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Mini Review

Idiopathic Dilated Cardiomyopathy

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Introduction

Cardiomyopathies are heart muscle diseases originated from a series of aggressions, such as genetic defects, cardiac myocyte injury or infiltration of myocardial tissue. Dilated cardiomyopathy (DCM) is characterized by an impairment of the left ventricular or biventricular contraction, caused by familial, genetic, viral, autoimmune, alcoholic, toxic, or of unknown cause. It is also associated with other recognized cardiovascular diseases, being considered a major cause of heart failure (HF) and the main indication for heart transplantation. Despite this, even in specialized centers with exhaustive diagnostic investigation, in only half of the cases, a specific cause is established for the disease. In its idiopathic form the evolution may not be progressive and different oucomes may be observed.

The time for stabilization of the disease may take years or even decades and it happens because of the effect of the reverse remodeling, a hypothsis recognized only in the last decade. As it is known, reverse remodeling may happen spontaneously or induced by medication. Genetic testing and endomyocardial biopsy may identify the etiology in many cases of idiopathic DCM, but they are not yet widely used in several countries because of the high costs, risks, and absence of specific therapy. More than 60 genes have been described as causing DCM, especially cytoskeleton cell genes and more recently sarcomere and Z-band genes, which were studied by its relation to the pathogenesis of hypertrophic cardiomyopathy (HCM) and later then discovered to DCM.

Laminins A and C are proteins of the intermediate filament family, being constituents of the nuclear lamina and therefore involved in several essential functions of the cell. Mutations of the LMNA gene, which encodes laminin A and C proteins, are the most frequently found in cases of idiopathic and familial DCM, with a prevalence of 5% to 10% in familial cases and 2% to 5% in sporadic cases [1-3]. Laminin A and C may have a change in structure which therefore results in multiple variants of its structure. However, in several studies it was verified that LMNA is not pathogenic by itself [3]. Nuclear architecture studies may be useful for a better understanding of the etiopathogeny of CMD related to variants of the LMNA gene.

Another important discussion is the discovery of three troponin subunits that cause the disease, namely TNNC1 (troponin C), TNNT2 (troponin T) and TNNI3 (troponin I) genes. These changes in the troponin complex are present in about 6% of DCM cases, and the clinical manifestations of these mutations are generally severe, causing sudden cardiac death and need for heart transplantation, which, on average, appears in the fourth decade of life [4,5]. Subsequent studies in experimental models have shown that the disease caused by troponin T changes results in calcium desensitization of the ATPase of the actomyosin, which in turn reduces the rate of contraction of the sarcomere and consequently its contractile force. Not always changes in the mutations in the cardiac troponin genes are pathogenic, and to bacome so, it requir genetic or environmental changes. Presenilin is an essential protein to γ-secretase, the enzyme responsible for the proteolytic processing of multiple proteins associated with the cell membrane. It is widely expressed in the brain, where it is responsible for the regulation of intracellular calcium currents and is implicated in the pathophysiology of Alzheimer's disease, but also expressed in the heart, where it is essential to cardiac morphogenesis. Mutations in PSEN1 and PSEN2 genes were proposed as possible causes of DCM. Thus, alterations of PSEN1 and PSEN2 genes are potential candidates for disease, as they increase intracellular protein aggregates, which in turn alter calcium homeostasis and provoke cytotoxicity [6,7]. Its' appearance in younger subjects suggests an early senility of the cardiac apparatus. Recently, studies have identified a polymorphism of the HSPB7 gene as being associated with increased susceptibility to DCM. HSPB7 is a gene encoding a small heat shock protein, cvHsp (also known as HspB7), usually activated when the cell is under stress, whether by elevated temperature, hypoxia or ischemia. Although the pathophysiological mechanism of this polymorphism is not well defined, its prevalence in patients included in the studies was 49% of cases of DCM [8].

The adequate investigation and the progression of the pathophysiological knowledge of DCM advances every year with new genetic discoveries. It's better understanding is very important for the introduce of appropriate treatment. Even though, nowadays in many centers, genetic research in these patients is still not a reality.

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