Evidence-based diagnosis of familial non-X-linked dilated cardiomyopathy

Prevalence, inheritance and characteristics

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Aims To assess the prevalence of familial non-X-linked dilated cardiomyopathy, to diagnose early asymptomatic cases and evaluate inheritance and characterize clinical phenotypes.

Methods and Results We screened 472 relatives of 104 consecutive patients diagnosed with dilated cardiomyopathy; males with X-linked dilated cardiomyopathy were excluded based on systematic immunohistochemical and molecular analysis. Relatives underwent clinical examination, electrocardiography, echocardiography and serum creatine-phosphokinase determination. Twenty-six index patients (25%) had familial disease: four youths (≤20 years) had rapidly progressive outcome and underwent emergency transplantation. In a sib-pair, the onset was with atrioventricular block. Inheritance was autosomal dominant in 15, undetermined in seven (four sib-pairs); mitochondrial DNA pathological mutations were found in four. The screening identified 23 newly diagnosed relatives in the familial group. Transplantation (P=0.04) and atrial fibrillation (P=0.04) were more frequent, and left bundle branch block (P=0.04) less frequent in index patients with familial than in those with non-familial disease. Several non-affected relatives had instrumental abnormalities potentially useful as pre-clinical markers: their prevalence was similar in both groups.

Conclusions The prevalence of familial, non-X-linked dilated cardiomyopathy was 25%. The immediate benefits of screening family members of index patients was early diagnosis in unaware symptomless affected relatives.

Key Words: Non-X-linked, evidence-based familial, dilated cardiomyopathy.

Introduction

Dilated cardiomyopathy is familial when at least two members of the family are affected¹⁴. The disease is genetically heterogeneous: X-linked, autosomal dominant and recessive as well as matrilinear forms have been reported². Among X-linked forms, dystrophin gene defects can be linked causally to familial dilated cardiomyopathies³. Less frequently, emerin gene defects cause myopathy with atrioventricular block and, occasionally, with dilated cardiomyopathy⁴. The Barth syndrome is another X-linked cardiomyopathy in paediatric subjects⁵. By linkage analysis, eight loci but no disease genes have been identified in families with both autosomal and recessive inheritance⁶-⁸. Analysing candidate genes, two actin gene mutations have been reported in two unrelated families⁹, a desmin gene mutation, in one family with ‘dilated cardiomyopathy restricted cardiac phenotype’¹⁰, and five mutations of the lamin A/C gene in five familial cardiomyopathies with conduction system disease¹¹. Rarely, defects of genes coding for dystrophin-associated glycoproteins cause peripheral myopathies and cardiomyopathies, mostly inherited as autosomal recessive traits¹². Finally, mitochondrial DNA defects have been causally linked or associated to dilated cardiomyopathy, both sporadic and familial¹³.

The overall reported prevalence of familial dilated cardiomyopathy ranges from 2% to 56%, including both X-linked and non-X-linked diseases¹⁴-²⁵. Discrepancies result from different approaches to family study: (1)
pedigree construction, on index patient interview\textsuperscript{[21,22]}, (2) clinical examination of relatives of patients suspected, on pedigree, to have a familial form\textsuperscript{[23]}, (3) clinical evaluation of all informed and consenting relatives (of consecutive patients diagnosed with dilated cardiomyopathy) who agree to be examined, independent of the interview data\textsuperscript{[1,14,24]}. This latter approach provides evidence-based diagnosis and reliable prevalence data of familial dilated cardiomyopathy, and identifies symptomless affected relatives.

This prospective study was set up to assess the prevalence of familial dilated cardiomyopathy, by evaluating patterns of inheritance, characterizing clinical phenotypes and diagnosing early asymptomatic or pre-clinical disease in relatives of index patients. The strategy of investigation was that of screening relatives of consecutive patients in whom X-linked diseases were systematically excluded with immunohistochemical and molecular methods.

**Methods**

Between January 1995 and April 1999, 104 patients diagnosed with dilated cardiomyopathy entered our informative and clinical programme for familial cardiomyopathies. All proband’s relatives, who accepted on informed consent to enter the screening (n=472), were evaluated with clinical examination, electrocardiographic and echocardiographic study and serum creatine-phosphokinase determination. Given that all males patients diagnosed with dilated cardiomyopathy since 1995 underwent systematic immunohistochemical and molecular screening for dystrophin defects (13/201=6.5\%\textsuperscript{[26]}, males with X-linked defects were systematically excluded from the present series.

**Diagnosis in index cases**

Dilated cardiomyopathy was diagnosed on World Health Organization criteria\textsuperscript{[27]}. Diagnostic and exclusion criteria have been previously reported in detail\textsuperscript{[28]}. Briefly, patients diagnosed with dilated cardiomyopathy had no significant coronary artery disease (luminal narrowing $\geq$50\%) by coronary angiography, absence of specific heart muscle disease or myocarditis by endomyocardial biopsy, and reduced (<45\%) left ventricular ejection fraction by cineangiography. The disease was defined as familial when at least two relatives were proven as affected\textsuperscript{[11]}. 

**Family study**

Index patients were informed on the possible familial condition of their disease and asked to inform their relatives on the possibility of receiving clinical evaluation to identify both symptomless patients and subjects with ‘pre-clinical’ signs. Relatives were further informed that the clinical significance and the predictive value of tested abnormalities still have unproven/uncertain diagnostic implications. Only fully informed and consenting subjects were included in the programme and are followed up at regular intervals. Patients and relatives who refused consent did not enter the study. Major reasons for refusal were geographical limitations, privacy and family conflicts. The study protocol has been approved by the scientific and ethical committee of our hospital.

**Pedigree analysis**

Detailed family history was obtained by interviewing both patients and relatives, and then combining and comparing information. For deceased subjects, the family was asked to provide clinical and pathological reports. Although highly suspicious, sudden death without pathological reports in subjects younger than 50 years was not considered sufficient, in kindreds with only one patient, to define the disease as familial. The family trees were obtained combining narrative data supported by clinical reports and clinical screening of relatives. Patterns of inheritance were defined according to Mendelian and matrilineal rules.

Given that the chronic heart failure characteristic of dilated cardiomyopathy is shared by several heart diseases, classification of a patient as affected by dilated cardiomyopathy requires a complete clinical work-up. Therefore, ancestors with a history of cardiac disease with heart failure cannot be accepted as affected by dilated cardiomyopathy unless the appropriate information is available. If this rule is accepted, the hereditary pattern of dilated cardiomyopathy will not be confused by inclusion of spurious cases in the hereditary trees.

**Evaluation of family members**

Each family member underwent assessment by medical history, clinical examination, 12-lead electrocardiogram, signal-averaged electrocardiogram, echocardiogram, as well as serum creatine-phosphokinase determination (normal values $\leq$180 mU . ml$^{-1}$). Family members potentially affected by dilated cardiomyopathy underwent coronary angiography to exclude coronary artery disease\textsuperscript{[28]}. Blood samples from all participants were collected and stored for molecular studies.

**Two-dimensional, M-mode and colour Doppler echocardiographic studies**

Chamber size and wall thickness were measured in the parasternal long axis view, at the level of the papillary muscles (echo equipment: Esaote Biomedica AU3). The predicted left ventricular end-diastolic diameter, corrected for age and body surface area, was calculated with the formula of Henry et al\textsuperscript{[29]}; corrected left ventricular end-diastolic diameter =45.3 $\times$ body surface area$^{0.3}$ $-$ 0.03 $\times$ age $-$ 7.2. The measured left ventricular end-diastolic diameter was expressed as a percentage
ratio: left ventricular end-diastolic diameter % = left ventricular end-diastolic diameter/corrected left ventricular end-diastolic diameter, with a value of 112% as the upper normal limit[29]. The following data were recorded as abnormal: (1) left ventricular end-diastolic diameter >112%; (2) reduced ventricular contractility with fractional shortening <25% or ejection fraction <45%.

Signal-averaged electrocardiogram

Electrocardiograms were recorded with HP Page Writer Xli M1700A equipment; data were analysed with Predictor I software (Corazonics Bispec, U.S.A.) (sampling frequency: 2000 Hz; bi-directional 40–250 Hz band pass filter)[30]. To obtain a noise level ≤0.5 μV, 150 and 300 beats of each lead were averaged. A minimal number of 250 beats was averaged (0–30–0–70). Time domain was analysed with a 40 Hz pass filter. Normal values were fixed at low amplitude signals of the terminal portion of the QRS complex <38 μV, root mean square voltage of the terminal 40 ms of the QRS complex >20 μV, total QRS complex duration: <112 ms. The combination of at least two abnormal values defined the presence of late potentials.

Exclusion criteria

Family members with one of the following diseases were unsuitable for definition of familial dilated cardiomyopathy: hypertension (defined as ≥160/100 mmHg at repeated measurements), insulin-dependent diabetes mellitus, valvular heart disease, coronary artery disease, congenital heart disease, thyroid dysfunction, anaemia, amyloidosis or sarcoidosis, hypertrophic cardiomyopathy, drugs and substances with a cardiotoxic effect and alcohol consumption ≥100 g per day. Hypertensive subjects (even pharmacologically controlled) with left ventricular dysfunction were excluded from this study.

Serum creatine-phosphokinase abnormalities

Increased serum creatine-phosphokinase (normal value: ≤180 mU . ml⁻¹) was considered a potential marker of subclinical myopathy; it was measured in the entire population and, in cases of abnormal levels, also after 3 days of limited physical activity when values were increased at the first testing.

Pathological and molecular study

All index patients underwent endomyocardial biopsy according to standardized procedures[31]. Samples were processed for light microscopy and ultrastructural study[32]. One frozen sample was used for molecular studies[33] and one for dystrophin immunostaining[13]. All males who came to our centre since 1995 entered a dedicated programme of molecular screening for dystrophin gene defects; affected males and their blood relatives were excluded from the present study. All patients with organelle abnormalities, both ultrastructural and histoenzymatical, and/or with maternal inheritance, were screened for mitochondrial DNA mutations[13]. Granulocytopenia was tested in all cases. Emerin defects were screened by immunostaining with antiemerin antibodies, and endomyocardial biopsies[24]. None of the 104 patients had emerin defects or Barth syndrome.

Follow-up

Index patients were followed-up for a mean time of 34-8 ± 37-9 months. All participants in the study were invited to refer to our centre with any new cardiovascular problem or symptom and to inform cardiologists of non-cardiovascular problems. Clinical controls for all family members are in progress.

Statistical analysis

The statistical analysis compared data from index patients and relatives of the two groups of familial and non-familial dilated cardiomyopathy. For categorical variables, we used the chi-squared test; continuous data, we used Student’s t-test for independent samples. The analysis was performed using the statistical package STATA 5.0 (1996).

Results

Familial dilated cardiomyopathy

Of the 104 index patients, 26 (25%) had familial non-X-linked dilated cardiomyopathy (Table 1). Based on clinical presentation and outcome, two major phenotypes were identified: the juvenile dilated cardiomyopathy and that with early atrioventricular block. The majority of familial cases did not fit with the above phenotypes.

Juvenile malignant phenotype. Four patients younger than 20 years of age, three males and one female, had clinical evolution from onset of symptoms to end-stage congestive heart failure in 2.5 ± 2.0 months. All underwent emergency transplantation. Inheritance was autosomal dominant in three families (the pedigree of one of these families is shown in Fig. 1A); a mitochondrial DNA pathological mutation was identified in one family. Parents had long-lasting (two fathers) and asymptomatic disease (one mother); three affected brothers of one index patient are symptomless after 12 months from the diagnosis.
Phenotype with early conduction defects in a sib-pair. Two brothers (43 and 53 years old, respectively) showed a disease onset with atrioventricular block. The disease progressed throughout refractory chronic heart failure after 5 and 10 years, respectively. The proband underwent transplantation and his brother is waiting for transplantation.

Remaining 21 patients. These did not show clinical features useful in subgrouping the disease according to peculiar phenotypes; inheritance was autosomal dominant in 12 (one example is shown in Fig. 1B), undetermined in six (three sib-pairs) (four examples are shown in Fig. 2). In three, pathological mitochondrial DNA mutations were identified.

Non-familial dilated cardiomyopathy

Of the 104 index patients, 78 (75%) (63 males and 15 females) did not have affected relatives in their families. Gender, age, onset, and clinical data and disease evolution did not allow a further subgrouping of these patients (Table 1).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Familial n=26</th>
<th>Non-familial n=78</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years) (range)</td>
<td>42±13-4 (15–57)</td>
<td>44.6±10-5 (16–65)</td>
<td>ns</td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>73/27</td>
<td>81/19</td>
<td>ns</td>
</tr>
<tr>
<td>Duration of disease (years)</td>
<td>4.8±9</td>
<td>3±5.6</td>
<td>ns</td>
</tr>
<tr>
<td>NYHA I-II</td>
<td>11 (42%)</td>
<td>45 (58%)</td>
<td>ns</td>
</tr>
<tr>
<td>NYHA III-IV</td>
<td>15 (58%)</td>
<td>33 (42%)</td>
<td>ns</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>7 (27%)</td>
<td>9 (11%)</td>
<td>0.04</td>
</tr>
<tr>
<td>LBBB</td>
<td>5 (19%)</td>
<td>31 (40%)</td>
<td>0.04</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>68±9.7</td>
<td>69±9.4</td>
<td>ns</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>24±8.4</td>
<td>26±8.7</td>
<td>ns</td>
</tr>
<tr>
<td>Outcome at 36 months follow-up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>3 (11%)</td>
<td>11 (14%)</td>
<td>ns</td>
</tr>
<tr>
<td>Transplant</td>
<td>12 (46%)</td>
<td>18 (23%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

NYHA=New York Heart Association; LBBB=left bundle branch block; LVEDD=left ventricular end-diastolic diameter; LVEF=left ventricular ejection fraction. Total number of index patients=104

The screening of the 317 relatives of patients with non-familial dilated cardiomyopathy identified two affected subjects in two unrelated families: one was a 48-year-old alcohol abuser (father of a 21-year-old female index patient) with clinical and echocardiographic diagnosis of dilated cardiomyopathy. The second was a 60-year-old male, brother of a transplanted patient. These two key relatives refused coronary angiography; they are in NYHA class II (Table 2). From family history, 11 subjects in the 64 families had died suddenly: four were younger than 50 (range 39–49) and seven were older (range 60 to 85 years). Clinical and/or autopsy documentation was not available for any of the deceased subjects. These narrative data were considered insufficient for evidence-based diagnosis of familial cardiomyopathy in families with only one proven patient.

Outcome data in index patients with familial and non-familial dilated cardiomyopathy

Heart transplantation and atrial fibrillation were significantly more frequent and left bundle branch block less frequent in index patients of familial than non-familial dilated cardiomyopathy (Table 1).
Prevalence data on instrumental abnormalities in ‘healthy’ relatives of index patients

The prevalence of cardiac abnormalities and increased serum creatine-phosphokinase in relatives of index patients with familial and non-familial dilated cardiomyopathy was similar (Table 2).

Discussion

By screening all informed and consenting relatives of 104 consecutive index patients diagnosed with non-X-linked dilated cardiomyopathy, we obtained a prevalence of evidence-based familial disease of 25%. Similar prevalence values were reported in family studies in which relatives of all index patients were examined, independent of informative histories or pedigrees\(^1\text{-}^{23}\). By screening relatives of patients suspected, on pedigree, as affected by familial disease, Grunig et al. found 10·8% confirmed, and 24·2% highly suspected of familial dilated cardiomyopathy\(^{14}\). Both strategies have major advantages: Michels et al.\(^1\) and Keeling et al.\(^{23}\) explored the possibility that familial dilated cardiomyopathy escapes detection when only interview data are used to assess the familial condition, while Grunig et al. enrolled a high number of patients and screened family members on a potentially informative pedigree\(^{14}\). Prevalence values are potentially biased, both under- and over-estimated, in non-prospective studies.

Figure 1 Two pedigrees of families with autosomal dominant pattern of inheritance. In family A, pathological mitochondrial DNA mutations were excluded; in family B, subject II7 died before being fully diagnosed with dilated cardiomyopathy. Black squares and circles: affected. Arrow: proband. Relatives with cardiac abnormalities: small red squares/circles: left ventricular end-diastolic diameter >112%; small green squares/circles: decreased fractional shortening; small blue squares/circles: late potentials; small yellow square/circles: increased serum CPK levels; combined abnormalities in the same subject: small black squares/circles.
Figure 2  Pedigrees of four familial dilated cardiomyopathies in which inheritance could be either autosomal dominant (A, C, D), or recessive (B) if abnormal instrumental markers are predictive of dilated cardiomyopathy: follow-up will clarify the pattern of inheritance. Mitochondrial DNA defects have been excluded in families B and D. Black squares and circles: affected. Arrow: proband. Relatives with cardiac abnormalities: small red squares/circles: left ventricular end-diastolic diameter >112%; small green squares/circles: decreased fractional shortening; small blue squares/circles: late potentials; small yellow square/circles: increased serum CPK levels; combined abnormalities in the same subject: small black squares/circles.
that enrol patients from historical databases: families with more than one affected member are highly motivated to enter clinical screening programmes, and highly suspicious pedigrees may increase priority in evaluation of informative families. In our opinion, the prevalence of familial dilated cardiomyopathy should be calculated when relatives of consecutive patients are screened, and when reliable documentation for unexamined patients is provided, independent of the family history that can be derived from interview of the index patients. For instance, nine of our 104 index patients (8% and 31/4%) have been diagnosed with familial dilated cardiomyopathy after identification of affected, unaware relatives.

The characterization of clinical phenotypes was quite difficult in our series. We identified one familial dilated cardiomyopathy with early atrioventricular block similar to two of the families reported by Grunig et al. and in one family by Mestroni et al. This rare phenotype, which was first reported in Ohio families, seems to differ from other dilated cardiomyopathies, given that there is a long interval between the appearance of atrioventricular block and of dilated cardiomyopathy. In this connection, defects of the lamin A/C gene have been causally linked with dilated cardiomyopathy with conduction system disease. The other major phenotype was the juvenile familial ‘malignant’ dilated cardiomyopathy: the four youngest patients of our series underwent emergency transplantation within a few months from onset of the disease. These data fully confirm the observations of Valantine et al. that familial juvenile dilated cardiomyopathy has a fast evolution to end-stage disease, worse than juvenile non-familial dilated cardiomyopathy in our series. Furthermore, the overall clinical profile of patients with familial dilated cardiomyopathy was more severe than that of patients with non-familial forms, with a significantly higher number of cases rapidly evolving to end stage disease and needing transplantation in the former.

Cardiac abnormalities, such as atrial fibrillation and left bundle branch block, although significantly different in the two groups of patients with familial and non-familial forms, did not provide information useful for the prognostic stratification of each patient. The significance of high serum creatine-phosphokinase levels remains obscure: in our series, this value was high in non-familial forms, with a significantly higher number of cases rapidly evolving to end stage disease and needing transplantation in the former.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Familial</th>
<th>Non-familial</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall population</td>
<td>155</td>
<td>317</td>
<td></td>
</tr>
<tr>
<td>Age (mean ± SD)</td>
<td>33 ± 18</td>
<td>32 ± 17</td>
<td></td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>79/76</td>
<td>140/177</td>
<td></td>
</tr>
<tr>
<td>Excluded</td>
<td>13 (8%)</td>
<td>36 (11%)</td>
<td></td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>2</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>6</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Hypertension+other disease</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Interatrial defect</td>
<td>0</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Valvular heart disease</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Suitable</td>
<td>142 (91%)</td>
<td>281 (88%)</td>
<td>ns</td>
</tr>
<tr>
<td>Affected</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-affected</td>
<td>119</td>
<td>279</td>
<td></td>
</tr>
<tr>
<td>Abnormalities in non-affected</td>
<td>49 (19%)</td>
<td>90 (27%)</td>
<td></td>
</tr>
<tr>
<td>LVEDD &gt;112%</td>
<td>17 (34%)</td>
<td>29 (32%)</td>
<td>ns</td>
</tr>
<tr>
<td>LV FS &lt;25%</td>
<td>3 (6%)</td>
<td>1 (1%)</td>
<td>ns</td>
</tr>
<tr>
<td>Late potential</td>
<td>20 (40%)</td>
<td>39 (43%)</td>
<td>ns</td>
</tr>
<tr>
<td>sCPK &gt;180 mU. ml⁻¹</td>
<td>19 (38%)</td>
<td>28 (31%)</td>
<td>ns</td>
</tr>
<tr>
<td>LAH or LBBB</td>
<td>2 (4%)</td>
<td>2 (2%)</td>
<td>ns</td>
</tr>
<tr>
<td>Single abnormality</td>
<td>38 (77%)</td>
<td>77 (85%)</td>
<td>ns</td>
</tr>
<tr>
<td>Combined abnormalities</td>
<td>11 (22%)</td>
<td>13 (14%)</td>
<td>ns</td>
</tr>
</tbody>
</table>

*Two males, 48 and 60 years old, both without angiography, the youngest with alcohol abuse history; LVEDD=left ventricular end-diastolic diameter; LV FS=left ventricular fractional shortening; sCPK=serum creatin-phosphokinase; LAH or LBBB=left anterior hemiblock or left bundle branch block; *no case among non-affected had increased LVEDD combined with decreased FS. Total number of relatives in dilated cardiomyopathy=417.

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six conscious of having some ‘cardiac problem’ or generically diagnosed with ‘cardiomyopathy’. All entered a regular diagnostic protocol, clinical follow-up and optimization of medical treatment/transplantation programme. Whether this low number of unexpected diagnoses justifies such a large programme, can be matter of discussion, especially when economic resources are limited or public health funding is not programmed for a new field of disease.

A potential benefit from studying relatives of index patients is the identification of ‘cardiac abnormalities’ reported as potentially useful for pre-clinical diagnosis. The only available data come from a series with 39-months of follow-up: 12 of 45 subjects with left ventricular enlargement (27%), and none of 13 subjects with decreased fractional shortening, developed dilated cardiomyopathy[24]. Therefore, left ventricular enlargement seems to be the only marker, among those tested, that predicts dilated cardiomyopathy in a given series. A longer follow-up might modify these percentages and raise the proportion of familial diseases: further studies in larger series are necessary to confirm the predictive value of left ventricular enlargement. The disease is not necessarily preceded by known cardiac abnormalities: three of the 15 (20%) patients who developed dilated cardiomyopathy in the course of the follow-up had no echocardiographic abnormalities 3 years before[24]. The potential predictive role of late potentials recognized with the signal average electrocardiogram did not allow a useful distinction to be made between familial and non-familial disease and needs further evaluation at follow-up. In any case, the pioneering study done by Baig et al.[24] is, at present, the only encouragement for continued screening of family members of dilated cardiomyopathy patients. A series of major and minor criteria (the latter based on mild cardiac abnormalities) has been recently proposed[35]: their application could contribute to the establishment of the predictive value of tested abnormalities.

Our study differs from earlier ones[14,23,25] because we excluded X-linked cardiomyopathies. In our centre all consecutive males diagnosed with dilated cardiomyopathy undergo screening for dystrophin defects, using both immunohistochemistry on endomyocardial biopsy and molecular analysis on peripheral blood DNA[26]. However, dystrophin defects rarely present at onset as dilated cardiomyopathy[36], only two of the numerous families investigated by Grunig et al.[14] and four of the patients evaluated by Mestroni et al.[25] had X-linked dilated cardiomyopathies. Furthermore, X-linked dilated cardiomyopathies are often associated with raised serum creatine-phosphokinase (information available at www.dmd.nl) making it likely that, in these patients, dystrophin defects are screened with respect to other patients.

Different considerations apply to dilated cardiomyopathy associated with mitochondrial DNA defects, even when mutations have all the necessary characteristics for a pathological definition[13]. Without the support of linkage analysis, the exclusive causative role of these mutations cannot be fully proven. In our families with pathological mitochondrial DNA mutations, an autosomal dominant pattern of inheritance cannot be excluded and, although it is likely that mitochondrial DNA defects play some role in the disease, nuclear gene mutations could coexist. For instance, in hypertrophic cardiomyopathy, the coexistence of two pathological mutations has recently been shown to affect the same gene[77], two disease genes[80] as well as the two DNAs, nuclear and mitochondrial[89].

In conclusion, it seems that all patients diagnosed with dilated cardiomyopathy are potentially affected by familial forms until relatives are proven to be non-affected. The diagnosis of familial disease should be evidence-based rather than derived from patient’s narratives. To reach consensus on the proportion of familial forms, uniform and rigorous diagnostic criteria have to be adopted in prospective studies enrolling consecutive patients. Familial dilated cardiomyopathy has a poorer clinical outcome than non-familial disease; this is especially the case for the juvenile phenotype. As for pre-clinical markers potentially helpful in identifying subjects who might develop the disease, further data should be obtained alongside those reported by Baig et al. on left ventricular enlargement[24]. It is clear that the clinical evaluation of family members has an immediate impact in the identification of symptomless patients, who are often unaware of their disease. Finally, all data coming from different studies done with similar criteria can constitute a pool for future research of disease genes in families, especially in those sharing similar phenotypes.


References


