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ORIGINAL ARTICLE

Arrhythmogenic Right Ventricular Cardiomyopathy: A Review of Living and Deceased Probands

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Background Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a potentially life-threatening genetic cardiomyopathy with a spectrum of clinical presentations including sudden cardiac death (SCD).

Methods Clinical and genetic data of 44 probands referred to a cardiac genetics clinic (2007–2017) who met 2010 Task Force Criteria (TFC) for ARVC diagnosis were included.

Results Thirty-three (33) (75%) male, 20 (45%) were referred by the Victorian Institute of Forensic Medicine. Presentation that lead to diagnosis included ARVC-related SCD (n = 19), SCD due to alternate cause of death (n = 1), aborted cardiac arrest (n = 6), stable symptomatic ventricular tachycardia (n = 14), palpitations (n = 3) and presyncope (n = 1). Left ventricular involvement (50%) was more common in the SCD subgroup (84% vs 21%, $p < 0.001$). Genetic testing (n = 39) revealed a pathogenic mutation in 16 (commonest: plakophillin-2 (n = 9)), a variant of uncertain significance (VUS) in 15, with no abnormality in eight. In the SCD subgroup, median age at death was 44.7 years and 74% were male. Genetic testing (n = 16) in this subgroup revealed a pathogenic mutation in six patients (commonest: desmoplakin (n = 4)). Comparison of the two commonest mutations (PKP2 and desmoplakin [DSP]) showed DSP mutation was more frequently associated with SCD ($p < 0.01$) and LV involvement ($p < 0.001$). Screening of 117 relatives has lead to ARVC diagnosis in 29 patients.

Conclusions Arrhythmogenic right ventricular cardiomyopathy has a heterogeneous and often severe clinical presentation. Sudden cardiac death and aborted cardiac arrest (ACA) are common, demonstrating electrical abnormalities appear early in the ARVC phenotype. Left ventricular involvement was common and may reflect a worse prognosis. Genetic testing is essential in family screening and may be helpful in risk assessment. Desmoplakin mutation is associated with LV involvement and may be indicative of worse prognosis and increased risk of SCD. Genetic screening of proband family members in a specialised multidisciplinary clinic is essential in early diagnosis of affected family members.

Keywords Arrhythmogenic right ventricular cardiomyopathy/dysplasia • Arrhythmic cardiomyopathy • Genetics • Sudden cardiac death (SCD)

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Introduction

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a genetic cardiomyopathy which can be difficult to diagnose due to its variable clinical presentations. The incidence of ARVC, also called arrhythmic cardiomyopathy (AC), is reported to be between 1:1,000 to 1:5,000 [1]. The 2010 ARVC Task Force Criteria (TFC) updated the original 1994 diagnostic criteria of McKenna et al. [2,3]. It encompassed both phenotypic and genetic characteristics but while 2010 TFC standardised many diagnostic features of ARVC, the diagnosis of ARVC in the early, subclinical phase still remains difficult. Life-threatening index clinical presentations are common in ARVC, with over 60% of index presentations due to ventricular arrhythmia (VA), aborted cardiac arrest (ACA) or sudden cardiac death (SCD) [4,5]. Nearly one quarter of ARVC diagnoses occur as a result of family screening, symptoms such as palpitations or presyncope and investigations documenting ventricular ectopics or nonsustained ventricular tachycardia (VT) [6]. Early diagnosis of ARVC is important because of its association with SCD [4,7].

Originally described as a developmental disorder/abnormality of the right ventricle (RV) [7], ARVC is now understood to be predominantly a cardiac desmosomal disease [8]. Desmosomes are protein structures that link adjacent cells and are an important part of intercalated disc proteins. They play a crucial role in myocardial electrical conductivity and structural stability as well as cell adhesion and regulation and calcium homeostasis [8,9]. Macroscopically, the characteristic histological finding is of fatty or fibrofatty infiltration in the ventricle. Classically, the condition was first thought to affect only the RV, however left-ventricular (LV) involvement is now well recognised in up to 76% of hearts examined at autopsy [1]. Histological patterns of the disease show two main types; a fibrolipomatous pattern with evidence of wall thinning, inflammation and fibrofatty replacement and a lipomatous pattern with preserved wall thickness and exclusive fatty replacement [4,10].

Inheritance is mostly autosomal dominant with variable penetrance and expressivity although recessive patterns also exist [1]. Environment and gender are further contributors to phenotype, with apparent disease modulation as affected individuals show a male preponderance (70%) [11] and family history is only confirmed in about 30% [12]. To date, the strongest evidence for an environmental influence is for exercise, with SCD in this condition being seen more in athletes [13]. In the largest autopsy series of SCD in athletes reported so far (n = 357), the incidence of ARVC was 13% [14]. It is also recognised that continued athletic activity in gene positive ARVC carriers augments clinical expression of the disease and recommendation against strenuous sporting activity is important for this group, even in genotype positive and phenotype negative family members [14,15]. Previous myocarditis has also been implicated in the aetiology of ARVC [16].

Genetic testing has demonstrated a number of mutations in disease-related genes, mostly in desmosomal genes coding for intercalated disc proteins, identified in over 50% of ARVC probands [1,15,17]. In recent years, uncommon non-desmosomal genes have also been described [1,5]. The phenotype is variable, and in combination with incomplete penetrance, adds to the challenge in diagnosis.

This paper discusses the clinical presentation and outcomes of investigations and genetic testing in 44 ARVC probands seen in the Cardiac Genetic Clinic (CGC) at the Royal Melbourne Hospital.

Methods

Study Population

All proband patients referred to the CGC between 2007 and 2017 who satisfied either the revised Task Force Criteria (TFC) for ARVC or had diagnostic pathological features of ARVC at postmortem (PM) were included in this study population. Data presented describes demographic variables (age and gender), clinical presentation, cardiac investigations including electrocardiograms (ECG), transthoracic echocardiograms (TTE) and cardiac magnetic-resonance imaging (CMR) findings and molecular genetic testing results. In the cases of deceased patients, postmortem findings are described.

Mode of clinical presentation was categorised into the following: SCD, ACA, syncope, stable symptomatic VT, palpitations or presyncope. Aborted cardiac arrest was defined as successful resuscitation from cardiac arrest. Stable symptomatic VT was diagnosed in patients that presented with documented VT but did not require cardiopulmonary resuscitation (CPR). The need for CPR converted the presentation into an ACA. Statistical analysis of categorical variables was performed using Chi Square testing with a p value <0.05 considered statistically significant.

Results

There were 44 individuals who met the TFC for ARVC diagnosis and were the first relative (proband) within their family to receive this clinical diagnosis. Thirty-four (34) of 44 probands consented to family screening. One hundred and seventeen (117) relatives were screened, with 29 subsequently diagnosed with ARVC within 16 proband families (47%).

Demographics and Mode of Presentation

The cohort consisted of 33 males and 11 females. More than half of the cohort first presented with either ARVC-related SCD (n = 19, 43%) or ACA (n = 6, 14%). Other presentations were stable symptomatic VT (n = 14, 32%), palpitations (n = 3, 7%) or presyncope (n = 1, 2%). One proband presented with SCD in context of concomitant illicit drug use and incidental ARVC diagnosis on postmortem (Table 1).

Phenotype Analysis of Probands

Available cardiac investigation results in the proband cohort are shown in Table 2. Electrocardiograph criteria were met in

Table 1 Baseline Demographics and Clinical Presentation.

Variable	N (%)
Male	33 (75%)
Mode of presentation	
- ARVC-related SCD	19 (43%)
- Other SCD[a]	1 (2%)
- ACA	6 (14%)
- Stable Symptomatic VT	14 (32%)
- Palpitations	3 (7%)
- Presyncope	1 (2%)

Abbreviations: SCD, sudden cardiac death; ACA, aborted cardiac arrest; VT, ventricular tachycardia; ARVC, arrhythmogenic right ventricular cardiomyopathy.
[a]SCD in context of concomitant illicit drug use with ARVC diagnosis on postmortem.

17 of 25 probands, of which most fulfilled major criteria (n = 14, 82%). Cardiac imaging characteristics were available in 25 probands, including one patient from the SCD group who was imaged antemortem (echocardiography demonstrating mild RV dilatation with preserved function). Imaging was with either CMR (n = 1), transthoracic echocardiography (TTE) (n = 9) or both (n = 15). Imaging criteria were fulfilled by 22 probands (88%). Criteria were met in 10 probands on both TTE and CMR, in seven on TTE alone and in five on CMR alone (Figure 1 in Supplementary Material). All 19 probands without cardiac imaging were in the SCD group.

Cardiac structural abnormalities were assessed in all 44 probands (PM alone = 19, imaging alone = 24, PM and imaging = 1) and LV involvement was confirmed in 22 (50%). It was significantly more common in the SCD subgroup compared to living probands (84% vs 21%, $p < 0.001$). Imaging revealed LV involvement on TTE alone (n = 2), CMR alone (n = 1) and both TTE and CMR (n = 2).

Genotype Analysis

Genetic analysis was undertaken in 39 (89%) probands (Table 3) with five patients not tested (see below). In 16 probands a known ARVC pathogenic mutation was identified, most often in plakophillin-2 (PKP2) (n = 9, 56% of positive mutations). A desmoplakin (DSP) mutation was observed in five subjects and a desmocollin-2 (DSC2) was seen in one subject. An incidental pathogenic mutation was found in one proband who was a carrier for LAMP2 (lysosomal associated membrane protein-2) mutation (Danon disease). A variant of uncertain significance (VUS) was identified in 15 probands and no mutation or variants were seen in the remaining eight. Left ventricular involvement did not differ according to mutation status (pathogenic mutation with LV involvement n = 8, 50%, no pathogenic mutation with LV involvement n = 11, 48%, p = 0.89). Three of the five

Table 2 Cardiac investigations and numbers satisfying modified TFC criteria.

Variable	N (%)
ECG	
- Total	25
◦ Major Criteria	14 (56%)
■ TWI V1-V3 (no BBB)	
◦ Minor criteria	1 (4%)
■ TWI V1-V3 with RBBB	2 (8%)
■ TWI V1/2 or V4/5/6	
Imaging	
- Total	25
◦ TTE only	9
◦ CMR only	1
◦ Both TTE and CMR	15
- Global or regional dysfunction and structural alterations on any imaging modality	22/25 (88%)
- No cardiac imaging	19
Left ventricular involvement	
- Total	22
◦ TTE alone	2
◦ CMR alone	1
◦ PM alone	16
◦ TTE and CMR	2
◦ TTE and PM	1

Abbreviations: TWI, T wave inversion; BBB, bundle branch block; RBBB, right bundle branch block; TTE, transthoracic echocardiogram; CMR, cardiac magnetic-resonance imaging; PM, postmortem; TFC Task Force Criteria; ECG, electrocardiograph.

Table 3 Genetic analysis – outcomes.

Variable	N (%)
Genetic testing performed	39
Pathogenic or likely pathogenic mutation found	
- Total	16 (41%)
◦ PKP2	9 (23%)
◦ DSP	5 (13%)
◦ DSC2	1 (3%)
◦ Other	1 (3%)
LV involvement and pathogenic or likely pathogenic mutation	
- Total	8
◦ DSP	5
◦ PKP2	1
◦ DSC2	1
◦ Other	1
Variant of uncertain significance (VUS)	15
● LV involvement and VUS	10

Abbreviations: PKP2, plakophillin-2; DSP, desmoplakin; DSC2, desmocollin-2; LV, left ventricle.

untested also had LV involvement. Comparison of the two commonest mutations (PKP2 and DSP) showed DSP mutation was associated with LV involvement ($p < 0.001$). In the five probands where genetic testing was not undertaken, the reasons were lack of family consent to test the deceased individual (n = 4) or other cause of death identified (n = 1).

Sudden Cardiac Death

The ARVC-related SCD probands (Table 4) had a median age at death of 44.7 (24.1 - 50.6) years. Of these 19 patients, 14 were male (74%). Genetic testing (n = 16) identified a pathogenic mutation in six (38%). The commonest mutation seen was DSP (n = 4) with a single case each of PKP2 and LAMP2 mutations. In comparison to eight PKP2-positive living probands, only one PKP2 mutation was seen in the SCD cohort. Comparison of the two commonest mutations (PKP2 and DSP) showed DSP mutation was more frequently associated with SCD ($p < 0.01$). A VUS was identified in eight (50%) and no abnormality identified in the remaining two patients. As previously stated, LV involvement at postmortem was seen in 84%, greater than the incidence on imaging in live probands (21%).

Postmortem Findings

Postmortem findings (Table S1 in Supplementary Appendix) demonstrated isolated fibrofatty RV involvement in three patients, isolated LV fibrofatty involvement in three patients with biventricular fibrofatty or fibrotic involvement in the remaining 14 patients. Of those with histological changes involving the LV, four had changes confined to the subepicardial region, three showed mid-wall fibrosis/fibrofatty change and 10 demonstrated both. There was no pattern to the region of LV involvement with more than one region (anterior, posterior, lateral, septal) involved in 14 patients (Figures 1 and 2).

Table 4 ARVC-related SCD cohort analysis.

SCD cohort	N (%) or median (IQR)
Total	19
Age at SCD (median)	44.7 (24.1-50.6)
Male and SCD	14 (74%)
SCD and genetic testing	
- Genetic testing completed	16
- Pathogenic or likely pathogenic mutation found	6
○ PKP2	1
○ DSP	4
○ DSC2	0
○ Other	1
- Variant of uncertain significance	8
- LV involvement on PM	16

Abbreviations: SCD, Sudden cardiac death; PKP2, plakophillin-2; DSP, desmoplakin; DSC2, desmocollin-2; LV, left ventricle; PM, postmortem.

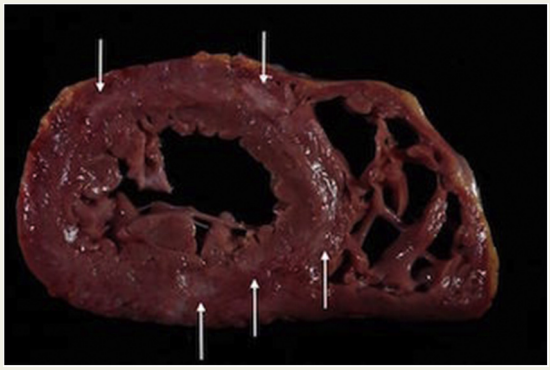

Figure 1 Macroscopic specimens of a deceased proband with arrhythmogenic right ventricular cardiomyopathy. Macroscopic figure demonstrates scattered subepicardial and mid-wall fibrosis within the left ventricle (white arrows).

Symptoms Preceding SCD

Eight (8) out of 20 who died suddenly had cardiac symptoms during life (Table 5). Four (4) of those eight subjects had sought medical attention with one having a very high ectopic count on Holter monitoring and all four having an abnormal resting ECG.

Discussion

This study describes the experience of 44 proband ARVC patients referred to the Royal Melbourne Hospital CGC, detailing clinical presentation and diagnostic features including the outcome of genetic testing. The study again highlights

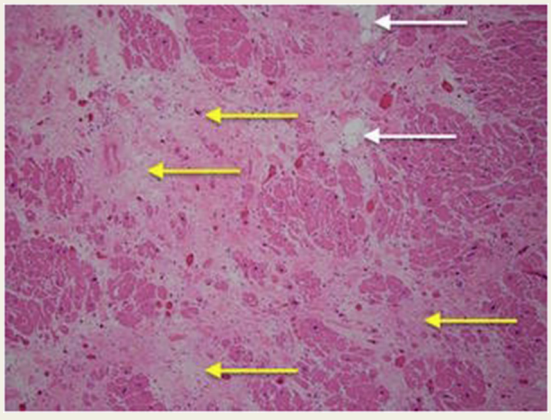

Figure 2 Microscopic specimens of a deceased proband with arrhythmogenic right ventricular cardiomyopathy. Microscopic figure demonstrates fibrosis (yellow arrows) and fatty infiltration (white arrows).

Table 5 Symptoms preceding SCD

Patient	Age at Death (yrs)	Sex	Symptoms before SCD	Action and PM findings	Gene test
1	49	Male	Syncope one year before SCD.	Did not seek medical attention. PM: 60% LAD stenosis, left dominant ARVC.	VUS
2	32	Male	Palpitations and chest pain two months before SCD.	Seen in ED of a major hospital. ECG showing T wave changes in RV leads and VEs. No follow-up undertaken. PM: Biventricular involvement.	DSP mutation
3	49	Male	Frequent palpitations.	Seen by a cardiologist. Holter monitor showed 3,267 VEs in 24 hours. Died before attending booked TTE appointment. PM: Biventricular involvement.	Negative
4	37	Female	Syncopal episode requiring resuscitation by husband several years before death.	Seen at a medical centre overseas. ECG showed, LAH, RBBB, sinus tachycardia and atrial ectopics. No follow-up undertaken. PM: Biventricular involvement.	Negative
5	57	Male	Syncopal episode 2 years ago. Dyspnoea on exertion for 1 week before SCD.	Did not seek medical attention. PM: RV fat and fibrosis, Myocyte necrosis. Concentric LVH.	Negative
6	44	Male	Chest pain and SOB for two weeks before SCD during sexual intercourse.	Seen by a cardiologist. TTE: Study performed in bigeminy with global LV dysfunction, RV dilatation with preserved function. ECG showed incomplete RBBB. PM: Biventricular involvement.	VUS
7	20	Male	Syncopal episode playing indoor soccer. Continued playing and suffered SCD.	No time to seek medical attention. PM: Biventricular involvement, fat and fibrosis.	MEM43 variant
8	65	Female	Syncopal episode in context of concomitant illicit drug use.	Did not seek medical attention. PM: dilated RV with extensive fatty Infiltration.	Untested

Abbreviations: SCD, sudden cardiac death; PM, postmortem; LAD, left anterior descending; VUS, variant of uncertain significance; RV, right ventricle; VE, ventricular ectopics; DSP, desmoplakin; TTE, transthoracic echocardiogram; LAH, left atrial hypertrophy; RBBB, right bundle branch block; LVH, left ventricular hypertrophy; ED, emergency department; RV, right ventricular; ECG, electrocardiograph.

the life-threatening nature of this genetic condition and a propensity for the diagnosis to be made after a SCD or life-threatening presentation in a significant number of affected subjects. This analysis demonstrates the complexity of this heterogeneous cohort with regards to genotype and phenotype, the difficulty in diagnosis and risk stratification and highlights the value of family screening.

In contrast to other publications, a greater proportion of this proband cohort had an index presentation of SCD. This reflects a referral bias in our series, which has a structured referral pathway from the Victorian Institute of Forensic Medicine (VIFM) ensuring at-risk families receive appropriate clinical assessment [18]. By way of illustration, SCD affected nearly half of the probands in this cohort, but only 5% of probands within a larger published cohort [5]. The incidence of ARVC is about 5% in an autopsy series of SCD [19]. In a large Australian and New Zealand prospective study of 490 SCD cases among children and young adults between the ages of 1 to 35 years, ARVC was the cause of death in 25 (5.1%) [20]. Genetic analysis showed pathogenic or probable pathogenic mutation in seven (DSP in four, PKP2 in two, DES in one). Interestingly, five of the seven showed no pathological changes in the heart at postmortem, supporting the concept that SCD in ARVC can occur during a concealed phase [21].

In other reports that include PM data, a higher incidence of SCD as the first presentation has also been noted (31 to 50% of cases) [22,23]. Out of 59 ARVC cases in The European Cardiomyopathy Registry, 35.7% families had a history of SCD, much higher than other cardiomyopathies [24].

Preventing SCD in ARVC patients requires implantable cardioverter defibrillator (ICD) implantation in appropriate patients and family screening of all probands. The cohort of Groeneweg et al. had ICDs implanted in nearly 80% (351 of 439 patients) of probands after diagnosis and 77% of those with an ICD suffered a sustained VA during follow-up (median 7 years) [5]. Another study observed 30 consecutive New Zealand patients diagnosed with ARVC over 7 years follow-up [25], with 26 having ICD insertion. This experience demonstrated appropriate ICD therapy in 50% of patients and no deaths. Implantable cardioverter defibrillator insertion for those who experience an ACA or ventricular arrhythmia is essential in order to alter the natural history of this disorder.

Eight (8) out of 20 who died suddenly had symptoms, ECG changes or Holter evidence of increased ventricular ectopics during life, of whom four had sought medical attention. It is not always appreciated that, in contrast to dilated cardiomyopathy, ARVC generally presents with arrhythmia. The peak incidence of ARVC is between the third and the fourth decade although the presentation can be from adolescence to an advanced age [26]. Appropriate, cost-effective investigation for ARVC should include ECG, Holter monitoring and echocardiography in patients presenting with cardiac symptoms that may be suggestive of ARVC.

Previous larger studies have analysed ARVC proband baseline characteristics including the presence of pathogenic mutations and their frequency. Similar male predominance has been described, including a 63% male prevalence in the largest proband study to date (n = 439) [5]. Others have also described a PKP2 gene mutation to be the commonest pathogenic mutation in these patients, with published estimates ranging between 73-78% of larger proband cohorts [5,27,28]. Previous publications have demonstrated a 30% incidence of ARVC in family members [12]. Utilising cascade testing after identification of a pathogenic mutation is helpful in family screening.

Genetic analysis assists in clinical diagnosis and family screening but may also be useful in predicting the natural history and associated risk stratification. This cohort demonstrates that DSP mutation is more frequently associated with SCD when compared to the more common PKP2 mutation ($p < 0.01$). PKP2 mutation has been shown to be associated with an earlier diagnosis and higher VA burden [29] whilst DSC2 mutation may result in a reduced VA burden relative to other genotypes [30]. Desmoplakin mutation is well-recognised to be associated with a left-dominant form of AC [31] and other genotype-phenotype associations include plakoglobin deletion in Naxos disease [32] and autosomal recessive DSP mutation in Carvajal syndrome [33]. Those without a recognised pathogenic mutation are more likely to present later in life, defined as age >50 years [34].

It is notable that LV involvement, which was previously thought to be a late feature in this disease, is now recognised as being sufficient to make the diagnosis [35,36,37]. Imaging had lower sensitivity to PM in identifying LV involvement (LV involvement seen in 19% on CMR, 21% on TTE, 80% at PM). Another explanation could be a link between LV involvement and SCD. This data possibly suggests that LV involvement may be over-represented both in SCD, as recently reported [38], and in genotype positive individuals [39]. Of note in our series, mutations in the PKP2 gene accounted for more than half of the mutations identified, but only one suffered SCD and demonstrated LV involvement on PM. Conversely, all five probands with DSP mutation in this study had SCD (n = 4) or ACA (n = 1) and were engaged in physical activity at time of cardiac event. Left ventricular involvement was demonstrated in all five (four on PM, one on TTE).

Left ventricular involvement is associated with adverse clinical outcomes including increased risk of VA [39,40,41]. This cohort demonstrates an increased proportion of SCD probands with LV involvement at PM but a low incidence of LV involvement on cardiac imaging in living probands. It is unclear at this stage whether specific CMR findings such as late-gadolinium enhancement plays a role in risk stratification of ARVC. Severity of left or right ventricular dysfunction is a recommended consideration in prophylactic ICD insertion [42] although it is not clearly associated with appropriate ICD therapies [43]. Current ARVC guidelines suggest consideration of ICD implantation if amongst other recognised risk factors, extensive LV or RV involvement is present (class IIb recommendation, level C evidence) [44].

Referral to a multidisciplinary genetic service that confirmed the diagnosis of ARVC in these 44 probands also led to family screening of 117 relatives and diagnosis of 29 additional ARVC cases which could otherwise have gone unnoticed. The diagnosis and ongoing cardiology care of these patients, many of whom were entirely asymptomatic, is aimed to improve their outcomes, in particular with advice regarding avoiding excessive exercise [15].

Limitations

This is a selected small population of patients that included a significant number of probands referred following SCD, however it highlights the fact that SCD is frequently the initial presentation in ARVC. The incidence of SCD or the natural history of ARVC should not be inferred from this cohort, as it may not be representative of an unselected population with this condition. Multiplex ligation-dependent probe amplification (MLPA) gene analysis was not performed in this cohort due to technical limitations, it is possible that some of the cases with no mutation identified represent a false-negative genotype [45]. Nonetheless, as a retrospective cohort analysis, it provides a snapshot of an Australian experience of ARVC probands diagnosed through a CGC.

Conclusion

This paper presents a 10-year experience of ARVC probands seen in the Cardiac Genetic Clinic of a major hospital. It highlights that sudden cardiac death is frequently the initial presentation of ARVC. Furthermore, some patients who die suddenly have preceding symptoms and the diagnosis of ARVC may be missed despite an abnormal ECG. Arrhythmias due to frequent ventricular ectopics are an important feature of ARVC in contradistinction to dilated cardiomyopathy. Left ventricular involvement is common and may reflect worse prognosis. Although the yield of genetic testing of ARVC is approximately 50%, it is essential in family screening and may be helpful in risk assessment. Our study shows that DSP mutation is associated with LV involvement and may be indicative of worse prognosis and increased risk of SCD. Family screening of the proband families in a multidisciplinary cardiac genetic service identifies at risk family members and allows intervention for better outcomes.

Disclosures

The authors have no disclosures to declare.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.hlc.2018.07.017.

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