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ACP_1 and ADA_1 Genetic Polymorphisms and Coronary Artery Disease. Effects on Age at Onset of Clinical Manifestations

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Abstract

Previous studies have shown an association of Coronary Artery Disease (CAD) with Acid Phosphatase locus 1 (ACP_1) and Adenosine Deaminase locus 1 (ADA_1) 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, ACP_1 genotype was determined in 130 subjects and ADA_1 genotype in 126 subjects by DNA analysis. SPSS programs performed statistical analyses.

The age at onset of CAD is lower in subjects with low ACP_1 activity genotypes and in those with low ADA_1 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 ACP_1 activity and/or ADA_1 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:

ACP_1; ADA_1; CAD; Age at onset

Introduction

Previous studies have shown an association of Coronary Artery Disease (CAD) with Acid Phosphatase locus 1 (ACP_1) [1] and with Adenosine Deaminase (ADA_1) [2,3]. The present analysis suggests an effect of these genetic systems on the age at onset of clinical manifestations of the disease.

ACP_1 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, ACP_1 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

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	All Subjects			Females			Males		
	Mean age (yrs)	S.E.	n°	Mean age (yrs)	S.E.	n°	Mean age (yrs)	S.E.	n°
ACP1									
Low activity genotypes (*A/*A and*A/*B) (A)	63.1	1.85	51	61.26	2.49	23	64.61	2.69	28
Medium activity genotype (*B/*B) (B)	67	1.36	59	68.53	2.62	19	66.8	1.59	40
High activity genotypes (*A/*C, *B/*C and *C/*C) (C)	69.45	2.7	20	69.67	3.87	13	68.86	3.22	7
Statistical analysis	A vs B vs C linear correlation p=0.027, eta =0.197 eta squared=0.040 A vs (B+C) difference between means p=0.036, eta=0.185 eta squared=0.040			A vs B vs C linear correlation p = 0.034 eta= 0.310 eta squared=0.095 A vs (B+C) difference between means p=0.023			A vs B vs C linear correlation p=0.371 eta=0.107 eta squared=0.011 A vs (B+C) difference between means p=0.860		
ADA1									
Low activity genotypes (carriers of ADA1*2 allele)	59.21	3.55	14	55.38	4.71	8	64.33	5.09	6
High activity genotypes (ADA1 *1/*1 genotype)	66.72	1.11	112	67.31	1.78	45	66.33	1.42	67
Statistical analysis	difference between means p=0.028, eta=0.146 eta squared=0.040			difference between means p=0.013, eta=0.338 eta squared=0.114			difference between means p=0.690, eta=0.047 eta squared=0.002		

Table 2: Age at onset of CAD in relation to ACP1 and ADA1 genetic polymorphisms

Several studies point to a significant link between atherosclerosis and the genetics of autoimmunity. ACP_1 has been found associated with several immune diseases including Coronary Artery Disease (CAD) suggesting an important relationship between this polymorphism and CAD possibly through the relationship of ACP_1 with ZAP70.

The ADA gene is located on chromosome 20 and it is constituted by 12 exons. A number of single nucleotide polymorphisms have been found within the coding and intronic regions of the gene [6]. The SNP (ADA_1) corresponding to the presence /absence of a Taq I site (4050-4053 exon 1, C22 G > A, Asp8Asn, rs 73598374) has been found associated with CAD [2,3]. This SNP at exon 1 corresponds to a known functional variant since the G > A transition results in the substitution of asparagine for aspartic acid at codon 8. This mutation is the molecular basis for the biochemical polymorphism at the ADA_1 locus described by Spencer et al., with two codominant alleles with activity decreasing in the order ADA_1*1 > ADA_1*2 [7].

ADA_1 catalyzes the irreversible deamination of adenosine to inosine contributing with adenosine kinase to the intra and extra-cellular concentration of adenosine. Carriers of ADA_1*2 allele show a low enzymatic activity as compared to ADA_1 *1/*1 genotype. Adenosine has an important role in glucose metabolism and immune functions and is a cardio-protective agent [8,9].

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_1 genotype was determined in 130 subjects admitted in the Hospital for the first episode of CAD. ADA_1 genotype was determined in 126 subjects at first episode. ACP_1 and ADA_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 (η^2) 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_1 and ADA_1. The age at onset of clinical manifestations is lower in subjects with low ACP_1 activity as compared to other ACP_1 genotypes and in carriers of ADA_1 *2 allele (associated with lower ADA enzymatic activity) as compared to ADA_1 *1/*1 genotype. Although the pattern appears similar in males and females, it is stronger in females than in males. For ACP_1 eta is 0.308 in females and 0.107 in males. For ADA_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_1 genotypes nor on the difference between low activity ADA_1 genotypes and high activity ADA_1 genotype.

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].

	All subjects			Females			Males		
Number of factors	Mean age at onset (yrs)	S.E.	n°	Mean age at onset (yrs)	S.E.	n°	Mean age at onset (yrs)	S.E.	n°
0	68.35	1.26	69	71.15	2.14	27	66.55	1.51	42
1	63.88	1.69	57	61.68	2.30	25	65.59	2.39	32
2	50.75	6.32	4	51.67	8.84	3	48.00	-	1
Statistical analysis linear correlation p=0.002 eta =0.290 eta squared=0.084				linear correlation p=0.001 eta=0.456 eta squared=0.208			linear correlation p=0.390 eta=0.185 eta squared=0.034		

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.

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

1. Banci M, Saccucci P, D Annibale F, Dofcaci A, Trionfera G, et al. (2009) ACP1 genetic polymorphism and coronary artery disease: an association study. Cardiology 113: 236-242. doi: 10.1159/000203405
2. Safranow K, Rzeuski R, Binczak-Kuleta A, Czyzycka E, Skowronek J, et al. (2007) ADA*2 allele of the adenosine deaminase gene may protect against coronary artery disease. Cardiology 108: 275-281. doi: 10.1159/000099096
3. Gloria-Bottini F, Safranow K, Banci M, Binczak-Kuleta A, Saccucci P, et al. (2013) The association of adenosine deaminase with coronary artery disease: Effect of gender and diabetes. Health 5: 166-169
4. Bottini N, Bottini E, Gloria-Bottini F, Mustelin T (2002) Low-molecular-weight protein tyrosine phosphatase and human disease: in search of biochemical mechanisms. Arch Immunol Ther Exp (Warsz) 50: 95-104.
5. Bottini N, Stefanini L, Williams S, Alonso A, Jascur T (2002) Activation of ZAP-70 through specific dephosphorylation at the inhibitory Tyr-292 by the low molecular weight phosphotyrosine phosphatase (LMPTP). J Biol Chem 277: 24220-24224
6. Tzall S, Ellenbogen A, Eng F, Hirschhorn R (1989) Identification and characterization of nine RFLPs at the adenosine deaminase (ADA) locus. Am J Hum Genet 44: 864-875
7. Spencer N, Hopkinson D, Harris H (1968) Adenosine deaminase polymorphism in man. Ann Hum Genet 32: 9-14. doi: 10.1111/j.1469-1809.1968.tb00044.x
8. Barankiewicz J, Danks AM, Abushanab E, Makings L, Wiemann T, et al. (1997) Regulation of adenosine concentration and cytoprotective effects of novel reversible adenosine deaminase inhibitors. J Pharmacol Exp Ther 283: 1230-1238
9. Asakura M, Asanuma H, Kim J, liao Y, Nakamaru K, et al. (2007) lmpact of adenosine receptor signaling and metabolism on pathophysiology in patients with chronic heart failure. Hypertens Res 30: 781-787. doi: 10.1291/hypres.30.781
10. Hansson GK (1999) Inflammation and immune response in atherosclerosis. Curr Atherosc Jer Rep 1: 150-155
11. Ostos MA, Recalde D, Zakin MM, Scott-Algara D (2002) lmplication of natural killer T cells in atheroselerosis development during a LPS-induced chronic inflammation. FEBS Lett 519: 23-29
12. Whitacre CC, Reingold SC, O Looney PA (1999) A gender gap in autoimmunity. Science 283: 1277-1278