International Journal of Cardiology 257 (2018) 371–377

Contents lists available at ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Common presentation of rare diseases: Arrhythmogenic right ventricular cardiomyopathy and its mimics

Adalena Tsatsopoulou [a,*], Eduardo Bossone [b]

[a] Nikos Protonotarios Medical Centre, Naxos 84300, Greece
[b] Heart Department, University Hospital, Salerno, Italy

ARTICLE INFO

Article history:
Received 22 October 2017
Received in revised form 4 January 2018
Accepted 11 January 2018

Keywords:
Arrhythmogenic right ventricular cardiomyopathy
Arrhythmogenic cardiomyopathies
Naxos syndrome
Desmosomal proteins
Juvenile sudden death
Right ventricular dysfunction

ABSTRACT

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is the most common phenotype described within the spectrum of arrhythmogenic cardiomyopathies. It usually presents in early adolescence with severe ventricular arrhythmias along with cardiac structural and functional alterations mainly of the right ventricular myocardium. Though the estimated prevalence of ARVC in the general population is only 1:5000, it represents one of the most common causes of juvenile sudden death. However, detection of early RV dysfunction in ARVC may be challenging requiring high clinical suspicion and an algorithmic approach. A thorough family history of juvenile sudden death, ventricular arrhythmias and ICD implants should always be sought. Diagnosis usually requires electrocardiographic interpretation as well as cardiac imaging. In this article, the key diagnostic steps in the assessment of ARVC and diagnostic red flags that aid its differential diagnosis are discussed.

1. Introduction

Right ventricular dysfunction occurs as the result of many genetic and acquired disorders. Their diagnosis can be challenging and requires a systematic approach to clinical assessment and investigation. In this article, we use a genetic disorder–arrhythmogenic right ventricular cardiomyopathy (ARVC)–to illustrate an approach that can be used in everyday practice to make the diagnosis of rare right ventricular disorders.

2. Arrhythmogenic cardiomyopathies

The term arrhythmogenic cardiomyopathy is used increasingly to describe a spectrum of primary heart muscle disorders characterized by ventricular arrhythmias accompanied by structural and/or functional alterations of ventricular myocardium. The RV myocardium is affected in most of these conditions, but left ventricular involvement is described in up to 66% in some series [1]. ARVC is considered to be the most frequent arrhythmogenic cardiomyopathy. It is a rare condition in the general population with an estimated prevalence of 1:5000, but is one of the more common causes of juvenile sudden cardiac death [2]. When first described it was termed Arrhythmogenic Right Ventricular Dysplasia as it was considered as a congenital dysgenesis of myocardium of the right ventricle [3]. However, it has been proved to be an inherited cardiomyopathy caused predominantly by mutations in genes encoding desmosomal proteins (i.e. plakophillin2, plakoglobin, desmoplakin, desmoglein2, and desmocollin2) [4]. The defining pathological process in ARVC consists of myocyte atrophy and degeneration with subsequent fibrous and fatty replacement of predominantly RV myocardium [5]. ARVC usually presents during the second decade of life mostly with signs or symptoms related to ventricular arrhythmias that typically originate from the right ventricle. The disease is often progressive and associated with hot phases characterized by increased RV arrhythmias and new ECG changes [6, 7]. End disease stage is characterized by development of RV dilatation and failure [4].

Naxos syndrome is a very rare form of ARVC associated with early appearance of palmo-plantar keratoderma and wooly hair caused by a recessive mutation in the desmosomal protein plakoglobin [8]. While almost unique to Cyclades, the disease provides a unique insight into the clinical course of other autosomal dominant forms of disease [9].

3. Diagnosis of ARVC

The diagnosis of ARVC is challenging as it requires a high index of suspicion and targeted evaluation not only for features diagnostic for ARVC but also for exclusion of other disorders presenting with similar symptoms and signs. In general, patients can present with sustained palpitations, syncope or chest pain or be diagnosed through family

* Corresponding author.
E-mail address: adalena@otenet.gr (A. Tsatsopoulou).

https://doi.org/10.1016/j.ijcard.2018.01.021
0167-5273/

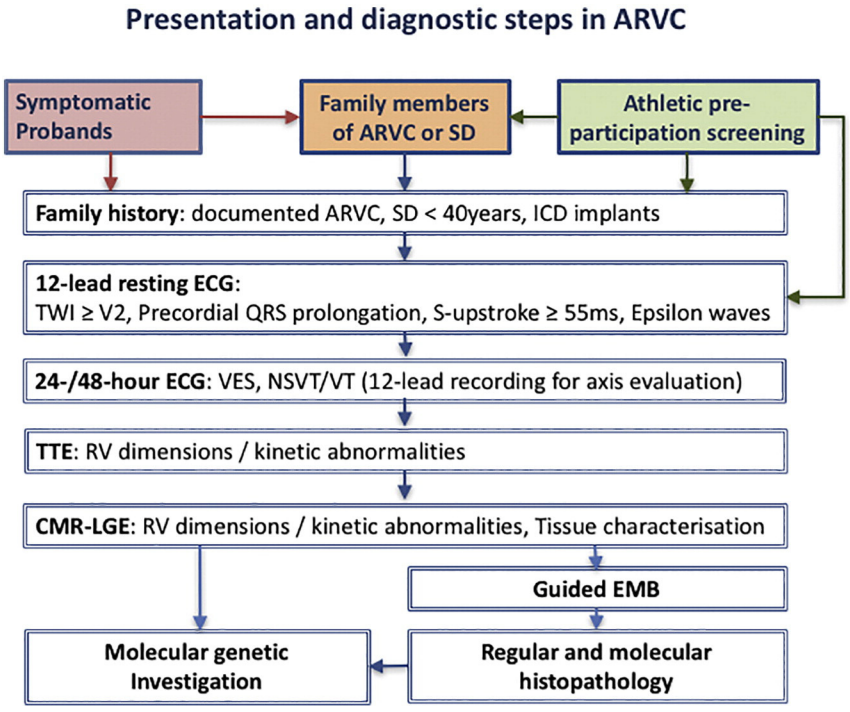

Fig. 1. ARVC: mode of presentation in colored rectangles; arrows indicate an algorithmic diagnostic approach. Abbreviations: ARVC, arrhythmogenic right ventricular cardiomyopathy; EMB, endo-myocardial biopsy; ICD, implantable cardioverter defibrillator; NSVT, non-sustained ventricular tachycardia; RV, right ventricular; SD, sudden death; TTE, transthoracic echocardiography; VES, ventricular extrasystoles; VT, ventricular tachycardia.

screening or following a routine ECG evaluation. An algorithmic approach is essential in reaching the diagnosis (Fig. 1).

The diagnosis of ARVC is based on consensus recommendations, originally proposed in 1994 and later revised in 2010 [10, 11]. They are relatively complex and rely on integration of family history, ECG interpretation, non-invasive imaging assessment of RV morphology and function, endomyocardial biopsy and molecular genetic analysis. RV morphology and function is assessed on two-dimensional color Doppler echocardiography (TTE) and/or cardiac magnetic resonance (CMR). Quantitative parameters based on comparison with normal data are included in the criteria [11].

4. Family history

A diagnosis of ARVC is supported by a family history of ventricular arrhythmias, juvenile cardiac arrest, unknown cause sudden death and/or potentially episodes of acute myocarditis. In addition, cutaneous abnormalities consistent with Naxos syndrome on the patient or close family members should not be missed.

5. Electrocardiography

5.1. Ventricular arrhythmias

ARVC typically presents with an episode of ventricular arrhythmias commonly arising from the right ventricle, as a result of re-entry at a site of myocardial damage. Ventricular arrhythmias ranging from ventricular extrasystoles (VES) to sustained ventricular tachycardia or ventricular fibrillation (VF) are considered a defining feature of the disease phenotype. An association between the total number of VES per 24 h and the arrhythmic potential for unstable ventricular arrhythmias has been demonstrated [12].

VES may be present prior to the characteristic histo-pathological changes in the myocardium [13]; this phenomenon has been attributed to early loss of junctional Connexin 43 that may affect electrical conduction contributing to a micro-re-entry mechanism [13]

VF is the predominant mechanism underlying sudden cardiac death in this disease and is related to active disease progression [14]. Ventricular arrhythmias and VF are usually less common in patients with long standing ARVC and extensive scarring in their myocardium [2, 15]. Therefore, symptomatic presentation of ventricular arrhythmias or a history of arrhythmic cardiac arrest in an otherwise normal myocardium should raise suspicion for early signs of development of the ARVC phenotype.

5.2. Repolarization abnormalities

T-wave inversion (TWI) in the anterior precordial leads has been considered an early and sensitive marker of disease expression as well as a prognostic marker [6]. TWI from V1 to V3 is observed in only 4% of healthy women and 1% of men while it is present in >70% of AVC patients and constitutes a major diagnostic criterion in otherwise healthy individuals older than 14 years of age [11]. In the presence of right bundle-branch block, T-wave inversion in V1, V2, V3, and V4 is uncommon in patients who do not have ARVC.

Precordial T-wave inversion should be sought in family screening as it might be the earliest indication of disease development in asymptomatic family members. In athletic pre-participation screening, identification of precordial or infero-lateral TWI warrants further investigation [16].

5.3. Depolarization abnormalities

Delayed depolarization of affected ventricular myocardium is a feature of ARVC and is commonly detected in the right precordial leads. Depolarization changes are expressed as prolonged (≥55 ms) terminal activation duration (TAD) of the QRS complex and epsilon waves. Epsilon waves have been defined as reproducible low-amplitude signals