Journal of Hematology & Thromboembolic Diseases

Forastiero, J Hematol Thromb Dis 2013, 1:4
http://dx.doi.org/10.4172/2329-8790.1000e103

Editorial Open Access

Trends in the Antiphospholipid Syndrome Criteria

Ricardo Forastiero*

Department of Physiology, Favaloro University, Division of Hematology, Thrombosis and Haemostasis, University Hospital, Favaloro Foundation, Buenos Aires, Argentina

The Antiphospholipid Syndrome (APS) is an autoimmune disease characterized clinically by the occurrence of either venous or arterial thrombosis in different vascular beds, and/or recurrent miscarriages in the first trimester, or fetal death in the second or third trimesters, or severe pre-eclampsia requiring delivery of a premature infant before 34 weeks of gestation. Cerebrovascular infarction is the most common clinical feature within the arterial circulation, whereas lower limb deep venous thrombosis and pulmonary embolism are the main locations within the venous circulation [1]. The detection of persistently elevated levels of antiphospholipid antibodies (aPL) is a requisite laboratory feature for the diagnosis of APS. The positivity for at least one aPL test: lupus anticoagulant (LA) by clotting assays and/or IgG/IgM anticardiolipin (aCL) and/ or IgG/IgM anti-β_2 glycoprotein I antibodies ($a\beta_2$GPI) by Enzyme-Linked Immunosorbent (ELISA) assays must be detected. aPL must be found on two or more occasions at least 12 weeks apart. In the 2006 updated APS criteria it is advised to classify APS patients in studies into one of the following categories: I, more than one laboratory criteria present (any combination); IIa, LA present alone; IIb, aCL present alone; IIc, $a\beta_2$GPI present alone [2].

aPL can occur in isolation or in association with other autoimmune conditions, particularly Systemic Lupus Erythematosus (SLE). The catastrophic APS is a rare variant of APS characterized by microthrombi in multiple organs. It is commonly triggered by several factors including infection, trauma, surgery, and the withdrawal of oral anticoagulation. Less than 1% of patients with the APS develop the catastrophic complication but it has a life-threatening clinical course. Sometimes aPL coagulopathy may start with a hemorrhagic syndrome when a severe thrombocytopenia, or an acquired thrombocytopathy, factor VIII inhibitor, or prothrombin deficiency is present.

According to the 2006 criteria for the classification of APS, a single positivity of any of the three aPL tests mentioned before fulfill the serologic criteria. More recently, however, several studies have shown that the risk of thrombosis increases with the number of positive tests in APS patients and also in asymptomatic carriers of persistent aPL. The concept of triple positivity (LA/aCL/$a\beta_2$GPI) conferring a higher risk for thromboembolic events and pregnancy losses has been proposed taking into account several retrospective and prospective studies. One recent study showed that this combination of aPL retrospectively increased the risk for thrombotic recurrences in patients without SLE [3]. With respect to thrombosis, triple aPL positivity conferred an odds ratio (OR) that ranges from 5.2 to 33.3. In contrast, none of the other combinations of aPL results reached statistical significance. A large, prospective multicentre study on triple aPL-positive APS patients reported a cumulative incidence of thrombosis of 12.2, 26.1, and 44.2% after 1, 5, and 10 years of follow-up, respectively [4]. In addition, it was reported that the annual incidence of the first thrombotic event was 5.3% per year among 104 triple aPL-positive patients with no history of thrombosis (aPL carriers) followed-up for a mean of 4.5 years [5]. Multivariate analysis also showed that male sex and other risk factors for VTE were independent predictors of a first thrombotic event. Thus, the likely occurrence of a first thrombotic event in carriers of a high-risk aPL-profile is considerable and is more frequent among male subjects and in the presence of additional risk factors for VTE. The risk of recurrent thrombosis is even higher in triple aPL-positive patients who were not on oral anticoagulation. Regarding obstetric complications, triple aPL positivity conferred an OR of 16.2 for late pregnancy loss and an OR of 34.4 for a subsequent pregnancy loss [6,7]. These findings reinforce the concept that patients with LA and the triple positive population have a more severe course of the disease. It is likely that the presence of triple positivity is due to antibodies directed against the Gly40-Arg43 epitope in the first domain of β_2GPI. At the present time, the detection of $a\beta_2$GPI-D1 seems to be a promising biomarker in diagnosis/risk assessment of APS, but more studies are needed to clearly define the clinical utility of its evaluation.

A number of studies have also suggested that testing for other aPL than those recommended in the last APS criteria may help to identify the syndrome. Among them, antibodies to prothrombin and the complex of prothrombin with phosphatidylserine (aPS/PT) have been proposed to be relevant to APS. In our prospective study in, 2005 [8] we showed that the triple positivity for LA, IgG $a\beta_2$GPI, and IgG antiprothrombin antibodies gave the highest annual rate of thrombosis (8.4%), that was statistically significant in multivariate analysis (OR, 2.6; 95% CI, 1.35-5.01). In a recent retrospective study, a large series of SLE patients was analyzed, and assessed the potential clinical usefulness of combining routinely tested aPL with new aPL specificities in an attempt to find a profile that will identify patients at higher risk of APS [9]. Among the 23 possible combinations of the six aPL tested, LA+$a\beta_2$GPI+aPS/PT had the best diagnostic accuracy for APS as a whole, and for both thrombosis and pregnancy loss. When comparing it to the combination suggested by the current criteria and all the other tested combinations, positivity for LA/$a\beta_2$GPI/aPS/PT had the best diagnostic performance in terms of specificity and predictive value in this SLE cohort.

Pengo et al. [10] proposed a modification of the categorization proposed in the last APS criteria, which takes into account the type (clotting tests or ELISA) and the number of positive assays:

a. Triple aPL positivity (positivity of LA, aCL, and $a\beta_2$GPI)

b. Double aCL and $a\beta_2$GPI positivity (in the absence of LA)

c. Single aPL positivity

Taken into account this increasing knowledge, it is now proposed that the definition of APS should include a different clinical risk to develop APS-related events:

1. definite APS in those patients with triple aPL positivity (high risk group).

2. probable APS in those patients with double aPL positivity (medium risk group).

3. non-APS in those patients with single aPL positivity (low risk group).

***Corresponding author:** Ricardo Forastiero, Hematologia, Universidad Favaloro, Solis 453, (C1078AAI) Buenos Aires, Argentina, Tel: +54 11 4378 1145; Fax: +54 11 4378 1349; E-mail: rforastiero@favaloro.edu.ar

Received July 25, 2013; **Accepted** July 27, 2013; **Published** July 29, 2013

Citation: Forastiero R (2013) Trends in the Antiphospholipid Syndrome Criteria. J Hematol Thromb Dis 1: e103 doi: 10.4172/2329-8790.1000e103

Likely this risk stratification would improve the clinical management of patients with aPL.

References

1. Wijetilleka S, Scoble T, Khamashta M (2012) Novel insights into pathogenesis, diagnosis and treatment of antiphospholipid syndrome. Curr Opin Rheumatol 24: 473-481.
2. Miyakis S, Lockshin MD, Atsumi T, Branch DW, Brey RL, et al. (2006) International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J Thromb Haemost 4: 295-306.
3. Hernández-Molina G, Espericueta-Arriola G, Cabral AR (2013) The role of lupus anticoagulant and triple marker positivity as risk factors for rethrombosis in patients with primary antiphospholipid syndrome. Clin Exp Rheumatol 31: 382-388.
4. Pengo V, Ruffatti A, Legnani C, Gresele P, Barcellona D, et al. (2010) Clinical course of high-risk patients diagnosed with antiphospholipid syndrome. J Thromb Haemost 8: 237-242.
5. Pengo V, Ruffatti A, Legnani C, Testa S, Fierro T, et al. (2011) Incidence of a first thromboembolic event in asymptomatic carriers of high-risk antiphospholipid antibody profile: a multicenter prospective study. Blood 118: 4714-4718.
6. Galli M (2012) Interpretation and recommended testing for antiphospholipid antibodies. Semin Thromb Hemost 38: 348-352.
7. Pengo V, Banzato A, Denas G, Jose SP, Bison E, et al. (2013) Correct laboratory approach to APS diagnosis and monitoring. Autoimmun Rev 12: 832-834.
8. Forastiero R, Martinuzzo M, Pombo G, Puente D, Rossi A, et al. (2005) A prospective study of antibodies to beta2-glycoprotein I and prothrombin, and risk of thrombosis. J Thromb Haemost 3: 1231-1238.
9. Sciascia S, Murru V, Sanna G, Roccatello D, Khamashta MA, et al. (2012) Clinical accuracy for diagnosis of antiphospholipid syndrome in systemic lupus erythematosus: evaluation of 23 possible combinations of antiphospholipid antibody specificities. J Thromb Haemost 10: 2512-2518.
10. Pengo V, Banzato A, Bison E, Denas G, Padayattil Jose S, et al. (2010) Antiphospholipid syndrome: critical analysis of the diagnostic path. Lupus 19: 428-431.

Citation: Forastiero R (2013) Trends in the Antiphospholipid Syndrome Criteria. J Hematol Thromb Dis 1: e103 doi: 10.4172/2329-8790.1000e103