Advances in Rheumatology

RESEARCH

Open Access

Clinical and laboratory characteristics of Brazilian versus non-Brazilian primary antiphospholipid syndrome patients in AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) clinical database and repository

Erivelton de Azevedo Lopes[1], Gustavo Guimarães Moreira Balbi[1,2], Maria G. Tektonidou[3], Vittorio Pengo[4], Savino Sciascia[5], Amaia Ugarte[6], H. Michael Belmont[7], Maria Gerosa[8], Paul R. Fortin[9], Chary Lopez-Pedrera[10], Lanlan Ji[11], Hannah Cohen[12], Guilherme Ramires de Jesús[13], D. Ware Branch[14], Cecilia Nalli[15], Michelle Petri[16], Esther Rodriguez[17], Nina Kello[18], Roberto Ríos-Garcés[19], Jason S. Knight[20], Tatsuya Atsumi[21], Rohan Willis[22], Maria Laura Bertolaccini[23], Doruk Erkan[24] and Danieli Andrade[1*] on behalf of APS ACTION

Abstract

Background: Antiphospholipid syndrome (APS) is characterized by episodes of thrombosis, obstetric morbidity or both, associated with persistently positive antiphospholipid antibodies (aPL). Studying the profile of a rare disease in an admixed population is important as it can provide new insights for understanding an autoimmune disease. In this sense of miscegenation, Brazil is characterized by one of the most heterogeneous populations in the world, which is the result of five centuries of interethnic crosses of people from three continents. The objective of this study was to compare the clinical and laboratory characteristics of Brazilian vs. non-Brazilian primary antiphospholipid syndrome (PAPS) patients.

Methods: We classified PAPS patients into 2 groups: Brazilian PAPS patients (BPAPS) and PAPS patients from other countries (non-BPAPS). They were compared regarding demographic characteristics, criteria and non-criteria APS manifestations, antiphospholipid antibody (aPL) profile, and the adjusted Global Antiphospholipid Syndrome Score (aGAPSS).

Results: We included 415 PAPS patients (88 [21%] BPAPS and 327 [79%] non-BPAPS). Brazilian patients were significantly younger, more frequently female, sedentary, obese, non-white, and had a higher frequency of livedo (25% vs. 10%, $p < 0.001$), cognitive dysfunction (21% vs. 8%, $p = 0.001$) and seizures (16% vs. 7%, $p = 0.007$), and a lower frequency of thrombocytopenia (9% vs. 18%, $p = 0.037$). Additionally, they were more frequently positive for lupus

*Correspondence: danieli.andrade@hc.fm.usp.br
[1] University of São Paulo, Av. Dr. Arnaldo 455, Third Floor, Room 3109, São Paulo 01246903, Brazil
Full list of author information is available at the end of the article

anticoagulant (87.5% vs. 74.6%, $p = 0.01$), and less frequently positive to anticardiolipin (46.6% vs. 73.7%, $p < 0.001$) and anti-ß2-glycoprotein-I (13.6% vs. 62.7%, $p < 0.001$) antibodies. Triple aPL positivity was also less frequent (8% vs. 41.6%, $p < 0.001$) in Brazilian patients. Median aGAPSS was lower in the Brazilian group (8 vs. 10, $p < 0.0001$). In the multivariate analysis, BPAPS patients still presented more frequently with livedo, cognitive dysfunction and sedentary lifestyle, and less frequently with thrombocytopenia and triple positivity to aPL. They were also less often white.

Conclusions: Our study suggests a specific profile of PAPS in Brazil with higher frequency of selected non-criteria manifestations and lupus anticoagulant positivity. Lupus anticoagulant (not triple positivity) was the major aPL predictor of a classification criteria event.

Keywords: Antiphospholipid syndrome, Primary antiphospholipid syndrome, Antiphospholipid antibodies, Lupus Anticoagulant, Anticardiolipin antibodies, Anti-beta-2 glycoprotein I antibodies

Background

Antiphospholipid syndrome (APS) is characterized by episodes of thrombosis, obstetric morbidity or both, associated with persistently positive antiphospholipid antibodies (aPL), namely lupus anticoagulant (LA), IgG or IgM anticardiolipin (aCL), and IgG or IgM anti-ß2-glycoprotein I (aß2GPI). According to the Sydney criteria, one must have at least one clinical criterion (arterial, venous or small vessel thrombosis and/or pregnancy morbidity) and one laboratory criterion (at least 1 positive aPL on 2 measures of at least 12 weeks apart) to be classified as APS [1]. APS can be further classified as primary (PAPS), when occurring without any underlying autoimmune disorder, or secondary/associated, when associated with chronic inflammatory conditions [2].

AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking (APS ACTION) is an organization that encompasses a group of scientists interested in APS, based in different countries. One of the main objectives of APS ACTION is to maintain an international aPL/APS registry and sample collection with longitudinal follow-up of aPL-positive patients worldwide [3].

Studying the profile of a rare disease in an admixed population is important as it can provide new insights for understanding an autoimmune disease [4]. For instance, genome wide association studies in Amerindian ancestry population with systemic lupus erythematosus (SLE) has brought new insights in the delineation of the genetic knowledge of the disease [4]. In this sense of miscegenation, Brazil is characterized by one of the most heterogeneous populations in the world, which is the result of five centuries of interethnic crosses of people from three continents [5].

Given that only a few studies evaluated geographical differences in clinical characteristics among APS patients, the main objective of this paper was to evaluate the epidemiological, clinical, and laboratory profile of patients with PAPS from Brazil in comparison to those from other countries with the data included in the APS ACTION clinical database and repository ("Registry").

Methods

This cross-sectional study was performed using data from the APS ACTION Registry. The study protocol was submitted for approval by the APS ACTION Committee. All patients included in this study signed a written informed consent during APS ACTION Registry recruitment.

For this analysis, in order to minimize confounding factors, we included only PAPS patients who fulfilled the Sydney classification criteria [1] aged 18 years old or older. Patients with APS associated with SLE or other autoimmune diseases, those with isolated aPL positivity without clinical criteria manifestations for APS, or those with insufficient data were excluded. Data was locked as of February 2nd, 2019.

First, we classified patients into two groups: (1) patients from Brazil (BPAPS); and (2) patients from other countries (non-BPAPS). The groups were compared regarding demographic profile (age, sex, and ethnicity), clinical criteria (thrombotic and/or obstetric event), frequency of arterial and venous thrombosis, non-criteria manifestations (skin ulcers, livedo reticularis, thrombocytopenia, aPL nephropathy, cognitive dysfunction, and seizures), aPL profile (LA, aCL, aß$_2$GPI, and triple aPL positivity), and risk factors for thrombosis at baseline (sedentary lifestyle, obesity, hypertension, hyperlipidemia, diabetes, smoking, and malignancy). Double positivity was defined as positivity to 2 of any of the 3 criteria aPL, irrespective of isotype. Triple positivity was defined as positivity to all 3 criteria aPL, irrespective of isotype. The adjusted Global Antiphospholipid Syndrome Score (aGAPSS), which is a surrogate marker for thrombosis, was calculated for each individual by the sum of the following criteria: 1 point for hypertension, 3 points for dyslipidemia, 4 points for LA positivity, 5 points for aCL (IgG or IgM) positivity, and 4 points for aß2GPI (IgG or IgM) positivity [6].

To be included in the APS ACTION Database, patients were persistently positive for at least one aPL within

12 months prior to the entry, defined as: LA test positivity was based on the International Society on Thrombosis and Haemostasis guidance; aCL and aß2GPI was considered positive if ≥ 40 units or above the 99th percentile [1]. Patients who were positive to all criteria aPL are described as triple positive.

All criteria and non-criteria APS manifestations and conventional cardiovascular risk factors (such as hypertension, diabetes, hyperlipidemia, and smoking) were recorded according to the definitions presented in the APS ACTION International Clinical Database & Repository Standard Operating Procedures: (a) Thrombocytopenia: platelets < 100,000 per microliter tested twice at least 12 weeks apart, (b) Cognitive dysfunction: considered present if there was clinical suspicion or abnormal neuropsychiatric testing; (c) Seizures: considered present if they were not provoked or symptomatic crises (for example, caused by hypoglycemia) and needed drug therapy; (d) Livedo reticularis: its presence was recorded as positive or negative; (e) Sedentary lifestyle: < 30 min daily of physical activity; (f) Obesity: body mass index (BMI) ≥ 30 kg/m^2; (g) Hypertension: systemic blood pressure ≥ 140/90 mmHg on two or more occasions or the use of anti-hypertensive medications; (h) Diabetes mellitus: serum glucose ≥ 126 mg/dL, oral glucose tolerance test (OGTT) ≥ 200 mg/dL or HbA1c ≥ 6.5% on two or more occasions, random glucose test ≥ 200 mg/dL in the presence of symptoms or signs of insufficient insulin, or the use of diabetes medications; (i) Hyperlipidemia: total cholesterol > 200 mg/dL, LDL-c > 130 mg/dL, triglycerides > 150 mg/dL or the use of lipid-lowering medications.

We performed a univariate analysis comparing patients from Brazil with those in other countries, using Student's t test, Mann–Whitney U test, chi-square test and Fisher's exact test, when applicable. Normality was evaluated using the Kolmogorov–Smirnov test. The significance threshold was set at 5%. We then performed a multivariate analysis using a model that included age, gender, race and variables with $p < 0.10$ in the univariate analysis.

Results

We identified 415 PAPS patients in the APS ACTION Registry that met inclusion criteria for PAPS; of them, 88 (21.2%) were BPAPS and 327 (78,8%) were non-BPAPS patients. The epidemiological, clinical, and laboratory profile of the two groups were summarized in Table 1. The distribution of patients by countries/regions (excluding Brazil) was the following: Europe (N = 208; 63.6%), United States (N = 88; 26.9%), Canada (N = 8; 2.4%), Jamaica (N = 2; 0.6%), Asia (N = 17; 5.2%), and Australia (N = 4; 1%).

Table 1 Demographics, clinical and laboratory characteristics of Brazilian APS patients versus other regions

	Brazil (n = 88)	Other Regions (n = 327)	p-value
Demographics			
Age	47.6 ± 11.3	50.7 ± 13.3	**0.048**
Sex (female)	70 (79.5%)	213 (65.1%)	**0.01**
Ethnicity (non-white)	61 (69.3%)	61 (23.3%)	**< 0.001**
Criteria APS manifestations			
Thrombotic APS	62 (70.5%)	239 (73.1%)	0.62
Thrombotic + Obstetric APS	20 (35.7%)*	41 (19.2%)**	0.25
History of any arterial events	37 (42%)	141 (43%)	0.86
History of any venous events	53 (60.2%)	164 (50.2%)	0.09
Catastrophic APS	0 (0.0%)	4 (1.2%)	0.30
Non-criteria APS manifestations			
Skin ulcers	6 (6.8%)	16 (4.9%)	0.47
Livedo	22 (25.0%)	34 (10.4%)	**< 0.001**
Thrombocytopenia	8 (9.1%)	60 (18.3%)	**0.037**
aPL Nephropathy	3 (3.5%)	12 (4.0%)	0.86
Cognitive dysfunction	18 (20.5%)	26 (8.0%)	**0.001**
Seizures	14 (15.9%)	22 (6.7%)	**0.007**
aPL profile			
Lupus anticoagulant (LA)	77 (87.5%)	244 (74.6%)	**0.01**
Anticardiolipin Antibodies (aCL)	41 (46.6%)	241 (73.7%)	**< 0.001**
Anti-Beta2-Glycoprotein1 (aB2GPI)	12 (13.6%)	205 (62.7%)	**< 0.001**
LA Only	45 (51.1%)	64 (19.6%)	**< 0.001**
aCL Only	8 (9.1%)	23 (7.0%)	0.52
aB2GPI Only	0 (0.0%)	13 (4.0%)	0.057
Double aPL positive	28 (31.8%)	91 (27.8%)	0.46
Triple aPL positive	7 (8.0%)	136 (41.6%)	**< 0.001**
Baseline thrombotic risk factors			
Sedentary lifestyle	71 (80.7%)	110 (33.6%)	**< 0.001**
Obesity	32 (36.4%)	72 (22.0%)	**0.006**
Hypertension	31 (35.2%)	99 (30.3%)	0.37
Hyperlipidemia	21 (23.9%)	91 (27.8%)	0.46
Diabetes	3 (3.4%)	21 (6.4%)	0.28
Smoking (ever)	25 (28.4%)	117 (35.8%)	0.20
Malignancy	0 (0.0%)	3 (0.9%)	0.37

Bold font refers to statistically significant differences found between groups

APS antiphospholipid syndrome, *CAPS* catastrophic antiphospholipid syndrome, *aPL* antiphospholipid antibodies

*N = 56; **N = 213

The overall mean age was 50.1 ± 13.1 years. The mean age for Brazilian patients was 47.6 ± 11.3 years vs. 50.7 ± 13.3 years for those from other countries ($p = 0.048$). Female gender was the most common in

both groups (79.5% vs. 65.1%, $p=0.01$), and non-Caucasian patients were more frequently described in the BPAPS (69.3% vs. 23.3%, $p<0.001$).

There was no significant difference between BPAPS and non-BPAPS regarding the clinical APS criteria. The rates of arterial and venous events were 42% vs. 43% ($p=0.86$) and 60% vs. 50% ($p=0.09$), respectively. Concomitance of obstetric APS manifestations was found in 36% of thrombotic BPAPS (vs. 19% of non-BPAPS, $p=0.25$). Cognitive dysfunction (CD) (21% vs. 8%, $p=0.001$) and seizures (15.9% vs. 6.7%, $p=0.007$) were more frequent in BPAPS when compared to non-BPAPS. In contrast, BPAPS patients were less likely to develop thrombocytopenia (9% vs. 18.3%, $p=0.037$).

Analysis of the antibody profile showed that BPAPS had a higher frequency of lupus anticoagulant (87.5% vs. 74.6%, $p=0.01$), and a lower frequency of aCL (46.6% vs. 73.7%, $p<0.001$) and aB2GPI (13.6% vs. 62.7%, $p<0.001$). When assessing the presence of a single antibody, patients with only aCL (9.1% vs. 7.0%, p 0.52) and only aß2GP1 (0 vs. 4.0%, p 0.52) were similar in both groups. However, patients with only LA positivity were more frequent in the BPAPS (51.1% vs. 19.6%, $p<0.001$). The rates of double aPL-positivity were similar between groups (31.8% vs. 27.8%, p 0.46), but triple aPL-positivity was less frequent in BPAPS (8% vs. 41.6%, $p<0.001$).

BPAPS patients were more often sedentary (81% vs. 33.6%, $p<0.001$) and obese (36.4% vs. 22%, $p=0.006$). No significant difference was found between the groups in relation to baseline thrombotic risk factors, such as hypertension (35.2% vs. 30%, $p=0.37$), hyperlipidemia (23.9% vs. 27.8%, $p=0.46$), diabetes (3.4% vs. 6.4%, $p=0.28$), ever smoking (28.4% vs. 35.8%, $p=0.20$), and malignancy (0.0% vs. 0.9%, $p=0.37$).

Finally, the median aGAPSS was 8 (IQR 4–9) for BPAPS and 10 (IQR 8–13) for non-BPAPS patients, which was statistically significant ($p<0.0001$).

For the multivariate analysis, the model included age, gender, race, livedo, thrombocytopenia, cognitive dysfunction, obesity and triple positivity. After adjustment, BPAPS still presented more frequently with livedo, cognitive dysfunction and sedentary lifestyle, and less frequently with thrombocytopenia and triple positivity to aPL. Also, the BPAPS population was less often white. The odds ratio (OR) for each variable is presented in Table 2.

Discussion

This is the first study that compares the epidemiological, clinical, and laboratory profile of PAPS patients from a genetically diversified country, such as Brazil, with patients from other countries.

We found that, even though non-BPAPS patients had a greater proportion of triple aPL-positivity, the rates of arterial and venous thrombotic events did not differ between BPAPS and non-BPAPS groups. Our study identified that BPAPS patients had a higher frequency of LA and a lower frequency of aCL and aβ2GPI. Additionally, the most frequent single isolated aPL in the BPAPS group was LA. This particular aPL profile was also previously reported in another Brazilian cohort [7].

It is widely known that LA is the aPL associated with the highest risk of thrombosis in APS patients [8, 9]. In a recently published study, Yin et al. analyzed 456 patients (66 APS patients vs. 390 controls) and found that isolated LA positivity was a strong predictor of vascular thrombosis (OR 7.3, CI95% 3.3–16.1), even better than triple positivity (OR 4.3, CI95% 1.6–12.2) [10]. Also, in previously published studies, LA, not triple positivity, was associated with a higher risk of thrombosis [11] and obstetric complications [12] in SLE patients. Thus, since rates of thrombotic events were similar between groups, we hypothesize that the lower triple positivity rates in the Brazilian group could be offset by its higher frequency of LA [13].

Previous Brazilian studies have also shown a high prevalence of livedo in APS patients [14]. Interestingly, in our cohort, livedo was more prevalent in BPAPS (25%), when

Table 2 Results of the multivariate analysis of BPAPS versus non-BPAPS patients

Variable	Odds ratio	Confidence interval 95%		Adjusted *p* value
		Lower limit	Upper limit	
White	0.09	0.05	0.18	< .001
Livedo reticularis	2.33	1.32	4.13	.004
Thrombocytopenia	0.34	0.12	0.92	.034
Cognitive dysfunction	1.49	1.03	2.17	.037
Sedentary lifestyle	7.30	3.72	14.35	< .001
Triple positive	0.08	0.03	0.22	< .001

Model: age, gender, race, livedo, thrombocytopenia, cognitive dysfunction, sedentary lifestyle, triple positivity to aPL

compared to non-BPAPS (10.4%). Considering that livedo is sensitive to cold exposure [15] and usually easier to be diagnosed in Caucasian patients due to skin contrast, it is intriguing that Brazilian patients present a higher frequency of livedo. A recent study on SLE patients found that all patients with livedo were positive to LA. Since LA positivity was higher in the BPAPS groups, this specific aPL profile may have contributed to the higher frequency of livedo in our cohort [16]. Further studies could help to elucidate the pathophysiological aspects of this APS vasculopathy.

In our study we also observed a lower frequency of thrombocytopenia in APS patients from Brazil (9.1% vs. 18.3%). These findings corroborate with previous reports that showed a frequency of 8.9% of thrombocytopenia in BPAPS patients [7]. The prevalence of thrombocytopenia in other countries varied more widely, ranging from 6 to 44% according to the cohort [17]. Genetic background could be a possible explanation for these differences.

Regarding neurological non-criteria manifestations, we found that the prevalence of seizures and cognitive dysfunction in the Brazilian population was significantly higher than that of the group of patients from other countries (15.9 vs. 6.7%, and 20.5 vs. 8.0%, respectively). In the Euro-Phospholipid Project study, a similar prevalence of seizures (7%) was observed in the European population of APS patients [3]. Regarding CD, Rosa et al. described an even higher prevalence of this manifestation in BPAPS patients (31.8%). In this study, the prevalence of CD in the matched healthy control group was only 5%, which suggests that this finding cannot be solely attributed to socioeconomic and educational conditions [18].

The proportion of non-white and female patients was higher in the BPAPS groups. There was also a statistically significant difference in the mean age between groups, but with no clinical relevance. Patients with APS have a high prevalence of metabolic syndrome, similar to other autoimmune diseases [19]. We observed that PAPS patients from Brazil were more often obese and sedentary when compared to the group of patients from other countries. In this regard, both genetic, environmental and socioeconomic status can be responsible for the differences found herein.

Our findings highlight the importance of considering the interethnic variations between different countries for decision making in PAPS. Especially for Brazilian patients, which were the focus of this study, we were able to understand their particularities, and this may help to stratify better their recurrence risk and provide better treatments based on that.

Our study has limitations. First, it was a retrospective analysis of records from a database, with a cross-sectional design; however, future analysis of the registry with prospective design will provide more reliable data. Second, aPL tests were performed locally in each center, not in the APS ACTION core labs; similarly, we will investigate geographical differences in the future based on core laboratory aPL data. Third, enrollment in APS ACTION is at the discretion of the investigator without requirement that, for example, all consecutively seen patients with aPL antibodies are enrolled allowing for biases across centers. However, no a priori reason for this to consequentially vary by geography. Fourth, while a referral bias cannot be totally ruled out, one should consider that most of the APS ACTION centers are mostly tertiary referral academic hospitals, all equally receiving the most severe cases of the syndrome, which may have led to selection bias and reduced external validity. Fifth, some variables were assessed subjectively (for example, sedentary lifestyle and cognitive dysfunction); nonetheless, since these data are derived from a registry, we were not able to reassess them with specific instruments throughout the conduction of this study. Finally, the database used did not provide information about the number of events per patient nor the rates of thrombosis in the presence of adequate anticoagulation for each group.

Conclusions

Our study suggests differences in the clinical and laboratory profile of patients with PAPS in an admixed population. In Brazil, PAPS occurs more often in women of non-white ethnicity, and patients are more sedentary and obese. Non-criteria manifestations, such as livedo, cognitive dysfunction and seizures, were more frequently reported in these patients. They also had a higher frequency LA, and a lower frequency of aCL, aβ2GPI, and triple aPL-positivity. This specific Brazilian aPL profile (high frequency of isolated LA, even with low frequency of triple positivity) may explain the comparable rates of vascular thrombosis between both groups. Further studies should explore potential genetic differences between homogenous and admixed APS populations.

Abbreviations

aß2GPI: Anti-ß2-glycoprotein I; aCL: Anticardiolipin antibodies; aGAPSS: Adjusted Global AntiPhospholipid Syndrome Score; APS: Antiphospholipid syndrome; aPL: Antiphospholipid antibodies; APS ACTION: AntiPhospholipid Syndrome Alliance for Clinical Trials and InternatiOnal Networking; BPAPS: Primary antiphospholipid syndrome patients from Brazil; CD: Cognitive dysfunction; IQR: Interquartile range; LA: Lupus anticoagulant; Non-BPAPS: Primary antiphospholipid syndrome patients from other countries (not Brazil); OGTT : Oral glucose tolerance test; OR: Odds ratio; PAPS: Primary antiphospholipid syndrome; SLE: Systemic lupus erythematosus.

Acknowledgements
The APS ACTION Registry was created using REDCAP provided by the Clinical and Translational Science Center at Weill Cornell Medical College (CTSC grant UL1 TR000457).

Authors' contributions
All of the authors provided critical review, relevant edits, and feedback to direct content during multiple rounds of review. All authors read and approved the final manuscript.

Funding
None.

Availability of data and materials
The datasets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
This study was performed using data from the APS ACTION Registry. During recruitment, each center received ethical approval of your local committee. The study protocol was submitted for approval by the APS ACTION Committee. All patients included in this study signed a written informed consent during APS ACTION Registry recruitment.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests regarding this paper.

Author details
[1]University of São Paulo, Av. Dr. Arnaldo 455, Third Floor, Room 3109, São Paulo 01246903, Brazil. [2]Federal University of Juiz de Fora, Minas Gerais, Brazil. [3]National and Kapodistrian University of Athens, Athens, Greece. [4]University Hospital Padova, Padua, Italy. [5]Center of Research of Immunopathology and Rare Diseases, University of Turin, Turin, Italy. [6]Hospital Universitario Cruces, Barakaldo, País Vasco, Spain. [7]Hospital for Joint Diseases, New York University, New York, NY, USA. [8]Clinical Immunology and Rheumatology Unit, IRCCS Istituto Auxologico Italiano, Milan, Italy. [9]CHU de Québec-Université Laval, Québec, QC, Canada. [10]Rheumatology Service, IMIBIC/Reina Sofia Hospital, University of Cordoba, Cordoba, Spain. [11]Rheumatology and Immunology Department, Peking University First Hospital, Beijing, China. [12]Haemostasis Research Unit, Department of Haematology, University College London, London, UK. [13]Universidade Do Estado Do Rio de Janeiro, Rio de Janeiro, Brazil. [14]University of Utah and Intermountain Healthcare, Salt Lake City, UT, USA. [15]Rheumatology and Immunology Unit, ASST Spedali Civili of Brescia, Brescia, Italy. [16]Johns Hopkins University School of Medicine, Baltimore, MD, USA. [17]Hospital Universitario, 12 de Octubre, Madrid, Spain. [18]Northwell Health, Great Neck, NY, USA. [19]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Hospital Clínic, Barcelona, Catalonia, Spain. [20]Division of Rheumatology, University of Michigan, Ann Arbor, MI, USA. [21]Hokkaido University Hospital, Sapporo, Japan. [22]Antiphospholipid Standardization Laboratory, University of Texas Medical Branch, Galveston, TX, USA. [23]Academic Department of Vascular Surgery, King's College London British Heart Foundation Centre of Excellence, School of Cardiovascular Medicine and Sciences, London, UK. [24]Barbara Volcker Center for Women and Rheumatic Disease, Hospital for Special Surgery, Weill Cornell Medicine, New York, NY, USA.

Received: 9 July 2021 Accepted: 11 October 2021
Published online: 28 October 2021

References

1. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, Cervera R, et al. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost. 2006;4:295–306.
2. Young-Macworth CG, Loizou S, Walport MJ. Primary antiphospholipid syndrome: features of patients with raised anticardiolipin antibodies and no other disorder. Ann Rheum Dis. 1989;48:362–7.
3. Erkan D, Lockshin MD. APS ACTION-antiphospholipid syndrome alliance for clinical trials and international networking. Lupus. 2012;21:695–8.
4. Alarcón-Riquelme ME, Ziegler JT, Molineros J, Howard TD, Moreno-Estrada A, Sanchez-Rodríguez E, et al. Genome-wide association study in an Amerindian ancestry population reveals novel systemic lupus erythematosus risk loci and the role of European admixture. Arthritis Rheumatol. 2016;68:932–43.
5. Durso DF, Bydlowski SP, Hutz MH, Suarez-Kurtz G, Magalhães TR, Pena SDJ. Association of genetic variants with self-assessed color categories in Brazilians. PLoS ONE. 2014;9:e83926.
6. Radin M, Schreiber K, Costanzo P, Cecchi I, Rocatello D, Baldovino S, et al. The adjusted Global AntiphosPholipid Syndrome Score (aGAPSS) for risk stratification in young APS patients with acute myocardial infarction. Int J Cardiol. 2017;240:72–7.
7. Signorelli F, Tupinambá H, Jesus G, Balbi GGM, Levy R. Thrombocytopenia is highly associated with specific antiphospholipid antibodies profile (P24). Lupus. 2019;28:31.
8. Galli M, Luciani D, Bertolini G, Barbui T. Lupus anticoagulants are stronger risk factors for thrombosis than anticardiolipin antibodies in the antiphospholipid syndrome: a systematic review of the literature. Blood. 2003;101:1827–32.
9. Devreese KMJ, de Groot PG, de Laat B, Erkan D, Favaloro EJ, Mackie I, et al. Guidance for the Scientific and Standardization Committee for lupus anticoagulant/antiphospholipid antibodies of the International Society on Thrombosis and Haemostasis. J Thromb Haemost. 2020;18:2828–39.
10. Yin D, de Groot PG, Ninivaggi M, Devreese KMJ, de Laat B. Clinical relevance of isolated lupus anticoagulant positivity in patients with thrombotic antiphospholipid syndrome. Thromb Haemost. 2020. https://doi.org/10.1055/a-1344-4271.
11. Petri M. Update on anti-phospholipid antibodies in SLE: the Hopkins' Lupus Cohort. Lupus. 2010;19:419–23.
12. Buyon J, Kim MY, Guerra MM, Laskin CA, Petri M, Lockshin MD, et al. Predictors of pregnancy outcomes in patients with lupus. A cohort study Ann Intern Med. 2015;163:153–63.
13. Pengo V, Biasiolo A, Pegoraro C, Cucchini U, Noventa F, Iliceto S. Antibody profiles for the diagnosis of antiphospholipid syndrome. Thromb Haemost. 2005;93:1147–52.
14. Diogenes MJN, Diogenes PCN, de Morais Carneiro RM, Neto CCR, Duarte FB, Holanda RRA. Cutaneous manifestations associated with antiphospholipid antibodies. Int J Dermatol. 2004;43:632–7.
15. Uthman IW, Khamashta MA. Livedo racemosa: a striking dermatological sign for the antiphospholipid syndrome. J Rheumatol. 2006;33:2379–82.
16. Ilgen U, Yayla ME, Ates A, Okatan IE, Yurteri EU, Torgultap M, et al. Antiphospholipid antibodies and non-thrombotic manifestations of systemic lupus erythematosus. Lupus. 2018;27:665–9.
17. Cervera R, Tektonidou MG, Espinosa G, Cabral AR, González EB, Erkan D, et al. Task Force on Catastrophic Antiphospholipid Syndrome (APS) and Non-criteria APS Manifestations (II): thrombocytopenia and skin manifestations. Lupus. 2011;20:174–81.
18. Rosa RF, Ugolini-Lopes MR, Gandara APR, Vendramini MBG, Campanholo KR, Dutra L, et al. Cognitive dysfunction and serum levels of brain-derived neurotrophic factor (BDNF) in primary anti-phospholipid syndrome (PAPS). Rheumatology (Oxford). 2021;60:179–87.
19. Medina G, Gutiérrez-Moreno AL, Vera-Lastra O, Saavedra MA, Jara LJ. Prevalence of metabolic syndrome in primary antiphospholipid syndrome patients. Autoimmun Rev. 2011;10:214–7.

Publisher's Note