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POSITION STATEMENT

Position Statement on the Diagnosis and Management of Familial Dilated Cardiomyopathy

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Key Points

- Genetic factors have an important role in the pathogenesis of dilated cardiomyopathy (DCM) and can be a primary cause of disease.
- *Clinical presentation*: The clinical presentation of familial DCM can be variable. In most kindreds, affected individuals present with symptoms and signs attributable to left ventricular dysfunction. In some cases, the family phenotype may include additional cardiac or extra-cardiac manifestations, including conduction-system abnormalities or skeletal myopathy. These features may provide clues to the underlying disease genes.
- *Clinical diagnosis*: The diagnosis of DCM is made using echocardiography or other imaging modalities such as magnetic resonance imaging. Approximately 25% of patients with ''idiopathic'' DCM are likely to have a genetic basis for disease and a detailed three-generation family history needs to be taken in all newly-diagnosed cases. First-degree family members of individuals with known or suspected familial DCM should undergo clinical screening with physical examination, 12-lead ECG and transthoracic echocardiography. A detailed medical history needs to be taken to identify any co-morbidities or acquired factors that might contribute to DCM development or exacerbate disease severity. In female family members, DCM may present during pregnancy or in the postpartum period.
- *Genetic testing:* Dilated cardiomyopathy is genetically heterogeneous with more than 40 genes associated with familial and sporadic disease. To date, the cost and relatively low yield (~20%) of screening known disease genes has limited the role of genetic testing for DCM patients in routine clinical practice. Current international guidelines recommend: (i) selective testing of the *LMNA* and *SCN5A* genes in patients with DCM and conduction-system disease and/or a family history of premature unexpected sudden death; and (ii) cascade testing of relatives in families in which a likely disease-causing variant is identified in the index case. Over recent years, the introduction of next-generation sequencing technologies has been a major advance that allows comprehensive and unbiased evaluation of an individual's genetic makeup. In DCM, these technologies have already increased the yield of potential mutations to ~50%. Surprisingly, truncating variants in the *TTN* gene have been identified in 15–25% of adult DCM cases, but whether these variants are sufficient alone to

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cause DCM remains to be clarified. As genetic testing becomes more affordable and available, it can be expected to play an increasingly important role in patient management. Interpretation of test results and understanding the clinical significance of genetic variants remains a major challenge.

- *Management:* In most families, treatment choices are not currently altered by the discovery of a causative gene mutation and clinically-affected individuals should receive standard pharmacological and device management. Asymptomatic family members should have baseline cardiac assessment and ongoing periodic cardiac screening for early detection of pre-clinical disease. When a pathogenic genetic variant has been identified in an affected individual, appropriate family members should be offered predictive genetic testing and genetic counselling. Genetic testing and family management is ideally undertaken by experienced personnel in the setting of a multidisciplinary clinic.

Changes from 2013 Document

These guidelines have been revised overall with expanded sections on the molecular genetics of DCM and sequencing options for genetic testing. The document now includes recommendations for paediatric DCM.

Clinical Characteristics

1. Definition and Prevalence

Dilated cardiomyopathy (DCM) is a myocardial disorder characterised by dilatation and systolic dysfunction of the left ± right ventricles. It is one of the most common forms of heart muscle disease with an estimated prevalence of 1:2500 [1]. DCM can be caused by diverse conditions that promote cardiomyocyte injury or loss, including viral myocarditis, alcohol excess, and chemotherapeutic drugs. In approximately 50% of cases, an underlying cause is unable to be identified and the condition is referred to as ''idiopathic'' DCM [2]. It is now recognised that approximately one in four patients with ''idiopathic'' DCM have a positive family history, which suggests a potential genetic aetiology [3]. A similar prevalence of familial disease (15–20%) has been observed in cohorts of children with DCM [4,5]. In kindreds in which DCM segregates with a Mendelian inheritance pattern, there is a high probability that a single inherited genetic variant is the primary cause of disease and this is termed ''familial'' DCM.

2. Clinical Presentation

Familial DCM may be inherited as an autosomal dominant, autosomal recessive, maternal or X-linked trait. Autosomal dominant is the most common pattern, with each child of an affected parent having a 50% chance of inheriting a disease-causing gene mutation, and 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 eg. conduction-system disorders, valvular abnormalities, congenital heart defects, left ventricular non-compaction, or with extracardiac manifestations eg. skeletal myopathy, partial lipodystrophy, sensorineural deafness.

3. Clinical Diagnosis

A diagnosis of familial DCM generally requires the presence of DCM in two or more affected individuals in a single family in the absence of another heritable cardiac or systemic cause of left ventricular dysfunction. Familial DCM should also be considered in kindreds in which first-degree relatives of DCM cases have unexplained sudden death at a young (<35 years) age [2,3]. Apart from family history, there are no specific clinical features that reliably distinguish familial from non-familial DCM [2,6].

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 families may include individuals who 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 family size is small, or if the clinical presentation differs between members of the same family. For example, in DCM with conduction-system disease due to *LMNA* mutations, family members may variably present with heart failure, arrhythmias, or sudden death [7,8]. The severity of disease and age of onset may differ between families and between members of the same family [9,10]. This may be influenced by sex, genetic modifier variants, comorbidities, and lifestyle factors. Dilated cardiomyopathy may be unmasked prematurely in genetically-predisposed females during the peripartum period [11]. While familial DCM generally shows high penetrance, some individuals may remain non-penetrant (ie. genotype-positive but with no clinical manifestations of disease) throughout life.

Family Screening

It has been 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 [12]. Measurement of creatine kinase levels is useful to identify subclinical skeletal muscle abnormalities and provides supportive evidence for the presence of an inherited myopathic disorder. Consideration of other causes of left ventricular dysfunction, including 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

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