Phenotypic expression of AVRD: how 12 lead ECG can predict left or right ventricle involvement.

A familiar case series and a review of literature

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ABSTRACT

Aims: Arrhythmogenic right ventricular cardiomyopathy (ARVC) is an inherited heart-muscle disease primarily affecting the right ventricle (RV) and potentially causing sudden death in young people. The natural history of the disease is firstly characterized by a concealed form progressing over a biventricular involvement. Three different cases coming from the same family are presented together with a review of the literature.

Methods and Results: Multi-parameter analysis including imaging and electrocardiographic analysis is presented since the first medical referral with follow-up ranging from 11 to 38 years. Case 1 presented a typical RV involvement in agreement with the ECG pattern. Case 2 presented a prevalent left ventricular involvement leading from the beginning to a pattern of dilated cardiomyopathy in agreement with his ECG evolution over the years. On the other side, Case 3 came to observation with a typical RV involvement (similar to Case 1) but with ECG evolution of typical left ventricle involvement (similar to Case 2). The genetic analysis showed a mutation in desmoglein-2 (*DSG2*) gene: p. Arg49His. Comparison between size and localization of ventricular dyskinesia at cardiovascular imaging and the surface 12 lead electrocardiography are proposed.

Conclusions: AVRC may lead to an extreme phenotypic variability in clinical manifestations even within patients coming from the same family in which AVRC is caused by the same genetic mutation. ECG progression over time reflects disease evolution and in particular cases may anticipate wall motion abnormalities by years.

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Abbreviation list: ARVC: Arrhythmogenic Right Ventricular Cardiomyopathy; ECG: electrocardiographic; CMR: cardiac magnetic resonance; HF: heart failure; EF ejection fraction; RV: right ventricle; LV left ventricle; VT: ventricular tachycardia; EPS: electrophysiologic study; *PKP2:* plakophilin-2; *DSC2*: desmocollin-2; DSP: desmoplakin; JUP: plakoglobin; RYR2: ryanodine receptor; SAECG: signal-averaged electrocardiogram; GLS: global longitudinal strain; LGE: late gadolinium enhancement.

INTRODUCTION

Arrhythmogenic Right Ventricular Cardiomyopathy (ARVC) is a rare inherited heart-muscle disease, characterized by myocardial atrophy, fibrofatty replacement, and ventricular arrhythmias, that primarily affects the right ventricle (RV)[1]. ARVC may lead with time to more diffuse RV and left ventricle (LV) involvement and may be difficult to distinguish clinically from dilated cardiomyopathy in the advanced stage[2-4]. Different genetic mutations and phenotypic expressions can lead to 3 distinct patterns of disease expression: classic, defined as isolated RV disease, or LV involvement in the presence of notable RV enlargement and/or dysfunction; left dominant with prominent LV manifestations in the setting of relatively mild right-sided disease; and biventricular, characterized by equal bilateral involvement[4]. The LV involvement increases incidence of clinical arrhythmic events and, compared with cases of isolated RV involvement, is associated with more severe

cardiomegaly, inflammatory infiltrates and heart failure (HF)[3-7]. Natural history of disease is divided in four phases. Firstly a subclinical phase with concealed structural abnormalities and no symptoms reported; in this phase sudden death might be the first manifestation. Secondly an overt RV electrical disorder with ventricular arrhythmias originating from the RV. Thirdly RV failure due to progressive loss of myocardium with severe dilatation and systolic dysfunction and lastly an end stage biventricular involvement that can mimic dilated cardiomyopathy[1]. Latest diagnostic criteria[8] have preferentially focused on RV analysis. Concealed phase is characterized by cellular injury that can trigger arrhythmic events. 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[9-11]. The subclinical phase of disease may also be detected by imaging studies, as it has been shown for 2D echocardiography with strain analysis[12]. However the ECG progression with time in AVRC patients and its correlation with LV or RV involvement has seldom been reported.

Aims of the present study were (1) to analyse the different phenotypic expression of ARVC and how the 12 lead ECG could predict LV or RV involvement in three AVRC patients of the same family and (2) to present a systematic review of the literature.

METHODS

Medical records of 3 adult cases, belonging to the same family, diagnosed with ARVC at the Division of Cardiology of “Città della Salute e della Scienza” Hospital, Turin, were analysed. Demographic data, presenting complaints, cardiac findings, electrocardiography, echocardiography, cardiac magnetic resonance (CMR) results and treatment data were

collected. Patients signed a written informed consent to proceed with data analysis. The genetic analysis evaluated 174 genes associated with cardiovascular disease using the "TruSight Cardio Sequencing Kit"; whereupon the genetic analysis focused on genes involved directly on ARVC, in particular: plakophilin-2 (*PKP2*), desmocollin-2 (*DSC2*), desmoplakin (*DSP*), plakoglobin (*JUP*), *TMEM43*-encoding transmembrane protein 43, ryanodine receptor 2 (*RYR2*).

RESULTS

We identified 3 cases of ARVC (3 adult males), from the same family with different phenotypic expression of the disease. None of the patients ever performed intensive physical activity and after the diagnosis they were advised to avoid moderate to intensive physical exercise. There was no difference in life style and cardiovascular profile risk among the three cases. In each patient epicardial coronary artery disease was ruled out by coronary angiography and CMR did not reveal any sign of different cardiomyopathy or myocarditis. First and second-degree relatives of these patients underwent ECG, signal-averaged electrocardiogram (SAECG), echocardiogram and CMR to exclude ARVC (Figure 1). Two sisters of Case 1 and 2 died at the age of 79 and 65 after acute ischemic stroke before performing a complete clinical evaluation; the ECGs didn't show any sign of ARVC. Among the family members who completed the evaluation none, excluding our three index cases, satisfied diagnostic criteria for AVRC (Figure 1).

Case 1

This is a 67-years-old male firstly referred to medical care in 1978 at the age of 29 with a history of dyspnea. ECG revealed negative T wave in V1-V4 precordial leads. Transthoracic

echocardiography showed a LV EF of 53% and reduced contractility and dilatation of RV. From 1983 he experienced palpitations with demonstration of sporadic ventricular ectopy on Holter-ECG analysis. In 1985 he presented with ventricular tachycardia (VT) with LBBB morphology, heart rate 200 bpm. LV angiography showed a preserved ejection fraction and RV angiography revealed a peri-annular diaphragmatic aneurism; myocardial biopsy showed monocytes infiltration and thickened endocardium. On the basis of clinical history, ECG and RV angiography, AVRC was diagnosed and beta blockers therapy with Nadolol started. In 1995 he experienced an ischaemic stroke, hence he started anticoagulation therapy with vitamin K antagonist. Because of symptomatic sustained palpitations, by 1996 nadolol was substituted with sotalol and the patient underwent 2 electrophysiologic studies (EPS) with induction and ablation of two different morphologies of VT coming from the RV. CMR showed dilated RV with accentuated trabecular pattern, diffuse fibrofatty infiltration of the RV free wall and aneurismatic dilatation of the RV outflow tract. SAECG showed 3 positive criteria out of 3.

Looking at the ECG evolution during this 38 year follow up, a progressive RV involvement is evident, with new onset right bundle branch block and epsilon wave in the right precordial leads and rightward QRS axis deviation on surface ECG. (Figure 2a). On the other side ECG signs of LV involvement are limited to R wave amplitude reduction in left lateral precordial leads and in D1 and aVL. This suggested predominant RV involvement, also confirmed by the recently repeated CMR, which showed dilated RV with reduced contractility (EF 17%), significant trabeculation, small aneurisms of infundibular and inferior-basal wall and along acute marginal wall, with adipose infiltration; LV anterior-basal and apical walls were thinned and dyskinetic, with adipose infiltration, but preserved EF (Figure 3, Appendix video 1). The last transthoracic echocardiogram (2015) showed not dilated LV, with EF of 51%, in

presence of hypokinesia of posterior-lateral wall; RV appeared significantly dilated (TDD 50 mm), with preserved longitudinal contractility (TAPSE 23 mm), but reduced global function (FSA 28%). The genetic analysis performed in 2016 showed a mutation in *DSG2* gene: p. Arg49His.

Case 2

This 70-years-old male suffered from extrasystolic palpitations since he was 30. Frequent polymorphic ventricular ectopic beats were recorded on Holter monitoring, which were reduced by beta-blocker therapy with propranolol. He was referred in 1993 for ischemic stroke. The ECG (1995) at the age of 49 years showed negative T waves the precordial leads up to V6 (Figure 2b), with demonstration of hypokinesia of anterior and apical wall at transthoracic echocardiogram. The CMR (1996) revealed fibrofatty infiltration in the infundibulum of RV, consistent with the diagnosis of ARVC. By 2006 he developed significant changes on CMR with spread fibrofatty involvement of LV, in particular of inferior interventricular septum and posterior-lateral wall, with reduction of global contractility. On the other side RV showed minimal abnormalities. Thereafter he progressively reduced his exercise tolerance in parallel with a greater involvement of LV and the consequent decline of LV EF. In particular, in the last 10 years CMR assessments showed wide involvement of the inferior and lateral regions with severe reduction of ventricular contractility (EF 25%), progressive thinning of ventricular wall and systolic bulging (Figure 3, Appendix video 1). ECG evolution, reflecting the progressive involvement of LV, was characterized by appearance of Q waves in DI, aVL, V5-V6 together with R wave amplitude reduction in the same leads and progressive enlargement of epsilon waves in antero-lateral leads; signs of RV involvement

were less evident (Figure 2b). He also suffered 2 demonstrated episodes of paroxysmal atrial fibrillation (in 2008 and 2009). From 2016 functional class worsened (NYHA III-IV) and the patient suffered 2 episodes of syncope, the last with demonstration of sustained VT, which was treated with cardioversion; he subsequently underwent EPS with induction and ablation of VT coming from the RV; also, an implantable cardioverter defibrillator was positioned. Last CMR revealed akinetic and thinned inferior and lateral LV wall leading to a severe contractile dysfunction (EF 25%); RV also showed diffused fibro-fatty infiltration, multiple systolic bulgings, with severe EF reduction (EF 25%). The genetic analysis performed in 2016 showed a mutation in *DSG2* gene: p. Arg49His.

Case 3

This 58-years-old male was referred in 1994 at the age of 38 due to the familiar history of ARVC (Case 1 and 2). The ECG showed possible epsilon wave in V1 and aVF. He performed CMR which showed slight dilatation of RV, with adipose infiltration of the apex and focal bulging of infundibular wall; LV was normal. SAECG showed 3 positive criteria out of 3. Considering familiar history, ECG, SAECG and CMR, he was diagnosed with ARVC and nadolol was started. In 2003 he underwent EPS, which resulted negative for VT induction. Subsequent CMRs in 2006 and 2012 showed a progression in RV involvement with adipose infiltration of anterior and infundibular wall, extension of bulging area to anterior, inferior and lateral wall, and reduction of RV EF to 40%. Despite imaging indicate a broad and apparently exclusive involvement of RV, the evolution of ECG in the last years shows a reduction of R waves amplitude in left precordial leads and presence of negative T waves up to V6, likewise the ECG evolution in Case 2 (Figure 2c). We were facing with contradictory

findings: imaging studies suggested a prevalent RV involvement (similar to Case 1) while ECG evolution suggested an important LV involvement (similar to Case 2). After the ECG showed LV involvement we needed to wait approximately three years before an asymptomatic involvement of the LV could be detected. In fact, the last echocardiogram (2016) showed LV wall motion abnormalities at global longitudinal strain (GLS) evaluation, located at medium-apical inferior and infero-lateral wall of the LV, and also mechanical dispersion of time to peak negative longitudinal strain in both RV and LV segments (Figure 4); this was confirmed by CMR which showed late gadolinium enhancement (LGE) in the same areas (Figure 3). The genetic analysis performed in 2016 showed a mutation in *DSG2* gene: p. Arg49His.

The presence of common diagnostic criteria and the description of indicators of LV involvement of all the three cases during the follow-up is presented in Appendix Table 1 and 2.

DISCUSSION

ARVC is a cardiomyopathy characterized by myocardial atrophy, fibrofatty replacement, and ventricular arrhythmias that usually primarily affects the RV[1]. It was initially considered to be strictly confined to the RV, but there is now a growing evidence that the LV can progressively be involved, so that it may be difficult in the advanced stage to distinguish clinically from dilated cardiomyopathy[2-5,7,13,14]. LV involvement in ARVC has been increasingly described, with reported prevalence of 16% in the first studies[15] increasing to 76-84% in last reports[3-7]. Lindstrom et al demonstrated, by myocardial perfusion scintigraphy and echocardiography,

LV abnormalities in 93% of their ARVC patients[16]. What was initially known as an isolated RV disease has been more recently shown by CMR data and pathology studies to be a wider spectrum of diseases. As a consequence, cardiologists are now focusing on a biventricular view rather than only on a right one and a more comprehensive term of "arrhythmogenic cardiomyopathy" has been proposed[17]. Sen-Chowdhry et al described 3 distinct patterns of disease expression, determined by different genetic mutations and phenotypic expressions: "classic", defined as isolated RV disease, or LV involvement in the presence of notable RV enlargement and/or dysfunction; "left dominant", with prominent LV manifestations in the setting of relatively mild right-sided disease; and "biventricular", characterized by equal bilateral involvement[4]. LV involvement is age dependent[3] and is associated with clinical arrhythmic events, more severe cardiomegaly, inflammatory infiltrates and HF[3-7].

McKenna et al. in 1994 developed for the first time diagnostic criteria based on medical history and on morphological, functional, and structural abnormalities[18]. These criteria focused on overt and severe disease, but lacked sensitivity for earlier forms. Moreover the possibility of LV involvement was admitted, but was not included in the diagnostic criteria. The sensitivity in early forms was improved with the 2010 diagnostic criteria[8]. Despite predominantly LV involving disease, with a particular ECG pattern (inferolateral T-wave changes, ventricular ectopy, or VT with right bundle-branch block morphology) and a particular imaging pattern (epicardial or mid-myocardial LGE by CMR) had been previously recognized [4,7,19,20], none of these criteria were included. The task force concluded that future revision of diagnostic criteria would have filled this gap including arrhythmias originating from LV, or imaging suggestive of LV fibro-fatty replacement, or loco-regional LV wall motion abnormalities as diagnostic features.

Several ECG abnormalities have been shown to develop over time reflecting disease progression and involvement of new myocardial areas, as QRS enlargement and T wave inversion in the precordial leads and epsilon waves[21,22]. ECG changes and arrhythmias may develop before histological evidence of myocyte loss or clinical evidence of RV dysfunction and are early and sensitive markers of disease expression in ARVC[9-11]. Epsilon wave is a marker of ventricular delayed activation due to late electrical depolarization of myocytes in the context of fibro-fatty tissue substitution and has been correlated with progressive RV involvement and therefore with a poor outcome[22-25]. It represents a major diagnostic criteria in 2010 Task Force Criteria when visible in right precordial leads (V1-V3)[8]. Gallo et al found that this marker was associated with the occurrence of sudden cardiac death, HF-related death and heart transplant[21]; accordingly Shulin Wu et al reported the presence of epsilon waves in 80% of patients at high-risk of cardiac mortality (previous sustained VT and RV failure) and in 51% of low-risk patients, without reaching statistical significance (p=0.16)[26]. The three cases we presented showed epsilon waves on the right precordial leads, however Case 2 developed epsilon waves also in the left precordial leads and in DI-aVL (Figure 2b, Appendix Table 2), reflecting the extended LV involvement by the fibro-fatty tissue substitution. This ECG evolution is not usually described in LV dominant or biventricular forms: Sen-Chowdhry et al, in a cohort of 200 probands (82% with LV involvement), reported epsilon waves in lateral leads only in 2 patients[4]; other reports described epsilon wave in V1-V3, and characteristic negative T wave in left precordial leads[3,4,7,14,27-34]. Epsilon wave detection in left precordial leads may be underestimated. On our opinion this should be included in future diagnostic criteria.

Similarly to epsilon wave, T wave inversion in leads V4-V5-V6 and low QRS voltages could

indicate progression over time, as reported by Gallo et al[21]. T-wave inversion beyond V3 are characteristic of subjects with more severe RV dilation and dysfunction[33,35-37], whereas negative T wave in lateral and inferior leads represent a typical sign of LV involvement in biventricular and LV dominant forms[3,4,7,14,27-32,34]. Furthermore, the progressive loss of contractile tissue, together with scar substitution of myocytes and the dilatation of the ventricles are associated with R wave reduction and Q/QS wave in the left precordial leads[32]: this phenomenon is particularly evident in Case 2 and 3. Noteworthy, similar to what already described for the RV, an occult phase of electrical involvement preceding the manifest contractile dysfunction can be recognized also for arrhythmogenic cardiomyopathy with prevalent LV involvement. In this report Case 3 showed ECG abnormalities typical of LV involvement before any imaging modality could detect them (Figure 2b e 2c, Appendix Table 2).

LV involvement can be detected by CMR and echocardiography with strain pattern analysis. The first plays a relevant role in the diagnostic process of suspected AVRC[18]. Fibrous replacement of the LV wall starts from the epicardial layer, this portion of the ventricular wall in poorly involved in the contraction process, then, fibro-fatty substitution of this portion do not lead to wall motion abnormalities detectable with traditional echocardiography. These injured areas can be easily detected with LGE at CMR[7,38]. Despite this, almost all studies in literature focused on the RV and only few assessed the LV involvement by CMR[4,39,40]. Revised 2010 diagnostic criteria for CMR are focused on RV and consider major criteria the presence of regional RV akinesia/dyskinesia/dyssychronous RV contraction and one of the following: dilatation of RV ≥110mL/m2 (or ≥100mL/m2 for female) or a reduced RV EF (≤40%); the presence of lower RV dilatation (100-110 ml/m2 for

male, 90-100 ml/m2 for female) or RV dysfunction (40-45%) is considered a minor criteria; tissue characterization of ventricular wall is only based on histological criteria[8]. Furthermore, in case of LV involvement the presence of LGE is really suggestive, but this is not included in last diagnostic criteria[8].

Surface echocardiography represents a fundamental tool in patients with suspected AVRC. Myocardial deformation analysis performed by the recently available methods of bi-dimensional strain analysis is emerging as a promising tool in numerous pathological conditions. Its application in the subclinical phase of disease is intriguing and already reported in AVRC patients[41,42]. In particular the evaluation of mechanical dispersion of ventricular segments is reported to improve the ability to identify high-risk patients[43,44]. Case 3 of our series was referred to our center with no wall motion abnormalities of LV reported at trans-thoracic echocardiography, despite this, application of strain methods analysis detected subclinical abnormalities in LV inferior wall (in particular basal and medium portion) and confirmed a clear involvement of RV free wall (Figure 4). Furthermore strain analysis revealed RV and LV mechanical dispersion. The LV involvement was then confirmed by the last CMR which showed a LGE in the same portions.

Molecular genetic analysis has provided considerable progress in understanding the pathophysiology of ARVC and many mutations have been identified in 8 genes. The majority of mutations are in 5 genes encoding proteins of the desmosome: *JUP*, *PKP2*, *DSP*, *DSG2*, *DSC2*; mutations in several non-desmosomal genes including *PLN*-encoding phospholamban and *TMEM43*-encoding transmembrane protein 43 have also been reported to cause ARVC[45]. Evidence for additional locus heterogeneity includes 4 loci for which no genes have yet been identified. The 3 Cases we presented had a mutation in *DSG2* encoded p. Arg49His

which is considered “pathogenetic” (1/12068 allele in controls on ExAC database). *DSG2* is the fourth recognized desmosomal gene causing ARVC and approximately 10% of patients with ARVC have mutations in *DSG2*[46,47]. Preliminary reports described an important, sometimes predominant, LV involvement with this mutation, with characteristic T wave inversion in inferior and left precordial leads and reduced R wave voltages in V5-V6[47-49]; otherwise a recent genotype-phenotype correlation study in 577 subjects described a LV dysfunction in 13% of *DSG2* mutation carriers (in contrast with 37% with *DSC* mutation, 40% with *DSP* mutation, and 67% with *PLN* mutation)[45]. The *DSG2* mutation were also found in 8% of sudden cardiac death victims in the absence of morphologic cardiac abnormalities at autopsy [50].

Despite the same genotype, a clearly different phenotype is evident. Case 1 showed a clear RV involvement with typical ECG signs of RV involvement. Case 2 had ECG signs of a clear LV involvement, in particular the progressive evolution to a QS morphology in left precordial leads together with left epsilon wave appearance (rarely reported). Imaging analysis in this patient showed a clear biventricular involvement with biventricular reduced ejection fraction. Case 3 was referred to our center with imaging tests suggestive for only RV involvement, but ECG showed a progression to rS in left precordial leads suggestive for LV involvement. After many years in which the ECG evolution was not followed by LV involvement at imaging studies, a subclinical wall motion abnormality of the LV was detected at the strain analysis and confirmed by the CMR.

Such a phenotype variability in disease expression in the same family is rarely reported[49]. ECG evolution could anticipates of years the future wall motion abnormalities onset, that, at the subclinical level, may be detected by strain echocardiographic analysis and contrast guided CMR.

CONCLUSIONS

ARVC represents an extremely heterogeneous disease in which not only RV is involved. We presented three cases of ARVC belonging to the same family but with different phenotypic expression, in particular in LV involvement. In these cases ECG changes reflect the disease progression demonstrated by imaging and also anticipate of years the wall motion abnormalities onset.

LIMITS

Our study has the limitation of observational study with patients evaluated in a single high experienced centre by a restricted group of physicians. Further studies are required to evaluate the diagnostic and prognostic impact of epsilon wave detection in left lateral precordial leads in AVRC patients. Larger sample size studies are also required to evaluate reliability of GLS analysis at surface echocardiography in AVRC patients and also to validate that certain ECG changes could predict LV involvement.

Figure Legends

Figure 1. Family tree.

Figure 2. ECG progression of the three cases from the diagnosis to the last control during follow-up. On the left are presented the peripheral leads, on the right the precordial leads.

Figure 3. Comparison of ECG and CMR of the three cases at similar age. In Case 1 ECG shows a predominant RV involvement (right bundle branch block, epsilon wave in the right precordial leads, rightward QRS axis deviation), confirmed by CMR: RV with significant trabeculation, small aneurisms of infundibular and inferior-basal wall and along acute marginal wall, with adipose infiltration; LV with thinned and discinetic anterior-basal and apical walls, with adipose infiltration. On the contrary, in Case 2 the ECG indicates a predominant LV involvement (Q waves in DI, aVL, V5-V6, with reduced R wave amplitude in the same leads and epsilon waves in antero-lateral leads), with a wide non-ischemic LGE on the inferior and the lateral regions, severe reduction of ventricular contractility (EF 25%), thinned ventricular wall and systolic bulging on CMR exam. Case 3 at a similar age shows an evident RV involvement with initial signs of LV involvement, both on the ECG (reduction of R waves amplitude in left precordial leads and negative T waves up to V6) and on the CMR (LGE areas at medium-apical inferior and infero-lateral wall of the LV).

Figure 4. Determination of longitudinal strain in apical view of LV and RV of Case 3. a) Two chambers apical view of LV. b) Four chambers apical view with determination of RV free wall longitudinal strain. Both RV and LV shows reduced global LS and mechanical dispersion.

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