

Arrhythmogenic Right Ventricular Dysplasia: Case Presentation and Review of the Literature

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Abstract

An 18 years old female died suddenly while sunbathing. Her family consulted an electro physiologist. He scanned the family for long QT, Brugada and ARVD. ECGs were performed on all the family members, which showed PVC's in one of her cousins, for whom a 24 hours recording ECG showed 200 polymorphic PVCs. Echocardiogram was normal, and Signal-Averaged ECG (SAECG) is negative, he adopted a "watch and see" strategy (Figure 1-2).

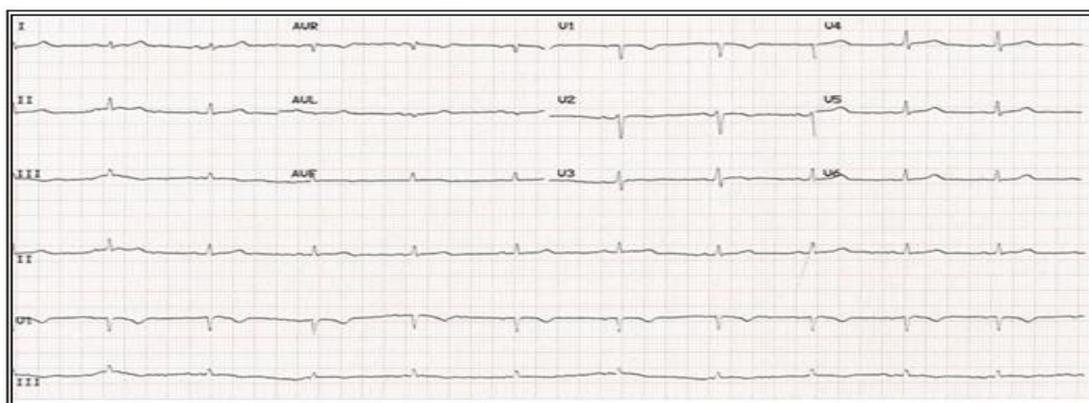


Figure 1:
ECG 12 leads microvoltage and T wave suggest myocarditis.

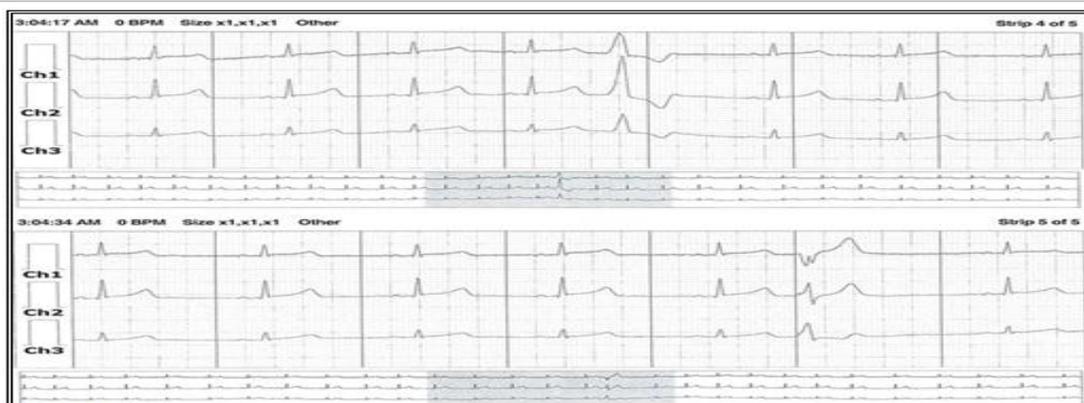


Figure 2:
24h recording ECG showing premature ventricular contraction suggesting different areas of origin .

A month later, the cousin passes out in the GYM with ventricular tachycardia at 230 bpm. Luckily, the Gym is at 3 min from an emergency department where she was successfully resuscitated. ECG post arrest was suggestive of ARVD (Figure 3). The physician was certainly disheartened by this near death experience, knowing that this won't be the last ARVD he misses. This cousin is a first degree relative of a sudden cardiac death victim without any other events in a family of seven siblings with a large extended family without sudden death. She only had premature beats. She was never syncopal.

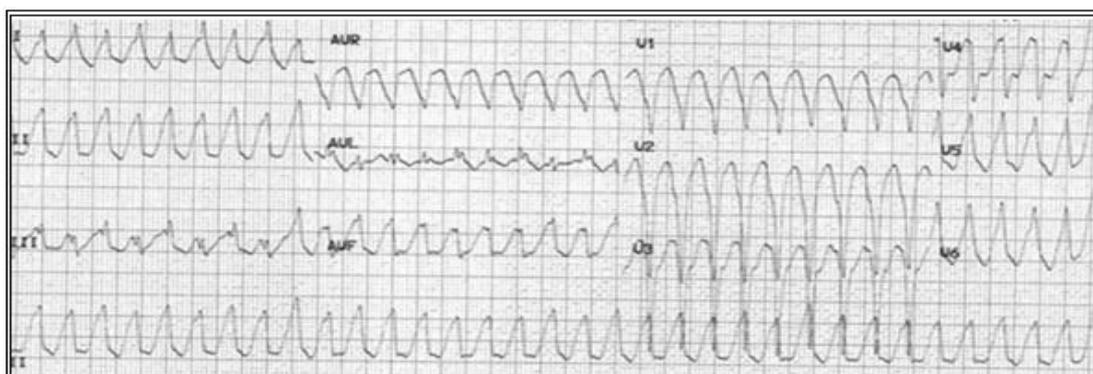


Figure 2:
12 leads ECG post cardiac arrest. Note alternance of QRS amplitude in lead III.

Following the ventricular tachycardia an ICD was implanted with two appropriate shocks in the last five years. CMR was positive in two siblings living abroad, one had an ICD implanted without therapies for 3 years follow up, and the other one is followed closely because of one minor criteria for ARVD.

Thorough tests and screening were performed in almost half of the first degree family members, and CMR confirmed ARVD in one cousin who lives in a different country.

Introduction

Arrhythmogenic Right Ventricular Dysplasia (ARVD) is a challenging clinical entity, due to its infrequent presentation, difficulty in diagnosis and the outcome of missing it could be lethal. First described in 1977 by Fontaine et al^[1]. And in 1982, with Marcus et al the clinical features of 24 French patients were first reported^[2].

Inherited by autosomal dominant transmission of affected desmosomes. Characterized by pathological presence of exceedingly large amount of fatty tissue and strands of cardiomyocytes bordered or embedded in interstitial fibrosis, constitutes the arrhythmogenic substrate, leading to life-threatening ventricular arrhythmias.

Regional wall motion abnormalities are the earliest signs of Right Ventricle (RV) myocardial damage that will progress later to global injury leading to RV dilation and failure, with Sudden Cardiac Death (SCD) in young adults as the major concern in the early stage of the disease. Although it mainly affects the RV, some variants of ARVD can also affect the left ventricle with or without involvement of the septum. The recessive form is extremely rare.

The aim of this article is a quick review on ARVD, how to recognize the clinical manifestation, how to diagnose it and how to approach relatives to SCD victims^[3].

Prevalence

Under-recognition makes the prevalence of ARVD indefinite, roughly estimated to be around 1 in 2000 to 1 in 5000 in the general adults population^[4]. Sudden Cardiac Death (SCD) is the major concern in ARVD, which accounts for approximately 3% to 5% of all cases of SCD in adults under the age of 65 years and even up to 20% in younger ages and among athletes who die suddenly^[5,6]. In fact, competitive sport doubled the risk of having ventricular tachycardia and death in comparison to recreational sport and inactive patients^[7].

30% to 50% of family members who were studied by non-invasive tests were found to have evidence of the disease^[5].

Clinical manifestations

The clinical profile of a patient with ARVD is very ambiguous, usually shows up between the 2nd and 5th decade, with a variety of presentation that mimic other diseases, including dyspnea, dizziness, palpitation, chest pain, but often heralded by syncope and SCD. On the other hand, patients may remain clinically asymptomatic for years, and the disease was found quiescent in the 3.7% of the general population^[8]; what render this disease difficult to recognize, specifically in sporadic cases with no family history of SCD.

In a large Cohort enrolling 100 patients diagnosed with ARVD^[6], follow up showed that palpitation, syncope and death were the most common reported symptoms at diagnosis (27%, 26%, and 23% respectively).

In patient presenting with palpitation, sustained or non-sustained Ventricular Tachycardia (VT) that arises from the Right ventricle (its inflow track, apex or outflow track; the “triangle of dysplasia”) with a Left Bundle Branch Block (LBBB) pattern were the most common arrhythmia^[9]. Less often, Supraventricular Tachyarrhythmia (SVT) is the solely finding. When it is present, atrial fibrillation accounts for more than 80% of cases^[10].

In familial ARVD with autosomal recessive pattern; palmoplantar Keratosis and woolly hair are commonly associated^[11].

Pathology

For the first time the genesis of fat and apoptosis was demonstrated by the San Diego’s group (Kim, Nature 2013), by cellular reprogramming of somatic cells to patient-specific induced pluripotent stem cells, enabling in vitro modelling of human genetic disorders^[12], and revealing the pathological hallmarks of ARVD; the progressive fibrofatty infiltration and the inappropriate desmosomal function when dealing with mechanical stress, leading to myocyte detachment and apoptosis primarily in the RV^[12].

This process is superimposed initially by inflammation, myocarditis, as active phase of ARVD^[13], which is the result of increased susceptibility to cardiotropic viruses which can explain “replacement fibrosis” on top of “interstitial” fibrosis.

The arrhythmic substrate is mainly conducted by three mechanisms: flare of myocarditis, fibrofatty infiltrates that facilitate macroreentry, and gap junction remodelling secondary to altered mechanical coupling^[14,15].

Genetics

Two established way of inheritance have been labelled in ARVD: autosomal dominant form, the most common one, and a rare autosomal recessive form, where ARVD takes part of a cardio-cutaneous syndrome; hyperkeratosis of palms and soles and woolly hair (Naxos disease and Carvajal syndrome)^[16,17].

Variety of genes may be implicated in ARVD and desmosomal mutations including: Junctional Plakoglobin (JUP; causally involved in Naxos Disease), desmoplakin (DSP; identified in autosomal dominant ARVD, due to a missense mutation linked to 6p24; also implicated in autosomal recessive Carvajal syndrome, due to mutation in the exon 24 of the desmoplakin gene)^[17], Plakophilin-2 (PKP2), TMEM43, Desmocollin-2 (DSC2), and Desmoglein-2 (DSG2). Individuals with PKP2 present at younger age and more likely to develop malignant arrhythmias^[4], giving a prognostic importance to genetic testing for ARVD^[18,19].

This recent molecular genetic approach of cardiomyopathies is at the same time of important benefit by improving the diagnostic tools, predictions^[20,21]; and a challenge to physicians to become able to integrate this recent knowledge into diagnosis and improving managements^[22,23].

Diagnosis

A sequence of electrocardiographic and imaging evaluations are recommended as initial approach to patient with high index of suspicion for ARVD; patients with no apparent heart disease who present with symptomatic or asymptomatic VT of LBBB configuration; survivors of SCD, especially the ones that occur during endurance sports^[24].

First, a non invasive approach is used with a 12-lead Electrocardiogram (ECG) and transthoracic echocardiography, SAE-CG, 24-hour ECG monitoring, exercise ECG testing, Cardiovascular Magnetic Resonance (CMR) imaging and genetic testing.

If still non diagnostic invasive procedure will follow such as; right ventricular contrast angiography, endomyocardial biopsy, electrophysiologic^[25].

Strong family history (unexplained premature death, arrhythmia symptoms and conduction disease) may increase the pre-test probability from 1: 2000-5000 to 1: 2^[26]. When a patient meets the diagnostic criteria for ARVD, clinical evaluation of at least first-degree relatives is seriously recommended^[27].

12-lead ECG findings in ARVD include the following^[28,29]: QRS prolongation in right precordial leads, V1 through V3, due to the delay in RV activation. Incomplete or complete Right Bundle Branch Block (RBBB), due to the conduction delay. Prolonged S wave upstroke (from the nadir of the S wave to the isoelectric baseline ≥ 55 msec). Epsilon wave is much more frequently observed

as a “slurring” at the base of QRS complexes more frequently found in right precordial leads, due to the delayed activation of some portion of the RV, is a major criterion in the 2010 revised Task Force criteria^[30], as well as, the inversion of the T waves in the right precordial leads (V1, V2, V3) in individual ≥ 14 years of age (in the absence of complete RBBB). These findings if not noted at presentation, the majority of patient will develop them in the upcoming 6 years of the disease progression^[31].

Signal-averaged ECG shows the following abnormalities: Filtered QRS duration ≥ 114 msec. Duration of terminal QRS < 40 micro V ≥ 38 msec. Root-mean-square voltage of terminal 40msec ≤ 20 micro V^[30].

Transthoracic echocardiography should be performed in all patient undergoing workup for ARVD^[32]. And the following are the noticed abnormalities: As major revised Task Force criteria^[30]; regional RV akinesia, dyskinesia, or bulges and 1 of the following, end diastolic RVOT ≥ 32 mm in the Parasternal Long Axis View (PLAX) or end diastolic RVOT ≥ 36 mm in the Parasternal Short Axis View (PSAX) or fractional area change $\leq 33\%$. As minor revised Task force criteria; regional RV akinesia or dyskinesia and 1 of the following: End diastolic RVOT ≥ 29 to < 32 mm in the PLAX, or end diastolic RVOT ≥ 32 to < 36 mm in the PSAX, or fractional area change $> 33\%$ to $\leq 40\%$.

CMR imaging is a valuable diagnostic tool in the evaluation of ARVD. Not commonly performed in all patients with suspicion of ARVD, especially if other tests have led to definite diagnosis of ARVD. However, when other means are non-diagnostic, CMR should be performed. It identifies global and regional ventricular dilation, dysfunction, intramyocardial fat, Late Gadolinium Enhancement (LGE) and focal wall thinning.

The conventional criteria that can be displayed with CMR as major criteria are: the high signal intensity on T1-weighted images of the fatty infiltration of the RV myocardium; regional wall motion abnormalities (akinesia or dyskinesia or dyssynchronous RV contraction); bulges of the RV and RVOT; dilatation of the RV and the RVOT (RV end-diastolic volume ≥ 110 ml/m² in men; ≥ 100 ml/m² in women); and global systolic dysfunction (depressed RV ejection fraction (RVEF $\leq 40\%$). As for minor CMR criteria: first, the RV wall motion abnormalities (as in major criteria) and lesser degrees of RV and RVOT dilatation (RV end-diastolic volume ≥ 100 ml/m² in men; ≥ 90 ml/m² in women); RVEF $\leq 45\%$ and global diastolic dysfunction^[30].

Right ventricular contrast angiography, is not routinely performed, only if we still miss the exact diagnosis by other imaging. It may provide valuable information about the RV structure and function^[33]. Findings include: hypertrophic trabeculae aligned transversely and detached by deep fissures; coarse trabeculae in the apical region; increased RV volume. And according to the revised Task Force criteria, the presence of regional RV akinesia, dyskinesia, or bulges by angiography is a major criterion^[30].

Electrophysiologic (EP) testing in ARVD is primarily used in refractory ventricular arrhythmias and not as a routine part of the diagnosis. The identification of low-voltage areas during EP testing is associated with increased risk of future ventricular arrhythmias^[34].

Endomyocardial Biopsy (EMB), only recommended when other non invasive diagnostic tools still inconclusive. It carries a rare risk of perforation because of fibrosis^[35]. The documentation of pathologic fibrofatty infiltration on EMB remains crucial and a major criterion in the modified Task criteria^[30].

Approach to relatives of sudden cardiac death victims

Recommending ICD implants for relatives of sudden cardiac death victims without definite criteria, will certainly lead to medical and psychological disasters. We came to a conclusion that at this point of time with the current knowledge, it is impossible to predict which relative will manifest the disease and who will not^[36-38].

In our opinion the best approach is to perform ECG's Holter monitoring and 2D echocardiograms on the willing relatives. In the presence of inverted T waves on the precordial leads or frequent PVC's on Holter or suspicious echocardiogram request a CMR. If the CMR is abnormal recommend ICD implant. If the CMR is normal you need to teach the patient that this does not exclude the disease^[39].

Patients should be instructed that they still need to follow up yearly, and to consult their physician as soon as possible if they experience syncope or palpitations. We should not be shy repeating the above mentioned non invasive tests on a regular basis^[27].

We recommend, for medico-legal purposes interpreting the tests with no findings of malignancy, rather than “Normal”.

Conclusion

In spite of the previously listed diagnostic tools, major and minor criteria of the modified Task force criteria, the diagnosis of ARVD remains a true challenge requiring a high index of clinical suspicion.

Genotyping is important for a positive diagnosis^[40], but with the most recent advance, we still lack a single diagnostic tool to clearly and easily identify ARVD.

Conflict of Interest: None.

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