

## Leading Article

# Antiphospholipid antibodies: which and when?

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Antiphospholipid antibodies (aPL) are a group of autoantibodies, mainly of the IgG and IgM class, directed predominantly against negatively charged phospholipids.<sup>1–4</sup> Several recent studies have found that patients with these antibodies are prone to repeated episodes of venous and arterial thrombosis, recurrent fetal loss, and thrombocytopenia.<sup>1,5</sup> In addition, there have been reports of the possible association of aPL with heart valve lesions,<sup>6</sup> haemolytic anaemia<sup>5,7</sup> and neurological events such as cerebrovascular accidents<sup>8</sup> and chorea.<sup>9</sup> Patients with these clinical and serological features have been defined as having the 'antiphospholipid syndrome'.<sup>10</sup>

However, in the clinical practice, two main questions remain to be elucidated for physicians. Firstly, which laboratory test is the best to detect aPL antibodies? Secondly, in which circumstances should these antibodies be sought?

With regard to the best technique, aPL may be detected by serological tests for syphilis (STS),<sup>11</sup> the lupus anticoagulant (LA) tests,<sup>12–14</sup> and the tests based on solid phase radioimmunoassay<sup>15</sup> or enzyme linked immunosorbent assay (ELISA)<sup>16,17</sup> using negatively charged phospholipids such as cardiolipin as antigen. STS rely on agglutination (e.g. VDRL) or complement fixation (e.g. Wasserman) assays to detect 'reagin',<sup>11</sup> the aPL present in syphilis. The LA tests depend on the ability of some groups of aPL to prolong phospholipid-dependent *in vitro* clotting tests, such as the activated partial thromboplastin time, the Russell viper venom clotting time and the prothrombin time determined using dilute thromboplastin.<sup>12–14</sup> Solid phase techniques have proved to be the most sensitive and reliable methods of detecting and measuring aPL.<sup>15–17</sup> Nevertheless, in our opinion, both LA tests and solid phase assay (e.g. ELISA) for anticardiolipin antibodies should be ordered, since in up to 20% of cases one may give a positive result but

not the other.<sup>18,19</sup> The detection of other negatively charged phospholipids, such as phosphatidylserine, phosphatidylinositol, and phosphatidic acid, gives little additional information.

In which clinical conditions should the determination of these antibodies be considered? Due to the wide spectrum of clinical manifestations related to these antibodies, this question remains unanswered. Nevertheless, the main indications may be as follows:

*Patients with systemic lupus erythematosus (SLE) and other autoimmune connective tissue disorders* SLE was the disease in which aPL were first studied in detail.<sup>20,21</sup> Subsequently, they have been found occasionally in other connective tissue disorders such as rheumatoid arthritis and vasculitis.<sup>4,22–24</sup> Their detection, particularly in moderate to high levels, could predict the development of the clinical manifestations previously described, namely venous and/or arterial thrombosis and fetal loss.<sup>25,26</sup> In addition, some authors have postulated that their early detection in patients with clinical manifestations suggesting SLE may constitute an alternative to the classical biological false positive STS in the American Rheumatism Association criteria for the classification of SLE.<sup>27,28</sup>

*Patients with recurrent fetal loss* The presence of aPL has been reported in up to 30% of an unselected population of women with repeated abortion.<sup>29,30</sup> The possibility, confirmed by several groups,<sup>31,32</sup> of attaining successful pregnancies with low-dose aspirin and/or prednisone therapy, has increased the interest for the detection of aPL in these women.

*Young patients with venous and arterial thrombosis* Preliminary studies have found aPL in up to 20% of young patients with venous and arterial thrombosis who do not suffer from SLE or any other well delineated autoimmune disorder. They have been defined as having a 'primary' antiphospholipid syndrome.<sup>33,34</sup> In addition, several authors have reported severe venous thrombosis after commencing

ing oral contraceptives in patients with aPL.<sup>35,36</sup> It would be wise to consider its determination in the screening of thrombotic risk factors in young women before contraceptive pills are prescribed.

**Patients with autoimmune thrombocytopenia** aPL have been found in patients with autoimmune thrombocytopenia associated with SLE and other connective tissue diseases.<sup>37</sup> In addition, they have been found in patients with clinical manifestations resembling idiopathic thrombocytopenic purpura<sup>38</sup> and thrombotic thrombocytopenic purpura.<sup>39</sup> It is possible that some of these patients will develop SLE during follow-up.

**Other associations** aPL have been reported in patients with many other conditions including

heart valve lesions,<sup>6</sup> chorea,<sup>9</sup> transverse myelopathy,<sup>40</sup> haemolytic anaemia,<sup>5,7</sup> neutropenia,<sup>5</sup> labile hypertension, toxæmia and a postpartum syndrome characterized by fever, pneumonitis, pleuritis, pulmonary infarctions and myocarditis.<sup>41</sup> Nevertheless, prospective studies involving a large number of patients are needed to assess if a significant relationship between these manifestations and aPL exists.

The description of the antiphospholipid syndrome appears to have linked rheumatology with a broad spectrum of medical disciplines, including gynaecology, neurology, and haematology, among others. The interactions between scientists from such disparate fields may prove useful to assess the full extent of this new and fascinating syndrome.

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