Cytomegalovirus Infection and Coronary Heart Disease

To the Editor:

We read with great interest the article by Ridker et al reporting no positive association between baseline cytomegalovirus (CMV) and herpes simplex virus serum antibodies and incidence of myocardial infarction or stroke in the Physician’s Health Study. We agree with the authors that prospective epidemiological data are scarce, and this study fills an important gap. However, we must point out that their citation of our previous study2 together with other “cross-sectional or retrospective studies” is misleading. Ridker et al state that in these previous studies, “evidence of exposure to these viruses was ascertained after rather than before the development of atherosclerosis.”1 In fact, in our study, antibodies were measured in serum that was collected 13 to 16 years before carotid atherosclerosis was measured, even though this was done “retrospectively.” Thus, the temporal relation between exposure and outcome in our historical (“nonconcurrent”) cohort study is similar to that in a “concurrent” prospective design.

We believe that our finding of a strong association between baseline CMV antibodies and subclinical carotid atherosclerosis (in individuals free of clinical disease) is consistent with the speculation by Ridker et al that “herpetic infection might lead to accelerated atherosclerosis progression without necessarily increasing rates of clinical thrombosis.”1 Negative seroepidemiological studies of infections and atherosclerosis may be the result of dilution bias due to nondifferential misclassification. CMV antibodies are poorly correlated with the presence of CMV DNA in atheroma specimens.3 Thus, even though Ridker et al report good repeatability of their antibody measurements, dilution bias cannot be ruled out. Moreover, Ridker et al characterized CMV status as positive/negative, without quantitative titration. CMV antibodies (like atherosclerosis) are highly prevalent in adult populations, and a dichotomous characterization may not be sensitive enough to identify individuals truly at risk. In our study,2 as well as in other studies,4 the associations were strongest for high antibody titers, which may indicate frequent reactivations of latent CMV infection. These reactivations may be the culprit in the promotion of atherogenesis.

Finally, Ridker et al claim that the homogeneity of their study population (US physicians) reduces the possibility of residual confounding. Although this is probably true, it also limits the generalizability of their results. As discussed elsewhere,5 CMV and other infections may be atherogenic because of their synergistic effect with other cardiovascular risk factors. A study restricted to a low-risk population may not have the power to detect associations that are present (or stronger) in higher-risk populations.

Response

In our analysis of initially healthy middle-aged men, we found no evidence of association between IgG antibody titer directed against herpes simplex virus (HSV) or cytomegalovirus (CMV) and the future risk of developing myocardial infarction or stroke.1 Indeed, our data indicated a possible inverse relation between CMV and subsequent risk that was unexpected and that may well have been due to chance, because the direction of association was not compatible with the a priori hypothesis based on proposed biological mechanisms and prior data. While we reported viral status as either positive or negative in our article, additional analyses based on magnitude of titers had no impact on our null findings.

As we indicated in our Discussion, we concur with Nieto and colleagues that data concerning thrombotic events should not be construed to exclude a potential role for infection in atherogenesis. For example, in their excellent study, Nieto and colleagues2 reported a graded association between baseline CMV antibody titers and the subsequent risk of developing carotid intimal-medial thickening, a marker of subclinical atherosclerosis; we apologize for characterizing this prospective study among the retrospective and cross-sectional studies cited. It would thus be of considerable interest to know whether clinical events were also increased in this cohort in relation to CMV titer.

At the same time, we believe that our homogeneous study population provides a useful setting in which markers of infection and inflammation as risk factors for atherothrombosis can be detected. After all, it is within this same prospective population sample that several markers of inflammation, including C-reactive protein, soluble intercellular adhesion molecule-1, and fibrinogen, have all been found to predict coronary risk.3–5

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Circulation. 1999;100:e139
doi: 10.1161/01.CIR.100.25.e139

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