Abstract

Objectives—To compare HLA distribution in familial and non-familial dilated cardiomyopathy, because a serum marker that could identify families at risk of developing dilated cardiomyopathy should be of use in screening for the disease.

Patients—100 patients with dilated cardiomyopathy.

Methods—200 first degree relatives from 56 of the proband families were screened for dilated cardiomyopathy by echocardiography. The HLA profile of the patients with dilated cardiomyopathy, as well as of the familial and non-familial subgroups, was compared with that of 9000 normal controls.

Results—The familial prevalence of dilated cardiomyopathy in this patient group was “definite” in 14 of 56 (25%) and “possible” in 25 of 56 (45%). The HLA-DR4 frequency in the 100 patients with dilated cardiomyopathy was similar to that in the 9000 controls (39% vs 32%). However, the DR4 subtype was significantly more common in the 25 probands with a familial tendency to dilated cardiomyopathy than in the 31 probands with non-familial dilated cardiomyopathy (68% vs 32%; P < 0.05).

Conclusions—The present finding supports an HLA linked predisposition to familial dilated cardiomyopathy. The HLA type DR4 was significantly more common in familial than in non-familial cases. The DR4 haplotype was associated with two thirds of the families at risk for dilated cardiomyopathy.

Methods

PATIENTS

Patients with dilated cardiomyopathy attending the National Cardiac Centre at the Mater Misericordiae Hospital and their first degree relatives were invited to attend a special clinic. To date 100 probands with dilated cardiomyopathy have been identified. The ultrasound criteria for the diagnosis of dilated cardiomyopathy were a left ventricular ejection fraction less than 50% combined with a left ventricular end diastolic dimension more than two standard deviations above the mean, corrected for the patient’s age and body surface area. All patients had angiographically normal coronary arteries. Patients with a known cause for heart muscle disease, for example coronary artery disease, hypertension, valvar, and congenital heart disease, as well as infective (myocarditis) and metabolic (thyroid disease) causes were excluded. Patients with a history of possible excessive alcohol consumption were included since they may have a genetic predisposition to develop dilated cardiomyopathy.

HLA typing which included class I (HLA-A, B) and class II (HLA-DR) was performed by the serological microtoxicity method at the National Blood Transfusion Service. The HLA distribution in patients was compared to a reference population of 9000 normal controls. Cross sectional, M mode, and Doppler echocardiographic examinations were performed by a single experienced operator on all patients. In keeping with convention, end systolic and end diastolic cavity dimensions, wall thickness, and fractional shortening were measured by M mode at the papillary muscle level in the parasternal short axis view.
Table 1  Prevalence of DCM in 56 screened proband families

<table>
<thead>
<tr>
<th>Definite DCM</th>
<th>Possible DCM</th>
</tr>
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<tbody>
<tr>
<td>Already diagnosed</td>
<td>56/56 (100%)</td>
</tr>
<tr>
<td>Both echo criteria*</td>
<td>9/16%</td>
</tr>
<tr>
<td>One of echo criteria</td>
<td>9/16%</td>
</tr>
<tr>
<td>Sudden death</td>
<td>6/11%</td>
</tr>
<tr>
<td>Total</td>
<td>25/56 (45%)</td>
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*Left ventricular ejection fraction < 50%; left ventricular internal diastolic diameter > 2 SD above mean.

FIRST DEGREE RELATIVES
To date, 200 first degree relatives from 56 proband families have attended for echocardiography. The disease was considered to be familial if at least one first degree relative was diagnosed as having dilated cardiomyopathy, as defined above. If a first degree relative fulfilled only one of the criteria for the diagnosis of dilated cardiomyopathy—that is, a left ventricular ejection below 50% or a left ventricular end diastolic dimension more than two standard deviations above the mean—they were entered into a "possible" category for further follow-up. Any families with a history of premature sudden death (unexplained at an age of less than 50 years) were also included in the "possible" category.

STATISTICS
Differences between proportions of patients and controls, and familial and non-familial patient subgroups, with regard to HLA distribution were compared using the \( \chi^2 \) test.

Results
FAMILY SCREENING
A total of 270 first degree relatives from 75 of the 100 patient families were potentially available for screening. Twenty five of the 100 patients either had no family members available for screening or did not wish their relatives to be contacted. So far, 200 of a possible 270 first degree relatives (74%), from 56 of the 75 proband families (75%), have been screened by echocardiography. Those not screened include relatives still to be contacted, non-attenders, and those residing abroad.

Of the 56 families screened, five (9%) had a first degree relative already diagnosed as having dilated cardiomyopathy, and a further nine (16%) had at least one relative who fulfilled both echocardiographic criteria for dilated cardiomyopathy. Thus the "definite" familial occurrence of dilated cardiomyopathy in this patient group was 14 of 56 (25%). In a further nine families (16%), one relative had a "possible" diagnosis of dilated cardiomyopathy, that is, only one of the two echocardiographic criteria was fulfilled. Six families (11%) gave a history of sudden unexplained death in a first degree relative and these were recorded as "possible" cases of dilated cardiomyopathy. Thus an additional 15 of 56 (27%) showed a "possible" familial tendency to dilated cardiomyopathy. Four families had more than one first degree relative with a definite or possible diagnosis of dilated cardiomyopathy. Therefore the familial occurrence of dilated cardiomyopathy in this patient group was "definite" in 14 (25%) and "possible" in a total of 25 (14 + 11) (45%) of the 56 proband families screened (tables 1 and 2).

HLA DISTRIBUTION
The HLA types in the 100 probands were compared with a reference population of 9000 normal controls from the National Transfusion Service. As compared to these controls, the total group of patients with dilated cardiomyopathy showed no significant differences in allele type. However, when only those dilated cardiomyopathy probands with a familial tendency were evaluated, the DR4 subtype was more common than in the whole patient population or in the controls (68% vs 39% vs 32%). There was no significant difference in the proportion of all patients with dilated cardiomyopathy who had the DR4 subtype compared with the general population. However, within the study group, the proportion of patients with familial dilated cardiomyopathy and HLA-DR4 (17 of 25; 68%) was greater than the proportion of patients with non-familial dilated cardiomyopathy and HLA-DR4 (10 of 31; 32%) (P < 0-05, table 3).

SCREEN DETECTED DILATED CARDIOMYOPATHY
Twenty two asymptomatic first degree relatives had abnormal echocardiographic examinations. Eighteen (82%) were male and the average age was 40 (range 17–60) years. The ECG was abnormal in only four (18%) of these cases, with two patients in atrial fibrillation and two showing non-specific ST changes. Fourteen (64%) of the screen detected cases were positive for the DR4 haplotype. Thus, as was shown for the probands with familial dilated cardiomyopathy, the screen detected relatives were significantly more likely than controls to have the HLA-DR4 subtype (64% vs 32%; P < 0-05).

Discussion
In this study of patients with dilated cardiomyopathy, 25% of cases were definitely familial in nature and 45% showed a possible familial tendency. This definite familial occurrence is similar to two other recent studies from the

<table>
<thead>
<tr>
<th>Available</th>
<th>Screened</th>
<th>Familial tendency</th>
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<tr>
<td>First degree relatives</td>
<td>270</td>
<td>200 (74%)</td>
</tr>
<tr>
<td>Proband families</td>
<td>75</td>
<td>56 (75%)</td>
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The evidence suggests that dilated cardiomyopathy can be associated with the host's immune response and the genetic factors that control this response. It is conceivable that familial dilated cardiomyopathy is the subgroup of patients with the disease with a defect in their immune response. This defect may then manifest itself as an autoantibody directed against the myocardium following an environmental stimulus, for example a viral illness. This theory is lent support by correlations between specific T cell gene alleles and HLA types and the presence of autoantibodies in familial cardiomyopathy. Organ specific cardiac antibodies have also been detected in symptom-free relatives of patients with dilated cardiomyopathy.7

Relatives of dilated cardiomyopathy patients with the DR4 subtype are at particular risk of developing the disease and should probably be screened regularly by echocardiography, as well as counselled regarding potential lifestyle and pharmacological interventions which might alter the natural history of the disease. Obviously, some relatives with a normal echo at a single screening may later develop dilated cardiomyopathy. Only an ongoing prospective study screening all available first degree relatives on a regular basis would determine the true prevalence of familial dilated cardiomyopathy and the usefulness of markers such HLA typing in identifying those families at greatest risk. When sufficient asymptomatic screen detected relatives with dilated cardiomyopathy are identified, randomised trials of ACE inhibition or immunotherapy to slow disease progression should be initiated.

This study was supported in part by a grant from the Mater Hospital Foundation.

5 Michels VV, Moll PP, Miller FA, et al. The frequency of familial dilated cardiomyopathy in a series of patients