Infection, Inflammation, and Atherosclerosis

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Only half of coronary artery disease,1,2 and half of carotid plaque measured by ultrasound,3 can be explained by the usual risk factors: age, sex, hypertension, hyperlipidemia, smoking, and diabetes. It is likely that much of unexplained atherosclerosis is genetic: a Swedish twin study showed that myocardial infarction below age 46 is almost entirely heritable.4 This suggests that few environmental factors remain to be discovered that would make a major contribution to atherosclerosis. Recently, the notion that infection may be important in atherosclerosis has been of interest.

A recent study has shown that C-reactive protein, a marker of inflammation, was a stronger predictor of cardiovascular events than was low-density lipoprotein cholesterol level.5 It has been postulated for more than a century that infection may be responsible for atherosclerosis;6 this issue has recently been reviewed by Fong.7 Organisms that have been implicated include Chlamydia pneumoniae, cytomegalovirus, Helicobacter pylori, and periodontal infections.

The mechanisms by which the association may be explained include increased coagulation,8,9 endothelial dysfunction,10 instability of plaque,11,12 and increased progression of atherosclerosis because of the influence of inflammation on plaque progression.13 In a rabbit model, infection accelerates atherosclerosis, and treatment with azithromycin prevents the effect.13

Growing evidence suggests that infection with C pneumoniae may be associated with increased risk of coronary events14–16 and more rapid restenosis after angioplasty.17 C pneumoniae has been identified in carotid endarterectomy specimens,18 and two studies have shown an association of Chlamydia antibody titers with stroke.19,20 Early studies of antibiotic treatment for C pneumoniae have shown mixed results.21–23

Evidence that C pneumoniae infection is associated with antigen mimicry of a heart muscle-specific protein24 has led to the hypothesis that perivascular inflammation around coronary arteries, caused by immune responses that have been misdirected against myocardial proteins, may explain the association of coronary artery disease and Chlamydia pneumoniae infection. This mechanism has been demonstrated in a rabbit model.25 If this is the case, Chlamydia pneumoniae infection may not predispose to carotid atherosclerosis or stroke.

Recently, Chiu et al12,18 have found evidence of multiple infections, including agents associated with periodontal infection (P gingivalis and S sanguis), in carotid endarterectomy specimens. In one study of 76 carotid endarterectomy specimens, they detected C pneumoniae in 71%, cytomegalovirus in 35.5%, and herpes simplex virus in 10.5% of specimens, versus none of 20 normal control carotid and aortic specimens obtained at autopsy. At least one organism was detected in 77.6% of the specimens, with a single organism present in only 46%; two organisms were present in 23.7% and all three in 7.9%. Plaques with thrombosis were more likely to have C pneumoniae (80.4%) or cytomegalovirus (57.8%) than were plaques without thrombosis (56.7% and 16.7%, respectively). Chiu12 found that organisms were localized in plaque shoulders and adjacent to apoptotic areas and were associated with plaque ulceration and thrombosis.

Singh et al26 recently found that a virulent strain of H pylori was associated with coronary events in the West of Scotland study cohort. Farsak et al27 found H pylori DNA in 37% of human endarterectomy specimens, but two other studies failed to find this organism in vascular tissues.28,29

Some of the relationship between infection and vascular disease may be genetic. Mannose binding lectin,30 a protein involved in immune defenses against infections including Chlamydia species,31–33 may be more common among patients with unexplained atherosclerosis.34 Hegele et al35 have shown that this polymorphism is associated with carotid plaque.

The strongest evidence for an association between infectious agents and cardiovascular disease is for C pneumoniae.7 Among more than 30 cross-sectional and retrospective studies, most show an association;36 however, a recent meta-analysis of 15 prospective studies found no significant association.37

In a condition with so many risk factors and genetic influences,38 it seems unlikely that infection will be the only or main cause of atherosclerosis and events. The role of these newly emerging risk factors or markers (such as C-reactive protein), and their relationship with “traditional” risk factors such as hypertension or lipids, remains unexplored. The uncertainty of their role and the types of infection or types of patients that should be treated must be explored in properly conducted, prospective studies.39 However, the findings to date are intriguing, and the hope that anti-infective therapy may reduce the burden of stroke is worth pursuing.
References

1. Futterman LG, Lemberg L. Fifty percent of patients with coronary artery disease do not have any of the conventional risk factors. Am J Cardiol. 1997;7:240–244.


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