Case report

Familial arrhythmogenic right ventricular dysplasia in afrocaribbeans: treadmill stress test the key to early diagnosis

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Abstract

Arrhythmogenic right ventricular dysplasia is a rare entity and a significant cause of sudden death especially in the Italian population and athletes. The familial form is uncommon especially in the Afro-Caribbean population. This Index family represents an Autosomal Dominant form in a maternal parent who had sudden death at 39 years of age. The Index case was diagnosed at 18 years with increasing palpitations since 8 years of age, becoming symptomatic two decades younger than her mother. This was confirmed using the Treadmill Stress test. This is the 1st Case of Familial Arrhythmogenic right ventricular dysplasia documented in an Afro-Caribbean family.

Learning objective

Familial Arrhythmogenic right ventricular dysplasia is a rare entity and a significant cause of sudden death especially in the Italian population and athletes. This the first case of Autosomal Dominant type of ARVD with variable penetrance, documented in an Afro-Caribbean family where diagnosis was aided by Ventricular Tachycardia occurring during a Treadmill Stress Test.

Keywords

Arrhythmogenic right ventricular dysplasia • Ventricular tachycardia • Familial • Gene

Imprint

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Introduction

Arrhythmogenic right ventricular dysplasia (ARVD) is a rare structural cardiac anomaly characterized by predominantly right ventricular free wall myocardial atrophy with fibro fatty replacement leading to ventricular arrhythmias and Sudden Death. First described by Giovanni Maria Lancisi (1736) who published in his book "De Hereditaria ad Cordis Aneurysmata Constitutione: De Cordis Prolapsu", the occurrence in four (4) generations of an Italian family, the classical symptoms and signs of palpitations, aneurysmal formation in dilated right ventricle, congestive cardiac failure and sudden death [1]. Sergio Dalla Volta (1961) published cases which had ventricular arrhythmias which occurred in right ventricles, which were ineffective in systole as there was "auricularization"

of the right ventricular pressure, where blood was transmitted to the pulmonary artery by atrial systole [2].

Over two and half centuries after the first description, Frank et al (1978) described the Electrocardiogram (ECG) findings in four (4) cases of right ventricular dysplasia with the first description of the Epsilon Wave after the QRS complex, seen in only 8% of confirmed ARVD. [1]. Marcus et al (1982) in 24 post mortem cases documented the worst end of the spectrum of Arrhythmogenic Right Ventricular Dysplasia and described the pathognomonic "Triangle of Dysplasia" in the inflow, apex and outflow of the right ventricle.

The early pathology can start in any part of the right ventricle and interventricular septum, which can explain the clinical, ECG and diagnostic phenotypic heterogeneity, which may not have all the classical findings of ARVD. These clinical, ECG and diagnostic findings may be difficult to ascertain in the attempt of early diagnosis of Familial ARVD, without using histology from an invasive cardiac muscle biopsy, with the attendant risk of perforation, before Sudden Death occurs and becomes the presenting feature [3]. Cardiac Magnetic Resonance Imaging (MRI) would not be cost effective, nor recommended, for repeated use in pre-pubertal or adolescent patients.

Prevalence of ARVD varies from 1:5000 in USA to 20:5000 in Italy and Germany and constitute up to 25%, of the main causes of Sudden Death in Italy amongst athletes under 35 years of age [4]. The familial occurrence has been substantiated by the detection of 12 gene abnormalities with over 800 pathogenetic mutations. The genes encode for five (5) desmosomal proteins and seven (7) non-desmosomal proteins, the most common of which was the ARVD (type 9) seen in up to 40% of cases, caused by mutations in PKP2 gene which encode plakophilin-2 protein. Desmosomal genes are protein parts of the cell membrane which facilitates the function and structural integrity of the cell. The ARVD gene type 1 has been found on chromosome 14q23-q24 with marked phenotypic heterogeneity. More than 50 % of cases of the genes identified with ARVD are familial, Autosomal Dominant with variable penetrance and phenotypic expression as in the Index case. Cutaneous-Cardiac phenotypes which are Autosomal recessive forms are associated with Naxos Disease and Carvajal Syndromes [5].

Case report

The Index case is an 18 years old Afro-Caribbean female at a tertiary level institution with a 10 year history of intermittent palpitations with increasing frequency, associated with dizziness and 9 years of retrosternal or praecordial "sharp sticking" chest pain not associated with palpitations. She functions at NYHA11 but becomes NYHA 111 on exertion. There was no history of syncope, seizure or deafness.

There was also no history of caffeine ingestion, energy drinks, high dose steroids, stimulants or illicit drugs.

The Index cases mother developed palpitations in her twenties and developed Complete Heart Block. She died at 39 years of age from Ventricular arrhythmias secondary to diagnosis of ARVD, when the index case was eight years old. The Index case was her only child.

On examination her weight was 49 kg and Height 174 cms with BMI of 16, and BSA 1.55m2. Cardiovascular examination revealed heart rate of 80/minute with normal volume and rhythm. Her Apex beat was at the 5th left intercostal space in the mid-clavicular line, normal in character. First and second heart sounds were normal; a grade 1/6 systolic murmur was noted in lower left sternal border. There were no signs of cardiac failure or pulmonary hypertension.

Investigations revealed Haemoglobin of 12.8 g/dl and packed cell volume of 38.2%. There were normal thyroid function tests.

The Chest-X Ray had normal cardiothoracic ratio with no filling of the anterior space, normal lung fields, normal ratio right and left bronchi and normal position of abdominal viscera ruling out Isomerism.

Transthoracic Echocardiogram showed RVAWd 0.5 cm, RVIDd 0.6 cm, IVSd 1.1 cm, LVIDd 3.9 cm, LVPWd 1.6 cm, IVSs 1.3 cm, LVIDs 2.4 cm and LVPWs 2.0 cm. Normal IVS/LVPW ratio, Normal LA-AO ratio, Normal Fractional shortening of 38% and Ejection Fraction of 70%. Right ventricular wall was non-homogenous. There was mild Tricuspid regurgitation and normal pulmonary artery pressures. Cardiac MRI, Cardiac CT and Gene studies are not available in the Index country.

The resting Electrocardiogram (ECG) showed heart rate of 71bpm, Sinus arrhythmia, and normal QRS duration of 90 msin, Normal Qtc of 0.398 ms and QRS axis of 89. P axis was -22 and T axis was 62. T wave was inverted in V1 only. There was early repolarization in V2 and V3. A small variant of an Epsilon (ie., Postsilon) wave in V3, V4, V5 and V6 was noted (Fig.1). These atypical Epsilon waves were not seen on other resting ECG's nor during the treadmill stress test. There were no Epsilon waves, or variants thereof, in V1 and V2.

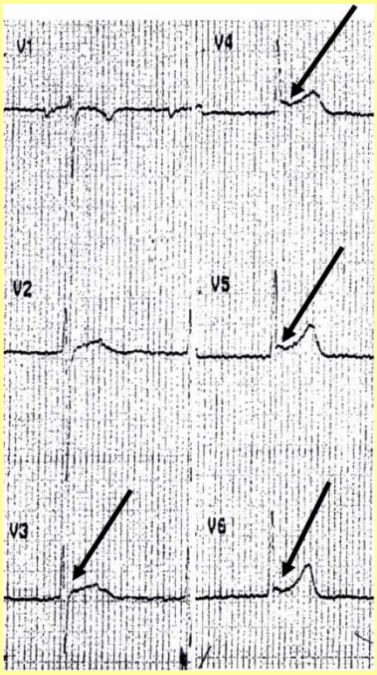

Figure 1. Variant Epsilon (Postsilon) Wave V3 - V6.

Bruce Protocol Treadmill Stress Test showed on ECG monitor, within 30 seconds of Stage 1, Atrial Flutter, Atrial Fibrillation and Isolated (premature ventricular contractions (PVC) (Fig. 2). Within two minutes there were more frequent isolated 2 to 1 wide QRS complex PVC (Fig.3) Within 3 minutes there were bizarre wide QRS complex Ventricular Tachycardia (VT)(Fig.4). Whilst the ECG abnormalities were noted, the Index case did not feel or complain of palpitations and fatigue in the first 3 minutes, which is an ominous sign, as this could be occurring without the patient's knowledge. The Index case complained of palpitations when VT commenced and continued to complain until 30 seconds after cessation of treadmill test. During the recovery period there was Atrial Flutter and Atrial Fibrillation intermittently up to 5 minutes, when the normal pre-test resting ECG occurred (Fig.5). The ECG abnormalities noted in Figures displayed, occurred in all leads simultaneously recorded, ruling out the possibility of artifact as a cause of abnormalities noted.

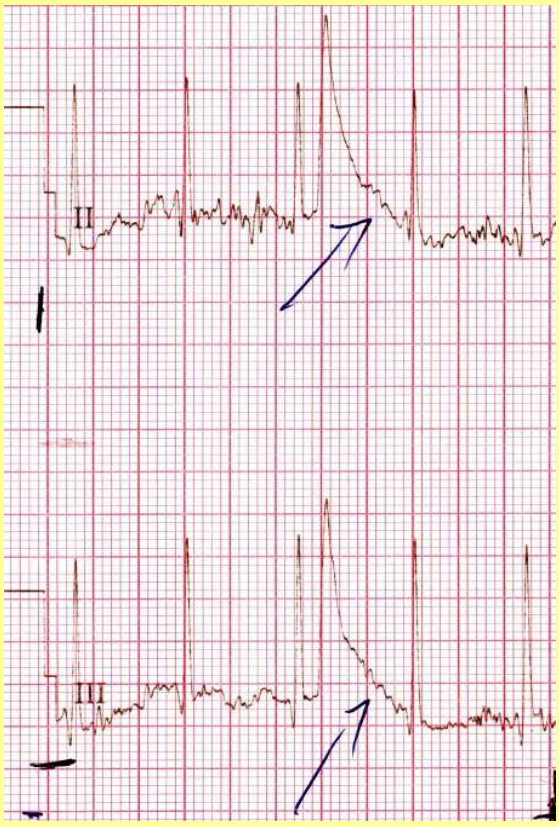

Figure 2. Atrial Dysrhythmias with Isolated PVC.

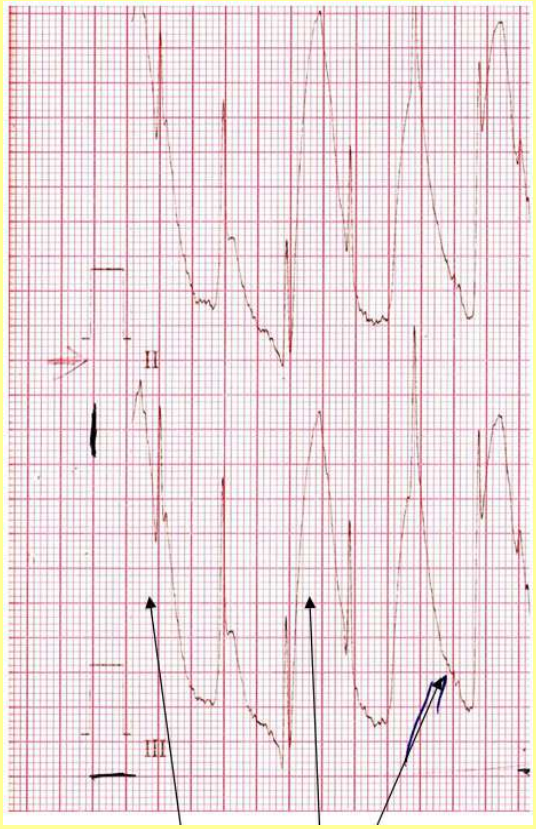

Figure 3. Isolated 2 to 1 Wide QRS Complex.

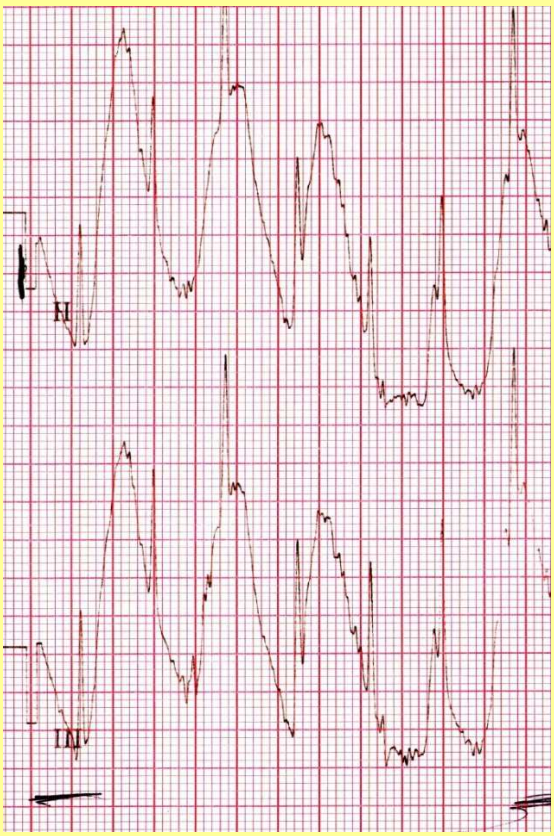

Figure 4. Ventricular Tachycardia (VT) with wide QRS complexes.

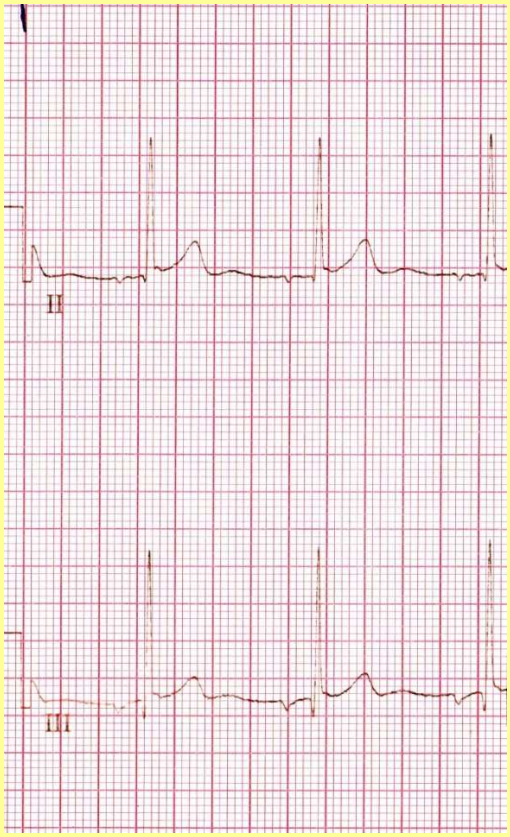

Figure 5. Resting ECG.

Medications initially started were cost effective anti-arrhythmic Digoxin and beta-blocker Atenolol. A Dual chambered implantable cardio vertex defibrillator was inserted. Index case is now maintained on beta-blocker only.

There continues to be recommended exercise restrictions, with no competitive sports or sustained exertion in Index case.

Discussion

The diagnosis of ARVD was based on a criteria first developed by McKenna et al (1994) which has been revised by the International Task Force in 2009. ARVD diagnosis needs 2 Major criteria or 1 major and 2 Minor criteria or 4 Minor criteria based on Family history of Sudden Death, and ARVD, ECG abnormalities, right ventricular arrhythmias, right ventricular structural or functional abnormalities with myocardial atrophy and fibro-fatty replacement. The 2009 diagnostic criteria included additional magnetic resonance imaging of the heart, genetic testing and new ECG abnormalities including LBBB morphology in ventricular arrhythmias. A new ECG criterion has also been developed as only 8% of ARVD cases have the classical Epsilon wave, which makes it more difficult to diagnose. Epsilon waves in ARVD are usually in V1- V3, but it would be possible to

understand that the ECG abnormality would be a direct reflection of the part of the ventricle involved in the early pathology, which can start in any part of the right ventricle and interventricular septum.

Basso et al noted that the most common ECG abnormality in 79% of cases is inverted precordial T wave especially in right precordial leads, as noted in VI of the Index case. Involvement of the interventricular septum occurs in 20% and left ventricle at autopsy in 47% of cases at the severe end of the spectrum of the disease [3, 6]. The Index case had 2 major and one minor criterion, Epsilon wave noted on one ECG, family history of death from ARVD and Ventricular Tachycardia during Treadmill Stress Test. The Ventricular Tachycardia was confirmed only during the Treadmill stress Test and hence helped to confirm the diagnosis of ARVD using the revised McKenna criteria.

There has been a diagnostic dilemma in determining what investigation or clinical assessment is needed to determine which family members would phenotypically inherit ARVD, prior to the occurrence of Sudden Death. There is no direct correlation noted between the genotype and when the phenotypic expression would occur. Sudden Death may be the presenting phenotypic expression. This anecdotal case suggests that Treadmill Stress tests, elucidating the Ventricular Arrhythmia in a controlled environment, could be the answer to early diagnosis of ARVD. Treadmill Stress Tests using the Modified Bruce Protocol annually after 10 years of age, or before the earliest age of Sudden Death in the Family with ARVD, could be the key to early detection and hence early treatment. Further large scale multicenter trials in descendants of ARVD, would be needed to elucidate if this method of assessment, starting in late childhood would be helpful in early diagnosis, leading to enhanced monitoring, treatment and prophylactic care.

The Epsilon waves in this Index Case are atypical of ARVD, in its appearance on the ECG and were not consistently seen in all ECG's completed within the year preceding the diagnosis. This confirms the finding of some authors who indicate also absence of Epsilon wave on some ECG's in the same patient but also beat to beat variability. There were no Epsilon waves (or variants thereof), ever seen in V1 and V2. Atypical variants of the Epsilon waves were only seen in V3, V4, V5 and V6 (Fig.1). The classical ARVD usually have Epsilon waves in V1 to V3. It is noted by some authors that there can be progression of Epsilon waves from V1 to V3 to all other leads with progression of the disease and that involvement of the myocardium may be non-homogenous, postulating that this could lead to variability in types of Epsilon waves and ECG leads that they are seen in. The new criterion for diagnosis is made easier without histology and or biopsy when not readily available. [1-3, 6]. The ECG abnormalities noted during the Treadmill test were initially not noticeable to the Index case indicating that Arrhythmias can be occurring without the patients awareness of Palpitations, leading to Syncope, Cardiac Arrest or even Sudden Death, without forewarning.

The etiological-pathological cause has been identified to be secondary to programmed "Apoptosis" of myocardial cells, metabolic degenerative with loss of myocardium, inflammatory with an inflammatory necrosis as seen in mice after coxsackie virus infection and sympathetic nerve disruption analogous to amine depletion. These theories and confirmed disease processes have not yet translated into curative therapy which at this time is purely symptomatic with increased survival with predominantly defribillators and improved drug therapy [7]. Some patients may present with Sudden Death and the new criteria is hoped to be helpful with early diagnosis of familial

asymptomatic cases, who can have palpitations without cognizance of family history of ARVD or occurrence of a new mutation of ARVD [4-7].

The literature is replete with studies in Italians, Greeks, Germans and Caucasians. The International Registry in 2006 in Europe and North America was beneficial in providing additional genetic evaluation with 5 new genes identified. This registry should now be extended to other countries where the ARVD diagnosis is made [1-7].

Thiene and Basso et al in his analysis of 38 families with detection of desmosomal genes DSP, PKP2, DGS2 and MM found increased left ventricular involvement and larger right ventricles in PKP2 and MM groups but there was no difference in long term morbidity or mortality between the groups confirming phenotypic heterogeneity. The Index family would benefit from Genetic testing to determine if the gene responsible belong to any of the 12 genes identified thus far, or if there is a different gene in the Afro-Caribbean population [1-8].

An index family that has an Autosomal Dominant Familial Arrhythmogenic right ventricular dysplasia displaying variable penetrance and phenotypic heterogeneity, confirmed with Ventricular Tachycardia during Treadmill Stress test, documented for the first time in an Afro-Caribbean family, in the English Medical Literature.

Statement on ethical issues

Research involving people and/or animals is in full compliance with current national and international ethical standards.

Conflict of interest

None declared.

Author contributions

The author read the ICMJE criteria for authorship and approved the final manuscript.

References

1. Thiene G, Nava A, Marcus FI. Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia In - Arrhythmogenic Right Ventricular Cardiomyopathy / Dysplasia. Marcus FI, Nava A, Thiene G Eds.Springer-Verlag Italia 2007. p.1

2. Dalla Volta S, Battaglia G, Zerbini E. "Auricularization" of right ventricular pressure curve. Am Heart J 1961:61;25-33

3. Marcus FI, Fontaine GH, Guiraudon G, Frank R, Laurenceau JL, Malergue C, et al. Right ventricular dysplasia: a report of 24 adult cases. Circulation 1982;65:384-398.

4. Pigozzi F, Rizzo M. Sudden Death in Competitive Athletes. Clin Sports Med 2008;27:153-181.

5. Campuzano O, Alcalde M, Allegue C, Iglesias A, Garcia-Pavia P, Partemi S, et al. Genetics of arrhythmogenic right ventricular cardiomyopathy. J Med Genet 2013;50:280-289.

6. Marcus FI, McKenna WJ, Sherrill D, Basso C, Bauce B, Bluemke DA, et al. Diagnosis of Arrhythmogenic Right Ventricular Cardiomyopathy. Circulation 2010;121:1533-1541.

7. Pilichou K, Remme CA, Basso C, Campian ME, Rizzo S, Barnett P. Myocyte necrosis underlies progressive myocardial dystrophy in mouse dsg2-related arrhythmogenic right ventricular cardiomyopathy. J Exp Med 009;206(8):1787-1802.

8. Basso C, Thiene G, Corrado D, Angelini A, Nava A, Valente M. Arrhythmogenic Right Ventricular Cardiomyopathy. Circulation 1996;94:983-991.