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CONCISE REPORT

Herpes zoster infection in childhood-onset systemic lupus erythematosus patients: a large multicenter study

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Objective: The aim of this multicenter study in a large childhood-onset systemic lupus erythematosus (cSLE) population was to assess the herpes zoster infection (HZI) prevalence, demographic data, clinical manifestations, laboratory findings, treatment, and outcome. **Methods:** A retrospective multicenter cohort study (Brazilian cSLE group) was performed in ten Pediatric Rheumatology services in São Paulo State, Brazil, and included 852 cSLE patients. HZI was defined according to the presence of acute vesicular-bullous lesions on erythematous/edematous base, in a dermatomal distribution. Post-herpetic neuralgia was defined as persistent pain after one month of resolution of lesions in the same dermatome. Patients were divided in two groups for the assessment of current lupus manifestations, laboratory findings, and treatment: patients with HZI (evaluated at the first HZI) and patients without HZI (evaluated at the last visit). **Results:** The frequency of HZI in cSLE patients was 120/852 (14%). Hospitalization occurred in 73 (61%) and overlap bacterial infection in 16 (13%). Intravenous or oral aciclovir was administered in 113/120 (94%) cSLE patients at HZI diagnosis. None of them had ophthalmic complication or death. Post-herpetic neuralgia occurred in 6/120 (5%). After Holm–Bonferroni correction for multiple comparisons, disease duration (1.58 vs 4.41 years, $p < 0.0001$) was significantly lower in HZI cSLE patients compared to those without HZI. Nephritis (37% vs 18%, $p < 0.0001$), lymphopenia (32% vs 17%, $p < 0.0001$) prednisone (97% vs 77%, $p < 0.0001$), cyclophosphamide (20% vs 5%, $p < 0.0001$) and SLE Disease Activity Index 2000 (6.0 (0–35) vs 2 (0–45), $p < 0.0001$) were significantly higher in the former group. The logistic regression model showed that four independent variables were associated with HZI: disease duration < 1 year (OR 2.893 (CI 1.821–4.597), $p < 0.0001$), lymphopenia <1500/mm^3 (OR 1.931 (CI 1.183–3.153), $p = 0.009$), prednisone (OR 6.723 (CI 2.072–21.815), $p = 0.002$), and cyclophosphamide use (OR 4.060 (CI 2.174–7.583), $p < 0.0001$). **Conclusion:** HZI is an early viral infection in cSLE with a typical dermatomal distribution. Lymphopenia and immunosuppressive treatment seem to be major factors underlying this complication in spite of a benign course. *Lupus* (2016) **25,** 754–759.

Key words: Infection; herpes zoster infection; childhood-onset systemic lupus erythematosus; multicenter cohort

Introduction

Herpes zoster infection (HZI) is a painful neurocutaneous disease caused by reactivation of the *Varicella zoster* virus, and has been described in adult systemic lupus erythematosus (SLE) patients.[1]

Data in childhood-onset systemic lupus erythematosus (cSLE) patients is limited due to the small representation of this complication in previous case series precluding an accurate comparison of patients with and without HZI to determine risk factors and outcomes.[1–4]

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In addition, glucocorticoid and cyclophosphamide use was not identified as a trigger for HZI in cSLE,[1,2] and the lack of information regarding current/cumulative dose hampers this interpretation.

Therefore, the aim of this multicenter study in a large cSLE population was to assess HZI prevalence, demographic data, clinical manifestations, laboratory findings, treatment, and outcome.

Methods

Study design and patients

This is a retrospective multicenter cohort study including 1017 cSLE patients followed in the ten pediatric rheumatology tertiary referral services of São Paulo state, Brazil. One hundred and sixty five patients were excluded due to incomplete medical charts ($n=96$), undifferentiated connective tissue disorder with three or fewer ACR criteria ($n=43$), isolated cutaneous lupus erythematosus ($n=11$), neonatal lupus erythematosus ($n=8$), drug-induced lupus ($n=5$), and other autoimmune diseases ($n=2$). The remaining 852 cSLE patients comprised the study group. All patients fulfilled the American College of Rheumatology (ACR) criteria,[5] with disease onset before 18 years of age[6] and current age under 25 years.

HZI was defined according to the presence of acute vesicular-bullous lesions on erythematous/edematous base, in a dermatomal distribution. Post-herpetic neuralgia was defined as persistent pain after one month of resolution of lesions in the same dermatome.[1] Data concerning HZI onset, dermatomal involvement and location, treatment, recurrence, and complications associated with HZI were also determined.

An investigator meeting was held for this study on 29 September 2012 in São Paulo city to define the protocol to harmonize clinical parameter definitions, disease activity and damage tools scoring, and outcome parameters. Investigators in each of the centers conducted data collection training locally. Data discrepancy was sorted out by one or more rounds of queries to check 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 HZI characteristics.

Demographic data, clinical evaluation, disease activity, disease damage and therapy

Demographic data included gender, ethnicity, current age, age at cSLE onset, and disease duration. SLE clinical manifestations were defined as constitutional symptoms (fever and weight loss), involvement of the reticulo-endothelial system (lymphadenopathy, hepatomegaly, and splenomegaly), mucocutaneous lesions (malar or discoid rash, photosensitivity, nasal or oral ulcers, vasculitis, and alopecia), musculoskeletal involvement (arthritis and myositis), serositis (pleuritis and pericarditis), nephritis (proteinuria $\geq$0.5 g/24 h, presence of cellular casts, hematuria $\geq$5 red blood cells per high power field and/or leukocituria $\geq$5 leukocytes per high power field), hematologic abnormalities (autoimmune hemolytic anemia, leukopenia (white blood cells count $<4000/mm^3$), lymphopenia (lymphocytes count $<1500/mm^3$) and thrombocytopenia (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.[7] Antiphospholipid syndrome (APS) was diagnosed according to the presence of arterial and/or venous thrombosis and antiphospholipid antibodies.[8]

High blood pressure was defined as systolic and/or diastolic blood pressures $\geq$95th percentile for gender, age, and height on at least three occasions.[9] Acute kidney injury was determined by sudden increase in serum creatinine above 2 mg/dL or by modified RIFLE (Risk, Injury, Failure, Loss of kidney function, and End-stage kidney disease) criteria.[10] Chronic renal disease was defined as structural or function abnormalities of the kidney for $\geq$3 months (with or without decreased glomerular filtration rate) or glomerular filtration rate $<$60 mL/min/1.73 m^2 for $\geq$3 months.[11]

Laboratorial assessment included erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood cell count, serum urea and creatinine, urinalysis, and 24-hour urine protein excretion. Complement levels (CH50, C3, and C4), anti-double-stranded DNA (anti-dsDNA), anticardiolipin antibodies (aCL), IgG and IgM antibodies, and lupus anticoagulant were carried out at each center. The cut-off values were considered abnormal according to the kit manufacturer.

SLE disease activity and cumulative damage were scored through the SLE Disease Activity Index 2000 (SLEDAI-2K)[12] and the Systemic

Lupus International Collaborating Clinics/ACR Damage Index (SLICC/ACR-DI),[13] respectively.

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

Patients were divided in two groups for the assessment of current lupus manifestations, laboratory findings, and treatment: patients with HZI (evaluated at the first HZI) and patients without HZI (evaluated at the last visit).

Statistical analysis

Results were presented as absolute number (frequency) for categorical variables and median (range) or mean ± SD for continuous variables. Categorical variables comparisons were assessed by Pearson χ^2 or Fisher's exact test. Continuous variables from cSLE patients with and without HZI were compared by Mann–Whitney test or *t* test. The significance levels of the independent variable were set at 5% ($p < 0.05$). Holm–Bonferroni correction for multiple comparisons was performed adjusting the significance level to $p < 0.002$. Logistic regression models were performed to identify independent variables associated with HZI. In the multiple model, we used as independent variables those that presented a level of 20% of significance in the univariate analysis. Results of the regression models were shown as the odds ratio (OR) and 95% confidence interval (95% CI).

Results

HZI was observed in 120/852 (14%) of cSLE patients. Information about previous chicken pox infection was available in 80/120 (67%), and it was reported by 51/80 (64%). History of varicella vaccination prior to lupus diagnosis was reported by 24/852 cSLE patients, and HZI occurred in 3/24 (12%) of those who had received this immunization. The involved sites were: thoraco-abdominal in 65 (54%), upper limbs in 13 (11%), lower limbs in 13 (11%), facial in nine (7%), buttocks in five (4%), back/lumbar regions in five (4%), cervical in three (2%), and genital one (1%). Postherpetic neuralgia was observed in six (5%) cSLE patients and recurrence in six (5%). Hospitalization occurred in 73 (61%) and overlap bacterial infection in 16 (13%). None of them had ophthalmic complications or death. Intravenous or oral aciclovir was administered in 113/120 (94%) cSLE patients at HZI diagnosis. Disease activity (SLEDAI-2K ≥6) was evidenced in 47/120 (39.2%) cSLE patients at HZI onset.

Demographic data, clinical manifestations, disease activity/damage scores, and laboratory parameters in 852 c-SLE patients according to the first HZI are shown in Table 1. After Holm–Bonferroni correction for multiple comparisons ($p < 0.002$), median of disease duration (1.58 vs 4.41 years, $p < 0.0001$) and current age (13.9 vs 17.0 years, $p < 0.0001$) were significantly lower in cSLE with HZI compared to those without this infection. The frequencies of fever (35% vs 5%, $p < 0.0001$), nephritis (37% vs 18%, $p < 0.0001$), arterial hypertension (27% vs 13%, $p = 0.001$), and lymphopenia (32% vs 17%, $p < 0.0001$) were more often observed in cSLE patients with HZI compared to those without HZI. The median of current SLEDAI-2K (6.0 (0–35) vs 2 (0–45), $p < 0.0001$), ESR (30 (3–120) vs 18 (1–135) mm/1st hour, $p < 0.0001$) and CRP (3.05 (0–103) vs 0.70 (0–3.64) mg/dL, $p = 0.001$) were significantly higher in patients with HZI (Table 1).

Current therapy of 852 cSLE according to the first HZI is illustrated in Table 2. After Holm–Bonferroni correction for multiple comparisons ($p < 0.002$), frequencies of the following treatments were significantly higher in patients with HZI compared to the ones without: prednisone (97% vs 77%, $p < 0.0001$) and intravenous cyclophosphamide (20% vs 5%, $p < 0.0001$). The median current prednisone dose/day (20 (3–80) vs 12.5 (1–90) mg/day, $p < 0.0001$) and in mg/kg/day (0.44 (0.5–3.8) vs 0.24 (0.02–3.0) mg/kg/day, $p < 0.0001$) were also significantly higher in cSLE patients with HZI *versus* those without this infection (Table 2).

The multiple regression model included five independent variables: disease duration <1 year, lymphopenia <1500/mm^3, SLEDAI-2K ≥6, prednisone, and cyclophosphamide use. Four of them remained significantly associated with HZI after analysis: disease duration <1 year (OR 2.893 (CI 1.821–4.597), $p < 0.0001$), lymphopenia < 1500/mm^3 (OR 1.931 (CI 1.183–3.153), $p = 0.009$), prednisone (OR 6.723 (CI 2.072–21.815), $p = 0.002$), and cyclophosphamide use (OR 4.060 (CI 2.174–7.583), $p < 0.0001$) (Table 3).

Discussion

This was the first study that identified immunosuppressants and lymphopenia as main factors for

Table 1 Demographic data, clinical manifestations, disease activity/damage scores and laboratory tests in 852 childhood-onset systemic lupus erythematosus (c-SLE) patients according to first herpes zoster infection (HZI)

Variables	*With HZI* n = *120 (%)*	*Without HZI* n = *732 (%)*	p
Demographic data			
Female gender	107 (89)	625 (85)	0.269
Caucasian, $n = 830$	80/117 (68)	512/713 (72)	0.447
Age at c-SLE onset, years, $n = 846/852$	11 (1.5–17.4)	12 (0.25–17.8)	0.011
Disease duration, years, $n = 846/852$	1.58 (0–19.1)	4.41 (0–21.7)	<0.0001[a]
Current age, years, $n = 849/852$	13.9 (0.91–20.58)	17 (2–25.9)	<0.0001[a]
Current clinical manifestations			
Constitutional features	40/110 (36)	54/729 (7)	<0.0001[a]
Fever, $n = 839$	39/110 (35)	38/729 (5)	<0.0001[a]
Weight loss >2 kg, $n = 815$	2/109 (2)	23/706 (3)	0.561
Reticuloendothelial system involvement, $n = 850$	7/112 (6)	24/728 (3)	0.171
Lymphadenopathy, $n = 839$	1/111 (1)	10/728 (1)	1.000
Hepatomegaly, $n = 841$	6/112 (5)	17/729 (2)	0.108
Splenomegaly, $n = 841$	1/112 (1)	5/729 (1)	0.577
Mucocutaneous involvement, $n = 840$	37/111 (33)	206/729 (28)	0.272
Musculoskeletal involvement, $n = 840$	12/111 (11)	43/729 (6)	0.051
Serositis, $n = 839$	3/111 (3)	12/728 (2)	0.435
Neuropsychiatric involvement, $n = 838$	4/11 (4)	63/727 (9)	0.067
Nephritis, $n = 831$	40/107 (37)	131/714 (18)	<0.0001[a]
Current autoimmune thrombosis (APS), $n = 807$	2/92 (2)	12/715 (2)	0.732
Other			
Arterial hypertension, $n = 833$	27/110 (27)	93/723 (13)	0.0010[a]
Acute renal failure, $n = 833$	4/111 (4)	27/722 (4)	1.000
Chronic renal failure, $n = 830$	4/108 (4)	21/722 (3)	0.555
Disease activity/damage			
SLEDAI-2K at c-SLE onset, $n = 780/852$	17 (3–45)	14 (0–58)	0.004
Current SLEDAI-2K, $n = 735/852$	6 (0–35)	2 (0–45)	<0.0001[a]
Current SLICC-ACR/DI, $n = 764/852$	0 (0–5)	0 (0–9)	0.258
Current laboratory tests			
ESR (mm/1st hour) at HZI or last visit, $n = 693/852$	30 (3–120)	18 (1–135)	<0.0001[a]
CRP (mg/dL) at HZI or last visit, $n = 536/852$	3.05 (0–103)	0.70 (0–364)	0.0010[a]
Autoimmune hemolytic anemia, $n = 812$	7/105 (7)	23/707 (3)	0.094
Leucopenia <4000/mm^3, $n = 784$	17/109 (16)	56/675 (8)	0.015
Lymphopenia <1500/mm^3, $n = 786$	36/111 (32)	115/675 (17)	<0.0001[a]
Thrombocytopenia, <150,000/mm^3, $n = 789$	5/110 (4)	31/679 (5)	0.993
Low C3, C4 and/or CH50, $n = 668$	29/64 (45)	237/604 (39)	0.345
Anti-ds-DNA autoantibodies, $n = 693$	38/73 (52)	222/620 (36)	0.007
Lupus anticoagulant, $n = 291$	1/20 (5)	37/271 (14)	0.489
Anticardiolipin IgM autoantibodies, $n = 329$	6/23 (26)	48/306 (16)	0.238
Anticardiolipin IgG autoantibodies, $n = 330$	3/22 (14)	58/308 (19)	0.777

[a]p-value according to Bonferroni correction for multiple comparisons ($p < 0.002$).
Results are presented in n (%) and median (range).
APS: antiphospholipid syndrome; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index 2000; SLICC/ACR-DI: Systemic Lupus International Collaborating Clinics/ACR Damage Index; ESR: erythrocyte sedimentation rate, CRP: C-reactive protein.

HZI, mainly in the first years of the disease course, in a large multicenter cohort of cSLE.

The advantage of the present study was the large representation of HZI in a multicenter cSLE cohort followed in ten tertiary and teaching hospitals in the State of Sao Paulo, Brazil. Standard procedures were ensured for data collection to minimize bias. The main limitations of this study were the retrospective nature and lack of polymerase chain reaction and viral culture for HZI confirmation. Nevertheless, the typical vesicles, along with dermatome distribution, support the correct diagnosis.[1,2]

A history of varicella vaccination prior to lupus diagnosis was rarely reported herein, due to the fact that varicella vaccination for children less than two years old only became available in the Brazilian public health care services in September 2013. Furthermore, herpes zoster vaccination is only available for elderly people.

Table 2 Current therapy of 852 childhood-onset systemic lupus erythematosus (c-SLE) patients according to to first herpes zoster infection (HZI)

Variables	*With HZI* n = *120 (%)*	*Without HZI* n = *732 (%)*	p
Nonsteroidal anti-inflammatory, *n* = 834	6/111 (5)	39/723 (5)	0.996
Glucocorticosteroids			
Prednisone use, *n* = 835	108/111 (97)	560/724 (77)	<0.0001[a]
Current dose, mg/day, *n* = 669/852	20 (3–80)	12.5 (1–90)	<0.0001[a]
mg/kg/day, *n* = 641/852	0.44 (0.5–3.8)	0.24 (0.02–3.0)	<0.0001[a]
Cumulative dose, gm, *n* = 700	18.86 (0.42–105.51)	16.93 (0.12–103.87)	0.785
Intravenous methylprednisolone, *n* = 833	15/109 (14)	61/724 (8)	0.071
Cumulative dose, gm, *n* = 451	5.6 (1–102)	9.0 (0.50–138.50)	0.044
Antimalarial drugs, n = 833	68/111 (61)	489/722 (68)	0.178
Immunosuppressive agents, n = 839	67/113 (59)	435/726 (60)	0.900
Azathioprine, *n* = 834	35/111 (31)	247/723 (34)	0.585
Cyclosporine, *n* = 838	2/112 (2)	28/726 (4)	0.412
Methotrexate, *n* = 837	6/112 (5)	65/725 (9)	0.202
Mycophenolate mofetil, *n* = 839	12/113 (11)	97/726 (13)	0.420
Cyclophosphamide, *n* = 838	23/113 (20)	35/725 (5)	<0.0001[a]
Cumulative dose, gm, *n* = 283	6.25 (1.46–36)	6.6 (0.26–84)	0.903
Others			
Intravenous immunoglobulin, *n* = 838	2/112 (2)	11/726 (1)	0.689
Rituximab, *n* = 837	0/113 (0)	1/724 (0)	1.000
Plasmapheresis, *n* = 839	0/113 (0)	5/726 (1)	1.000

[a]*p*-value according to Bonferroni correction for multiple comparisons ($p < 0.002$).
Results are presented in *n* (%).

Table 3 Independent variables in the multiple regression model associated with the first herpes zoster infection (HZI) in 852 childhood-onset systemic lupus erythematosus (c-SLE) patients

Independent variables	*OR (95% CI)*	p
Disease duration <1 year, *n* = 846	2.893 (1.821–4.597)	<0.0001
Lymphopenia <1500/mm^3, *n* = 786	1.931 (1.183–3.153)	0.009
Prednisone use, *n* = 835	6.723 (2.072–21.815)	0.002
Cyclophosphamide use, *n* = 838	4.060 (2.174–7.583)	<0.0001

OR: odds ratio; 95% CI: 95% confidence interval.

The frequency of HZI observed herein is lower than that reported in Chinese cSLE[2] and Japanese adult SLE patients with HZI (46%).[14] This finding is, however, similar to that reported for cSLE in the USA,[4] raising the possibility of a higher susceptibility to this viral infection in Asians.

HZI seems to be an early cSLE complication, particularly in the first two years after lupus diagnosis,[1,2] contrasting with adults, in whom this infection is a late complication.[1,15]

Regarding HZI clinical features, the most important dermatomal involvement was thoracic, as also observed in cSLE and adult SLE patients.[1,15] Of note, approximately one fifth of the patients had limb involvement, a site not reported in former reports of cSLE.[1–4] In addition, no episodes of disseminated HZI, ophthalmic involvement, or death were observed, suggesting a mild complication during the disease course. Importantly, post-herpetic neuralgia was observed in only 5% of cSLE with HZI in the present study, a lower frequency compared to adult SLE with this infection (19%–24%).[1,15]

Lymphopenia may explain in part the susceptibility to this viral infection, since it was present in approximately one third of the patients. Disease activity was not an associated factor with HZI in the multivariate analysis, contrasting with other studies that reported disease activity more often noticed in children than in adult SLE with HZI.[1]

We have identified herein that underlying immunosuppressive drugs are an additional predisposing factor for HZI in cSLE patients, particularly glucocorticoid and cyclophosphamide.[1,2,15] This novel finding was not recognized in preceding reports due to the fact that they did not assess current and cumulative doses.[1–4] Indeed, nearly all cSLE patients were under moderately high doses of prednisone, and one fifth of them were receiving cyclophosphamide. Nevertheless, cSLE had a satisfactory outcome, probably due to prompt intravenous or oral acyclovir therapy.

In conclusion, HZI is an early viral infection in cSLE, with a typical dermatomal distribution. Lymphopenia and immunosuppressive treatment seem to be major factors underlying this complication, in spite of a benign course.

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