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Prevalence and associations of anti-phosphatidylserine/prothrombin antibodies with clinical phenotypes in patients with primary antiphospholipid syndrome
aPS/PT antibodies in primary antiphospholipid syndrome

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ABSTRACT

Objective: The clinical significance of anti-phosphatidylserine/prothrombin (aPS/PT) in antiphospholipid syndrome (APS) is still controversial. We assessed the prevalence of aPS/PT antibodies, their association with other anti-phospholipid antibodies (aPL) and with different APS clinical phenotypes.

Methods: We included 95 primary APS patients according to the Sydney classification criteria, and patients with thrombocytopenia and/or hemolytic anemia who also fulfilled the serological APS criteria. We tested aCL, anti-β2GP-I and aPS/PT antibodies (both IgG and IgM isotypes) and lupus anticoagulant (LA). We used $\chi 2$ test, Spearman's correlation coefficient, Mann-Whitney *U* test and logistic regression.

Results: Seventy-seven percent of patients had thrombosis, 50% hematologic involvement and 25% obstetric events (non-exclusive groups). Twenty patients had only hematologic features. The prevalence of IgG and IgM aPS/PT antibodies was 61% and 60%, respectively. Patients with LA+ had a higher prevalence and higher titers of IgG and IgM aPS/PT antibodies. aPS/PT antibodies correlated with aPL antibodies including LA. IgG aPS/PT antibodies were associated with thrombosis (OR 8.6 [95% CI 2.13–33.8, p = 0.002]) and pure hematologic features (OR 0.2, CI 95% 0.05–0.97, p = 0.004). IgM anti-β2GP-I antibodies conferred high risk for both hematologic (OR 7.9, 95% CI 1.88–34.61, p = 0.006) and thrombotic involvement (OR 7.4, 95% CI 1.76–31.12, p = 0.006).

Conclusions: aPS/PT antibodies were highly prevalent and correlated with other aPL antibodies. IgG aPTS/PT conferred a high risk for thrombosis, but not for pure hematologic involvement. aPS/PT antibodies may be a useful serological tool in the diagnosis and phenotypic characterization of APS patients.

1. Introduction

The antiphospholipid syndrome (APS) is a systemic autoimmune disease characterized by thrombosis and/or pregnancy morbidity in the presence of persistently positive antiphospholipid (aPL) antibodies. The updated Sydney APS classification criteria only include anticardiolipin antibodies (aCL), anti-β2glycoprotien-I (anti-β2GP-I) and lupus anticoagulant (LA) as part of the serological criteria [1]. Nevertheless, aPL antibodies also comprise a family of other autoantibodies such as anti-phosphatidylserine/prothrombin (aPS/PT), anti-vimentin, anti-annexin, anti-phosphatidylethanolamine and antibodies directed against domain I of the β2GP-I molecule [2].

Several studies have shown conflicting results regarding the presence and clinical significance of aPS/PT in APS patients. A recent systematic review showed that aPS/PT antibodies are a strong risk factor for arterial and venous thrombosis [3], while other authors have shown that these autoantibodies are independently associated with recurrent abortions and premature delivery [4]. In contrast, the clinical significance of aPTS/PT antibodies in non-criteria APS clinical manifestations, particularly thrombocytopenia and hemolytic anemia,

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remains largely unknown [5].

The aim of our study was to assess the prevalence of IgG and IgM aPS/PT antibodies, to evaluate their correlation with other aPL, particularly LA, and to determine their association with thrombotic, obstetric and pure hematologic features, in a well-established cohort of patients with primary APS.

2. Methods

We included consecutive patients with primary APS who attended (2015–2016) our Rheumatology Clinic at the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, a tertiary referral care center in Mexico City. All patients fulfilled the revised APS classification Sydney criteria [1]. We also included patients with thrombocytopenia and/or autoimmune hemolytic anemia who also fulfilled the Sydney APS serological criteria [1]. Patients were excluded if they had any other concomitant autoimmune connective tissue disease.

Thrombotic and obstetric features were defined according to the Sydney classification criteria [1]. We defined thrombocytopenia as a persistent platelet count of $< 100 \times 10^9$ platelets/L and autoimmune hemolytic anemia as the presence of low hemoglobin, direct positive Coombs' test, corrected reticulocyte count above 2%, elevated indirect bilirubin, elevated DHL and low haptoglobin levels.

Patients' clinical records were thoroughly reviewed according to a pre-established protocol. We retrospectively collected demographic data, thrombotic events ("thrombotic phenotype"), obstetric events ("obstetric phenotype") and the presence of pure hematologic features ("pure hematologic phenotype").

2.1. aPL serological testing

A blood sample was drawn to test aCL (IgG and IgM) and anti-β2GP-I (IgG and IgM) antibodies by ELISA (*INOVA* Diagnostics; San Diego, USA) according to manufacturer's recommendations. Positivity was considered for titers > the 99th percentile for aCL (IgG: > 8.4 UGPL, IgM: > 13.1 UMPL) and anti-β2GPI (IgG: > 8.4 U/mL, IgM: > 14.3 U/mL) according to the Sydney APS serological criteria [1].

aPS/PT antibodies (IgG and IgM isotypes) were determined in the same sample by a quantitative commercially available ELISA (INOVA Diagnostics; San Diego, USA). Serum samples were diluted 1:100. All wash steps were done with TBS-Tween. Results are expressed as Units derived off a standard curve (0 − 100). All ELISAs were processed in a DSX System (DYNEX Technologies). The cut-off values (90th percentile), calculated on 60 healthy subjects (42 women, 32 ± 12 years) were > 15.7 U and > 19.5 U, for IgG and IgM isotypes, respectively. With this cut off, we observed a sensitivity (SE) of 67%, specificity (SP) of 97%, *positive predictive value (PPV)* of 89% and a negative predictive value (NPV) of 88% for the IgG isotype. For the IgM isotype, the SE was 67%, SP 88%, PPV 84% and NPV 88%. ROC analysis using these cut-off values, showed an AUC for the IgG isotype of 0.8 (SE = 69%, SP = 97%), and an AUC for the IgM isotype of 0.94 (SE 56%, SP = 97%). However, as the literature in Asian and Caucasian population have used a higher cut-off (> 30 U) for both aPS/PT isotypes, we also performed a sub-analysis using this cut-off.

As most patients were on oral anticoagulants at time of study, LA status was recorded from the medical charts. LA was determined by LA/1 screening reactant and a confirmatory test LA/2 according to published international guidelines [6].

Our study was approved by the Institutional Review Board of the Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. All patients gave their informed signed consent to participate according to the Declaration of Helsinki.

2.2. Statistical analysis

Categorical variables were compared using either X^2 or Fisher's Exact test when appropriate. Continuous variables were compared using Student's *t*-test or *Mann–Whitney U test*. We reported non-parametric correlations using Spearman's correlation coefficient and also evaluated kappa coefficient. We also used *logistic regression* analysis for each of the clinical phenotypes. Results are reported in OR and 95% CI. A two-tailed $P < 0.05$ was considered significant. All analyses were done with SPSS for Windows version 20.0.

3. Results

We included 95 patients, most of them females (n = 67, 70.5%), with a mean age of 44.4 ± 14.7 years and a median disease duration of 7.3 years (range 0.5–26.6). The main clinical features were thrombosis (n = 74, 77.8%), hematologic involvement (n = 48, 50.5%) and obstetric complications (n = 24, 25.2%) (non-mutually exclusive groups). Among the 48 patients with hematologic features, 40 had thrombocytopenia, three hemolytic anemia, five had both features and 20 had pure hematologic involvement (i.e. thrombotic and obstetric-free events). Of patients with thrombosis, 18 had arterial events and 56 had venous thrombosis. Thirty-seven patients (38.9%) were on aspirin and 64 (67.3%) on oral anticoagulants at time of study.

The prevalence of conventional aPL antibodies and aPS/PT antibodies are shown in Table 1. As seen, LA activity was present in 70.2% of patients. The frequency of aPS/PT was 61% and 60% for IgG and IgM isotypes, respectively. IgM + isotype alone was present in only 9.5% of patients. When a cut-off of > 30 U for both IgG and IgM aPS/PT isotypes was used, the prevalence dropped to 50.5% for IgG and 52.6% for IgM. The prevalence for the single IgM (+ve) group did not change. The overall median titers of IgG aPS/PT were 40.5 U (range 6.2–333.0) and 35 U for IgM (range 7.7–317.0).

Table 1
Serological features of primary APS clinical phenotypes.

Antibody	All cohort n = 95	Thrombotic[b] n = 74	Obstetric[b] n = 24	Pure hematologic n = 20
LA (n, %)	58/84 (70.2)	48/65 (73.8)	16/22 (76.2)	10/18 (55.5)
aCL IgG +[a] (n,%)	54 (56.8)	46 (62.1)	19 (79.1)	8 (40)
aCL IgM (n,%)	30 (31.5)	21 (28.9)	22 (91.7)	9 (45)
Only aCL IgM + (n, %)	10 (10.5)	7 (9.4)	4 (16.6)	3 (15)
aβ2GP-I IgG +[a] (n, %)	41 (43.1)	36 (48.6)	10 (41.6)	5 (25)
aβ2GP-I IgM (n,%)	20 (21)	11 (14.9%)	9 (37.5)	9 (45)
Only aβ2GP-I IgM + (n, %)	10 (10.5)	3 (4.1)	3 (12.5)	7 (35)
aPS/PT IgG (n, %)	58 (61)	51 (68.9)	15 (62.5)	7 (35)
aPS/PT IgM (n,%)	57 (60)	43 (58.1)	11 (45.8)	14 (70)
Only aPS/PT IgM + (n, %)	10 (10.5)	3 (41.0)	3 (12.5)	7 (35)

[a] Independent of IgM status.
[b] Thrombotic and obstetric groups are not mutually exclusive.

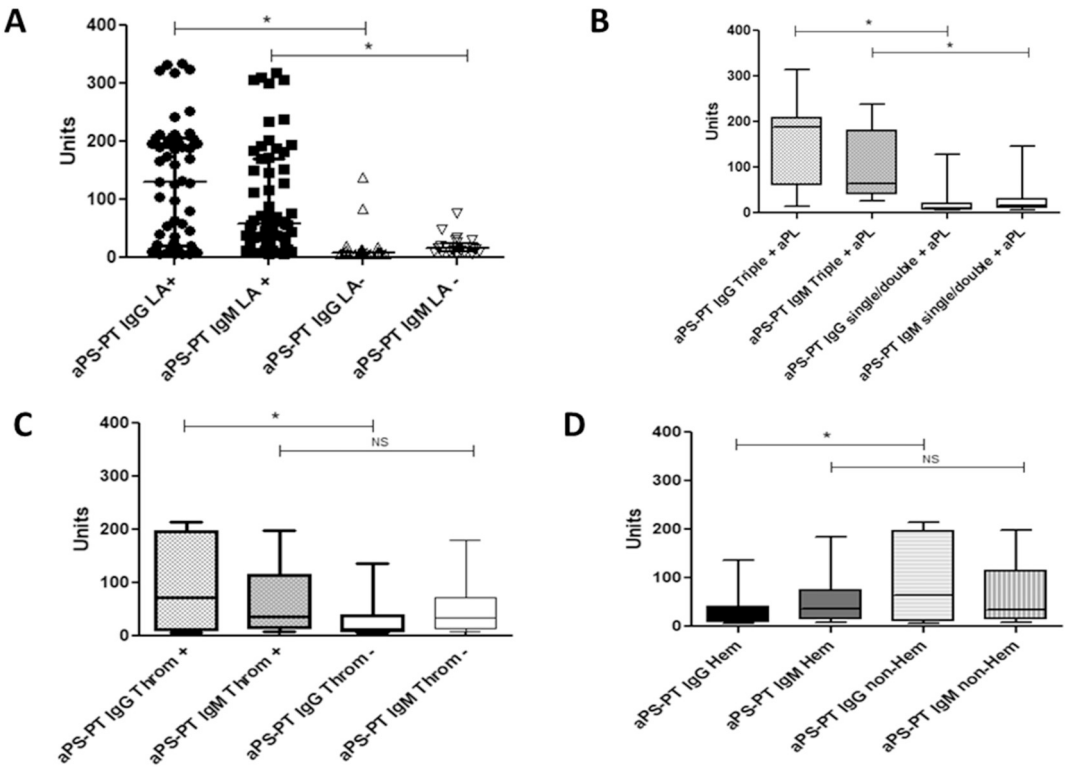

Fig. 1. Panel A: aPS/PT levels in APS with (black symbols) or without (open symbols) Lupus Anticoagulant. The graph shows the median and interquartile range (horizontal black bars). * p values < 0.05. Panel B: aPS/PT and triple marker in primary APS. The graph shows the median and interquartile range (black bars). *p values < 0.05. Panel C: Titers of aPS/PT in APS and thrombosis. The graph shows the median and interquartile range (black bars). * p values < 0.05. NS = non-significant. Panel D: Titers of aPS/PT in APS and pure hematologic features. The graph shows the median and interquartile range (black bars). * p values < 0.05. NS = non-significant.

3.1. aPS/PT serological associations

We found a significant difference in the frequency and titers of aPS/PT in APS LA+ patients (n = 59) compared with LA negative patients (n = 25). The first group had a higher prevalence of IgG aPS/PT (79.3% vs. 16%, p = 0.0001) and IgM aPS/PT (81.5% vs. 31.8%, p = 0.001), as well as higher titers of IgG aPS/PT (130.5 U vs. 8.2 U) and IgM aPS/PT (58.5 U vs. 16.6 U, p = 0.0001) (Fig. 1A).

In addition, we found moderate agreement between the presence of LA and both aPS/PT isotypes (κ = 0.58 p = 0.0001 for IgG, and κ = 0.47 p = 0.001 for IgM).

We also analyzed the association between triple positive marker (LA, aCL and anti-β2GP-I) with aPS/PT antibodies. These results are shown in Fig. 1B. As seen, triple-positive patients had higher titers of aPS/PT antibodies than single or double aPL positive patients.

The correlations of the IgG and IgM aPS/PT antibodies with conventional aPL are shown in Table 2. Overall, we found a significant positive correlation of both aPS/PT isotypes with aCL and anti-β2GPI antibodies.

3.2. aPS/PT clinical phenotypes

When we compared patients with (n = 74) or without thrombosis (n = 21), we found higher titers (72.1 U vs. 12.2 U, p < 0.05) (Fig. 1C) as well as a higher frequency of IgG aPS/PT in patients with thrombosis (68.9% vs. 33.3%, p = 0.003). Although the prevalence of IgM aPS/PT (independent of the IgG status) was similar between the groups with or without thrombosis (58.1% vs. 66.7%, p = 0.04), the prevalence of single IgM+ aPS/PT was lower in patients with thrombosis (4.1% vs. 33.3%, p = 0.001).

We also found a higher prevalence of IgG aCL (62.2% vs. 38.1%, p = 0.01) and IgG anti-β2GP-I (48.6% vs. 23.8%, p = 0.04) in patients with thrombosis. In contrast, patients with thrombosis had a lower prevalence of IgM anti-β2GP-I (independent of the IgG anti-β2GP-I status) (4.6% vs. 42.9%, p = 0.005) and single IgM anti-β2GP-I positivity (2.7% vs. 33.3%, p = 0.0001) in patients with thrombosis. The multivariate regression analysis for the thrombotic phenotype showed that IgG aPS/PT (OR 8.6 95% CI 2.13–33.8, p = 0.002) and IgG anti-β2GP-I antibodies (OR 7.4 95% CI 1.76–31.12, p = 0.006) remained associated with thrombosis. We did not find significant differences regarding other aPL antibodies nor between arterial/venous thrombosis.

When we compared patients with pure hematologic features (n = 20) vs. patients without them (n = 75), we found that hematologic patients had a higher prevalence of IgM anti-β2GP-I (45% vs. 14.7%, p = 0.003) as well as higher prevalence of positivity for single IgM anti-β2GP-I (35% vs. 2.7%, p = 0.0001). In contrast, a lower prevalence of IgG aPS/PT antibodies (35% vs. 68.5%, p = 0.006) and a higher prevalence of positive IgM aPS/PT antibodies (35% vs. 4%,

Table 2
Correlations of titers of aPS/PT and other aPL antibodies.

aPS/PT-IgG	ρ[a]	p value
aPS/PT IgM	+0.59	0.0001
aCL-IgG	+0.62	0.0001
aβ2GP-I IgG	+0.63	0.001
aβ2GP-I IgM	+0.35	0.001
aCL-IgM	+0.20	Non-significant
aPS/PT- IgM		
aCL-IgG	+0.57	0.0001
aCL-IgM	+0.42	0.001
aβ2GP-I IgG	+0.48	0.001
aβ2GP-I IgM	+0.59	0.0001
aPS/PT-IgG	+0.59	0.0001

[a] Spearman's correlation coefficient.

Table 3
aPS/PT autoantibodies and clinical associations.

Study	Subjects	Ethnicity	aPS/PT IgG	aPS/PT IgM	Clinical association	Method's data
Atsumi 2000 [10]	Systemic autoimmune diseases n = 124 (included 21 primary APS and 24 secondary APS) HC n = 36	Asian	Overall 10.9% Primary APS 19%	Overall 4.9% Primary APS 10%	Overall APS manifestations (thrombosis, obstetric events or thrombocytopenia) with both isotypes	In-house ELISA Cut-off IgG/IgM 2.0 U/13.0 U (mean + 5SD)
Nojima 2004 [11]	SLE n = 126 HC n = 80	Asian	38.1%	Not evaluated	Cerebral infarction	In-house ELISA Cut-off 403.2 OD (mean + 3SD)
Bertolaccini 2005 [12]	SLE n = 212 HC n = 100	Caucasian	Overall 31% Only IgG+ 16%	Overall 31% Only IgM+ 6%	Thrombosis with both Isotypes	In-house ELISA Cut-off IgG/IgM 2.0/11.0 U (mean + 3SD)
Bertolaccini 2005 [13]	SLE/APS n = 56 SLE with thrombosis but not APS n = 56 SLE n = 56	Caucasian	SLE/APS 46.4% SLE/thrombosis no APS 1% SLE 8%	SLE/APS 39.2% SLE/thrombosis no APS 1% SLE 1%	Thrombosis with both Isotypes	In-house ELISA Cut-off IgG/IgM 2.0/11.0 U (mean + 3SD)
Tsutsumi 2006 [14]	SLE n = 139 HC n = 148	Asian	No specified	Not specified	Thrombosis	ELISA commercial MBL manufact. Cut off IgG > 17.8 U (mean + 2SD)
Nojima 2006 [15]	SLE n = 175 HC n = 80	Asian	43.4%	Not evaluated	Thrombosis (arterial and venous) No association with obstetric events	In-house ELISA Cut-off 403.2 AU (mean + 3SD)
Bardin 2007 [16]	Subjects with thrombosis n = 152 (90 negative for LA, aCL, anti-B2GPI and hereditary thrombophilic abnormalities, 62 APS) HC n = 120	Caucasian	55% in the aPL+ group 2% in the aPL- group	Not evaluated	Thrombosis	In-house ELISA Cut-off > 97th percentil
Hoxha 2012 [9]	APS n = 158 HC n = 100	Caucasian	27.8%	42.4%	Thrombosis, obstetric events. IgG isotype for venous thrombosis and IgM isotype for arterial thrombosis	ELISA commercial INOVA manufact. Cut-off IgG/IgM > 40 U/mL
Bertolaccini 2013 [17]	Consecutive patients n = 257 (19 with primary APS and 25 with SLE/APS)	Caucasian	31% (isotype non specified) 40% among LA+ patients		Either IgG and IgM were associated with thrombosis and obstetric events	In-house ELISA Cut-off IgG/IgM 2 U/11 U (mean + 3SD)
Vlagea 2013 [18]	Suspected autoimmune disease (n = 295; 95 primary APS, 45 secondary APS)	Caucasian	Primary APS 35.7% Secondary APS 40%	Primary APS 32.6% Secondary APS 31.1%	Both isotypes associated with venous thrombosis. IgG isotype associated with obstetric events	In-house ELISA Cut-off IgG/IgM 10 and 15 AU/mL (mean + 10SD)
Fabris 2014 [26]	Patients with a medical prescription for aPS/PT n = 421 HC n = 52	Caucasian	22.4%	75%	Not evaluated	ELISA commercial - INOVA manufact. Cut-off IgG/IgM > 40 U 30–40 U borderline
Sciascia 2014 [19]	SLE n = 75 (37 with APS) HC n = 100	Caucasian	44% (Commercial) 33.4% (In-house)	30.7% (Commercial) 25.3% (In-house)	Both isotypes associated with thrombosis and IgM isotype associated with pregnancy loss	ELISA in house and commercial - INOVA manufact. In house cut-off IgG: 2 U, IgM: 11 U, mean + 3SD Commercial ELISA IgG/IgM > 30 U
Zigon 2015 [4]	Patients with obstetric events n = 402 (169 with APS) HC = 222	Caucasian	9.5% in APS	7.1% in APS	Pregnancy outcomes	ELISA in house Cut off > 99th percentile
Heikal 2015 [24]	Patients at risk for APS n = 104 (8 primary APS, 3 secondary APS)	American	62.5% in primary APS 33.3% in secondary APS	No evaluated	Not evaluated	ELISA commercial - INOVA manufact. Cut-off IgG/IgM > 30 U
Hoxha 2016 [8]	Primary APS n = 197 HC = 100	Caucasian	29.9%	60%	Both isotypes associated with thrombosis, obstetric events and thrombotic microangiopathy	ELISA commercial - INOVA manufact Cut-off IgG/IgM 61.4/56.3 U

(*continued on next page*)

Table 3 (*continued*)

Study	Subjects	Ethnicity	aPS/PT IgG	aPS/PT IgM	Clinical association	Method's data
Amengual 2017 [20]	APS n = 126 (77 primary and 46 secondary) Replication cohort n = 96	Asian, Caucasian	58% (INOVA) and 43% (MBL) in primary APS 55% (INOVA) adn 41%(MBL) in replication cohort	No evaluated	IgG isotype associates with thrombosis (arterial and venous) No association with obstetric events.	ELISA commercial - INOVA manufact Cut-off IgG > 30 U - MBL manufact Cut-off IgG > 12 U
Shi 2018 [21]	APS patients n = 186 (67 primary and 119 secondary)	Asian	72.6%	66.7%	Venous thrombosis (only IgG isotype). Obstetric events	ELISA commercial - INOVA manufact. Cut-off IgG/IgM > 30 U
Our study 2018	Primary APS n = 95	Mestizo	61%	60%	aPS/PT IgG isotype associated with thrombosis. aPS/PT IgG isotype less prevalent in thrombocytopenia	ELISA commercial - INOVA manufact Cut-off IgG/IgM (90th percentile) 15.7/19.4 U

HC: Healthy controls.

p = 0.001) was found in patients with pure hematologic features. Interestingly, titers of IgG aPS/PT were lower in patients with pure hematologic features (12.3 U vs. 64 U, p = 0.02), but the IgM titer was similar (36.5 U vs. 34.7 U, p = 0.7) (Fig. 1D). The logistic regression analysis for this clinical phenotype confirmed that IgM anti-β2GP-I antibodies were a risk factor associated with pure hematologic features (OR 7.9 [95% CI 1.88–34.61] p = 0.006) whereas IgG aPS/PT antibodies were not (OR 0.2, CI 95% 0.05–0.97, p = 0.004).

When we compared patients with or without obstetric features, the prevalence of aPS/PT antibodies was 62.5% vs. 54.9% (p = 0.51) for the IgG isotype, 45.8% vs. 26.8% (p = 0.08) for the IgM isotype and 12.5% vs. 9.9% (p = 0.71) for single IgM+ isotype. We did not find a statistical difference in titers of IgG or IgM aPS/PT in patients with or without obstetric events (108 U vs. 21 U, p = 0.2, and 45.8 U vs. 30.5 U, p = 0.2; respectively). Similarly, we did not find any significant difference in the prevalence of LA, aCL and anti-β2GP-I antibodies in this group.

Finally, using a cut-off of > 30 U for both IgG and IgM aPS/PT isotypes, IgG aPS/PT antibodies were more frequent in patients with thrombosis (58.1% vs. 23.8%, p = 0.006), less frequent in the pure hematologic group (25% vs. 57.3%, p = 0.01), and had a similar distribution in the obstetric group (62.5% vs. 46.5%, p = 0.17). We did not find any difference regarding the IgM aPS/PT isotype (alone or in combination with the IgG isotype).

4. Discussion

For almost two decades, multiple studies have attempted to define the diagnostic utility of aPS/PT antibodies and their clinical associations in patients with primary or secondary APS [7–25]. Thus, different aPS/PT ELISA assays have been developed with their corresponding variations in cut-off values and in vitro assay conditions (Table 3). Overall, it is known that the aPS/PT prevalence ranges from 27 to 51% in primary APS, 47–53% in secondary APS and 10–33% in negative-APS SLE patients [8–10]. Here, we found a 60% prevalence for both isotypes in a well-established cohort of patients with primary APS. We also found that their prevalence decreased to 50% when a higher cut-off (> 30 U) was used, as suggested in previous studies from Caucasian and Asian populations. The specificity of aPS/PT antibodies for the classification of APS is 98% for IgG and 97% for IgM, while the sensitivity is 29% and 48% for IgG and IgM isotypes, respectively [8].

The clinical associations of aPS/PT with thrombosis have also been the subject of extensive international effort. Both isotypes are strong independent risk factors for arterial and venous thrombosis [3,8–22]. We confirmed that IgG aPS/PT antibodies, but not IgM aPS/PT, are strongly associated with thrombosis.

The study of IgG and IgM aPS/PT in patients with APS associated pregnancy morbidity has rendered discrepant results. For instance, many authors have reported that IgG/IgM aPS/PT positivity is a high risk for obstetric complications such as prematurity and pregnancy loss [4,8,9,18–21]. Other authors have not found this association [15,20]. Our study is in agreement with these latter two studies. Patient selection may explain those discrepancies.

As known, thrombocytopenia and hemolytic anemia are considered non-criteria clinical manifestations in patients with APS [1]. To date, only two studies have addressed, albeit partially, the role of aPS/PT antibodies in patients with APS and hematologic features. For instance, almost 20 years ago in the original description of the aPS/PT ELISA, Atsumi and cols found a strong association of both aPS/PT isotypes with APS regardless of the presence or absence of thrombocytopenia [10]. It is possible then that their results may have been driven by the thrombotic and obstetric groups. Nojima et al., on the other hand, did not find an association of aPS/PT antibodies in small group of SLE patients with thrombocytopenia [15]. To the best of our knowledge then, our study is the first to date that directly addresses the characterization of aPS/PT antibodies in a selected group of APS patients with pure hematologic

phenotype. These are patients with thrombocytopenia and/or hemolytic anemia who also met the revised Sapporo APS laboratory criteria [1], but more importantly, they have not developed thrombotic events after long-term follow up. Under these strict inclusion criteria, we found that hematologic APS patients had a lower prevalence of IgG aPS/PT than patients with thrombotic APS (35% vs. 68.5%, p = 0.006) and that their IgG aPS/PT titers were five-fold lower compared to patients with thrombotic manifestations (p = 0.02). Hematologic APS patients also had a three-fold higher prevalence of IgM anti-β2GP-I (p = 0.003) and a stronger higher prevalence of single positive IgM anti-β2GP-I (35% vs. 2.7%, p = 0.0001). It is well known that aPS/PT are more frequently found in patients with LA [15,17,18,21,24]. Here, we confirmed that LA positive patients had a higher prevalence of IgG aPS/PT than LA negative patients (79.3% vs. 16%, p = 0.0001). We previously demonstrated that APS patients with pure hematologic phenotype had a lower prevalence of LA than hematologic patients who later developed thrombotic events [23]. In parallel with the findings reported here, we interpret these results to mean that hematologic APS is a distinct clinical entity characterized by the presence of non-thrombogenic IgM anti-β2GP-I antibodies and absence of LA activity. Our study also indirectly emphasizes the notion that aPS/PT testing may be helpful to confirm the presence of LA activity, particularly in patients on vitamin K-dependent oral anticoagulants, with inconclusive LA results [24] or with difficult LA testing interpretation [25].

5. Conclusion

aPS/PT antibodies were highly prevalent and correlated with LA in a cohort of patients with primary APS. We confirmed the association of IgG aPS/PT antibodies as a risk factor for thrombosis in our population, whereas the presence of this antibody was less prevalent among patients with pure hematologic features who also fulfilled the Sydney serological criteria. Thus, pure hematologic APS patients have a different aPS/PT serological profile than the conventional APS patients with thrombosis. In this vein, our study adds new knowledge not only to better understand the role of aPS/PT antibodies in the detection of thrombotic-prone patients, but their absence strengthens our proposal that pure hematologic APS is a distinct phenotypic entity. In sum, our study supports the notion that IgG aPS/PT may be an additional serological tool in the classification of APS patients and may help to improve the diagnosis of its thrombotic and hematologic phenotypes.

Declaration of interest

None.

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Statement of conflict of interest

All authors acknowledge that we meet criteria for authorship and will sign a statement attesting to authorship, declare no conflicts of interest. We will release the copyright should the manuscript be accepted for publication.

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