

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy – an Overview

Introduction

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C), which occurs at an estimated prevalence of as high as 1:1000 individuals (1), is characterized clinically by ventricular arrhythmia, most commonly arising from the right ventricle (RV), and histologically by replacement of normal myocardial tissue in the RV by fibrotic adipose tissue. Ventricular arrhythmias associated with ARVD/C account for about 20% of sudden cardiac death (SCD) in young individuals and athletes (2, 3). SCD can be prevented through use of an implantable cardioverter defibrillator (ICD), and occurrence of SCD events may be reduced by avoidance of mechanical stress due to physical exertion. However, at-risk individuals who may benefit from an ICD and lifestyle adjustments may be difficult to identify, since SCD can be the presenting symptom. Genetic testing can facilitate detection of at-risk individuals in familial forms of ARVD/C, which account for nearly 50% of all cases (4). Family members carrying familial mutations detected in the index patient for the family are at highly increased risk of ARVD/C, while family members not carrying familial mutations are at lesser risk. In the index patient, genetic testing can help to establish whether a specific case of ARVD/C is familial or not, by screening for presence of a germline mutation in the genes known to be associated with ARVD/C. A familial versus a sporadic nature of ARVD/C may otherwise not always be clear, since ARVD/C shows variable expressivity and penetrance, ranging from 20-100% (5-9).

Familial ARVD/C typically shows autosomal dominant inheritance and has been associated with mutations in any one of at least eight genes (see Table 1). Rare autosomal recessive forms of familial ARVD/C usually occur in the context of non-cardiac manifestations, such as palmoplantar keratoderma and woolly hair in Carvajal syndrome (10) and Naxos disease (11).

Table 1: Genetic Causes of Familial ARVD/C (8-21)

Gene (Protein)	% ARVD/C (inheritance)
<i>PKP2</i> (plakophilin 2)	10-43% (AD)
<i>DSG2</i> (desmoglein 2)	10% (AD)
<i>DSP</i> (desmoplakin)	6-16% (AD); <1% (AR)*
<i>DSC2</i> (desmocollin 2)	1-5% (AD)
<i>JUP</i> (plakoglobin)	<1% (AR)*
<i>RYR2</i> (cardiac ryanodine receptor 2)	<1% (AD)
<i>TGF-B3</i> (transforming growth factor beta 3)	3% (AD)
<i>TMEM43</i> (transmembrane protein 43)	<1% (AD)*

AD (autosomal dominant); AR (autosomal recessive)
*presumed rare; reported as founder mutations in single population

Molecular Pathophysiology

Among the ARVD/C-associated genes, *PKP2*, *DSG2*, *DSP*, *DSC2*, and *JUP* code for desmosomal proteins. Desmosomes are specialized multi-protein complexes that make up intercellular junctions mainly in tissues subject to mechanical stress, including the epidermis and myocardium. By providing cell-cell adhesion, desmosomes serve as the “cement” that holds cells together. In addition, they participate in cell signaling networks which are known to affect cell fate, proliferation, and apoptosis. Disruption of either function has been proposed to underlie the disease mechanism of ARVD/C. In a simple model, loss of cell adhesion results in apoptosis of myocytes and localized fibrosis (22). A more complex model (23) proposes that defects in gap-junction signaling give rise to abnormal electrical conductivity that leads to arrhyth-

mias. *RYR2*, *TGF-B3*, and *TMEM43* code for non-desmosomal proteins. The exact function of *TMEM43* is not known; however, *TMEM43* contains a response element for PPAR-gamma, an adipogenic transcription factor, suggesting a link between defects in *TMEM43* and the replacement of normal myocardium with fibrotic adipose tissue observed in ARVD/C patients.

Clinical Presentation

ARVD/C typically presents with palpitations and/or syncope, although cardiac arrest may also be the presenting manifestation (reviewed in (24)). A higher occurrence of cardiac arrest has been associated with *DSP*-related ARVD/C (17). Characteristic of ARVD/C, an EKG usually shows RV arrhythmias triggered by physical effort. There may also be left ventricular (LV) arrhythmias, making the disease look more like dilated cardiomyopathy (24). *DSG2*- and *DSC2*-related ARVD/C may present with predominant LV involvement (7, 8, 15). Age-of-onset of ARVD/C is usually in the thirties, but *PKP2*-related ARVD/C often shows a significantly lower (by ~8 years) age-of-onset than other forms of ARVD/C (13). In addition, *PKP2* mutations that lead to early-disease onset are usually also associated with higher penetrance, ie, they cause disease in most mutation carriers. However, penetrance of *PKP2*-related ARVD/C can remain incomplete even above 70 years of age (25). In *TMEM43*-related ARVD/C, age-of-onset varies by sex, with males presenting in their thirties and females presenting in their forties. Compared to other forms of ARVD/C, penetrance of *TMEM43*-related ARVD/C is typically complete by age 63 in males and age 76 in females (9). *TMEM43*-related ARVD/C is also more severe than other forms of ARVD/C. The median life expectancy of patients with *TMEM43*-related ARVD/C was reported to be significantly reduced due to a high incidence of SCD in several Norwegian families with *TMEM43*-related ARVD/C, which was about twice as likely in males as in females (9, 21).

Diagnosis

Diagnosis of ARVD/C is based on so-called Task Force Criteria (TFC – see Table 2; (4,

26). A positive diagnosis is indicated by presence of two major criteria, one major plus two minor criteria, or four minor criteria. Major criteria include family history of ARVD/C, electrocardiogram depolarization/conduction abnormalities, structural alterations, and presence of fibro-fatty tissue in the heart. Minor criteria generally constitute milder versions of the major criteria. A clinical diagnosis of familial ARVD/C can be confirmed through genetic testing, since published studies have shown a causal relationship to certain variants in *PKP2*, *DSG2*, *DSP*, *DSC2*, and *TMEM43* (reviewed in (22)). Once the familial mutation is known, genetic testing can also distinguish asymptomatic mutation carriers from non-carriers in an affected family. This distinction is important since mutation carriers, even if asymptomatic, are at high risk of ARVD/C and should be closely monitored for development of ARVD/C, while non-carriers are not at increased risk of ARVD/C. Depending on the family history and the type of mutation present, asymptomatic mutation carriers may even be candidates for ICD implantation. In contrast, non-carriers of familial mutations are at lesser risk of ARVD/C, although an increased risk cannot completely be excluded, given that recessive forms of ARVD/C have been reported.

Treatment

ARVD/C is typically treated with antiarrhythmic drugs, such as sodium blockers, beta-blockers, sotalol, amiodarone, or verapamil alone or in combinations. Risk of SCD may also be reduced by certain lifestyle adjustments, such as avoiding physical exertion. ICD implantation is commonly considered for patients who have been diagnosed with ARVD/C and have had an aborted SCD or are at high risk of SCD, based on presence of severe RV dysfunction, LV involvement, hemodynamically unstable VT/VF, pleomorphic VT, epsilon potential, late potential, and family history of SCD and/or ARVD/C (27). In a study tracking the efficacy of ICD in prevention of cardiac arrest, ICD intervention averted SCD in 72% patients with severe ARVD/C over a 36-month period (28). However, since ICD implantation is invasive, requires frequent clinical follow-up, and may cause side effects such as inappropriate defibrillation/shock, the

risk-benefit ratio has to be carefully considered. In severe cases of ARVD/C, heart transplantation may be necessary.

Table 2: ARVD/C Diagnostic Criteria (TFC)

Group	Major Criteria	Minor Criteria
Structural/Functional RV abnormality	Severe RV dilation with little or no LV involvement; localized RV aneurysm	Mild RV dilation with normal LV; regional RV hypokinesia
Tissue characterization	Replacement of myocardium by fibro-fatty infiltrate	No criteria reported
EKG depolarization/conduction abnormality	Epsilon waves or localized prolongation (>110ms) of QRS complex in right precordial leads	Late potentials on signal-averaged EKG
EKG repolarization abnormality	No criteria reported	Inverted T waves on EKG; aged >12 years; absence of right bundle branch block
Arrhythmias	No criteria reported	Left bundle branch block type ventricular tachycardia on EKG; frequent ventricular extrasystoles (>1000/24h) on Holter monitoring
Family History of ARVD/C	Family history confirmed by autopsy or surgery	Family history of SCD (>35 years of age) due to suspected ARVD/C; family history of ARVD/C clinically diagnosed based on TFC

Adapted from (22, 24)

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