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Case Report

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Fragmented QRS and sudden death in a patient with arrhythmogenic right ventricular dysplasia/cardiomyopathy

Luis A. Rodríguez López, MD; Eliany Rodríguez Moreno, MD; Juan M. Cruz Elizundia, MD; Yohan M. Díaz Sardiñas, MD; Reinaldo Gavilanes Hernández, MD; Dr. Ruben R. Quenta Tarqui✉, MD; Jhosely A. González Achacollo, MD; and Carlos Santana Santana, MD

Department of Cardiology, Cardiocentro Ernesto Che Guevara. Santa Clara, Villa Clara, Cuba.

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Acronyms
ARVD: Arrhythmogenic right ventricular dysplasia
ECG: Electrocardiogram
SCD: Sudden cardiac death
VT: Ventricular tachycardia

ABSTRACT

The arrhythmogenic right ventricular dysplasia or cardiomyopathy is a genetic heart disease whose diagnosis is often a challenge for the clinician. It is one of the most common causes of sudden cardiac death in adolescence and in young adults. We present the case of a patient with a history of malignant ventricular arrhythmias and recovered sudden cardiac death due to arrhythmogenic right ventricular dysplasia, with QRS fragmentation in the right precordial leads, as a marker of the presence of a suitable substrate for the emergence of spontaneous ventricular fibrillation. The pathogenesis, diagnosis and treatment of this disease are discussed.

Keywords: QRS fragmentation, Sudden death, Arrhythmogenic right ventricular dysplasia

Fragmentación del QRS y muerte súbita en paciente con displasia arritmogénica del ventrículo derecho

RESUMEN

La miocardiopatía o displasia arritmogénica del ventrículo derecho es una cardiopatía de origen genético cuyo diagnóstico supone, a menudo, un reto para el clínico. Es una de las causas más comunes de muerte súbita cardíaca en la adolescencia y en los adultos jóvenes. Se presenta el caso de un paciente con historia de arritmias ventriculares malignas y de muerte súbita cardíaca recuperada, por displasia arritmogénica del ventrículo derecho, con fragmentación del QRS en las derivaciones precordiales derechas, como marcador de la presencia de un sustrato propicio para el surgimiento de la fibrilación ventricular espontánea. Se comenta la patogenia, el diagnóstico y el tratamiento de esta enfermedad.

Palabras clave: Fragmentación del QRS, Muerte súbita, Displasia arritmogénica del ventrículo derecho

✉ *RR Quenta Tarqui*
Cardiocentro Ernesto Che Guevara
Calle Cuba 610
e/ Barcelona y Capitán Velasco.
Santa Clara 50200. Villa Clara, Cuba.
E-mail address:
rubenqt@ucmex.vcl.sld.cu

INTRODUCTION

Since the arrhythmogenic right ventricular dysplasia (ARVD) was first described by Dalla Volta *et al*[1] in 1961, and subsequently characterized by Fontaine *et al*[2] in 1977, up to the present, that it has been included in the cardiomyopathies classification of the World Health Organization[3], the

contributions to the literature on this disease has been numerous[4,5]. Initially, the descriptions focused on the arrhythmic substrate of certain areas of the right ventricle, the so-called "triangle of dysplasia" ; but now the spectrum has expanded to give way to diffuse manifestations in the aforementioned ventricle, to the only left ventricular and biventricular disease in the advanced phase of the disease, often indistinguishable from dilated cardiomyopathy[6]. The prevalence varies widely according to the series described and there is controversy about the geographical distribution of the disease. In the Veneto regions of Italy, a prevalence of 1 case per 1000 or 10000 people is estimated. Corrado *et al*[7] point out that it can cause up to 20% of sudden cardiac deaths (SCD) in young adults and Italian athletes, and it affects males most often. In USA it represents 5% of the SCD in under 65 years old and 3-4% in athletes[8,9].

The ARVD is a disease of the cardiac muscle of genetic origin whose diagnosis is often a challenge for the clinician. The classic description usually refers to the final stage of the disease, in which the myocardium, fundamentally from the right ventricle, has been replaced by fibroadipose tissue; for this reason, the initial phases of the disease, which are not as vast in semiology, usually go unnoticed. Unfortunately, the risk of fatal outcome is not low[10].

CASE REPORT

This is the case of a 54-year-old man with white skin and without cardiovascular risk factors, toxic habits, previous valvular disease or other heart disease, which was sent to the arrhythmia department presenting loss of consciousness, of short duration, related to physical exertion and stress, and eventually ventricular tachycardia (VT), which degenerated into ventricular fibrillation recovered after electrical cardioversion. The 12- lead basal electrocardiogram (ECG) showed an incomplete right bundle branch block pattern with negative T waves and QRS width bigger than 110 msec; also, epsilon wave and QRS fragmentation in right precordial (**Figure 1**).

The echocardiogram showed right ventricular dilatation (54 mm) with thickened free wall and presence of whitish appearance in some areas, which could be related to fibroadipose infiltration (**Figure 2**). An ARVD was diagnosed, a treatment with amiodarone was indicated and an implantable cardioverter defibrillator was placed; the evolution was favorable.

COMMENTS

The ARVD is a heritable disorder, having family incidence until 50% of cases, with an autosomal dominant pattern of transmission, varying degrees of penetration and polymorphic phenotypic expression. However, an autosomal recessive form has also been described[1-5]. It can be associated to a palmoplantar keratoderma and to a wooly hair (Naxos disease)[6]. This type of ARVD is caused by a mutation in the plakoglobin gene, whose product is a component of desmosomes and adherens junctions, and the Carvajal's syndrome, with the same cutaneous phenotype prevalence of left ventricular in families from India and Ecuador[6,7].

The first mutation causing a non-syndromic ARVD was described by Rampazzo *et al*[8] in 2002. This mutation was identified in the desmoplakin gene, which codes a component of the desmosome. In 2004, Gerull *et al*[9] described 25 mutations of the chimeric desmosomal or plakophilin gene; later, there were identified other mutations that presuma-

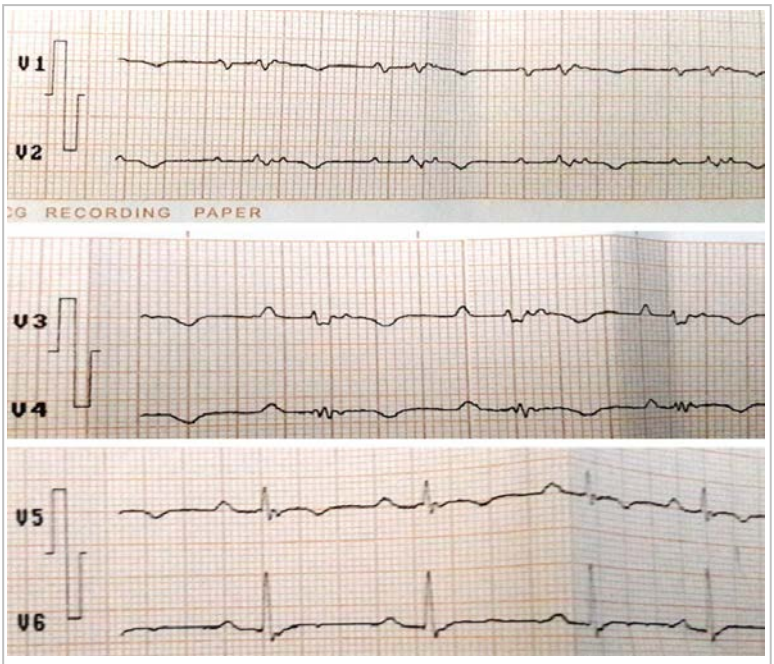

Figure 1. Electrocardiogram in right precordial with epsilon wave and wide QRS, with fragmentation.

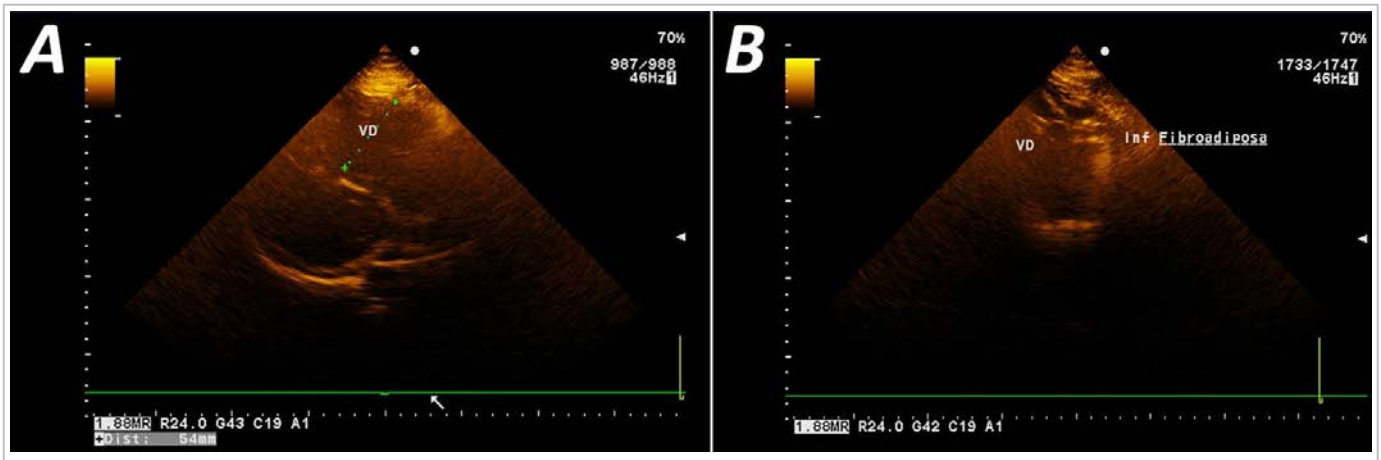

Figure 2. Transthoracic echocardiogram. **A.** Severe dilatation of right ventricle. **B.** Fibroadipose infiltration of anterior wall. VD, right ventricle.

bly caused disease in the plakoglobin and desmoplakin, as well as other desmosomal genes (the ones of desmocollin 2 and desmoglein 2) in patients with non-syndromic ARVD. Nowadays, the desmosomal dysfunction is considered to be the final common pathway in the pathogenesis of the ARVD, since the structural and functional integrity of the brain tissue is based on desmosomes, adherens junctions and gap junctions located on the intercalary disks[10].

In the chromosomal map there have been located different genetic variants of the ARVD and over 140 disease-causing mutations have been described, most of them corresponding to encoding desmosomal proteins. Some non-desmosomal genes have also been associated with an autosomal dominant ARVD, including the gene of the transforming growth factor β-3 (TGFβ3)[11], which modulates the expression of cellular contact proteins and the ryanodine 2 receptor gene. (RyR2) [11,12]. The RyR2 gene, which was first described in eight families, encodes receptors that mediate the release of calcium from the sarcoplasmic reticulum; however, there are still divergent views as to whether or not it should be considered in patients with mutations of this gene that they suffer ARVD or catecholaminergic polymorphic VT. The mutation that has been described more recently is the TMEM43 gene, which causes an ARVD variant of complete penetration, very lethal (ARVD type 5) [13-15].

The degeneration and death of the miocardiocytes are the anatomopathological consequence of these adhesion protein mutations, with the consequent progressive substitution by adipose and fibroadipose tissue. In the inflammatory theory, supported by the appearance of inflammatory infiltrates in necropsy series, the myocardial damage would be explained by a continuous process of damage and repair as a chronic myocarditis[13-15].

The clinical manifestations of the ARVD are variable and depend on cardiac instability and progressive ventricular dysfunction. They will range from asymptomatic patients, SCD as the first manifestation, ventricular and supraventricular arrhythmias, to right or biventricular heart failure. The presence of an imbalance in adrenergic innervation has been described as a possible coadjuvant in the genesis of arrhythmias; in this way, the propensity for ventricular arrhythmias increases in situations of exposure to catecholamines, especially during exercise[11].

The most frequent alterations in the ECG are the inversion of the T wave (V_1-V_3), present in up to 50% of the individuals. The condition beyond V_3 indicates additional involvement of the left ventricle[12]. There are different anomalies of ventricular depolarization, incomplete right branch block is more frequent (18%) than complete (15%); the prolongation of the QRS more than 110 msec in V_1 and V_2 is a more specific finding, and epsilon waves are observed at the end of the QRS and at the beginning of ST, which correspond to delayed electric potentials and small amplitude originated in areas of healthy tissue surrounded by infiltrated fibroadipose[13]. The QRS width and fragmentation in the right precordials allow to predict, independently, the presence of dilation and right ventricular dysfunction and even dysrhythmias[14].

This QRS fragmentation is defined as the presence of notches or low voltage waves (R') at the terminal portion of the QRS or ST segment start, at least two contiguous leads. Morita *et al*[10] showed

that they represent a marker of the presence of a substrate conducive to the emergence of spontaneous ventricular fibrillation, with a sensitivity of 93% and specificity of 90%.

The definitive diagnosis of the ARVD requires the pathological confirmation of the transmural fibroadipose substitution, by means of surgical or necropsy samples. The patchy and progressive nature of the disease means that the endomyodocardial biopsy has limited utility. There is no single test to establish the diagnosis of the ARVD[3-7]; this is established after a functional, morphological and electrocardiographic evaluation, whereby currently recognized major and minor criteria are determined[15-1]. In 2002, a modification to these criteria for the diagnosis of the ARVD was proposed, in first-degree relatives of an index case[16]. In this situation, the presence of a reversal of the T wave in right precordials (V_2-V_3), late potentials in the ECG of signal averaging, VT with morphology of the left bundle branch block (LBBB), or the observation of functional or morphological changes of the right ventricular in imaging scans must be all considered major criteria with higher diagnostic value for family ARVD[16]. Subsequently, a new modification of these criteria was published, in order to increase the sensitivity by using emerging diagnostic modalities, advances in genetics of the ARVD and introducing quantitative parameters[18].

The ARVD is usually manifested as episodes of VT originated in the RV, i.e., they have LBBB morphology in adolescents or young adults apparently healthy. Ventricular arrhythmias may be asymptomatic and detected by routine ECG or may cause palpitations, syncope or SCD. It has been estimated that the ARVD accounts for up to 5-20% of cases of SCD in individuals under 35 years of age[18].

Although the information regarding natural history is limited, in general four stages are registered[7,19,20]:

I. The early or silent phase, usually asymptomatic, although the debut may present with SCD.
II. Unstable phase with predominance of symptomatic arrhythmias, usually with LBBB morphology, highly suggestive of right ventricular origin.
III. Phase of the right ventricular failure with relative conservation of the left's function.
IV. Final phase with progressive biventricular dilation, often indistinguishable from dilated cardiomyopathy. The most frequent complications at this stage are the thromboembolic and atrial fibrillation.

In the last two decades, the arrhythmias originated in the RV have attracted the attention of the scientific world for several reasons, mainly because they tend to affect younger patients and can lead to SCD. The pathophysiological mechanism of these arrhythmias has not been fully clarified and sometimes allows different interpretations. In addition, the intriguing world of genetics is increasingly involved in the pathogenic, diagnostic and prognostic aspects of some of these arrhythmias. The fibroadipose tissue infiltration is a substrate for electrical instability leading to ventricular arrhythmia ranging from ventricular extrasystoles isolated to sustained VT or ventricular fibrillation[1-4]. There are multiple electrical predictors for the occurrence of ventricular arrhythmias and SCD[10,21-23], the QRS of longer duration, QRS fragmentation and epsilon wave were present in our patient.

The main objective of the therapeutic strategy in these patients is prevention of the SCD, to which we have three main therapeutic strategies: antiarrhythmic drugs, catheter ablation and using implantable cardioverter defibrillator[24,25].

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