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Full Length Article

IgG phosphatidylserine/prothrombin antibodies as a risk factor of thrombosis in antiphospholipid antibody carriers

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ABSTRACT

The clinical significance of IgG/IgM antiphosphatidylserine/prothrombin (aPS/PT) antibodies was prospectively evaluated in a cohort of 191 antiphospholipid antibody (aPL) carriers using commercial ELISA assays. IgG aPS/PT antibodies were detected in 40 (20.9%) and IgM aPS/PT in 102 (53.4%) of the carriers. Both IgG and IgM aPS/PT antibodies were significantly associated with triple aPL positivity (Lupus anticoagulants [LAC] plus anti-β2Glycoprotein I plus anticardiolipin antibodies) ($p = 0.0000$ for both). There was a significant prevalence of IgM aPS/PT in the individuals with isolated LAC positivity ($p = 0.005$). Fourteen of the aPL carriers (7.3%) developed a first thrombotic event. There was a significant prevalence of IgG aPS/PT antibodies but not of IgM aPS/PT in the thrombotic patients ($p = 0.015$). The cumulative incidence rate of thrombotic events was significantly higher in the IgG aPS/PT positive ($p = 0.035$) but not in the IgM aPS/PT positive carriers. Logistic regression analysis assessing the independent effect of IgG /IgM aPS/PT antibodies, triple aPL positivity, genetic/acquired thrombosis risk factors and autoimmune disorders on thrombosis development uncovered a significant association only for the risk factors (Odds Ratio = OR: 12.451, 95% Confidence Interval = CI: 2.519–61.537, $p = 0.002$) and for triple aPL positivity (OR: 4.725, 95% CI: 1.135–19.674, $p = 0.033$). Logistic regression evaluating the independent effect of IgG and IgM aPS/PT on thrombosis development uncovered a significant association only for the former (OR: 3.962, 95% CI: 1.174–13.37, $p = 0.026$). The risk score for thrombosis in aPL carriers could be more effective if IgG aPS/PT antibodies are added to triple aPL positivity and thrombosis risk factors.

1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune disease that is characterized by vascular thrombosis and/or well defined obstetric complications [1]. Anti-β2-Gycoprotein I antibodies (aβ2GPI), anticardiolipin antibodies (aCL) and lupus anticoagulants (LAC) are considered as laboratory criteria for APS classification. Testing for other antiphospholipid (aPL) antibodies with solid phase assays is not included in standard workups [2], since they have not yet been standardized and there is only limited evidence demonstrating their clinical utility in APS patients. Some studies have nevertheless demonstrated that antibodies directed against the phosphatidylserine/prothrombin complex (aPS/PT) are associated with thrombosis and the obstetric complications of APS [3–5]. Basing on their deductions, on a systematic review of published studies and on an analysis of scoring systems designed to quantify the risk of thrombosis and/or obstetric manifestations in APS and in other autoimmune diseases, some investigators have hypothesized that including aPS/PT antibodies [6–9] in standard protocols could improve thrombotic risk assessment. As no studies have examined the usefulness of aPS/PT antibodies as biomarkers of vascular risk in subjects fulfilling the laboratory but not the clinical criteria for APS classification (*i.e.*, aPL carriers), the current one prospectively evaluated the clinical significance of IgG and IgM aPS/PT antibodies in a cohort of aPL carriers attending our centre.

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2. Methods

2.1. Study population

One hundred and ninety-one aPL carriers attending the Rheumatology outpatient clinic of the University of Padua Medical Centre were considered eligible for the study. Their laboratory criteria were those of the Sapporo consensus [10] for the 75 carriers enrolled before February 2006 and those of the Sydney consensus [1] for the 116 carriers enrolled after that date. None of them presented the clinical manifestations of APS. Plasma and serum samples were collected at the beginning of the clinical follow-up when aPL were confirmed and stored at −80 °C until the aPS/PT assays could be carried out. All the participants were provided information about the study's modality and objectives and were asked to sign statements consenting to participate and authorizing the investigators to review their medical records. The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.2. Antibody detections

Commercial ELISA kits [kindly provided by INOVA Diagnostics (USA)] were used, following the manufacturer's instructions, for the detection of IgG and IgM aPS/PT antibodies. The cut-off values for medium-high levels were > 30 Elisa Units for both isotypes. In a group of 100 aPL carriers whose the sera were available the IgG and IgM aPS/PT antibody results were confirmed at least 12 weeks apart. Home-made ELISA methods were used, as described elsewhere, for the detection of IgG/IgM aβ2GPI and IgG/IgM aCL antibodies [11]. In accordance with international guidelines, LAC was assessed by means of a series of coagulation tests using dilute Russell's viper venom and the Silica clotting time as screening tests [12].

2.3. Statistical analysis

The Chi-square test was used at univariate analysis to evaluate any associations between the categorical variables. A Kaplan–Meier survival analysis and the log-rank test were carried out to analyse the cumulative incidence of the first thrombotic event in the aPL carriers with and without IgG/IgM aPS/PT antibodies. Cox logistic regression and backward conditional logistic regression were used to assess the independent effect of IgG/IgM aPS/PT antibodies, triple aPL positivity, thrombosis risk factors and autoimmune disorders on thrombosis; the results were adjusted for confounding variables (age and sex). Another logistic regression analysis evaluated the independent effect of IgG and IgM aPS/PT antibodies on thrombosis, again, adjusted for confounding variables (age and sex). A $p < 0.05$ value was considered statistically significant. All statistical analyses were performed using the 22.0 version of the Statistical Package for the Social Sciences software (Chicago, IL, USA).

3. Results

One hundred and ninety-one aPL carriers enrolled between 2000 and 2018 were monitored for a mean time of 81.1 months ± 18.4 SD (range 12–216 months). The patients' demographic and clinical characteristics are outlined in Table 1.

The IgG aPS/PT antibodies resulted positive in 40 of the aPL carriers (20.9%), the IgM aPS/PT antibodies resulted positive in 102 (53.4%), and IgG + IgM aPS/PT antibodies resulted positive in 33 (17.3%). Positive IgG and IgM aPS/PT antibody results were confirmed in 88.2% and 93.8%, respectively, of the cases. Negative IgG and IgM aPS/PT antibody results were confirmed in all cases (100%) for both.

The IgG aPS/PT antibodies were significantly associated to triple aPL positivity (LAC plus IgG/IgM a-β2GPI plus IgG/IgM aCL antibodies) (Table 2); the IgM aPS/PT antibodies were significantly associated to

Table 1
The demographic and clinical characteristics of the study population.

Characteristics (No. 191)	Frequency
Mean age (years) ± SD	38.4 ± 11.3
Female no. (%)	177 (92.7)
Male no. (%)	14 (7.3)
Reasons for initial testing: no. (%)	
- Screening before pregnancy	26 (13.6)
- Prolonged aPTT	40 (20.9)
- Family history for autoimmunity	11 (5.8)
- Autoimmune diseases: no. (%)	115 (60.2)
Systemic lupus erythematosus	26 (22.6)
Undifferentiated connective tissue disease	23 (20.0)
Thrombocytopenia	12 (10.4)
Thyroiditis	27 (23.5)
Sjögren's syndrome	7 (6.1)
Dermatomyositis	3 (2.6)
Psoriatic arthritis	6 (5.3)
Discoid lupus	1 (0.9)
Multiple sclerosis	2 (1.7)
Systemic sclerosis	3 (2.6)
Rheumatoid arthritis	3 (2.6)
Celiac disease	1 (0.9)
Still disease	1 (0.9)
Risk factors for thromboembolic events: no.179 (%)	
- Arterial thrombosis[a]	35 (19.5)
- Venous thrombosis[b]	19 (10.6)

[a] The risk factors for arterial thrombosis: diabetes mellitus, hypertension, hypercholesterolemia, obesity, smoking habit, and family history.
[b] The risk factor for venous thrombosis: recent surgical intervention, perioperative immobilization, oral estroprogestinic treatment, pregnancy, malignancy, family history, thrombophilia, and previous venous thromboembolism.

Table 2
Comparison of antiphospholipid antibody profiles in IgG/IgM aPS/PT positive and negative carriers.

	IgG aPS/PT + (n 40)		IgG aPS/PT – (n 151)		*p* value
	n	%	n	%	
(IgG/IgM) aβ2GPI + (IgG/IgM) aCL + LAC	27	(67.7)	28	(18.5)	0.000*
(IgG/IgM) aCL + LAC	3	(7.5)	8	(5.3)	0.881
(IgG/IgM) aβ2GPI + LAC	2	(5.0)	0	–	0.059
(IgG/IgM) aβ2GPI + (IgG/IgM) aCL	2	(5.0)	44	(29.1)	0.003*
LAC	1	(2.5)	13	(8.6)	0.329
(IgG/IgM) aCL	2	(5.0)	29	(19.2)	0.054
(IgG/IgM) aβ2GPI	3	(7.5)	29	(19.2)	0.127

	IgM aPS/PT + (n 102)		IgM aPS/PT – (n 89)		p value
	n	%	n	%	
(IgG/IgM) aβ2GPI + (IgG/IgM) aCL + LAC	45	(44.1)	10	(1.1)	0.000*
(IgG/IgM) aCL + LAC	8	(7.8)	3	(3.4)	0.311
(IgG/IgM) aβ2GPI + LAC	2	(1.9)	0	–	0.538
(IgG/IgM) aβ2GPI + (IgG/IgM) aCL	16	(15.7)	30	(33.7)	0.006*
LAC	13	(12.7)	1	(1.2)	0.005*
(IgG/IgM) aCL	13	(12.7)	18	(20.2)	0.229
(IgG/IgM) aβ2GPI	5	(4.9)	27	(30.3)	0.000*

Abbreviations: aPS/PT antiphosphatidylserine/prothrombin antibodies; aPS/PT +, carriers with positive antiphosphatidylserine/prothrombin antibodies; aPS/PT -, carriers with negative antiphosphatidylserine/prothrombin antibodies; aβ2GPI, anti-β2Glycoprotein I antibodies; aCL, anticardiolipin antibodies; LAC, lupus anticoagulants.

Table 3
Demographic and clinical characteristics of the 14 aPL carriers who developed a first thrombotic event during the study period.

N	Sex	Age	Autoimmune diseases	Type of event	Risk factors	Prophylaxis
1	F	39	Still disease, Human Immunodeficiency Virus	Deep vein thrombosis	Contraceptive pill	None
2	F	51	Systemic Lupus Erythematosus	Deep vein thrombosis	Hypercholesterolemia	Low-dose aspirin
3	F	40	Systemic Sclerosis	Stroke	None	None
4	M	43	Systemic Lupus Erythematosus	Stroke	Smoking	None
5	M	39	Systemic Lupus Erythematosus	Deep vein thrombosis	Hypertension	None
6	F	43	Systemic Lupus Erythematosus	Arterial thrombosis	None	None
7	F	58	Thrombocytopenia, thyroiditis	Transient ischemic attack	Smoking	None
8	F	69	Sjögren's syndrome	Deep vein thrombosis	Surgery	None
9	F	29	Thrombocytopenia	Deep vein thrombosis	Pregnancy	Prophylactic heparin
10	F	51	Undifferentiated connective tissue disease	Myocardial infarction	Hypertension, Smoking	Low-dose aspirin
11	M	61	Thyroiditis, morphea	Deep vein thrombosis	None	None
12	F	58	Thrombocytopenia	Arterial thrombosis	HypercholesterolemiaSmoking	Low-dose aspirin
13	F	29	Systemic Lupus Erythematosus	Deep vein thrombosis	Diabetes	Low-dose aspirin
14	F	32	–	Deep vein thrombosis	Pregnancy	None

Table 4
Anti IgG/IgM aPS/PT antibodies, aPL profiles, thromboembolic risk factors and autoimmune disorders in the aPL carriers who did not develop thrombosis and in those become APS.

	aPL carriers (n 177) n (%)	aPL carriers become APS (n 14) n (%)	p value
IgG aPS/PT	33 (18.6)	7 (50)	0.015*
IgM aPS/PT	91 (51.4)	11 (78.6)	0.092
(IgG/IgM) aβ2GPI + (IgG/IgM) aCL + LAC	45 (25.4)	10 (71.4)	0.0008*
(IgG/IgM) aCL + LAC	10 (5.6)	1 (7.1)	0.715
(IgG/IgM) aβ2GPI + LAC	2 (1.1)	0	0.335
(IgG/IgM) aβ2GPI +(IgG/IgM) aCL	44 (24.8)	2 (14.3)	0.571
LAC	13 (7.3)	1 (7.1)	0.613
(IgG/IgM) aCL	31 (17.5)	0	0.182
(IgG/IgM) aβ2GPI	32 (18.1)	0	0.170
Thromboembolic risk factors	40 (22.6)	11 (78.6)	0.0000*
Autoimmune disorders	102 (57.6)	13 (92.9)	0.021*

Abbreviations: aPS/PT antiphosphatidylserine/prothrombin antibodies, aPL, antiphospholipid antibodies; aβ2GPI, anti-β2Glycoprotein I antibodies; aCL, anticardiolipin antibodies; LAC, lupus anticoagulants.

both triple aPL positivity and isolated LAC.

Fourteen of the aPL carriers (7.3%) experienced a first thrombotic event during the study period. The incidence rate of thrombosis was 1.4% patient-year. The clinical features, the genetic/acquired risk factors for thrombosis and the prophylaxis being used in the aPL carriers developing thrombosis are outlined in Table 3. While in Table 4 is indicated that the 14 aPL carriers developing thrombosis had triple aPL positivity in ten cases, double positivity in three and single positivity in one. The cumulative incidence rate of the thrombotic events was significantly higher in the IgG aPS/PT positive aPL carriers with respect to their negative counterparts (Fig. 1A), but there were no differences in the cumulative incidence rate of thrombotic events between the IgM positive and the IgM negative aPS/PT subjects (Fig. 1B). While there was a significantly higher prevalence of IgG aPS/PT antibodies in the aPL carriers who became APS patients, the same cannot be said for the IgM aPS/PT antibodies (Table 4). Triple aPL positivity and thromboembolic risk factors and autoimmune disorders also significantly prevailed in the aPL carriers who developed thrombotic events (Table 4).

The logistic analysis assessing the independent effect of IgG and IgM aPS/PT antibodies, triple aPL positivity, thrombosis risk factors and autoimmune disorders on thrombosis uncovered a significant association only for triple aPL positivity (OR: 4.725, 95% CI: 1.135–19.674, $p = 0.033$) and the thrombosis risk factors (OR: 12.451, 95% CI: 2.519–61.537, $p = 0.002$). Logistic regression analyzing the independent effect of IgG and IgM aPS/PT on thrombosis uncovered a significant result only for the former (OR: 3.962, 95% CI: 1.174–13.37, $p = 0.026$).

4. Discussion

There are several studies examining the usefulness of aPS/PT antibodies as biomarkers of vascular or obstetric risks in subjects fulfilling laboratory and clinical criteria for APS also of different ethnic groups [3,5,9]. However, to the best of our knowledge there are no studies concerning the clinical value of aPS/PT antibodies in aPL carriers without the clinical manifestations of APS.

The frequency of IgG aPS/PT antibodies in the aPL carriers studied here was lower than that of the IgM aPS/PT antibodies (20.9% *vs*

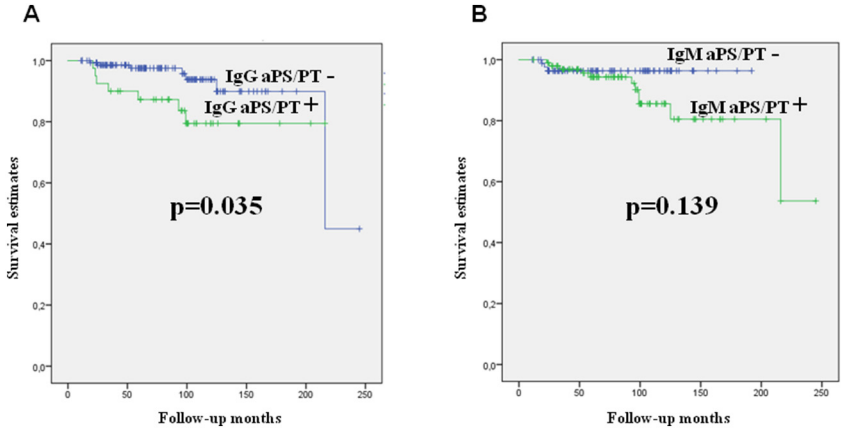

Fig. 1. Kaplan-Meier survival analysis and the log rank test revealed that the cumulative incidence of thromboembolic events was significantly higher in (A) the IgG antiphosphatidylserine/protrombin antibody positive carriers (IgG aPS/PT +) with respect the IgG antiphosphatidylserine/prothrombin antibody negative carriers (IgG aPS/PT -) but not in (B) the IgM antiphosphatidylserine/protrombin antibody positive carriers (IgM aPS/PT +) with respect the IgM antiphosphatidylserine/prothrombin antibody negative carriers (IgM aPS/PT -).

53.4%) but, as demonstrated by confirmation testing, both antibodies appeared stable over time. Both IgG and IgM aPS/PT were significantly associated to triple aPL positivity, which is considered a marker of clinical severity in APS [13,14]. This finding could contribute to identifying vascular risk in these "silent" aPL-positive cases. However, the prevalence of IgM aPS/PT was significantly higher even in the carriers who resulted positive for isolated LAC. Due to the low clinical value of isolated LAC both in APS patients and aPL carriers [15–17], this association reduces the clinical relevance of IgM aPS/PT antibodies in aPL carriers. This finding was confirmed by the significant association of IgG aPS/PT but not of IgM aPS/PT antibodies in the carriers who developed a first thrombotic event. Kaplan–Meier survival analysis also showed a significant cumulative incidence of thrombosis in the carriers testing positive for IgG but not for IgM aPS/PT antibodies. The significance of the high frequency of medium-high levels of IgM aPS/PT in aPL carriers remains currently unknown. Although, at least in part, it could be due to the high frequency (60.2%) in our aPL carriers of autoimmune disorders where in literature a higher prevalence of IgM with respect to IgG aPS/PT is described [3,8].

The univariate analysis showed in the aPL carriers a significant association with the first thrombotic event of IgG aPS/PT, triple aPL positivity, thromboembolic risk factors and autoimmune disorders. According to some studies, the logistic regression analysis results showed that only triple aPL positivity and acquired/genetic risk factors for thromboembolic events [15,18–19] are independent risk factors for thrombosis in aPL carriers, but when it was used to evaluate the independent effect of IgG and IgM aPS/PT for thrombosis, only the former resulted significant. Therefore, the addition of IgG aPS/PT antibodies to the other pro-thrombotic and pro-inflammatory risk factors could be a useful tool for a better risk assessment in aPL carriers and could thus suggest their detection. The association that was found between IgM aPS/PT antibodies and isolated LAC and the fact that their prevalence was not significant in aPL carriers developing thrombosis suggest that they could be useful in identifying aPL carriers at low risk for thrombosis

The study's limits are linked to the use of a non-standardized ELISA assay and the unavailability of reference sera. In fact, in the literature there is only one study comparing a homemade non-standardized ELISA method with a commercial kit and concludes that the commercial one is a reproducible and accurate test for the detection of aPS/PT antibodies, bringing also the advantage of shorter running times [20].The homogeneity of the study cohort, composed exclusively of aPL carriers prospectively monitored in a single centre over a long time period (81.1 mean months) and possessing an incidence rate of thrombosis similar to the one reported in the literature can be considered its strengths.

If these findings will be confirmed by other large-scale studies IgG aPS/PT antibodies could be included in the list of risk factors predictive of a first thrombotic event in aPL carriers. While IgM aPS/PT antibodies may be useful to identified aPL carriers at low-risk for thrombosis.

Author contributions

MT and AR designed the study, and co-wrote the manuscript. EM and MF collected the data. ES performed statistical data processing, MF, TDR, CA, and AH followed the patients. All authors checked and approved the version to be submitted.

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Conflict of interest notification

None of the authors have any conflicts to declare.

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