Association between a B19 parvovirus infection and the severity of coronary atherosclerosis

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Title: Association between a B19 parvovirus infection and the severity of coronary atherosclerosis.

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Short title: B19 parvovirus and coronary atherosclerosis

Conflict of interest: none declared.

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Introduction

Beside the well-established risk factors for the development of coronary atherosclerosis, such as gender, hypertension, dyslipidemia, diabetes and smoking, there have been studies showing a correlation between infections and coronary artery disease (CAD). There is a substantial amount of data suggesting a possible involvement of Chlamydia pneumophilae [1], HSV-2 [2], CMV [3], Helicobacter pylori [4] or Porphyromonas gingivalis [5] in the development or exacerbation of atherosclerosis. It is postulated they might exert an atherogenic effect by causing systemic proinflammatory conditions. Nevertheless, none of the above mentioned pathogens targets the human endothelium [1]. One pathogen with a direct tropism to human endothelial cells is the B19 parvovirus (B19PV). B19PV has been shown not only to infect endothelial cells, but also to impair their regeneration [6]. Since atherosclerosis is strongly dependent on endothelial dysfunction, this suggests B19PV could be involved in the development of. B19PV infections are common. Results of an epidemiology study indicate a B19PV infection has affected 80% of the Polish population at the age of 40 [7]. Clinical presentations of a B19PV infection range from erythema infectiosum in children to arthropathy or myocarditis in adults; with a suggested involvement in the pathogenesis of rheumatoid diseases. However, a B19PV infection may often be asymptomatic or give influenza-like symptoms only [8].

The aim of this study was to determine whether there is an association between anti-B19PV IgG antibodies and the severity of coronary artery disease.

Methods

This was an observational study conducted in 2012 at the Department of Heart Surgery, Vessel Surgery and Transplantation, Jagiellonian University, Collegium Medicum. We included 76 consecutive patients qualified for coronary artery bypass grafting (CABG) due to
stable coronary artery disease (CAD). The only exclusion criterion was qualification for an urgent procedure. All patients were thoroughly informed and provided written consent to participate in the study. The study was approved by the Jagiellonian University Ethics Committee. The project received funding from an institutional grant to AW, EP, JP.

Patients were screened for typical risk factors of atherosclerosis and history of myocardial infarction. Coronary angiograms were analyzed and the Gensini Score was used for quantitative analysis of coronary atherosclerosis [9].

**PVB19PV diagnostics.** Venous blood was collected before CABG, centrifuged and the supernatants were stored in -80°C. The level of anti-B19PV IgG antibodies was measured using ELISA (recomWell Parvovirus B19PV IgG kit; Mikrogen, Germany). Based on the results, patients were divided into a B19PV IgG – positive (patients who had undergone the infection) and B19PV IgG – negative group (patients with no evidence of an infection).

**Statistical analysis.** Normal distribution of continuous variables was assessed using the Shapiro-Wilk test. For the association of nominal values the Pearson Chi² test was used. The U - Mann-Whitney test was used in case of one nominal and one continuous variable (no continuous variables showed a normal distribution in both groups). A p of <0.05 was considered significant.

**Results and discussion**

The results are presented in Table 1. 63 out of 76 patients tested positively for the presence of B19PV IgG antibodies (82.9%), consistently with epidemiological data [7]. The distribution of CAD risk factors was typical and did not differ between seropositive and seronegative patients. We found that seropositive patients were significantly more likely to have a history of myocardial infarction (36.5% vs. 7.7%, p = 0.049). We also observed a significantly larger atherosclerotic burden in the seropositive group, (Gensini Score 98 vs. 70, p = 0.049).
Based on the assessed indicators of CAD severity, it seems plausible a B19PV infection may influence the development of coronary atherosclerosis. Since one of the first stages and hallmarks of atherosclerosis is endothelial dysfunction, it is possible that infectious agents targeting the endothelium and causing inflammation, such as B19PV, might contribute to the development of atherosclerotic plaques. There is, in fact, some data supporting this thesis [10]. Liu et al. performed a serology analysis of 565 individuals with CAD or healthy controls and demonstrated that anti-B19PV IgG positive results were significantly more frequent in the CAD as compared to the control group [11]. An interesting study by Niccoli et al. has shown that the presence of B19PV DNA on a balloon used to predilate coronary lesions was a predictor of MACE defined as a composite of cardiac death, MI and clinically driven target lesion revascularization [12].

B19PV genetic material can be found in cells in a quiescent state, at levels that do not exert immune response [13]. It has been demonstrated that a simultaneous infection with B19PV and adenoviruses can augment the expression of B19PV proteins within endothelial cells [14]. It is, therefore, possible that an isolated B19PV infection of the endothelium does not have the potency to lead to a clinically relevant effect on atherosclerosis and requires a co-infection with other viruses.

B19PV material can be found in around 1% of myocarditis patients [15]. Still, none of the patients in our group had a history of myocarditis. This might be due to the fact that most of the B19PV infections are asymptomatic or give influenza-like symptoms and may have remained unnoticed/undiagnosed. Since the median patient age was above 60 and myocarditis usually affects 20-40 year-olds, it is possible that some myocardial infections had occurred in the B19PV-positive group in the distant past and were not diagnosed at that time of presentation.
In conclusion, our results show B19PV-seropositive patients had a larger atherosclerotic burden measured by the Gensini Score and were more likely to have suffered from a myocardial infarction. This was a preliminary study concerning a small group of patients. Therefore, conclusions must be treated cautiously and require a confirmation in a larger group. Still, as arterial endothelial cell dysfunction underlies the development of atherosclerosis, it seems the association between B19PV infection and CAD is an interesting research field.

References


### Tables

<table>
<thead>
<tr>
<th></th>
<th>Anti-B19PV IgG positive (n = 63)</th>
<th>Anti-B19PV IgG negative (n = 13)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, median</td>
<td>63 (47;80;14)</td>
<td>62 (51;82;18)</td>
<td>0.65 (U-M-W)</td>
</tr>
<tr>
<td>Gender: male, n (%)</td>
<td>51 (81.0)</td>
<td>10 (77.0)</td>
<td>0.40 (Pearson Chi²)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>50 (79.4)</td>
<td>13 (100.0)</td>
<td>0.40 (Pearson Chi²)</td>
</tr>
<tr>
<td>Dyslipidemia, n (%)</td>
<td>44 (69.8)</td>
<td>11 (84.6)</td>
<td>0.57 (Pearson Chi²)</td>
</tr>
<tr>
<td>Diabetes, n (%)</td>
<td>22 (34.9)</td>
<td>4 (30.8)</td>
<td>0.12 (Pearson Chi²)</td>
</tr>
<tr>
<td>Active smoking, n (%)</td>
<td>38 (60.3)</td>
<td>8 (61.5)</td>
<td>0.84 (Pearson Chi²)</td>
</tr>
<tr>
<td>Pre-op LVEF, median</td>
<td>52 (35;70;6)</td>
<td>52 (40;70;6)</td>
<td>0.91 (U-M-W)</td>
</tr>
<tr>
<td>History of MI, n (%)</td>
<td>23 (36.5)</td>
<td>1 (7.7)</td>
<td>0.049 (Pearson Chi²)</td>
</tr>
<tr>
<td>Gensini Score, median</td>
<td>98 (46.5;152.5;33.5)</td>
<td>70 (45;134;38)</td>
<td>0.049 (U-M-W)</td>
</tr>
</tbody>
</table>

Table 1. Patient characteristics with relations to B19PV IgG seropositivity/seronegativity.

IgG – immunoglobulin G; MI – myocardial infarction; Pre-op LVEF – pre-procedural left ventricle ejection fraction; SD – standard deviation, U-M-W – U – Mann-Whitney test.