SLICC classification criteria for juvenile systemic lupus erythematosus: a cross sectional study

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ABSTRACT

Objectives: To verify the sensitivity and specificity of the criteria for systemic lupus erythematosus, proposed by the Systemic Lupus International Collaborating Clinics (SLICC) and compare it to the ACR lupus criteria, in a pediatric population.

Patients and methods: This is an observational cohort study, with a descriptive analysis of data from a Pediatric Rheumatology center, including 23 patients with Juvenile Systemic Lupus Erythematosus (jSLE) and a control group of 24 patients with Juvenile Idiopathic Arthritis (JIA), both groups recently diagnosed and virgin of treatment. Information on signs and symptoms was obtained on the diagnostic consult, and the ACR and SLICC criteria were applied to both groups. Statistical analysis on descriptive data was performed, presenting them in absolute and relative frequency and calculating sensitivity and specificity for each set of criteria.

Results: By comparing the ACR and SLICC criteria, we obtained higher sensitivity and accuracy using the SLICC criteria (100% and 97.9%, respectively) and equal specificity. Individually, the positive ANA criterion had 100% sensitivity but only 58.3% specificity in both classifications. The other criteria showed low sensitivity and high specificity when individually analyzed; renal disorder, leukopenia or lymphopenia, positive anti-DNA antibody and low complement level were the only criteria with sensitivity above 50%. Arthritis was the least specific criterion.

Conclusion: our results were similar to previous studies with both children and adults, and classification criteria should be used with caution. The SLICC criteria showed high sensitivity and specificity for the classification of jSLE.

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Keywords: Juvenile systemic lupus erythematosus; SLICC; American College of Rheumatology; Classification criteria; Childhood

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune disease, involving multiple organs and systems, associated with the presence of auto-antibodies. Worldwide incidence is estimated to be of 5:100.000 persons, with 15-20% of cases beginning in early childhood or adolescence (up to 18 years old)[1,2].

In the pediatric population, systemic symptoms are more frequent and severe, with higher frequency of renal disorder when compared to adult SLE[2].

In 1971 the American College of Rheumatology (ACR) elaborated a classification criteria for SLE, in order to facilitate disease identification and systematize studies, since this disease manifests itself through a wide array of signs and symptoms. This classification was published in 1982 and revised by the same group in 1997[3,4]. According to the criteria proposed by the ACR, to classify a disease as SLE, the patient must have at least four out of eleven defined criteria[4].

In 2012, the Systemic Lupus International Collaborating Clinics (SLICC) published a new proposal for SLE classification criteria, emphasizing cutaneous lupus, neurological symptoms, urinary sediment alterations, and immunologic patterns. According to the new criteria, to classify a disease as SLE, it is mandatory to have at least four out of a total of seventeen criteria, with at least one clinical and one laboratorial criterion or, alternatively, a renal biopsy histopathology compatible with lupus nephritis, associated with positive ANA or anti-DNA antibody[5,6].

These new criteria showed higher sensitivity (94% vs 86%, $p < 0.0001$), but lower specificity (84% versus 96%, $p < 0.0001$) when compared to the ACR criteria[4]. Although some studies in the pediatric population have

already been published, given the importance and worldwide acceptance of the criteria proposed by the SLICC group, we considered it relevant to conduct this study, analyzing its sensitivity and specificity in comparison to the previous criteria proposed by the ACR[7-9].

PATIENTS AND METHODS

PATIENTS

We conducted a cross sectional study, with descriptive analysis of data from a tertiary Pediatric Rheumatology clinic. Study population included: 1) 23 patients with confirmed diagnosis of Juvenile Systemic Lupus Erythematosus (jSLE); 2) a control group of 24 patients with Juvenile Idiopathic Arthritis (JIA). We used a convenient sample of new cases of JIA and jSLE (up to one month following diagnosis), seen in the years of 2014 and 2015 in our service. Inclusion criteria were: patients up to 18 years old for jSLE and 16 years old for JIA, followed in our service, with clinically confirmed diagnosis of either disease, established according to the attending Pediatric Rheumatologist discretion, using both clinical e immunological alterations suggestive of the disease, since there is no current gold standard test for jSLE diagnosis[4,10].

We defined as exclusion criteria: presence of more than one auto-immune disease; absence of complete clinical and laboratorial data.

METHODS

Signs and symptoms were obtained through patient history and physical examination at first consult, taking into account: skin lesions, oral ulcers, alopecia, synovitis, serositis and neurological disorder. Laboratory exams to verify hematologic, renal or immunological abnormalities were analyzed. In all cases physical examination was carried out by a pediatric rheumatology certified specialist. In some cases complementary exams were deemed necessary and performed, such as chest x-ray and echocardiography.

Clinical and laboratorial data were compiled through a standardized questionnaire for posterior application and analysis of the ACR and SLICC criteria, to classify jSLE in both sample groups.

The data were stored in an electronic spreadsheet in Microsoft Excel© and Stata 11© formats and statistical analysis was performed, calculating the absolute frequency, relative frequency, sensitivity and specificity of each set of criteria.

The study was approved by the local research ethics committee. A written informed consent form and an agreement form were signed by parents or legal guardians and by patients, respectively.

RESULTS

We included 23 patients with jSLE and 24 patients with JIA with a maximum time of 1 month since diagnosis. From the total of 47 patients, only eight (17%) were male, all of them in the JIA group. The mean age on diagnosis was 9.8 ± 4.8 years. Mean time of symptoms until diagnosis was 9.8 ± 13.7 months. Demographic and clinical data of patients in the jSLE and the JIA groups are presented in Table I.

Table II shows the frequency of each ACR criterion in patients with jSLE and JIA and Table III shows the frequency of each SLICC criterion for the same patients.

When we compared the criteria proposed by the ACR and the SLICC group, we obtained higher sensitivity and accuracy with the SLICC criteria (100% and 97.9% respectively), and equal specificity (Table IV).

When we evaluated each criterion individually, the positive ANA criterion had 100% sensitivity but only

TABLE I. DEMOGRAPHIC AND CLINICAL DATA OF PATIENTS WITH JSLE AND JIA

Data	jSLE N=23	JIA N=24
Female gender	23	16
Age at onset, mean (years±SD)	11.5±3.9	7.9±5.0
Time to diagnosis (months±SD)	10.7±17.5	9.0±9.3
Number of ACR SLE criteria:		
Mean	5	1.4
Minimum	2*	0
Maximum	8	4
Number of SLICC SLE criteria		
Mean	6.3	1.4
Minimum	2*	0
Maximum	12	4

jSLE: juvenile systemic lupus erythematosus; JIA: juvenile idiopathic arthritis; ACR: *American College of Rheumatology*; SLICC: *Systemic Lupus International Collaborating Clinics*
*Positive ANA + renal biopsy histopathology compatible with SLE nephritis

TABLE II. PRESENCE OF CRITERIA PROPOSED BY ACR FOR PATIENTS WITH JSLE AND JIA

	jSLE (N=23)		JIA (N=24)		Total (N=47)	
Criteria	**n**	(%)	**n**	(%)	**n**	(%)
Malar rash	11	(47.8)	1	(4.2)	12	(25.5)
Discoid lupus	0	(0)	0	(0)	0	(0)
Photosensitivity	10	(43.5)	1	(4.2)	11	(23.4)
Oral ulcers	6	(26.1)	0	(0)	6	(12.8)
Arthritis	9	(39.1)	22	(91.7)	31	(65.9)
Serositis	10	(43.5)	0	(0)	10	(21.3)
Neurologic symptoms	1	(4.3)	0	(0)	1	(2.1)
Renal disorder	14	(60.9)	0	(0)	14	(29.8)
Haematological	16	(69.6)	0	(0)	16	(34)
Immunological	15	(65.2)	1	(4.2)	16	(34)
ANA	23	(100)	10	(41.7)	33	(75)

jSLE: juvenile systemic lupus erythematosus; JIA: juvenile idiopathic arthritis; ACR: *American College of Rheumatology*; ANA: antinuclear antibody

TABLE II. PRESENCE OF THE SLICC CRITERIA IN PATIENTS WITH JSLE AND JIA

	jSLE (N=23)		JIA (N=24)		Total (N=47)	
Criteria	**n**	(%)	**n**	(%)	**n**	(%)
Acute cutaneous lupus	11	(47.8)	1	(4.2)	12	(25.5)
Chronic cutaneous lupus	1	(4.3)	0	(0)	1	(2.1)
Oral ulcers	6	(26.1)	0	(0)	6	(12.8)
Alopecia	6	(26.1)	0	(0)	6	(12.8)
Arthritis	9	(39.1)	22	(91.7)	31	(65.9)
Serositis	10	(43.4)	0	(0)	10	(21.2)
Neurological	1	(4.3)	0	(0)	1	(2.1)
Renal disorder	14	(60.9)	0	(0)	14	(29.8)
Hemolytic anemia	7	(30.4)	0	(0)	7	(14.9)
Leucopenia/lymphopenia	12	(52.2)	0	(0)	12	(25.5)
Thrombocytopenia	4	(17.4)	0	(0)	4	(8.5)
ANA	23	(100)	10	(41.7)	33	(70.2)
Anti-dsDNA	12	(52.2)	0	(0)	12	(25.5)
Anti-Sm	5	(21.7)	0	(0)	5	(10.6)
Antiphospholipid antibodies	6	(26.1)	1	(4.2)	7	(14.9)
Low complement	14	(60.9)	1	(4.2)	15	(31.9)
Direct Coomb's test	5	(21.7)	1	(4.2)	6	(12.8)

jSLE: juvenile systemic lupus erythematosus; JIA: juvenile idiopathic arthritis; ACR: *American College of Rheumatology*; SLICC: *Systemic Lupus International Collaborating Clinics*; ANA: antinuclear antibody

58.3% specificity in both classifications (Tables V and VI). Other criteria showed low sensitivity and high specificity when analyzed individually. Renal disorder, leukopenia or lymphopenia, positive anti-DNA antibody and low complement were the only criteria with sensitivity above 50%. Arthritis was the least specific criterion.

DISCUSSION

In this study we compared the classification criteria for SLE proposed by the ACR with the criteria proposed by the SLICC group. A few studies have been published evaluating the SLICC criteria for jSLE, however, they

TABLE IV. SENSITIVITY, SPECIFICITY AND ACCURACY OF THE ACR AND SLICC SLE CLASSIFICATION CRITERIA

	Sensitivity	Specificity	Accuracy
jSLE			
ACR	87.5%	95.8%	91.5%
SLICC	100%	95.8%	97.9%

jSLE: juvenile systemic lupus erythematosus; ACR: *American College of Rheumatology*; SLICC: *Systemic Lupus International Collaborating Clinics*

TABLE V. SENSITIVITY AND SPECIFICITY OF EACH ACR CRITERIA

Criteria	Sensitivity	Specificity
Malar rash	47.8%	95.8%
Discoid lupus	0.0%	100%
Photosensivity	43.5%	95.8%
Oral ulcers	26.1%	100%
Arthritis	39.1%	8.3%
Serositis	43.5%	100%
Neurologic symptoms	4.3%	100%
Renal	60.9%	100%
Haematological	69.6%	100%
Immunological	65.2%	95.8%
ANA	100%	58.3%

ACR: *American College of Rheumatology*; ANA: antinuclear antibodies

were all of a retrospective nature[7-9]. We believe that the strength in our study was the application of both criteria in patients at the moment of their respective jSLE or JIA diagnoses, and previous to treatment. Other studies have been carried out through the revision of charts, but in patients already on medical treatment[7-9,11,12].

Studies comparing sensitivity and specificity of the SLE classification criteria have been done both in adult and pediatric populations, and up to this moment, three studies for adults[11-13] and three for children[7-9] have been published.

The Amezcua-Guerra *et al.* study, performed with adult patients, reported higher sensitivity with the ACR criteria, compared to the SLICC criteria; specificity was the same for both[11]. In its turn, the Ighe study, also performed with adult patients, showed that the SLICC criteria presented higher sensitivity than the ACR criteria,

TABLE VI. SENSITIVITY AND SPECIFICITY OF EACH SLICC CRITERIA

Criteria	Sensitivity	Specificity
Acute cutaneous lupus	47.8%	95.8%
Chronic cutaneous lupus	4.3%	100%
Oral ulcers	26.1%	100%
Alopecia	26.1%	100%
Arthritis	39.1%	8.3%
Serositis	43.4%	100%
Neurological	4.3%	100%
Renal disorder	60.9%	100%
Hemolytic anemia	30.4%	100%
Leucopenia/lymphopenia	52.2%	100%
Thrombocytopenia	17.4%	100%
ANA	100%	58.3%
Anti-dsDNA	52.2%	100%
Anti-Sm	17.4%	100%
Antiphospholipid antibodies	26.1%	95.8%
Low complement	60.8%	95.8%
Direct Coomb's test	21.7%	95.8%

SLICC: *Systemic Lupus International Collaborating Clinics;* ANA: antinuclear antibodies

but had more frequent classificatory errors in the control group[12].

Studies with children showed higher sensitivity of the SLICC criteria compared to the ACR ones. In the study by Fonseca *et al.*, both criteria showed similar specificity, and in the study by Sag *et al.*, the specificity of the SLICC criteria was lower, with a smaller margin of error in the control group[8,9].

In our service, two female patients were classified as jSLE based on the SLICC criteria, since they had a renal biopsy compatible with lupus nephropathy and positive immunology. These girls would not have been classified as jSLE using the ACR criteria. Another patient did not fulfill criteria using the ACR (3 out of 11) but had enough criteria according to the SLICC classification (6 out of 17), since she presented alopecia, autoimmune hemolytic anemia, lymphopenia, positive ANA, positive anti-Sm antibody and low complement. In the control group, only one patient would have been wrongly classifed as jSLE, using both the ACR and the SLICC criteria.

When we evaluate sensitivity and specificity of the criteria individually, only the presence of ANA had high sensitivity in the SLE group, although with low speci-

ficity (58.3%), since we can find a positive ANA in other autoimmune diseases and even in healthy population[14]. The other criteria had low sensitivity when considered individually.

We consider limitations to our study: the fact that we did not include patients with other rheumatic diseases other than JIA in our control group; the relatively small number of patients; the fact that they all came from a single center; and the choice to classify patients that had been recently diagnosed, since both SLE criteria are cumulative, allowing patients that were not classified as jSLE to be categorized as such in the future, depending on new signs and symptoms that may arise. In this respect, we can mention patients with supposed JIA (chronic arthritis and a positive ANA), who can develop other symptoms and be diagnosed as jSLE later on. However, we chose to use the criteria in this population since, although not elaborated as diagnostic criteria, we understand that many pediatricians and family care physicians might use them to guide clinical decisions – as such, a set of criteria that has higher sensitivity and specificity in newly diagnosed patient might facilitate referral of patients in primary care to a proper Pediatric Rheumatology center, while minimizing diagnostic errors.

In conclusion, our results are similar to the ones found in studies performed with children and adults – the criteria proposed by the SLICC group had high sensitivity and specificity for the classification of jSLE. Classificatory criteria should be used with caution, and we reinforce that a patient might be diagnosed with jSLE even if he or she does not fulfill the classification criteria. Still, a set of criteria with high sensitivity and specificity might aid in patient care, and the SLICC group criteria seems to meet this demand.

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REFERENCES

1. Silverman E, Eddy A. Systemic lupus erythematosus. In: Cassidy JT, Petty RE, Laxer RM, Lindsey CB. Textbook of Pediatric Rheumatology. Philadelphia: Saunders, 2011. p. 315-343.
2. Bastos WA, Liphaus BI. Lupus eritematoso sistêmico. In: Terreri MTRA; Sacchetti SB. Reumatologia para o pediatra – Série atualizações pediátricas. São Paulo: Atheneu, 2008. p. 59-72.
3. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, et al. The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982; 25:1271–1277.
4. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus [letter]. Arthritis Rheum 1997; 40 (9): 1725.
5. Petri M. Review of classification criteria for systemic lupus erythematosus. Rheum Dis Clin North Am 2005; 32 (2): 245-254.
6. Petri M, Orbai AM, Alarcón GS, Gordon C, Merrill JT, Fortin PR, et al. Derivation and validation of the Systemic Lupus International Collaborating Clinics classification criteria for systemic lupus erythematosus. Arthritis Rheum 2012; 64(8):2677-2686.
7. Gutiérrez-Suárez R, Ruperto N, Gastaldi R, Pistorio A, Felici E, Burgos-Vargas R, et al. A proposal for a pediatric version of the Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index based on the analysis of 1,015 patients with juvenile-onset systemic lupus erythematosus. Arthritis Rheum 2006; 54(9):2989-2996.
8. Sag E, Tartaglione A, Batu ED, Ravelli A, Khalil SMA, Marks SD, et al. Performance of the new SLICC classification criteria in childhood systemic lupus erythematosus: a multicenter study. Clin Exp Rheumatol 2014; 32: 440-444.
9. Fonseca AR, Gaspar-Elsas MIC, Land MGP, Oliveira SKFO. Comparison between three systems of classification criteria in juvenile systemic lupus erythematous. Rheumatology (Oxford) 2015; 54(2): 241-247.
10. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International league of associations for rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31(2):390-392.
11. Amezcua-Guerra lM, Higuera-Ortiz V, Arteaga-Garcia U, Gallegos-Nava S, Hubbe-Tena C. Performance of the 2012 SLICC and the 1997 ACR classification criteria for systemic lupus erythematosus in a real-life scenario. Arthritis Care Res 2015; 67(3):437-441.
12. Ighe A, Dahlstrom O, Skogh T, Sjowall C. Application of the 2012 Systemic Lupus International Collaborating Clinics classification criteria to patients in a regional Swedish systemic lupus erythematosus register. Arthritis Res Ther 2015; 17(1):3.
13. Ines l, Silva C, Galindo M, López-Longo FJ, Terroso G, Romão VC, et al. Classification of systemic lupus erythematosus: Systemic Lupus International Collaborating Clinics versus American College of Rheumatology criteria. A comparative study of 2055 patients from a real-life, international SLE cohort. Arthritis Care Res 2015; 67(8):1180-1185.
14. Hilário MOE, Len CA, Roja SC, Terreri MT, Almeida G, Andrade LE. Frequency of antinuclear antibodies in healthy children and adolescents. Clin Ped 2004; 43:637-642.