CASE REPORT

Phenotypic variation among siblings with arrhythmogenic right ventricular cardiomyopathy

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SUMMARY

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is primarily a familial disease with autosomal dominant inheritance. Incomplete penetrance and variable expression are common, resulting in broad disease spectrum. Three patterns of phenotypic expression have been described: (1) "classic" subtype, with predominant right ventricle involvement, (2) "left dominant" subtype, with early and dominant left ventricle involvement, and (3) "biventricular" subtype, with both ventricles equally affected. Genotype-phenotype associations have been described, but there are other genetic and non-genetic factors that can affect disease expression. We describe two different phenotypic expressions of ARVC in a family.

INTRODUCTION

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited cardiomyopathy characterised by fibro-fatty replacement of the myocardial tissue in the right ventricle (RV). ARVC typically affects the RV. However, early and predominant left ventricle (LV) involvement is increasingly being recognised. Confirmation of diagnosis remains a challenge, as it requires information from multiple sources as proposed by the 2010 task force criteria.[1] We report two cases of ARVC in a family with different phenotypic expression of the disease.

CASE REPORT

Case 1

A 28-year-old woman was referred for palpitations and syncope. She had previous history of hyperthyroidism. Her anti-thyroid medications had been stopped for a year. She had a younger brother who was recently diagnosed to have dilated cardiomyopathy. At the time of presentation, she had no family history of sudden death.

Clinical examination was unremarkable. Her thyroid function test was normal (T4: 15.4pmol/L, TSH: 0.847mIU/L). Her 12-lead electrocardiogram (ECG) showed no overt abnormalities and 24-hour Holter revealed 2723 premature ventricular contractions (2.8% of total beats). Transthoracic echocardiogram showed right ventricle dilatation with moderate tricuspid regurgitation. The RV systolic pressure was normal at 22mmHg. There was no significant left heart pathology (Figure 1a). She subsequently underwent cardiac magnetic resonance imaging. Cardiac magnetic resonance showed increased RV volumes. The indexed RV end-diastolic volume was 123ml/m^2. There was mild RV hypokinesia (Figure 1b). The RV ejection fraction was 39.8%. The LV volumes and function were normal. Late gadolinium enhancement images showed no hyperenhancement of the myocardium.

A few days after the scan, she experienced palpitations. 12-lead ECG, done at the emergency ward, showed non-sustained ventricular tachycardia (VT) of left bundle branch block morphology (Figure 1c). The ECG also showed Epsilon wave in lead V1 and T wave inversion in lead V1 through V5. She was started on oral amiodarone. Based on the 2010 task force criteria,[1] the diagnosis of ARVC was definite for her (four major and two minor criteria). She was counselled for implantable cardioverter defibrillator insertion. She declined initially but changed her mind after the sudden death of her younger brother (Case 2). She remains well until the time of publication.

Case 2

A 25-year-old man was referred for biventricular dysfunction. He was otherwise asymptomatic. He had no significant past-medical history. He was admitted two weeks earlier after a road-traffic accident. He sustained manubriosternal joint dislocation and avulsion of T5 vertebra. Both injuries were managed conservatively. Transthoracic echocardiogram was performed during admission to exclude cardiac contusion. It showed dilatation and reduced systolic function of both ventricles (Figure 2a). His cardiac enzymes were normal. 12-lead ECG showed Epsilon wave in lead V1, poor R wave progression and T wave inversion in the inferior and precordial leads (Figure 2c).

His coronary angiogram showed normal coronaries. Cardiac magnetic resonance imaging was performed. On volumetric analysis, the volumes of both ventricles were increased, and the systolic function of both ventricles was markedly reduced. The indexed LV- and RV-end diastolic volume was 140ml/m2 and 189ml/m2 respectively. The ejection fraction of LV and RV was 29% and 22% respectively. Late gadolinium enhancement images showed subepicardial to mid-wall enhancement at the inferolateral wall of the LV (Figure 2b). He was started on heart failure therapy and managed as dilated cardiomyopathy. His diagnosis was later revised to ARVC when his elder sister (Case 1) was diagnosed with the

This article was accepted: 17 May 2019
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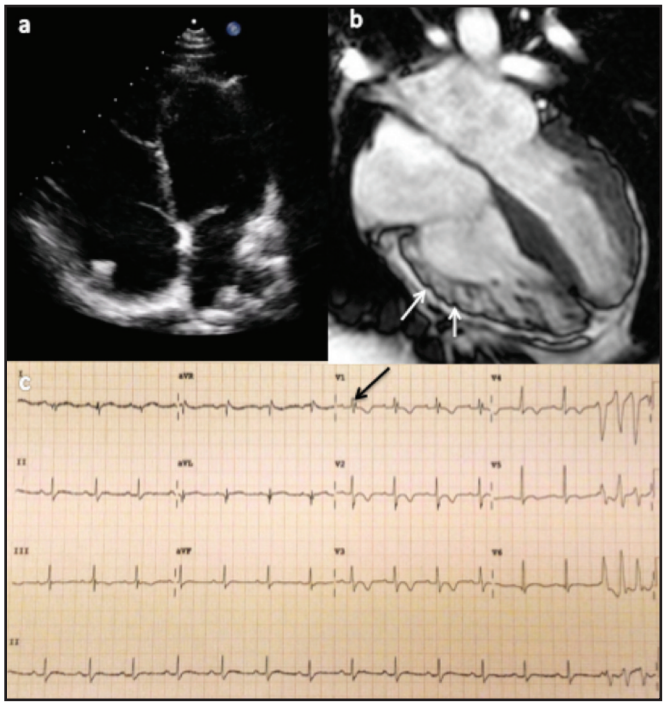

Fig. 1: Case 1, "classic" ARVC: (a) Apical 4-chamber view of transthoracic echocardiogram showing right ventricle and right atrial dilatation; (b) Apical 4-chamber view of cardiac magnetic resonance imaging showing microaneurysms (white arrows) of the right ventricle; (c) 12-lead ECG showing non-sustained VT of left bundle branch morphology, Epsilon wave in lead V1 (black arrow) and T-wave inversion in lead V1 through V4.

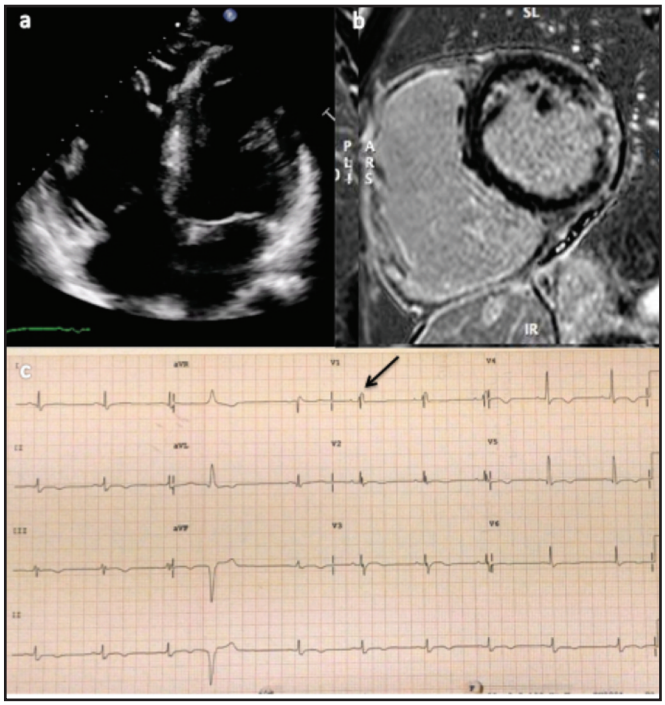

Fig. 2: Case 2, "biventricular" ARVC: (a) Apical 4-chamber view of transthoracic echocardiogram showing biventricular dilatation; (b) Late gadolinium enhancement short-axis images showing subepicardial to mid-wall enhancement of the LV inferolateral wall; (c) 12-lead ECG showing Epsilon wave in lead V1 (black arrow), poor R wave progression, T wave inversion in lead V2 through V5 and lead II, III, aVF, and premature ventricular contraction.

condition. He was advised for implantable cardioverter defibrillator implantation but declined. He did not turn up for subsequent clinic visits and was non-adherent to treatment. Three years after the diagnosis, he was found dead by his friends at his residence. The family declined post-mortem.

Family screening was carried out, using 12-lead ECG and transthoracic echocardiogram, for the parents and other siblings. None of them was found to have clinical manifestation of the disease.

DISCUSSION

ARVC is primarily a familial disease with autosomal dominant inheritance. Incomplete penetrance and variable expression are common, resulting in diverse clinical manifestation. Mutations of the following genes have been identified to cause ARVC: plakophilin-2 *(PKP2)*, desmoglein-2 *(DSG2)*, desmocollin-2 *(DSC2)*, desmoplakin *(DSP)*, junctional plakoglobin *(JUP)*, transforming growth factor beta-3 *(TGFB3)* and transmembrane Protein-43 *(TMEM43)*.[2] Five of these genes *(DSP, PKP2, DSG2, DSC2*, and *JUP)* encode proteins that are important to desmosome structure and function. Majority of cases are caused by mutations in these five desmosomal genes. The *PKP2* gene is the most common causal gene, accounting for approximately one-quarter of cases.[3]

As illustrated in our two cases, the clinical presentation of ARVC is highly variable, even among immediate family members. There are many factors that can affect disease expression. Genotype-phenotype correlation studies have shown association between specific mutation(s) with certain phenotype pattern. For example, LV involvement is more frequent in families with chain-termination mutations and/or *DSP* disease,[4] and patients harbouring *PKP2* mutations have earlier onset of symptoms and arrhythmic events.[2] Although genetic factor is an important determinant of disease expression, non-genetic factors such as viral myocarditis and intensity of exercise have also been implicated.[3] In this family, the elder sister presented with "classic" ARVC subtype, with the disease confined to the RV. Her primary clinical presentation was palpitations due to VT. The younger brother presented with "biventricular" subtype, with both ventricles equally affected, making it difficult to distinguish from dilated cardiomyopathy initially.

LV involvement in ARVC was initially thought to occur only at advanced stage of the disease. However, there is now growing evidence to show that it can occur early with or without overt RV involvement.[4] A distinctive feature of ARVC is the propensity towards arrhythmic events. Patients typically present with arrhythmia rather than heart failure, and VT can occur in the absence of severe LV dysfunction. This feature can help to differentiate ARVC from dilated cardiomyopathy. But in our second case, his LV was severely

affected at the time of presentation that other features, such as positive family history and characteristic ECG changes, were needed for definite diagnosis. On hindsight, his ECG changes should have raised suspicion of the diagnosis, but the biventricular involvement made it difficult to be confidently certain. Although he reported no symptoms, the presence of severe biventricular involvement conferred him a higher risk of sudden cardiac death compared to his sister.[3] Implantation of implantable cardioverter defibrillator for him would have prevented his unfortunate death.

Due to issue of high cost, genetic testing was not performed for the patients and family. Approximately 50% of patients with definite ARVC harbour mutations in one of the genes responsible for the disease.[3] Identification of pathogenic mutation in index cases allows cascade screening of family, thus identifying members who currently have morphologically normal heart but at risk of developing ARVC in later life ("concealed" phase).[2] However, about 50 to 70% of mutation carriers will never develop ARVC.[5] Therefore a positive test does not translate to definite occurrence of disease in later life, but a negative test provides assurance that the members are most likely unaffected.

In summary, these two cases highlight that phenotypic variation of ARVC can exist among family members, and that the biventricular subtype can be mistaken for dilated cardiomyopathy if other characteristic features are not explored. Course and prognosis of disease may differ greatly among family members, and hence treatment needs to be individualised.

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