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STATE-OF-THE-ART PAPER

Clinical and Genetic Issues in Familial Dilated Cardiomyopathy

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Idiopathic dilated cardiomyopathy (IDC) is characterized by left ventricular dilatation and systolic dysfunction after known causes have been excluded. Idiopathic dilated cardiomyopathy occurring in families, or familial dilated cardiomyopathy (FDC), may occur in 20% to 50% of IDC cases. Sixteen genes have been shown to cause autosomal dominant FDC, but collectively may account for only a fraction of genetic causation; it is anticipated that additional genes causative of FDC will be discovered. Familial dilated cardiomyopathy demonstrates incomplete penetrance, variable expression, and significant locus and allelic heterogeneity, making clinical and genetic diagnosis complex. Echocardiographic and electrocardiographic screening of first-degree relatives of individuals with IDC and FDC is indicated, as detection and treatment are possible before the onset of advanced symptomatic disease. Genetic counseling for IDC and FDC is also indicated to assist with family evaluations for genetic disease and with the uncertainty and anxiety surrounding the significance of clinical and genetic evaluation. Genetic testing is not yet commonly available, but its emergence will provide new opportunities for presymptomatic diagnosis. (J Am Coll Cardiol 2005;45:969–81) © 2005 by the American College of Cardiology Foundation

Idiopathic dilated cardiomyopathy (IDC) is a diagnosis that continues to puzzle many cardiovascular specialists. The diagnosis of IDC is one of exclusion; that is, all obvious or detectable causes should be excluded before its assignment. Yet thoughtful clinicians recognize that some cause, albeit unseen or undetected, underlies the myocardial dysfunction. Multiple causes have been suggested and include previous viral infections, excessive alcohol exposure, severe hypertension, and autoimmune or other phenomena.

An alternative cause, also unseen and difficult to detect, is underlying genetic disease. The clinical and genetic data to support genetic causation, and preliminary recommendations for cardiovascular specialists to deal with this disease, are the focus of this review. That cardiovascular disease can be caused by mutations in genes that encode for key proteins important in cardiovascular biology has been elegantly described for other myocardial diseases, most notably for hypertrophic cardiomyopathy (HCM), now recognized largely as a genetic disease of contractile proteins (1). Other genetic cardiovascular diseases include the long QT syndrome (2), arrhythmogenic right ventricular dysplasia (3), and Marfan syndrome (4). Recent clinical studies have also suggested that bicuspid aortic valve is heritable (5), and atrial fibrillation may be familial in 5% to 15% (6) to 30% (7) of cases.

Genetic disease also underlies a considerable proportion of what has been previously understood to be IDC. The clinical and molecular genetic data gleaned from studies of familial dilated cardiomyopathy (FDC, defined as the presence of IDC in two or more family members) indicate that gene mutations, largely single base changes in key autosomal genes, cause FDC and IDC. The identity of the genes involved, their mutation frequency, mechanisms of disease, and phenotype/genotype correlations are beginning to emerge.

FDC CLINICAL AND FAMILY STUDIES

A genetic basis for IDC was thought to be distinctly uncommon until the mid-1980s. Familial transmission in 1% to 2% of subjects with IDC had been postulated from earlier scattered case reports (for earlier reviews, see references 8–15). Before the widespread availability of echocardiography to screen family members, the research devoted to hereditary cardiomyopathy had difficulty sorting hypertrophic from dilated cardiomyopathy (DCM). Other recent overviews of FDC are available (16–23).

The recognition that DCM may aggregate in families has evolved significantly since the early case reports (8,24–41) (Table 1). Based on family history, two initial studies in 1982 and 1985 reported FDC rates of 2% and 6.5% respectively (8,25) (Table 1). In 1988, a small prospective echocardiographic-based study suggested a much higher rate of 33% (27). That same year in children >2 years of age, the FDC rate was observed to be 25% (28). In 1992, prospective echo screening of first-degree relatives in patients diagnosed with IDC estimated the rate of FDC at 20.3% (32). In this study, 315 relatives of the 59 index patients with IDC underwent screening with echocardiography, including coronary angiography in those ≥40 years of age to exclude coronary artery disease. Idiopathic dilated

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Abbreviations and Acronyms

AD = autosomal dominant
CK = creatine kinase
CLIA = Clinical Laboratories Improvement Act
DCM = dilated cardiomyopathy
ECG = electrocardiography
FDC = familial dilated cardiomyopathy
HCM = hypertrophic cardiomyopathy
HF = heart failure
IDC = idiopathic dilated cardiomyopathy
LVE = left ventricular enlargement

cardiomyopathy was found in 18 relatives (20.3% of the index patients) by echocardiography, whereas only 5% had been suspected of having familial disease based on family history alone. Of the 18 relatives, 12 were asymptomatic and 15 were given new diagnoses.

In 1997, a prospective study of 56 probands estimated the "definite" FDC rate at 25%, where "definite" was defined as a first-degree relative with a diagnosis of IDC, or both an echocardiographic left ventricular end-diastolic dimension >2 standard deviations above the mean and an ejection fraction <50% (37). An additional 27% of probands had a first-degree relative with one of these two echocardiographic criteria, or premature sudden death (unexplained <50 years of age); these were categorized as "possible" FDC. The sum of both "definite" and "possible" FDC rates was 52% (37).

Two reports (38,39), published simultaneously in 1998, indicated that FDC rates among patients with IDC ranged from 35% (38) to 48% if left ventricular enlargement (LVE) was included as a clinical indicator of FDC (39) (Table 1). In the former study (38), family history was obtained in 445 of 481 consecutive subjects (92.5%) with IDC. Dilated cardiomyopathy was discovered in 65 subjects from 48 of the 445 families (10.8%) as determined by full cardiac evaluation or at autopsy. Of the 65 subjects observed to have DCM during the study, 38 were newly identified by prospective screening. In an additional 108 of the 445 families (24.2%), FDC was eventually diagnosed on the basis of sudden cardiac death (75 families), heart failure (HF) (23 families), or abnormal echocardiography (10 families). In the remaining 289 families (65%), no evidence of familial disease was observed. The latter study (39) identified 110 consecutive patients with documented IDC; of these, 408 subjects from 89 different families (an average of 4.6 members per family) agreed to undergo full clinical screening. Forty-five of the relatives screened had LVE; 7 of the 45 had DCM (LVE and decreased systolic function). With LVE included as early evidence of disease, the prevalence of FDC among index patients with IDC was 48% (39).

Clinical screening, regardless of family history, was offered to 350 patients with IDC in Trieste, Italy, identified between 1991 and 1997 (40), and 281 family members from 60 families were investigated based on their geographic proximity. Thirty-nine of the 60 families (65%) had familial disease. When familial disease was compared to nonfamilial disease, only a younger age of onset was predictive. The investigators concluded that although FDC was frequent, no particular clinical or morphologic features of individual patients distinguished FDC from IDC, and thus family screening was required to detect it.

FDC DISEASE GENES AND CHROMOSOMAL LOCI

Autosomal dominant (AD). Familial dilated cardiomyopathy has been reported most commonly (approximately 90%) with AD inheritance (40). The genetic and clinical heterogeneity suggests causation by a single gene, with multiple other genetic and environmental factors altering its expressivity (40). To date mutations in 16 autosomal genes (42–66) have been suggested to be causative of FDC and have been categorized as FDC and FDC with conduction system disease (Table 2). The former category has no specific or unique phenotypic features. The latter category includes families with mutations in lamin A/C who frequently present with sinoatrial and atrioventricular node dysfunction, heart block commonly requiring pacemakers, atrial fibrillation, and other supraventricular arrhythmias; later DCM, ventricular arrhythmias, and death from sudden cardiac death or pump failure are observed. Based on these preliminary reports (Table 2), mutations in the lamin A/C and beta-myosin heavy chain genes may each be responsible for 5% to 10% of FDC. However, these estimates have been derived from patients and their families seen in specialist or referral clinics that may not be representative of overall population frequencies. Actin (67–69) and desmin (69) genes appear to be quite uncommon causes (<1%) of IDC and FDC. Preliminary estimates of the frequencies of the other FDC genes are largely based upon the primary reports (Table 2), but appear to be less common causes of FDC than the lamin A/C and beta-myosin heavy chain genes. Studies designed to survey disease gene frequencies in larger populations will be required to clarify these issues.

X-linked. X-linked FDC is reported to account for approximately 5% to 10% of FDC (Table 2) (38–40), usually resulting from mutations in the dystrophin gene that have been identified in several families displaying X-linked inheritance (70–78). In some cases, DCM has also been noted to be the only or presenting feature in individuals who have Becker muscular dystrophy or in female carriers (79,80). Furthermore, Becker muscular dystrophy and IDC have been seen in the same family (81), suggesting that it may be difficult to draw conclusions about phenotype from genotype. Individuals with X-linked FDC may have skeletal muscle weakness, and whereas most have elevated creatine kinase (CK) levels, normal levels have been reported (40). Dystrophin mutations have also been identified in male patients diagnosed with IDC, suggesting that this may be a rare cause of sporadic cases (20,82).

Mutations in the gene G4.5, which encodes the tafazzin