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Antiphospholipid Syndrome – An Evolving Story of a Multisystemic Disease

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1. Introduction

Antiphospholipid syndrome (APS) is an autoimmune multisystemic disorder characterized clinically by recurrent thrombosis and pregnancy morbidity and serologically by the presence of antiphospholipid antibodies (aPL) including anticardiolipin (aCL) and anti-β2 glycoprotein I (anti-β2GPI) antibodies and lupus anticoagulant (LA) [1]. Historically, aPL antibodies were classified based on the clinical laboratory test in which they were detected, i.e. LA and aCL antibodies. It is now widely accepted that aPL antibodies are a heterogenous group of antibodies that react with a myriad of phospholipids (PLs), PL-protein complexes and PL binding proteins. The main antigenic target of these antibodies is recognized to be β2glycoprotein I (β2GPI), which along with prothrombin accounts for more than 90% of the antibody binding activity in APS patients. Other potentially significant antigenic targets include tissue plasminogen activator (tP/A), phosphatidylserine (PS), plasmin, annexin 2, activated protein C (APC), thrombin, antithrombin (AT) and annexin A5 [2,3].

In the general population, APS is the most common cause of acquired thrombophilia and is a recognized risk factor for the development of deep vein thrombosis (DVT) with or without pulmonary embolism, new strokes in individuals below the age of 50 and recurrent fetal loss [4]. The prevalence of DVT occurrence in the general population is estimated at 2-5%, 15 - 20% associated with APS, suggesting that the prevalence of venous thrombosis associated with APS may be as high as 0.3-1% of the general population [4]. APL antibodies are present in 30-40% of systemic lupus erythematosus (SLE) patients and up to a third of these patients (10-15% of SLE patients) have clinical manifestations of APS, especially venous or arterial thromboses [5,6].

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The APS related thrombotic events range in severity from the relatively benign superficial thrombophlebitis to myocardial infarction, stroke and catastrophic APS (CAPS) [7]. APS also accounts for a significant proportion of recurrent pregnancy loss in SLE patients, indeed, aPL are now regarded as the most frequent acquired risk for a treatable cause of recurrent pregnancy loss and for pregnancy complications (early and severe pre-eclampsia) [5,8].

The first description of aPL antibodies dates back to 1952, when Moore et al described patients suffering from SLE with a persistently false positive VDRL flocculation test for syphilis, a test based on the detection of antibodies against cardiolipin (CL) extracted from beef heart [7]. In the same year, Conley et al [8,9] described two SLE patients with a peculiar circulating inhibitor of coagulation [10]. These “anticoagulants” could inhibit in vitro coagulation assays, but did not influence the activity of coagulation factors and were not associated with a bleeding diathesis. Feinstein and Rapaport introduced the term LA to describe this phenomenon in 1972 [10]. Although the relation between thrombosis and the presence of these anticoagulants in SLE patients was already noticed in 1963 [11], it took until 1980 before the association between LA and thrombosis was widely recognized [12]. As LA was found to be associated with a persistently false positive syphilis test, this led to the development of an aCL immunoassay and the establishment of the association between thrombosis and aCL anticardiolipin [13]. From this time on, patients presenting with thrombosis and/or pregnancy loss in combination with persistently positive aCL antibodies and/or circulating LA were considered to have the APS [14,15]. Subsequently, patients with systemic lupus erythematosus (SLE) and related connective tissue diseases (CTD) that had abnormal LA tests, were labeled as ‘secondary’ APS (SAPS) in the presence of these conditions and ‘primary’ (PAPS) in their absence [16]. A study of patients with SLE showed that aCL positivity preceded the onset of a more severe form of SLE, as well as SLE complicated with thrombosis, pregnancy loss and thrombocytopenia [5]. However, studies have found no difference between PAPS and SAPS with respect to the clinical complications, the timing of those complications, the prognosis or frequency of positive aCL, LA or other autoantibody tests. In addition, management of PAPS and SAPS is the same and prognosis does not appear to differ [17].

2. Traditional and non-traditional manifestations of APS

APS is classically characterized by vascular thromboses or obstetric morbidity in association with the presence of aPL antibodies [1]. Vascular thromboses include venous thromboses resulting clinically in deep venous thrombosis and/or pulmonary emboli while arterial thromboses may present with ischemia affecting limbs, cerebral vascular accidents or transient ischemic attacks and small-vessel thrombosis may result in cutaneous ulceration [1,18]. Presence of thrombosis should be confirmed with a diagnostic angiogram, Doppler ultrasound, pulmonary scintigraphy, histopathology or computed tomography (CT) or magnetic resonance imaging (MRI) of the brain depending on the clinical context [1].

In a longitudinal cohort of patients with APS, transient ischemic attacks (TIA)s and cerebrovascular accidents (CVA)s were the most common thrombotic events occurring in 2.4% and 2.3% respectively of patients with established APS followed by pulmonary embolism and deep venous thrombosis over a period of 5 years [18]. Obstetric manifestations of APS include fetal loss with loss after 10 weeks of gestation being more strongly associated with APS, placental insufficiency potentially resulting in
decreased gestational weight or fetal distress and preterm delivery and development of pre-eclampsia and frank eclampsia [1]. Early pregnancy loss occurs in 17.1% and late pregnancy loss occurs in 6.7% of pregnancies in women with established APS while 35% of successful pregnancies were premature and 13.7% had intrauterine growth restriction [18].

Catastrophic APS (CAPS) is the rare but life-threatening development of wide-spread intravascular thrombosis seen in less than 1% of patients with APS [18-20]. Patients present acutely with multi-organ system failure, evidence of small vessel thrombosis and presence of positive aPL antibodies [19,20]. Death occurs in approximately 45% of patients during the acute event with primary causes being cerebral involvement, cardiac involvement, infections, multiorgan failure, pulmonary involvement and abdominal involvement [20]. Infection is the most common trigger identified in CAPS being present in approximately 20% of patients [20].

Patients with APS may also develop manifestations not included in the classification criteria. Neurologic symptoms other than strokes or TIAs including chorea, dementia, transverse myelitis, multiple sclerosis and epilepsy have been attributed to APS although studies are contradictory [1,18,21]. Livedo reticularis occurs more commonly in APS and may progress to livedo vasculitis with purpuric lesions, nodules and painful ulcerations [1,18,22]. Presence of livedo reticularis appears to carry an increased risk of arterial thrombosis, CVA and pregnancy loss [22].

Thrombocytopenia is the most common hematologic manifestation, occurring in over 30% of patients with APS [22]. Cardiac involvement frequently manifests as valvular disease with presence of mitral or tricuspid valve thickening or regurgitation and presence of valvular vegetations [19]. APS is also associated with a thrombotic microangiopathy of the renal arterioles and glomeruli known as APS nephropathy, which leads to hypertension, nephrotic range proteinuria, hematuria and progressive renal insufficiency [1].

3. Current diagnostic algorithms

a. “Criteria” aPL tests.

Current classification criteria for definite APS require the use of three “standardized” laboratory assays to detect aPL antibodies. These assays include aCL, both IgG and/or IgM by enzyme-linked immunoabsorbent assay (ELISA), the anti-β2GPI IgG and/or IgM by ELISA and the LA [1]. These tests, when positive, represent criteria for diagnosis when at least one of the two major clinical manifestations (thrombosis or pregnancy losses) is present according to the revised Sapporo criteria (Table 1).

Laboratory testing for aPL antibodies is one of the most problematic areas in the field of APS. The confirmation of diagnosis of the APS relies on laboratory tests, since clinical manifestations such as thrombosis and pregnancy losses may occur for many reasons not related to the presence of aPL antibodies. Most importantly, patients with APS who have experienced thrombosis and/or pregnancy losses need a specific therapy that is often lifelong and must be personalized, requiring careful monitoring of additional risk factors to prevent recurrences of APS manifestations. Given the potential serious side effects of anticoagulant therapy, a solid diagnosis is essential in planning management.
a) Lupus anticoagulant (LAC)  
Positive on two or more occasion at least 12 weeks apart, detected according to the guidelines of ISTH

b) Anticardiolipin (aCL) antibody  
Positive for IgG or IgM isotype in serum or plasma, present in medium and high titer on two or more occasions, at least 12 weeks apart, measured by standardized ELISA.

c) Anti-β2GPI antibody  
Positive for IgG or IgM isotype (in titer > the 99th percentile) on two or more occasions, at least 12 weeks apart measured by standardized ELISA


Table 1. Laboratory Criteria for APS (Revised Sapporo Criteria).

Although international consensus guidelines for the determination of LA have been published and revised, the existence of “standardized” tests for detection of aCL and anti-β2GPI has remained elusive. Furthermore, despite over 7000 publications related to the clinical use of aPL antibody tests, a consensus on clinical recommendations has been difficult to achieve. This difficulty appears related to sub-optimal design in clinical studies and a lack of laboratory standardization in areas such as the following: 1) units of measurement, 2) calibration curves, 3) determination of cut-off values, and 4) laboratories not performing the tests according to established guidelines. Significant inter-assay and inter-laboratory variation in the results of both aCL and anti-β2GPI testing still exists, affecting the consistency of the diagnosis of APS [23].

Over the years, international workshops have worked hard to standardize the laboratory test in this area. These workshops include the APL European forum, the Australasian Anticardiolipin Working Party (AAWP), the College of American Pathologists (CAP), the National External Quality Assessment Scheme (NEQAS), and the Standardization Subcommittee (SSC) on lupus anticoagulant and phospholipid-dependent antibodies of the International Society of Thrombosis and Hemostasis (ISTH). While some laboratories can obtain reliable testing results, there is still wide inter-laboratory variation despite all the efforts at standardization. This situation may result from laboratories performing aPL assays with their own protocols or using commercial kits that do not conform to the proposed guidelines for these tests. Furthermore, standardization of tests or re-evaluation of standardization is important since APS is related to serious complications like thrombosis and pregnancy loss; missing a diagnosis because of laboratory variability could have serious medical consequences. The use of semi- or fully-automated analyzers and commercial kits instead of in-house assays poses additional challenges to the process of standardization [23].

To address the challenges on aPL testing described above, an international “Criteria aPL Task Force” (Task Force) of researchers and scientific leaders in the field was formed prior to the 13th International Congress on Antiphospholipid Antibodies in Galveston, TX, April 2010 (APLA 2010). The “Criteria” aPL Task Force was further divided into three subgroups, which were charged by the APLA 2010 Congress Chair to address, in an evidence-based manner, various topics related to the testing of aCL, anti-β2GPI and LA. To accomplish its mission, the Criteria aPL Task Force considered published information, the results of a survey distributed among APLA 2010 congress attendees and the discussions that occurred during a special preconference workshop at APLA 2010. On the basis of this approach, the
Task Force reached several conclusions and proposed recommendations discussed below and summarized in Table 2; this information has recently been published [24-26].

### Table 2. “CRITERIA” aPL Task Force Recommendations.

b. “Non-Criteria” aPL Tests.

As indicated above, the revised classification criteria for the diagnosis of APS include the positivity of at least one of the three ‘Criteria’ aPL tests [1]. However, the use of these tests
may not guarantee full sensitivity and specificity to confirm a diagnosis of APS. In clinical practice, there are indeed many ‘false positives’ with aPL tests, especially the aCL ELISA, which can give positive results in clinical conditions besides APS; these conditions include infectious disease (i.e., syphilis), malignancy and other autoimmune diseases. On the other hand, there are patients with a clinical pattern strongly suggestive of APS, but persistently negative for ‘Criteria’ tests. In addition the “criteria” aPL tests may not identify the “pathogenic” subpopulations of aPL.

Several autoantibodies have been demonstrated to bind directly to negatively charged phospholipids other than CL (individually or as a phospholipid mixture) or to other proteins in the coagulation cascade (i.e., prothrombin and/or phosphatidylserine-prothrombin complexes); antibodies can also interfere with anticoagulant activity of the annexin A5. However, the clinical and diagnostic utility of these newly developed assays as well as their standardization requires much further study. In some cases, these new assays lack standardization and there are not international units of measurements.

A “Non-Criteria” aPL Task Force assembled prior to APLA 2010 was charged by the Congress Chair to address, in an evidence-based manner, the status of various new tests being developed for confirmation of diagnosis of APS. The results and recommendations of that task force have been recently published elsewhere [27].

4. Antigenic targets of antiphospholipid antibodies: Phospholipids and phospholipid binding proteins

As stated previously, aPL represent a heterogeneous group of antibodies with reactivity to not only PLs but also proteins, in particular those able to bind and form complexes with PLs [2]. Historically, serological activity against cardiolipin (CL) (Figure 1a), an anionic PL found in mitochondrial membranes, was one of the earliest key descriptive features of APS and although still important is overshadowed by β2GPI, which is now recognized as the main antigenic target of pathogenic aPL [2]. Indeed, β2GPI along with prothrombin (PT) account for more than 90% of the antibody binding activity in APS patients and it is unsurprising that antibodies against these 2 abundant proteins involved in hemostasis are most consistently associated with LA activity [28]. β2GPI consists of five contiguous domains (Figure 1b), the first proposed to be the binding site for pathogenic anti-β2GPI antibodies and the fifth the binding site for anionic and hydrophobic phospholipids such as phosphatidylserine (PS), lyso (bis) phosphatidic acid (LBPA), and CL exposed on cell surfaces and protein receptors [2,29]. The role that apoptosis plays in the exposure of these phospholipids on the cell surface and the subsequent interaction with β2GPI has been proposed as a possible mechanism for the production of pathogenic aPL in APS patients [30]. An interesting pathogenic role for oxidized low-density lipoprotein (ox-LDL)/β2GPI complexes bound by aPL in the initiation and progression of atherogenesis has been described [31,32].

Several models have been put forward for pathogenic anti-β2GPI Abs complexed with β2GPI activating monocytes, ECs, trophoblasts and platelets via simultaneous binding to PLs and candidate protein receptors to induce production of tissue factor and proinflammatory cytokines [33-36]. In vivo and in vitro studies have demonstrated the role of annexin A2 (AnnA2), in association with Toll-like receptor 4 (TLR4) and/or apolipoprotein ER2’
(ApoER2') that act as co-receptors containing intracellular signaling domains, in the activation of ECs, monocytes and cells of the decidua and trophoblast [37-39]. Candidate receptors on platelets include ApoER2' and the glycoprotein Ibα (GPIbα) subunit of the GPIb-IX-V receptor and Sikara et al have demonstrated a putative role for platelet factor 4 (PF4) in the stabilization and binding of dimeric β2GPI /anti-β2GPI complexes to platelet membranes [40,41].

Many serine proteases that function in maintaining hemostasis are targets of autoantigens in APS patients. These include activated protein C (APC), prothrombin, antithrombin (AT) and many coagulation factors including factors IXa, IIa and II [42]. There is evidence to suggest
that antibodies directed against AnnA5, an abundant cationic protein that functions as a natural anticoagulant especially in placental tissue, can cause placental thrombosis and fetal resorption in mice, although there is conflicting evidence of the significance of these antibodies in APS patients [43,44]. A recently described protein antigenic target, vimentin, has been suggested to play a putative role in platelet and leukocyte activation in APS patients but further characterization of the role of this cytoskeletal protein is necessary [45].

5. Origins of APS: Infection-associated APS and molecular mimicry

The failure of normal T cell tolerance mechanisms seems to be an important component for the development of autoimmunity in several diseases. In APS, there is evidence to suggest that molecular mimicry can induce production of pathogenic APL antibodies, presumably because of a breakdown in normal peripheral tolerance mechanisms [46]. Although aPL were first characterized by their ability to bind CL, it is now well accepted that these antibodies recognize various PL and protein antigenic complexes [1,2].

Indeed, efforts to induce high titer production of pathogenic aPL in animal models succeeded only after immunization with heterologous β2GPI rather than pure phospholipids [47]. This led researchers to believe that perhaps in vivo binding of foreign PL-binding proteins resembling β2GPI to self phospholipids in APS patients may lead to the formation of immunogenic complexes, against which aPL antibodies are produced. Gharavi et al in 1999 synthesized a 15 amino acid peptide, GDKV, which spanned an area of the fifth domain of β2GPI known to be a major PL-binding site of the molecule, and demonstrated the peptide’s ability to induce pathogenic aPL and anti-β2GPI antibody production in mice [48]. A monoclonal antibody with aPL and anti-β2GPI activity generated from these GDKV-immunized mice was shown to be pathogenic using in vivo models for thrombus enhancement and microcirculation [49]. The resulting search for candidate peptides in microorganisms that exhibited functional and sequence similarity to the PL-binding domain of β2GPI produced the peptides TIFI and VITT from cytomegalovirus (CMV), TADL from adenovirus (AdV) and SGDF from Bacillus subtilis. All these peptides had strong similarities with GDKV and induced high titers aPL and anti-β2GPI production in mice. Subsequent in vivo and in vitro experiments confirmed the pathogenicity of antibodies induced in TIFI-immunized mice [50-52].

Further supporting evidence for molecular mimicry as a possible mechanism for APS development was provided by a study evaluating the APS-related pathogenic potential of microorganisms carrying sequences related to a hexapeptide, TLRVYK, known to be specifically recognized by a pathogenic monoclonal anti-β2GPI Ab [53]. Following immunization with Haemophilus influenzae, Neisseria gonorrhoeae or tetanus toxoid; high titers of antibodies of anti-peptide (TLRVYK) and anti-β2GPI activity were observed in BALB/c mice. These affinity-purified antibodies were then infused into naive mice at day 0 of pregnancy. At day 15, these mice had significant thrombocytopenia, prolonged activated partial thromboplastin times (aPTT) and increased frequency of fetal loss compared to controls [53].

Infections are thought perhaps to be the most prominent environmental trigger for aPL production and APS development. Syphilis was the first infectious disease recognized to be linked to aPL production and this infectious type aPL is for the most part non-pathogenic
However, several subsequent reports have shown that many other infections not only trigger aPL production but are associated with APS manifestations as well [55,56]. CMV, parvovirus B19, Human immunodeficiency virus (HIV), Hepatitis B and C viruses, Human T-cell lymphoma/leukemia virus (HTLV) and Varicella Zoster Virus (VZV) are just a few of the infectious agents that have reported associations with aPL production and APS manifestations [56]. A recent study has demonstrated that protein H of Streptococcus pyogenes can bind β2GPI, inducing conformational changes, exposing hidden epitopes and in so doing then enable production of anti-β2GPI antibodies [57].

Rauch et al have recently put forward a hypothesis regarding the dual role of the innate immune system in the initiation and progression of APS based on their work. This hypothesis highlights the central part played by toll-like receptors (TLRs), especially TLR4, in inducing a break in tolerance, aPL production and epitope spread to several autoantigens [58]. Utilizing lupus prone mice treated with CMV derived peptides in the presence of TLR7 or TLR9 agonists and other lupus prone mice deficient in TLR7 or both TLR7 and TLR9, our group has demonstrated for the first time that both these TLRs are involved in aPL production in β2GPI immunized mice [59].

6. Genetics of APS

Animal models and family and population studies have been used to highlight genetic associations with APS disease characteristics and the occurrence of aPL antibodies in patients. In 1992 Hashimoto et al described an animal model of lupus associated APS in NZW x BXSB F1 (W/B F1) male mice that displayed spontaneous production of IgG aCL antibodies which exhibit co-factor (β2GPI) dependent binding to cardiolipin [60]. Interestingly, analysis of the genes utilized in the production of pathogenic aCL in these mice showed preferential usage of certain V_H (variable region of heavy immunoglobulin chain) and V_K (variable region of kappa light immunoglobulin chain) genes, whereas other non-pathogenic aCL utilize random V gene combinations possibly indicating that pathogenic aCL production in these mice is antigen driven rather than germline encoded [61]. Genome-wide analysis using microsatellite markers in these mice and their progeny revealed that the generation of each disease character was controlled by two independently segregating major dominant alleles producing full expression as a complementary gene action. Although there was complete genetic concordance between the occurrence of antiplatelet Abs and thrombocytopenia, other disease characteristics were independently controlled by different combinations of two dominant alleles suggesting that no single genetic factor can explain the pathogenesis of APS [62]. Papalardo et al have recently shown, using MHCII deficient mice and MHCII deficient mice transgenic for human MHCII haplotypes, that MHCII is necessary for producing aPL after immunization with β2GPI and certain haplotypes are more effective than others [63].

Since 1980, several studies have described families with high incidences of primary APS associated with LA, aCL and other autoantibodies [64-66]. The most consistent HLA associations in families with APS are HLA-DR4 and DRw53; other less consistent associations include DR7, DQw3, DQw7, A30, CW3 and B60 [67-70]. In non-familial population studies HLA-DR4 and DRw53 were also consistently associated with APS disease characteristics in addition to DR7 and DQB1*0302 [71-73].


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The antiphospholipid syndrome has been described for the first time by Graham Hughes in 1983 as a condition connected with thromboses or foetal losses and antiphospholipid antibodies presence. From that time there has been a great progress in knowledge, including antiphospholipid antibodies characterisation, their probable and also possible action, clinical manifestations, laboratory detection and treatment possibilities. This book provides a wide spectrum of clinical manifestations through Chapters written by well known researchers and clinicians with a great practical experience in management of diagnostics or treatment of antiphospholipid antibodies' presence.

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