

Editorial

The Antiphospholipid Syndrome

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Introduction

The antiphospholipid syndrome (APS) is an autoimmune thrombophilic condition characterized by the presence in blood of antibodies that recognize phospholipid-binding proteins. The clinical manifestation of APS include arterial and venous thromboembolic events and/or obstetric complications (especially recurrent fetal losses) [1,2]. The antiphospholipid antibodies (aPLA) associated with the disease include the lupus anticoagulant (LA), anti-cardiolipin (a-CL), and anti- β 2glycoprotein-I (a- β 2GP-I) [3]. APS and aPLA can occur in isolation (primary) or in association with systemic lupus erythematosus (secondary) [2]. The recognition of aPLA by endothelial cells (EC), monocyte and platelets is one of the pathogenic mechanisms contributing to APS. LA is clinically the most relevant among all aPLA tests. LA belongs to a group of autoantibodies direct against proteins with affinity for negatively charged phospholipid (PLs) [2]. The in vitro anticoagulant effect of LA is explained by the assumption that this antibody competes with clotting factors for anionic PLs [2]. Since β 2GP-I-dependent LAs are antibodies directed against β 2GP-I, such competition can only be explained by an increased affinity of β 2GP-I for PLs upon antibody binding to this protein [2]. Recently, two tests have been recommended by recent guidelines for LA detection: activated partial thromboplastin time (aPTT) and/or diluted prothrombin time (dRVVT) [4].

Antigenic targets and pathogenesis of APS

The main antigens are β 2-glycoprotein I (β 2-GPI) and prothrombin although a number of autoantibodies recognize other PL-binding proteins like protein C (PC), protein

S (PS), annexin V, complement factor H, high- and low- molecular-weight kininogen, prekallikrein, Factor IX, tissue factor pathway inhibitor (TFPI), Factor VII/VIIa [1]. There are "anticoagulant" surface-mediated processes with which aPLA are thought to interfere. One anticoagulant pathway involves PC activated by thrombin on endothelial thrombomodulin, and PS. Activated PC in association with PS cleaves factor Va and factor VIIIa on the PL surface and thereby inactivates the intrinsic tenase and prothrombinase reactions. Occupancy of the surface by immune complexes could impede these interactions and thereby promote coagulative activation [2]. Indeed, LAs can induce "activated protein C resistance". A second anticoagulant mechanism involves TFPI. This protein binds to negatively charged PL and to factor Xa on PL. This protein complex then links to the TF-factor VIIa complex, and shuts off further TF-mediated clotting. Occupancy of the PL surface by immune complexes may impede this interaction, leading to prolonged thrombin generation [2]. The a β 2-GPI autoantibodies bind to and activate EC, monocytes, and platelets and induce endothelial microparticles release [5,7,8]. Activation of these cells results in a shift toward a prothrombotic state. Toll like receptor 2 (TLR2) and TLR1 or TLR6, and CD14 contribute to monocyte activation of aPLA. In particular, TLR2, TLR1, and TLR6 are involved in aPLA recognition by human monocytes. The CD14-dependent internalization of TLR2 by aPLA in monocytes triggers NF- κ B activation inducing TF expression and upregulating TF activity [5,7,8]. Proteomic analysis has identified the vimentin (VIM) as a key antigen in the APS. VIM is an intermediate filament cytoskeletal protein, which is expressed by neutrophils, T cells, monocytes and EC. Anti-VIM/CL antibodies were found in 92% of patients with APS [8]. Other target proteins are

plasminogen activator inhibitor type-1 (PAI-1) linked to APS thrombogenesis. Immunoglobulin G isotype activates p38 mitogen-activated protein kinase (MAPK) causing the upregulation of TF activity and inducing the expression of vascular endothelial growth factor (VEGF) [8]. The α - β 2-GPI antibodies are associated with increased risk of thrombosis and are predominantly the IgG isotype, particularly IgG2 subclasses [5,6].

Diagnostic criteria for APS

The presence of aPLA alone does not constitute APS. Definitive APS is defined by the simultaneous presence of clinical and laboratory criteria as agreed upon International criteria for APS (Sapporo criteria) in 1998 and revised in 2006 [9] (Figure 1, [6] with permission). The clinical criteria are one or more objectively confirmed episodes of vascular thrombosis at any site and/or pregnancy morbidity defined as more than one unexplained death of a morphologically normal foetus, more than one premature birth of a morphologically normal neonate, or more than 3 unexplained consecutive spontaneous abortions before the 10th week of gestation [2,9]. The laboratory criteria are IgG and/or IgM aCL or α β 2-GPI or documentation of LA [9]. The laboratory abnormality must be present on two or more occasion at least 12 weeks apart [9] (Table 1, [1] with permission).

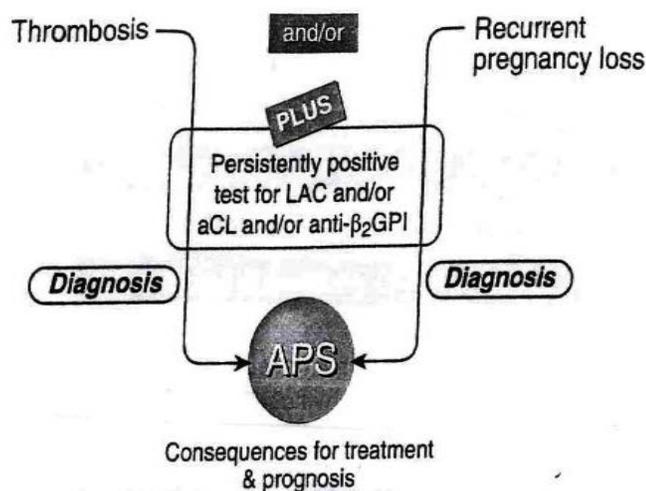


Figure 1. The updated classification criteria for APS.

Laboratory Diagnosis of aPLA

According to the last revision of the “Sapporo” laboratory criteria [10], the APS requires the presence of at least one of the three aPLA (i.e. LA, IgG and/or IgM aCL and IgG and/or IgM α β 2-GPI antibodies) [9]. The revised criteria provided details about the titres (> 40 GPL or MPL or $>$ the 99th percentile for aCL and $>$ the 99th percentile for α β 2-GPI) and the persistence in time (presence on at least two occasion at least 12

weeks apart) of the antibodies [9,11]. Interestingly, LA is the strongest risk factor for thrombosis and recurrent fetal loss whereas aCL antibodies show some significant associations only at high titres. The G rather than the M isotype is significantly associated with the clinical events for both aCL and α β 2-GPI antibodies [11]. It has been reported that “triple LA positivity”, defined by the presence of LA and high titres of aCL and α β 2-GPI antibodies, correlated with both thrombosis and pregnancy morbidity more strongly than single or double positivities [12].

Overview of the assays

The Lupus Anticoagulant/Phospholipid-Dependent Antibodies Subcommittee of the Scientific and Standardization Committee of the ISTH has recommended criteria for the diagnosis of LA [13]. The recommendation is to perform two different tests, such as the activated partial thromboplastin time (aPTT) and the dilute Russel’s viper venom time (dRVVT) [13]. The LA assay system chosen has to comply with the 3-step strategy defined in the International Society of Thrombosis and Haemostasis criteria [14] (a) Screening test: demonstration of the prolongation of a phospholipid-dependent clotting time beyond the upper limit of the reference interval; (b) Mixing test: confirmation of the presence of an inhibitor and the exclusion of a coagulation factor deficiency; and (c) Confirmation that the inhibitor is phospholipid-dependent and no directed against a specific coagulation factor. The mixing test involve combining the patient’s plasma with normal plasma (1:1) and assessing the influence of this procedure on clotting time, the theoretical underpinning being that if prolongation of clotting time is the result of a coagulation factor deficiency, it will correct to normal, whereas with LA, correction requires larger volumes of normal plasma [6,14]. Although ELISA-based methods were developed to detect aPLA, LA detected by coagulometric tests has been shown to be strongly associated with thrombosis [4]. There is growing belief that β 2-GPI-dependent aPLA are strongly associated with thrombosis [2,4]. For this reason, various attempts have been made to specifically detect β 2-GPI-dependent LAs. Two methods of β 2-GPI-dependent LA identification were described [15,16]. The α β 2-GPI antibodies may be divided into high and low avidity and the former is associated with thrombosis [6]. In the obstetric APS, testing positive on all 3 assays (LA, β 2-GPI, and CL-ELISAs) is associated with a greater risk for thrombosis [17,18].

Clinical management Scenarios

Several studies have shown an important risk of thrombosis relapse in APS [17,18]. The prevention and treatment of thrombosis in patients with established APS is low molecular weight heparin (LMWH) followed by long-term oral anticoagulation [2,1]. The Canadian study [20] and

the Warfarin in the Antiphospholipid Syndrome (WAPS) trial [21] established that the appropriate INR is 2.0 to 3.0 for thromboprophylaxis. High-intensity anticoagulation (INR 3.0-4.0) is recommended after the first arterial thromboembolic event, and in the recurrence of venous thrombosis [1]. There is significant debate regarding treatment of cerebrovascular events associated with aPLA, with some anticoagulating these patients as they would other patients with arterial or venous thrombosis, while others treat with aspirin alone [1].

therapy improves outcomes is of modest quality. The optimal doses for LMWH and ASA are 75 to 100 mg of ASA per day plus prophylactic-dose LMWH. For women with obstetric APS and no history of thrombosis, thromboprophylaxis during the postpartum period should be considered [23]. If a woman has APS and is anticoagulated for prior thrombosis, it is suggested switching to therapeutic-dose LMWH before six weeks gestation. Full-intensity anticoagulation is important during the pregnancy and the post partum period [23].

Table 1. Summary of the Sydney Consensus Statement on Investigation Classification Criteria for the APS[13].

Antiphospholipid antibody syndrome (APS) is present if at least one of the clinical criteria and one of the laboratory criteria that follow are met.

Clinical criteria

Vascular thromboses:

1. One or more documented episodes of arterial, venous, or small vessel thrombosis—other than superficial venous thrombosis—in any tissue or organ. Thrombosis must be confirmed by objective validated criteria. For histopathologic confirmation, thrombosis should be present without significant evidence of inflammation in the vessel wall.
2. Pregnancy morbidity
 - (a) One or more unexplained deaths of a morphologically normal fetus at or beyond the 10th week of gestation, with normal fetal morphology documented by ultrasound or by direct examination of the fetus, or
 - (b) One or more premature births of a morphologically normal neonate before the 34th week of gestation because of: (i) eclampsia or severe pre-eclampsia defined according to standard definitions, or (ii) recognized features of placental insufficiency, or
 - (c) Three or more unexplained consecutive spontaneous abortions before the 10th week of gestation, with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded.

In studies of populations of patients who have more than one type of pregnancy morbidity, investigators are strongly encouraged to stratify groups of subjects according to a, b, or c above.

Anticoagulant treatment is generally not sufficient to treat the catastrophic APS (CAPS), a form of the disorder that is marked by the disseminated macro and microvascular occlusions resulting in multi-organ failure [1]. CAPS, which occurs in less 1% of patients presenting APS, is defined by thrombotic occlusions in at least three organ/tissues occurring within a week (“thrombotic storm”), with laboratory confirmation of aPLA. Even with optimal treatment, the mortality rate is approximately 48%. Patients with CAPS generally require supplementing anticoagulant treatment with plasma-pheresis and immunosuppression. Treatment approaches have included intravenous IgG, corticosteroids, cyclophosphamide, and azathioprine. Rituximab has been tried in patients who have been refractory to other treatments [1].

For the pregnant women with APS, the American College of Chest Physicians (ACCP) [22] evidenced-based guidelines recommends low-dose aspirin (ASA) on confirmation of pregnancy [23,24]. The evidence that combined (LMWH+ASA)

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