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Review

Genetic causes of dilated cardiomyopathy ☆

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ABSTRACT

Dilated cardiomyopathy is a disease of the myocardium characterized by left ventricular dilatation and/or dysfunction, affecting both adult and pediatric populations. Almost half of cases are genetically determined with an autosomal pattern of inheritance. Up to 40 genes have been identified affecting proteins of a wide variety of cellular structures such as the sarcomere, the nuclear envelope, the cytoskeleton, the sarcolemma and the intercellular junction. Novel gene mutations have been recently identified thanks to advances in next-generation sequencing technologies. Genetic screening is an essential tool for early diagnosis, risk assessment, prognostic stratification and, possibly, adoption of primary preventive measures in affected patients and their asymptomatic relatives. The purpose of this article is to review the genetic basis of DCM, the known genotype–phenotype correlations, the role of current genetic sequencing techniques in the discovery of novel pathogenic gene mutations and new therapeutic perspectives.

1. Introduction

Dilated cardiomyopathy (DCM) represents an important health issue both in the in adult and pediatric population, with high rates of morbidity, mortality and hospital admissions. DCM is a severe disease of the heart muscle that is characterized by dilatation of the left ventricle and reduced left ventricular systolic function [1]. Genetic forms of DCM account for approximately 40% of cases [2], whereas the etiology of a wide portion of cases remains still unknown and it is considered idiopathic. In this group, the possibility to identify novel genetic mutations represents an intriguing challenge for the current advanced techniques of high-throughput genetic sequencing. Genetic screening for rare specific variants is an essential diagnostic tool not only in affected subjects but also in their asymptomatic relatives, including at risk siblings and children of affected patients, in order to improve early diagnosis, risk assessment for prognostic stratification and to identify patients who may benefit from primary prevention strategies such as regular cardiac monitoring, early institution of heart failure medications, and consideration of implantable cardioverter-defibrillators in those with a genetic-related increased risk of life threatening malignant arrhythmias.

The purpose of this article is to review the genetic basis of DCM, the known genotype–phenotype correlations and the role of current genetic sequencing techniques in the discovery of novel pathogenic gene mutations. Finally, we will discuss future developments including novel therapeutic perspectives.

2. Epidemiology of DCM in the adult and pediatric populations

DCM is a heart-muscle disorder characterized by systolic dysfunction and dilatation of the left ventricle with normal left ventricular wall thickness. DCM may present with biventricular involvement (Fig. 1A and B), even though the presence of a dilated and dysfunctional right ventricle is neither necessary nor sufficient for the diagnosis. Systolic dysfunction may lead to cardiac thrombus formation (Fig. 1C) that confers a risk of systemic embolization. DCM represents an important health issue both in the adult and pediatric population, with high rates of morbidity, mortality and hospital admissions: DCM can lead to progressive heart failure and represents the most frequent indication for heart transplantation [3].

The prevalence of DCM in the general population remains undefined. This disorder develops at any age, in either sex, and in people of any ethnic origin [4]. It is among the most common causes of cardiomyopathy with an estimated prevalence of 1:2500, and incidence of 7:100,000. In adults, males are more frequently affected than females with an approximately 3:1 ratio of males to females [5,6]. More recent estimates suggest a substantially higher prevalence of approximately ≥1 in 250 individuals [2]. In the pediatric population, DCM is the predominant type of cardiomyopathy [7] and its incidence is higher in the first year of life [8]. The majority of cases are idiopathic, followed by familial forms [4], which, in 6.8% of cases, are due to inborn errors of metabolism mainly regarding metabolic disorders, oxidative phosphorylation defects and systemic carnitine deficiency [9].

☆ The authors report that they have no relationship to disclose.

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In the pediatric cohort, a comprehensive clinical evaluation is important to exclude secondary causes of cardiomyopathies. In some cases, such as cardiomyopathy related to anomalous coronary connections to the pulmonary artery and tachycardia-induced cardiomyopathy, surgical treatment in the former and ablation in the latter may be curative [10,11]. Furthermore, hormonal and nutritional causes should be excluded, as it was observed that vitamin D deficiency is associated with reversible pediatric dilated cardiomyopathy [12].

3. Diagnostic criteria of idiopathic and familial dilated cardiomyopathy

Criteria for the diagnosis of DCM are the presence of left ventricular fractional shortening <25% and/or left ventricular ejection fraction <45%, and left ventricular end-diastolic dimensions >117% of the predicted value by the Henry formula [1,13]. The diagnosis of familial dilated cardiomyopathy is made in the presence of two or more affected individuals in a single family or in the presence of a first-degree relative of a dilated cardiomyopathy patient, with well-documented unexplained sudden death at <35 years of age [1]. In idiopathic DCM and familial DCM, the exclusion of potential secondary causes of ventricular dilatation and dysfunction (systemic arterial hypertension, coronary artery disease, valvular diseases, active myocarditis, chronic excess of alcohol consumption, sustained and rapid supraventricular arrhythmias, systemic disease, pericardial diseases, cor pulmonale, congenital heart diseases) is needed before reaching a DCM diagnosis. There are no significant clinical differences between idiopathic and familial forms of DCM except for the earlier age of onset and slightly higher left ventricular ejection fraction in the latter group [14]. Notably, also idiopathic DCM can have a genetic cause and lack the familial transmission due to small family size, lack of information, low penetrance, or de novo mutations.

4. Genetic determinants of dilated cardiomyopathy and genotype–phenotype correlations

Genetic forms of DCM account for nearly half of cases and are characterized by profound genetic heterogeneity, as about 40 causative genes have been identified so far [2,15]. These genes encode for a wide variety of proteins of the sarcomere, cytoskeleton, nuclear envelope, sarcolemma, ion channels and intercellular junctions. Specific mutations of these genes alter various pathways and cellular structures and negatively affect the mechanism of muscle contraction, functioning and sensitivity of ion channels to electrolytes, calcium homeostasis and generation–transmission of mechanic force in the myocardium. The fact that this genetic heterogeneity results in a common phenotype has been explained by Bowles and Towbin with the “Final Common Pathway” hypothesis: different mutations alter various proteins involved in a common pathway whose disruption leads to DCM, even the arrhythmogenic form [16,17].

The main pattern of inheritance in pediatric genetic forms of DCM is the autosomal recessive. In adult population, familial genetic forms of DCM account for 30–48% of cases, their main pattern of inheritance is autosomal dominant (56%) [14] and they are usually characterized by incomplete and age-related penetrance, and variable expression. The clinical phenotype, in terms of age of presentation, clinical characteristics and severity, is heterogeneous not only among different families, but also among members of the same family. Patients may be asymptomatic for several years before the development of overt progressive heart failure requiring transplantation. Arrhythmias, conduction system

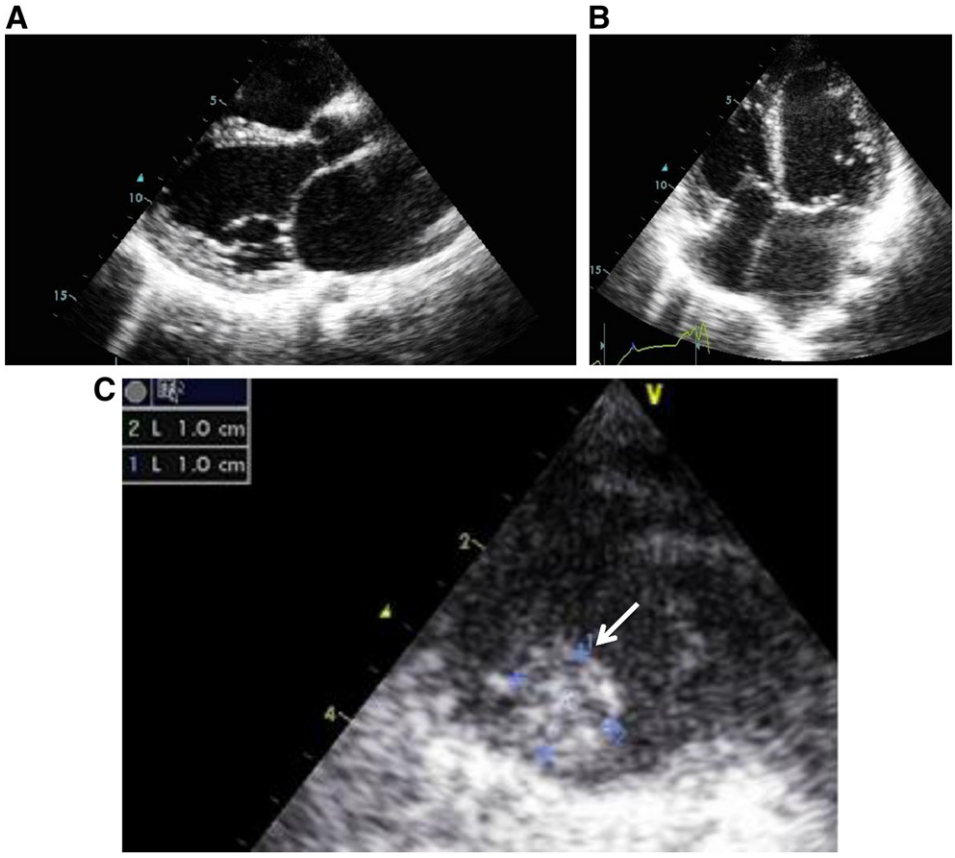

Fig. 1. Echocardiographic findings in pediatric DCM. (A) Parasternal long axis view in a 13 year-old patient with DCM and severe biventricular dysfunction showing enlargement of the cardiac chambers. (B) Four chamber echocardiogram shows biventricular dilation, biatrial enlargement and a marked trabecular meshwork in the lateral wall. (C) Echocardiography showing a large mobile thrombus (arrow).