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The Potential of Antibodies Against the Phosphatidylserine/Prothrombin Complex as a Biomarker in Antiphospholipid Syndrome.

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Abstract

Introduction

Antibodies against the phosphatidylserine/prothrombin complex aPS/PT are autoantibodies recognizing an epitope formed in the phosphatidylserine/prothrombin complex as a result of conformational changes resulting from the combination and not present in any of the initial components of the complex. Its presence is predominantly observed in patients with thrombotic complications, particularly in those suffering from antiphospholipid syndrome (APS), systemic

lupus erythematosus (SLE), and other connective tissue disorders. The new epitope is clinically relevant, as it plays a role in the mechanism and effects of autoantibody binding to phospholipids and their cofactors. Testing for aPS/PT, in conjunction with other APS markers, is recommended to assess the risk of thrombotic events.

Purpose

The object of this review is to assess whether aPS/PT complex serves as an effective diagnostic marker in the pathogenesis of complications associated with APS and other connective tissue disorders.

Material and methods

This review evaluates data from medical databases such as PubMed, NCBI or BMJ using the search term 'aPS/PT'.

Conclusion

The presence of aPS/PT may be considered an independent risk factor for thrombosis. However, further research is needed to fully validate its clinical relevance in various clinical scenarios.

Keywords: Anti-phosphatidylserine/prothrombin complex antibodies; Antiphospholipid syndrome; Systemic Lupus Erythematosus, Lupus anticoagulant; Thrombosis.

List of Abbreviations:

- aPS/PT: Phosphatidylserine/prothrombin complex antibodies
- APS: Antiphospholipid syndrome
- LAC: Lupus anticoagulant
- APLAs: Antiphospholipid antibodies
- aCL: Anticardiolipin antibody
- aβ2GPI: Anti-β2-glycoprotein I antibody
- SLE: Systemic Lupus Erythematosus

Introduction

APS is an autoimmune disease driven by circulating autoantibodies that recognize cell surface phospholipids and phospholipid binding proteins. As a result of this autoimmune process, the patients are subjected to a higher risk of potential thrombotic events or pregnancy morbidity. Moreover, there is a risk of occurrence of other autoimmune and inflammatory complications [19]. In order to diagnose a patient with APS, APLAs are necessary, however, they have to coexist with thrombotic symptoms. Despite the definition, there are few cases of APS development without fulfilling diagnostic criteria. [14][32]. Originally laboratory criteria of APS "Classification Criteria" consisted of only aCL IgG/IgM and LAC [26]. In 2006, classification criteria were enhanced by presence of aβ2GPI IgG/IgM antibody due to the extension of the requirement of persistent presence to 12 weeks. [17].

Recent data has shown cases where patients present with typical clinical features of APS but lack persistent positivity for APLAs, leading to the inclusion of additional antibodies in the diagnostic process. As a result, the concept of seronegative APS (SNAPS) has gained recognition, notably through the work of researchers Hughes and Kamath. [28].

Manifestation of increased risk for thrombotic complications and pregnancy morbidities can be present in both SNAPS patients and classic APS patients. [20]. In rare instances, APS can progress to catastrophic antiphospholipid syndrome (CAPS), which involves widespread microvascular thrombosis and multi-organ failure, a life-threatening condition. [23][29].

Extensive research into anti-prothrombin antibodies has led to the discovery of the aPS/PT antibody complex as a significant target for aPL antibodies. Currently, aPS/PT antibodies are emerging as a promising marker for APS [8][16], and their inclusion in future diagnostic criteria may enhance the ability of healthcare providers to diagnose and manage patients suspected of having this condition.

Seropositive APS

APS is characterized by recurrent venous and/or arterial thromboembolic events or pregnancy morbidity. [8][24]. The presence of specific autoantibodies is essential. While the exact mechanism underlying these autoantibodies remains unclear, current research suggests they target particular phospholipid-binding proteins. Animal models have confirmed the

prothrombotic nature of these autoantibodies, and recent studies have offered valuable insights into potential prothrombotic pathways. [1]

Seronegative APS

SNAPS is often diagnosed when a patient shows clinical signs of APS, such as recurrent thrombosis, miscarriage, or unexplained thrombocytopenia, but repeatedly tests negative for standard antiphospholipid antibodies. Diagnosis is made by exclusion, after ruling out other causes of thrombosis, such as genetic thrombophilias or malignancy. [26]

Following the understanding of SNAPS, the risk of vascular and pregnancy complications in APS has been further explored. APS is strongly associated with thrombotic events, which can be venous, arterial, or microvascular. These complications contribute significantly to morbidity and mortality, highlighting the need for early and accurate diagnosis.

APS - vascular complications

The risk of vascular events in APS is enhanced. It may present as venous thromboembolism, arterial thromboembolism, particularly in younger individuals, and microvascular thrombosis. In case of those complications, further trials supporting the diagnosis are essential. A histopathologic examination is crucial for diagnosing microvascular thrombosis, and coexisting risk factors should be considered in the management of these patients. [7]

APS - pregnancy complications

Pregnancy-related complications include eclampsia, severe pre-eclampsia, by promoting placental insufficiency and endothelial dysfunction [7]

Pregnancy loss is common in the case of patients with APS, especially in the second or the third trimester. Genetic and chromosomal defects are the most common causes of early pregnancy loss (<10 weeks of gestation), however, they could happen in patients with APS. [10]. Clark et al demonstrated persistently positive lupus anticoagulants in 2.7% of women with

recurrent pregnancy loss.[9] In case of late gestational loss (>20 weeks), the association in a few studies tends to reach almost 10% of positivity of one or more APLAs, although this data is not sufficient. [9] According to the PROM-ISSE study the presence of LAC correlated with thromboembolism during pregnancy, ≥1 stillbirth (beyond 32 weeks), intrauterine growth retardation, and the HELLP syndrome, but not with ≥2 spontaneous abortions (≤12 weeks). [21]

Criteria of APS:

Clinical Criteria:

1. Vascular thrombosis, confirmed by imaging or histopathologic analysis, affecting any organ.
2. Pregnancy morbidity, including unexplained fetal death, premature birth due to eclampsia, or unexplained spontaneous abortion

Laboratory criteria:

1. Positive aCL IgG and/or IgM at medium to high titer (>40 GPL or MPL), or >99th percentile
2. Presence of LAC in plasma, detected on two or more occasions at least 12 weeks apart
3. Positive aβ2GPI in serum or plasma, at a titer >99th percentile

[26][35]

Seronegative APS antibodies

In cases of SNAPS, antibodies directed against other phospholipids, such as phosphatidylethanolamine (PE), phosphatidic acid (PA), and phosphatidylserine (PS), or proteins like vimentin and annexin, are implicated. The presence of aPS/PT antibodies is a potential marker for APS in seronegative cases. [28]

aPS/PT antibodies

Prothrombin is converted to thrombin by extrinsic thromboplastin during the second stage of blood clotting. [30]. There is a considerable amount of data, obtained from many retrospective studies, that gives unsettled evidence concerning the clinical significance of anti-prothrombin antibody (aPT). Thus, in a comparison between 106 subjects who experienced either a non-fatal myocardial infarction or cardiac death and 106 subjects without coronary disease, Vaarala *et al*. found that a high level of aPT (highest tertile of distribution) predicted a 2.5-fold increase in the risk of cardiovascular events. [33] On the other hand, Atsumi *et al*. did not find any correlation between clinical manifestation of aPT and APS in an evaluation of 265 APS patients. [2]. The existence of these discrepancies may be caused by differences in study design, population or measurement methods.

More recently, two prospective studies validated the role of aPT in predicting the first or recurrent risk of thrombosis in patients with APS. [6][15] Considering a group of 142 LAC positive patients, Forastiero *et al*. found a higher rate of thrombosis in patients with positive anti-PT compared with patients without anti-PT (8.6% *vs*. 3.5% per patient year). The highest incidence of thrombosis was detected in patients positive for both aβ2GPI and aPT. [18] Moreover, a 15-year longitudinal prospective study by Bizzaro *et al*. identified IgG aPT antibody as the most useful thrombosis predictor in SLE patients. [15] Another intriguing issue is represented by the different potential role of IgG/IgM aPS/PT compared to aPT. Indeed, a high correlation between APS classical antibody panel and aPS/PT IgG/IgM suggests that this marker may be useful in the evaluation of APS. [15].

The clinical significance of aPT and aPS/PT was evaluated by testing for the presence of these antibodies in 212 SLE patients and in 100 healthy individuals. Results show that aPT and aPS-PT were found in 47% of the patients (aPT in 31% and aPS-PT in 31%). Their presence did not correlate with that of aCL, aβ2GPI, LAC and/or anti-protein S. IgG but not IgM aPT were more frequently found in patients with thrombosis than in those without. IgG and IgM aPS-PT were also more frequent in patients with thrombosis (venous and/or arterial) than in those without. Levels of IgG aPT and IgG and IgM aPS-PT were higher in patients with thrombosis than in those without. More significantly, 48% of the patients with aPL-related clinical features who were negative for standard tests had aPT. [5].

Recently, the clinical significance of aPS/PT antibodies was prospectively evaluated in a cohort of 191 aPL carriers: [31].

IgG aPS/PT antibodies were detected in 40 (20.9%) and IgM aPS/PT in 102 (53.4%) of the carriers. 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. Similar results were obtained in a second study evaluating 152 patients with a previous thrombosis of whom 90 were SN-APS; 10% of SN-APS patients in this study were positive for aPS/PT. [3].

The association with recurrent early or late abortions and with premature delivery were observed in patients' aPS/PT positive, irrespectively of other aPLs. [22.] In a recent study, the presence of IgG and IgM aPS/PT was detected in 9 out of 17 affected by SN-APS. [27] Similarly, strong evidence was given by two retrospective studies on SN-APS patients. 50% of patients tested positive for aPS/PT in both. [13][36].

For example, a study was undertaken in a referral center in Mexico City. The aim was to determine the prevalence of aPS/PT with other aPLs, especially LAC, and thrombosis. According to the Sydney classification criteria and potential hematologic features, 96 patients with primary APS were recruited. Thrombosis was associated with aPS/PT IgG antibodies (87.7% vs. 61.1%, p=0.003) but not with aPS/PT IgM (73.6% vs. 81.8%, p=0.37). At the logistic regression analysis, the aPS/PT IgG antibodies remained associated with thrombosis after adjusting for all other aPL antibodies, odds ratio 8.6 95% CI 2.1 - 33.8, p=0.002. [4]

The relevance of aPS/PT as a risk factor for thrombosis was evaluated in Sudanese and Swedish patients with SLE. Various antibodies, including aPS/PT, aCL, and anti-β2GPI, as well as LAC in the Swedish cohort, were assessed, and carotid plaque diameters were measured. Sudanese SLE patients showed higher levels of IgM aPS/PT, but when using national cut-off values, the frequency of positivity was similar to that in Swedish patients across all isotypes. In the Swedish cohort, all isotypes of aPS/PT were associated with venous thromboembolism (VTE), while only IgA aPS/PT was linked to arterial thrombosis. aPS/PT antibodies were strongly associated with LAC and, independently, emerged as the best predictor for VTE. Double positivity for aPS/PT and anti-β2GPI was linked to a higher VTE risk than conventional triple positivity. Carotid plaque diameters showed no association with any antiphospholipid antibodies APLAs. [12].

Moreover, aPS/PT complexes and other non-criteria anti-phosholipid antibodies were compared between LAC-positive and negative as well as APS and non-APS patients. The study referred to 486 patientents tested for LAC and APLAs. In this trial there were 3 groups based on LAC and serology positivity: single-positives for LAC, aCL or aB2GPI; double-positives for aCL and aB2GPI; triple-positives for LAC, aCL and aB2GPI. As a result, based on APS diagnosis aPS/PT IgM indicated the highest area under the curve (AUC) (0.87; 0.79-0.95) compared to other APLAs. aPS/PT superiorly predicted the LAC presence and APS diagnosis. [16]

In another study, 186 Chinese patients with APS, 48 with SNAPS, 176 disease controls (79 SLE, 29 Sjogren's syndrome, 30 ankylosing spondylitis, 38 rheumatoid arthritis) and 90 healthy donors were examined. aPS/PT IgG and IgM, IgG/IgM/IgA aCL and IgG/IgM/IgA anti-β2-glycoprotein I (anti-β2GPI) antibodies were tested by ELISA. As a result, 86.0% of APS patients were positive for at least one aPS/PT isotype. 72.6% were positive for IgG aPS/PT, 66.7% positive for IgM aPS/PT, and 53.2% positive for both. Approximately half of the SNAPS patients were positive for IgG and/or IgM aPS/PT. Highly significant associations between IgG aPS/PT and venous thrombotic events (odds ratio = 6.72) and IgG/IgM aPS/PT and pregnancy loss (OR=9.44) were found. Levels of IgM aPS/PT were significantly different in APS patients with thrombotic manifestations and those with fetal loss (p=0.014). The association between IgG/IgM aPS/PT and LAC was significant (p<0.001). When both were positive, the OR for APS was 101.6. Notably, 91.95% (80/87) of LAC-positive specimens were positive for IgG and/or IgM aPS/PT, suggesting aPS/PT is an effective option when LAC testing is not available.

In essence, anti-PS/PT antibody assays demonstrated high diagnostic performance for Chinese patients with APS and some APS patients negative for criteria markers. [34]

In the next trial, 160 APS patients next to 128 seronegative patients were included. aPS/PT IgG were significantly associated with aCL IgG, anti-beta 2 GPI IgG and LAC (p<0,0001 for all). On the other hand, however, aPS/PT IgM were associated significantly only with LAC (p<0,0001). The correlation between IgG aPS/PT and both aCL IgG and anti-beta 2 GPI levels (p=0,42 and p=0,40 respectively. Both IgG and IgM aPS/PT were more frequent in triple than in double and in single positivity (p<0,0001). In conclusion, aPS/PT were independent risk factors for LAC. aPS/PT antibodies were found in 9,4% of the seronegative APS patients and 2% of healthy control (p=0,043). aPS/PT was significantly more frequent in cases affected by thrombosis, with respect to the pregnancy morbidity subset (p=0,01). [35]

In the subsequent trial, only IgA aPS/PT was identified as a thrombotic risk factor. The study involved 254 patients, including 91 with APS, 40 with APS secondary to SLE, 47 with SLE, 57 with rheumatoid arthritis, and 19 with Sjögren's syndrome. Among the participants, 55 experienced arterial thrombosis, 60 had venous thrombosis, and 54 faced obstetric complications. Statistical analysis revealed that IgA aPS/PT was significantly associated with both arterial thrombosis ($p=0.025$) and venous thrombosis ($p=0.002$), but no such association was found with obstetric complications ($p=0.0534$). Additionally, IgA aPS/PT showed a stronger correlation with LAC activity ($p<0.001$; odds ratio 4.7) compared to other antibodies. [36].

A recent metaanalysis attempted to reevaluate the prevalence of aPS/PT in patients with APS, especially in those who tested positive for LAC. According to PRISMA guidelines, a systematic search of PubMed, Web of Science, and the Cochrane Library from January 1990 to September 2021 was carried out. Proportions and 95% confidence intervals (CIs) were calculated using a random-effects model. Publication biases were evaluated via visualization of funnel plots along with Egger's and Begg's tests. [38]

It is worth mentioning that Begg’s and Egger’s tests are used to assess the relationship between observed treatment effects and their standard errors. A strong association suggests the presence of publication bias. [11]

In a recent retrospective study twenty-one articles about the prevalence of aPS/PT in 1853 patients were analyzed. Pooled prevalence of aPS/PT IgG alone, IgM alone, and IgG/M were 50.0%, 45.0%, and 65.0%, respectively. According to Egger's and Begg’s tests there was no significant publication bias detected. When the prevalence of aPS/PT was calculated in homogeneous aPLs, a much higher rate of pooled prevalence of aPS/PT IgG/M in patients positive for LAC (84.5%) and in those with triple positivity (83.4%) was found. This data provides us with information that proves a high rate of aPS/PT positivity in patients with APS, especially in those positive for LAC. [38]

A recent retrospective study analyzed 21 articles on the prevalence of aPS/PT in 1,853 patients. The pooled prevalence rates for aPS/PT IgG alone, IgM alone, and IgG/M were 50.0%, 45.0%, and 65.0%, respectively. No significant publication bias was detected according to Egger's and Begg’s tests. When the prevalence of aPS/PT was assessed in homogeneous aPLs, a much higher pooled prevalence was found for aPS/PT IgG/M in patients positive for LAC

(84.5%) and those with triple positivity (83.4%). This data highlights the high rate of aPS/PT positivity in patients with APS, particularly among those positive for LAC. [37]

In a more recent study, 95 primary APS patients, diagnosed according to the Sydney classification criteria, and patients with thrombocytopenia and/or hemolytic anemia who also met the serological APS criteria. Tests for aCL, anti-β2GP-I, aPS/PT (both IgG and IgM isotypes), and LAC were conducted. The $\chi 2$ test, Spearman's correlation coefficient, Mann-Whitney U test, and logistic regression were applied. Seventy-seven percent of patients had thrombosis, 50% experienced hematologic involvement, and 25% had obstetric events (non-exclusive groups). Twenty patients had only hematologic features. The prevalence of IgG and IgM aPS/PT was 61% and 60%, respectively. LAC-positive patients had a higher prevalence and higher titers of both IgG and IgM aPS/PT. aPS/PT was found to correlate with aPL antibodies, including LAC. A significant association was observed between IgG aPS/PT and thrombosis (OR 8.6 [95% CI 2.13-33.8, p = 0.002]), as well as pure hematologic features (OR 0.2, CI 95% 0.05-0.97, p = 0.004). These findings demonstrate a high prevalence and correlation of aPS/PT with other aPL antibodies, with IgG aPS/PT conferring a significant risk for thrombosis but not solely for hematologic involvement. [25]

The next study aimed to determine whether most high-risk thrombotic APS patients test positive for anti-β2-glycoprotein and aPS/PT. However, the precise impact of these antibodies on thrombin generation and activated protein C resistance (aPCr) remains insufficiently understood and often contradictory.

The study results revealed a significant anticoagulant effect of aPS/PT. When activated protein C (aPC) was introduced into the system, aPCr was notably increased in cases compared to controls for both anti-β2GPI and aPS/PT. However, this effect was significantly more pronounced with aPS/PT. Anti-β2GPI antibodies exhibited a mild anticoagulant and moderate procoagulant effect on thrombin generation, along with moderate aPC resistance. In contrast, aPS/PT antibodies demonstrated a strong anticoagulant effect, and a robust aPCr was observed. [29]

Conclusion

After considerable research and findings presented by multiple studies, there is efficient data to rate aPS/PT as a marker that may potentially be necessary to fully diagnose patients with APS and detect possible risk factors of this disease. However, clinical significance of aPS/PT should be further extensively explored, not only for research purposes, but also in order to rate it as a candidate for one of the enzyme-linked immunosorbent assay (ELISA)-based confirmatory tests for APS associated LAC. It is important to note that aPS/PT are in early stages of research. The influence of aPS/PT and its significance in patients from different ethnic groups is still unknown, but the diagnostic potential may be impactful in upcoming years. Therefore, aPS/PT antibodies may play a major role in future clinical trials and become a useful serological tool in the diagnosis and phenotypic characterization of APS patients. Moreover, further elaboration on diagnostic and therapeutic implications, as well as the unique role of aPS/PT, could strengthen its utility for clinicians and researchers.

Disclosure

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data in the study and is responsible for the integrity of the data and the accuracy of the data analysis.

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