Unlikely Association between Clinically Apparent Herpesvirus Infection and Coronary Incidence at Older Ages

The Framingham Heart Study

Richard J. Havlik, William C. Blackwelder, Richard Kaslow, and William Castelli

Experimental studies in chickens have shown a relationship of a herpesvirus to atherosclerosis. The hypothesis of an association in humans was tested by using data on the history of cold sores and other manifestations of herpes infections reported by 658 male and 919 female participants (ages 58 to 89) in the Framingham Heart Study from 1977 to 1979 and on the prevalence and subsequent 6-year incidence of coronary heart disease (CHD). Approximately 40% of the men and 52% of the women reported a history of ever having "fever blisters or cold sores." Overall, there was no association between a history of such oropharyngeal manifestations and prevalent CHD. Only in the subgroup of women with recurrent infections was there a suggestion of a possible relationship (relative risk = 1.5, 95% confidence interval 1.0 to 2.1). Among members of the cohort without CHD at baseline there was no association between the history of cold sores, chicken pox, shingles, or infectious mononucleosls and 6-year CHD incidence. However, a possible interaction among women with recurrent herpes, lower levels of serum cholesterol, and incidence of angina pectoris without myocardial infarction was suggested in post hoc analyses. These data from the Framingham cohort do not support the notion that any self-reported clinically manifest herpesvirus infection has a strong etiological role in older persons, but they do raise issues to be addressed in any further research. (Arteriosclerosis 9:877-880, November/December 1989)

Among the 246 possible causes of atherosclerosis summarized by Hopkins and Williams, viroemia, but not specifically herpesvirus infection, is mentioned as a suggested risk factor for coronary heart disease (CHD). During the past 15 years there have been reports of other viruses associated with atherosclerosis, and a report of the specific relationship between one type of herpesvirus in chickens and atherosclerosis appeared in 1978. The herpesvirus of Marek's disease was inoculated in young chickens with or without the addition of an elevated cholesterol diet; these were compared with control chickens given normal feed or a cholesterol-enriched diet. Chickens with combined virus inoculation and cholesterol feeding showed the greatest number of atherosclerotic lesions. These findings prompted the editorial comment, "Surprisingly, there seems to be a great lack of epidemiological data on infections in relation to CHD and this might be a profitable area of study." More recently there have been further animal experiments and a relevant epidemiological study. In the latter study the prevalence of cytomegalovirus antibodies was higher in cardiovascular surgery patients than in controls, but the prevalence of other herpesvirus antibodies was not different in the two groups.

In 1977, investigators at the National Institute of Allergy and Infectious Diseases began to explore the relationships of HLA types and clinical expressions of certain herpes infections through a special study in the Framingham population. Using specific data collected for that study on the history of manifest oral/labial herpes simplex virus type (HSV-1) and other herpes infections on approximately 1600 participants, along with routine data for ascertainment of CHD, we searched for a possible association between a history of herpes infections and the prevalence and incidence of CHD.

Methods

Population

The Framingham Heart Study is a longitudinal investigation of risk factors for cardiovascular and other diseases. It has been in operation since 1948 and is based in Framingham, Massachusetts. Biennial examinations are performed on the cohort, which originally numbered 5209. At the time of the 15th round of examinations, occurring primarily during the period between 1977 and 1979, a questionnaire was administered to approximately 1600 participants who were ages 58 to 89 as part of a study of the potential relationship of herpesvirus infections to HLA...
types. At the time of the examination, blood pressure, cholesterol level, and smoking history were ascertained. Titers of antibodies to HSV-1, HSV-2, varicella-zoster virus, and cytomegalovirus were determined for 402 persons. At each examination, the individual participants was followed for the onset of CHD, either fatal or nonfatal, during the subsequent 6 years.

**Questionnaire**

The participants were asked questions on their history of herpes labialis (fever blisters or cold sores), whether the lesions were recurrent, and how often they occurred. Questions on a history of zoster (shingles), varicella (chickenpox), and infectious mononucleosis were also asked.

**Statistics**

We compared CHD prevalence and incidence rates for those with and those without a history of herpesvirus infection including the subset with recurrent manifestations by using relative risks (RRs) and 95% confidence intervals. To adjust simultaneously for the possible influences of age, blood pressure, cholesterol level, and smoking, we used the logistic regression model and estimated coefficients by the method of Walker and Duncan. In addition, we did further analyses which stratified on the type of CHD endpoint and the serum cholesterol levels.

**Results**

Of the total of 1657 persons ages 58 to 89, 1024 were 58 to 69 years old, 450 were 70 to 79 years old, and 183 were 80 to 89 years old. The proportion of women increased in the three age groups: 55%, 61%, and 66%, respectively.

A total of 265 of 658 men (40%) and 481 of 919 women (52%) reported a history of fever blisters or cold sores. Among the 746 persons reporting such a history, 116 (15.5%) reported a history of fever blisters or cold sores. The same proportion (15.5%) of the 831 participants with no history of CHD at the time of Examination 15. The same proportion (15.5%) of the 831 participants with no history of blisters or cold sores had CHD (Table 1).

Among the 301 women reporting recurrent cold sores, 50 (16.6%) had CHD at the time of Examination 15, compared to 49 of 438 (11.2%) with no history of cold sores (relative risk = 1.5, 95% confidence interval 1.0 to 2.1). Information on recurrences was unavailable for three men and three women. Differences in age and other CHD risk factors (cholesterol, blood pressure, and smoking) did not explain the relationship. In contrast, the proportion of men with prevalent CHD was somewhat lower in those reporting recurrent cold sores than in those with no history. When the analysis was limited to those with the onset of nonfatal disease at or before 50 years of age, CHD prevalence results were similar for those with and those without a cold sore history (data not shown).

### Table 1. Recurrence of Cold Sores and Coronary Heart Disease Prevalence in Framingham

<table>
<thead>
<tr>
<th>Coronary heart disease prevalence at exam 15</th>
<th>History of cold sores or recurrence</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Any history (Recurrent)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td></td>
<td>129</td>
<td>116</td>
<td>245</td>
</tr>
<tr>
<td>No</td>
<td></td>
<td>702</td>
<td>630</td>
<td>1332</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>831</td>
<td>746</td>
<td>1577</td>
</tr>
</tbody>
</table>

### Table 2. Recurrence of Cold Sores and Coronary Heart Disease Prevalence in Framingham

<table>
<thead>
<tr>
<th>Coronary heart disease incidence at exam 15</th>
<th>History of cold sores or recurrence</th>
<th>Males</th>
<th>Females</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>Any history (Recurrent)*</td>
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<td></td>
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<tr>
<td>Yes</td>
<td></td>
<td>64</td>
<td>60</td>
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<tr>
<td>No</td>
<td></td>
<td>638</td>
<td>570</td>
<td>1208</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>702</td>
<td>630</td>
<td>1332</td>
</tr>
</tbody>
</table>

*The "Recurrent" group is a subset of the "Any history" group.

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There was no association between a history of fever blisters or cold sores, whether recurrent or not, and 6-year CHD incidence in either women or men (Table 2). The CHD rate in those with a history of cold sores was 9.5% compared to 9.1% for those with no such history. Stratification by recurrence in the last year or by age 70 and over did not materially alter the results. However, stratification by serum cholesterol level (less than or equal to 240 mg/dl) suggested a possible interaction. The relative risk for CHD incidence in women with the lower cholesterol level and recurrent cold sores was 2.3 (95% confidence interval 0.9 to 5.9). When the endpoint, angina pectoris without myocardial infarction, was selected from the total CHD endpoints, the relative risk was 5.2 (95% confidence interval 1.1 to 24.7).

We found no association of other clinically apparent herpesvirus infections (shingles, chicken pox, or infectious mononucleosis) with CHD prevalence or incidence (data not shown). Only 167 of 1603 persons reported having had shingles, and 13 of 1612 persons reported having had mononucleosis. The number who reported having had chicken pox was substantial (662 of 1135), but there were many unknowns. Incidence rates for both men and women combined for those with and without a baseline history of shingles were 8.9% compared to 9.2% (RR = 1.0, 95% confidence interval 0.5 to 1.7); for a baseline history of chicken pox, 8.6% and 9.6%, respectively (RR = 0.9, 95% confidence interval 0.6 to 1.3); and for a baseline history of mononucleosis, 8.3% versus 9.2%, respectively (RR = 0.9, 95% confidence interval 0.1 to 5.9).

Discussion

An attempt was made to demonstrate an association between self-reported clinical manifestations of HSV-1 infection and CHD in a human population-based study. Although prevalence data at baseline showed a cross-sectional relationship in a subgroup of women, no consistent prospective relationship was found for either gender in this group of older persons in Framingham. The older age structure of the population precluded considering issues related to the initiation of disease in a younger population.

Various analytic approaches were used to discover relationships that may have been less obvious. At baseline, questions were asked about recurrences and about the frequency of such recurrences. Since the pathogenesis of arterial lesions in chickens depended on active viral infection, the human subgroup with recurrent activity might have been expected to be at greatest risk. Other than the modest association between CHD prevalence and reported recurrent disease in women, there was no indication of an association between risk of CHD and recurrent HSV-1 infection. However, stratification by risk of cholesterol level and use of various CHD endpoints did sometimes give “significant” results. However, such subgroup analyses done in a post hoc manner could result in spurious findings. 13

The presence of an apparent relationship between recurrent HSV-1 infection in women only and the prevalence, but not incidence, of CHD is not easily explained. There is no a priori reason why any association should be limited to either men or women, although women may have a higher frequency of HSV-1 infection. However, if a different physiologic or emotional response to stress in women generally leads to a different clinical expression of HSV-1 infection, then recurrent exacerbations of herpesvirus infection in women may have been a consequence, rather than an etiological factor, in the development of CHD. In Framingham, most of the CHD, even in older women, took the form of angina pectoris. 10 Perhaps the reaction to the recurrent chest pain accounted for recurrent expression of HSV-1. More extensive information on the timing of recurrence and CHD status would be necessary to test such an explanation.

Only clinical measures and endpoints were used in this study. We may have missed an association with clinically inapparent, but biologically important, infection. It is worth noting that data from this population have previously demonstrated a clear association between a positive history of cold sores and higher antibody titers to HSV-1; approximately 90% (190 of 211) of participants with a positive history also had detectable titers to HSV-1. Furthermore, there was a dose-response relationship, i.e., those reporting more frequent recurrence of cold sores had higher geometric mean titers. 9 Nevertheless, a relationship might be more readily recognized by distinguishing serologically or virologically between infected and uninfected persons and by documenting CHD with pathologic and angiographic data. For example, in one such study, herpesvirus probes were used on specimens of aortic wall taken from patients undergoing coronary bypass surgery. 7 The herpes simplex viral mRNA was found in some of the specimens. There was no evidence for the presence of other herpes-like viruses from hybridization studies with either cytomegalovirus or the Epstein-Barr viral probes. However, in another study, cytomegalovirus antigen was evident within arterial smooth muscle cells. 14 It has been speculated that viruses can reach the intimal smooth muscle cells and may initiate or enhance cell proliferation. This process might produce the nidus for increased concentrations of cholesterol and cholesterol esters. However, in a secondary analysis of data from our study, we actually found a stronger relationship in those with serum cholesterol levels equal to or less than 240 mg/dl. It is possible that an effect of herpesvirus infection might be more evident in those without other risk factors. Studies of individuals at younger ages with less atherosclerosis might also be more revealing. Again, in the Framingham Study, however, when the analysis was limited to those with the onset of disease at an early age, no relationship was found.

Our investigation in a population-based study provided little support for a relationship between CHD and previous occurrence of clinically active herpesvirus infection. The negative overall results of both cross-sectional and longitudinal analyses based on clinical history are consistent with the antibody prevalence study in cardiovascular surgery patients. 8 However, our subgroup analyses did identify women with prevalent CHD, lower cholesterol levels, and incident angina as having more frequently recurring herpes infections. Since both her-
pesvirus infections and atherosclerosis are ubiquitous in this population, the importance of any possible relationships should not be minimized. The results of this study should not dissuade other investigators from performing more specific etiologic studies.

Acknowledgments
The authors thank Diane Yerg and Maria Deloria for programming assistance.

References

Index Terms: coronary heart disease • herpesviruses • HSV-1 • Framingham Heart Study
Unlikely association between clinically apparent herpesvirus infection and coronary incidence at older ages. The Framingham Heart Study.
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doi: 10.1161/01.ATV.9.6.877

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