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J Rheumatol 2004;31;2099-2101
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Anticardiolipin Test and the Antiphospholipid (Hughes) Syndrome: 20 Years and Counting!

It has been 20 years since The Lancet published the first report on the anticardiolipin (aCL) test\(^1\) that identified a group of patients subject to recurrent arterial and/or venous thromboses and recurrent pregnancy losses (RPL). It spawned a wave of interest in what came to be known as the antiphospholipid syndrome (APS).

In the early 1980s, Graham Hughes and his team published a number of studies that showed an association of aCL with stroke, deep vein thrombosis, RPL, livedo, seizures, chorea, renal and liver vein thrombosis, thrombocytopenia, and pulmonary hypertension\(^2\). This was initially called the aCL syndrome, but as aCL were found to cross-react with other negatively charged phospholipids, it came to be known as the antiphospholipid (aPL) syndrome\(^3\). Hughes pointed out that the syndrome could occur in patients who did not have systemic lupus erythematosus, and introduced the term primary APS for non-lupus patients at the British Society for Rheumatology meeting in 1987. The interest this subject has generated has amazed even the most optimistic. Presentations on APS are now commonplace and draw large audiences at rheumatology, obstetrics/gynecology, hematology, neurology, and other meetings. APS is now said to be the most common cause of acquired thrombotic disorders and the commonest treatable cause of RPL.

The study of aPL has been full of surprises. In 1990, 2 groups found that most aPL did not only bind negatively charged phospholipids, but a serum protein termed \(\beta_2\)-glycoprotein I (\(\beta_2\)-GPI)\(^5,6\). This protein binds negatively charged phospholipids and is thought to be a natural anticoagulant. The finding led to speculation that aPL might promote thrombosis by interfering with the anticoagulant properties of \(\beta_2\)-GPI. Since 1990, subsets of these antibodies have been shown to bind a host of other serum proteins, including prothrombin. Hence, aPL comprise a family of autoantibodies specific for a variety of serum proteins and phospholipids. Even more intriguing is the demonstration by Gharavi and colleagues that immunization of mice with \(\beta_2\)-GPI generated both anti-\(\beta_2\)-GPI and aCL\(^7\). Subsequent studies showed that these mice were subject to enhanced thrombosis and fetal loss. As intriguing was the observation that bacterial and viral peptides homologous to amino acid sequences of \(\beta_2\)-GPI could induce aCL that also caused thrombosis, pregnancy loss, and presence of the LAC. In addition, the finding of aCL-positive patients with clinical complications who were LAC-negative illustrated the greater sensitivity of the new test in identifying these patients.

In 1984, Hughes and colleagues sponsored the first international meeting on aPL and since then, 10 meetings have been held entirely devoted to this subject in cities throughout the world, attracting hundreds of physicians and scientists. Presentations on APS are now commonplace and draw large audiences at rheumatology, obstetrics/gynecology, hematology, neurology, and other meetings. APS is now said to be the most common cause of acquired thrombotic disorders and the commonest treatable cause of RPL.

The study of APS is not without controversy. The standardization and interpretation of aCL and LAC test results remain contentious even after 20 years of investigation. These have been the subjects of more standardization workshops than any other autoantibody test. The aCL test is very sensitive and patients with a variety of disorders can have false-positive results. Patients with APS tend to have higher...
levels of the antibody (usually IgG) that persist for prolonged periods of time. To increase specificity for APS, it was reasoned that a measuring scale should be developed that would enable determination of aCL level by isotype (IgG, IgM, IgA). Utilizing a unique approach of mixing various quantities of positive and negative sera, a group of calibrators were developed from which aCL levels could be derived and results reported in specific units. Further and more specific tests for APS such as the anti-β2-GPI assay will probably also be limited by interlaboratory variations in results. Newer and more specific tests for APS such as the anti-β2-GPI assay will probably also be subject to interlaboratory variations, representing the general limitations of the ELISA itself and how it is performed.

Unique animal models have been developed that provide insights into pathogenesis and treatment of the disorder. Several studies have shown that these antibodies enhance thrombus formation, activate endothelial cells, and cause pregnancy loss in mice. A variety of causal mechanisms have been proposed suggesting that these antibodies might induce expression of intracellular adhesion molecules [intercellular adhesion molecule-1 (ICAM-1), vascular cell adhesion molecule-1, E- and P-selectin] on endothelial cells, and these would have a procoagulant effect. Of note, ICAM-1 and E- and P-selectin knockout mice are not subject to aPL-induced thrombosis. Investigators have also reported that aPL enhance platelet activation and aggregation in vitro. Recent publications have shown that complement activation (more specifically C3 and C5) is required in aPL-mediated platelet and endothelial cell activation and in the determination of the receptor involved in these processes. Understanding these mechanisms better may result in the use of less toxic agents.

There are still many unanswered basic and clinical questions about APS, including disease mechanisms at the molecular level and whether or not minor manifestations, such as livedo reticularis, are predictive of more serious complications. The next 20 years should be just as exciting as the last.

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REFERENCES