Familial Idiopathic Cardiomegaly

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Among causes of cardiac enlargement of obscure origin that confront the clinician and pathologist alike are subendocardial fibroelastosis, inflammatory myocardopathies, glycogen-storage disease, amyloidosis, muscular subaortic stenosis, asymmetrical hypertrophy of the heart, idiopathic myocardopathy, and familial cardiomegaly. Familial cardiomegaly, originally named in 1949 by Evans, has been the subject of many communications, primarily in the European literature, but it is little better understood now than after the original report. Various theories to explain the cardiomegaly include cardiac involvement with toxoplasma and trypanosomiasis, a myocardiopathy similar to that seen in Friedreich ataxia but without neurologic involvement, glycogen-storage disease, and an inheritable disorder of the myocardium transmitted as a Mendelian dominant, with sex linkage. Similar to the enigma of causation, the question of the specificity of the clinical picture and of the autopsy findings has been controversial with a familial occurrence being the only unequivocal common denominator. Unfortunately, relatively little emphasis has been devoted to the character and specificity of the morphologic findings, with the majority of reports having appeared in clinical literature.

It is the purpose of this paper to present the clinical and necropsy studies of two sisters who died in young adulthood of progressive cardiac disease. Family history and the significance of specific anatomic findings are discussed with a few remarks regarding etiology.

Case Reports

Case 1

This 21-year-old white girl was well until age 17 years, when she noticed nervousness, tremor of the hands, and a "throbbing" in her neck. At age 18½ years she was told her heart was enlarged, and she received digitalis for 2 months. At age 20 she noticed decreased effort tolerance. In January 1949, at age 21 years, she was hospitalized for dyspnea and hemoptysis. Two sputum cultures were positive for tubercle bacilli, but the diagnosis of tuberculosis was not further substantiated. In March 1949 she noticed ankle swelling.

There was no history of scarlet fever, acute rheumatic fever, chorea, or tonsillitis. Vertigo and cyanosis had not been present in her childhood years, and she had tolerated an appendectomy at age 15 without difficulty.

Abnormal findings were limited to the heart, which was enlarged both to the left and to the right. Ectopic ventricular beats were heard but there were no murmurs.

Electrocardiograms showed left axis deviation and an accelerated atrioventricular conduction pattern suggestive of Wolff-Parkinson-White syndrome. A diagnosis of idiopathic cardiac hypertrophy was made at cardiac fluoroscopy. A complete blood count, erythrocytic sedimentation velocity, and basal metabolism rate were all normal.

The patient gained weight (from 114 to 134 pounds) despite digitalization. On one visit to the clinic jaundice with hepatomegaly was noted. On July 1, 1949, she had an episode of syncope.

On August 19, 1949, she was admitted to the University of Minnesota Hospitals with severe congestive heart failure. She also gave a history of occasional hemoptysis and had noted swelling of the right arm. Physical findings included a pulse of 110, blood pressure of 90/70, and temperature of 98.6 F. At this time a gallop rhythm was noted at the apex but again no murmurs were audible. Physical findings in the right upper extremity were suggestive of thrombophlebitis of the axillary vein.

On August 20, 1949, the patient had a grand mal seizure following an intravenous injection of aminophylline. The patient's congestive heart failure failed to respond, she became semicomatose, and died on September 8, 1949.

At necropsy there was moderate pitting edema of the lower extremities and slight cyanosis of the lips and nailbeds. Approximately 1 liter of clear straw-colored fluid was present in each pleural space and in the peritoneal space, and 50 ml. were in the pericardial sac. No pleural or pericardial adhesions were present.

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The heart weighed 400 Gm. and was globular in shape. The epicardial surface was pale gray and firm, grayish nodules were present that extended into the myocardium and were surrounded by muscle of softer-than-normal consistency. The thickness of both ventricular walls varied markedly. The very dilated right ventricle measured 2 to 3 mm. anteriorly near the apex and was 5 mm. in other areas. The left ventricular wall varied from 5 to 15 mm. and revealed diffuse patchy fibrosis. The interventricular septum likewise showed rather marked, fine, patchy fibrotic change. In the thinned areas the fibrosis was much more evident. Underlying the fibrotic area of the left ventricle was a mural thrombus. Remaining endocardium, valves, and coronary arteries were unremarkable.

The lungs were heavy, weighing 470 and 425 Gm. each. Several wedge-shaped fresh pulmonary infarcts were noted in each lung, but no large pulmonary emboli were found. The lungs exuded bloody fluid when cut. In the right lower lobe were several small, white, nodular areas surrounding a 1-cm. subpleural firm nodule. This nodule contained a thick white fluid in its central portion. No lymphadenopathy was noted.

The liver weighed 1,600 Gm. and grossly revealed the pattern of severe passive congestion. The kidneys and spleen were unremarkable except for several depressed fibrotic areas over their surfaces.

In the right superior parietal area of the brain, a 1.5-cm. circumscribed, firm area was noted with petechiae scattered through it. Other portions of the brain and remaining organs were unremarkable.

On microscopic examination multiple sections of myocardium stained with hematoxylin and eosin showed severe muscular degeneration with early fibrous replacement in many areas (fig. 1). Hypertrophy, with pallor, granularity and vacuolization of the muscle fibers, was noted. The nuclei were often swollen or pyknotic and of bizarre shape (fig. 2). A few scattered small mononuclear cells were present in areas of degeneration. A periodic acid-Schiff stain for glycogen in the myocardial vacuoles revealed only very minimal positive material. A Giemsa stain of some sections revealed no toxoplasma.

The cerebral and pulmonary lesions proved to be typical granulomatous reactions with central necrosis, and epithelioid and Langhans' giant cells. An acid-fast stain of the lung revealed no organisms, however. Pulmonary infarcts were present, and sections of liver and spleen showed passive congestion. The remainder of the microscopic examination was normal.

Case 2

This patient, a 17-year-old sister of case 1, gave a history of easy fatigability of many years' duration. At age 12 years cardiomegaly was noted on a routine chest x-ray. At age 14 she began to have mild exertional dyspnea, which progressed slowly over the next 3 years. Congestive heart failure was diagnosed and treated with digitalis, low-salt diet, and diuretics. She also noted vertigo but had no syncopeal episodes. There was no history of cyanosis or rheumatic fever.

On physical examination abnormal findings included pulsating neck veins, cardiomegaly without murmurs, protodiastolic gallop rhythm, and hepatomegaly. The clinical impression was familial myocardiopathy.

Electrocardiograms revealed a typical Wolff-Parkinson-White syndrome. Complete blood count, erythrocyctic sedimentation rate, and urinalysis were normal. The patient responded to treatment with digitalis and diuretics, and quinidine was given to prevent arrhythmias.

Three weeks later, on November 6, 1959, the patient was hospitalized because of increasing congestive heart failure and episodes suggestive of paroxysmal supraventricular tachycardia.

Physical findings were essentially unchanged with the exception that posterior basilar rales and pedal edema were noted. Again a protodiastolic gallop rhythm was heard, but no murmurs were audible. During her hospitalization the patient became jaundiced. She also had symptoms of a schizophrenic reaction. Treatment for her congestive heart failure was without success and she died on December 2, 1959.

At necropsy 3,000 ml. of clear straw-colored fluid were removed from the pleural spaces, 2,000 ml. from the peritoneum, and 100 ml. from the pericardial sac.
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Figure 2
Case 1. Section from periphery of fibrotic area seen in figure 1. Note the degenerating, pale, finely vacuolated muscle cell near the upper margin. Giant bizarre nuclei are also present in the muscle cells. Hematoxylin and eosin stain.

The heart was globular and massively enlarged to 920 Gm. No pericardial adhesions were present. The ventricular walls were thickened. The left ventricular wall varied in thickness from 20 to 25 mm., and the right ventricular wall measured 10 mm. at its thickest cross section (fig. 3). Dense white fibrous bands extended through the left and right ventricles. The interventricular septum revealed severe fibrous replacement. No evidence of acute necrosis or gross areas of removal of necrotic muscle were found. The remaining myocardium was pale and somewhat soft. No fibrosis of atrial muscle was evident grossly. The endocardium of both ventricles was mildly thickened, but even after formalin fixation it did not appear like sub-endocardial fibroelastosis. Fresh-appearing mural thrombi were seen in both ventricles. Examination of valves and of coronary circulation revealed no congenital or acquired abnormalities.

Weights and appearances of lungs, liver, and spleen were characteristic of severe acute and chronic passive congestion. A small fresh infarct of the left kidney was also present. The remaining organs were grossly normal.

Microscopic examination of left ventricular tissue revealed massive replacement of structure by dense bands of fibrous connective tissue (fig. 4). Remaining muscle fibers were often pale and granular or contained clear vacuoles of irregular shape and size. Their nuclei were often of unusual size and shape, and occasional giant nuclei were noted. A mild mononuclear infiltrate was seen in only a few sections. In the right ventricle and atria only the loose early fibrotic change and severe vacuolization were present. The sections of interventricular septum revealed dense hyaline scar. Special stains were negative for amyloid with methyl violet, negative for fat with Sudan stains, negative for glycogen with Best's carmine, and negative for toxoplasma and other organisms with Giemsa stain.

Mural thrombi were verified on microscopic examination of both ventricles. The endocardium was not remarkably altered in any area.

Sections of lungs, liver, spleen, and pancreas showed evidence of passive congestion, both acute and chronic. A small fresh infarct was present in the right kidney.

The large cells of the nuclei tuberes laterales of the brain were significantly altered. The neurons were severely swollen, and their distended cytoplasm was filled with faintly eosinophilic granules. Nissl-stained sections showed only faint staining of these granules. Fat stains, periodic acid-Schiff stain, and Bielschowsky stain revealed no abnormal structures. Phosphotungstic acid-hematoxylin stain showed no surrounding glial reaction. This entire appearance is without adequate explanation.*

The family history of these two sisters was extensively studied. Their mother died at age 34, in 1946. She had been hospitalized elsewhere in 1944 for "myocardial heart disease and asthma."

*These sections were examined by Dr. L. J. Rubinstein of the London Hospital Medical College and by the Armed Forces Institute of Pathology. It is their opinion that no similar abnormality has previously been reported in the literature.
In 1946 she was rehospitalized and a diagnosis of "myocarditis" was made. She was discharged with a poor prognosis and died at home. No autopsy was obtained. One brother of the sisters died at age 16, when he was hit in the anterior chest by a baseball. He had been well prior to that time.

The patient's father, age 54, two sisters, age 28 and 30, one brother, age 15, and all five nieces and nephews, age 2½ to 9 years, were examined. In no case was there any history suggestive of heart disease. Physical examination, electrocardiogram, and x-ray studies of the heart failed to show any abnormalities except that the father was slightly hypertensive. One brother, age 20, was not available for these studies, but he was known to be healthy and there was no history of heart disease.

Comment

The final, and most complete, classification of disease entities characterized by cardiomegaly must fall to the pathologist. The usual causes of an enlarged heart are well known and need not be dwelt upon here. Reports of idiopathic cardiomegaly have recently become more numerous. This syndrome appears unrelated to any known cardiovascular anomaly or to the aging process. It is characterized by a cardiac demise in a young adult with a large heart and is considered basically a myocardial disease. Autopsy reveals massive enlargement and dilatation of the heart, predominantly left-sided, and with or without fibrosis. Hypertrophy of myocardial fibers with patchy vacuolization and fibrosis is seen microscopically. No evidence of significant endocardial or epicardial abnormality is noted.

Dr. William Evans described an interesting variant of this complex in 1949. The presence of a definite familial tendency was suggested with his presentation of three families with cardiomegaly and symptomatic heart disease. Since that time several other families have been presented as examples of this idiopathic familial cardiopathy. A recent excellent review by Beasley of some 38 cases in 14 families would seem to verify the existence of such an entity. The two cases described in this report along with their family background are offered as further evidence of such a familial disease.

Clinical Comment

It is apparent that many of the reported cases of familial cardiomegaly had unrecognized heart disease for some years as was documented in our second case. The age of onset of symptoms is highly variable, but is usually between the ages of 5 and 20 years. Dyspnea on exertion, palpitation, giddiness, and syncopal episodes are common symptoms before overt congestive heart failure is manifest.

On physical examination most of these patients appear to be of normal habitus and are well nourished. Abnormal findings include generalized cardiomegaly without a murmur. In those cases that do show murmurs, they most often are of low intensity and questionable significance. No murmurs were heard in either of the two present cases. A protodiastolic gallop or triple rhythm is often heard. As the disease progresses, the signs of left- and right-sided congestive heart failure become increasingly evident. There are no signs or symptoms that are pathognomonic of familial cardiomegaly, however, and the disease may be manifest clinically only by sudden unexplained death.

Useful laboratory studies are limited to the x-ray and electrocardiogram. The former shows generalized cardiomegaly with left-sided preponderance but without pulmonary congestion initially. Electrocardiographic findings are quite varied, but most commonly an
abnormal conduction pattern is found. This may be manifest as intraventricular block (usually left bundle), partial atrioventricular block or as the Wolff-Parkinson-White syndrome. The latter should especially alert the clinician to the possibility of familial cardiomegaly although it occurs in other conditions such as Ebstein’s anomaly.9

The age at death varies but most reported cases have died before 30 years of age.10 Death usually results from intractable heart failure or the development of an arrhythmia such as paroxysmal supraventricular tachycardia.

Pathologic Comment

In comparing the cases presented here with those in the literature one notes the following points.

Hearts of previously autopsied cases have been markedly enlarged, weighing up to 1,134 Gm., with an average of 658 Gm.8 The 920-Gm. heart of our case 2 certainly would fit in the classification of cardiomegaly, and the smaller 400-Gm. heart, though only moderately enlarged by weight, appeared markedly enlarged owing to dilatation of the chambers. This rather marked difference in weight is unexplained but suggests that a long-term process is involved with heart size possibly dependent on the ability of the patient to withstand the progressive cardiac deterioration. This view is somewhat borne out by examination of the literature, in that cases with the longest history of symptoms also had the largest hearts. This is also true in the present cases with cardiomegaly noted in our second case 5 years prior to demise. Increased weight is not a true indication of heart size, however, and the importance of marked dilatation of the heart has been stressed by many observers.

Fibrosis varied from dense hyaline scar, predominantly left-sided, to loose, more recently developed fibrosis in other areas. The smaller heart was also the least fibrotic and showed much looser fibrosis in the present cases. By Evans’ criteria, fibrosis must be present in cases designated as familial cardiomegaly.4 However, cases discussed in 194211 showed no fibrosis, yet were considered as the first recorded examples of this familial entity. Garrett suggested that the disease should be categorized by the presence or absence of fibrosis. He noted that both fibrotic and non-fibrotic cases have not been observed in the same family.12 Such a superficial distinction has little merit in the face of the similarity of these cases in all other respects. This variable appears to be a manifestation of only one factor, possibly a time factor.

Vacuoles were prominent within muscle fibers in both cases presented. These were noted in islands of retained muscle fibers surrounded by fibrosis and also in the atria and right ventricle where fibrosis was not so marked. Vacuolization has been described both with and without associated fibrosis6,13 and is thought to represent degenerative, possibly ischemic, change in muscle fibers. The contents of these vacuoles do not stain with periodic acid-Schiff, Best’s carmine, or fat stains.

Although endocardial disease is not a significant component of this complex, mural thrombosis was present in both of our cases. A high incidence of mural thrombosis and secondary embolization is not noted in previous cases. Flynn and Mann14 postulated, however, that the dilated ventricle in a failing heart results in decreased emptying and a subsequent decreased oxygen content of blood to nourish endocardial and subendocardial tissues. The damage may result in mural thrombosis and possible Thebesian vein thrombosis.

Etiologic considerations may be divided into four main groups: infectious, allergic, mechanical and chemical, and congenital. The possibility of a myocarditis as the underlying cause of progressive myocardial disease was entertained frequently in discussions of earlier isolated cases of cardiomegaly.15,16 With the familial aspects of the syndrome apparent, an infectious etiology has become less attractive, though Sommers17 presented three cases in a family in all of which enlarged hearts showed active inflammation. Two families described by Paulley et al.5 showed a high inci-
edence of positive serologic tests for toxoplasmosis as well as high familial incidence of cardiomegaly and cardiac symptomatology. The organism was never isolated, however, by examination of autopsy specimens or by inoculation studies. Doubt has also been expressed\textsuperscript{12, 13} that these serologic tests signify toxoplasma infection and over the postulated existence of a special strain involving only myocardium that Paulley has suggested. Multiple microscopic sections from both hearts in the present cases also failed to reveal any toxoplasma pseudocysts. The presence of active tuberculosis in our case 1; in one of Evans’ original cases,\textsuperscript{4} and in a recent case described by Beasley\textsuperscript{8} is of some interest. That these were all recent acute infections is apparent from the descriptions, and most likely are related to the cardiac abnormality only by hastening the patient’s inevitable demise. Infection in other recorded cases could hardly be suspected as an etiology without fever, predisposing illness, or microscopic evidence of an inflammatory reaction.

Allergic diseases such as rheumatic fever and the collagen diseases have been considered. The lack of valvular, vascular, or epicardial changes speaks strongly against such a relationship. The general lack of findings in other organs, the absence of fever, joint symptoms, skin lesions, and a predisposing hypersensitivity reaction in association with the cardiopathy are also of importance. Of the collagen diseases, systemic scleroderma has more in common with familial cardiomegaly than any other. Diffuse fibrosis of heart muscle with a lack of inflammatory reaction is noted in both. Both may be associated with clinical heart failure, conduction abnormalities, and radiographic cardiac enlargement. Here the similarity ends, however. Scleroderma heart disease is most common as a part of systemic scleroderma and occurs mainly in the fourth and fifth decades. No specific familial tendency has been noted. Hearts do not undergo the massive enlargement seen in familial cardiomegaly. Fibrosis is more often fine and interstitial in type and does not show the predominant left-sided increase noted in familial cardiomegaly. Microscopic differences are also apparent with a quite cellular and often very vascular fibrous tissue infiltration with secondary muscular degeneration and replacement in scleroderma. Remaining isolated muscle fibers often appear quite normal, despite being surrounded by fibrous tissue.\textsuperscript{18} The fibrosis in the present two cases differs markedly from this, and suggests a degenerative myocardial abnormality with a secondary replacement fibrosis.

Mechanical and chemical changes in the heart can also cause cardiomegaly. Absence of hypertension, coronary disease, congenital defects, valvular disease, or electrolyte abnormality rules out a likely relationship in this category.

Recent interest in incomplete subaortic stenosis has been expressed by several authors. A report by Brent et al.\textsuperscript{1} described two families with such a clinical entity. All were characterized by cardiomegaly, heart failure, and the presence of heart murmurs. Walther et al.\textsuperscript{10} suggested that the progressive familial cardiomegaly with left ventricular hypertrophy may lead to a partial outflow obstruction. Such obstruction could then be a stimulus for further severe hypertrophy. Descriptions of the hearts in most cases of idiopathic cardiomegaly, however, include marked dilatation as well as hypertrophy of the cardiac chambers. This plus the absence of murmurs in a large proportion of patients with familial cardiomegaly would make unlikely a mechanism like subaortic stenosis.

Of interest, also, is the work of McAllen,\textsuperscript{16} who cited two cases of longstanding potassium deficiency that resulted in severe diffuse myocardial fibrosis. The hearts were not enlarged significantly, however, and degenerative lesions with necrosis and inflammatory cells could be seen even in the longstanding deficiencies.

Last and most important, is the possibility of a congenital defect of the myocardium. The two most important abnormalities related to cardiomegaly are Friedreich’s ataxia and Von Gierke’s disease. The latter has been mentioned and discarded by most previous au-
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thors because of the following characteristics of Von Gierke's disease that are not found in idiopathic cardiomegaly: Involvement of heart with death prior to 1 year of age; defect in glycogenolysis, i.e., ketosis, hypoglycemia, and abnormal glucose tolerance tests; and massive glycogen deposits in multiple organs on autopsy. Evans found a moderate amount of glycogen in the heart of one of his original cases but thought it was insignificant and could be seen in any degenerative condition such as heart failure. No significant increase in glycogen was found in the present case 2. (Only case 2 was studied with alcohol fixation and Best's carmine stain.)

Friedreich ataxia is often associated with cardiac abnormalities and was suggested by Evans as a related familial congenital abnormality. Electrocardiographic findings in 38 cases of Friedreich ataxia were reported by Evans in an earlier publication, with significant abnormality in 10 of these. Dorothy Russel described myocardial in four cases of Friedreich ataxia at autopsy. Hypertrophy with left predominance, diffuse fibrosis, and scattered degenerative areas with inflammation were present. Familial tendency of Friedreich ataxia is apparent, but no family has been found showing isolated cardiomegaly in one member and Friedreich's disease in another.

Campbell and Turner-Warwick have postulated a genetic basis for idiopathic cardiomegaly and suggested that it is inherited as a Mendelian dominant. Inheritance only through the maternal half of a family has been demonstrated in several two-generation studies, suggesting sex-linked transmission. Although no autopsy study of the mother was made in the family presented here, involvement of the mother's heart by an abnormality of myocardial nature is suggested. Such a family relationship would not offer any proof of a sex-linked transmission, but would fit the general scheme of such a concept.

Of interest is the possible relationship of infantile hypertrophy of the heart to adult myocardial disease. The infantile variety also shows a marked familial tendency but no family has been described showing an adult-infant disease pattern. That the infantile hypertrophic disease is basically myocardial is suggested by the work of Black-Schaffer and Turner. They postulated an abnormal cell division of myocardium, which may result in the loss of efficiency of the myocardium due to shortened fibers. Secondary dilatation and hypertrophy would result, with formation of endocardial fibrosis in some cases. Although a basic shortcoming of adult cardiomegaly as a congenital abnormality is the long latent period, one could still postulate a basic myocardial defect originating in development. Such a concept would necessitate the reaching of "critical size" as described by Linzbach, after which marked myocardial change takes place. Whether this change involves an anoxic phenomenon due to progressive hypertrophy and decreased vessel-fiber ratio or is due to a basic myocardial fiber abnormality, possibly enzymatic, with dilatation and degeneration is not known. With present increased interest in histochemical techniques, enzymatic studies in subsequent cases may be of real value in clarifying a very cloudy disease complex. In order to accomplish such studies, however, this disease entity must be recognized at the autopsy table or earlier in order that valid metabolic studies be completed.

Summary

Two young adult sisters are described with clinical and pathologic findings of myocardial disease. These cases along with a suggestive family history are presented as examples of familial idiopathic cardiomegaly. Pathologic findings are compared and contrasted with those in the literature, and etiologic concepts are discussed. It is concluded that a congenital myocardial abnormality is the most likely etiology and suggestions for further studies are presented.

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References


Though old Fort Crawford on the upper Mississippi has vanished, the results of the experiments Beaumont conducted within its walls have come down to us with undiminished luster through more than a hundred years and are an enduring portion of America's gifts to science. "Truth, like beauty," Beaumont wrote, "when unadorned is adorned the most, and in prosecuting these experiments and inquiries I believe I have been guided by its light." Such is the ideal and such is the faith of the frontiersman in science, and in so far as he is loyal to his convictions he will leave behind him, as Beaumont did in his records, lasting contributions from his fleeting years.—Walter B. Cannon, M.D., The Way of An Investigator. New York, W. W. Norton & Company, Inc., 1945, p. 29.
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