Autoimmunity Reviews 16 (2017) 132–135

Contents lists available at ScienceDirect

Autoimmunity Reviews

journal homepage: www.elsevier.com/locate/autrev

Review

Anti-RO/SSA and *anti*-La/SSB antibodies: Association with mild lupus manifestations in 645 childhood-onset systemic lupus erythematosus

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ARTICLE INFO

Article history:
Received 5 September 2016
Accepted 10 September 2016
Available online 14 December 2016

Keywords:
Anti-Ro/SSA autoantibodies
Anti-La/SSB autoantibodies
Sjögren syndrome and childhood-systemic lupus erythematosus
Multicenter cohort

ABSTRACT

Background: To our knowledge there are no studies assessing *anti*-Ro/SSA and anti-La/SSB autoantibodies in a large population of childhood-systemic lupus erythematosus (cSLE) patients.
Methods: This was a retrospective multicenter cohort study performed in 10 Pediatric Rheumatology services, São Paulo state, Brazil. Anti-Ro/SSA and *anti*-La/SSB antibodies were measured by enzyme linked immunosorbent assay (ELISA) in 645 cSLE patients.
Results: Anti-Ro/SSA and *anti*-La/SSB antibodies were evidenced in 209/645 (32%) and 102/645 (16%) of cSLE patients, respectively. Analysis of cSLE patients with and without anti-Ro/SSA antibodies revealed higher frequencies of malar rash (79% vs. 71%, $p = 0.032$), photosensitivity (73% vs. 65%, $p = 0.035$), cutaneous vasculitis (43% vs. 35%, $p = 0.046$) and musculoskeletal involvement (82% vs. 75%, $p = 0.046$) in spite of long and comparable disease duration in both groups (4.25 vs. 4.58 years, $p = 0.973$). Secondary Sjögren syndrome was observed in only five patients with this antibody (2.5% vs. 0%, $p = 0.0035$), two of them with concomitant *anti*-La/SSB. The presence of associated autoantibodies: *anti*-Sm (50% vs. 30%, $p < 0.0001$), anti-RNP (39% vs. 21%, $p < 0.0001$) and anti-ribossomal P protein (46% vs. 21%, $p = 0.002$) was also significantly higher in patients with *anti*-Ro/SAA antibodies. Further evaluation of cSLE patients with the presence of *anti*-La/SSB antibodies compared to those without these autoantibodies showed that the frequency of alopecia (70% vs. 51%, $p = 0.0005$), anti-Sm (59% vs. 31%, $p < 0.0001$) and *anti*-RNP (42% vs. 23%, $p < 0.0001$) were significantly higher in the former group.
Conclusions: Our large multicenter cohort study provided novel evidence in cSLE that *anti*-Ro/SSA and/or anti-La/SSB antibodies were associated with mild manifestations, particularly cutaneous and musculoskeletal. Secondary Sjögren syndrome was rarely observed in these patients, in spite of comparable frequencies of *anti*-Ro/SSA and/or anti-La/SSB reported for adult SLE.

Contents

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http://dx.doi.org/10.1016/j.autrev.2016.12.004
1568-9972/

1. Introduction

Systemic lupus erythematosus (SLE) is a chronic condition with a broad clinical spectrum, which can affect multiple organs and systems [1–6]. One hallmark of the disease is the presence of autoantibodies directed against several cellular antigens, such as histone, non-histone, cytoplasm and nuclear proteins [1–7].

Ro/SSA and La/SSB are extractable nuclear antigens, and *anti*-Ro/SSA and anti-La/SSB autoantibodies were reported in 30–40% and 7–45% of adult SLE patients, respectively [8–10]. Cutaneous [7–9] and musculoskeletal involvements [7,9] were common clinical manifestations in these patients. Anti-Ro/SSA and *anti*-La/SSB antibodies were also observed in childhood-onset SLE (cSLE) patients, but frequencies seem to be lower than the reported in adults at disease diagnosis or during disease course [5,6,10–13]. However, demographic, clinical and laboratorial associations of *anti*-Ro/SSA and anti-La/SSB autoantibodies in cSLE patients are lacking since data is limited to case reports and small cohorts [5,6,10–13].

Therefore, the aim of this multicenter cohort study was to evaluate the possible association between the presence of *anti*-Ro/SSA and/or anti-La/SSB antibodies with demographic, clinical and laboratorial features in cSLE patients.

2. Methods

2.1. Study design and patients

This was a retrospective multicenter study performed in 10 Pediatric Rheumatology services, São Paulo state, Brazil. The population included 645 cSLE patients and *anti*-SSA/Ro and anti-SSB/La antibodies were measured. All patients fulfilled the American College of Rheumatology (ACR) criteria [14], with disease onset before 18 years of age [6].

The protocol for this study was defined, including clinical and laboratory parameters, in an investigator meeting in São Paulo. Demographic data included age at last visit, disease duration, gender and cumulative clinical descriptors and custom definitions, as previously described [6].

Juvenile Sjögren's syndrome was established according to the American-European Consensus Group [15]. Neuropsychiatric lupus comprised 19 syndromes according to ACR classification criteria, and was subdivided in peripheral and central nervous system involvement [16]. Antiphospholipid syndrome was diagnosed according to the preliminary criteria for the classification of pediatric antiphospholipid syndrome [17].

Anti-SSA/Ro and *anti*-SSB/La antibodies were measured by Enzyme Linked Immunosorbent Assay (ELISA). Antinuclear antibodies (ANA) were tested by indirect immunofluorescence; *anti*-double-stranded DNA (anti-dsDNA) by indirect immunofluorescence or ELISA; anti-Smith (anti-Sm) and anti-RNP by passive hemagglutination or ELISA; and anti-ribosomal P (anti-P) autoantibodies by ELISA. Autoantibodies detections were performed at each center and the cutoff values were defined according to the commercial kit.

Systemic Lupus International Collaborating Clinics/ACR-Damage Index (SLICC-ACR/DI) [18] was used to score disease damage at last visit.

2.1.1. Statistical analysis

Descriptive statistics were presented as an absolute number (frequency) for categorical variables and median (minimum and maximum values) for continuous variables. Categorical variables were assessed by Pearson χ-Square or by Fisher test. Continuous variables were analyzed according to Mann–Whitney test. We adopted the significance level of 5% in all statistical analysis.

3. Results

Anti-Ro/SSA and *anti*-La/SSB antibodies were evidenced in 209/645 (32%) and 102/645 (16%) of cSLE patients, respectively.

Table 1 included demographic data, cumulative clinical manifestations, autoantibodies, disease damage score at last visit in 645 c-SLE patients according to the presence or absence of *anti*-Ro/SSA antibody. Frequencies of malar rash (80% vs. 72%, $p = 0.032$), photosensitivity (73% vs. 65% $p = 0.035$), cutaneous vasculitis (43% vs. 35%, $p = 0.046$) and musculoskeletal involvement (82% vs. 75%, $p = 0.046$) were significantly higher in patients with the presence of *anti*-Ro/SSA antibodies compared to those without, in spite of long and comparable disease duration in both groups (4.2 vs. 4.6 years, $p = 0.973$). Juvenile Sjögren syndrome was rare and observed in only five patients with this antibody (2% vs. 0%, $p = 0.0035$) and two of them presented concomitant *anti*-La/SSB. Thrombocytopenia was less frequently observed in patients with *anti*-Ro/SSA positive compared to those without these autoantibodies (19% vs. 28%, $p = 0.012$) (Table 1).

Anti-Ro/SSA autoantibodies were associated with the presence of *anti*-Sm (50% vs. 30%, $p < 0.0001$), *anti*-RNP (39% vs. 21%, $p < 0.0001$) and anti-ribossomal P protein (46% vs. 21%, $p = 0.002$) (Table 1).

Further evaluation of cSLE patients with anti-La/SSB antibodies showed that the frequency of alopecia (70% vs. 51%, $p = 0.0005$), *anti*-Sm (59% vs. 31%, $p < 0.0001$) and anti-RNP autoantibodies (42% vs. 23%, $p < 0.0001$) was significantly higher in patients with this antibody specificity compared to that without these autoantibodies (Table 2).

Additional evaluation of cSLE patients with concomitant *anti*-Ro/SSA and anti-La/SSB antibodies revealed a higher frequency of alopecia (71% vs. 51%, $p = 0.0008$), *anti*-Sm (59% vs. 29%, $p = 0.0001$) and anti-RNP autoantibodies (45% vs. 21%, $p = 0.0001$) and a lower frequency of anti-dsDNA (55% vs. 70%, $p = 0.009$) compared to those without these antibodies.

4. Discussion

Our study provided novel evidence in cSLE patients that anti-Ro/SSA and/or anti-La/SSB antibodies were associated with mild manifestations, particularly cutaneous and musculoskeletal. Juvenile Sjögren syndrome was rarely observed in these patients.

This large multicenter cSLE population using a standardized protocol allowed a more accurate analysis of the clinical significance of these antibodies in cSLE in spite of the retrospective design.

We confirmed that the frequency of *anti*-Ro/SSA and anti-La/SSB antibodies in the present unique mixed ethnic background Brazilian population is similar to the previously reported for European, Canadian and American populations [5,6,10–12] minimizing the relevance of the genetic inheritance in the expression of these antibodies.

Table 1
Demographic data, cumulative clinical manifestations, autoantibodies and disease damage score at last visit in 645 childhood-onset systemic lupus erythematosus (c-SLE) patients according to the presence or absence of anti-Ro/SSA antibody.

Variables	With anti-Ro/SSA ($n = 209$)	Without anti-Ro/SSA ($n = 436$)	P
Demographic data			
Age at last visit (years), $n = 645$	17.6 (2–25)	17 (0–25.9)	0.288
Disease duration (years), $n = 642$	4.2 (0.08–17)	4.6 (0–23.4)	0.973
Male gender, $n = 645$	28/209 (13)	70/436 (16)	0.379
Constitutional manifestations, $n = 644$	158/209 (76)	321/435 (74)	0.623
Reticuloendothelial manifestations, $n = 644$	87/209 (42)	175/435 (40)	0.735
Mucocutaneous involvement, $n = 644$	196/209 (94)	407/435 (94)	0.916
Malar rash, $n = 641$	166/209 (80)	309/432 (72)	0.032
Discoid lupus, $n = 642$	23/208 (11)	47/434 (11)	0.931
Photosensitivity, $n = 642$	153/209 (73)	281/433 (65)	0.035
Mucosal ulceration, $n = 642$	97/209 (46)	221/433 (51)	0.272
Alopecia, $n = 642$	126/209 (60)	226/433 (52)	0.054
Vasculitis, $n = 644$	90/209 (43)	152/435 (35)	0.046
Musculoskeletal involvement, $n = 645$	171/209 (82)	326/436 (75)	0.046
Serositis, $n = 642$	72/209 (34)	155/433 (36)	0.738
Nephritis, $n = 643$	143/209 (68)	284/434 (65)	0.453
Neuropsychiatric involvement, $n = 644$	113/209 (54)	205/435 (47)	0.099
Autoimmune thrombosis (APS), $n = 616$	8/197 (4)	24/419 (6)	0.385
Sjögren syndrome, $n = 645$	5/209 (2)	0/436 (0)	0.0035
Cumulative hematological abnormalities			
Autoimmune hemolytic anemia, $n = 640$	59/208 (28)	108/432 (25)	0.364
Leukopenia $<4000/mm^3$, $n = 640$	109/209 (52)	196/431 (45)	0.113
Lymphopenia $<1500/mm^3$, $n = 639$	146/209 (70)	278/430 (65)	0.191
Thrombocytopenia, $<100.000/mm^3$, $n = 641$	39/209 (19)	120/432 (28)	0.012
Cumulative autoantibodies evaluation			
Antinuclear antibodies (ANA), $n = 643$	208/208 (100)	433/435 (99)	1.000*
Anti-dsDNA, $n = 641$	158/208 (76)	302/433 (70)	0.102
Anti-Sm, $n = 631$	101/202 (50)	130/429 (30)	<0.0001
Anti-RNP, $n = 615$	77/197 (39)	89/418 (21)	<0.0001
Anti-ribosomal P (*anti*-P), $n = 167$	21/46 (46)	26/121 (21)	0.002
Current disease damage score at last visit			
SLICC/ACR-DI ≥ 1, $n = 587$	63/192 (33)	140/395 (35)	0.530
Neuropsychiatric $n = 587$	15/192 (8)	43/395 (11)	0.242
Skin $n = 587$	5/192 (3)	13/395 (3)	0.651
Peripheral vascular $n = 587$	4/192 (2)	8/395 (2)	1.000
Ocular $n = 587$	23/192 (12)	39/395 (10)	0.436
Renal $n = 587$	16/192 (8)	33/395 (8)	0.993
Musculoskeletal $n = 587$	16/192 (8)	46/395 (12)	0.221
Cardiovascular $n = 587$	6/192 (3)	6/395 (2)	0.220
Pulmonary $n = 587$	3/192 (2)	5/395 (1.3)	0.721
Gastrointestinal tract $n = 587$	0/192 (0)	1/395 (0.3)	1.000
Gonad $n = 587$	0/192 (0)	1/395 (0.3)	1.000
Diabetes mellitus $n = 587$	1/192 (0.5)	0/395 (0)	0.327

Results are presented in n (%) and median (range), APS — antiphospholipid syndrome; SLICC/ACR-DI — Systemic Lupus International Collaborating Clinics/ACR-Damage Index.

We demonstrated herein that *anti*-Ro/SSA and/or anti-La/SSB antibodies are associated in cSLE patients with cutaneous and musculoskeletal involvements. With regard to the skin manifestation, this association was particularly relevant with malar rash, photosensitivity and cutaneous vasculitis. Likewise, in adult SLE the presence of anti-Ro/SSA antibodies was associated with cutaneous vasculitis [8], photosensitivity [9] and polyarthritis [7].

Of note, these autoantibodies in cSLE were not associated with major organ involvement, such as renal and neuropsychiatric abnormalities as also described in adult SLE [8]. On the contrary, these patients seem to have mild lupus without a higher frequency of cumulative damage in spite of long disease duration. Reinforcing this finding, cSLE patients with positive *anti*-Ro antibodies had lower frequency of thrombocytopenia, a known severe manifestation of lupus [19]. Interestingly, the presence of anti-Ro/La/Sm/RNP was previously associated with more benign form of adult lupus nephritis [20]. In fact, we observed that *anti*-Ro/SSA and anti-La/SSB antibodies were also associated with *anti*-Sm, *anti*-RNP and anti-ribossomal P protein in cSLE.

Secondary Sjögren syndrome was rarely diagnosed in our cSLE patients contrasting to adult SLE patients (3–18%) [8,21], and all of our patients had anti-Ro/SSA antibodies. Interestingly, frequencies of these antibodies did not seem to account for this low incidence of secondary Sjögren, since *anti*-Ro/SSA and anti-La/SSB antibody frequencies were comparable to the reported in adult SLE patients [8,21]. Importantly, the use of international criteria for Sjögren's syndrome definition provided a more uniform characterization of this syndrome [15].

In conclusion, *anti*-Ro/SSA and/or anti-La/SSB antibodies were associated with mild manifestations without a relevant cumulative damage. Secondary Sjögren syndrome was rarely diagnosed in these patients in spite of the comparable frequencies of anti-Ro/SSA and/or anti-La/SSB reported for adult SLE.

Fundings

This study was supported by grants from Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq 301805/2013-0 to RMRP, 303752/2015-7 to MTT, 301479/2015-1 to CSM, 305068/2014-8 to EB and 303422/2015-7 to CAS), Federico Foundation (to EB, RMRP and CAS) and by Núcleo de Apoio à Pesquisa "Saúde da Criança e do Adolescente" da USP (NAP-CriAd) to CAS.

Acknowledgements

Our gratitude to Ulysses Doria-Filho for the statistical analysis. The authors thank the following Pediatric Rheumatology Divisions and colleagues for including their patients: Pediatric Rheumatology Unit,

Table 2
Demographic data, cumulative clinical manifestations, autoantibodies and disease damage score at last visit in 645 childhood-onset systemic lupus erythematosus (c-SLE) patients according to the presence or absence of *anti*-La/SSB antibody.

Variables	With anti-La/SSB ($n = 102$)	Without anti-La/SSB ($n = 543$)	*P*
Demographic data			
Age at last visit (years), $n = 645$	17.8 (2.1–25)	17(0–25.9)	0.110
Disease duration (months), $n = 642$	57 (1–204)	54 (0–281)	0.791
Male gender, $n = 645$	14/102 (14)	84/543 (15)	0.764
Constitutional manifestations, $n = 645$	81/102 (79)	398/543 (73)	0.218
Reticuloendothelial manifestations, $n = 645$	46/102 (45)	216/543 (40)	0.324
Mucocutaneous involvement, $n = 645$	98/102 (96)	505/543 (93)	0.379
Malar Rash, $n = 645$	81/102 (79)	394/543 (73)	0.177
Discoid lupus, $n = 645$	15/102 (15)	55/543 (10)	0.168
Photosensitivity, $n = 645$	75/102 (74)	359/543 (66)	0.167
Mucosal ulceration, $n = 645$	58/102 (57)	266/543 (49)	0.746
Alopecia, $n = 645$	72/102 (71)	280/543 (52)	0.0005
Vasculitis, $n = 645$	42/102 (41)	200/543 (37)	0.435
Musculoskeletal involvement, $n = 645$	82/102 (80)	415/543 (76)	0.442
Serositis, $n = 645$	43/102 (42)	184/543 (34)	0.114
Nephritis, $n = 645$	71/102 (70)	356/543 (66)	0.493
Neuropsychiatric involvement, $n = 645$	56/102 (55)	262/543 (48)	0.235
Autoimmune thrombosis (APS), $n = 616$	6/99 (6)	26/517 (5)	0.624
Sjogren Syndrome, $n = 645$	2/209 (1)	3/543 (0.5)	0.179
Cumulative hematological abnormalities			
Autoimmune hemolytic anemia, $n = 645$	27/102 (26)	134/543 (25)	0.051
Leukopenia $<4000/mm^3$, $n = 645$	53/102 (52)	252/543 (46)	0.331
Lymphopenia $<1500/mm^3$, $n = 645$	70/102 (69)	354/543 (65)	0.570
Thrombocytopenia, $<100.000/mm^3$, $n = 645$	23/102 (22)	136/543 (25)	0.707
Cumulative autoantibodies evaluation			
Antinuclear antibodies (ANA), $n = 643$	102/102 (100)	539/541 (100)	1.000
Anti-dsDNA, $n = 645$	80/102 (78)	380/543 (70)	0.094
Anti-Sm, $n = 645$	60/102 (59)	171/543 (31)	0.0001
Anti-RNP, $n = 645$	43/102 (42)	123/543 (23)	0.0001
Anti-ribosomal P (*anti*-P), $n = 176$	10/23 (43)	37/153 (24)	0.074
Current disease damage score at last visit			
SLICC/ACR-DI ≥ 1, $n = 586$	34/88 (39)	169/498 (34)	0.397
Neuropsychiatric	9/88 (10)	49/499 (10)	0.848
Skin	3/88 (3)	15/499 (3)	0.742
Peripheral vascular	2/88 (2)	10/499 (2)	0.698
Ocular	14/88 (16)	48/499 (10)	0.089
Renal	7/88 (8)	42/499 (8)	1.000
Musculoskeletal	8/88 (9)	54/499 (11)	0.710
Cardiovascular	4/88 (4)	8/499 (2)	0.089

Results are presented in n (%) and median (range), APS - antiphospholipid syndrome; SLICC/ACR-DI - Systemic Lupus International Collaborating Clinics/ACR-Damage Index.

FMUSP (Cristina Miuki Abe Jacob, Gabriela Blay, Gabriela Nunes Leal, Gabriella Erlacher Lube de Almeida, Heloisa Helena de Souza Marques, João Domingos Montoni da Silva, Joaquim Carlos Rodrigues, Juliana Caíres de Oliveira Achili Ferreira, Laila Pinto Coelho, Lucia Maria A Campos, Luciana dos Santos Henriques, Mariana Ferriani, Maria Helena Vaisbich, Nadia Emi Aikawa, Victor Marques, Werther Brunow de Carvalho); Pediatric Rheumatology Unit, UNIFESP (Anandreia Simões Lopes, Aline Alencar, Claudio Arnaldo Len, Daniela Petry Piotto, Giampaolo Faquin, Gleice Clemente, Maria Odete Esteves Hilário, Octavio Augusto Bedin Peracchi, Vanessa Bugni); Division of Rheumatology, FMUSP (Juliane A Paupitz, Glauce Leão Lima); UNESP (Priscila R. Aoki, Juliana de Oliveira Sato, Silvana Paula Cardin, Taciana Albuquerque Pedrosa Fernandes), Irmandade da Santa Casa de Misericórdia de São Paulo (Eunice Okuda, Maria Carolina dos Santos, Silvana Brasilia Sacchetti), State University of Campinas (Simone Appenzeller, Maraísa Centeville, Renata Barbosa), Ribeirão Preto Medical School — University of São Paulo (Francisco Hugo Gomes, Gecilmara Salviatto Pileggi, Paola Pontes Pinheiro, Luciana Carvalho), Hospital Infantil Darcy Vargas (Jonatas Libório, Luciana Tudech Pedro Paulo), Hospital Municipal Infantil Menino Jesus (Simone Lotufo).

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