Familial Dilated Cardiomyopathy: A Genetic Enigma

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Dilated cardiomyopathy (DCM) is a disease of the cardiac muscle, characterized by dilatation and impaired contractility of the left or both ventricles, with progressive development of congestive heart failure (CHF) and occurrence of serious arrythmiologic events. Diagnosis is made by exclusion of underlying cardiac diseases, such as coronary artery disease, valvulopathies or arterial hypertension. A great variety of factors (toxic, infectious, metabolic, immunologic etc) have been etiologically implicated in DCM. This correlation is of great importance, as myocardial damage may be reversible in some of these cases. However, DCM is often characterized, as "idiopathic", as no etiologic factor is revealed, despite constant diagnostic research.

Diagnosis of familial DCM (FDCM) is made, when DCM is diagnosed in at least two members of the same family. Until recently, the frequency of FDCM was underestimated, because of the lack of diagnostic indices for early diagnosis in asymptomatic relatives and the limited genetic penetration of the disease. Systematic screening and follow-up of the relatives of patients with "idiopathic" DCM has contributed to an increasing identification of new cases, because of early diagnosis of asymptomatic or subclinical forms of the disease. Recent studies report that 20% to 35% of DCM cases are considered to be familial[1-3].

Genetic control of certain families with FDCM has contributed to the identification of certain gene mutations, responsible for the production of abnormal muscle cell proteins. These proteins are usually substances of cytoskeleton or the sarcomere and some of these mutations have already been implicated with skeletal myopathies (Table 1)[4].

Phenotype

Clinical presentation of FDCM is characterized by a great diversity. According to recent reviews, patients with FDCM could be divided into four major categories: (1) DCM with rapid progress in young men, (2) DCM with mainly left ventricular dysfunction, (3) DCM with early conduction system disease and (4) DCM with sensorineural hearing loss[5]. A form of DCM with segmental hypokinesia has also been described, while some cases cannot be classified into any of these categories[3]. Skeletal myopathy can be present in all of the previous phenotypic categories[5].

Diagnosis is usually made at a young age (20-50 years). A symptom of CHF is the initial manifestation in the vast majority of patients (75%-85%)[6]. Heart failure may be advanced even at admission. Biventricular dilatation and contractility impairment are detected. Heart muscle weight is usually increased, indicating hypertrophy, although left ventricular wall thickness may be within normal range, due to the dilatation of the ventricles.

Familial form of DCM seems to appear at a significantly younger age than

Table 1. Gene mutations correlated with familial dilated cardiomyopathy.

Chromosome	Protein	Skeletal muscles involvement	Type of dilated cardiomyopathy (DCM)	Correlation with muscular dystrophy
Xp21 (X-linked)	Dystrophin	Mild	DCM with rapid progress in young men	Muscular dystrophies Becker and Duchenne
Xp28 (X-linked)	Emerin	None-mild	»	Muscular dystrophy Emery-Dreifuss
Xp28 (X-linked)	Taphazin	Mild	»	Barth syndrome
1q11-23, 1q21-23, 1p1-q21 (autosomal dominant)	Lamin A/C	None-mild	DCM with early conduction disease	Muscular dystrophy Emery-Dreifuss
2q35 (autosomal dominant)	Desmin	None-Severe	»	"Desmin myopathy"
2q14-q22, 3p22-25, 6q23	Unknown	Unknown	»	
6q23-24 (autosomal dominant)	Unknown	Severe	DCM with sensorineural hearing loss	
Mitochondrial DNA	–	Mild	»	
1q3	Troponin T	Unknown	DCM with left ventricular dysfunction	
17q12-21.33	alpha-sarcoglycan	Unknown	»	
5q33-q34	delta-sarcoglycan	None-Subclinical	»	
14q11.2-12	β-MHC	None	»	
15q14	Actin	Unknown	»	
10q22	Metavinculin	Unknown	»	
1q32, 2q31, 2q11-22, 2q31, 3p22-25 9q13-22, 10q21-23,	Unknown	Unknown	»	

idiopathic[3]. However, patients with similar genotypic anomalies, or even members of the same family may develop heart failure at different ages, which confirms the phenotypic heterogeneity of the disease. Furthermore, the great portion of patients' relatives, identified during family screening, present asymptomatic left ventricular dilatation and never develop clinical DCM[7]. This phenotypic diversity among patients with common genetic abnormalities (reported even between monozygotic twins) is referred to as

"epigenetic inheritance", demonstrating the existence of underlying epigenes, that modify the gene expression[6].

Genetics

Genetic analysis of families with DCM has revealed a variety of gene mutations, associated with abnormal myocyte protein production, many of which had already been correlated with skeletal myopathies[8]. During the last decade, a geat effort has been made to link specific gene defects to specific phenotypic forms of FDCM, in order to plan further therapeutic approach.

In young men with rapidly progressive DCM, a dystrophin gene mutation has been identified. The dystrophingene is situated on the X-chromosome, explaining the prevalence of the disease in male patients[9,10]. Dystrophin "stabilizes" the sarcomere, by attaching the actin of cytoskeleton to the extracellular matrix, via a glycoprotein complex (csarcoglycans and destroglycans). Dystrophin gene mutations have been implicated previously with Duschenne and Becker muscular dystrophies[5,11], in whom cardiomyopathy is frequently noted . In addition, a subgroup of patients with dystrophin-related DCM has abnormally elevated serum levels of muscular creatine phosphokinase, which seems to be a sign of pure prognosis[12]. It must be added, that DCM has also been described in association with genetic defects of the production of the sarcoglycans[13,14].

Conduction abnormalities associated with DCM have been correlated with Emery-Dreifuss muscular dystrophy and have been attributed to mutation of genes encoding nuclear envelope proteins[15,16]. Certain mutations have been identified in genes emerine (X-linked transmission)[17,18] and lamine A/C (autosomal dominant transmission)[19-21]. Defectective production of these proteins results in myocardial nucleus destabilization and nuclear "death". Furthermore, implication of nuclear envelope proteins in a regulation mechanism of gene expression has also been described[6, 19]. Patients with lamine-related DCM seem to have poor prognosis, as only 31% of mutation carriers are reported to have event-free survival at the age of 45 years, in comparison to 75% of non-carriers[22].

Conduction abnormalities associated with DCM have also been described in desmin cardiomyopathy[23,24]. Desmin is a cytoskeleton protein that forms intermediate filaments and links adjacent myofibrils, playing an important role in the attachment, stabilization and force transmission of the sarcomeres. Phenotypic expression is depended on patient's sex; male patients present DCM with or without conduction abnormalities, while female carriers present usually skeletal myopathy, without cardiac involvement[25]. According to recent reports, this form of FDCM seems to be rare[26].

Sensorineural hearing loss in patients with DCM has been attributed to whether certain autosomic mutation (6q 23-24)[27] or to mitochondrial DNA mutation (A3243G)[28]. Mitochondrial DNA defects could affect tissues or organs with high oxidative metabolism, presenting as seizures, stroke, optic atrophy, neuropathy, myopathy, cardiomyopathy, sensorineural hearing loss, diabetes mellitus and other clinical manifestations[29]. Alstrom syndrome is an autosomal recessive disorder, characterized by conerode dystrophy, hearing impairment, diabetes mellitus, obesity and cardiomyopathy, which is developed in early childhood[30].

A novel form of lethal inherited DCM has recently been described in association with phospholamban (PLN) gene mutations. PLN is a transmembrane phosphoprotein that inhibits the cardiac sarcoplasmic reticular Ca^{2+}-ATPase (SERCA2a). SERCA2a is a pump that regulates the calcium release from the sarcoplasmic reticulum. Dephosphorylated PLN inhibits SERCA2 pump activity, while PLN phosphorylation (through the β-adrenergic receptor pathway) relieves this inhibitory effect. Two different mutations of PLN gene have been described: the PLN (R9C)[31] and the PLN-L39stop[32]. Both have been demonstrated to result in severe form of DCM and premature death. Furthermore, a phenotypic heterogeneity of PLN-L39stop mutation has been reported in heterozygous individuals, as heterozygosity has been associated with both ventricular hypertrophy and DCM[32]. Environmental perturbations and unidentified genetic modifiers have been suggested as possible underlying mechanisms.

Genetic analysis of families with DCM continuously adds new promising candidates to the list of gene-related forms of DCM. Actin[33], β-myosin heavy chain[34], troponin-T[35], metavinculin[36] and alpha T-catenin[37] are some of these. Some of the gene mutations, implicated in FDCM, have also been identified in sporadic cases of DCM. There are reports in literature about sporadic DCM cases caused by gene defects of desmin[25], actin[26], dystrophin[38] and beta-

and delta-sarcoglycan[39,40]. The correlation of gene mutations and sporadic cases has not been clarified yet. It has been hypothesized that the absence of observed genetic transmission in these cases may be attributed to *de novo* gene mutations or "masked" cases of FDCM, meaning a reduced penetrance or insufficient family data[41].

This genetic heterogeneity is also characteristic in the other form of inherited cardiomyopathies, the hypertrophic cardiomyopathy (HCM). HCM is a disease of the sarcomere (often characterized as "sarcomyopathy" in literature). Most common mutations related with HMC have been reported for the genes encoding beta-myosin heavy chain, alpha-tropomyosin, troponin I, troponin T, actin and myosin binding protein-C (MyBP-C)[42,43]. Different mutations of the same gene can manifest as either DCM or HCM, settling the hypothesis of a "final common pathway" in inherited cardiomyopathies[44,45]. The phenotypic heterogeneity of PLN-L39stop mutation heterozygosity has already been described, while mutation of the same gene, delta-sarcoglycan has been correlated with both HCM and DCM in hamsters[46]. Furthermore, cases of DCM diagnosed in elderly patients have been attributed to the "burn-out" phase of HCM[47].

Therapeutics and expectations

Clinical management of patients with FDCM aims at the pharmaceutical control of symptoms (diuretics, inotropes) and prevention of the disease progression (angiotensine converting enzyme inhibitors, aldosterone andagonists, beta-blockers). Physicians should also consider anticoagulant therapy, as patients with DCM are at higher risk of thromboembolic complications. Vitamin K antagonists should be given to patients with moderate ventricular dilatation and systolic dysfunction, despite the lack of prospective randomised trials[5]. Sudden cardiac death risk can be decreased by amiodarone, although implantable cardioverter-defibrillators are indicated in patients with aborted cardiac arrest or sustained ventricular tachycardia and low ejection fraction (<35%)[48]. Transplantation is the last choice for patients with end-stage heart failure.

Family screening and follow-up is the cornerstone of early diagnosis and effective management of FDCM. Characteristically, it is reported that 29% of asymptomatic relatives of patients present ultrasound abnormalities (usually left ventricular dilatation), while 27% of them will manifest clinical DCM in future[49]. It is not clear yet, whether these persons should receive preventive treatment or not, but it is certain that they should undergo systematic follow-up[50,51]. Organization and financial support of follow-up programmes for the patients and their relatives remains the basic problem[52].

Genetic intervention is the hope for the future. The genotypic heterogeneity of the disease makes this effort complicated. Efforts in animal models with inherited forms of DCM have been described. Most implicate the TO-2 strain hamsters, which have genetic defects of delta-sarcoglycan gene and show similar clinical and genetic backgrounds to human cases. The normal gene transfer has been successfully achieved by using recombinant adeno-associated virus vector (rAAV)[53]. The same vector has also been used as a mediator in transferring micro-dystrophin recombinant cDNA in mdx mice with dystrophin related muscular dystrophy[54].

New candidates are continuously added to the list of gene mutations, related to the certain forms of FDCM. The expectation of early and safe identification of genetic defects will be the background of gene therapy in future.

Conclusions

The screening test of patient's relatives with DCM has recently determined the real magnitude of the familial form of the disease, contributing simultaneously to the early recognition of asymptomatic relatives. In addition, the identification of families with genetic abnormalities and the correlation of specific gene mutations with the phenotypic variants of the disease have revealed the genetic heterogeneity of the disease. The possibility of molecular diagnosis and genetic intervention are the expectations for the future. Up to now, clinical and molecular investigations have confirmed that FDCM is a genetic enigma of which only a small part has been solved.

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