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Autoimmune hepatitis in 847 childhood-onset systemic lupus erythematosus population: a multicentric cohort study

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Abstract

Objective: To evaluate autoimmune hepatitis (AIH) in a multicenter cohort of childhood-onset systemic lupus erythematosus (cSLE) patients.

Methods: This retrospective multicenter study included 847 patients with cSLE, performed in 10 Pediatric Rheumatology services of São Paulo state, Brazil. AIH was defined according to the International Autoimmune Hepatitis Group criteria (IAHGC). The statistical analysis was performed using the Bonferroni's correction ($p < 0.0033$).

Results: AIH in cSLE patients confirmed by biopsy was observed in 7/847 (0.8%) and all were diagnosed during adolescence. The majority occurred before or at cSLE diagnosis [5/7 (71%)]. Antinuclear antibodies were a universal finding, 43% had concomitantly anti-smooth muscle antibodies and all were seronegative for anti-liver kidney microsomal antibodies. All patients with follow-up ≥18 months (4/7) had complete response to therapy according to IAHGC. None had severe hepatic manifestations such as hepatic failure, portal hypertension and cirrhosis at presentation or follow-up. Further comparison of 7 cSLE patients with AIH and 28 without this complication with same disease duration [0 (0–8.5) vs. 0.12 (0–8.5) years, $p = 0.06$] revealed that the frequency of hepatomegaly was significantly higher in cSLE patients in the former group (71% vs. 11%, $p = 0.003$) with a similar median SLEDAI-2 K score [6 (0–26) vs. 7 (0–41), $p = 0.755$]. No differences were evidenced regarding constitutional involvement, splenomegaly, serositis, musculoskeletal, neuropsychiatric and renal involvements, and treatments in cSLE patients with and without AIH ($p > 0.0033$).

Conclusions: Overlap of AIH and cSLE was rarely observed in this large multicenter study and hepatomegaly was the distinctive clinical feature of these patients. AIH occurred during adolescence, mainly at the first years of lupus and it was associated with mild liver manifestations.

Keywords: Autoimmune hepatitis, Childhood systemic lupus erythematosus, Hepatomegaly, Multicenter study

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Introduction

Childhood-onset systemic lupus erythematosus (cSLE) is an autoimmune and inflammatory disease that affects multiple organs and systems, including liver [1–3].

Of note, autoimmune hepatitis (AIH) is characterized by elevated hepatic enzymes, hypergammaglobulinemia, presence of autoantibodies and liver histology abnormalities, particularly interface hepatitis and lymphocytic infiltrates [4, 5]. To our knowledge the prevalence of overlap AIH and cSLE in a large population was not studied and analysis of this very rare association is restricted to few case reports or case series [1, 3, 6, 7].

Therefore, the objective of this multicenter cohort study was to evaluate cSLE and AIH and the possible association with demographic data, cumulative clinical manifestations, treatments and outcomes in a large cSLE population in Latin America.

Methods

This study was conducted in 10 Pediatric Rheumatology services in the state of São Paulo, Brazil including a population of 847 cSLE patients [8]. All patients fulfilled the American College of Rheumatology (ACR) criteria for SLE [9], with disease onset before the age of 18. The Ethical Committee of each University Hospital approved this study. An investigator meeting was held for this study in São Paulo city to define the protocol according to the clinical parameters and disease activity tool scoring. At least one investigator with Brazilian Board Pediatric Rheumatology Certifying Examination supervised data collection in each center, reviewed paper files and tried to solve discrepancies among investigators of these centers. Four rounds of queries were performed to check for accuracy and sort out discrepancies among groups.

Patients' medical charts were systematically reviewed according to demographic data, clinical features and AIH characteristics, laboratorial abnormalities, therapeutic data and outcomes. AIH was diagnosed according to International Autoimmune Hepatitis Group criteria (IAHGC) [4, 5]. Every medical visit from cSLE diagnosis to last visit or death was reviewed in each center. Percutaneous needle liver biopsy was performed in these centers in cSLE patients with elevation of liver enzymes (not related to hepatotoxic drugs, metabolic disease, alcohol or viral disease), associated with hypergammaglobulinemia and presence of at least one autoantibody [antinuclear antibodies (ANA), anti-type I liver-kidney microsomal (anti-LKM-1) antibody or liver and stomach tissue substrates and anti-smooth muscle antibody (anti-SMA)].

Descriptors of SLE Disease Activity Index 2000 (SLEDAI-2 K) were used to define clinical manifestations [10], and custom definitions as previously reported [8]. Cumulative clinical manifestations included constitutional involvement [defined as fever and lymphadenopathy (peripheral lymph node enlargement > 1.0 cm)], hepatomegaly [based on physical exam with liver edge ≥2 cm below the right costal margin or imaging (ultrasound or computer tomography when available)], splenomegaly [based on physical exam with palpable spleen or imaging (ultrasound or computer tomography when available)], musculoskeletal involvement, serositis, neuropsychiatric and renal involvement. Neuropsychiatric Lupus included 19 syndromes according to ACR classification criteria [11].

Antinuclear antibodies (ANA) were tested by indirect immunofluorescence. Anti-type I liver-kidney microsomal (anti-LKM-1) antibody on frozen sections of rodent kidney, liver and stomach tissue substrates and anti-smooth muscle antibody (anti-SMA) by indirect immunofluorescence on rat liver and kidney tissue sections on frozen sections of rodent kidney, liver and stomach tissue substrates. The cut-off values from the kit manufacturer were used to define abnormal.

Drug treatment data (prednisone, intravenous methylprednisolone, chloroquine diphosphate, hydroxychloroquine sulfate, methotrexate, azathioprine, cyclosporine, mycophenolate mofetil, intravenous cyclophosphamide, intravenous immunoglobulin and rituximab) were also recorded.

Patients were divided in two groups with similar disease duration: cSLE patients with AIH (evaluated at AIH diagnosis) and cSLE patients without AIH (evaluated at last visit).

Statistical analysis

Results were presented as absolute number (frequency) for categorical variables and median (range) or mean ± standard deviation for continuous variables. Categorical variables comparisons were assessed by Pearson χ-Square or Fisher's exact test. Continuous variables from cSLE patients with and without AIH were compared by Mann-Whitney test or t test as appropriate. Statistical analysis was performed using Bonferroni correction ($p < 0.0033$).

Results

Demographic data, clinical and laboratorial features, outcomes and treatments in cSLE patients with AIH are described in Table 1. AIH in cSLE patients confirmed by biopsy was observed in 7/847 (0.8%) and all were diagnosed during adolescence. The majority occurred before or at cSLE diagnosis [5/7 (71%)]. Antinuclear antibodies were a universal finding, 43% had concomitantly anti-SMA and all were seronegative for anti-LKM-1 antibodies. All 7 patients with follow-up ≥18 months (4/7) had complete response to therapy according to IAHGC. None of cSLE patients with AIH had severe hepatic manifestations such as hepatic failure, portal hypertension, cirrhosis or deceased at presentation or at follow-up (Table 1).

Liver biopsy was performed in only 7/847 (0.8%) cSLE that fulfilled the AIH criteria (IAHGC) [4, 5]. Regarding

Table 1 Demographic data, clinical and laboratorial features, outcomes and treatments in childhood-onset systemic lupus erythematosus (cSLE) patients with autoimmune hepatitis (AIH)

	Cases						
	1	2	3	4	5	6	7
Demographic data							
Age, years	12.5	12.3	10.3	15	10.3	15.6	11.7
Female gender	+	+	+	+	+	+	–
Time between AIH and cSLE, years	−1.5	0	−4.75	0	2.3	8.5	0
cSLE duration, years	0	0	0	0	2.3	8.5	0
Clinical/laboratorial features							
Constitutional symptoms	–	+	+	+	+	+	+
Jaundice/ascites	+/–	–/–	+/–	+/–	–/–	+/–	+/–
Hepatomegaly/Splenomegaly	–/–	+/+	–/–	+/+	+/–	+/–	+/+
AST, IU/L	93	652	35	345.7	245	4466	1260
ALT, IU/L	113	268	122	244.6	552	1411	949
GGT, IU/L	258	604	91	51.2	613	69	606
Hypergammaglobulinemia	+	+	+	+	+	+	+
ANA > 1:80	+	+	+	+	+	+	+
Anti-SMA > 1:80	+	+	+	–	–	–	–
Anti-LKM1 > 1:80	–	–	–	–	–	–	–
Viral hepatitis markers	–	–	–	–	–	–	–
Alcohol intake	–	–	–	–	–	–	–
Liver histology with interface hepatitis and lymphocytic infiltrates	+	+	+	+	+	+	+
Outcomes							
Liver failure/portal hypertension/cirrhosis	- /–/–	- /–/–	- /–/–	- /–/–	- /–/–	- /–/–	- /–/–
Death	–	–	–	–	–	–	–
Therapy							
AIH complete response therapy (> 18 months)	+	NP	+	NP	+	+	NP
cSLE treatments	PD, AZA	PD, AZA, AM	PD, AZA, AM	PD, AZA	PD, AZA, AM	PD, AZA	PD

AST aspartate aminotransferase (normal value 15–40 IU/L), *ALT* alanine aminotransferase (normal value 10–40 IU/L), *GGT* gamma glutamyl transferase (normal value 3–25 IU/L), *ANA* antinuclear antibodies, anti-SMA - anti-smooth muscle antibody, anti-LKM1 - anti-liver kidney microsomal antibody type1, *NP* not possible, *PD* prednisone, *AZA* azathioprine, *AM* antimalarial

the remaining 840 cSLE patients without AIH, 86% patients were females. The median of age was 12 years (0.25–18) and the median of disease duration was 5 years (0–23). Leukopenia (45%), thrombocytopenia (21%), ANA (99%), anti-dsDNA antibodies (71%) and anti-Sm antibodies (32%) were observed in these cSLE patients.

Deaths occurred in 69/840 (8%) cSLE patients that were not affected by AIH. Infections accounted for 54/69 (78%) of overall deaths and 70% of these had concomitant disease activity. Other causes of death were: nephritis (acute kidney injury or chronic renal disease) (9%), alveolar hemorrhage (4%), massive intracranial bleeding (1.4%), multiple thrombosis due to catastrophic antiphospholipid syndrome (1.4%), B-cell lymphoma (1.4%) and unknown etiologies (4%).

Further analysis of 7 cSLE patients with AIH compared to 28 cSLE patients without AIH and with the same disease duration [0 (0–8.5) vs. 0.12 (0–8.5) years, $p = 0.06$] revealed that the frequency of hepatomegaly was significantly higher in cSLE patients with AIH compared to those without AIH (71% vs. 11%, $p = 0.003$). The median of age at diagnosis [12.25 (10.3–15.6) vs. 12.9 (3.3–19.7) years, $p = 0.650$] and SLEDAI-2 K score [6 (0–26) vs. 7 (0–41) years, $p = 0.755$] were similar in both groups. No differences were evidenced between constitutional involvement, splenomegaly, serositis, musculoskeletal, neuropsychiatric and renal manifestations, and treatments in cSLE patients with and without AIH ($p > 0.0033$) (Table 2).

The comparisons of last visit of cSLE patients with AIH ($n = 7$) versus last visit of cSLE without AIH ($n = 840$) revealed similar age [12.25 (7.1–15) vs. 11.83 (0.25–17.8) years, $p = 0.94$] and disease duration [4.3 (0.58–11.8) vs. 4.58 (0–23.4) years, $p = 0.56$] in both groups. The frequency

Table 2 Demographic data, disease activity, cumulative clinical manifestations and treatments in childhood-onset systemic lupus erythematosus (cSLE) patients with autoimmune hepatitis (AIH) at diagnosis compared to those without AIH evaluated at last visit

Variables	cSLE with AIH (at AIH diagnosis) ($n = 7$)	cSLE without AIH (at last visit) ($n = 28$)	*P*
Demographic data			
Age at diagnosis, years	12.25 (10.3–15.6)	12.9 (3.3–19.7)	0.650
Disease duration, years	0 (0–8.5)	0.12 (0–8.5)	0.060
Disease activity parameter			
SLEDAI-2 K	6 (0–26)	7 (0–41)	0.755
Cumulative clinical manifestations			
Constitutional involvement	6 (86)	7 (25)	0.006
Hepatomegaly	5 (71)	3 (11)	**0.003***
Splenomegaly	3 (43)	1 (4)	0.019
Musculoskeletal involvement	4 (57)	3 (11)	0.018
Serositis	0 (0)	4 (7)	1.000
Neuropsychiatric involvement	0 (0)	5 (18)	0.559
Renal involvement	2 (29)	11 (39)	0.689
Treatment			
Prednisone dose, mg/kg/day	1.07 (0.5–2.4)	0.9 (0.1–2.8)	0.365
Antimalarial use	3 (43)	14 (50)	1.000
Immunosuppressive use	6 (86)	8 (29)	0.009

Results are presented in n (%) and median (range), **P* - value according to Bonferroni correction for multiple comparisons ($p < 0.0033$), SLEDAI-2 K - SLE Disease Activity Index 2000

of female gender (85.7% vs. 85.9%, $p = 1.0$) and median of SLEDAI-2 K [4 (2–10) vs. 2 (0–45), $p = 0.45$] and SLICC-ACR/damage index [0 (0–1) vs. 0 (0–9), $p = 0.77$] were also similar in both groups. The frequencies of chronic renal failure (0% vs. 6.1%, p = 1.0), prednisone (100% vs. 97%, $p = 1.0$), azathioprine (86% vs. 61%, $p = 0.26$), methotrexate (29% vs. 23%, $p = 0.66$), mycophenolate mofetil (14% vs. 21%, $p = 1.0$) and intravenous cyclophosphamide (0% vs. 42%, $p = 0.05$) were alike in both group. The lower frequency of death in AIH patients did not reach statistical significance (0% vs. 8%, $p = 1.0$).

The Kaplan-Meier overall survival curve was significantly higher in cSLE patients with AIH compared to those without this complication ($p = 0.001$). After 11.6 years of disease onset the survival percentage of cSLE patients with AIH was 100% and for those without AIH was 83% (Fig. 1).

Discussion

This multicenter study demonstrated that overlap of AIH and cSLE is a very rare association. This liver autoimmune disease occurred mainly at the first years of cSLE diagnosis, without liver complication and associated with mild disease manifestations.

The strength of this study was the large cohort including 10 different Pediatric Rheumatology and tertiary centers of cSLE. All AIH patients fulfilled the IAHGC definite criteria (score > 15) with typical histological features in liver biopsy [4, 5]. We also used a standardized cSLE protocol with definitions for clinical and disease activity parameters [10]. The limitations were the possible missing data due to retrospective design, the collinearity of the variables and the limited indication for liver biopsy.

We have confirmed and extended previous observation that liver involvement is rarely observed in cSLE and adult SLE patients, with a variety of clinical and laboratorial manifestations [1, 12–16]. The rigorous selection criteria of AIH and cSLE patients excluding viral infections, malignancies and alcohol intake was relevant to avoid other confounding etiologies of hepatitis [1, 7, 12, 14].

AIH was solely observed in adolescents and the majority occurred before or at cSLE diagnosis. Hepatomegaly was a distinctive feature of AIH in this age group contrasting with our previous observation that liver enlargement was usually not common in adolescent at lupus diagnosis [17]. Hepatomegaly was not associated with liver congestion, fatty infiltration, viral hepatitis, metabolic disorders, thrombosis or hepatotoxic drugs usage, since histological findings excluded these issues. The concomitant presences of jaundice, splenomegaly and hypergammaglobulinemia reinforced the AIH diagnosis [1], as observed in more than 50% of cases.

AIH occurred in cSLE patients with mild lupus manifestations. Of note, the majority of our patients had a

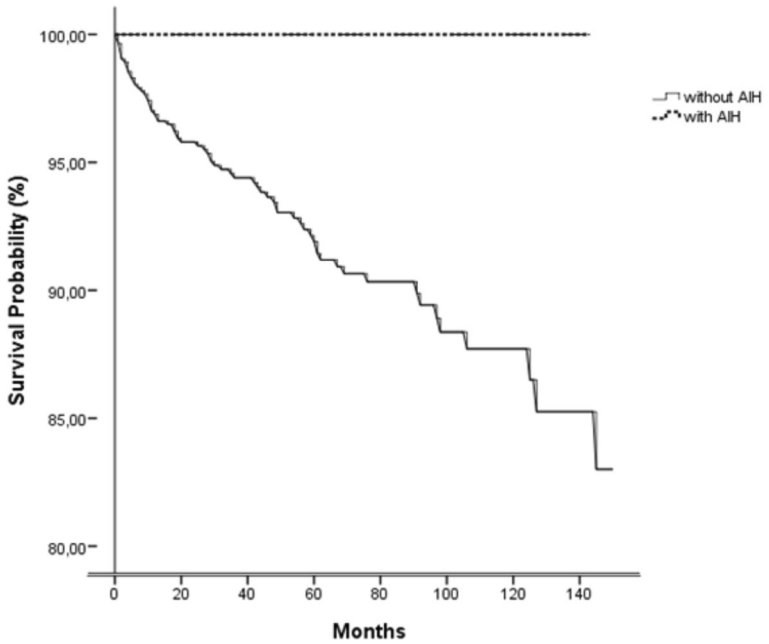

Fig. 1 Kaplan-Meier overall survival curve in childhood-onset systematic lupus erythematosus patients with autoimmune hepatitis (AIH) compared to those without this complication

complete response to the classical AIH prednisone and azathioprine combination therapy. Reinforcing this finding none of our patients had hepatic failure, portal hypertension and cirrhosis suggesting that AIH phenotype in lupus was a non-severe pattern [1, 3]. Additionally, none of our cSLE patients had anti-LKM1 antibodies.

Conclusion

Overlap AIH and cSLE was rarely observed in this large multicenter study and hepatomegaly was the distinctive clinical feature of these patients. AIH occurred during adolescence, mainly at the first years of lupus and it was associated with mild liver manifestations.

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Availability of data and materials

Not applicable

Authors' contributions

VAB, BM, ACP, ARS, LPC, JCOF, RMRP, MTT, CSM, NEA, APS, KK, LMC, AMS, VPF, DPP, EB and CAS analyzed and interpreted the patient data regarding autoimmune hepatitis in childhood onset systemic lupus erythematosus. VAB, BM, ACP, EB and CAS were the major contributor in writing the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was approved by our Ethics Committee.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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