CLINICAL VIGNETTE

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy: Diagnostic and Management Overview

Amir B. Rabbani, M.D.; James S. Lee, M.D.; and Ravi Dave, M.D.

Case

A 19-year-old was referred to cardiology with a chief complaint of recurrent syncope. The episodes were preceded by lightheadedness and dizziness, followed by brief loss of consciousness with return to her baseline within thirty seconds. She described occasional rapid heart rate and palpitations, and she denied a family history of early cardiac disease. Physical examination and laboratory workup were unremarkable. The patient was instructed to follow conservative measures for management of vasodepressor symptoms.

The patient returned to cardiology several weeks later with another syncopal episode. An ECG showed T-wave inversion in V1, and a notched, isoelectric T-wave in lead V2 (Figure 1). A 30-day event monitor showed infrequent premature atrial contractions. Transthoracic echocardiogram found basal right ventricular diameter at end diastole of 4.33 cm (normal < 4.1 cm) and the mid-cavitary right ventricular dimension of 3.8 cm (normal < 3.7 cm) (Figure 2a). The proximal right ventricular outflow tract dimension was borderline normal at 3.3 cm (normal < 3.3 cm) (Figure 2b). Cardiac magnetic resonance (CMR) imaging showed thinning of the myocardium in the free lateral wall of the right ventricle, chamber dilatation, and hypokinetic motion with reduced right ventricular ejection fraction on cine imaging (Figure 3).

Given the high suspicion for arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) based on echo and MRI imaging, genetic testing was performed revealing her to be heterozygous for an autosomal dominant ryanodine receptor 2 (RYR2) mutation. The patient was diagnosed with ARVD/C with two major and three minor criteria based on the 2010 revised task force criteria (Table 1). Subsequently, a single chamber implantable cardioverter defibrillator was placed. The patient was started on a beta blocker with resolution of her syncopal episodes.

Background

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is a rare, inherited cardiomyopathy that can lead to right ventricular failure, ventricular arrhythmias, and sudden cardiac death (SCD) in young patients and athletes.[1] The disease is characterized by progressive replacement of the right ventricular myocardium with fibrofatty tissue.[2] The right ventricle is most frequently involved; however, left dominant forms also have been identified, potentially leading to biventricular heart failure.[3] Mortality varies with larger community-based patient cohorts reporting rates of <1% per year with higher mortality reported in higher-risk cohorts.[4] The mechanism of SCD is cardiac arrest due to sustained ventricular tachycardia or ventricular fibrillation, which may be the first manifestation of ARVD/C in young people.[5] Independent predictors of poor outcome include malignant arrhythmic events (SCD, cardiac arrest due to ventricular fibrillation, appropriate ICD interventions, or ICD therapy), and unexplained syncope has been associated with increased arrhythmic risk in some studies.[6] ARVD/C is a familial condition in over 50% of cases and typically is transmitted as an autosomal dominant trait with variable penetrance. Histological examination reveals islands of surviving myocytes interspersed with fibrous and fatty tissue.[7] The seven most common genetic mutations associated with ARVD/C are listed in Table 2.[8]

Diagnosis

While there is no gold standard, diagnosis of ARVD/C is based on a scoring system with major and minor criteria based on echocardiographic, MRI, and ECG abnormalities, as well as tissue pathology, characteristic ventricular arrhythmia, and family history.[9] Patients are given the diagnosis of ARVD/C if they have four points (major criteria = 2 points, minor = 1 point). Patients with three points have probable ARVD/C. Endomyocardial biopsy is rare in the current era due to existence of high resolution cardiac MRI imaging.[10]

While 40-50% of patients have a normal ECG at presentation, at six years' follow-up nearly all patients have one or more ECG findings during normal sinus rhythm.[11] QRS prolongation in leads V1 to V3 is consistent with delayed right ventricular activation, and prolonged S wave upstroke from the nadir of the S wave to the baseline >55msec are highly specific for ARVD/C (in the absence of right bundle branch block). Epsilon waves (reproducible wave between end of the QRS complex and the onset of the T wave) in the right precordial leads have been identified in 30% of ARVD/C confirmed patients. T wave inversions are also apparent in over half patients in leads V1 to V3 based on degree of RV enlargement.

The majority of patients are diagnosed based on a combination of noninvasive ECG and imaging testing.[12] Echocardiographic changes include RV chamber enlargement and decreased

function as characterized by fractional area change. The sensitivity and specificity of the right ventricular outflow tract (RVOT) measured >32mm in diastole are 75% and 95%, respectively. Cardiac MRI has also been utilized for morphologic and functional assessment of the RV. Right ventricular end diastolic volume normalized for body surface area >110 ml/m^2 in males or >100 ml/m^2 in females has a sensitivity and specificity of 68-76% and 90-98% respectively.[13] Electrophysiological study (EPS) is mainly used to differentiate ARVD/C from idiopathic right ventricular outflow tract tachycardia, as well as provide information regarding VT inducibility in patients undergoing ICD implantation.[14]

Treatment

Although no large, randomized controlled trials currently exist, general consensus is that patients with ARVD/C who are high or intermediate risk for life-threatening ventricular arrhythmias should receive an ICD (Table 3). Risk factors that place patients at particularly high risk for life-threatening ventricular arrhythmias include syncope, non-sustained ventricular tachycardia, and moderate to severe RV dysfunction, LV dysfunction or both. Patients without major risk factors but who are deemed to be in the 1-10% risk range based on morphologic, ECG, and proband characteristics should be considered for ICD implantation on a case-by-case basis.

Beta blockers play an important role in management of patients with ARVD/C in all patients. Beta blockade in some studies decreased the risk of exercise-induced adrenergic stimulation of ventricular arrhythmias and may play a role in the management of heart failure and myocardial dysfunction.[15] Anti-arrhythmic medications such as sotalol and amiodarone are most often used in patients who are receiving ICD therapies due to ventricular arrhythmias refractory to beta blockade. If medical therapy fails, catheter therapy for ventricular arrhythmias can be offered with VT-free survival of 70% at five years.[16] Importantly, all patient should be advised to avoid exercise as most SCD occurs in ARVD/C patients during physical exertion.[17] Exercise avoidance both reduces the incidence of ventricular arrhythmias as well as halting disease progression.

Summary

ARVD/C is an inherited cardiomyopathy characterized by distinctive morphologic, ECG, and genetic abnormalities that can lead to life-threatening arrhythmias and sudden cardiac death. The diagnosis can be challenging and involves a multi-modality approach. Establishing an accurate diagnosis based on the 2010 modified task force criteria is critical given the need for ICD implantation in these patients. Treatment strategies are aimed at reducing symptoms and avoiding SCD from lethal arrhythmias. A cure for ARVD/C currently does not exist but will be based on further investigation into the molecular and genetic pathogenesis of the disease.

Figures and Tables

Figure 1: ECG showing T wave inversions and flattening (red arrows) in V1 and V2, and notched QRS complex in V2 (black arrow).

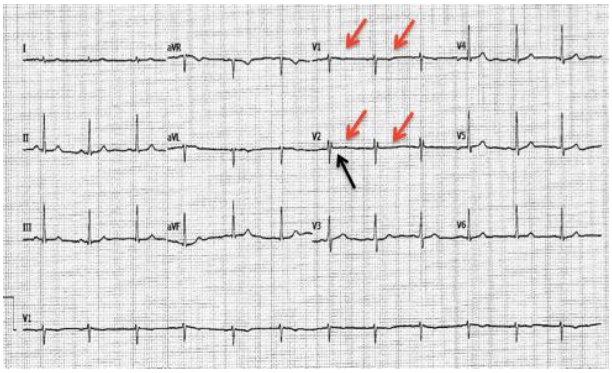

Figure 2: Apical 4 chamber view showing enlargement of the right ventricle. The basal right ventricular diameter (RVD1) and mid cavitary right ventricular diameters (RVD2) are enlarged. The basal to apical diameter (RVD3) is within normal limits (A). The proximal right ventricular outflow tract diameter is borderline normal (B).

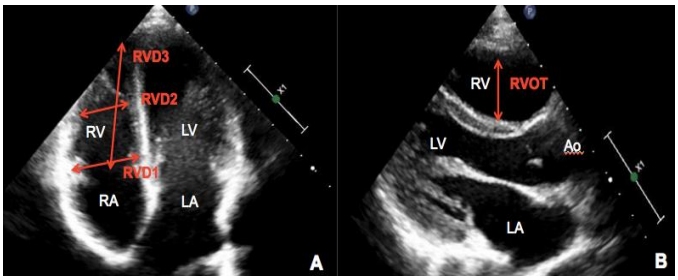

Figure 3: Apical four chamber (A) and short axis (B) cardiac MRI views showing dilatation of the right ventricle, decreased right ventricular function, and thinning of the right ventricular free wall (red arrows).

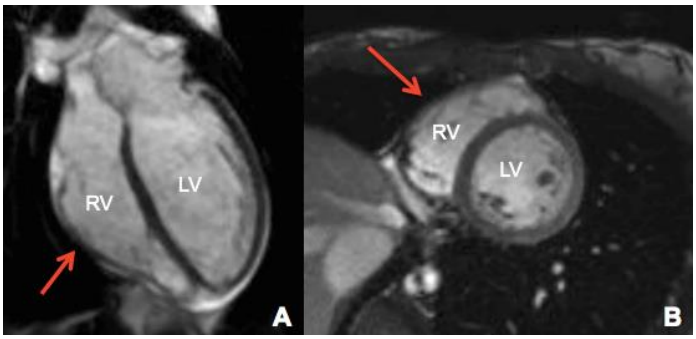

Table 1: 2010 Task Force Criterial for ARVD/C. Definite diagnosis: 2 major or 1 major and 2 minor criteria or 4 minor from different categories. Borderline: 1 major and 1 minor or 3 minor criteria from different categories. Possible: 1 major or 2 minor criteria from different categories.

	Major Criteria	Minor Criteria
Global or Regional Dysfunction and Structural alterations	**Echo Criteria** Regional RV wall motion abnormalities AND: PLAX RVOT ≥ 32 mm or PSAX RVOT ≥ 36 mm, or Fractural area change ≤ 33% **MRI Criteria** Regional RV wall motion abnormality or RV EF ≤ 45%	**Echo Criteria** Regional RV wall motion abnormalities AND PLAX RVOT ≥ 29 mm < 32 mm PSAX RVOT ≥ 32 mm < 36mm Fractional area change > 33% ≤ 40% **MRI Criteria** Regional RV wall motion abnormality or RV EF ≤ 40%
Tissue characterization of wall	Residual myocytes < 60% by morphometric analysis. Fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy	Residual myocytes < 60-75% by morphometric analysis. Fibrous replacement of the RV free wall myocardium in ≥ 1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Repolarization abnormalities	Inverted T waves (V1, V2 and V3)	Inverted T waves in V1 and V2 or in V4, V5 and V6. Inverted T waves in leads V1, V2, V3, and V4 in presence of RBBB
Depolarization/conduction abnormalities	Epsilon wave (V1-V3)	Late potentials by SAECGB ≥1 or three parameters filtered QRS duration ≥ 114 ms, terminal QRS < 40 μV ≥ 38 ms, root-to-mean-square voltage of terminal 40 ms ≤ 20 μV Terminal activation duration of QRS ≥ 55 ms measured from nadir S wave to end of QRS, including R' in V1, V2, V3
Arrhythmias	VT of LBBB morphology with superior axis	VT of RVOT configuration, LBBB morphology w/ inferior axis > 500 PVCs per 24 h.
Family history	ARVD/C in 1st degree relative, mutation associated with ARVD/C	ARVD/C in 1st degree relative, SCD (<35 yo) due to suspected ARVD/C in 1st degree relative, ARVD/C in 2nd degree relative

*SAECG = signal averaged ECG, PLAX = parasternal long axis, PSAV = parasternal short axis, RVOT = right ventricular outflow tract, BSA = body surface area, LBBB = left bundle branch block, VT = ventricular tachycardia

Table 2: Genetic mutations associated with ARVD/C including gene locus and prevalence.

Gene	Locus	Prevalence (%)
Plakophili-2 (PKP2)	12q11	11-43
Desmoglein-1 (DSG2)	18q12	12-40
Desmoplakin (DSP)	6p24	6-16
Desmocollin-2 (DSC2)	18q12	1-5%
Plakoglobin (JUP)	17q21	Rare
Cardiac ryanodine receptor (RYR2)	1q42	Rare
Transmembrane protein 43 (TMEM43)	2p25	Unknown

Table 3: Indication for ICD implantation. Estimated yearly risk of arrhythmic event 10% in high risk group, between 1 and 10% in intermediate risk group, and < 1% for low risk.

	Clinical Characteristics	Indication for ICD
High Risk	-Aborted SCD due to VF -Sustained VT -Severe dysfunction of RV, LV or both	ICD indicated (class I)
Inter-Mediate Risk	≥1 risk factor: Syncope NSVT Moderate dysfunction of RV, LV or both	ICD should be considered (class IIa)
Low Risk	-No risk factors -Health gene carriers	ICD not indicated (class III)

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