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Arrhythmogenic right ventricular cardiomyopathy/dysplasia: Analysis based on six cases

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Abstract

Background: *We sought to investigate the profile of symptoms and results of investigations among six cases of suspected arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D).*

Methods: *The diagnosis of ARVC/D was made on the basis of standardised diagnostic criteria proposed by the study group on ARVC/D of the European Society of Cardiology. A study was conducted involving six patients with suspected ARVC/D that were diagnosed and treated at our centre in the years 1992–2004.*

Results: *All patients presented with a typical history and with similar complaints and symptoms: limitation of exercise toleration, palpitations, dizziness, presyncope and syncope. In all six cases ECG abnormalities were detected, namely T wave inversion, prolonged QRS complexes in V1–V3 or/and epsilon waves. Echocardiographic abnormalities were also detected in all cases in the form of global or segmental dilation and a reduction in right ventricular ejection fraction, morphological irregularity of the endocardium and tricuspidal valve insufficiency. On the basis of diagnostic criteria we diagnosed ARVC/D in four cases and the borderline variant of ARVC/D in the remaining two.*

Conclusions: *ARVC/D is a heart muscle disease with varied and complex presentation. The profile of symptoms and the results of investigations and diagnostic procedures are varied and can assume various combinations. Accurate diagnosis can be established in most cases as a result of the non-invasive and widely-used techniques of ECG, 24-hour Holter monitoring and echocardiography.* (Cardiol J 2007; 14: 396–401)

Key words: cardiomyopathy, right ventricle, diagnosis

Introduction

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a primary myocardial disease [1] characterised by a generalised or focused right ventricular myocytes replacement by fibrous-fatty tissue [2, 3]. Secondary ARVC/D can progress to left ventricular involvement and may culminate in biventricular heart failure. The most common clinical presentation of this irregularity, which most commonly prevails among people under 35 years of age and athletes, is of life-threatening ventricular and supraventricular arrhythmias. Monomorphic tachycardia was detected in all our cases with left bundle branch block (LBBB). In 7–29% of patients the first manifestation of disease is sudden cardiac death [4]. The diagnosis of ARVC/D must be considered when a young, otherwise

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healthy, person complains of dizziness, palpitations, presyncope or syncope, which characteristically occur during exercise, or in a patient who presents with syncope who has a family history of ARVC/D.

A number of cases are not recognised because they are often, especially at the beginning, asymptomatic or difficult to diagnose with conventional methods. With regard to this, a prospective investigation on sudden cardiac death in Italy revealed that over 20% of fatal events in young people and over 25% of fatalities in athletes were caused by ARVC/D [2–4].

A genetic background has been demonstrated in 30–50% cases [5]. The disease is typically inherited as an autosomal dominant trait with variable penetration and incomplete expression. Most of the genes identified code desmosomal family proteins with a remarkably predominant yield of plakophilin-2 mutations [6, 7]. Recently plakoglobin has been identified as the first gene responsible for the autosomal recessive variant of the disease (the so-called "Naxos disease") [8, 9]. In the remaining sporadic cases a variety of etiologies is being considered. Among the theories explaining the transdifferentiation of myocytes in fibrous-fatty tissue are the inflammatory theory, which maintains that the disease results from myocarditis, the degenerative hypothesis, which holds that myocyte death is a consequence of inherited metabolic or ultrastructural defect, and the apoptotic hypothesis, which is supported by the high level of CPP-32, a cysteine protease required for apoptosis [2, 10, 11].

In diagnosing ARVC/D, apart from the presentation of the complaint and the family history referred to above, characteristic abnormalities in ECG, Holter monitoring, echocardiography, late potential analysis, computerised tomography, magnetic resonance imaging (MRI), electrophysiological examination and endomyocardial biopsy [1–4] are all very helpful.

Methods

Objective

We sought to investigate the profile of symptoms as well as the results of investigations and diagnostic procedures among people with suspected ARVC/D.

Diagnostic criteria of arrhythmogenic right ventricular cardiomyopathy/dysplasia

Standardised diagnostic criteria have been proposed by the study group on ARVC/D of the European Society of Cardiology and by the International Society and Federation of Cardiology. According to the task force guidelines, the diagnosis of ARVC/D is based on the presence of major and minor criteria encompassing genetic, ECG, arrhythmic, morphofunctional and histopathological factors (Table 1) [12].

On the basis of this classification a diagnosis of ARVC/D would be certain in the presence of two major criteria, one major plus two minor or four minor criteria from different groups. The presence of one major plus one minor or three minor criteria is the basis for diagnosing the borderline variant of ARVC/D.

Methods

A study was conducted involving six patients (three women and three men) with suspected ARVC/D, diagnosed and treated at our centre (2nd Chair and Department of Cardiology, Medical University of Łódź) in the years 1992–2004. The group ranged from 25 to 60 years (with a mean of 37 years).

The following data were recorded:

— detailed description of the presentation of the complaint: dizziness, palpitations, presyncope, syncope, stenocardia, limitation of exercise toleration, family history;
— ECG: repolarisation and depolarisation abnormalities;
— echocardiography: all patients were investigated with transthoracic echocardiography with classical projection. The morphology and measurements of the right and left ventricles and the flow with colour Doppler were assessed. We looked for right ventricular segmental or regional dilatation, aneurysms or morphological abnormalities;
— exercise test and 24-hour Holter monitoring with late potentials analysis;
— MRI (only carried out in one case);
— invasive diagnostic methods: coronary angiography, endomyocardial biopsy and electrophysiological research, depending on clinical indications.

Results

All patients presented with a typical history of limitation of exercise toleration, palpitations, dizziness, presyncope and syncope. In one patient the history revealed sudden cardiac arrest in the mechanism of ventricular fibrillation (documented), while in another patient there was evidence of ARVC/D in the family history (sudden cardiac death in his brother due to ARVC/D, diagnosed post mortem at autopsy).

ECG abnormalities were detected in all cases:

— T wave inversion in the precordial leads exploring the right ventricle V1–V3 in four patients (Fig. 1);
— epsilon wave in one patient;

Table 1. Criteria for diagnosis of arrhythmogenic right ventricular cardiomyopathy/dysplasia.

	Major criteria	Minor criteria
I. Global or regional dysfunction and structural alterations	Severe dilation and reduction of RV ejection fraction; localised RV aneurysms (akinetic or dyskinetic areas with diastolic bulging)	Mild global RV dilation or ejection reduction with normal LV; regional RV hypokinesis
II. Tissue characterisation of walls	Fibrous-fatty replacement of myocardium on endomyocardial biopsy	
III. Repolarisation abnormalities		Inverted T waves in right precordial leads V2–V3 (people aged over 12 years; in absence of RBBB
IV. Depolarisation abnormalities	Epsilon waves or localised prolongation (> 110 ms) of the QRS complex in right precordial leads V1–V3)	Late potentials
V. Arrhythmia		Left bundle branch block type ventricular tachycardia (ECG, Holter, exercise testing); frequent ventricular extrasystoles more than 1000/24 h in Holter
VI. Family history	Familial disease confirmed at necropsy or surgery	Familial history of premature sudden death (< 35 year) or clinical diagnosis based on present criteria

RV — right ventricle, LV — left ventricle, RBBB — right bundle branch block

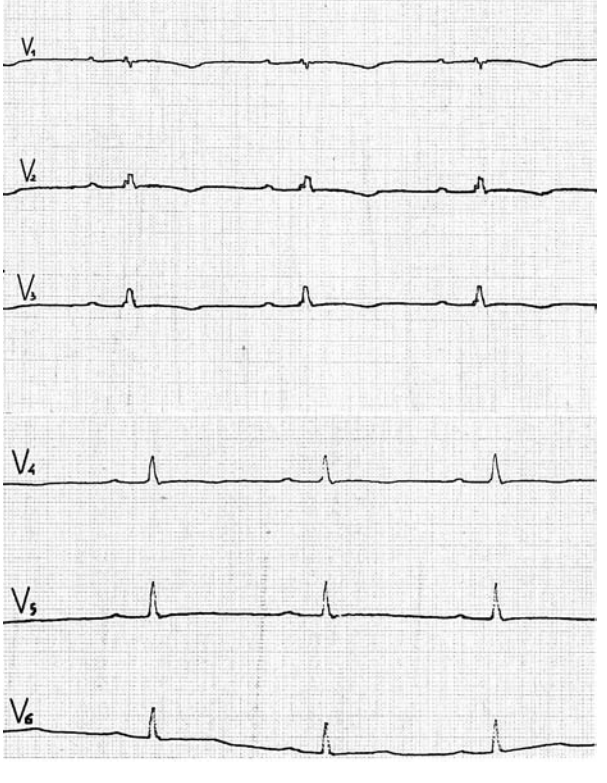

Figure 1. ECG — precordial leads. Repolarisation abnormalities — inverted T waves in right precordial leads V2–V3.

— prolonged QRS complex to more than 110 ms in the V1–V3 leads in one patient.

In one of the recorded ECGs we documented ventricular arrhythmia (bigeminy) but not the LBBB type, while in another ECG atrial fibrillation was apparent.

In 24-hour Holter monitoring we observed repeated supraventricular tachycardia in four of our patients and ventricular arrhythmias, ranging from isolated premature ventricular beats (Lown II, III or IVa) to non-sustained and sustained ventricular tachycardia with an LBBB morphology, in four patients (Lown IVB). Late potentials were detected in two patients.

Echocardiographical abnormalities were detected in all our cases in the form of global or segmental dilatation and a reduction in right ventricular ejection fraction, morphological irregularity of the endocardium (moderator band hyper-reflectivity or trabecular derangement) or tricuspidal valve insufficiency (I–II°) (Fig. 2–4).

Results were obtained for only one ventriculography, showing dilatation of the right ventricle with enhanced trabeculosis, two endomyocardial biopsies, showing fibrous-fatty replacement with degeneration of the myocytes, and one MRI result, which showed a dilated right ventricle with a lighter signal (indicative of fat) from the free wall (Table 2).

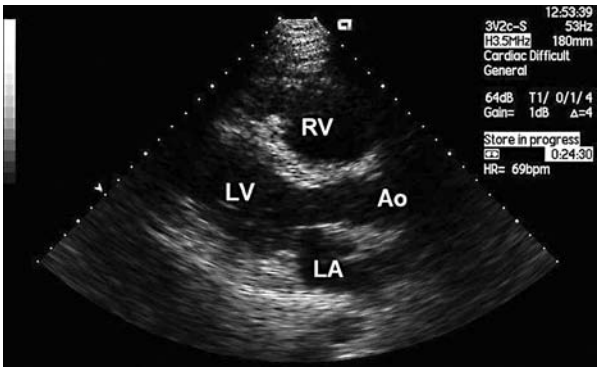

Figure 2. Transthoracic two-dimensional echocardiogram recorded in a patient with arrhythmogenic right ventricular cardiomyopathy/dysplasia. Parasternal long-axis view showing dilation of the right ventricle; RV — right ventricle, LV — left ventricle, LA — left atrium, Ao — aorta.

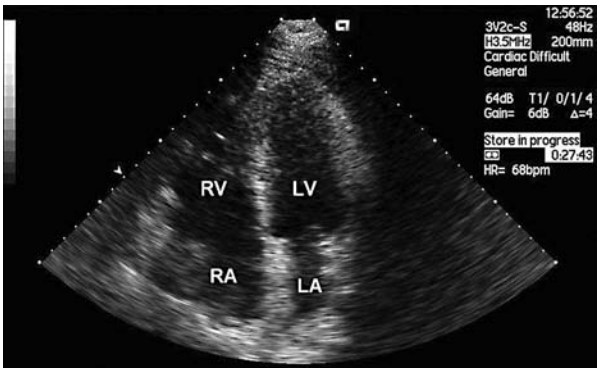

Figure 3. Transthoracic two-dimensional echocardiogram recorded in a patient with arrhythmogenic right ventricular cardiomyopathy/dysplasia. An apical four-chamber view showing dilation of the right ventricle and right atrium; RV — right ventricle, LV — left ventricle, LA — left atrium, RA — right atrium.

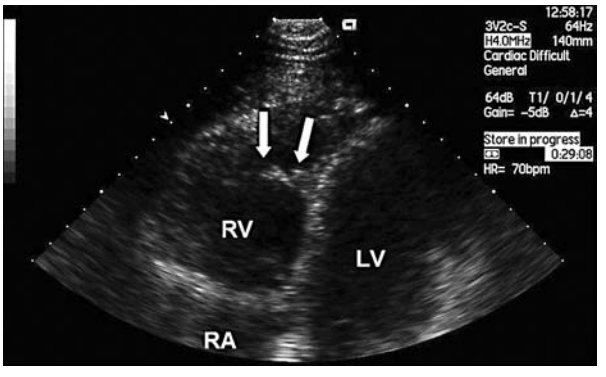

Figure 4. Transthoracic two-dimensional echocardiogram recorded in a patient with arrhythmogenic right ventricular cardiomyopathy/dysplasia. An apical modified four-chamber view, showing dilation of the right ventricle and marked thickening of the moderator band (arrows); RV — right ventricle, LV — left ventricle, LA — left atrium, RA — right atrium.

Discussion

The study is a presentation of six clinical cases with ARVC/D diagnosed on the basis of the criteria proposed by the study group on ARVC/D of the European Society of Cardiology and by the International Society and Federation of Cardiology [11]. The disease may be suspected on the basis of a typical history and physical examination. In most cases we receive confirmation of the underlying pathology without MRI or invasive testing such as endomyocardial biopsy, which involves a high risk of complications.

The ECG abnormalities typical for ARVC/D, mostly fulfilling minor diagnostic criteria, were detected in all our cases in ECG and 24-hour Holter monitoring. Despite its low sensitivity and specificity ECG abnormalities are present in up to 90% of

Table 2. Summary of recorded data of the six analysed cases.

Patient	ECG (depolarisation abnormalities)	ECG (repolarisation abnormalities)	ECHO	Endo-myocardial biopsy	NMR	Lown score (IVB)	Familial history
1	–	+	++	ND	ND	–	–
2	+	–	++	ND	ND	–	–
3	–	+	+	++	ND	+	–
4	++	–	+	ND	++	+	–
5	++	+	+	ND	ND	+	++
6	+	+	++	++	ND	+	–

+: abnormalities fulfilled minor diagnostic criteria; ++: abnormalities fulfilled major diagnostic criteria; ND — not done

ARVC/D patients [13, 14]. The most common abnormality consists of T wave inversion, often associated with a slight ST-segment elevation < 0.1 mV, in the precordial leads V1–V3 exploring the right ventricle. These repolarisation changes, detected in four of our patients, may be a normal variant in children aged below 12 years or may be secondary to a right bundle branch block. Relatively the most sensitive and ARVC/D-specific ECG diagnostic markers are epsilon waves (post-excitation potentials of small amplitude that occur at the end of QRS complex found in up to 30% of cases of ARVC/D) and localised prolongation of the QRS complex in V1–V3 to more than 110 ms (found in up to 60% of cases of ARVC/D) [2, 3, 13]. These abnormalities were observed in two of the cases analysed.

Another very helpful and useful method of diagnosing ARVC/D is echocardiography. This technique, which is non-invasive, widely available, low in cost and easy to perform and interpret, has played a crucial role in imaging structural and functional abnormalities of the right ventricle. Generally, these irregularities in ARVC/D are moderate and easily overlooked, which is why right ventricle function should be measured at several points, including the inflow and outflow tract, because of the focal nature of the disease [15]. The development of new echocardiographic techniques such as three-dimensional, harmonic imaging and tissue echo Doppler will minimise the number of false negative results [14]. The echocardiographic findings most suggestive of ARVC/D include dilatation of the right ventricle with localised aneurysms and dyskinesis in the inferior basal region [14, 15]. Right ventricle end diastolic and end systolic diameter is another very useful echocardiographic parameter in establishing the diagnosis of ARVC/D, as well as the ratio of the right to left ventricle end diastolic diameters (a ratio > 0.5 for the right ventricle/left ventricle end diastolic diameter has a sensitivity of 86% and a specificity of 93% for the diagnosis of ARVC/D) [16]. There are numerous reports of the use of echocardiography to aid diagnosis of ARVC/D. These studies have found that the presence of right ventricular dysfunction by two-dimensional echocardiography had a high specificity and predictive value for ARVC/D [15, 17, 18]. Echocardiographical abnormalities, fulfilling major or minor diagnostic criteria, were detected in all our cases.

Magnetic resonance imaging has recently been added to the techniques used to diagnose ARVC/D. It is a potentially useful test because it can distinguish fat from muscle. Cine MRI also provides a good contrast between the blood and the myocardial wall and can, therefore, provide information about right ventricular motion and function. On the other hand MRI does not improve on echocardiography in revealing morphological and functional changes in the right ventricle, whereas adipose tissue detection is usually uncertain and cannot claim to be one of the diagnostic criteria [19, 20]. A definitive diagnosis of ARVC/D relies on the histological demonstration of substitution of the right ventricular myocardium by fatty or fibrous-fatty tissue at endomyocardial biopsy (or autopsy in post-mortem examination), although its sensitivity and specificity is low owing to the segmental nature of the ARVC/D lesions and difficulty in differentiating ARVC/D from other causes of fatty infiltration of the right ventricular myocardium [21]. Because an accurate diagnosis had been made earlier which met standardised diagnostic criteria, and in view of lack of availability and the high cost, we performed only one MRI examination. In one patient we established the diagnosis of ARVC/D on the basis of an invasive diagnostic method, namely endomycardial biopsy (the result of another biopsy was only a confirmation of the accuracy of the diagnosis made earlier).

In summary, on the basis of diagnostic criteria, we diagnosed ARVC/D in four cases and the borderline variant of ARVC/D in the remaining two.

Conclusions

Arrhythmogenic right ventricular cardiomyopathy/dysplasia is a heart muscle disease with a highly unspecified presentation. The profile of symptoms and investigation results are varied and can assume different combinations. In most of the cases presented we made an accurate diagnosis of ARVC/D on the basis of echocardiographic and ECG abnormalities, fulfilling the major or/and minor European Society of Cardiology and the International Society and Federation of Cardiology diagnostic criteria.

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