Idiopathic familial myocardiopathy in three generations: A clinical and pathologic study

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Hypertrophic or non-dilated cardiomyopathy frequently has a familial incidence1-4 and demonstrates an autosomal dominant mode of inheritance. In contrast, in congestive or dilated cardiomyopathy it is rare to find families in which more than one member is affected,5-6 and virtually all cases of congestive cardiomyopathy are considered sporadic. This report describes clinical and morphologic features of an idiopathic non-hypertrophic myocardiopathy which differs from sporadic idiopathic congestive cardiomyopathy both by its clinical presentation and its occurrence in three and possibly five generations of a single family (Table I). The autosomal dominant pattern of inheritance for the cardiac abnormalities in this family, and the lack of distinctive structural abnormalities in the hearts of the three direct line descendents which were studied at autopsy suggest the possibility of a genetic metabolic abnormality of myocardium as a causative factor in this family and in some sporadic cases of idiopathic myocardiopathy.

Case report

On March 29, 1973, approximately one year after the unexpected death of her son, a previously healthy 44-year-old mother of three collapsed suddenly while playing tennis. She was brought into a local hospital in ventricular fibrillation, was converted to sinus rhythm by electroshock, but died four days later having not regained consciousness. She was known to have had a systolic murmur since childhood, first evaluated when she was three years old and believed to be functional. Because of vague chest pain, an evaluation 10 years before her death revealed a systolic murmur in the pulmonic area, a normal-sized heart, and borderline abnormalities of the ST segment on electrocardiogram (ECG). One year before her death an ECG during exercise showed nonspecific ST segment abnormalities and premature ventricular contractions. Although she denied any symptoms other than occasional chest pain, over the eight-year period before her death she had had two unexplained fainting spells.

At autopsy her heart weighed 385 grams, had a globular configuration, mild acute fibrinous pericarditis, and left ventricular dilatation and hypertrophy. There was no disproportionate septal hypertrophy. The mitral valve showed thickening and rolling of its margins (Fig. 1) with chordal shortening but no commissural fusion. The left ventricular endocardium was involved by a diffuse endocardial fibroelastosis (Fig. 2). Histologic examination of myocardium showed scattered fibrosis, prominent perinuclear lipofuchsin accumulation in muscle cells. Basophilic degeneration, present in moderate degree, was evident by light microscopy which by
Fig. 1. Views of left side of the heart of the index case (No. 4) showing the globular configuration of the left ventricle, endocardial fibroelastosis especially prominent in the left ventricular (LV) outflow area, and rolling of the margins of the mitral valve leaflets secondary to mitral regurgitation. A. Outflow tract of left ventricle. AV = aortic valve. B. Opened left atrium (LA) and left ventricle.

Fig. 2. Histologic sections from heart shown in Fig. 1. A. Marked endocardial fibroelastosis. The endocardium is approximately five times thicker than normal and contains prominent elastic lamellae, stained black. (Verhoff-van Gieson stain; original magnification ×375.) B. Myocardium showing strongly PAS positive intracellular material characteristic of basophilic degeneration (BD). (Periodic-Acid Schiff stain; original magnification ×125.) B, lower panel. Transverse section of myocardial cell with basophilic degeneration. (Toluidine blue stain; original magnification ×750.) C. The rolled margin of the mitral valve showing changes characteristic of long-standing mitral regurgitation. (Verhoff-van Gieson stain; original magnification ×25.)

Methods

Medical genealogical study. The sudden unexpected death of this 44-year-old woman approximately one year after the sudden death of her previously healthy 20-year-old son suggested that a heritable cardiac disorder might exist within some segment of this family. To explore this hypothesis a detailed family tree was constructed and medical information was sought.
Table I. Clinical data in five generations

<table>
<thead>
<tr>
<th>Patient number, age &amp; sex</th>
<th>Clinical history</th>
<th>Electrocardiogram</th>
<th>Clinical course</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 52F</td>
<td>Active unrestricted life</td>
<td>+</td>
<td>Sudden death due to “fatty degeneration of the heart”</td>
</tr>
<tr>
<td>2 57F</td>
<td>Occasional “heart attacks” because of “heart of someone who drank too much coffee” over 2 years PTD; otherwise well.</td>
<td>+</td>
<td>Sudden death due to “acute cardiac dilatation”</td>
</tr>
<tr>
<td>3 60F</td>
<td>Wolff-Parkinson-White syndrome; active unrestricted life; “spell” 1 month PTD: premonition of death</td>
<td>0</td>
<td>Sudden death</td>
</tr>
<tr>
<td>4 44F</td>
<td>Vague chest pains x 8 yrs.; palpitations, mild dyspnea on exertion 2 years. PTD</td>
<td>+</td>
<td>Sudden death</td>
</tr>
<tr>
<td>5 49F</td>
<td>Active life; no symptoms</td>
<td>+</td>
<td>Alive and well</td>
</tr>
<tr>
<td>6 20M</td>
<td>None until fatigue, flu-like syndrome 4 days before death</td>
<td>+</td>
<td>Acute heart failure and unexpected death</td>
</tr>
<tr>
<td>7 23F</td>
<td>None except for occasional vague chest pain; active life</td>
<td>+</td>
<td>Alive and well</td>
</tr>
<tr>
<td>8 24F</td>
<td>Active unrestricted life</td>
<td>+</td>
<td>Alive and well</td>
</tr>
<tr>
<td>9 26F</td>
<td>Active unrestricted life</td>
<td>+</td>
<td>Alive and well</td>
</tr>
</tbody>
</table>

Symbols and abbreviations: ? = unknown; + = present; 0 = not present; - = not done; LV = left ventricle; EF = ejection fraction; PTD = prior to death.

on relatives of the deceased woman including offspring, parents, and grandparents on both sides of each family. Heart disease and cardiac deaths were preponderant in one segment of the family, and could be traced back five generations in a direct line. A detailed historical search of this branch of the family was undertaken which included interviews of family members in three generations, review of medical records and death certificates in all five generations, and prospective medical examinations, including electrocardiograms and chest x-rays in all living family members. Living family members who demonstrated any cardiac abnormality underwent
Idiopathic familial myocardial interstitial fibrosis

GENERATION

CASE I

Q PROBABLE MYOCARDIOPATHY
\( \square \) DEFINITE MYOCARDIOPATHY
\( \bigcirc \) SUDDEN DEATH

Fig. 3. Family tree. Case numbers refer to patients in text and on Table I. Numbers below circles and squares refer to individual's age as of 1976, or age at time of death.

Further evaluation including exercise stress testing, echocardiography, cardiac fluoroscopy, and in one instance cardiac catheterization.

Autopsy studies. Complete autopsies were obtained on three first-degree relatives in three different generations with cardiac disease. The hearts were reviewed grossly and by light microscopy. Histological stains performed included hematoxylin and eosin, Congo Red, Periodic acid-Schiff, phosphotungstic acid hematoxylin, Verhoeff's elastin and sudan IV. Electron microscopy was performed on formalin-fixed tissue from two of the three hearts. Conduction system was examined by a method described previously and adapted from Hudson.

Results of a genealogical study

Family tree. The family tree of the segment of the family under study is shown in Fig. 3. The generations are designed I to V and clinical details of corresponding family members with definite or probable cardiomyopathy are summarized in Table I. The proband, the 44-year-old woman (Case 4), is in the fourth generation of the family.

Generation I. The earliest recorded ancestor with cardiac disease in this family (Generation I) was the proband's great-grandmother who died before the turn of the century at age 52 of "fatty degeneration of the heart" which was apparently a clinical diagnosis. Little is known about her clinical details except that she had a longstanding heart murmur, and died at an unexpectedly early age. Family records indicate that all her siblings (the exact number is not clear) lived into their 70's or 80's.

Generation II. The second generation of this family consisted of four children, and two of them died cardiac deaths. One, a son, died in his early 20's also before 1900, of clinically diagnosed "valvular disease of the heart." The other, a daughter (Case 2) died at age 57 of "acute cardiac dilatation and chronic myocarditis" and had a history of what were probably premature ventricular contractions. The other two members of Generation II were apparently well, living into old age.

Generation III. Seven offspring comprised the third generation of this family. The mother (Case 3) of the index case was the third born of these seven siblings. During a hospitalization approximately 20 years before her death, she was noted to have a Wolff-Parkinson-White syndrome, but led a generally vigorous active life. At age 60, she died suddenly in her sleep. In retrospect there was
Fig. 4. A, Histologic sections of myocardium from mother of index case (No. 3) showing extensive basophilic degeneration of the myocardium. (Periodic-acid Schiff stain; original magnification ×125.) B, Longitudinal section of muscle cells shown in A with basophilic degeneration. (Toluidine blue stain; original magnification ×750.)

...some suspicion that she may have had a premonition of death, and one month before her death she suffered a transient spell "resembling petit mal." At autopsy the only significant abnormality was in her heart, which had four chamber dilatation and a focally thickened and grayish white left ventricular endocardium. The valves were minimally thickened, and the coronary arteries were widely patent. Myocardium showed severe focal replacement fibrosis, extensive basophilic degeneration (Fig. 4), and prominent perinuclear lipofuchsin deposits present in many cardiac muscle cells. Except for basophilic degeneration, no other abnormalities of myocardial fine structure could be seen by electron microscopic examination of previously formalin-fixed myocardium. Death was attributed to a myocardial disease of unknown etiology.

Although details of all her siblings are not available she, like her mother, had a brother who died in his early twenties of "acute myocarditis" and mitral insufficiency after three months of cardiac symptoms and associated systemic emboli. Another brother died shortly after birth of "apnea neonatorum," but it is not known whether cardiac disease was present. There was no known cardiac disease in the other four members of this generation.

Generation IV. The fourth generation of this family consists of the three offspring of Case 3, the 60-year-old woman who died in her sleep, and includes the index case (Case 4) reported above who was the second oldest of her children. The first member of this generation, also a daughter (Case 5), has clinical findings similar to those of other family members including a short PR interval, nonspecific ST-T wave changes, and exercise-related premature ventricular contractions. By echocardiogram she has a mildly dilated left ventricular cavity (5.5 cm.) and no evidence of asymmetric hypertrophy. She remains clinically well and asymptomatic at age 49. The third child in this generation, a 43-year-old male physician, is well without evidence of cardiac abnormality by physical examination, electrocardiogram, electrocardiographic stress test, or echocardiogram.

Generation V. Eight offspring of these three children comprise the fifth generation of this family, and four of the eight have evidence of a cardiac abnormality similar to that present in the previous generations. Within this fifth generation was the 20-year-old son (Case 6) of the index case who died unexpectedly approximately one year before his mother. This young college student had been in excellent general health and had recently passed a physical examination for admission to the lacrosse team. Four days before his death he complained of unusual fatigue, and subsequently developed a flu-like illness. Twenty-four hours after admission to the college infirmary, he died unexpectedly with left-sided congestive heart failure. At autopsy, his heart, weighing 540 grams, showed biventricular dilatation and hypertrophy, focal fibrosis, and a thinned gray-white endocardium. The posterior tricuspid leaflet was adherent to the septal endocardium and the mitral valve had nodular thickening and rolling of its free margin. The coronary arteries were normal. Death was attributed to congestive heart failure caused by primary myocardial disease with endocardial fibroelastosis of unknown etiology.
This deceased young man had two younger siblings. His sister (Case 7) is an asymptomatic athletic young woman who has had a precordial systolic murmur since birth, nonspecific ST and T wave abnormalities, and exercise-aggravated multifocal premature ventricular contractions (Fig. 5). On several occasions she has had a short PR interval (< .12 sec.) with a normal QRS duration. Her heart is normal-sized by chest radiograph and by echocardiogram the left ventricular cavity size is at the upper limits of normal. The third sibling in this family is a young brother who is entirely free of any detectable cardiac abnormality by examination, chest radiograph, rest and stress electrocardiogram, echocardiogram, and Thallium 201 myocardial perfusion scan. Also within the fifth generation of this family are the three children of Case 5, the sister of the index case, two of whom have evidence of a similar myocardial disorder including systolic
murmurs, short PR intervals, and minor ST segment abnormalities on electrocardiogram. One of these two sisters (Case 8) also had a normal cardiac silhouette by chest radiograph and like her mother, aunt, and cousin (Case 7), multifocal premature ventricular contractions worsened by exercise. By echo she has a mildly dilated and hypodynamic left ventricle with an ejection fraction of 41 per cent and no evidence of asymmetric hypertrophy (Fig. 6). She was the only family member to undergo cardiac catheterization, which demonstrated normal pressures, a slightly enlarged left ventricle, and generalized moderately impaired over-all left ventricular contractility. The two other members of Generation V are offspring of the unaffected brother of the index case and both are free of cardiac abnormalities by physical examination and noninvasive laboratory studies including electrocardiograms, chest radiographs, and echocardiograms.

**Therapy.** In two members of Generation V (Cases 7 and 8) anti-arrhythmic therapy was instituted. After three baseline ECG stress tests and 24-hour Holter monitoring, anti-arrhythmic agents were started and repeat stress tests were performed. Propranolol had little effect on the arrhythmias. Both quinidine and diphenylhydantoin (Dilantin) were effective in suppressing the in-exercise multifocal premature ventricular contractions and in decreasing postexercise extrasystoles. Because of side effects related to quinidine, dilantin was chosen for long-term therapy in both patients. Dilantin in a dose of 300 mg. a day has been well tolerated, and repeat stress tests at six months and one year's time have continued to show that ectopy is suppressed during, and diminished after, maximal exercise compared to the pretreatment studies.

In contrast to these two patients, anti-arrhythmic therapy was unsuccessful instituted in one member of generation IV (Case 5). Quinidine was not tolerated and resulted in syncope, and Dilantin and procainamide had no effect on the frequency of her premature ventricular contractions.

**Discussion**

A similar type of cardiomyopathy, distinctive both in its clinical presentation, its course, and its morphology, developed in several members of at least three and possibly five generations of an otherwise healthy family. The clinical manifestations of this familial myocardial disease are distinct from the usual forms of “sporadic” congestive cardiomyopathy. Rather than being the chronic debilitating disorder lasting for a few years usually seen with idiopathic congestive cardiomyopathy, this familial cardiomyopathy ran a relatively long but benign subclinical course with those affected appearing healthy, vigorous, and asymptomatic. With most dilated congestive cardiomyopathies, murmurs, electrocardiographic abnormalities, and arrhythmias become manifest along with symptoms of heart failure and signs of cardiac dilatation and do not precede them. In the patients described here, however, precordial murmurs were most often detected in the first few years of life, and conduction and rhythm disturbances were detected without associated heart failure or gross cardiac dilatation. Even in the family members who died suddenly, symptoms during life were minimal and signs of heart failure were present, if at all, for only a brief time before death. The clinical picture of this cardiomyopathy also suggests that the same disorder may occur with variable severity in different affected family members. Although two family members died prematurely in their 20's and 40's, respectively, one lived into her 60's suggesting that the disorder can be compatible with a normal or near normal life span.

The familial pattern of this myocardial disease suggests an autosomal dominant mode of inheritance. Of the 11 direct descendents of the mother of the index case, six had evidence of cardiac abnormalities. It is not clear, however, whether this disorder has a sex predominance. Although female sex predominates in the affected family members, women predominate in the offspring. It is of note, however, that the one affected male who had the most severe form of the disease with death at age 20 also had congestive heart failure terminally. The direct line descendents in Generations II, III, and V, each had a brother dying in his early 20's of cardiac failure. In Generation III there was also a male sibling who died at birth but cardiac disease was not documented. Although detailed medical records or autopsy information are only available on one of the three likely affected males, one might wonder whether the cardiac abnormalities in this family were manifested in a milder form in the affected females.

The over-all picture of the familial cardiomyopathy described here with autosomal dominant
Idiopathic familial myocardiopathy

inheritance and variable penetrance, associated with murmurs, electrocardiographic abnormalities, a paucity of symptoms, and sudden cardiac death appears superficially similar to the pattern of hypertrophic cardiomyopathy, but echocardiographic, cardiac catheterization, and morphologic studies indicate that it is rather more akin to a congestive, dilated type of cardiomyopathy. Nonetheless, morphologic observations on the family members from three different generations reaffirm the clinical impression that it comprises a most unusual form of dilated cardiomyopathy. The three hearts studied at autopsy showed similar morphologic abnormalities that varied only in degree. Left ventricular hypertrophy and dilatation, endocardial fibroelastosis, and relative mitral insufficiency with secondary rolling and shortening of the leaflet margins was most prominent in the heart of the 20-year-old, intermediate in that of the 44-year-old mother, and most mild in his 61-year-old grandmother, suggesting again that the disease in its most severe form led to early death but in its milder form was consistent with a near normal life span. The complex of morphologic features in these three hearts resembles both the idiopathic endocardial fibroelastosis of children, and the idiopathic dilated cardiomyopathy of adults. Although the latter is rarely familial, endocardial fibroelastosis of children may be inherited in an autosomal recessive pattern. Unlike the familial myocardiopathy described here, idiopathic endocardial fibroelastosis usually manifests itself within the first few years of life with symptoms of heart failure and at times conduction disturbances, and leads to death within a matter of months to a few years. Some patients have been reported to live to the second decade but these represent a distinct rarity.

Although the cause of endocardial fibroelastosis is unsettled, it may be a consequence and not a cause of left ventricular dilatation resulting from an underlying myocardial weakness. Endocardial fibroelastosis is known to exist in a "secondary" phenomenon in a variety of congenital and acquired diseases associated with ventricular dilatation, particularly when present early in life. Similarly, the endocardial fibroelastosis present in the three hearts under study may be a response to long-standing, mild ventricular dilatation, as was documented angiographically in one clinically asymptomatic family member.

An unusual morphologic feature of the myocardial disease in this family is the marked basophilic degeneration seen in the hearts of the grandmother and present to a moderate degree in the mother. Basophilic degeneration is a focal myocardial disorder characterized by the deposition of a glycogen-like granular substance within the central portions of myocardial fibers. A mild degree of basophilic degeneration is present in over 80 per cent of hearts, particularly with advanced age, but there are certain disease entities in which basophilic degeneration exceeds that expected from age alone and may in such instances be related to myocardial dysfunction. In myxedema heart disease in which there is a generalized myocardial hypodynamic state (generally believed to be sufficient for diminished metabolic demands), basophilic degeneration of myocardium is generally increased and may be related to abnormal glycogen metabolism. Some patients with sporadic and familial idiopathic congestive myocardiopathy have also been reported to have extensive basophilic degeneration of myocardium but, as in our patients, it is uncertain whether the degenerative changes in myocardium are morphologic manifestations of an underlying metabolic defect causing muscle weakness, or are unassociated or secondary changes.

Another feature distinguishing this familial cardiomyopathy from the sporadic congestive myocardiopathy is the degree of myocardial fibrosis. In idiopathic congestive cardiomyopathy, fibrosis is usually minimal and limited mainly to the interstitium. Frank replacement fibrosis unassociated with coronary artery disease is unusual, although it may be seen in some rare cardiomyopathies such as that associated with scleroderma. The degree of myocardial fibrosis present in these three hearts exceeds that usually seen in idiopathic myocardial disease. The fact that the fibrosis, endocardial fibroelastosis, and basophilic degeneration appear to become more prominent with age suggests that none of these is the primary disorder, although they may, in fact, reflect an underlying primary myocardial disturbance.

The arrhythmias and repolarization abnormalities, the major clinical manifestations of this cardiomyopathy, showed a striking similarity among affected family members. Familial arrhythmias and conduction disturbances have been reported in a variety of settings. Families
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with isolated repolarization abnormalities such as the long QT interval associated with sudden death have been reported.14, 25 Idiopathic ventricular tachycardia has been described in siblings without detectable heart disease themselves who were part of a family with hereditary congestive myocardopathy.26, 27 There have also been reports of congenitally malformed conduction systems associated with sudden death in several family members with otherwise normal hearts,74 and the mitral valve prolapse syndrome which may be associated with arrhythmias and sudden death, in some families may be transmitted as an autosomal dominant trait.28, 30

The finding of a pre-excitation syndrome in at least five of these family members described here may be important. Since the first report of the Wolff-Parkinson-White syndrome,15 it has been recognized to be associated with certain congenital disorders including Ebstein's anomaly, atrial septal defect, ventricular septal defect, and tetralogy of Fallot.32-34 Although a number of reports have associated familial cardiomyopathies with Wolff-Parkinson-White syndrome,6, 31-34 almost always the cardiomyopathy is of a hypertrophic variety. A recent echocardiographic study demonstrated associated cardiac abnormalities in almost one quarter of patients with Wolff-Parkinson-White syndrome, including two patients with hypertrophic cardiomyopathy and one with congestive cardiomyopathy.26 Since Wolff-Parkinson-White syndrome was first described, other variants of the Wolff-Parkinson-White syndrome have been recognized as related pre-excitation syndromes, including the short PR interval with a normal QRS duration (Lown-Ganong-Levine syndrome) which is prevalent in the family described here. Whether the pre-excitation syndrome associated with idiopathic cardiomyopathy results from a specific nodal bypass tract or from intranodal abnormalities related to the underlying myopathic process is uncertain.

Clinical and pathologic cardiac findings in this family raise questions about idiopathic non-hypertrophic cardiomyopathy which are worthy of consideration. First, congestive cardiomyopathies may be familial and using the ECG as a screen one may be able to detect subtle, subclinical abnormalities in the myocardium of first degree relatives of patients with seemingly sporadic congestive cardiomyopathy. Only a detailed family search and prospective clinical evaluation of all living family members uncovered the striking inheritance pattern of the disorder described here. Secondly, this family demonstrates that dilated cardiomyopathy, like hypertrophic cardiomyopathy, may be subclinical, have a benign course, and go virtually unrecognized during life. And thirdly, the findings in this family point out that the class of disorders deemed "idiopathic dilated cardiomyopathies," are a heterogeneous group likely to be of multiple etiologies and pursuing varied clinical courses. That dilated cardiomyopathies may be associated with an autosomal dominant pattern of inheritance and a relatively homogeneous clinical and pathologic expression suggests that a unitary biochemical defect yet to be discovered may lead to an intrinsic weakness of myocardial contraction.

Summary

A peculiar non-hypertrophic myocardiopathy is described which occurred in three and possibly five generations of a single family. Clinical features included systolic murmurs, electrocardiographic abnormalities, and sudden cardiac death with a paucity of symptoms of cardiac dysfunction. Pathological studies in three generations showed a striking similarity of cardiac findings including globular and dilated ventricles, endocardial fibroelastosis, and mitral valve thickening. Myocardium in two showed basophilic degeneration and fibrosis. A retrospective genealogic analysis and a prospective clinical evaluation of living family members suggested an autosomal dominant mode of inheritance with variable penetrance. The cause of this heritable myocardiopathy is presumably a mutant gene; the biochemical defect to which the mutant gene gives rise remains unknown.

REFERENCES

Idiopathic familial myocardiopathy


