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Original Article

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Clinical and Genetic Characteristics of Arrhythmogenic Right Ventricular Cardiomyopathy Patients: A Single-Center Experience

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Abstract

Background: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited progressive cardiomyopathy. We aimed to define the long-term clinical outcome and genetic characteristics of patients and family members with positive genetic tests for ARVC in a single tertiary care cardiac center in Saudi Arabia.

Methods: We enrolled 46 subjects in the study, including 23 index-patients (probands) with ARVC based on the revised 2010 ARVC Task Force Criteria (TFC) and 23 family members who underwent a genetic test for the ARVC between 2016 and 2020.

Results: Of the probands, 17 (73.9%) were males with a mean age at presentation of 24.95 ± 13.9 years (7 to 55 years). Predominant symptoms were palpitations in 14 patients (60.9%), and syncope in 10 patients (43.47%). Sustained ventricular tachycardia (VT) was documented in 12 patients (52.2%). The mean left ventricular ejection fraction (LVEF) by echocardiogram was 52.81±6.311% (30-55%), and the mean right ventricular ejection fraction (RVEF) by cardiac MRI was 41.3±11.37% (23-64%). Implantable cardioverter-defibrillator (ICD) implantation was performed in 17 patients (73.9%), and over a mean follow-up of 13.65 ± 6.83 years, appropriate ICD therapy was noted in 12 patients (52.2%). Genetic variants were identified in 33 subjects (71.7%), 16 patients and 17 family members, with the most common variant of plakophilin 2 (PKP2) in 27 subjects (81.8%).

Conclusions: ARVC occurs during early adulthood in Saudi patients. It is associated with a significant arrhythmia burden in these patients. The *PKP2* gene is the most common gene defect in Saudi patients, consistent with what is observed in other nations. We reported in this study two novel variants in *PKP2* and desmocollin 2 (DSC2) genes. Genetic counseling is needed to include all first-degree family members for early diagnosis and management of the disease in our country.

Keywords: Arrhythmogenic right ventricular cardiomyopathy; Genetics; PKP2 variant; Heart failure

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Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC), also known as arrhythmogenic right ventricular dysplasia (ARVD), is an inherited cardiomyopathy [1].

ARVC primarily affects the right ventricle (RV) with akinetic or dyskinetic areas involving the free wall of the ventricle, fibrofatty replacement of the myocardium, and accompanying ventricular arrhythmias (VAs), which commonly originate in the RV. However, ARVC has been described as an isolated left ventricular (LV) disease [2].

The typical age of presentation is between the second and the fourth decade of life. ARVC is characterized by VAs ranging from premature ventricular complexes (PVCs) to ventricular tachycardia (VT), typically of RV origin, and may result in RV failure and progress to congestive heart failure at a later stage. ARVC is a recognized cause of sudden cardiac death (SCD) in young individuals [3].

ARVC variants in at least 13 genes are seen in 30-60% of patients [4]. Most of these genes are involved in the function of desmosomes, which are specialized adhesive junction that interacts with the cytoskeleton and participates in cross-talk with gap and adherens junctions. Desmosomes consist of a symmetrical protein complex with each end residing in the cytoplasm of one of a pair of adjacent cells, anchoring intermediate filaments in the cytoskeleton to the cell [5]. A large majority of variants in ARVC patients have been found in genes encoding different components of the cardiac desmosome, i.e., plakophilin 2 (PKP2), desmocollin 2 (DSC2), desmoglein 2 (DSG2), desmoplakin (DSP), and plakoglobin (JUP), suggesting that ARVC/D is primarily a disease of dis-

turbed desmosomal function. However, variants in other genes (non-desmosomal genes) have also been reported in ARVC, including transmembrane protein 43 (TMEM43), desmin (DES), and titin (TTN), indicating genetic heterogeneity [6, 7]. Several ARVC cases were found to be caused by multiple variants in the same gene (compound heterozygosity) or variants in different genes (digenic inheritance), which could result in an earlier onset and increased disease severity [6]. ARVC is inherited predominantly as an autosomal dominant in its classical form and as autosomal recessive in non-classical form with cardiocutaneous disease such as Naxos disease, which is associated with palmoplantar keratoderma and woolly hair [8] and Carvajal syndrome [9]. We previously described the clinical characteristic of ARVC in Saudi Arabia [10]. However, genetic testing was only performed in 60% of patients in the previous study. In the current study, we include only patients with genetic testing and their family members with available genetic testing results. We will concentrate on the genetics of these patients. Furthermore, the duration of follow-up is longer in the current study. Only 10 patients were included in this study from the previous cohort.

This study aimed to define the long-term clinical outcome and genetic characteristics in a cohort of Saudi patients and family members for ARVC in a single tertiary care cardiac center in Saudi Arabia.

Materials and Methods

Study population

The study population comprised 23 index-patients (probands) fulfilling the 2010 ARVC Task Force Criteria (TFC) [11] for definite diagnosis and 23 family members with available data of genetic testing for ARVC enrolled in the ARVC registry at King Faisal Specialist Hospital & Research Centre, Riyadh. The study has been approved by the Research Ethics Committee (REC) at King Faisal Specialist Hospital & Research Center (KFSH&RC), Riyadh. The study was conducted in compliance with the ethical standards of the responsible institution on human subjects, as well as with the Helsinki Declaration.

Clinical analysis

A retrospective analysis of clinical and genetic data of ARVC patients and family members, including each individual's demographic data and medical history was conducted. These data were obtained by reviewing medical records, electronic clinical evaluations, and device clinic charts. Genetic counselors with a special interest in ARVC obtained a detailed family history for pedigree analysis through patient interviews.

Molecular genetic analysis

All index-patients underwent genetic testing of PKP2, DSP, DSG2, DSC2, and JUP with direct sequencing of the entire coding regions or the next generation multi-gene panel. First-degree family members were screened for the variant found in their respective index patients, if any.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation (SD), and categorical variables were reported as frequency (%). SPSS statistical software (version 20; SPSS Inc., Chicago, IL) was used for the analyses.

Results

Presenting clinical characteristics, clinical course, and long-term outcome

Table 1 summarizes the major presenting clinical features of the 23 probands. Our patient cohort consists of 23 probands, 17 were males (73.9 %), with a mean age at the diagnosis of 24.95 ± 13.9 years (ranging from 7 to 55 years). The clinical presentation was palpitations in 14 patients (60.9%), dizziness in four patients (17.4 %), shortness of breath in six patients (26.1%), and syncope in 10 patients (43.5%). Sustained VT was seen in 12 patients (52.2%), and three were survivors of sudden cardiac arrest (13%). Family history of ARVC was present in four patients (17.4%), and a family history of SCD was present in six patients (26.1%). A history of consanguinity was present in six patients (26.1%).

The electrocardiogram (ECG) depolarization changes meeting major diagnostic criteria were found in nine patients (39%), and ECG repolarization changes meeting major diagnostic criteria were found in 17 patients (73.9%).

Echocardiogram changes meeting major diagnostic criteria were found in nine patients (39%), and cardiac magnetic resonance imaging (MRI) was performed in 11 patients (47.8%) and showed changes compatible with major diagnostic criteria in six patients (54.5%). The mean left ventricular ejection fraction (LVEF) by echocardiogram was 52.8±6.3% (30-55%), and the mean right ventricular ejection fraction (RVEF) by cardiac MRI was 41.3±11.37% (23-64%). LV involvement with LVEF of < 40% was present in three patients (13%).

Medical management, antiarrhythmic medications, electrophysiologic studies and ablation procedures are summarized in Table 1.

Seventeen patients (73.9%) underwent implantable cardioverter-defibrillator (ICD) implantation, of whom 13 patients (56.5%) had ICD implanted for secondary prevention of SCD (three patients were survivors of SCD, and 10 patients had sustained VT). Of note, two survivors of SCD also had VT during hospitalization. One patient (4.3%) died from non-cardiac causes during the follow-up. Over a mean follow-up of 13.65 ± 6.83 years, 12 of the 17 patients (70.6%) had received appropriate therapy for sustained VAs.

The 23 family members consisted of 11 males (47.8%) with a mean age of 34.4 ± 13 years (23 - 50 years) with a history of palpitations in five patients (31.25%). There was no

Table 1. Clinical Characteristics of the Probands

Characteristics	No. or value (%)
Age	24.95 ± 13.9 years (7 to 55 years)
Gender	17 males (73.91%)
Clinical presentation	
Palpitations	14 (60.9%%)
Shortness of breath	6 (26.1%)
Dizziness	4 (17.4%)
Syncope	10 (43.5%)
VT	12 (52.2%)
SCD	3 (13%)
Family history of SCD	6 (26.1%)
Family history of ARVC	4 (17.4%)
Diagnostic workup	
ECG	
Epsilon wave	9 (39%)
T-wave inversion in V1-3 or beyond	17 (73.9%)
Echocardiogram meeting major diagnostic criteria	9 (39%)
LVEF	52.8±6.3% (30-55%)
Cardiac MRI meeting major diagnostic criteria	6/11 (54.5%)
RVEF	41.3±11.4% (23-64%)
Medications	
Beta-blockers	12 (52.2%)
ACEIs/ARBs	10 (43.5%)
MRC	1 (4.5%)
Sotalol	8 (34.8%)
Flecainide	2 (9.1%)
Amiodarone	7 (30.4%)
ICD therapy	17 (73.9%)
EPS procedures	
PVCs ablation	3 (13%)
VT ablation	7 (30.4%)
SVT ablation	4 (17.4%)
Follow-up	13.22 ± 6.83 years (2 - 25 years)
VT/VF on follow-up	12/17 (70.6%)
Mortality	1 (4.3%) non-cardiac cause

ACEIs/ARBs: angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers; ARVC: arrhythmogenic right ventricular cardiomyopathy; ECG: electrocardiogram; EPS: electrophysiology study; ICD: implantable cardioverter-defibrillator; LVEF: left ventricular ejection fraction; MRC: mineralocorticoid receptor antagonist; MRI: magnetic resonance imaging; PVCs: premature ventricular complexes; RVEF: right ventricular ejection fraction; SCD: sudden cardiac death; SVT: supraventricular tachycardia; VF: ventricular fibrillation; VT: ventricular tachycardia.

definite case of ARVC in these subjects.

Genetic testing result

Genetic testing was performed on all patients and available first-degree family members. Out of 113 eligible first-degree family members for ARVC screening, only 23 subjects (20%) underwent workup, including genetic testing, despite having genetic counselors and providing screening of family members for free.

Variants were identified in 71.7% of all study subjects (33 subjects, including 16 patients and 17 family members). The most common variants detected were in PKP2 in 81.8%

of all positive results (27 subjects, including 13 patients and 14 family members), followed by DSP in 9% (three subjects, including two patients and one family member) and DSC2 in 9% (three subjects, including one patient and two family members) (Table 2) [12-26].

The discovered genetic variants in our study were deemed pathogenic in seven probands, likely pathogenic in four, and of uncertain significance in three and novel (it has not been reported in the literature before) in two (Table 2).

None of our family members with positive genetic testing have had a definitive ARVC diagnosis.

Discussion

In this study, we observed ARVC occurrence in a young age with male predominance. ARVC affects males more than females. About two-thirds of our patients were males. Male gender predominance in ARVC with male to female ratio of 3:1 has been reported previously [27, 28].

ARVC generally affects young patients with a mean age of 30 years, whereas it rarely manifests before the age of 12 or after the age of 60 years [6, 28-31]. However, a higher mean age in the late 30s to 40s years has been noted in another study [32].

Most of our patients presented with palpitations, and VT was a common presenting event. Previous studies have shown that individuals with ARVC present with palpitations (67%), syncope (32%), atypical chest pain (27%), or RV failure (6%). However, some patients are asymptomatic (6%) [32].

ARCV is a leading cause of SCD, accounting for 11-22% of cases of SCD in the young athlete patient population [33, 34]. Thirteen percent of our patients were survivors of cardiac arrest.

Regarding diagnostic workup, all our patients were diagnosed based on non-invasive tests, including ECG, echocardiogram, cardiac MRI, and family history.

ECG is an essential diagnostic test for the ARVC diagnosis. The presence of epsilon waves (described as post-excitation potentials of small amplitude that occur at the end of the QRS complex) in V1-3 is a major ARVC diagnostic criterion noted in about 30% of ARVC cases [35].

ECG repolarization abnormities with T wave inversion in V1-3 or beyond in individuals > 14 years of age in the absence of complete right bundle-branch block is another major ARVC diagnostic criterion seen in 55% to 94% in different ARVC series [35-37]. ECG repolarization was also frequent in our patients.

The echocardiogram is a beneficial, non-invasive diagnostic test to assess structural changes in ARVC [38-40]. Echocardiogram changes meeting major diagnostic criteria present in 39% of our patients.

Cardiac MRI has the advantage of assessing the RV (and LV) function, size, global or regional wall motion abnormalities, and quantifying of myocardial wall thinning and hypertrophy [41, 42]. Cardiac MRI was performed in about half of our patients, showing changes compatible with major diagnostic criteria in about half of them.

Table 2. Probands and Family Members With Positive Genetic Testing

Proband	Family members with positive gene	Consanguinity	Gene	Transcript	Variant	Zygosity	ClinVar Classification	Reference
1	5	No	*PKP2*	NM_004572.4	c.2274delG p.Asn759Ilefs*41	Hetero	Likely pathogenic	[14]
2	2	Yes	*PKP2*	NM_004572.4	c.2274delG p.Asn759Ilefs*41	Hetero	Likely pathogenic	[14]
3	1	No	*PKP2*	NM_004572.4	c.2274delG p.Asn759Ilefs*41	Hetero	Likely pathogenic	[14]
4	-	No	*PKP2*	NM_004572.4	c.2274delG p.Asn759Ilefs*41	Hetero	Likely pathogenic	[14]
5		No	*PKP2*	NM_004572.4	c.663C>A p.Tyr 221* Stop codon	Hetero	Pathogenic	[15, 16]
6		Yes	*PKP2*	NM_004572.4	c.663C>A p.Tyr 221* Stop codon	Hetero	Pathogenic	[7, 16-18]
7		Yes	*PKP2*	NM_004572.4	c.663C>A p.Tyr 221* Stop codon	Hetero	Pathogenic	[6, 16-18]
8		Yes	*PKP2*	NM_004572.4	c.663C>A p.Tyr 221* Stop codon	Hetero	Pathogenic	[7, 16-18]
9		Yes	*PKP2*	NM_004572.4	c.663C>A p.Tyr 221* Stop codon	Hetero	Pathogenic	[7, 16-18]
10	-		*PKP2*	NM_004572.4	c.148_151delACAG, p. T50SfsTer61	Hetero	Pathogenic	[12, 13, 19, 20]
11	5	Yes	*PKP2*	NM_004572.4	c.148_151delACAG, p. T50SfsTer61	Hetero	Pathogenic	[12, 13, 19, 20]
12	1	No	*PKP2*	NM_004572.4	c. 277G>T p.Val93Phe	Hetero	Uncertain significance	[21, 22]
13	-	Yes	*PKP2*	NM_004572.4	c.1837A>T Asn 613 Tyr	Hetero	Not reported	This study
14	2	No	*DSC2*	NM_024422.6	c.589T>C p.Cys 197 Arg	Hetero	Not reported	This study
15	1	No	*DSP*	NM_004415.4	c. 1067C>T p.Thr356Met	Hetero	Uncertain significance	[23, 24]
16		Yes	*DSP*	NC_000006.12	c.273+5G>A	Hetero	Uncertain significance	[25, 26]

Biventricular involvement with LV fibrofatty replacement and involvement have been found in as much as in 70% of the cases of ARVC [1, 43]. It is usually age-dependent and associated with more severe cardiomegaly, arrhythmogenic events, inflammatory infiltrates, and heart failure [1, 43]. LV involvement with LVEF < 40% was present in 13.6% of our patients. A coronary angiogram or cardiac computed tomography (CT) was used to rule out coronary artery disease in patients with impaired LVEF. Patients with typical dilated cardiomyopathy or other cardiomyopathies changes by cardiac MRI were excluded.

Patients with ARVC have a high burden of arrhythmia. ICD therapy is the most effective preventive measure for SCD [7]. Of our patients, 73.9% underwent ICD implantation. Over half of our patients received appropriate ICD therapy for sustained VAs during follow-up. About one-third of our patients underwent electrophysiology studies and PVCs/VT ablations. Furthermore, 77.3% of the patients were on antiarrhythmic medications. The Heart Rhythm Society (HRS) 2019 expert consensus statement on arrhythmogenic cardiomyopathy (ACM) provides a class IIb recommendation for amiodarone and sotalol in individuals with ACM to control arrhythmic symptoms or reduce ICD shocks. In the absence of other antiarrhythmic drugs, flecainide with beta-blockers receives a class IIb recommendation in individuals with ARVC and ICD and preserved LV and RV function to control refractory VAs to other therapies [44].

Genetic evaluation

ARVC has been documented in families since the early 1980s. In 1985, three out of five siblings in one family were diagnosed with ARVC, and it was postulated that ARVC has an autosomal dominant inheritance with an incomplete penetrance pattern [45]. We have a low rate of first-degree family members screening. Genetic discrimination, i.e., adverse treatment based solely on the genotype or family history of individuals without disease symptoms or the stigma of having a chronic illness in the family, appears to be responsible for the lack of interest in having ARVC screening in the ARVC family members. Another interesting observation is the absence of clinical ARVC disease in positive family members so far. The clinical picture and natural history of familial ARVC have been reported in 37 ARVC families. Of the 365 subjects enrolled in this study, 151 (41%) were affected, 157 (43%) were unaffected, 17 (5%) were healthy carriers, and 40 (11%) were uncertain [46].

The first ARVC diagnostic criterion published in 1994 included familial disease confirmed at necropsy or surgery as a major criterion [47]. A familial history of premature sudden death (< 35 years of age) due to suspected ARVC or a familial history based on clinically diagnosed disease is included as minor criteria [47]. Furthermore, the 2010 ARVC Task Force included the identification of a pathogenic variant categorized as associated or probably associated with ARVC as a major diagnostic criterion [11].

In 1998, linkage analysis in nine families with Naxos disease found a single mutant gene mapped to 17q21 (homozygous genotype) [48]. Two years later, a homozygous deletion variant in JUP was identified in 19 patients with Naxos disease [8].

Subsequently, other desmosome genes were identified as a cause of ARVC. DSP was confirmed as a causative gene in 2002 [49], PKP2 in 2004 [12], and DSG2 and DSC2 variants were reported in 2006 [13, 50].

ARVC may occur due to non-desmosome genes, including transforming growth factor-β3 (TGFB3) [51], the cardiac ryanodine receptor RYR2 [52], TTN [53], TMEM43 [54], and DES [55]. Additional ARVC genes are identified using candidate gene sequence approaches instead of linkage analysis [56].

The *PKP2* gene is responsible for about 70% of all ARVC variants in previous studies [7, 12]. We have similar *PKP2* gene predominance in Saudi patients.

Strengths and limitations of this study

To our knowledge, this is the first study describing long-term follow-up with a concentration on the genetics of ARVC in Saudi Arabia. The main limitation of this study is the small number of subjects, but ARVC is a rare disease. The other limitation is the retrospective nature of the study. It is also a single-center study; however, we are a tertiary care hospital with referrals from the kingdom.

Conclusions

ARVC occurs during early adulthood in Saudi patients. It is associated with a significant arrhythmia burden. ARVC is familial and genetic testing is essential in all cases. The *PKP2* gene is the most common gene defect in Saudi patients, consistent with what is observed in other nations. We reported in this study two novel variants in *PKP2* and *DSC2* genes. Genetic counseling is needed to include all first-degree family members for early diagnosis and management of the disease in our country.

Acknowledgments

None to declare.

Financial Disclosure

None to declare.

Conflict of Interest

The authors declared no conflict of interest for all authors.

Informed Consent

Consent was waived by REC as the study is retrospective.

Author Contributions

Bandar Saeed Al-Ghamdi: conception or design of the work, drafting of the manuscript, and final approval of the version to be published; Faten Alhadeq, Aisha Alqahtani, and Monther Rababh: data collection; Nadiah Alruwaili: data collection, data analysis, and interpretation; Sara Alghamdi: data analysis and interpretation; Waleed Almanea: final approval of the version to be published; Zuhair Alhassnan: conception or design of the work, critical revision of the article, and final approval of the version to be published.

Data Availability

The authors declare that data supporting the findings of this study are available within the article.

Abbreviations

ARVC: arrhythmogenic right ventricular cardiomyopathy; ARVD: arrhythmogenic right ventricular dysplasia; DES: desmin; DSC2: desmocollin 2; DSG2: desmoglein 2; DSP: desmoplakin; EF: ejection fraction; ICD: implantable cardioverter-defibrillator; JUP: plakoglobin; LV: left ventricle/ventricular; MRI: magnetic resonance imaging; PKP2: plakophilin 2; PVCs: premature ventricular complexes; RV: right ventricle; SCD: sudden cardiac death; TTN: titin; TMEM43: transmembrane protein 43; VAs: ventricular arrhythmias; VT: ventricular tachycardia

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