Lupus (2017) 26, 484–489
journals.sagepub.com/home/lup

SPECIAL ARTICLE

Anti-ribosomal P antibody: a multicenter study in childhood-onset systemic lupus erythematosus patients

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Objectives: Anti-ribosomal P protein (anti-P) autoantibodies are highly specific for systemic lupus erythematosus (SLE). However, the evaluation of this autoantibody in childhood-onset SLE (cSLE) populations has been limited to a few small series, hampering the interpretation of the clinical and laboratorial associations. Therefore, the objective of this multicenter cohort study was to evaluate demographic, clinical/laboratorial features, and disease damage score in cSLE patients with and without the presence of anti-P antibody. **Methods:** This was a retrospective multicenter study performed in 10 pediatric rheumatology services of São Paulo state, Brazil. Anti-P antibodies were measured by ELISA in 228 cSLE patients. **Results:** Anti-P antibodies were observed in 61/228 (27%) cSLE patients. Frequencies of cumulative lymphadenopathy (29% vs. 15%, $p = 0.014$), acute confusional state (13% vs. 5%, $p = 0.041$), mood disorder (18% vs. 8%, $p = 0.041$), autoimmune hemolytic anemia (34% vs. 15%, $p = 0.001$), as well as presence of anti-Sm (67% vs. 40%, $p = 0.001$), anti-RNP (39% vs. 21%, $p = 0.012$) and anti-Ro/SSA antibodies (43% vs. 25%, $p = 0.016$) were significantly higher in cSLE patients with anti-P antibodies compared to those without these autoantibodies. A multiple regression model revealed that anti-P antibodies were associated with autoimmune hemolytic anemia (odds ratio (OR) = 2.758, 95% confidence interval (CI): 1.304–5.833, $p = 0.008$) and anti-Sm antibody (OR = 2.719, 95% CI: 1.365–5.418, $p = 0.004$). The SLICC/ACR damage index was comparable in patients with and without anti-P antibodies ($p = 0.780$). **Conclusions:** The novel association of anti-P antibodies and autoimmune hemolytic anemia was evidenced in cSLE patients and further studies are necessary to determine if anti-P titers may vary with this hematological manifestation. *Lupus* (2017) **26,** 484–489.

Key words: Systemic lupus erythematosus; anti- ribosomal P protein antibodies; neuropsychiatric lupus; autoimmune hemolytic anemia; childhood

Introduction

Anti-ribosomal P protein (anti-P) autoantibodies recognize three ribosomal phosphoproteins, called P0, P1, and P2.[1] These autoantibodies are highly specific for systemic lupus erythematosus (SLE).[2,3] Clinical associations reported were disease activity, neuropsychiatric,[4,5] and renal involvements.[3–5]

The prevalence of anti-P in childhood-onset SLE (cSLE) populations varies from[4,6-9] 20% to[10] 42%, a frequency higher than described in adult-onset SLE (aSLE) patients.[3,8–10] However, the evaluation of this autoantibody in cSLE populations has been limited to a few small series,[4,6–10] hampering the interpretation of the clinical and laboratorial associations.

Therefore, the objective of this multicenter cohort study was to evaluate demographic, cumulative clinical/laboratorial features, and disease damage score in cSLE patients with and without the presence of anti-P antibody.

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10.1177/0961203316676386

Methods

Study design and patients

This was a retrospective multicenter study performed in 10 pediatric rheumatology services of São Paulo state, Brazil, and included 228 cSLE patients that underwent anti-P antibody evaluation. All patients fulfilled the American College of Rheumatology (ACR) criteria,[11] with disease onset before 18 years of age.[12]

An investigator meeting in São Paulo defined the protocol for this study that included clinical and laboratory parameters, as previously described.[13–18] Neuropsychiatric lupus, which includes 19 syndromes according to ACR classification criteria, can be subdivided into peripheral and central nervous system involvement.[19] Antiphospholipid syndrome was diagnosed according to the preliminary criteria for the classification of pediatric antiphospholipid syndrome.[20] High blood pressure was defined as systolic and/or diastolic blood pressures ≥95th percentile for gender, age, and height on ≥3 occasions.[21] Acute kidney injury was determined by sudden increase in serum creatinine above 2 mg/dL or by modified RIFLE (risk, injury, failure, loss of kidney function, and end-stage kidney disease) criteria.[22] Chronic renal disease was defined as structural or function abnormalities of the kidney for ≥3 months (with or without decreased glomerular filtration rate) or glomerular filtration rate <60 mL/min/1.73 m^2 for ≥3 months.[23]

The anti-P antibody was measured by ELISA, antinuclear antibodies (ANA) tested by indirect immunofluorescence, anti-dsDNA by indirect immunofluorescence or ELISA, anti-Sm and anti-RNP by passive hemagglutination or ELISA, anti-SSA/Ro and anti-SSB/La by counterimmunoelectrophoresis or ELISA, and anticardiolipin (aCL) IgG and IgM by ELISA, carried out at each center. The cutoff values were defined according to kit manufacturer. Lupus anticoagulant (LA) was detected according to the guidelines of the International Society on Thrombosis and Hemostasis.[24] At last visit, the Systemic Lupus International Collaborating Clinics/ACR damage index (SLICC-ACR/DI) was evaluated.[25]

Statistical analysis

Descriptive statistics are presented as an absolute number (frequency) for categorical variables and median (minimum and maximum values) for continuous variables. Categorical variables were assessed by Pearson's chi-squared test or by Fisher test. Continuous variables were analyzed according to Mann–Whitney test. Logistic regression models were performed to identify independent variables associated with the presence of anti-P antibodies. In the multiple model, we used as independent variables those that presented a level 20% of significance in the univariate analysis. Results of the regression model are shown as the odds ratio (OR) and 95% confidence interval (95% CI). We adopted a significance level of 5% in all analyses.

Results

Anti-P antibody was evidenced in 61/228 (27%). Demographic data, cumulative clinical manifestations, and disease damage score at last visit in c-SLE patients according to presence of anti-P autoantibody are shown in Table 1. Frequencies of cumulative lymphadenopathy (29% vs. 15%, $p = 0.014$), acute confusional state (13% vs. 5%, $p = 0.041$), mood disorder (18% vs. 8%, $p = 0.041$), and autoimmune hemolytic anemia (34% vs. 15%, $p = 0.001$) were significantly higher in cSLE patients with anti-P antibodies compared to those without these autoantibodies. The median SLICC/ACR-DI scores were comparable in patients with and without anti-P antibodies ($p > 0.05$, Table 1).

Frequencies of anti-Sm (67% vs. 40%, $p = 0.001$), anti-RNP (39% vs. 21%, $p = 0.012$), and anti-Ro/SSA antibodies (43% vs. 25%, $p = 0.016$) were significantly higher in cSLE patients with the presence of anti-P antibodies compared to those without these autoantibodies (Table 2).

A multiple regression model revealed that anti-P antibody was associated with autoimmune hemolytic anemia (OR = 2.758, 95% CI: 1.304–5.833, $p = 0.008$) and anti-Sm antibody (OR = 2.719, 95% CI: 1.365–5.418, $p = 0.004$) (Table 3).

Discussion

A novel association of anti-P antibodies and autoimmune hemolytic anemia was identified in cSLE patients. We also confirmed the association of anti-P and anti-Sm antibodies.

The advantages of the present study were as follows: the multicenter study included a large cSLE population; the assessment of 19 standardized neuropsychiatric syndromes was according to ACR classification criteria;[19] and evaluation of

Table 1 Demographic data, cumulative clinical manifestations, and disease damage score at last visit in 228 cSLE patients according to presence of anti-P autoantibody

Variables	*Anti-P positive* (n = *61*)	*Anti-P negative* (n = *167*)	p
Demographic data			
Age at last visit, years, $n = 228$	18 (2–25)	17.8 (2–25.3)	0.230
Disease duration, years, $n = 228$	5 (0.1–23)	6 (0.1–22)	0.447
Female gender, $n = 228$	54/61 (88)	145/167 (87)	0.733
Constitutional manifestations, $n = 228$	39/61 (64)	99/167(59)	0.525
Fever, $n = 227$	35/61 (57)	94/166 (57)	0.919
Reticuloendothelial manifestations, $n = 228$	24/61 (39)	44/167 (26)	0.058
Lymphadenopathy, $n = 227$	18/61 (29)	25/166 (15)	0.014
Hepatomegaly, $n = 228$	13/61 (21)	28/167 (17)	0.429
Splenomegaly, $n = 227$	7/61 (11)	12/166 (7)	0.306
Mucocutaneous involvement, $n = 228$	58/61 (95)	155/167 (93)	0.764
Rash, $n = 228$	46/61 (75)	125/167 (75)	0.931
Discoid lupus, $n = 228$	10/61 (16)	22/167 (13)	0.536
Photosensitivity, $n = 228$	44/61 (72)	116/167 (69)	0.696
Mucosal ulceration, $n = 227$	30/61(49)	65/166 (39)	0.175
Alopecia, $n = 227$	32/61 (52)	77/166 (46)	0.417
Vasculitis, $n = 227$	25/61 (41)	47/166 (28)	0.069
Musculoskeletal involvement, $n = 228$	50/61 (82)	139/167 (83)	0.822
Arthritis, $n = 228$	49/61 (80)	138/167 (83)	0.688
Myositis, $n = 227$	5/61 (8)	13/166(8)	1.000
Serositis, $n = 227$	26/61 (43)	53/166 (32)	0.134
Pleuritis, $n = 227$	18/61 (29)	32/166 (19)	0.099
Pericarditis, $n = 227$	15/61 (25)	40/166 (24)	0.939
Nephritis, $n = 228$	29/61 (47)	81/167 (48)	0.898
Arterial hypertension, $n = 226$	19/61 (31)	51/165 (31)	0.973
Acute renal failure, $n = 227$	12/61 (20)	22/166 (13)	0.230
Chronic renal failure, $n = 227$	3/61 (5)	8/166 (5)	0.975
Renal replacement therapy, $n = 193$	5/50 (10)	6/143 (4)	0.157
Neuropsychiatric involvement, $n = 228$	30/61(49)	90/167(54)	0.528
Central nervous system, $n = 228$	29/61 (47)	89/167 (53)	0.442
Acute confusional state, $n = 227$	8/61 (13)	8/166 (5)	0.041
Aseptic meningitis, $n = 227$	0/61 (0)	2/166 (1)	1.000
Cerebrovascular disease, $n = 225$	2/61 (3)	1/164(1)	0.179
Demyelinating syndrome, $n = 227$	0/61 (0)	0/166 (0)	–
Headache, $n = 227$	19/61 (31)	58/166 (35)	0.593
Movement disorder chorea, $n = 227$	2/61 (3)	4/166 (2)	0.661
Myelopathy, $n = 227$	0/61 (0)	3/166 (2)	0.566
Seizure disorders, $n = 228$	8/61 (13)	30/167(18)	0.384
Anxiety disorder, $n = 227$	4/61 (7)	5/166 (3)	0.255
Cognitive dysfunction, $n = 227$	2/61 (3)	8/166 (5)	0.055
Mood disorder, $n = 227$	11/61 (18)	14/166 (8)	0.041
Psychosis, $n = 226$	9/61 (15)	19/165 (12)	0.512
Peripheral nervous system, $n = 227$	3/61(5)	9/166 (5)	1.000
Guillain–Barré syndrome, $n = 228$	0/61(0)	0/167(0)	–
Autonomic disorder, $n = 226$	1/61(2)	0/165(0)	0.270
Mononeuropathy, single/multiplex, $n = 228$	2/61(3)	3/167(2)	0.614
Myasthenia gravis, $n = 225$	0/61 (0)	0/164(0)	–
Neuropathy, cranial, $n = 228$	0/61 (0)	1/167(1)	1.000
Plexopathy, $n = 226$	0/61 (0)	0/165(0)	–
Polyneuropathy, n = 226	0/61(0)	5/165(3)	0.327
Visual disturbance, $n = 227$	0/61 (0)	3/166 (2)	0.566
Autoimmune thrombosis (APS), $n = 222$	2/59 (3)	15/163 (9)	0.251
Disease damage score			
SLICC/ACR-DI at last visit n = 213	0 (0–7)	0 (0–6)	0.780

Results are presented as *n* (%) or median (range); APS – antiphospholipid syndrome; SLICC/ACR-DI – Systemic Lupus International Collaborating Clinics/ACR damage index.

Table 2 Cumulative hematological abnormalities, laboratory results, and treatments at last visit in 228 cSLE patients according to presence of anti-P autoantibody

Variables	*Anti-P positive* (n = *61*)	*Anti-P negative* (n = *167*)	p
Cumulative hematological abnormalities			
Autoimmune hemolytic anemia, $n = 226$	21/61 (34)	25/165 (15)	0.001
Leukopenia < 4000/mm^3, $n = 227$	21/61 (34)	53/166 (32)	0.722
Lymphopenia < 1500/mm^3, $n = 226$	35/60 (58)	81/166 (49)	0.205
Thrombocytopenia < 100,000/mm^3, $n = 227$	10/61 (16)	37/166 (22)	0.331
Cumulative autoantibodies			
ANA, $n = 225$	61/61 (100)	163/164 (99)	1.000
Anti-dsDNA, $n = 227$	43/61 (70)	112/166 (67)	0.665
Anti-Sm, n = 189	34/51 (67)	55/138 (40)	0.001
Anti-RNP, $n = 180$	20/51 (39)	27/129 (21)	0.012
Anti SSA/Ro, $n = 183$	22/51 (43)	33/132 (25)	0.016
Anti SSB/La, $n = 183$	11/51 (22)	21/132 (16)	0.366
LA, $n = 137$	3/37 (8)	17/100 (17)	0.191
aCL IgM, $n = 150$	4/42 (9)	22/108 (20)	0.115
aCL IgG, $n = 150$	5/44 (11)	23/106 (22)	0.139

Results are presented as *n* (%).

Table 3 Independent variables in the multiple regression models associated with anti-P autoantibody in 228 cSLE patients

Independent variables	*OR (95% CI)*	p
Autoimmune hemolytic anemia, $n = 226$	2.758 (1.304–5.833)	0.008
Anti-Sm autoantibodies, $n = 189$	2.719 (1.365–5.418)	0.004

OR – odds ratio; 95% CI – 95% confidence interval.

these autoantibodies was by a method commonly used in clinical practice with high sensitivity and specificity.[3] A limitation of the present report is the fact that it was a retrospective study with missing data.

The frequency of anti-P autoantibodies in cSLE patients observed in the present study was similar to that reported for pediatric SLE populations.[4,7–9,26–30]

An original and important finding of this study was the association with autoimmune hemolytic anemia, suggesting that the anti-P may target erythrocytes. Possible underlying mechanisms include apoptosis, cross-reactivity, and enhanced proinflammatory cytokine production induced by this antibody.[3] However, the clinical relevance of this hematological finding must be confirmed in prospective studies.

Proposed explanations for multiple autoantibody production observed in our cSLE patients may be due to random polyclonal B cell activation, widespread abnormal expansion of a B cell subset and an antigen-driven immune response. Association between anti-P and anti Sm autoantibodies were also previously reported in both human SLE and in mice.[5,27]

The higher frequency of mood disorders and acute confusional state in anti-P positive patients in the univariate analysis did not remain in multivariate assessment. Anti-P antibody activity fluctuation may account for this discrepancy since the retrospective evaluation of cumulative neuropsychiatric involvement performed herein may hamper the interpretation of attribution for psychiatric and cognitive dysfunction.[29] Indeed, a more appropriate study design indicates that anti-P in cSLE patients is associated with psychosis,[27] anxiety disorders,[4] and cognitive impairment.[29]

In conclusion, the novel association of anti-P antibodies and autoimmune hemolytic anemia was evidenced in cSLE patients and further studies are necessary to determine if anti-P titers may vary with this hematological manifestation.

Acknowledgments

The authors wish to thank Ulysses Doria-Filho for the statistical analysis.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: this work was supported by Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq; grant numbers 301805/2013-0, 303752/2015-7, 301479/2015-1, 305068/2014-8, and 303422/2015-7), the Federico Foundation, and by Núcleo de Apoio à Pesquisa "Saúde da Criança e do Adolescente" da USP (NAP-CriAd).

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