Antibodies to phosphatidylserine/prothrombin complex and the antiphospholipid syndrome

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Antiphospholipid antibodies (aPL) are an heterogeneous family of immunoglobulins targeting phospholipid-binding plasma proteins or their complex with phospholipids [1]. In clinical practice, anticardiolipin antibodies (aCL), anti-β2 glycoprotein I (aβ2GPI) antibodies and the lupus anticoagulant (LA) have been the most established tests for the diagnosis of Antiphospholipid Syndrome (APS) [2].

The clinical relevance of aPL assays for autoantibodies other than the routinely used is currently under debate [3] and the utility of testing for new aPL specificities in identifying APS in patients with thrombosis and/or pregnancy morbidity, particularly in those who are repeatedly negative for the currently used tests is now being investigated [4]. Among the "so called" non-criteria aPL tests [5], antibodies to prothrombin have been proposed as potential marker to help in assessing the risk for both thrombosis and pregnancy morbidities in patients suspected of APS.

Antibodies to prothrombin can be detected by ELISA using prothrombin coated onto irradiated plates (aPT) or the phosphatidylserine/prothrombin complex as antigen (aPS/PT) and they have been both related with the clinical manifestation of APS [6, 7]. Current evidence supports the concept that they belong to distinct populations of autoantibodies. Nevertheless, they can both be detected simultaneously in one patient [8].

Clinical utility of aPS/PT in the diagnosis of APS

The association between APS and antibodies to prothrombin, detected either as aPT or aPS/PT, has been evaluated with conflicting results [9-14]. However, emerging evidence seems supporting the clinical utility of aPS/PT in the diagnosis of APS [15].

One of the first efforts aiming to clarify the clinical value of aPS/PT was done by Atsumi and co-workers [7]. They showed that the presence of aPS/PT conferred a

risk for APS of 3.6 in a cohort of 265 Japanese patients with systemic autoimmune diseases[7]. After these first observations, many reports have confirmed the association between aPS/PT and clinical manifestations of APS [4, 6, 15, 16].

Zigon et al [17]. reported that aPS/PT was the strongest independent risk factor for the presence of aPL-related obstetric complications in a cohort of 156 patients with systemic autoimmune diseases.

Sanfelippo et al [18] tested aPS/PT in large cohort of 728 patients suspected of having APS, in the absence of of aCL or anti-β2GPI. Of the tested samples, 41 had elevated levels of aPS/PT with thrombotic events occurring in 50% of the cases (11 out of the 22 patients with accessible medical histories). These results support the concept that testing for aPS/PT in patients negative for aCL, anti-β2GPI and the LA can contribute to the identification of APS in patients that may go otherwise undetected with current testing essays.

Data from our group also support the importance of aPS/PT as a diagnostic marker of APS [14]. We evaluated several possible aPL specificities combinations aiming to identify the profile with the best diagnostic accuracy for APS. This study included 230 SLE patients, all tested for six aPL derived in 23 possible combinations of results. The profile including LA + anti-β2GPI + aPS/PT held the best diagnostic accuracy for APS as a whole and, individually, for each thrombosis and pregnancy loss (OR 3.73 [95% CI 1.82-5.38]; OR 3.75 [95% CI 2.13-6.62] and OR 4.82 [95% CI 2.17-10.72], respectively) and the best specificity when compared with all the other attainable combination of tests, including the current classification criteria profile.

When systematically reviewing the topic analyzing data on more than 7000 patients and controls from 38 studies analyzing aPT and 10 studies analysing aPS/PT, our

group found that aPS/PT was associated with both arterial and/or venous thrombosis and this association is stronger for aPS/PT when compared to aPT (OR 5.11 [95%CI 4.2-6.3] vs. 1.82 [95%CI 1.44-2.75], respectively)[19].

Recently, three score systems have been formulated to quantify the risk of thrombosis/obstetric events in APS, aiming to help physicians to stratify patients according to risk [20-22]. Two of those scores included antibodies to aPS/PT among the variables computed when assessing the risk for thrombosis or pregnancy morbidity [21, 22]. Positivity for aPS/PT was found to be an important variable when assessing the risk by using the GAPSS, suggesting that the addition of these antibodies can help in predicting APS-related clinical manifestations risk.

A Task Force of worldwide scientists in the field recently met, discussed and analysed critical questions related to “criteria” and “non-criteria” aPL tests in an evidence-based manner during the 14th International Congress on Antiphospholipid Antibodies APLA 2013, September 18-21, Rio De Janeiro, Brazil). When aPS/PT were discussed, the depute sub-group concluded that a) testing for aPS/PT can contribute to assess the risk of thrombosis b) testing for aPS/PT can contribute to a better identification of patients with APS c) results (confirmed after multivariate analysis) do not substantially differ between groups, suggesting that aPS/PT are truly relevant in APS [23].

Taken all these data together, available evidence tends to support the importance of testing for aPS/PT in routine practise. However, some methodological issues appertaining to all aPL are still under debate as subject of concern. Future studies focusing on harmonization and standardization of tests used to detect aPS/PT are urgently needed. Potentially, the use of reference material for these,

as well as all aPL detection, will help to address many of the problems caused by a lack of standardization of aPL assays.

In conclusion, although some controversial data still exist, most of the available studies support the association between aPS/PT and the clinical manifestations of the APS. Many groups are currently working towards further characterisation of aPS/PT and their mechanisms of action, though, additional laboratory and clinical studies are needed to conclusively define the relevance and prognosis impact of testing for these antibodies in the daily routine clinical practise.

The possibility of aPS/PT becoming an additional serological classification criterion for APS is under debate, especially when considering how to identify APS patients negative for classical aPL.

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