ACP1 and ADA1 Genetic Polymorphisms and Coronary Artery Disease. Effects on Age at Onset of Clinical Manifestations

Gloria-Bottini Fulvia1, Banci M1, Saccucci P2, Neri A1, Magrini A1, Bottini E1

1Department of Biomedicine and Prevention, University of Tor Vergata, Rome, Italy
2Department of Cardiology, Valmontone Hospital, Valmontone, Rome, Italy

Abstract

Previous studies have shown an association of Coronary Artery Disease (CAD) with Acid Phosphatase locus 1 (ACP1) and Adenosine Deaminase locus 1 (ADA1) genetic polymorphisms. Both systems are involved in immune reactions and several studies point to a significant autoimmune component in the pathogenesis of CAD. In the present note we have investigated the role of the two polymorphisms on age of onset of the disease.

Hundred and thirty patients admitted to Valmontone Hospital for the first episode of CAD have been studied. Informed consent was obtained by the patients to participate in the study that was approved by the Sanitary Direction of the Hospital.

In patients at the first episode of CAD, ACP1 genotype was determined in 130 subjects and ADA1 genotype in 126 subjects by DNA analysis. SPSS programs performed statistical analyses.

The age at onset of CAD is lower in subjects with low ACP1 activity genotypes and in those with low ADA1 activity genotypes. The association is stronger in females than in males. The effects of the two systems appears additive with a lower age of onset in subjects carrying the two factors associated with lower age at onset and a higher age in subjects with no factor. The pattern is stronger in females than in males.

Gender differences in autoimmunity are well documented: women with low ACP1 activity and/or ADA1 genotype seem to have a high risk of early clinical manifestations as compared to women carrying genotypes with high activity. These differences support the hypothesis of significant autoimmune component in the pathogenesis of CAD.

Keywords: ACP1; ADA1; CAD; Age at onset

Introduction

Previous studies have shown an association of Coronary Artery Disease (CAD) with Acid Phosphatase locus 1 (ACP1) [1] and with Adenosine Deaminase (ADA1) [2,3]. The present analysis suggests an effect of these genetic systems on the age at onset of clinical manifestations of the disease.

ACP1 gene is located on chromosome 2 and encodes the Low Molecular Weight Protein Tyrosine Phosphatase (LMWPTP). The gene shows three co dominant alleles *A, *B and *C: the corresponding 6 genotypes show an activity increasing in the order *A/*A<*A/*B<*B/*B≤*A/*C<*B/*C<*C/*C. The enzyme has several functions: (i) as flavin mononucleotide phosphatase catalyzes the conversion of flavin mononucleotide to riboflavin contributing to the regulation of flavo-enzymes activity and energy metabolism; (ii) dephosphorylating insulin receptor and band 3 protein modulates the glycolytic rate; (iii) dephosphorylating a negative regulatory Tyr-292 of ZAP-70, ACP1 strengthens T cell receptor signaling [4,5].

Parameter | % Proportion
--- | ---
Infarction | 40.5%
Major Coronary Lesions | 83.2%
Bypass | 35.2%
Angioplasty | 27.1%

Table 1: Clinical data in subjects with CAD
Table 2: Age at onset of CAD in relation to ACP\textsubscript{1} and ADA\textsubscript{1} genetic polymorphisms

<table>
<thead>
<tr>
<th></th>
<th>All subjects</th>
<th>Females</th>
<th>Males</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean age</td>
<td>S.E.</td>
<td>n°</td>
</tr>
<tr>
<td>Low activity genotypes (*A/*A and *A/*B) (A)</td>
<td>63.10</td>
<td>1.85</td>
<td>51</td>
</tr>
<tr>
<td>Medium activity genotype (*B/*B) (B)</td>
<td>67.00</td>
<td>1.36</td>
<td>59</td>
</tr>
<tr>
<td>High activity genotypes (*A/*C, *B/*C and *C/*C) (C)</td>
<td>69.45</td>
<td>2.70</td>
<td>20</td>
</tr>
<tr>
<td>Statistical analysis A vs B vs C linear correlation p=0.027 eta=0.197 eta squared=0.040</td>
<td>A vs B vs C linear correlation p = 0.034 eta=0.310 eta squared=0.095</td>
<td>A vs B vs C linear correlation p=0.023 eta=0.371 eta squared=0.060</td>
<td></td>
</tr>
<tr>
<td></td>
<td>difference between means p=0.036 eta=0.185 eta squared=0.040</td>
<td>difference between means p=0.095 eta=0.107 eta squared=0.011</td>
<td>difference between means p=0.233 eta=0.107 eta squared=0.002</td>
</tr>
</tbody>
</table>

Material and Methods

We have studied 130 patients admitted to Valmontone Hospital for the first episode of Coronary Artery Disease. 55 were females and 75 males. Part of these subjects have been included in previous studies [1,3]. Informed consent was obtained from the patients to participate to the study that was approved by the Sanitary Direction of the Hospital. Clinical data of subjects examined are shown in Table 1.

ACP\textsubscript{1} genotype was determined in 130 subjects admitted in the Hospital for the first episode of CAD. ADA\textsubscript{1} genotype was determined in 126 subjects at first episode. ACP\textsubscript{1} and ADA\textsubscript{1} genotypes were determined by DNA analysis as previously described.[1,3].

Statistical analyses were carried out by commercial software (SPSS). Eta (η) is a measure of association and eta squared (η²) represents the proportion of variance of dependent variable that is explained by the independent variable.

Results

Table 2 shows the age of subjects admitted to the Hospital for the first episode of CAD in relation to the genotypes of ACP\textsubscript{1} and ADA\textsubscript{1}. The age at onset of clinical manifestations is lower in subjects with low ACP\textsubscript{1} activity as compared to other ACP\textsubscript{1} genotypes and in carriers of ADA\textsubscript{1} *2 allele (associated with lower ADA enzymatic activity) as compared to ADA\textsubscript{1} *1/*1 genotype. Although the pattern appears similar in males and females, it is stronger in females than in males. For ACP\textsubscript{1}, eta is 0.388 in females and 0.107 in males. For ADA\textsubscript{1}, eta is 0.338 in females and 0.047 in males.

As shown in table 3 the effect of the two genotypes in subjects admitted to the Hospital for the first episode of CAD appears additive with a lowest age in subjects carrying the two factors associated with lower age at onset and the highest age in subjects with no factor. Although the pattern is similar in males and females, it is much stronger in females than in males. In females eta is 0.456, eta squared is 0.208 while in males eta is 0.185 and eta squared is 0.034.

We have considered in females the effect of the following variables: hypertension, obesity and diabetes. No statistically significant effect of these variables was observed neither on the difference between low activity and medium-high activity ACP\textsubscript{1} genotypes nor on the difference between low activity ADA\textsubscript{1} genotypes and high activity ADA\textsubscript{1} genotype.
Table 3: The relationship between age at onset of clinical manifestations of CAD and the number of genetic factors for which an earlier onset of manifestation has been observed.

<table>
<thead>
<tr>
<th>Number of factors</th>
<th>Mean age at onset (yrs)</th>
<th>S.E.</th>
<th>n°</th>
<th>Mean age at onset (yrs)</th>
<th>S.E.</th>
<th>n°</th>
<th>Mean age at onset (yrs)</th>
<th>S.E.</th>
<th>n°</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>68.35</td>
<td>1.26</td>
<td>69</td>
<td>71.15</td>
<td>2.14</td>
<td>27</td>
<td>66.55</td>
<td>1.51</td>
<td>42</td>
</tr>
<tr>
<td>1</td>
<td>63.88</td>
<td>1.69</td>
<td>57</td>
<td>61.68</td>
<td>2.30</td>
<td>25</td>
<td>65.59</td>
<td>2.39</td>
<td>32</td>
</tr>
<tr>
<td>2</td>
<td>50.75</td>
<td>6.32</td>
<td>4</td>
<td>51.67</td>
<td>8.84</td>
<td>3</td>
<td>48.00</td>
<td>-</td>
<td>1</td>
</tr>
</tbody>
</table>

Statistical analysis

linear correlation p=0.002
eta =0.290 eta squared=0.084

Discussion

The present analysis shows a statistically significant positive correlation between ACP$_1$ activity and age at onset of CAD: low activity ACP$_1$ genotypes are associated with early onset of clinical manifestations while high activity genotypes are associated with late onset of manifestations. Such correlation is statistically significant in females but not in males. Since low ACP$_1$ activity is associated in females to early onset and probably to early mortality also, this could result in an apparent relative increase of ACP$_1$ genotypes with high activity in the surviving subjects with CAD. The data also indicate that ADA$_1$ *2 allele is associated in females to early onset of clinical manifestations and probably to early mortality. This could result in an apparent relative decrease of subjects carrying this allele in surviving subjects [1,2].

The analysis confirms the involvement of ACP$_1$ and ADA$_1$ in the risk of CAD and suggests an additive effect of the two systems on age at onset of the disease.

Several studies point to a significant autoimmune component in the pathogenesis of atherosclerosis [10,11]: gender differences in autoimmunity are well documented and it has been suggested that in diseases with autoimmune component males and females should be examined separately [12].

The limitation of the study is represented by the relatively low number of subjects examined and by the lack of information on the distribution of ACP$_1$ and ADA$_1$ in subjects not surviving the first episode of CAD.

From the practical point of view the determination of ACP$_1$ and ADA$_1$ genotypes may help to detect subjects with high risk of early manifestations of CAD.

References


