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Original article

Liver and spleen biometrics in childhood-onset systemic lupus erythematosus patients

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ABSTRACT

Objective: To evaluate liver and spleen dimensions in childhood-onset systemic lupus erythematosus (c-SLE) patients and healthy controls.
Methods: 30 c-SLE patients and 30 healthy control volunteers underwent abdominal ultrasound. The following two liver measurements were performed in left hepatic lobe: craniocaudal and anteroposterior and three in right hepatic lobe (RHL): posterior craniocaudal (PCC-RHL), anterior craniocaudal and anteroposterior. Three spleen dimension measurements were also evaluated: longitudinal, transverse and anteroposterior. Demographic, clinical and laboratorial data, SLEDAI-2K, ECLAM, SLAM and treatment were assessed.
Results: Mean current age was similar in c-SLE and controls (170.31 ± 27.81 vs. 164.15 ± 39.25 months; $p = 0.486$). The mean of PCC-RHL dimension was significantly higher in c-SLE compared to controls (13.30 ± 1.85 vs. 12.52 ± 0.93, $p = 0.044$). There were no differences between the other hepatic biometrics and splenic parameters ($p > 0.05$). Further analysis in c-SLE patients according to PCC-RHL dimension $\geq$13.3 cm versus <13.3 cm showed that the median of SLEDAI-2K [8 (0–18) vs. 2 (0–8), $p = 0.004$], ECLAM [4 (0–9) vs. 2 (0–5), $p = 0.019$] and SLAM [5 (1–13) vs. 2 (0–14), $p = 0.016$] were significantly higher in patients with higher PCC-RHL dimension, likewise the frequencie of nephritis (77% vs. 29%, $p = 0.010$). Liver enzymes were similar in both groups ($p > 0.05$). Positive correlation was observed between SLEDAI-2K and PCC-RHL ($p = 0.001$, $r = +0.595$). Negative correlation was evidenced between disease duration and longitudinal dimension of spleen ($p = 0.031$, $r = -0.394$).
Conclusion: Our data raises the possibility that disease activity could lead to a subclinical and localized hepatomegaly during the disease course. Long disease duration resulted to spleen atrophy in c-SLE patients.

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Biometria do fígado e do baço em pacientes com lúpus eritematoso sistêmico de início na infância

Palavras-chave:
Hepatomegalia
Atrofia do baço
Ultrassonografia
Biometria
Lúpus eritematoso sistêmico
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RESUMO

Objetivo: Avaliar as dimensões do fígado e do baço em pacientes com lúpus eritematoso sistêmico de início pediátrico (LESp) e controles saudáveis.

Métodos: 30 pacientes com LES-i e 30 voluntários saudáveis controle foram submetidos a uma ultrassonografia do abdome. Foram realizadas duas medições do fígado no lobo hepático esquerdo (craniocaudal e anteroposterior) e três no lobo hepático direito (LHD) (craniocaudal posterior [CCP-LHD], craniocaudal anterior e anteroposterior). Foram também avaliadas três medidas das dimensões do baço: longitudinal, transversal e anteroposterior. Foram avaliados dados demográficos, clínicos e laboratoriais, SLEDAI-2K, ECLAM, SLAM e tratamento.

Resultados: A idade média foi semelhante nos pacientes com LES-i e controles (170,31 ± 27,81 vs. 164,15 ± 39,25 meses; $p = 0{,}486$). A média da dimensão CCP-LHD foi significativamente maior no grupo LES-i em comparação aos controles (13,30 ± 1,85 vs. 12,52 ± 0,93, $p = 0{,}044$). Não houve diferenças nos outros parâmetros biométricos do fígado e do baço ($p > 0{,}05$). Uma análise especifica realizada apenas nos pacientes com LESp de acordo com a dimensão CCP-LHD ≥13,3 cm versus <13,3 cm mostrou que a mediana do SLEDAI-2K [8 (0–18) vs. 2 (0–8), $p = 0{,}004$], ECLAM [4 (0–9) vs. 2 (0–5), $p = 0{,}019$] e SLAM [5 (1–13) vs. 2 (0–14), $p = 0{,}016$] era significativamente maior em pacientes com maior dimensão CCP-LHD, do mesmo modo que a frequência de nefrite (77% vs. 29%, $p = 0{,}010$). As enzimas hepáticas foram semelhantes nos dois grupos ($p > 0{,}05$). Foi observada uma correlação positiva entre o SLEDAI-2K e a dimensão CCP-LHD ($p = 0{,}001$, $r = +0{,}595$). Evidenciou-se uma correlação negativa entre a duração da doença e a dimensão longitudinal do baço ($p = 0{,}031$, $r = -0{,}394$).

Conclusão: Os dados levantam a possibilidade de que a atividade da doença pode levar a uma hepatomegalia subclínica e localizada durante o curso da doença. A duração da doença resultou em atrofia do baço em pacientes com LES-i.

Introduction

Hepatomegaly and/or splenomegaly occur in 20–50% childhood-onset systemic lupus erythematosus[1] (c-SLE) patients at disease onset, usually associated with disease activity. Involvement of the reticuloendothelial system may also be associated with abnormal liver function tests.[2,3]

Abdominal ultrasound can be used to assess liver[4] and spleen measurements in children and adolescents without risk of radiation.[5] However, a systematic evaluation of these visceral organ dimensions has not been performed in c-SLE population, particularly during the disease course.

Therefore, the objectives of our study were to evaluate liver and spleen dimensions in c-SLE patients and healthy controls and to assess possible associations between abnormalities in liver and spleen sizes with demographic data, clinical features, disease activity, cumulative damage and treatment.

Materials and methods

Patients and controls

From May to June 2012, 58 c-SLE patients were followed at our Pediatric Rheumatology Service. All of the patients fulfilled the American College of Rheumatology criteria for c-SLE.[6] The exclusion criteria were current acute or chronic infections, autoimmune hepatitis, other concomitant disease with hepatosplenomegaly, cancer or unwilling to participate. Out of them, 15 were excluded due to current acute infections, 9 due to unwillingness to participate and 4 due to autoimmune hepatitis. Therefore, the cross-sectional study was conducted in 30 c-SLE patients. The control group included 30 healthy control volunteers recruited from the primary care clinic nearby our tertiary hospital. The control volunteers were submitted to clinical evaluation, and liver and spleen biometrics. Local ethics committee of our university hospital approved this study, and informed consent was obtained from all participants.

Liver and spleen biometrics

Abdominal ultrasound was carried out by an experienced and trained, specialist (SMS) using a 1–6 mHz convex multifrequency transducer (LOGIC E9® – General Electric, USA). The following two liver measurements were performed in left hepatic lobe (LHL): craniocaudal (CC-LHL) and anteroposterior (AP-LHL), and three in right hepatic lobe (RHL): posterior craniocaudal (PCC-RHL), anterior craniocaudal (ACC-RHL) and anteroposterior (AP-RHL). Three spleen dimension

measurements were also evaluated: longitudinal, transverse and anteroposterior.

Demographic data, clinical, laboratorial and treatment assessment

Demographic data included current age, disease duration and *gender*. Weight and height were evaluated. Body mass index (BMI) was defined by weight in kilograms/height in meters^2 (kg/m^2). Body surface area (BSA in m^2) was calculated according to the formula: (weight in kilograms$^{0.425}$ × height in centimeters$^{0.725}$) × 0.007184.

SLE clinical manifestations were defined as: hepatomegaly (liver edge >2 cm below the right costal margin), splenomegaly (palpable spleen below the left costal margin), mucocutaneous lesions (malar or discoid rash, oral ulcers or photosensitivity), articular involvement (non-erosive arthritis), neuropsychiatric disease (seizure or psychosis), renal involvement (proteinuria ≥ 0.5 g/24 h, presence of cellular casts, and/or persistent hematuria ≥ 10 red blood cells per high power field), serositis (pleuritis or pericarditis), and hematologic abnormalities (hemolytic anemia, leukopenia with a white blood cell count < 4000 mm^{-3}, lymphopenia < 1500 mm^{-3} on two or more occasions and thrombocytopenia with platelet count < 100,000 mm^{-3} in the absence of drugs or infection).

Disease activity was evaluated according to SLE Disease Activity Index 2000 (SLEDAI-2K),[7] European Consensus Lupus Activity Measurement (ECLAM),[8] and Systemic Lupus Activity Measure (SLAM) scores.[9] Cumulative damage using the SLE International Collaborating Clinics/ACR Damage Index (SLICC/ACR-DI).[10]

Erythrocyte sedimentation rate (ESR) was performed by Westergreen method and C-reactive protein (CRP) by nephelometry. Anti-double-stranded DNA (anti-dsDNA) was detected by indirect immunofluorescence using *Crithidia luciliae* as substrate. Presence of anticardiolipin antibodies (aCL) IgG and IgM was analyzed by enzyme-linked immunosorbent assay (ELISA). Lupus anticoagulant (LAC) was detected according to the guidelines of the International Society on Thrombosis and Hemostasis.[11]

Data concerning the cumulative and current dosage of prednisone, hydroxychloroquine, methotrexate, azathioprine, intravenous cyclophosphamide, cyclosporine and mycophenolate mofetil were determined.

Statistical analysis

Results were presented as the mean ± standard deviation (SD) or median (range) for continuous and number (%) for categorical variables. Data were compared by Mann–Whitney test in continuous variables to evaluate differences among c-SLE and control group, and among SLE subgroups. For categorical variables, differences were assessed by Fisher's exact test. Spearman rank correlation coefficient was used for correlations between disease activity scores and liver and spleen parameters. The level of significance of independent variable was set at 5% ($p < 0.05$).

Results

Table 1 includes demographic data, liver and spleen biometrics in c-SLE patients and healthy controls. The mean current age was similar between the c-SLE and controls (170.31 ± 27.81 vs. 164.15 ± 39.25 months; $p = 0.486$), likewise the frequency of female gender (77% vs. 63%, $p = 0.398$) and median of BSA ($p = 0.875$). The mean of PCC-RHL dimension was significantly higher in c-SLE compared to controls (13.30 ± 1.85 vs. 12.52 ± 0.93, $p = 0.044$) (Table 1). There were no differences between the other hepatic biometrics and splenic parameters ($p > 0.05$). None of c-SLE and healthy controls had jaundice, ascites, pruritus, bleeding, liver or spleen thrombosis or sonographic hepatic steatosis.

Further analysis in c-SLE patients according to PCC-RHL dimension ≥13.3 cm (Table 2) (mean of this biometric measurement in 30 c-SLE patients) versus <13.3 cm showed that the median of SLEDAI-2K [8 (0–18) vs. 2 (0–8), $p = 0.004$], ECLAM [4 (0–9) vs. 2 (0–5), $p = 0.019$] and SLAM [5 (1–13) vs. 2 (0–14), $p = 0.016$] were significantly higher in patients with higher PCC-RHL dimension, likewise the mean of ESR (33.7 ± 16 vs. 22.0 ± 13 mm/h, $p = 0.038$). The frequencies of nephritis were significantly higher in patients with PCC-RHL dimension ≥13.3 cm versus <13.3 cm (77% vs. 29%, $p = 0.010$). The mean of BSA was also significantly higher in the former group (1.56 ± 0.23 vs. 1.37 ± 0.26m^2, $p = 0.043$). The median of serum liver enzymes were similar in both groups ($p > 0.05$).

Only one c-SLE patient had hepatosplenomegaly (liver edge 4 cm below the right costal margin and spleen edge 4 cm

Table 1 – Demographic data, liver and spleen biometrics in childhood-onset systemic lupus erythematosus (c-SLE) patients and healthy controls.

Variables	c-SLE ($n = 30$)	Controls ($n = 30$)	p
Demographic data			
Current age, months	170.31 ± 27.81	164.15 ± 39.25	0.486
Female gender	23 (77)	19 (63)	0.398
BMI, kg/m^2	21.15 (17.4–35.3)	22.1 (18.6–29.6)	0.721
BSA, m^2	1.56 (0.94–2.02)	1.49 (1.32–2.03)	0.875
Liver biometrics			
CC-LHL, cm	7.73 ± 1.48	7.57 ± 1.21	0.648
AP-LHL, cm	5.22 ± 0.79	5.38 ± 0.68	0.405
PCC-RHL, cm	13.30 ± 1.85	12.52 ± 0.93	0.044
ACC-RHL, cm	8.33 ± 1.27	8.25 ± 1.04	0.698
AP-RHL, cm	11.40 ± 1.60	10.74 ± 0.98	0.060
Spleen biometrics			
Longitudinal, cm	9.85 (7.0–16.9)	9.50 (8.1–11.9)	0.387
Transverse, cm	3.50 (2.8–5.8)	3.75 (2.0–6.0)	0.524
AP, cm	6.70 ± 1.09	6.64 ± 0.85	0.793

Results are presented in median (range) or mean ± standard deviation and *n* (%).
BMI, body mass index; BSA, body surface area; CC, craniocaudal; LHL, left hepatic lobe; AP, anteroposterior; PCC, posterior craniocaudal; RHL, right hepatic lobe; ACC, anterior craniocaudal.

Table 2 – Demographic data, disease parameters, clinical and laboratorial features and treatment in childhood-onset systemic lupus erythematosus (cSLE) patients according to posterior craniocaudal of right hepatic lobe (PCC-RHL) dimension.

	PCC-RHL ≥13.3 cm (*n* = 13)	PCC-RHL <13.3 cm (*n* = 17)	*p*
Demographic data			
Current age, month	173.49 ± 23.05	167.87 ± 31.45	0.592
Disease duration, month	36.0 (7.2–104.4)	40.8 (4.8–156.0)	0.869
BMI, kg/m^2	21.1 (17.4–35.3)	21.4 (16.9–32.9)	0.483
BSA, m^2	1.56 ± 0.23	1.37 ± 0.26	0.043
Female gender	11 (85)	12 (71)	0.326
Disease parameters			
SLEDAI-2K	8 (0–18)	2 (0–8)	0.004
ECLAM	4 (0–9)	2 (0–5)	0.019
SLAM	5 (1–13)	2 (0–14)	0.016
SLICC-ACR-DI	0 (0–1)	0 (0–1)	0.242
Clinical and laboratorial features			
Hepatosplenomegaly	0 (0)	1 (6)	1.0
Articular	2 (15)	3 (18)	0.633
Mucocutaneous	6 (46)	6 (35)	0.547
Hematological	5 (38)	4 (23)	0.314
Serositis	1 (8)	1 (6)	0.687
Neuropsychiatric	2 (15)	0 (0)	0.179
Nephritis	10 (77)	5 (29)	0.010
ESR, mm/h	33.7 ± 16	22.0 ± 13	0.038
CRP, mg/dL	7.4 (0.1–20.8)	0.8 (0.1–12.9)	0.094
AST, IU/L	20 (11–55)	21 (11–63)	0.322
ALT, IU/L	31 (11–47)	33 (7–61)	0.622
Anti-dsDNA	3 (23)	0 (0)	0.070
IgM ACL	3 (23)	1 (6)	0.204
IgG ACL	3 (23)	2 (12)	0.367
LAC	0 (0)	2 (12)	0.313
Treatment			
Current prednisone	12 (92)	12 (71)	0.156
Dose, mg/day	20 (10–50)	15 (3–30)	0.089
Cumulative dose, g	24.85 (7.1–54.5)	19.72 (6.1–451.3)	0.477
Current azathioprine	4 (31)	7 (41)	0.421
Current mycophenolate mofetil	7 (54)	4 (23)	0.093
Current methotrexate	2 (15)	2 (12)	0.591
Current hydroxychloroquine	11 (85)	17 (100)	0.179

Results are presented in median (range) or mean ± standard deviation and *n* (%).
BMI, body mass index; BSA, body surface area; SLEDAI-2K, Systemic Lupus Erythematosus Disease Activity Index 2000; ECLAM, European Consensus Lupus Activity Measurement; SLAM, Systemic Lupus Activity Measure; SLICC/ACR-DI, Systemic Lupus International Collaborating Clinics/ACR Damage Index; AST, alanine aminotransferase; ALT, aspartate aminotransferase; ACL, anticardiolipin antibody; LAC, lupus anticoagulant.

below the left costal margin), however the PCC-RHL was <13.3 cm.

Correlations were evidenced between SLEDAI-2K and PCC-RHL ($p = 0.001$, $r = +0.595$), SLEDAI-2K and CC-LHL ($p = 0.015$, $r = +0.440$), SLEDAI-2K and ACC-RHL ($p = 0.017$, $r = +0.431$), and SLEDAI-2K and AP-RHL dimensions ($p = 0.029$, $r = +0.399$), as well as observed between SLEDAI-2K and longitudinal spleen dimension ($p = 0.042$, $r = +0.373$). Also, it was found a positive correlation between SLAM and PCC-RHL ($p = 0.020$, $r = +0.422$), SLAM and CC-LHL ($p = 0.047$, $r = +0.365$), ECLAM and PCC-RHL ($p = 0.018$, $r = +0.430$), ECLAM and CC-LHL ($p = 0.008$, $r = +0.475$), as well as found between ECLAM and longitudinal spleen dimension ($p = 0.047$, $r = +0.365$).

Negative correlation was evidenced between disease duration and longitudinal dimension of spleen ($p = 0.031$, $r = -0.394$).

Discussion

To our knowledge, this was the first study that specifically addressed liver and spleen biometrics in pediatric lupus population, and showed subclinical hepatomegaly in patients with disease activity associated with BSA. Moreover, long period of disease duration may be related to splenic atrophy in c-SLE patient.

The great advantage of the present study design was the systematic assessment of various liver and spleen dimensions in c-SLE patients and healthy controls. The similar age, gender and BSA in c-SLE and control groups were relevant, since these parameters may influence these organs sizes.[5] The rigorous selection criteria of our patients and controls without infections, cancer,[12] autoimmune hepatitis,[2,13] and other

concomitant chronic diseases with hepatosplenomegaly are important since these abnormalities may also influence the dimensions. However, the main limitations of this study were the small number of patients, the lack of laboratory exams evaluation in control group and the lack of assessement of splenic function, since c-SLE patients could present functional asplenia.[14]

Hepatomegaly is a common finding at disease onset in c-SLE patients and adult SLE.[2,3,15] During disease course, liver enlargement in lupus patients, either children or adults, may be associated with hepatic congestion, fatty infiltration, autoimmune and viral hepatitis, metabolic disorders, thrombosis or hepatotoxic drugs usage.[2,15,16]

Our patients had localized right-liver hypertrophy associated with disease activity, suggesting the same systemic pathogenesis mechanism. These patients had mild and subclinical liver enlargement probably due to liver congestion, liver chronic inflammation and hypervascularization. Of note, this enlargement was associated with severe disease and correlated with various clinical and laboratory disease parameters. Indeed, the autopsy registry data of the liver showed that hepatic congestion, liver chronic inflammation and/or liver arteritis were observed in 77% of adult and c-SLE patients and may be reflecting lupus activity.[15] Positive correlation was also found between disease activity parameters and longitudinal spleen dimension, despite the absence of clinical and sonography splenomegaly.

Damage to hepatocyte cell seems not to be relevant herein, since none of our patients had elevated levels of liver enzymes. Moreover, corticosteroid use, a known cause of hepatomegaly and fatty liver disease, may have not contributed to enlargement of this organ in the present study.[2,15]

Both pediatric and adult SLE patients may present splenic atrophy.[14,17] Importantly, our children and adolescent lupus patients with long disease duration presented spleen size reduction, thus indicating splenic atrophy during the disease course. A previous study evaluating adult SLE patients found that splenic atrophy had no correlation with disease duration.[17] However, the mechanisms of spleen atrophy and functional asplenia are still not clear in pediatric and adult SLE populations and further studies will be necessary.

In conclusion, our data raises the possibility that disease activity could lead to subclinical and localized hepatomegaly. We hypothesize that liver is a potential target organ for active lupus during the disease course. Long disease duration resulted to spleen atrophy in c-SLE patients.

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Conflicts of interest

The authors declare no conflicts of interest.

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