REVIEW ARTICLE

Arrhythmogenic Cardiomyopathy. Genes and Desmosomal Proteins

Miocardiopatía arritmogénica. Genes y proteínas desmosómicas

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ABSTRACT

In 1996 this disease was introduced into the WHO classification of cardiomyopathies with the term “arrhythmogenic cardiomyopathy”. By the end of the 70s the right ventricle (RV) was identified as a substrate for the development of arrhythmias. The replacement of the myocardium by fibrofatty tissue and the hereditary nature of this condition were described in the 1980s. Later findings led to the identification of several genes involved in the production of desmosomal proteins participating in intercellular coupling, which led to defining arrhythmogenic cardiomyopathy as a desmosomal disease. Electrocardiography and echocardiography are fundamental tools, and invasive angiocardiography was used to detect dyskinesia-akinesia and right ventricular aneurysms. Endomyocardial biopsy was established as the gold standard for the diagnosis due to its ability to detect transmural replacement by fibrofatty tissue. The advent of cardiac magnetic resonance imaging (CMRI) with late gadolinium enhancement reveals morphological and functional abnormalities and tissue damage. The understanding of intercalated disc structure involved in intercellular coupling has made it possible to determine that, apart from desmosomes, several desmosomal proteins, as adherens junctions, gap junctions and ion channels are integrated into a unit known as the " area composita". The area composita constitutes an amalgam between supporting elements and ion channels that participate in action potential propagation, which has led to develop the concept that intercalated discs are constituted by "adhesion/excitability nodes". The clinical implications in the development of malignant arrhythmias are obvious.

Key words: Arrhythmogenic Right Ventricular Dysplasia - Desmosomes - Ventricular Fibrillation

RESUMEN

Desde 1996 esta enfermedad figura en la clasificación de las miocardiopatías de la OMS con el nombre de “miocardiopatía arritmogénica”. A fines de la década del 70 se estableció que el ventrículo derecho (VD) puede ser el sustrato para el desarrollo de arritmias. En la década del 80 se describió el reemplazo del miocardio por tejido fibroadiposo y su naturaleza hereditaria. Posteriores descubrimientos permitieron la identificación de varios genes implicados en la producción de proteínas desmosómicas que participan en el acoplamiento intercelular lo cual llevó a definir a la miocardiopatía arritmogénica como una enfermedad desmosómica. El electrocardiograma y el ecocardiograma resultaron fundamentales y la angiocardiografía invasiva se utilizó para detectar disquinesia-aquinesia y aneurismas del VD. La biopsia endomiocárdica se perfiló como el gold standard para el diagnóstico, debido a su capacidad para detectar el reemplazo transmural por tejido fibroadiposo. El advenimiento de la resonancia magnética cardíaca (RMC) con realce tardío de gadolinio ha permitido revelar no solamente anomalías morfológico-funcionales sino también daño tisular. El conocimiento de la estructura del disco intercalar, involucrado en el acoplamiento intercelular ha permitido determinar que no solamente los desmosomas estarían comprometidos, sino que habría varias proteínas constituyentes tanto de los desmosomas, como de las uniones adherentes, las uniones gap, y los canales iónicos, integradas en una unidad conocida como “área composita”. Ésta constituye una amalgama entre elementos de sostén y canales iónicos que participan en la propagación del potencial de acción, lo que ha permitido desarrollar el concepto de disco intercalar compuesto por los llamados “nodos excitoadhesivos”. Las implicancias clínicas en el desarrollo de arritmias malignas son obvias.

Palabras clave: Displasia Ventricular Derecha Arritmogénica - Desmosomas - Fibrilación ventricular

In 1996 a new disease was introduced into the WHO classification of cardiomyopathies, (1) leaving aside the concept of this entity as a congenital defect. The identification of the left ventricular variant led to coin the term “arrhythmogenic cardiomyopathy” (ACM). (2) The adjective arrhythmogenic defines the pathognomonic characteristic of this non-ischemic heart muscle disease.

In the last century, towards the end of the 70s, Fontaine et al. noticed that the right ventricle (RV) could constitute the substrate for the development of arrhythmias with left bundle branch block morphology. (3,4) In 1982, Frank Marcus et al. published a series of patients with a new syndrome characterized by RV remodeling with aneurysms localized in the inflow tract, apex and outflow tract (triangle of dysplasia) (Figure 1) because the myocardium was replaced by fibrofatty tissue. (5) Nava et al. described the hereditary nature of ACM. (6) In Italy, Nava described a dominant inherited form, later named the "Veneto disease", (7) which

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consisted of a genetically determined cardiomyopathy since its clinical manifestations were absent at birth and became evident between 10 and 12 years of age.

Sports activity increases five times the risk of sudden death in carriers. (8) In Italy, the incidence of sudden death due to ACM is 27% among athletes, with a significant reduction since ECG has been implemented as a screening tool in the evaluation of candidates for sports. (9)

Arrhythmogenic cardiomyopathy involves an acquired loss of myocardial tissue followed by fibrofatty replacement in the setting of a myocyte death and repair process (10) due to apoptosis. (11) Although myocardial inflammation is a common finding, its characterization as a consequence of necrosis or as a primary immunological phenomenon is still controversial. (12) Moreover, adipocytes have a mesenchymal origin. (13)

In the Greek island of Naxus, a recessive form of the disease was discovered, with palmoplantar keratosis and woolly hair. (14) In 1996 Ruiz et al. studied junction plakoglobin (JUP) in knockout mice and demonstrated that the absence of JUP affects the development of desmosomes in the heart. The human plakoglobin gene is located on chromosome 17q21. (15)

In Ecuador, the dermatologist Carvajal-Huerta found a recessive mutation in the gene encoding desmoplakin (DSP) in a similar familial syndrome with dilated cardiomyopathy. (16) The gene encoding DSP also became a candidate for the dominant form of ACM. Subsequently, other mutations were identified in the dominant form of ACM: plakophilin-2, desmoglein-2, desmocollin-2 and plakoglobin, confirming it is a desmosomal disease. (17) Multiple compound or heterozygote mutations imply a more severe prognosis, but the productivity of genetic testing does not exceed 50%. (18)

Thus, ACM was definitely linked to genes encoding for desmosomal proteins. Electron microscopy demonstrated disruption of the intercalated discs as a common final pathway for cell death. (19)

The diagnostic criteria were defined in 1994 and updated in 2010. (20,21) Electrocardiography and echocardiography resulted fundamental diagnostic tools. Invasive angiocardiography was used to detect dyskinesia-akinesia and RV aneurysms. (22)

Endomyocardial biopsy was established as the gold standard for diagnosis due to its ability to detect transmural replacement by fibrofatty tissue. (23) This test plays a critical role in the differential diagnosis with diseases that mimic ACM, as myocarditis, sarcoidosis, and idiopathic RV tachycardia. The advent of cardiac magnetic resonance imaging (CMRI) with late gadolinium enhancement reveals morphological and functional abnormalities and tissue damage; it also plays a fundamental role in the diagnosis of isolated left ventricular involvement. (24,25)

Genetic screening is now a routine diagnostic tool in relatives of probands with ACM who have at least one mutation, to search for relatives who are mutation carriers, and is an effective bridge between the laboratory and the patient. State-of-the-art genetic sequencing has enabled rapid and accurate screening and generates index cases either by clinical identification or in postmortem molecular investigation. (26)

Advice against physical activity is one of the most effective measures to prevent sudden death in ACM. (27) Implantable cardioverter defibrillator (ICD) also saves lives in patients with this disease. The indication for implantation depends on the prognosis; it is mandatory in patients with syncope, sustained ventricular tachycardia or previous heart attacks. (28,29)

Drug therapy is routinely used, either isolated or associated with ICD. (30). Ablation is also included among the treatment options, although it is considered a palliative procedure due to the recurrence of arrhythmias. (31) Heart transplantation is the last

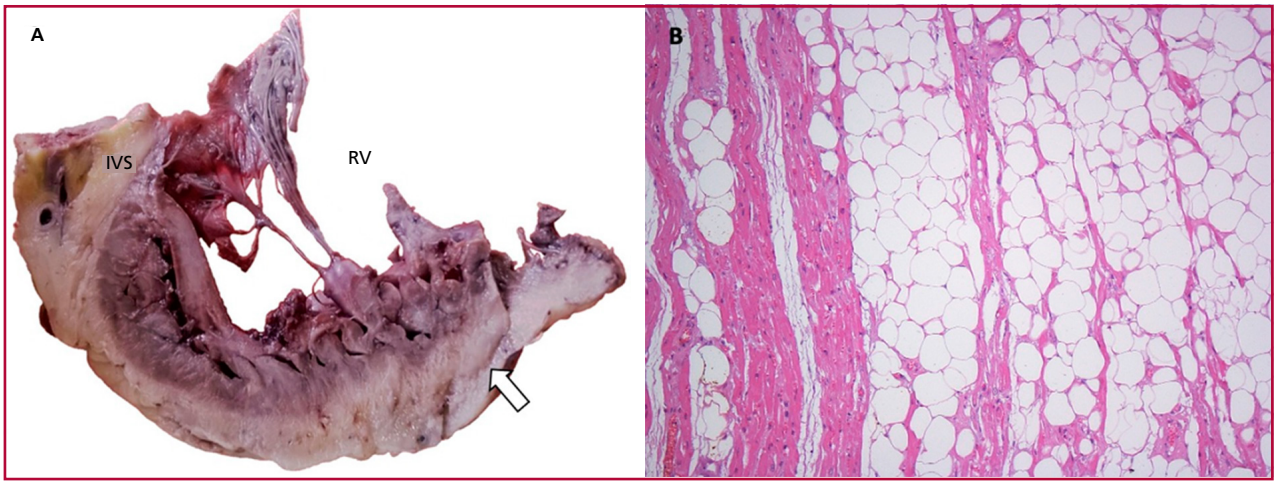

Fig. 1. 29-year-old, otherwise healthy man, with no personal or family history, with unwitnessed sudden death. **A.** Right ventricle (RV) with thin free wall and lard-like tissue (arrow) replacing the myocardium and extending to the interventricular septum (IVS) and left ventricle. **B.** Histological examination showing extensive replacement of the myocardium by fatty tissue, scarce atrophic bundles and residual myocardial fibers separated in small fascicles. HE 200x.

option reserved for end-stage congestive heart failure or unbearable electrical storm.

MOLECULAR MECHANISMS

Among the research perspectives, curative therapy should focus on the molecular mechanism involved in the pathogenesis of the disease. (32) Intercalated discs are highly organized complex structures which connect cardiomyocytes to one another and consist of gap junctions bridging the cytoplasm of the cells, adherens junctions that interconnect the cell cytoskeletons, and desmosomes that connect with the intermediate filament of the cells. Finally, ion channels are also present in the intercalated discs. The genetic abnormalities involving the components of the intercalated discs are responsible for the development of arrhythmias.

The characteristics of the intercalated disc are mainly determined by the properties of its multifunctional proteins within an integrated unit, called the "area composita" which includes adherens junctions, gap junctions, desmosomes and ion channels. Ion channels and gap junctions generate and propagate the action potential.

Deficiencies in these proteins can lead to contractility abnormalities and arrhythmias, demonstrating the interdependence between the intercalated disc components. The lateral membrane has a different composition. Its structural functional component is the costamere and includes focal adhesions linking sarcomeres to the extracellular matrix. Despite the differences, the intercalated disc and lateral membrane have several proteins in common, such as vinculin and α-actinin, and ion channels.

The adherens junction connects actin filaments from adjacent cells and is involved in transducing mechanical signals. The transmembrane protein N-cadherin is the main constituent of adherens junctions. It homodimerizes with N-cadherins from adjacent cells as an intercellular zipper, while calcium ions ensure the rod shape of this junction. N-cadherin also possesses regulatory functions and a mechanosensing role.

β-catenin directly interacts with the C-terminal cytoplasmic domain of N-cadherin. By associating with α-catenin and vinculin, it connects adherens junctions to the actin cytoskeleton. Also, β-catenin plays a central role in cadherin-mediated signaling and can activate the canonical Wnt signaling pathway. The canonical Wnt pathway is crucial in cardiac development but has also been proposed as the key mechanism in certain cardiomyopathies.

While adherens junctions transmit mechanical forces to the cytoskeleton, desmosomes are more robust thanks to their connection to mechanically resilient intermediate filaments. The intercellular part of the cardiac desmosome is built up by the cadherins desmoglein-2 (DSG2) and desmocollin-2 (DSC2). The plaque proteins plakoglobin (JUP) and plakophilin-2 (PKP2), and desmoplakin (DSP) connect desmin to the desmosome. The hyperadhesive state of the desmosome, when DSC2 and DSG2 are bound, depends on the presence of calcium ions.

PKP2 is the main protein, associated with gap junctions and necessary for the organization of the intercalated disc and desmosomal function. Together with JUP, PKP2 mediates attachment to intermediate filaments. PKP2 knockdown causes a decrease in conduction velocity and an increased propensity to develop re-entry arrhythmias.

PKP2 mutations are most common in hereditary ACM. Plakoglobin is present in both desmosomes and adherens junctions. Desmoplakin connects the desmosomes to the type III intermediate filament protein desmin. The main mutations in genes encoding desmosomal proteins in ACM include PKP2 and DSP, along with cadherins DSG2 and DSC2; mutations in JUP are less common. CDH2 encodes N-cadherin and belongs to a superfamily of proteins that mediate cell–cell adhesion in a calcium-dependent manner.

The fact that cadherin-2, like its desmosomal cadherin counterparts, plays a major role in the structure of the intercalated disc is based on the CDH2 cardiac-specific mouse model with deletion of N-cadherin in the adult mouse heart causing dissolution of the intercalated disc structure, including loss of both desmosomes and adherens junctions, demonstrating that desmosome integrity is N-cadherin or cadherin-2 dependent. These mice present atypical forms of dilated cardiomyopathy and ventricular arrhythmia that resulted in sudden death.

Arrhythmic propensity is probably due to a reduced and heterogeneously distributed connexin-43, causing loss of functional gap junctions and partial cardiomyocyte uncoupling, and highlighting the prominent role of cadherin-2 in the intercalated disc. This remodeling with concomitant reduction of desmosomal proteins, connexin-43, and cadherins has also been demonstrated in ventricular tissues of patients with ACM.

The loss of PKP2 expression has been shown to alter the amplitude and kinetics of the sodium current. This evidence suggests a model in which the intercalated disc would be constituted by “adhesion/excitability” nodes formed by aggregates of sodium channels and N-cadherins. (33)

Finally, in view of the important investigations described in the present study, we have recently indicated that the absence of routine clinical and cardiological examinations hinders the correct characterization of the potentially lethal nature of ACM. (34)
Meanwhile, the study of the disease continues.

Conflicts of interest

None declared.

(See authors' conflict of interests forms on the web/Additional material.)

Ethical considerations

Not applicable.

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