Short Communication

Hepatitis A Virus and Coronary Artery Diseases

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Abstract

Many studies have reported on the association between human coronary artery disease (CAD) and certain persistent bacterial and viral infections. The aim of the present analysis was to investigate the possible association between HAV infection and angiography proven CAD. Blood from 200 patients undergoing coronary angiography was tested for antibodies to HAV by enzyme immunosorbent assay at Madani Heart Hospital, Tabriz University of Medical Sciences, Iran. CAD prevalence was 90% in HAV seropositive and 84.4% in HAV seronegative patients (Pv= 0.2). This analysis demonstrated that HAV seropositivity is not a risk factor for CAD.

Keywords: Coronary Artery Diseases ● Hepatitis A Virus ● Inflammation ● Infection

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Introduction

Hepatitis A is caused by infection with hepatitis A virus (HAV), a 27-nm RNA virus that is classified as a picornavirus. HAV is commonly believed to be eliminated from the body after the acute infection, and there are no other target tissues in which this virus is known to reside or to produce a disease. Hepatitis A continues to occur at relatively high levels in Iran. Arteriosclerosis is the main cause of coronary heart disease which, in turn, is the most common cause of death in the industrialized world. An acute event in coronary heart disease is typically precipitated by thrombosis occurring at the site of arteriosclerotic plaque disruption. Arteriosclerotic plaques consist of a fibrous cap overlying a lipid-rich core. Substantial evidence now exists indicating that inflammation plays an important role in atherogenesis. An intensive search for the stimuli that trigger and maintain the inflammatory process is underway. The results of epidemiologic studies are of relevance to this concept which proposes possible atherogenic roles for such pathogens as cytomegalovirus (CMV), Chlamydia pneumonia, Helicobacter pylori, herpes simplex virus and HAV. There is one important shared characteristic of the infectious agents implicated in the development of atherosclerosis: they all are intracellular pathogens and can establish long-term, persistent infection or induce long-lasting effects, such as persistent circulating antibodies. HAV was thought to be a reasonable candidate pathogen to test hypothesis. The aim of the present study was to determine the association between HAV seropositivity and CAD.

Methods

Patients were enrolled between October 2007 and November 2008. Participation was voluntary and written informed consent was obtained from each subject. The study cohort consisted of consecutive subjects who were admitted for coronary angiography because of chest pain or because of non-invasive testing compatible with myocardial ischemia. A total of 200 patients were interviewed according to a standard questionnaire about clinical characteristics and conventional risk factors for coronary artery disease such as smoking, hypertension, hypercholesteremia, and diabetes mellitus. CRP was determined by an immunoradiometric assay (range: 0.05–10 mg/l). Testing for serum IgG anti-bodies to HAV were done using a commercially available enzyme immunosorbent assay (ELISA) method (HAV-Kit, DIA.PRO, Italy). All laboratory analyses were carried out in a blinded fashion. Coronary angiography studies were performed behind this association according to the standard technique. CAD was defined as a luminal diameter stenosis > 50% of at least one major coronary artery. One cardiologist blinded for laboratory data reviewed the films. The patients with acute ischemic syndromes within the previous 4 weeks were excluded. The results for normally distributed continuous variables are expressed as mean±S.D. Statistical analysis was performed using ANOVA or by the unpaired t-test in case of continuous variables between different groups. In case of dichotomous variables, the chi-square test or proportional comparison was used where appropriate.

Results

Two hundred sera submitted for HAV screening in Madani Heart Center, Tabriz University of Medical Sciences. Of 200 patients 128 were men and 72 women and mean age of the patients was 49± 10. All serum samples used in this study were tested for anti-HAV antibody using ELISA kit. Of the 200 patients 179 (89.5%) had anti-HAV Ig G antibodies (table). CAD prevalence was 90% in HAV seropositive and 84.4% in HAV seronegative patients (pv =0.2). The elicited risk factors for patients with CAD included man gender, hypertension, hypercholesteremia, diabetes mellitus and smoking. Mean high sensitive CRP value among CAD patients was 10.8± 5.2 and in normal angiography population group it was 5.01 ± 4.1 (pv 0.001).
Coronary Artery Diseases Prevalence and Serostatus of Anti-Hepatitis A Virus Antibodies.

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<th>CAD</th>
<th>NO CAD</th>
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<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
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<tr>
<td>Anti-HAV positive</td>
<td>179 (89.5)</td>
<td>141 (90.9)</td>
</tr>
<tr>
<td>Anti-HAV negative</td>
<td>21 (10.5)</td>
<td>14 (9.1)</td>
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<tr>
<td>Total</td>
<td>200 (100)</td>
<td>155 (77.5)</td>
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CAD, Coronary Artery Diseases; HAV, Hepatitis A Virus Antibody

Discussion

The etiological complexity and the remarkable epidemiological and social importance of atherosclerosis have given rise to extensive research on its pathogenesis. Although increasing data exists indicating that inflammation plays an important role in atherogenesis. However, the triggers that start and maintain the inflammatory process have not been definitively identified. In this case-control study with 155 patients with CAD and 45 patients undergoing coronary angiography and showing no sign of CAD (used as controls), HAV was studied in association with CAD. However, we found no facts in this study that hepatitis A IgG seropositivity was associated with CAD. Thus, despite suggestive evidence from some clinical reports, this investigation has failed to prove an association of hepatitis A IgG seropositivity and CAD. In a recent article, Zhu et al suggested a causal role for HAV infection in atherogenesis, on the basis of a significantly higher prevalence of CAD among subjects living in the Washington DC area who have serum IgG antibodies to HAV. The same research group reported a high relative hazard for myocardial infarction or death among individuals positive for IgG antibodies to HAV. Ethnic differences (white vs. non-white) did not influence the results in these studies. Zhu et al believed that anti-HAV antibodies are associated with CAD prevalence and with elevated CRP levels raise the possibility that HAV can establish a chronic, persistent infection that leads to chronic inflammation that has significant biologic consequences. To our knowledge, no prior evidence has been published suggesting that HAV can persist in its host or found a chronic, subclinical inflammatory condition. We disagree with the findings previously reported that hepatitis A infection is probably an important contributor for CAD. Another important methodological subject of Zhu et al works may be the choice of a very small reference group. In the study of Zhu et al, who reported a strong association between six combined seropositivity, which followed a dose–response pattern, and subsequent myocardial infarction or death among CAD patients, only 4% (n = 36) of the subjects served as reference group. The combined effect of residual confounding and random variation due to a very small reference group may explain in part the positive results. These issues may also explain the unexpected statistically significant associations. Except for acute hepatitis, there are no other target tissues in which this virus is known to reside or to produce a disease. Persistent anti-HAV antibodies are commonly believed not to reflect persistent viral infection and long-term induction of inflammation. Thus, it does not seem to be credible that there is association between seropositivity for anti-HAV IgG antibodies and CAD. In this study the overall seropositivity for anti-HAV IgG antibodies was 89.5% whereas Zhu and colleagues was 52% and Auer and colleagues was 81.7%. A weakness of the present study is its relatively small size. As a result, we might have missed a very weak association between hepatitis A IgG seropositivity and CAD. Hence, any conclusion derived from such a study must be considered preliminary and hypothesis-generating rather than hypothesis-proving. Since serologic markers of HAV infection provide tools to follow the natural course of disease and hither to, there was no concrete evidence supporting the infection of HAV in endothelial cells. We examined just one widely used serologic marker instead of more sensitive HAV-RNA detection with the hypothesis that circulating HAV associated antigens might be the risk factors for atherosclerosis. We suppose that our study has several strengths in comparison with previous published studies. Compared to currently published studies with partly positive findings (two cross-sectional and one prospective nested case-control study), we selected only cases with a recent
diagnosis of CAD, excluded patients with acute ischemic syndromes, and carefully controlled potential confounders. The control group was not just a representative sample from the clinic as in other studies, but was enrolled from the same geographic area as the cases and frequency matched with patients according to age and gender factors. In summary, our results are well-matched with the hypothesis that prior HAV infection is not associated with the development of CAD.

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References