

Antiphospholipid syndrome

# Seronegative antiphospholipid syndrome

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History repeats itself

The antiphospholipid syndrome (APS; Hughes syndrome) is now 20 years old.<sup>1,2</sup> The clinical features are well defined, and include the tendency to both arterial *and* venous thrombosis, to recurrent miscarriages, and to occasional thrombocytopenia.

So too are the features which give the syndrome such a distinctive flavour, setting it apart from other coagulopathies—the severity of the headaches and migraine, the memory loss, the “atypical multiple sclerosis”, the prominence of the livedo reticularis, the heart valve involvement.<sup>3</sup>

Traditionally, raised levels of antiphospholipid antibodies (aPL), especially IgG aPL, are associated with the increased thrombotic risk characteristic of the syndrome. However, as always in real clinical practice, there are often discrepancies between antibody levels and clinical disease expression.

As awareness increases, and the number of patients with APS grows, it comes as no surprise that “seronegative APS” provides the focus of day to day clinical discussion—the patient with migraine, stroke, several previous miscarriages, thrombocytopenia, and livedo reticularis, whose aPL tests are doggedly negative.

Over half a century ago we grappled with “seronegative” rheumatoid arthritis. Then, with the era of antinuclear antibody testing came “seronegative lupus”. Both were clinical expressions of honesty, and both “seronegative” epithets served useful purposes.

What of “seronegative APS”. Three possibilities spring to mind. Firstly, the diagnosis may be wrong—the patient has a different coagulopathy. Secondly, it may be a “laboratory” problem; conventional testing failing to pick up cases with antibodies directed against different phospholipids or protein cofactors. Thirdly, it is conceivable that previously positive aPL tests have now reverted to negative.

A wrong clinical diagnosis is always the first consideration, although some cases, such as the example given here, hardly fit with any other known coagulopathy (or other diagnosis). Yet the example of Sneddon’s syndrome teaches us that there *are* some subjects with stroke and livedo who have persistently negative aPL tests.

Is conventional testing foolproof? Like all biological assays, there are large and well documented variations and pitfalls. Ever since the introduction of the first immunoassay for anticardiolipin antibodies (aCL) in 1983,<sup>4</sup> there has been close international collaboration, with regular standardisation exercises and workshops. It is universally recognised that the routine screening tests—the anticardiolipin and lupus anticoagulant, may miss some cases. Antibodies may be directed for example against other phospholipids such as phosphatidylethanolamine, or against components of the protein C pathway or annexin V. The discovery of  $\beta_2$ -glycoprotein I ( $\beta_2$ GPI) cofactor raised hopes that screening would become more comprehensive and that anti- $\beta_2$ GPI testing might pick up numbers of cases of APS negative by older tests. The experience has been disappointing, the extra yield of “seronegative” cases being small.<sup>5</sup>

Our own laboratory experience in testing a large cohort of patients with APS and lupus supports this. Cases of aCL negativity but with positive anti- $\beta_2$ GPI antibodies were exceptionally rare.<sup>6</sup> Neither was IgA aPL testing of significant extra help in these cases.<sup>7</sup>

Is it possible that previously positive aPL titres become negative—either acutely by “consumption” during an acute thrombotic episode, or slowly, over time. There is little reproducible evidence to suggest the former. Also, while in our longitudinal studies, mean aPL levels tend to drift down somewhat over the years (unpublished observations), acute changes are unusual.

Despite this, there are clinical cases of, for example, pulmonary hypertension, where a previous history of migraine or recurrent pregnancy loss has been supported by the finding of a false positive Venereal Disease Research Laboratory test in the old clinical charts.

The use of the term “seronegative APS” could be viewed as an inducement to clinical sloppiness. As a catch-all to embrace all those diagnostically suggestive cases who fail to meet classification criteria.<sup>8</sup> But diagnosis and classification are separate disciplines. The history of “seronegative RA” and “seronegative lupus” has provided useful lessons, and suggests a positive approach towards “seronegative APS”.

Clinical observation can still lead the way when it comes to defining disease groups, whatever the shortfalls of the laboratory support.

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