Arrhythmogenic right ventricular dysplasia and sudden death. Report of two cases

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Received: 18.02.2009/ Accepted in revised form: 9.04.2009

Abstract: Arrhythmogenic right ventricular dysplasia or cardiomyopathy (ARVD or ARVC) is a heart muscle disease, often familial, characterized by structural and functional abnormalities of the right ventricle due to replacement of the myocardium by fatty and fibrous tissue. Clinical presentation of ARVD/ARVC usually consists of arrhythmias of right ventricular origin that include isolated premature ventricular beats, sustained ventricular tachycardia, and ventricular fibrillation that can lead to sudden death. The development of arrhythmogenic right ventricular dysplasia or cardiomyopathy appears to be related to the following two processes: (1) myocyte degeneration (including apoptosis and transdifferentiation), which may be inherited, and (2) interstitial inflammation, which may be infectious (probable postvital) or autoimmune in origin. Fatty infiltration, which is the hallmark of the disorder, is considered to represent a secondary phenomenon. Gene mutations have recently been identified and suggest an underlying ion channel disorder. Fatty infiltration is nearly transmural and accompanied by thinning of the muscular wall. Grossly, fatty infiltration generally spares the right ventricular trabeculations the ventricular septum and the left ventricular free wall.

Authors present two cases, a 52-year-old and a 35-year-old women, previously healthy, with sudden death. In both cases, marked fatty infiltration of the right ventricular myocardium was observed.

Key words: arrhythmogenic right ventricular dysplasia, sudden death

Knowledge about the role of the right ventricle in health and disease historically has lagged behind that of the left ventricle. Less muscular, restricted in its role to pumping blood through a single organ, and less frequently or obviously involved than the left ventricle in diseases of epidemic proportions such as myocardial ischemia, cardiomyopathy, or valvulopathy, the right ventricle has generally been considered a mere bystander, a victim of pathological processes affecting the cardiovascular system [1].

The right ventricle is affected by and contributes to a number of disease processes, including perhaps most notably pulmonary hypertension caused by a variety of lung or pulmonary vascular disease (cor pulmonale). Other diseases affect the right ventricle in different ways, including global, left ventricular – or right ventricular – specific cardiomyopathy; right ventricular ischemia or infarction; pulmonary or tricuspid valvular heart disease; and left-to-right shunts [1].

Arrhythmogenic right ventricular dysplasia or cardiomyopathy [ARVD or ARVC] is a heart muscle disease, often familial, characterized by structural and functional abnormalities of the right ventricle due to replacement of the myocardium by fatty and fibrous tissue.

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Clinical presentation of ARVD usually consists of arrhythmias of right ventricle origin that include isolated premature ventricular beats, sustained ventricular tachycardia, and ventricular fibrillation that can lead to sudden death [2, 3]. ARVD is an uncommon disorder characterized by right ventricular dilatation and fibrofatty replacement of the right ventricular myocardium [4]. Although it has been estimated that the disease afflicts about 1 in 5000 persons in the United States, the exact prevalence is unknown [5].

In 80% the cases the initial manifestation occurs before the age of 40 years and includes palpitations, presyncope or syncope, transient or sustained ventricular tachycardia, cardiac arrest, congestive heart failure, or sudden unexpected death [5, 6, 7]. In many cases of sudden death, there is no prior history of an underlying cardiac disorders [4].

**Report of two cases**

**Case 1** A 35-year-old woman was hospitalized in the Urological Clinic of Tg. Mureș for a left kidney calculus and hidronephrosis. After the surgical intervention, the patient started suddenly to complain of thoracic pains, extreme anxiety and dispnea and died in less than 1 hour.

A forensic autopsy was performed.

The right ventricle was markedly dilated, and very thin (the maximal thickness of right ventricle 0.2 cm) with transmural adipous invasion (Fig. 1, 2).

The heart weighted 280 g, maximum thickness of left ventricle was 0.9 cm. The right coronary artery was markedly hypoplasic (circumference 0.3-0.4 cm).

**Case 2** A 52 year old woman collapsed suddenly on a public side-way and died before the arrival of an ambulance. The personal medical history provided no relevant information. Post-mortem toxicological investigation was negative for common toxic substances (including alcohol). The autopsy revealed the presence of moderately to markedly dilated and thin (maximal thickness 0.3 cm) right ventricle. Transmural adipous invasion of the right ventricle wall was present at various levels on serial sections. The heart weight was within the normal range (340 g).
Low-power microscopic examination of right ventricular free wall revealed extensive adiposity and small island of subendocardial myocytes (Fig. 3).

Discussion

Multiple theories regarding the genesis of ARVD has been described [8]. In the dysontogenetic theory, the absence of myocardium is considered to be the consequence of a congenital aplasia or hyperplasia of the right ventricular wall, leading to a parchment-like aspect. The eponym Uhl anomaly has been commonly used in memory of the 8-month-old infant described by Uhl in 1952, with “almost total absence of the myocardium of the right ventricle” [8].

Only 27 years have elapsed from the time that the clinical profile of arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) was first described [9]. Since then, this entity has been found to have prevalence of about 1 in 5000 persons [10] and is well recognized in the United States, Europe, and Asia. The usual clinical presentation of ARVD/C is that of palpitations, nonsustained ventricular tachycardia, and sustained ventricular arrhythmias. Uncommonly, sudden cardiac death may be the first manifestation of the disease [11].

Arrhythmogenic right ventricular cardiomyopathy is characterized by myocyte loss due to necrosis or apoptosis, as well as fatty or fibrofatty replacement. [5, 6, 7]. It primarily affects the right ventricular free wall and may be focal or diffuse. The disease tends to progress from subepicardium to subendocardium and is eventually associated with wall thinning, focal aneurysm formation, and chamber dilatation.

Although ARVD may be diagnosed at any age, sudden deaths tend to occur between the ages of 15 and 45 years, with a mean age of about 30 years [12, 13, 14]. Men are affected slightly more often than women. In a series of 200 cases reported by Tabib et al. [14] the mean age was 34 years (range, 5-64 years), and 108 (54%) was male.

The development of ARVD appears to be related to the following 2 processes: [1] myocyte degeneration (including apoptosis and transdifferentiation), which may be inherited, and [2] interstitial inflammation, which may be infections (probably postviral) or autoimmune in origin [5, 6, 7, 15, 16]. Both processes may be operative in some patients. Fatty infiltration, which is the hallmark of the disorder, is considered to represent a secondary phenomenon. It has been postulated that myocardial cell death in ARVD might represent a programmed death (“cell suicide”) known as apoptosis [13]. This theory is very attractive because it offers a reasonable explanation for the peculiar right ventricular involvement [17].

Link age analysis indicated that ARVD is a genetically heterogeneous disorder, but in only about half of the patients can chromosomal defects be identified. For the autosomal dominant form, defects have been localized to 1q42-q43 (ARVD2), 2q32 (ARVD4), 3q23 (ARVD5), 10q22 (ARVD7), 10p12-p14 (ARVD6), 14q12-q22 (ARVD3) and 14q23-q24 (ARVD1) [18,19]. Corresponding gene mutations have recently been identified and suggest an underlying ion channel disorder [19]. A rare autosomal recessive form of ARVD, occurring with Naxos disease (skin abnormalities and woolly hair), has been associated with defects at 6p24 and 17q21 [18, 19, 20]. Dalal et al. [21] and van Tintelen et al. [22] address the prevalence and clinical expression of mutation in the plakophilin-2 gene (PKP2) in ARVD patient populations of comparable size and fulfilling the task force diagnostic criteria [23].
The ECG repolarization abnormalities are inverted T waves in right precordial leads (V2 and V3) in people aged >12 year and in absence of right bundle branch block. Fibro-fatty replacement of myocardium on endomyocardial biopsy [23].

Annually in the United States, sudden unexpected death accounts for about half of all cardiovascular deaths, or approximately 350 000 cases [24]. The underlying cases vary with age. During the first 3 decades, myocarditis, cardiomyopathy, and coronary artery anomalies predominate as causes of sudden unexpected death. However, for persons older than 30 years, coronary atherosclerosis with ischemic heart disease is the most common cause [4]. Although ARVD is considered a rare disorder, it accounted for 10% of all cases of sudden unexpected cardiac death in the study of Tabib et al. [14]. However, in we cases of sudden or unexpected deaths, the incidence of ARVD is very rare.

References