The human immune response is highly complex, dictated by incompletely understood genetic and environmental factors, and it appears to be important in contributing to several forms of cerebrovascular disease. Antiphospholipid-protein antibodies (aPL) have been implicated in immune-mediated clotting in both arterial and venous beds and are considered to be the most common hematological condition associated with ischemic stroke. However, given the vast number of conditions associated with aPL production, including systemic lupus erythematosus, HIV, syphilis, other infections, malignancy, immunizations, and medications, it is clear that aPL are quite a heterogeneous family of immunoglobulins that vary in specificity, isotype, subclass, titer, and associated mechanisms of action. aPL may also be seen in otherwise healthy individuals. Thus, there has been great difficulty in sorting out the potentially important aPL from the nonspecific immune system “noise.” A major breakthrough in the field came in 1990 when 3 groups identified the need for a cooperative phospholipid binding protein in order to detect most, but not all, aPL antibodies. Based on limited data, it has been suggested that infection-related aPL may be less pathogenic and that these aPL do not require a cofactor (apolipoprotein H, also called β2 glycoprotein-1 [β2GP1]) for their detection with ELISA. β2GP1 is a cationic plasma glycoprotein with a molecular mass of 50 kDa and a plasma concentration of ≈200 μg/mL. Cofactor-dependent aPL may allow identification of a more specific group of antibodies involved in thrombo-occlusive disease. These differences in aPL may also contribute to the lack of consistent data on their relationship to ischemic stroke (IS).

Two new, intriguing, and important pieces to the aPL puzzle appear in this issue of *Stroke*. Both articles attempt to tease out the more specific from the nonspecific aPL using a nested case-control study design. A prospective study using cofactor-dependent anticyclosporin antibodies (aCL) has shown that these antibodies are independently associated with incident stroke and myocardial infarction (MI). The other article suggests that infection-related aPL may be less pathogenic and that these aPL do not require a cofactor (apolipoprotein H, also called β2 glycoprotein-1 [β2GP1]) for their detection with ELISA. β2GP1 is a cationic plasma glycoprotein with a molecular mass of 50 kDa and a plasma concentration of ≈200 μg/mL. Cofactor-dependent aPL may allow identification of a more specific group of antibodies involved in thrombo-occlusive disease. These differences in aPL may also contribute to the lack of consistent data on their relationship to ischemic stroke (IS).

A clear strength of the study is the prospective nature and long follow-up period, yet changes in more classical risk factor status and aCL status over time (possibly a disproportionate prevalence in either group) may have affected the outcome of an ischemic event and/or diluted the effect of a less-potent risk factor such as aCL. Yet, why the impact of
aCL weakens with longer follow-up can only be speculated, as can the more pronounced risk of stroke with aCL in nonsmokers and more pronounced risk of MI with aCL in smokers. These points along with the lack of a dose response could call into question a strong cause-and-effect relationship.

A Novel Explanation: Hint of a Seasonal Effect

The other article that addresses potentially different types of aPL takes a novel approach—testing seasonal variability of aCL and antiphosphatidylserine antibodies (aPS). Again using a nested case-control study, aCL and aPS titers were obtained from 900 IS patients and >1000 controls over 7 years. Striking seasonal differences in the proportion of positive titers were found in controls, possibly mirroring the seasonality of certain infections. The authors suggest that the origins of aPL in individuals with and without IS may differ.

A major contributor to the increased odds of stroke in patients with aPL may be the lower frequency of aPL in controls during the summer months. Statistical “noise” (variance) due to increased production of nonpathogenic aPL may have reduced the potency of the relationship between aPL and stroke during the non-summer months.

One would expect both IS patients and controls to have similar frequencies of nonpathogenic aPL throughout the year. Thus, IS patients would be expected to have higher frequencies of aPL during the winter (nonpathogenic and pathogenic aPL) compared with the summer (only pathogenic aPL). However, this was not found in the study. Perhaps, the important trigger of pathogenic aPL occurs more commonly during the summer (and not the winter).

The stimuli that trigger aCL and aPS may not be identical (they are not perfectly concordant9), and there was no significant seasonal trend for aPS IgM (possibly due to a weaker power of subgroup analysis). A caveat is that these data were based on the month that the antibody was drawn, and there was no direct data on the seasonal infection rates in the week prior to IS. Perhaps, the more pronounced risk of stroke with aCL in thrombo-occlusive events.

References

2001: A Prospective, Seasonal Odyssey Into Antiphospholipid Protein Antibodies
Steven R. Levine and Bradley S. Jacobs

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The online version of this article, along with updated information and services, is located on the World Wide Web at:
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