Antigens of the Major Histocompatibility System in Ischemic Heart Disease and Idiopathic Dilated Cardiomyopathy

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Summary

Background: Although dilated cardiomyopathy (DCM) is a disease of unknown and probably multifactorial etiology, a change in immune mechanisms is presumably significant, with many abnormalities in humoral and cellular responses having been reported. The heart thus becomes the target organ for an initial episode of myocardial damage that triggers an autoimmune response.

Hypothesis: The purpose of this study was to analyze the frequency of different human leukocyte antigens in patients with a diagnosis of well-advanced DCM and ischemic heart failure, comparing them with a control group of presumably healthy subjects.

Methods: The group with dilated cardiomyopathy consisted of 50 patients (7 women and 43 men), aged from 14 to 64 years. The group with ischemic heart disease included 76 patients (4 women and 72 men), with ages ranging from 34 to 64. The control group, consisting of 1,337 presumably healthy subjects from the Spanish Mediterranean area, was recruited based on paternity studies.

Results: Compared with the control group, we found in DCM a greater incidence of B15 (20 vs. 6%) and DQ3 (83 vs. 50%) antigens. In ischemic heart disease we found a lower in-

cidence of A1 (3 vs. 22%), B8 (5 vs. 12%), and DQ2 (16 vs. 50%) in comparison with the control group.

Conclusions: In the Spanish Mediterranean area, the presence of antigens B-15 and DQ3 would be associated with advanced DCM. The absence of antigens A1, B8, and DQ2 would be associated with the occurrence of severe ischemic heart disease.

Key words: human leukocyte antigens, dilated cardiomyopathy, ischemic heart disease

Introduction

Dilated cardiomyopathy (DCM) is a disease of unknown and probably multifactorial etiology. However, it is presumed that a change in immune mechanisms plays a significant part,^{1–5} since many abnormalities in the humoral^{4,5} and cellular^{1–3} responses have been reported, so that the heart becomes the target organ for an initial episode of myocardial damage that will trigger an autoimmune response.⁶ It is believed that this response is influenced by immunological factors.^{6,7} Dilated cardiomyopathy has been related to abnormalities in lymphocyte function, including defects in natural killer cells⁸ and in lymphocyte suppressive function.^{2,9} It has also been related to the response of cytotoxic antithymocytic T cells¹⁰ and to antibodies against beta receptor¹¹ and heart tissue.¹² Given the relationship between the types of major histocompatibility system (HLA) and many autoimmune diseases, some studies have attempted to find a possible association between DCM and a specific type of HLA.^{13–20} The one most frequently associated with DCM has been HLA-DR4.²¹

Attempts have also been made to relate ischemic heart disease (IHD) to a specific HLA, based on the concept that genetic influences would contribute to the susceptibility to coro-

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nary atherosclerosis, regardless of risk factors. Conflicting results have been found, usually bearing no relationship to HLA,^{14, 22, 23} although one study has shown HLA-DR6 to be the most common.²⁴

There are two general kinds of HLA: class I antigens which encompass loci A, B and C, and class II antigens, consisting of the loci of area D/DR, DQ, and DP. The genetic products of class I are used for antigen recognition by cytotoxic T cells, whereas those of class II have a regulatory capacity.

Knowing that these antigens are transmitted by heredity and are therefore different in different geographical areas, the purpose of this study was to analyze in our area (Spanish Mediterranean) the frequency of the various HLAs in patients with DCM and IHD compared with a control group. They are also compared with the results of other authors, although the distribution of HLA types varies, depending on the population areas studied.

Methods

Patients

The study group consisted of patients eligible for heart transplantation referred to our hospital, all of whom were from the Mediterranean area, particularly from the Valencia Region. All patients studied are currently transplanted, thus allowing the pathologic study of the specimen to be made.

The group with DCM (Group 1) consisted of 50 patients, 7 women and 43 men, with ages ranging from 14 to 64 years (mean 50 years). The diagnosis was made in dilated hearts with poor generalized contractility after ruling out secondary reasons such as amyloidosis, hemochromatosis, or valvular disease. The diagnosis of idiopathic DCM was confirmed by the pathologic study of the necropsy specimen after heart transplantation, which showed no coronary lesions or any other disease as the cause of this entity. Cases showing diffuse interstitial inflammatory infiltration and/or myocyte necrosis were not included in the study.

The group with IHD (Group 2) consisted of 76 patients, 4 women and 72 men, with ages ranging from 28 to 64 years (mean 54 years). Previous diagnosis was made using coronary angiography, which showed diffuse multivessel lesion, apart from a history of angina pectoris or myocardial infarction. The subsequent study of the heart confirmed the diagnosis, showing the typical atheroma plaques of this disease.

The control group was recruited from 1,337 presumably healthy subjects in this geographical area, obtained in paternity studies.²⁵ All patients were free of any disease known to have a predilection for specific HLAs (such as type I diabetes mellitus, rheumatoid arthritis, ankylosing spondylitis, Graves' disease, myasthenia gravis, or rheumatic disease).

Measurement Technique

Human leukocyte antigen typing was performed in peripheral blood lymphocytes isolated from 20 ml of heparinized whole blood using Ficoll-Hypaque gradient.²⁶ Purified B

TABLE I Incidence of human leukocyte antigens in dilated cardiomyopathy, ischemic heart disease and control group

	Dilated cardiomyopathy (n = 50) No. (%)	Ischemic heart disease (n=76) No. (%)	Control group (n=1337) No. (%)
HLA-A			
A1	10 (20)	5 (3) ^a	291 (22)
A2	30 (60)	29 (38)	618 (46)
A3	10 (20)	12 (16)	261 (20)
A9	11 (22)	14 (18)	296 (22)
A10	3 (6)	10 (13)	159 (12)
A11	5 (10)	14 (18)	175 (13)
A24	5 (10)	0 (0)	204 (13)
A28	2 (4)	4 (5)	97 (7)
A29	8 (16)	17 (22)	195 (15)
A30	8 (16)	8 (11)	148 (11)
A31	2 (4)	1 (1)	54 (4)
A32	5 (10)	4 (5)	89 (7)
A33	2 (4)	2 (3)	56 (4)
HLA-B			
B5	13 (26)	12 (16)	240 (18)
B7	4 (8)	10 (13)	209 (16)
B8	3 (6)	4 (5) ^a	155 (12)
B12	19 (38)	31 (41)	433 (32)
B13	2 (4)	3 (4)	43 (3)
B14	3 (6)	6 (8)	149 (11)
B15	10 (20) ^a	3 (4)	78 (6)
B16	2 (4)	3 (4)	106 (8)
B17	6 (12)	4 (5)	106 (8)
B18	8 (16)	10 (13)	196 (15)
B21	7 (14)	7 (9)	191 (14)
B22	2 (4)	1 (1)	44 (3)
B27	4 (4)	7 (9)	87 (6)
B35	8 (16)	14 (18)	250 (19)
B37	2 (4)	2 (3)	45 (3)
B40	2 (4)	6 (8)	101 (8)
B41	1 (2)	1 (1)	25 (2)
HLA-DR			
DR1	11 (22)	18 (24)	266 (20)
DR2	9 (18)	13 (17)	288 (22)
DR3	8 (18)	13 (17)	334 (25)
DR4	11 (22)	15 (20)	241 (18)
DR5	20 (40)	17 (22)	361 (27)
DR6	9 (18)	15 (20)	184 (14)
DR7	20 (40)	21 (28)	440 (33)
DR8	1 (2)	3 (4)	23 (2)
DR9	0 (0)	2 (3)	12 (1)
DR52	2 (4)	1 (1)	23 (2)
HLA-DQ			
DQ1	26 (51)	49 (65)	742 (55)
DQ2	18 (37)	12 (16) ^a	667 (50)
DQ3	41 (83) ^a	36 (47)	668 (50)

^a $p < 0.05$.

lymphocytes²⁷ were used for HLA-DR. Phenotyping of HLA A, B, and C antigens was performed by microcytotoxicity

FIG. 1 Graph shows the human leukocyte antigen incidence in both groups (between control and both ischemic heart disease and dilated cardiomyopathy). DCM = dilated cardiomyopathy, IHD = ischemic heart disease, * = $p < 0.05$.

(cell lysis) in lymphocyte suspension, and that of HLA-DR by microlymphocytotoxicity with prolonged incubation in the purified B lymphocytes.

Statistical Analysis

The chi-square test was used to compare the values. When the number of cases was small, Yates' correction and Fisher's exact test were used. A value of $p < 0.05$ was considered significant.

Results

We found some significant differences between the incidence of antigens of these diseases and those of the control group (Table I, Fig. 1).

With regard to DCM, we found statistically significant differences compared with the control group. The incidence of HLA B15 and DQ3 antigens was significantly higher in Group 1.

In IHD, the incidence of antigens such as HLA A1, B8, and DQ2 was significantly lower than that in the control group.

Discussion

Both DCM and IHD were studied to ascertain their possible relationship with certain HLAs: in the former, due to changes in immune mechanisms probably triggered by a myocardial insult¹⁻¹² (e.g., a viral infection), and in the latter due to the influence of genetic factors on susceptibility to coronary atherosclerosis, regardless of risk factors.^{14, 22, 24}

This study was performed to determine whether there is an association between the presence of certain HLAs and advanced IHD and DCM. To do so, we compared the frequency with which different HLAs occur in patients with severe systolic dysfunction with a documented diagnosis of DCM or IHD with that of a control group of presumably healthy subjects from the Spanish Mediterranean area.

Some studies on other population groups have reported different associations between these diseases and different antigens of the HLA system.^{13, 14, 17, 18, 25} In DCM, two antigens were found with greater frequency in this study than in the general population (B15 and DQ3), and no antigen showed a lower incidence. There are widely differing results in DCM reported in the literature, with a greater incidence of antigens DR4,^{13, 17, 21} A2 and A,¹⁴ DQB1-0503,²⁸ DQ4,¹⁷ B27,¹⁸ and a lower incidence of haplotypes A-25,¹⁴ DQB1-0303,²⁸ DRW-6,¹⁷ and DR6Y.¹⁸ However, other authors found no greater incidence of certain HLAs among patients with DCM than in their respective controls.^{22, 23} In IHD, we found a lower incidence of A-1, B8, and DQ2, with no antigen showing an increased occurrence compared with the controls. Also in this heart disease, a review of the studies published shows widely different antigen frequencies, although the studies are less emphatic than those referring to DCM. Some authors relate it to the DRW6²⁴ antigen, whereas others find no correlation.^{14, 22}

Comparing our results with those of other authors, we find that there is very little coincidence. We attribute this to the fact that the populations studied are very different. These differences are probably due to the ethnic heterogeneity of the populations used. We consider this observation to be of practical interest when attempting to assess the different antigen frequencies found in the normal and sick population. Thus, when we wish to analyze possible associations of antigens with certain diseases, the control group must have the same characteristics as the diseased population studied. In our case, the patients studied were different from those of most studies reviewed, conducted in countries such as Great Britain,²² U.S.A.,^{14, 17, 24} Scandinavian countries,¹³ France,¹⁵ or Japan,²⁸ with marked ethnical differences from our population (Spanish Mediterranean area). Therefore, to give validity for a certain population group to the most common antigens found in areas that are very different to that under study could lead to serious errors; therefore it is advisable that the study groups of certain areas should have their own control groups.

On the other hand, when analyzing the results, we must bear in mind that all patients with both heart diseases showed severe systolic dysfunction (they are all currently transplanted), with ejection fraction quantified by radionuclides of 18 ± 6 for Group 1 and of 21 ± 7 for Group 2. This can lead to errors, since in patients with these diseases, but with a lower degree of involvement, the incidence of the different HLAs may possibly not be the same; also, there could be subjects in the control group with nondocumented ischemia, since they were not subjected to any type of coronary disease detection, a fact that could place a limitation on the study.

Conclusions

In the geographical area of the Spanish Mediterranean coast, the presence of B15 and DQ3 antigens is associated with the occurrence of advanced dilated cardiomyopathy. The absence of antigens A1, B8, and DQ2 is associated with a greater incidence of highly advanced ischemic heart disease.

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