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Comparison of urinary parameters, biomarkers, and outcome of childhood systemic lupus erythematosus early onset-lupus nephritis

Daniele Faria Miguel[1], Maria Teresa Terreri[2], Rosa Maria Rodrigues Pereira[3], Eloisa Bonfá[3], Clovis Artur Almeida Silva[4], José Eduardo Corrente[5], Claudia Saad Magalhaes[6*] and for the Brazilian Childhood-onset Systemic Lupus Erythematosus Group

Abstract

Background: Urinary parameters, anti-dsDNA antibodies and complement tests were explored in patients with childhood-Systemic Lupus Erythematosus (cSLE) early-onset lupus nephritis (ELN) from a large multicenter cohort study.

Methods: Clinical and laboratory features of cSLE cases with kidney involvement at presentation, were reviewed. Disease activity parameters including SLEDAI-2 K scores and major organ involvement at onset and follow up, with accrued damage scored by SLICC-DI, during last follow up, were compared with those without kidney involvement. Autoantibodies, renal function and complement tests were determined by standard methods. Subjects were grouped by presence or absence of ELN.

Results: Out of the 846 subjects enrolled, mean age 11.6 (SD 3.6) years; 427 (50.5%) had ELN. There was no significant difference in the ELN proportion, according to onset age, but ELN frequency was significantly higher in non-Caucasians ($p = 0.03$). Hematuria, pyuria, urine casts, 24-h proteinuria and arterial hypertension at baseline, all had significant association with ELN outcome ($p < 0.001$). With a similar follow up time, there were significantly higher SLICC-DI damage scores during last follow up visit ($p = 0.004$) and also higher death rates ($p < 0.0001$) in those with ELN. Low C3 (chi-square test, $p = 0.01$), but not C3 levels associated significantly with ELN. High anti-dsDNA antibody levels were associated with ELN ($p < 0.0001$), but anti-Sm, anti-RNP, anti-Ro, anti-La antibodies were not associated. Low C4, C4 levels, low CH50 and CH50 values had no significant association. High erythrocyte sedimentation rate (ESR) was associated with the absence of ELN ($p = 0.02$).

Conclusion: The frequency of ELN was 50%, resulting in higher morbidity and mortality compared to those without ELN. The urinary parameters, positive anti-dsDNA and low C3 are reliable for discriminating ELN.

Keywords: Anti-dsDNA antibodies, Childhood-onset systemic lupus erythematosus, Complement, C3, C4, Lupus nephritis

* Correspondence: claudia.saad@unesp.br
[6]Pediatric Rheumatology Division, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP), Botucatu, Brazil
Full list of author information is available at the end of the article

Background

Childhood systemic lupus erythematosus (cSLE) accounts for nearly 10–15% of all cases of SLE. It affects multiple organ systems including the kidneys, central nervous system, hematopoietic cells and skin [1] .

Lupus nephritis has been identified in 20–75% of childhood patients, indicating the worse prognosis when compared to adult patients [2–6]. However, most of the reported series evaluated lupus nephritis along the disease course. Only two series correlated silent lupus nephritis identified by renal biopsies at disease onset with serum biomarkers, including products of complement activation, as C3 and C4 levels [3, 7].. Ethnicity is one of the parameter associated to disease severity and systemic involvement [7] and there was no similar study in Latin America population. Therefore, we addressed the issue, exploring urinary parameters, renal function, anti dsDNA antibodies and complement tests in patients with childhood-Systemic Lupus Erythematosus (cSLE) and early-onset lupus nephritis (ELN), from a large multicenter national cohort study.

Methods

A large multicentric database including historical cohorts of cSLE cases, classified by the American College of Rheumatology (ACR) 1997 criteria, in 10 of the Brazilian cSLE Study Group centers, from 2013 to 2016, was analyzed for secondary data [8]. Parameters of cSLE activity were SLE Disease Activity Index 2000 (SLEDAI-2 K) scores at disease onset [9], major organ involvement such as glomerulonephritis, vasculitis, neuropsychiatric lupus, hematologic and cardio-vascular involvement and disease damage scores by Systemic Lupus International Collaborating Clinics/ACR-Damage Index (SLICC/DI) [10], at the last follow up visit.

Laboratory data, including antibody tests, urinary parameters and complement tests were obtained using standard methods in each laboratory of participating centres. Renal involvement status was defined according to pediatric definitions and guidelines [11, 12], as estimated by the physicians in the retrospective data collection. Glomerulonephritis was considered if either urine leukocytes, red blood cells, casts or renal function impairment above the normal range were present. Acute renal failure was defined as any sudden increase of serum creatinine above 2 mg/dl. Chronic renal failure was established with glomerular filtration rate lower than 60 ml/min/1.73 m2 of body surface, with or without any structural or functional damage, observed by abnormal biomarker or imaging, and occurring beyond 3 month of duration.

Initial c-SLE renal and extra-renal manifestations, including events recorded during the first six months after the diagnosis, the presence of arterial hypertension, abnormal urinalysis results, 24-h urinary protein excretion, renal function, acute and chronic renal failure status were used for comparison of the groups of cSLE with and without ELN. C3, C4, CH50, antinuclear antibodies (ANA), anti-double-stranded DNA (anti-dsDNA), anti-Sm, RNP, Ro/SSA and La/SSB tests results were also compared [8]. The clinical diagnosis of ELN required the presence of active urinary sediment based on SLEDAI-2 K criteria by Gladman et al. [9] during the first six month of the diagnosis. We selected the SLEDAI-2 K tool in order to standardize comparison of nephritis activity over time. Renal biopsy and histopathology evaluations by light microscopy and immunofluorescence, were performed independently, in each of the centres, and evaluated by local pathologists, classifying renal lesions by the World Health Organization (WHO) criteria or 2004 ISN/RPS criteria, scoring active and chronic lesions [11]. Subjects were classified according to the presence or absence of ELN, estimated by either clinical or biopsy findings.

Descriptive and parametric statistics, T-test and chi-square, were used for comparison of the groups of cSLE with and without ELN, at disease onset. The statistics tests were performed using SAS software v. 9.2 and values were considered significant if $p < 0.05$.

Results

Out of 852 subjects selected in the primary study from Gomes et al. [8], 846 with mean age of 11.6 (SD 3.6) years, with a comprehensive clinical assessment, were enrolled. Of those, 427 (50.5%) presented early-onset ELN and 419 (49,5%) did not present with ELN. Renal biopsy was performed in 228 of the cases, but only 181 were classified according to WHO criteria or 2004 ISN/RPS criteria, in addition to standard histopathology parameters [13]. Of those with renal biopsy, histopathology classification by WHO-2004 resulted in the proportion of 11 (6%) class I, 45 (25%) class II, 25 (14%) class III, 76 (42%) class IV, 21 (11%) class V and 3 (2%) class VI.

Table 1 illustrates demographic data, clinical features, laboratory, urinary parameters and outcome, in cSLE patients with and without ELN. No significant difference was found between male and female subjects, and no significant difference was found in each group of onset age, < 6 years, 6–12 and > 12 years. But, there was a significant difference related to the ethnic background. ELN frequency was significantly higher in non-Caucasian ($p = 0.03$). For ethnic classification, 20 subjects had missing data. Renal parameters, as 24 h-proteinuria, hematuria, pyuria, urine casts and arterial hypertension were compared, resulting in significant difference for those with ELN ($p < 0.001$), as well as presentation with acute renal failure ($p < 0.001$) and chronic renal failure ($p < 0.0002$). Low complement, defined by low C3, C4 or CH50 activity, was found in nearly 70% of those tested. Low C3 ($p = 0.01$) but not C3 levels, was associated significantly with ELN. Low C4, C4 levels or

Table 1 – Demographic and clinical features, laboratory parameters, disease activity, damage scores and death rates comparison in childhood-onset Systemic Lupus Erythematosus (c-SLE) patients with and without early onset lupus nephritis (ELN)

Variables	n of cases 427	cSLE with ELN	n of cases 419	cSLE without ELN	*p*-Value
Onset age (y)		11.6 ± 2.8		11.7 ± 3.2	0.65
0–6 y *n* (%)		17 (3.9)		21 (5)	0.74
6–12 y *n* (%)		206 (48.2)		196 (46.7)	0.74
> 12 y *n* (%)		198 (46.3)		194 (46.3)	0.74
Female *n* (%)		357 (83.6)		360 (86)	0.18
Caucasian *n* (%)	407	274 (67.3)	405	304 (72.5)	0.03*
Non-Caucasian *n* (%)	407	133 (32.7)	405	101 (24.9)	0.03*
SLEDAI-2 K (mean, SD) median		(20 ± 8) 20		(12 ± 7) 11	< 0.001*
Acute renal failure (ARF) *n* (%)		94 (22)		0	< 0.001*
Chronic renal failure (CRF) *n* (%)		17 (4)		0	0.0002*
Arterial hypertension n (%)		181 (42.3)		18 (4.2)	< 0.001*
Haematuria *n* (%)		309 (72.3)		56 (13.36)	< 0.001*
Pyuria *n* (%)		223 (52.2)		49 (11.7)	< 0.001*
Urine Casts *n* (%)		153 (35.8)		21 (5)	< 0.001*
Proteinuria *n* (%)		191 (44.7)		67 (16)	< 0.001*
24 h Proteinuria (g/day) (mean, SD)	191	(1.5 ± 2.9)	225	(0.12 ± 0.18)	< 0.001*
Low C3 *n* (%)	301	198 (65.7)	303	174 (57.4)	0.01*
Low C4 *n* (%)	265	183 (69)	280	183 (65.3)	0.07
Low CH50 *n* (%)	91	62 (68.1)	54	35 (65)	0.07
C3 (mg/dl) (mean, SD)	301	(60 ± 36)	303	(73 ± 38)	0.05
C4 (mg/dl) (mean, SD)	265	(12 ± 14)	280	(12 ± 10)	0.18
CH50 (U/ml) (mean, SD)	91	(87 ± 79)	54	(110 ± 84)	0.07
ESR mm/h (mean, SD)	343	(42 ± 35)	346	(49 ± 32)	0.02*
CRP mg% (mean, SD)	179	(5 ± 7)	217	(4 ± 6)	0.49
Anti-dsDNA antibodies *n* (%)	381	286 (75)	397	253 (63.7)	0.0001*
Anti-Sm antibodies *n* (%)	312	106 (34)	317	124 (39)	0.14
Anti-RNP antibodies *n* (%)	295	73 (24.7)	298	79 (26.5)	0.46
Anti-Ro/SSA antibodies *n* (%)	280	88 (31.4)	298	93 (31.2)	0.88
Anti-La/SSB antibodies *n* (%)	274	37 (13.5)	290	41 (14)	0.90
SLICC/DI (range) median		(0–9) 1		(0–3) 0	0.004*
Disease duration (y) (mean, SD)		(4.2 ± 3.6)		(4.2 ± 3.5)	0.80
Death n (%)	404	99 (24)	419	18 (4)	< 0.0001*

CH50–50% hemolytic activity of Complement, SLEDAI-2 K- SLE Disease Activity Index 2000, SLICC/DI - Systemic Lupus International Collaborating Clinics/ACR-Damage Index, anti-dsDNA - anti-double-stranded DNA
* significant values of p< 0.05

CH50 activity had no significant difference in the same comparison (Table 1).

Positive anti-dsDNA antibody test was associated with ELN ($p < 0.0001$), but all other autoantibodies, such as positive anti-Sm, anti-RNP, anti-Ro/SSA, anti-La/SSB, were not associated with early-onset ELN. Erythrocyte sedimentation rate (ESR) was significantly lower in cSLE with ELN compared to those without ELN ($p = 0.02$). We found no statistically significant difference in other major organ involvement in those with ELN compared to those without ELN. Only statistical trend was observed in the comparison of neuropsychiatric manifestations in those with ELN, tested by chi-square test ($p = 0.06$).

Further analysis of these patients, during the last follow-up, revealed that death rates were significantly higher in the group with ELN ($p < 0.0001$). Overall cSLE median follow up time was nearly four years; it

was comparable between those with and without ELN (Table 1). SLICC-DI scored during the last follow up visit had significant difference, being higher in those with ELN ($p = 0.004$).

Discussion

This large multicenter study confirms and expands the findings of previous reports ponting to lupus nephritis as a relevant feature of cSLE. It further demonstrates that ELN is characterized by high frequency arterial hypertension, hematuria proteinuria, low C3, anti-dsDNA and a significant proportion of acute renal failure. It is in keeping with recent reports comparing renal involvement in cSLE versus adult onset SLE [14, 15]. The clinical picture mostly likely represents proliferative glomerular lesions. In fact, more than half of the patients had class III to V by WHO classification categories. This is in accordance with former case series reports, from different ethnic backgrounds populations. Comparable death rates and end-stage renal disease were also seen [2, 3, 14].

Our study contributes to the current knowledge of ELN in cSLE, reflecting in accrued damage, scored by SLICC damage index and mortality. In our series and previous reports, ELN is a predominant feature of cSLE, in particular when compared to adult series [14, 15]. ELN was confirmed by a comprehensive assessment of standardized clinical and laboratory measures, in a large multicentric study, from a population of mixed ethnic background, where non-Caucasians had higher frequency of ELN.

The role of complement as biomarker of ELN was explored. Complement and immunoglobulin deposition is a characteristic finding in ELN renal biopsies and low serum C3 and C4 have been considered as disease activity biomarkers. But, it was rarely reported in pediatric patients [7, 16, 17]. Activation of the classical complement system by immune complex contributes to inflammation and tissue injury. However, the measurement of C3 and C4 serum levels has several drawbacks. The range of C3 and C4 in the normal plasma is wide, consumption during activation can lead to increased synthesis due to acute phase reaction, resulting in no net change. Although complement serum levels do not differentiate between consumption and production, they are used worldwide for assessing lupus activity.

Our study has the limitations of a retrospective assessment, diagnosis delay or limitation of obtaining renal biopsy, as well as classifying those renal biopsies in different centers and also limited resources for laboratory tests as C3, C4 and CH50 determination. Other study limitations were those of retrospective assessments where new biomarkers were not studied. Also, the longitudinal comparison of final renal outcome as association with chronic renal failure, dyalisis and transplantation could not be addressed in this sample, but there is work is in progress in the expanded database, addressing this research question. In spite of these caveats, paired comparison between those presenting with ELN and without ELN was possible in a robust sample, in a series with a medium follow up time of four years.

Conclusion

The frequency of ELN was 50%, it was predominant in non Caucasians and resulted in higher morbidity and mortality. The urinary parameters, positive anti-dsDNA and low C3 are practical and reliable biomarkers, for discriminating ELN.

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Authors' contributions

All the authors provided substantial contribution to the study design, data acquisition, analysis, data interpretation and final approval of the manuscript.

Authors information

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Availability of data and materials

The authors can provide all the source data and analysis.

Ethics approval and consent to participate

It was granted as a national multicentric protocol under n 264.656/CAAE 09231912.2.2003.541 on May 6th 2013.

Consent for publication

It was given according to ethical standards and authorship policy.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Universidade Estadual Paulista (UNESP) Faculdade de Medicina de Botucatu, Botucatu, Brazil. [2]Pediatric Rheumatology Division, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP), São Paulo, Brazil. [3]Rheumatology Division, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil. [4]Children's Institute, Hospital das Clinicas HCFMUSP, Faculdade de Medicina, Universidade de São Paulo, São Paulo, Brazil. [5]Biostatistic Department, Instituto de Biociencias, Universidade Estadual Paulista (UNESP), Botucatu, Brazil. [6]Pediatric Rheumatology Division, Faculdade de Medicina de Botucatu, Universidade Estadual Paulista (UNESP), Botucatu, Brazil.

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