopyrin-associated periodic syndromes and hereditary or acquired C1 esterase inhibitor deficiency were also not systematically evaluated.

Other autoimmune disorders have been associated with CSU, including dermatomyositis, polymyositis, Sjögren syndrome and juvenile idiopathic arthritis [28]. We describe a low frequency of CSU in a large population of cSLE patients. Of note, the majority of cSLE patients presented this skin manifestation before or at disease onset, as was also observed previously in case reports of adult and cSLE patients [6, 8].

Interestingly, our study indicated that CSU may be linked to active cSLE, with a predominance of constitutional, mucocutaneous and musculoskeletal involvement, without a high frequency of severe lupus manifestations.

We also evaluated antithyroid antibodies, which are the most common autoantibodies reported in adults (14–33%) and children (4.3%) with chronic urticaria [5, 24, 29–32]. Twenty percent of the cSLE patients with CSU evaluated had autoimmune thyroid disease; this contrasts with the 7% of this endocrine abnormality previously reported in a cohort study regarding the overall cSLE population at a single center [13]. The pathophysiology of this disorder is unknown, but the immune dysregulation may be related to autoimmunity or to chronic inflammatory processes [5].

The frequency of CSU in cSLE is within the expected range reported in other populations of children and adolescents (0.1–3%) [31, 33]. There are, however, no systematic studies regarding the prevalence of CSU in the Brazilian pediatric population. In addition, the analysis of the influence of race was hampered by the small representation of non-Caucasian patients in our sample.

CSU may be triggered by lupus treatment medications, particularly nonsteroidal anti-inflammatory drugs [9, 28, 29], but none of our patients was under this therapy at CSU onset. The majority of cSLE patients were treated with H1-antihistamines, according to the literature recommendations [28, 29]. Moderate glucocorticoid dose and/or intravenous methylprednisolone pulse were required to treat our lupus patients with CSU and the majority did not need immunosuppressive agents.

In conclusion, urticaria was linked to early cSLE. We also demonstrated that this skin manifestation is associated with lupus moderate/high disease activity without major organ involvement.

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Disclosure Statement

The authors have no conflict of interest that is directly relevant to the content of this manuscript.

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