Anticardiolipin antibodies and cerebral infarction

In the course of his comprehensive editorial on antiphospholipid antibodies and cerebral infarction, Greaves' recommendations on whom to test for lupus anticoagulant and anticardiolipin antibodies are incompatible with the evidence he cites.1 Our own findings regarding the relevance of anticardiolipin antibodies in a stroke population would also suggest that the advice to test all patients with stroke below the age of 50 years is no longer valid.

Anticardiolipin antibody assays are the only widely available laboratory assay of antiphospholipid antibody. Most published data on the influence of anticardiolipin antibodies on the risk of arterial or venous thrombosis have been retrospective and uncontrolled;2 prospective studies have been confined mainly to highly selected groups of patients—typically “young” patients (below an arbitrary age of 40-50 years), male:female ratio 1:2-5,24% were positive for IgG, 17% for IgM, and 28% for IgA. There was no significant overlap between isotype positivity: a total of 95% of patients described significant isotype titres to one or more isotypes. This contrasted with a control population in whom only 2% had mild elevation of IgG levels. There was no correlation between antibody titre and age for any isotype (IgG r = 0.26, IgM r = -0.05, IgA r = -0.10), and the mean ages of positive and negative groups did not differ significantly (unpaired r-test: IgG+ 67 years, IgG- 72 years, p = 0.07; IgM+ 66, IgM- 68, p = 0.68; IgA+ 67, IgA- 68, p = 0.46).

Significant findings of a high prevalence of elevated anticardiolipin titres and lack of correlation to age at any age have been reported by others testing unselected stroke populations.3 There is no evidence from unselected populations of a special association with thrombotic stroke in young people. Interpretation of retrospective data or series of highly selected patients as demonstrating such an association is inappropriate. No specific treatment can be recommended for patients found to have elevated antibody titres, because, again, all reported data are from highly selected or retrospective series.4

Elevated titres of anticardiolipin antibodies may be demonstrated in many conditions other than antiphospholipid syndrome: for example, following infection or immunisation, related to drug exposure, in non-thrombotic neurological conditions such as the Guillain-Barre syndrome, chronic liver disease, or in lymphoproliferative disorders. No mechanism whereby these antibodies could cause thrombosis has been convincingly demonstrated.5 There is also no convincing evidence to explain why antibodies of identical specificity should cause thromboses under some circumstances (patients with stroke) but not in others, such as in primary immunisation. As Greaves states, we are far from being able to assign causality to anticardiolipin antibodies. Given their apparently ubiquitous presence in disease states they may represent little more than a non-specific immune response to tissue damage. An attempt to treat patients with an elevated anticardiolipin titre with potent immunosuppressive therapy or anticoagulation is inappropriate given the lack of evidence that such elevation genuinely defines a distinct pathological entity.

The body of the editorial acknowledges the poverty of evidence in the field, yet recommends testing of all patients under the age of 50 for antiphospholipid antibodies. We believe that this policy will only serve to exacerbate the confusion with the interpretation and management of stroke patients in whom such antibodies are found: it may also lead to a false sense of security in achieving a "diagnosis" which in reality may not be more than the erroneous description of an epiphenomenon of the stroke itself.

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Dr Greaves replies: I am grateful to Muir and colleagues for giving me the opportunity to reiterate and clarify my views on the possible relationships between antiphospholipid antibodies (APA) and stroke, which has been the subject of confusion regarding the laboratory approach to the detection of APA, the nature of these antibodies, and their possible medical significance. Muir, Alwan, and Squire state that the “only widely available laboratory assay” for APA is the anticardiolipin assay. This is incorrect, and reliance on anticardiolipin assays alone may lead to more than the reasonable conclusions regarding the possible significance of APA. Screening for APA must include the use of at least two coagulation assays for lupus anticoagulant. Many subjects with APA, including some fulfilling the criteria for the diagnosis of the primary antiphospholipid syndrome, and others with systemic lupus erythematosus, only give positive results for APA in coagulation-based assays.7 The performance of the recommended tests, in particular the kaolin clotting time and the diluted Russell’s viper venom time and the kaolin clotting time is well within the capabilities of any haematology laboratory.8 National quality- control schemes have been developed, and the distribution of anticardiolipin titres in healthy subjects is non-parametric; without information regarding the composition of the control population and their choice of levels for the upper limit of normal, any interpretation of the results is meaningless.

Muir, Alwan, and Squire outline some results of their own anticardiolipin assays. They describe “significantly elevated” titres of APA in a high proportion of patients with lacunar stroke. They point out that the distribution of anticardiolipin titres in healthy subjects is non-parametric; without information regarding the composition of the control population and their choice of levels for the upper limit of normal, any interpretation of the results is meaningless. Furthermore the well-recognised requirement for the demonstration of persistence with time, of positive tests, is apparently ignored in this study. These considerations, together with the failure to use adequate laboratory methods, render the study of Muir, Alwan, and Squire unhelpful.

The pathogenicity of APA, Muir and colleagues comment that “there is also no convincing evidence to explain why antibodies of identical specificity should cause thrombosis”. The question of specificity has not been resolved, but to consider these antibodies as uniform in this regard is erroneous. The authors appear to be unaware of the considerable evidence that APA are reactive not with negatively charged phospholipid phosphatidyl serine, but with epitopes on proteins which are themselves avidly phospholipid bound.9 These include prothrombin, Fv-glycoprotein 1 and, probably, Protein S. It is now well recognised that these proteins is important in physiological haemostatic and anticoagulant mechanisms thus providing a clear potential link between ‘antiphospholipids’ and thrombo- sis. Despite these recent findings, it is acknowledged that causality has not been established. I refer Muir, Alwan and Squire to my supposition that APA may act as surrogates markers for other, as yet unidenti- fied, cytotoxic antibodies. For example, it has been conclusively demonstrated that serum samples from subjects with primary antiphospholipid syndrome and systemic lupus erythematosus often contain antibody reactive with vascular endothelial cells, as well as those apparently binding to cardiolipin.10 Muir, Alwan, and Squire claim a lack of evidence for a special association of APA with stroke and appear willing to dismiss a large body of evidence on this. For example Brey et al found APA in 46% of 46 unselected subjects under the age of 50 years, of age presenting with transient cerebral ischaemic attack or stroke, compared with 8% of 26 matched neurological cases without