Editorial Comment

Chlamydia in Atherosclerosis

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Among the many theories of the pathogenesis of atherosclerosis has been a possible role for infection. However, the possibility that a viral infection initiates or perpetuates damage to the arterial wall has received less attention than other more widely recognized risk factors. Recently, a newly described Chlamydia species, Chlamydia pneumoniae, strain TWAR, has been associated with atherosclerosis in seroepidemiological studies. The Chlamydiae are classified as bacteria but grow only intracellularly. C. pneumoniae causes pneumonia, bronchitis, pharyngitis, and sinusitis and is transmitted from human to human via the respiratory tract. It does not cause sexually transmitted disease (Chlamydia trachomatis) or infect birds and lower mammals (Chlamydia psittaci).

See p 1130

There have now been several studies of an association of antibody against C. pneumoniae and cardiovascular disease (CVD). Saikku and colleagues first reported such an association when they compared 40 patients with acute myocardial infarction (MI) and 36 patients with chronic coronary artery disease (CAD) with 40 control subjects drawn from a population in Helsinki. They found both an increased frequency and elevated titers of microimmunofluorescence antibody in the IgG and IgA serum fractions against TWAR antigen in the patients. Antibody against the lipopolysaccharide (LPS) containing a Chlamydia antigen was found only in the MI patients. Subsequently, the Finnish investigators showed that immune complexes containing the LPS were found more frequently in 44 patients with MI than in 44 control subjects. They then extended their observation to a larger number of patients with sera collected before an MI through study of prospectively collected sera in the Helsinki Heart Study. This study was of hyperlipidemic persons treated with drug or placebo for cholesterol reduction over a 5-year period. Sera were tested from 105 persons who had cardiac endpoints (MI or sudden death) and time-matched control subjects from the study without such events. The sera that were tested included those drawn 3–6 months before the cardiac event. In this study, an association of disease and antibody was found for antibody in the IgA serum fraction (but not IgG) and for immune complexes containing Chlamydia LPS. The differences among the individual measurements were of borderline statistical significance, especially after adjustment for risk factors. However, when the presence of IgA antibody and/or immune complexes was used for comparison, a more highly significant association was found that was to an extent independent of other cardiac risk factors (smoking, hypertension, cholesterol).

The Finnish group’s paper in this issue of the journal extends the association of immune complexes to 46 patients with angiographically verified chronic CAD compared with random control subjects collected in Helsinki. However, in addition to finding more frequent immune complexes with Chlamydia LPS (41% versus 15%), they also dissociated circulating immune complexes and identified C. pneumoniae protein–specific antibody. The difference between cases and controls was of greater statistical significance for those with either one or both of the immune complexes (74% versus 24%). The antibody in the “protein-specific immune complexes” was shown to be specific for C. pneumoniae both in the serological test and by immunoblot. This adds another probable marker of C. pneumoniae infection to the others previously associated with CAD.

There have now been reports from other groups supporting the association of TWAR antibody and CVD. Thom and colleagues studied patients with angiographically determined CAD and compared their antibody status with persons with normal coronary arteries on angiogram and subsequently with normal population control subjects from the same health maintenance organization as the patients. Those studies showed a significant association of TWAR antibody in the microimmunofluorescence test in the IgG serum fraction with CAD. Melnick et al has presented data using sera from the Atherosclerosis Risk in Communities (ARIS) study, in which the cases were asymptomatic persons determined to have carotid wall thickening by ultrasound imaging and the control subjects were persons from the same study with normal carotid arteries. The persons with the carotid abnormalities more frequently had TWAR IgG antibody.

Although the antibody association with disease in each of these studies had odds ratios of ≥2.0, in some of the studies, the numbers of subjects were relatively small, and in most of the studies, design compromises were necessary. Except in their first study, the Finnish group did not find an association with antibody in the IgG serum fraction, but the association was present with antibody in the IgA fraction. The American studies did not measure IgA antibody. The Finnish group’s finding of the immune complex containing LPS and now...
TWAR protein–specific antibody has added another dimension to these seroepidemiological studies.

Can it be concluded from these studies that there is an association between infection with *Chlamydia pneumoniae*, strain TWAR, and CVD? The most impressive finding is that in different laboratories using different techniques and studying patients in different stages of CVD, there was always an association of antibody (or immune complexes) specific for *C. pneumoniae* with disease. The association of *Chlamydia* with CVD does not lack biological plausibility, because each of the *Chlamydia* species (*C. trachomatis*, *C. psittaci*, *C. pneumoniae*) has been found as the cause, albeit rarely, of myocarditis, pericarditis, and endocarditis.

The possibility of *C. pneumoniae* infection’s playing a role in the pathogenesis of atherosclerosis has received important additional support from the recent findings of A. Shor, C-C Kuo, and their colleagues. They have used morphological and molecular biological techniques to demonstrate the presence of *C. pneumoniae* organisms in atherosclerotic lesions of coronary arteries and aorta. One of the characteristics of the TWAR organism that differentiates it from the other *Chlamydia* species is a pear-shaped elementary body seen on electron microscopy.10 Shor et al11 observed structures in atheromatous lesions reminiscent of these pear-shaped elementary bodies. When sections from such lesions were examined by immunocytochemical stain with TWAR-specific monoclonal antibody, it was demonstrated that the TWAR organism was present in the atheroma. Subsequently, a total of 36 coronary arteries with atheroma were examined by both immunocytochemistry and the polymerase chain reaction for TWAR-specific DNA. The organism was demonstrated in 20 of the 36 specimens by one or both of the methods.12 The organisms were found in atheromatous lesions from early (fatty streaks) to late (fibrocalcific) stages but not in normal vessels of the same individuals or in persons without disease. The observation has been extended to lesions in aortas and to tissue removed at coronary atherectomy collected in Seattle.13,14 The organisms were found in both macrophages and smooth muscle cells.

*C. pneumoniae* was first described less than 10 years ago, and its role in acute respiratory infection is still being worked out. Data showing an association with atherosclerosis are intriguing and certainly indicate the need for vigorous investigation. However, there is as yet no basis for conclusions concerning a pathogenetic role for the organism in atherosclerosis.

References


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