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UPDATE ON ARRHYTHMOGENIC VENTRICULAR DYSPLASIA.

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ABSTRACT

The Arrhythmogenic Ventricular Dysplasia (AVD) is a rare hereditary primary cardiomyopathy causing many diagnostic problems by the limits of current knowledges and instrumental opportunities.

The authors present a review about the most recent advances in the field of pathogenesis and diagnosis.

The pathogenesis relates to mutations in desmosomal genes, proteins involved in intercellular adhesion and in intracellular signal transduction, but also in no-desmosomal genes mutations have been described.

ECG, echocardiography, angiocardiography and RM have diagnostic limitations, such as endomyocardial biopsy, due to defects in sensitivity or specificity.

The AVD is a complex disease and there are still several and significative limitations both in the knowledge of pathogenesis than in diagnosis.

KEYWORDS: Arrhythmogenic Ventricular Dysplasia, Diagnosis, Pathogenesis

INTRODUCTION

The Arrhythmogenic Right Ventricular Dysplasia / Cardiomyopathy (ARVD / C) was described in 1982 for the first time[1] and it is characterized by a progressive fibro-adipose sub-epicardial replacement, especially in the right ventricle (RV)[2-4]. However, today it is no longer spoken exclusively ARVD, but AVD because the left ventricular involvement is frequent (10-28%)[5, 6].

The estimated prevalence is 1/5,000 individuals[7]. It generally occurs between the second and fourth decade of life[8] and it represents up to 5% of all sudden deaths in young adults in the United States and up to 25% of exercise-related deaths in Veneto region (Italy) [9, 10].

According to the classification of the American Heart Association it is a primary cardiomyopathies, genetically determined[11]. Many genetic mutations have been identified, related mainly to abnormalities of the desmosomal proteins and the most common form is a mutation in plakophilin-2 [12].

ARVD is diagnosed by using the Revised Task Force criteria 2010, which were based on structural alteration, tissue characterization, repolarization-depolarization/conduction abnormalities, arrhy-thmias, and family history[13]: definite diagnosis is made by completing two major criteria, or one major and two minor criteria, or four minor criteria from different categories.

The Authors present a review of the most current knowledges about the pathogenesis and diagnostical picture of the disease.

DISCUSSIONS

After the discovery of pathogenic mutations in desmosomal genes in families of persons with ARVD / C, it is now widely accepted as the primary mechanism of the disease is the disruption of desmosomal structure[12, 14-17].

The desmosomes are protein structures that consent the structural attachment between the cells and mediate the intracellular transduction of signals [18]. They are multi-protein complex expressed in epithelial and cardiac tissues and they guarantee a strong cell-cell adhesion through interactions between the desmoglein-2 (DSG2) and desmocollin-2 (DSC2)[19,20]. These interactions stabilize cadherins at the membrane[21,22] and cadherins interact with catenins and plakophilins, described as mediators of intracellular signaling[23].

The molecular pathogenesis of AVD concerns heterozygous mutations in the genes that encode cardiac desmosomal proteins DSG2 and DSC2, but also plakophilin-2 (PKP2), plakoglobin (JUP) and desmoplakin (DSP)[24].

Some studies have seen in plakoglobin and Wnt/beta-catenin signaling two histological characteristics of AVD-related adipogenesis and fibrogenesis[18,25,26], as also confirmed by transgenic animal models which reproduce the phenotype of the disease[18,27].

Samples of AVD heart present smaller desmosomes with more inter membrane space by electron microscope, probably because of an overall reduction of the length and adhesive properties of desmosomes[14,26]. Another support to this theory are recent studies frequently reporting plakoglobin levels reduced in the intercalated discs[28,29].

However, also non-desmosomal mutations may be involved[30-35]: the c.40_42delAGA (p.Arg14del) mutation of no-desmosomal phospholamban (PLN) gene[36-38] e c.40_42delAGA founder mutation[35]; in ryanodine receptor (RYR2), classically implicating in catecholaminergic polymorphic ventricular tachycardia and involving in the release of calcium from the sarcoplasmic reticulum [39]; mutations in transmembrance protein 43 (TMEM43) gene [31], as part of a adipogenic path in which the dysregulation may explain the progressive fibro-adipose replacement of the myocardium[40]; Transforming Growth Factor β pluripotent (TGFβ3) gene overexpression implicated in TGFβ3-induced myocardial fibrosis, but a direct causal role has yet to be confirmed[30].

The specific mechanism, by which these mutations can result in the clinically visible variety of expression of the disease, has been subject of many hypotheses.

The mutations would cause the death of cardiomyocytes and this would result in fibro-adipose replacement of normal myocardium. In fact clinical evidence showed a progressive loss of biventricular myocardial[41-43] and biopsy studies showed a remodeling of the intercalated disc, minus number of desmosomes, increased desmosomal-gap and improperly located desmosomes[14]. And the disproportionate involvement of the RV would be due to the increased vulnerability of the thin walls[44, 45].

Disorders of desmosomal signals also have been considered as implicated in causing electrical changes, slowing of conduction, and, finally, the loss of cardiomyocytes resulting in fibrogenesis and adipogenesis. In studies on DSP +/- mice the suppression of DSP caused the inhibition of signaling Wnt - catenin β1[18] and activation of this pathway has demonstrated increasing the myogenesis signal while suppression started adipogenesis signal. So the breaking of desmosomes would make cardiomyocytes incapable of supporting mechanical stresses resulting in cell death[46]. According to an alternative theory the fibro-adipose infiltration would result by a suppression of Wnt β1 - catenin signaling which is

initiated by dislocation of plakoglobin of the cell nucleus, resulting in a switch of cardiac progenitor cells for adipogenesis[47].

Lastly, according to another theory about the cardiomyocytes necrosis there would be the myocarditis. Inflammatory cells are commonly observed in biopsies (up to 75%)[41, 48] and they are particularly numerous during the acute phase of the disease, playing an important role in causing arrhythmias[41,49,50]. This would explain the chest pain, ECG abnormalities, and the release of myocardial enzymes (troponin) particularly during activity phases of disease[51]. But this inflammation may be a consequence of proinflammatory cytokines produced by apoptosis or, alternatively, caused by a viral infection.

AVD patients show non-specific anatomical pictures as RV myocardial atrophy with thinning of the wall, aneurysms, and global expansion of the RV[52].

The use of echocardiography in the definition of the RV volumes is limited[53] beacuse evaluations of regional or segmental dilation, wall thinning and reduction of RV function or formation of RV aneurysms are often subjective and qualitative, and still there are controversies about the importance of the various morphological features of disease[54]. Although many echocardiographic findings were associated with AVD, many of these studies involved a small number of cases[55] and some have been undertaken before the criteria of the Task Force, generating doubts about the non-uniformity of the study populations[56,57]. These studies[55,56,58] found that the presence of RV dysfunction by two-dimensional echocardiography has high specificity and predictive value[55], however a clear set of echocardiographic diagnostic criteria have not yet been decided.

The current ECG invasive techniques are usually limited to RV, they lose the arrhythmogenic epicardium substrate of the disease, important for disease[59], and are dangerous[60]. RV is for the most part electrically silent during conventional surface ECG, generating weak forces mostly hidden by the effects of LV depolarization [61]. So the early manifestation of the disease can be completely masked.

The angiocardiography provides information on global and regional RV function[62], with dilated, poorly contracting (decreased EF) and localized dyskinetic areas[63], but it is an invasive technique and, therefore, its use is limited in follow-up.

Magnetic resonance imaging (MRI) has been widely used[64-66], however, the studies were limited by the small number of patients and by non-uniform criteria for patient selection. Although MRI provides RV exquisite details and the evidence of fibro-adipose degeneration is very specific, but it has a low sensitivity[67].

The endomyocardial biopsy is required for demonstrating histopathologic features if the diagnosis is unclear or exclude a competitor diagnosis.

As already mentioned, the histological changes of disease in autopsy cases described a fat and fibro-adipose replacement of the myocardium[50].

However, it has been demonstrated that the only presence of adiposity is not compatible with the diagnosis of AVD because the adipose infiltration of the heart occurs physiologically and increases with age and body weight. The Task Force has revised the criteria that include a fibroadipose replacement with <60% residual myocytes as an important diagnostic criterion and, therefore, as a minor diagnostic criterion the presence of only fat in the absence of fibrosis [68].

However, the evidence has a low diagnostic sensitivity for several reasons, including the irregular distribution of the disease and the high rate of sampling error. The thin dyskinetic areas of RV free wall are more likely sites to provide an optimal sample, but these areas can present a higher risk of perforation and tamponade.

A recent study showed that small immunohistochemical analysis about the distribution of the desmosomal protein in samples of endomyocardial biopsy may have high sensitivity (91%) and specificity (82%) for the diagnosis [28], but, after an initial euphoria, excitement dropped rapidly when it was subsequently recognized that sarcoidosis and giant cell myocarditis can have similar patterns[69]. In addition cardiologists are cautious biopsying the RV free wall and the septum is usually intact in this disease.

CONCLUSIONS

The AVD is a complex disease and there are still several and significative limitations both in the knowledge of pathogenesis than in diagnosis.

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