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Clinical Presentation, Cardiac Magnetic Resonance Findings, and Prognosis of Patients with Arrhythmogenic Right Ventricular Cardiomyopathy – An Experience from Pakistan

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ABSTRACT

Objectives: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart-muscle disease, characterized by fibro-fatty replacement and ventricular arrhythmias, that primarily affects the right ventricle (RV). We aimed to look at the clinical presentation, cardiac magnetic resonance (CMR) imaging findings and prognosis of patients with ARVC in Pakistan.

Material and Methods: It is a retrospective observational study, 17 consecutive patients with CMR and other findings consistent with ARVC, were enrolled from 2010 to 2019 at a single center.

Results: Out of 17 patients, 12 (70.6%) were male with a mean age of 33.5 ± 17.5 years. Family history of sudden cardiac death was present in 3 (17.7%) patients while one (5.9%) patient had family history of ARVC. Syncope was the first presenting symptom in eight (47.1%) patients. On 12 leads ECG, T wave inversion in precordial leads was found in 6 (35.4%) patients, and epsilon wave was present in only 3 (17.7%) patients. On echocardiogram, 13 (76.5%) patients had dilated RV with reduced systolic function. On CMR, majority of patients (n = 14, 82.4%) were found to have RV dilatation with regional dyskinesia and fatty infiltration, 9 (52.9%) of them had left ventricular involvement also. Follow-up was available for 14 patients (82.4%) with a mean follow-up period of 35.5 ± 19.7 months. Three (21.4%) of them died and 10 (71.4%) got admissions for heart failure during follow-up period.

Conclusion: Arrhythmia related events are the main presenting symptoms of ARVC in this region, and left ventricular involvement in ARVC is not rare in this population. The mortality is relatively high, probably due to advanced disease at the time of presentation and less medical facilities available.

Keywords: Arrhythmogenic, Cardiomyopathy, Prognosis, Pakistan

INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart-muscle disease, characterized by myocardial atrophy, fibro-fatty replacement, and ventricular arrhythmias, that primarily affects the right ventricle (RV).[1] With time, ARVC leads to diffuse RV and left ventricle (LV) involvement and may be difficult to distinguish clinically from dilated cardiomyopathy.[2,3]

Different distinct patterns of the disease have been reported, which include isolated RV disease, prominent LV manifestations in the setting of relatively mild right-sided disease;

and biventricular disease.[4] The LV involvement is associated with more severe cardiomyopathy, inflammatory infiltrates, and heart failure.[4,5] Natural history of disease is divided into four phases. A subclinical phase (with concealed structural abnormalities and no symptoms but sudden death might be the first manifestation in this phase), followed by an overt RV electrical disorder with ventricular arrhythmias originating from the RV. Third, RV failure due to progressive loss of myocardium with severe dilatation and systolic dysfunction and finally an end stage biventricular involvement that can mimic dilated cardiomyopathy.[6]

Electrocardiographic (ECG) changes and arrhythmias may develop before histological evidence of myocytes loss or clinical evidence of RV dysfunction and are early and sensitive markers of disease expression in ARVC.[6] The subclinical phase of disease may also be detected by imaging studies, and cardiac magnetic resonance (CMR) imaging is one of the most sensitive imaging modality which not only helps in morphological and functional assessment but also helps in tissue characterization.[7]

There are no data on ARVC from our population. Our hospital has been the pioneer of cardiac imaging in the country. It serves as the only center offering CMR facility to a large area of population and hence has been a referral center for CMR in patients with suspected ARVC. We aim to study the clinical presentation, CMR findings, and prognosis of patients with ARVC. This will help us understand the characteristics and prognosis of ARVC in our population.

MATERIAL AND METHODS

Study design

This is a retrospective observational study.

Study population

This study was approved by the hospital ethical review committee. Forty-three patients with clinical signs and symptoms suggestive of ARVC who were referred to Aga khan university hospital, Karachi, Pakistan, for CMR from 2010 to 2019, were evaluated for inclusion criteria. Seventeen patients who met the CMR criteria for ARVC[8] [Table 1] were retrospectively included in this study and rest of them were excluded from the study. The diagnosis of ARVC was based on a set of criteria recommend by the revised Task Force Criteria.[9] All included subjects had to meet two major, or one major plus two minor, or four minor diagnostic criteria to be diagnosed with ARVC. Data were collected by reviewing patients' charts and investigations and variables of interest were recorded using a dedicated pro forma.

Follow-up

Follow-up was done at variable intervals after diagnosis of ARVC. Clinical information and variables of interest were documented on a dedicated pro forma by a physician during telephone contact or ambulatory visits.

CMR protocol

CMR was performed using a 1.5T Siemens Avanto scanner. A breath hold steady-state free-precession ECG-triggered sequence was used to evaluate global LV and RV function. In each patient, two long axis views (one vertical and one horizontal) and a set of contiguous short-axis views were acquired from the mitral plane to the apex with the following parameters: Slice thickness 7 mm, distance factor 25%, field of view 34 cm, matrix 192 × 192, flip angle 80, TR/TE 58.74/1.12, and bandwidth 930 hz/px. In addition, two RV outflow tract (RVOT) views, one RV view showing inflow and outflow and axial stack for right ventricular slices were acquired.

Selected views of Turbo spin-echo T1-weighted images with and without FAT suppression were also acquired for each patient to look for fatty infiltration of the myocardium. Late gadolinium-enhanced (LGE) images were obtained 8–10 min after bolus injection of gadolinium. Images were acquired in the same short-axis, long-axis, and RV views as used for cine CMR. The inversion time was optimized to null signal from the normal myocardium.

CMR analysis

All the images were analyzed by a reader who is qualified and experienced in cardiovascular imaging. The analysis of CMR images was done on third party software – Medis Q mass. The endocardial and epicardial borders of the LV and RV were drawn manually on the series of short-axis cine slices, at end-diastole, and end-systole to obtain end-diastolic volume (EDV), and end-systolic volume (ESV), respectively. The left and right ventricular ejection fraction (EF) was calculated from the EDV and ESV, and presented as percentages.

CMR challenges, findings in ARVC, and differential diagnosis

ECG irregularities and breath-holding issues are the main challenges during image acquisition in patients with suspected ARVC and may result in suboptimal image quality. Sometimes it is difficult to differentiate epicardial fat from fatty infiltration of the myocardium. Intramyocardial fat may also occur in older, obese patients and is not specific for ARVC in the absence of functional abnormalities.

CMR findings in ARVC include RV wall thinning, RVOT enlargement, prominent trabeculae, ventricular dilation,

Table 1: Revised 2010 task force criteria for ARVC.

1. Global or regional dysfunction and structural alterations
Major
2D Echo criteria Regional RV akinesia, dyskinesia, or aneurysm AND 1 of the following measured at end diastole PLAX RVOT≥32 mm (PLAX/BSA≥19 mm/m^2), or PSAX RVOT≥36 mm (PSAX/BSA≥21 mm/m^2), or Fractional area change≤33% CMR criteria Regional RV akinesia or dyskinesia or dyssynchronous RV contraction AND 1 of the following RV EDV/BSA≥110 mL/m^2 (male) or≥100 mL/m^2 (female RV ejection fraction≤40% RV Angiography Criteria Regional RV akinesia, dyskinesia, or aneurysm
Minor
2D Echo Criteria Regional RV akinesia or dyskinesia or dyssynchronous RV contraction AND 1 of the following measured at end diastole PLAX RVOT ≥29–<32 mm (PLAX/BSA ≥16– <19 mm/m^2), or PSAX RVOT ≥32–<36 mm (PSAX/BSA ≥18– <21 mm/m^2), or Fractional area change>33%≤40% CMR criteria Regional RV akinesia or dyskinesia or dyssynchronous RV contraction AND 1 of the following: RV EDV/BSA ≥100–110 mL/m2 (male) or ≥90–100 mL/m^2 (female) RV ejection fraction >40–≤45%
2. Tissue characterization of wall
Major
Residual myocytes<60% by morphometric analysis (or<50% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample, with or without fatty replacement of tissue on endomyocardial biopsy
Minor
Residual myocytes 60–75% by morphometric analysis (or 50%–65% if estimated), with fibrous replacement of the RV free wall myocardium in ≥1 sample with or without fatty replacement of tissue on endomyocardial biopsy
3. Repolarization abnormalities
Major
Inverted T waves in right precordial leads (V1, V2, and V3) or beyond in individuals >14 years of age (in the absence of complete RBBB QRS≥120 ms)
Minor
Inverted T waves in V1 and V2 in individuals >14 years of age (in the absence of complete RBBB) or in V4, V5, and V6 Inverted T waves in leads V1, V2, V3, and V4 in individuals >14 years of age in the presence of a complete RBBB
4. Depolarization/conduction abnormalities
Major
Epsilon wave (reproducible low-amplitude signals between end of QRS complex to onset of T wave) in the right precordial leads (V1-V3)
Minor
Late potentials by SAECG in ≥1 of 3 parameters in the absence of a QRS of ≥110 ms on standard ECG: Terminal activation duration ≥55 ms measured from the nadir of the S-wave until the end of all depolarization deflections (including R') in V1, V2, or V3
5. Arrhythmias
Major
Non-sustained or sustained VT of LBBB morphology with superior axis
Minor
Non-sustained or sustained VT of RVOT configuration, LBBB morphology with inferior axis or of unknown axis >500 PVCs per 24 h on Holter monitoring

(*Contd...*)

Table 1: (*Continued*).

6. Family history
Major
ARVC in first degree relative who meets Task Force Criteria
ARVC confirmed pathologically at autopsy or surgery in first degree relative
Identification of pathogenic mutation categorized as associated or probably associated with ARVC in the patient under evaluation
Minor
History of ARVC in first degree relative in whom it is not possible to determine whether the family member meets Task Force Criteria
Premature sudden death (<35 years of age) due to suspected ARVC in a first degree relative
ARVC confirmed pathologically or by current Task Force Criteria in second-degree relative

ARVC: Arrhythmogenic right ventricular cardiomyopathy, RVOT: Right ventricular outflow tract, RV: Right Ventricle, EDV: End-diastolic volume, BSA: Body surface area, SAECG: Signal-averaged electrocardiogram

global or regional systolic dysfunction, regional or focal areas of dyskinesia, and fibro-fatty replacement. These abnormalities especially occur in predilection sites including the RV base and LV lateral wall. Common differentials of ARVC include conditions causing RV dilatation and dysfunction, Uhl's anomaly, myocarditis, sarcoidosis, dysplastic tricuspid valve, and RV infarct.

Statistical analysis

We recorded the demographic details, presenting symptoms, family history, and results of investigations. After creating a database, we encoded our data. All statistical analyses were performed using the Statistical Package for the Social Sciences version 23. Continuous variables were expressed as mean value ± standard deviation and categorical variables were expressed as frequencies and percentage.

RESULTS

Table 2 shows the baseline characteristics, ECG and 24 h ambulatory ECG findings in patients with ARVC. The majority (70.6%) of patients were male with a mean age of 33.9 ± 17.5 years. Three (17.7%) of them had a family history of sudden cardiac death (SCD) and only one (5.9%) had family history of ARVC. The majority (47.1%) of patients presented with syncope, followed by palpitations (35.3%).

The most common ECG finding was T wave inversion in precordial leads in 6 (35.3%) patients, followed by right bundle branch block in 4 (23.5%) patients, epsilon wave was found in only 3 (17.7%) patients. On 24 hour ambulatory ECG monitoring, 5 (29.4%) patients had non-sustained ventricular tachycardia (VT), 5 (29.4%) patients were found to have premature ventricular complexes, and one (5.9%) patient showed sustained VT.

Table 3 shows the echocardiographic and CMR findings in patients with ARVC. On echocardiogram, mean left ventricular EF was 54.6 ± 4.1%. The majority of patients

Table 2: Baseline characteristics.

Demographics	
Mean age (years)	33.9±17.5
Males (%)	12 (70.6)
Symptoms (%)	
Palpitations	6 (35.3)
Syncope	8 (47.1)
Dyspnea	2 (11.8)
Pedal edema	1 (5.9)
Family history (%)	
SCD	3 (17.7)
ARVC	1 (5.9)
12 leads ECG findings (%)	
Epsilon waves	3 (17.7)
RVH	1 (5.9)
RBBB	4 (23.5)
T wave inversion in precordial leads	6 (35.3)
Records not available	3 (17.7)
24 h ambulatory ECG (Holter) (%)	
PVCs	5 (29.4)
Non-sustained VT	5 (29.4)
Sustained VT	1 (5.9)
Records not available	6 (35.3)

SCD: Sudden cardiac death, ARVC: Arrhythmogenic right ventricular cardiomyopathy, ECG: Electrocardiographic, RVH: Right ventricular hypertrophy, RBBB: Right bundle branch block, PVCs: Premature ventricular complexes, VT: Ventricular tachycardia

(n = 13, 76.5%) had dilated RV with reduced RV systolic function, three patients (17.6%) had dilated RV with normal systolic function, and one patient (5.9%) was found to have normal sized RV with reduced systolic function. LV was dilated in only two patients (11.8%) [Figure 1].

On CMR, all patients (n = 17, 100%) had LGE in the RV while fatty infiltrates were found in 14 (82.4%) patients [Figure 2]. Dilated RV with systolic dysfunction and regional dyskinesia was found in 14 (82.4%) patients, 2 (11.8%) patients had normal size RV with regional dyskinesia and systolic dysfunction, and 1 (5.9%) patient had regional right ventricular dyskinesia with normal size RV and

normal systolic function [Figure 3]. Left ventricular involvement was found in more than half of the patients (n = 9, 52.9%).

Follow-up

Follow-up was available in 14 (82.4%) patients with a mean follow-up period of 35.5 ± 19.7 months [Table 4]. Half of the patients (n = 7, 50%) had at least one episode of VT on follow-up and only 4 (28.6%) patients underwent implantable cardioverter defibrillator (ICD) implantation for secondary prevention. All patients needed hospitalization during follow-up period and number of mean hospital admissions was 2.3 ± 1.0. Ten (71.4%) of the patients admitted for heart failure, 3 (21.4%) patients required admissions due to syncope/arrhythmia. Three (21.4%) of the 14 patients died during follow-up period, one (7.1%) had SCD and 2 (14.3%) died due to decompensated heart failure.

Table 3: Echo and CMR findings.

Echocardiogram findings (%)	
Mean EF	54.6±4.1
Patients with LV dilatation	2 (11.8)
Patients with only RA enlargement	13 (76.5)
Patients with Bi-atrial enlargement	4 (23.5)
Patients with RV dilatation without systolic dysfunction	3 (17.6)
Patients with RV dilatation with systolic dysfunction	13 (76.5)
RV systolic dysfunction without dilatation	1 (5.9)
CMR findings (%)	
Patients with fatty infiltration	14 (82.4)
Late gadolinium enhancement	17 (100)
Normal sized RV with regional akinesia or Dyskinesia and preserved RV systolic function	1 (5.9)
Dilated RV with systolic dysfunction and regional akinesia/dyskinesia	14 (82.4)
Normal size RV with systolic dysfunction and regional dyskinesia/akinesia	2 (11.8)
LV envolvement	9 (52.9)

CMR: Cardiac magnetic resonance, EF: Ejection fraction, LV: Left ventricle, RA: Right atrial, RV: Right ventricle

Table 4: Follow-up.

Follow-up (n=14)	
Mean duration of follow-up (months)	35.5±19.7
Hospital admissions during follow-up (mean)	2.3±1.0
Patients underwent ICD implantation (%)	4 (28.6)
Deaths (%)	3 (21.4)
Reason of hospitalization (%)	
Arrhythmia	3 (21.4)
Heart failure	10 (71.4)
Others	1 (7.1)
Cause of death (%)	
SCD	1 (7.1)
Decompensated heart failure	2 (14.3)

ICD: Implantable cardioverter defibrillator, SCD: Sudden cardiac death

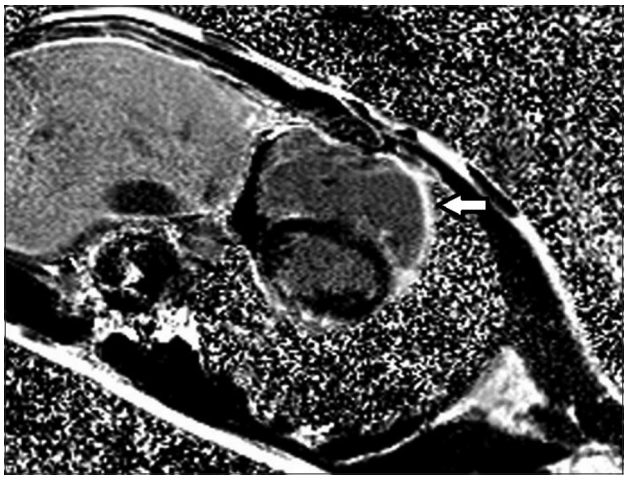

Figure 1: A 27-year-old man with a history of syncope. Cardiac magnetic resonance delayed enhanced image with gadolinium, showing hyper enhancement (arrow) in the right and left ventricular walls.

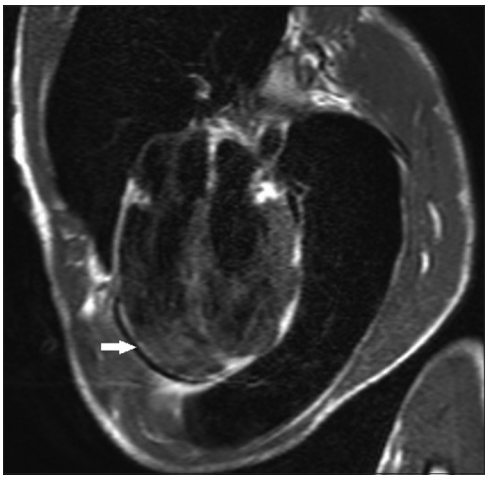

Figure 2: A 23-year-old woman with syncope. Cardiac magnetic resonance Turbo spin-echo T1-weighted image, showing fatty infiltration (arrow) of the myocardium.

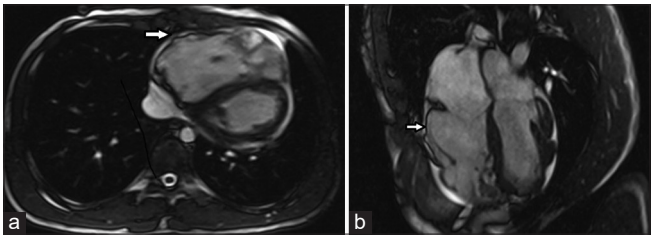

Figure 3: (a and b) A 23-year-old woman with syncope. Cardiac magnetic resonance steady-state free precession still frames, showing focal aneurysmal areas (arrow) in the right ventricular free wall.

DISCUSION

This is the first study from this region, looking at the clinical presentation, CMR findings, and prognosis of patients with ARVC. The study results would help us understand the clinical presentation of ARVC and its prognosis in our population.

The prevalence of ARVC is one in 2000–5000 individuals.[8] Classically, ARVC presents between the second and fourth decade of life. Syncope, palpitations, and SCD are the common presentations.[9] In our study, the mean age of patients was 33.9 years, and the main clinical presentation was syncope, followed by palpitations. In a study of 100 patients with ARVC, Dalal *et al*. reported an incidence of SCD of 23% in ARVC; other common presentations were palpitations (27%) and syncope (26%).[10]

The most common ECG finding of T wave inversion in precordial leads in our study is also in accordance with the literature which showed that T-wave inversion in the right precordial leads is present in up to 87% of adult patients with RV dominant ARVC and this is directly associated with RV dilatation and may extend to the left precordium with time.[11,12]

Echocardiography is usually the first-line imaging modality used for ARVC evaluation, as is the case in this study. However, echocardiography has its limitations in assessing the RV due to its complex geometry. On echocardiogram, right ventricular dilatation was the characteristic feature of ARVC in this study. In the literature, RV dilatation was found in more than 50% of patients, and it was directly associated with arrhythmic events.[13]

CMR has now emerged as the imaging modality of choice in ARVC. CMR allows not only the morphological and functional evaluation but also the tissue characterization of the myocardium. RV abnormalities in ARVC have been extensively described in the literature.[14]

One important finding of our study is the LV involvement in more than 52.9% of patients on CMR. LV involvement has been reported in ARVC subjects, with the majority having the advanced disease. Recent studies have shown that potential LV involvement may develop ahead of significant RV dysfunction in patients with ARVC, although RV dysfunction presents earlier because of its thin and distensible features, which allow it to be primarily affected.[15]

One reason for LV involvement in more than half of the patients could be the late presentation and delayed diagnosis due to less awareness and suboptimal medical facilities in this part of the world. This further signifies the importance of this study.

High mortality (21.4%) during follow-up in this study could be due to advanced disease at the time of presentation or due to less medical facilities available in the region. In a study from New Zealand, 30 patients with ARVC were followed for a mean follow-up of 7.4 years, and only two (6.6%) patients died during follow-up.[16]

Only four (28.6%) patients underwent ICD implantation for secondary prevention in our study while 26 patients underwent ICD implantation in the New Zealand study.[16] ICD implantation is an expensive but lifesaving treatment for secondary prevention and awareness about this treatment option needs to be increased among patients and cardiologists.

The findings of this study would have implications on clinical decision making and would help improve the outcomes of patients with ARVC in this region.

Limitations

This is a retrospective, single-center study conducted at a tertiary care hospital. The sample size is small, and follow-up is available in 14 out of 17 patients.

CONCLUSION

Arrhythmia related events are the main presenting symptoms of ARVC in this region. CMR is the best non-invasive imaging modality for ARVC, and left ventricular involvement in ARVC is not rare in this population. The mortality is relatively high probably due to advanced disease at the time of presentation and less medical facilities available in this region.

Declaration of patient consent

Institutional Review Board (IRB) permission obtained for the study.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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