Guidelines for the Diagnosis and Management of Familial Dilated Cardiomyopathy

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Clinical Characteristics

Definition and Prevalence

Dilated cardiomyopathy (DCM) is a myocardial disorder characterised by dilatation and contractile dysfunction of the left and right ventricles. DCM may be caused by a diverse range of conditions that promote cardiomyocyte injury or loss, e.g. coronary artery disease, viral myocarditis, alcohol excess. In approximately 50% of cases, an underlying cause is unable to be identified. This group has traditionally been termed “idiopathic” DCM. It is now recognised that approximately one-third to one-half of cases of “idiopathic” DCM have a positive family history, suggesting that an inherited gene defect might be the cause of the disorder (“familial DCM”).

Clinical Presentation

Familial DCM may be inherited as an autosomal dominant, autosomal recessive, maternal or X-linked trait; autosomal dominant inheritance is present most commonly. In autosomal dominant inheritance, each child of an affected parent has a 50% chance of inheriting a disease-causing gene mutation, with males and females equally at risk. Clinically affected individuals generally present with symptoms and signs of heart failure or arrhythmias. Some families have a clinical presentation (phenotype) that is characterised by DCM alone, while in others, DCM may be associated with additional cardiac manifestations, e.g. conduction-system disorders, valve defects, atrial/ventricular septal defects, left ventricular non-compaction, or with non-cardiac manifestations, e.g. skeletal myopathy, partial lipodystrophy, sensorineural deafness.

Clinical Diagnosis

The diagnosis of familial DCM is made when DCM (with or without associated features) is present in the setting of a positive family history (at least two family members affected). There are no specific clinical features that reliably distinguish familial from non-familial DCM.

Family History

A detailed family history and a high level of clinical suspicion are essential. While inherited gene defects alone may be sufficient to cause disease, some individuals in families may have concurrent risk factors for DCM that may confound the recognition of familial disease. In addition, familial clustering may not be immediately apparent if the clinical presentation differs between members of the same family. For example, in DCM with conduction-system disease, some individuals may present with heart failure, while others may have a history of arrhythmia symptoms, pacemaker implantation or sudden death. The severity of disease, and the age of onset, may differ between families and within members of the same family. While familial DCM generally shows high penetrance, some individuals may remain non-penetrant (i.e. genotype-positive but with no clinical manifestations of disease) throughout life.

Family Screening

It is currently recommended that all first-degree family members of individuals with “idiopathic” DCM, and of individuals with suspected familial DCM on the basis of a positive family history, should undergo clinical screening with physical examination, 12-lead ECG and transthoracic echocardiography to identify familial disease and to determine the number of affected individuals within families. Measurement of CK levels is useful to identify subclinical skeletal muscle abnormalities and provides supportive evidence for the presence of an inherited myopathic disorder. Exercise treadmill testing and/or coronary angiography may be indicated in family members aged over 50 years who are found to have a new diagnosis of DCM, to distinguish a familial from a non-familial cause.

Molecular Genetics

Familial DCM Disease Genes

Familial DCM is a genetically heterogeneous disorder. To date, more than 30 chromosomal loci have been associated with various forms of autosomal dominant DCM, with the disease-causing genes identified in approximately two-thirds of these loci. These disease genes encode a variety of proteins in the cardiomyocyte sarcomere, cytoskeleton, sarcolemma, and nucleus. These findings indicate that diverse molecular mechanisms may trigger familial DCM.
A gene defect may not develop manifestations of disease related to penetrance, i.e. family members who are born with familial DCM exhibit disease early in life (earlier than six months to five years). Familial DCM exhibits age-related penetrance, and may range from six to ten years. Familial DCM disease genes are acquired, rapid and inexpensive methods for mutation screening will be needed before genetic diagnosis in individual families can become part of routine patient management in this disorder.

Management

Affected Individuals
Clinically affected family members with DCM should receive standard pharmacological management as indicated by the severity of symptoms and signs of heart failure. In families with DCM and conduction-system disease, young family members who present with conduction-system disturbances (sinus bradycardia, atrioventricular conduction block, atrial fibrillation) should be followed for arrhythmias that might necessitate pacemaker implantation and for the onset of DCM in later life. Electrocardiographic changes (left ventricular dilation and/or mild impairment of contractile function) has been identified. The significance of these echocardiographic changes is not yet clear. It is not known whether these changes represent mild subclinical disease that is unlikely to change, or early signs of progressive disease. The optimal management of these individuals is also unknown. The ability to recognise early disease has important management implications, since early intervention may prevent, or attenuate progression to symptomatic heart failure. A clinical trial to evaluate pharmacologic intervention in this subgroup of family members is currently underway.

Asymptomatic Family Members

Longitudinal Follow-Up: Periodic cardiac screening (ECG and transesophageal echocardiography) of family members of probands with familial DCM is recommended, to identify arrhythmias and asymptomatic abnormalities of left ventricular size and function. The frequency of follow-up assessments should be determined in each individual case by factors such as the typical age of onset of disease in symptomatic family members, and “suspicious” echocardiographic changes (e.g. borderline normal, or suggestive of early heart failure [see below]), and may range from six to twelve months to five years. Familial DCM exhibits age-related penetrance, i.e. family members who are born with a gene defect may not develop manifestations of disease until later in life. The age of onset of disease in families is variable, with clinical signs appearing from the second to ninth decades. Young family members with a normal ECG and echo, particularly offspring of an affected parent, should not be dismissed as “unaffected” and require ongoing medical surveillance.

“Early Disease”: As part of clinical screening for molecular genetics studies, a previously unrecognised subgroup of family members with asymptomatic echocardiographic changes (left ventricular dilation and/or mild impairment of contractile function) has been identified. The significance of these echocardiographic changes is not yet clear. It is not known whether these changes represent mild subclinical disease that is unlikely to change, or early signs of progressive disease. The optimal management of these individuals is also unknown. The ability to recognise early disease has important management implications, since early intervention may prevent, or attenuate progression to symptomatic heart failure. A clinical trial to evaluate pharmacological intervention in this subgroup of family members is currently underway.

Counselling
All family members potentially at risk of disease should receive lifestyle modification advice, e.g. avoidance of alcohol excess, regular moderate exercise, etc. Female family members who are considering pregnancy should have initial cardiological review and regular follow-up during pregnancy, since familial DCM may be unmasked or accelerated in the peripartum period, especially in the last trimester and first six months postpartum. The diagnosis of a genetic disorder in a family and the possibility of testing for the disorder raise a number of issues. Involvement of genetics professionals (clinical genetics and genetics counsellors) should be considered.

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Further reading

Appendix A
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