MATTERS ARISING

Anticardiolipin antibodies and cerebral infarction

In the course of his comprehensive editorial on coagulation disorders 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 misplaced.

Anticardiolipin antibody assays are the only widely available laboratory assay of antiphospholipid antibody. Most published data on the influence of anticardiolipin antibodies in stroke have been retrospective and uncontrolled²; prospective studies have been confined mainly to highly selected groups of patients—typically “young” patients (below an arbitrary age of 40–50 years) after a first ever ischaemic stroke.³ Significantly elevated titres of immunoglobulin G or IgM anticardiolipin have been found in many cases, and it has been argued that the presence of antibodies is of pathogenetic importance, by means of causing a prothrombotic tendency.

We have screened consecutive, unselected admissions to an acute stroke unit for anticardiolipin antibodies of IgG, IgM or IgA isotype using a standardised in-house assay. Of 108 patients with confirmed stroke or transient ischaemic attack (TIA) on clinical or CT grounds (mean age 67 years, male:female ratio 1.25), 24% were positive for IgG, 17% for IgM, and 28% for IgA. There was no significant overlap between isotype positivity: a total of 53% of patients demonstrated significantly elevated 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 t -test: IgG + 67 years, IgG– 72 years, $p = 0.07$; IgM + 66, IgM– 68, $p = 0.68$; IgA + 67, IgA– 68, $p = 0.46$).

Similar findings of a high prevalence of elevated anticardiolipin titres and lack of relation to age have been reported by others testing unselected stroke populations.⁴ 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.⁵

Elevated titres of anticardiolipin antibodies may be demonstrated in many conditions unassociated with thrombosis—for example, following infection or immunisation, related to drug exposure, in non-thrombotic neurological conditions such as

the Guillain-Barré syndrome, chronic liver disease, or in lymphoproliferative disorders. No mechanism whereby these antibodies could cause thrombosis has been consistently demonstrable.⁶ There is also no convincing evidence to explain why antibodies of identical specificity should cause thrombosis under some circumstances (patients with stroke) but not in others, such as post-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 pathophysiological 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 existing problems 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 amount to little more than the description of an epiphenomenon of the stroke itself.

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- 3 Brey RL, Hart RG, Sherman DG, Tegeler CH. Antiphospholipid antibodies and cerebral ischaemia in young people. *Neurology* 1990;40:1190–6.
- 4 Chakravarty KK, Byron MA, Webley M, et al. Antibodies to cardiolipin in stroke: association with mortality and functional recovery in patients without systemic lupus erythematosus. *Q J Med* 1991;79:397–405.
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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. Their comments indicate a degree of confusion regarding the laboratory approach to the detection of APA, the nature of these antibodies, and their possible mechanisms of pathogenicity.

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 could lead to erroneous 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.¹ The performance of the recommended tests, in particular the kaolin cephalin clotting time, the dilute Russell’s viper venom time and the kaolin clotting time is well within the capabilities of any haematology laboratory.² National quality-control surveys have demonstrated that these assays are performed widely.^{2,3} Indeed some haematologists also supervise the performance of the solid phase assays for anticardiolipin, previously the province of immunology laboratories, in order to provide a full diagnostic screen for APA. As indicated in my editorial, such a comprehensive laboratory approach is essential for accurate diagnosis.

Muir, Alwan, and Squire outline some results of their own anticardiolipin assays. They describe “significantly elevated” titres of anticardiolipin in a high proportion of patients with stroke. It is well known 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 level for the upper limit of normal, the data described are uninterpretable. 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.

Regarding 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 primarily, but with epitopes on proteins which are themselves avidly phospholipid bound.^{4,5} These include prothrombin, β_2 -glycoprotein 1 and, probably, protein S. It is noteworthy that each of these proteins is important in physiological haemostatic and anticoagulant mechanisms thus providing a clear potential link between ‘antiphospholipids’ and thrombosis. 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 surrogate markers for other, as yet unidentified, 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.⁶

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.*⁷ found APA in 46% of 46 unselected subjects under 50 years of age presenting with transient cerebral ischaemic attack or stroke, compared with 8% of 26 matched neurological cases without