Viewpoint

Another Brick in the Wall Through the Knowledge of Desmoplakin Cardiomyopathy: Three Siblings Case Reports

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Abstract

Desmoplakin (DSP) is a pivotal component of the desmosome, a cell junction complex anchoring intermediate filaments. In the heart molecular architecture, desmosomes play a relevant role in cellular adhesion and force transducer through the myocardium. Mutations in the DSP gene cause distinct arrhythmogenic cardiomyopathy with myocardial injury, left ventricular fibrosis, further systolic dysfunction, and a high incidence of ventricular arrhythmias.

We describe the clinical cases of three siblings with DSP cardiomyopathy diagnosed after the index patient had been referred to an inherited cardiac disease investigation due to recurrent myocarditis. A novel nonsense variant in the DSP gene was diagnosed, and the patients were treated to avoid sudden cardiac death.

Introduction

The Desmoplakin (DSP) gene encodes a protein that anchors cardiac desmosomes to intermediate filaments, which is crucial to force transmission through the myocardium.[1] Its mutations have been originally associated with Carvajal Syndrome (recessive mutation in the DSP gene with disruption in DSP-intermediate filament interactions leading to dilated cardiomyopathy, woolly hair, and keratoderma[2] and arrhythmogenic right ventricle cardiomyopathy (ARVC).[3,4] However, left-dominant arrhythmogenic cardiomyopathy (LDAC) has been characterized as a distinct phenotype of the DSP variant with left ventricular dysfunction and increased propensity to ventricular arrhythmias and sudden cardiac death (SCD), which is frequently misdiagnosis as Dilated Cardiomyopathy (DCM) or viral myocarditis.[5] Biventricular involvement has also been described.[6]

Keywords

Desmoplakins; Genetic Predisposition to Disease; Heart Failure.

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The pathophysiology of Arrhythmogenic Cardiomyopathy has not been completely elucidated yet. Nevertheless, the abnormalities of cell-cell adhesion possibly cause cardiomyocyte death by either necrosis or apoptosis and, consequently, fibrofatty replacement. The desmosomal proteins might also be related to cell signaling, which may modulate pathological gene expression. There is evidence of deregulated intracellular signaling, probably associated with junctional plakoglobin shift to intracellular sites.[7] Desmosomes' interactions with the nucleus, gap junctions, and ion channels possibly account for fibroadipogenesis, slowing conduction, and electrical heterogeneity, respectively, and therefore may play a role in ventricular arrhythmias.[8] In this paper, we report a series of cases of a novel DSP pathogenic variant in three siblings with a noteworthy intrafamilial history of cardiomyopathy.

Case Reports

In the index case, a 19-year-old white male presented to the emergency room with chest pain and vomiting. The physical examination was unremarkable. His electrocardiogram on entrance showed mild early ventricular repolarization (Figure 1), C-reactive protein was 0.1 mg/ml (normal <6 mg/ml), and troponin elevation. The initial diagnosis hypothesis was myopericarditis and, therefore, empirically treated with ibuprofen and colchicine. The patient was referred to a cardiological and rheumatological etiology assessment. Neither systolic dysfunction (left ventricle ejection fraction - LVEF 63%) nor pericardial effusion was present on his transthoracic echocardiogram. Rheumatic and infectious serology were negative. Six and nine months after the primary clinical manifestation, the patient had experienced new episodes of chest pain, both treated with ibuprofen and colchicine, this time prescribed for six months. The initial hypothesis of myopericarditis was also initially made due to the recurrence of the symptoms.[2]

A cardiac magnetic resonance (CMR) was done. It showed a preserved ejection fraction of both left and right ventricles despite the presence of epicardial late gadolinium enhancement (LGE) on the basal and medial portions of the inferior wall on the basal portion of the inferoseptal wall, on the middle and basal portions of the anterior wall and the middle portion of the anterolateral wall (Figure 2). At this point, a beta-blocker and an angiotensin-converting enzyme inhibitor were prescribed.

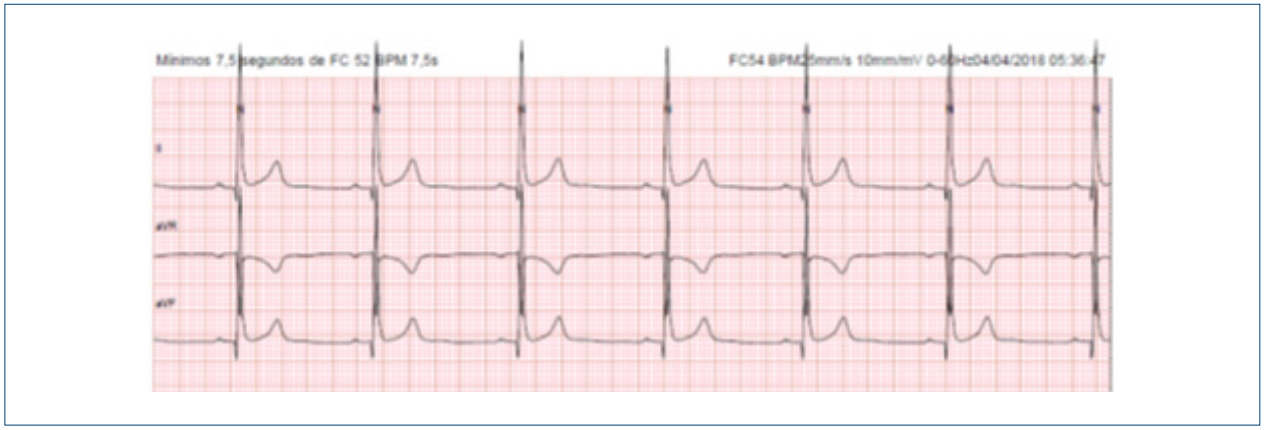

Figure 1 – *Index patient electrocardiogram.*

Nonetheless, three months later, another episode of mild chest pain drove the patient to the hospital, this time with a significant elevation of the troponin level (13 μg/L). A new rheumatological investigation was performed but persisted negative for auto-immune diseases. The CMR was repeated, and the final diastolic diameter was 5,7 cm (previously it was 5,6 cm) and a final diastolic volume of 88 ml/m² of body surface exceeding 5% of the expected for his body surface, but with preserved both systolic (LVEF 55%), and diastolic function.

The patient was referred to an inherited cardiac disease investigation. The panel evaluated 49 genes using molecular analysis by new sequencing generation (Illumina HiSeq®). The study revealed the nonsense variant Chr6:7.580.313 A>AGGTC of the DSP gene in heterozygosis, which promotes the substitution of the amino acid methionine at position 1299 for glycine and, at this point, change of the reading matrix, leading to premature interruption of protein translation (p.Met1299Gly fs * 7). This variant was classified as definitely pathogenic according to the laboratory analysis.

This specific variant has been described in the medical literature before, and DSP's variants are strongly associated with SCD.[1,9] Therefore, Holter monitoring was indicated as a screening for arrhythmias. On the exam, there were 995 episodes of premature ventricular contractions (PVCs), of which 991 were isolated and 2 were paired. Considering these results, a subcutaneous implantable cardioverter-defibrillator (ICD) was implanted as the primary prophylaxis of SCD. Clinical and genetic assessments of his two brothers were performed; the younger was 17 years old, and the older was 24 years old. Both siblings presented the pathogenic variant of the DSP gene.

Younger sibling

The patient was asymptomatic and had no comorbidities. His physical exam was normal. There were unspecific ventricular repolarization abnormalities on the anterior wall in his electrocardiogram. The transthoracic echocardiogram showed mild diffuse hypokinesia in the LV, with an ejection fraction of 44%, along with mitral and tricuspid regurgitation without hemodynamic repercussions. Holter exhibited 1418 PVCs, of which 1372 were isolated and 22 paired. Finally, CMR (Figure 3) revealed laminar areas of LGE affecting predominantly the epicardium of the anterior walls, anteroseptal, lateral, and anterolateral segments in the left ventricular mild and basal segments, and a discrete reduction in systolic function, with an LVEF of 46.6%. After the workup, treatment with ramipril and bisoprolol was initiated and subsequently titrated to optimal doses. Considering the potential risk of SCD, a subcutaneous ICD was implanted.

Older sibling

The older patient was also asymptomatic, although obesity and hypertriglyceridemia were present. The physical exam was normal, except for the body mass index of 35 kg/m². The electrocardiogram revealed a first-degree atrioventricular block. His Holter showed two isolated ventricular PVCs. On the echocardiogram, mild diffuse hypokinesia in the LV was present, with an LVEF of 50%, along with mitral valve prolapse.

Likewise his brother, epicardial LGE was observed on his CMR (Figure 4) in the mid and apical segments of inferoseptal and inferior walls of the LV, with preserved LVEF and mild RV dysfunction (RVEF 35,5%). Thus, bisoprolol and ramipril were initiated, and a subcutaneous ICD was implanted. During the first year of follow-up, none of the patients had ventricular arrhythmias, ICD shock, chest pain, or dyspnea. After medical therapy optimization, the transthoracic echocardiogram of the younger sibling revealed an increase in LVEF to 51%.

Despite the family history of cardiomyopathy, both the father and paternal grandfather of the patient had been deceased due to other causes. Their father had died from non-Hodgkin lymphoma complications five years before the first episode of chest pain of the index case. Therefore, data on DSP gene variants could not be entirely retrieved on their ascendants. Their paternal aunt had tested negative for this DSP gene variant. The pedigree is shown in Figure 5.

Discussion

Although DSP gene mutations have been historically thought of as part of the ARVC spectrum, Smith *et al.*[1] hypothesized that it represents a distinguished set of arrhythmogenic cardiomyopathy, which is markedly

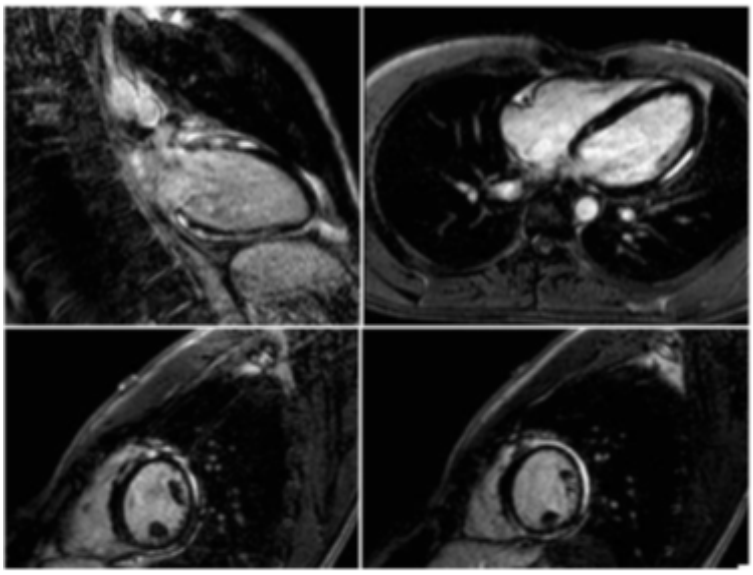

Figure 2 – *Cardiac magnetic resonance of the index patient.*

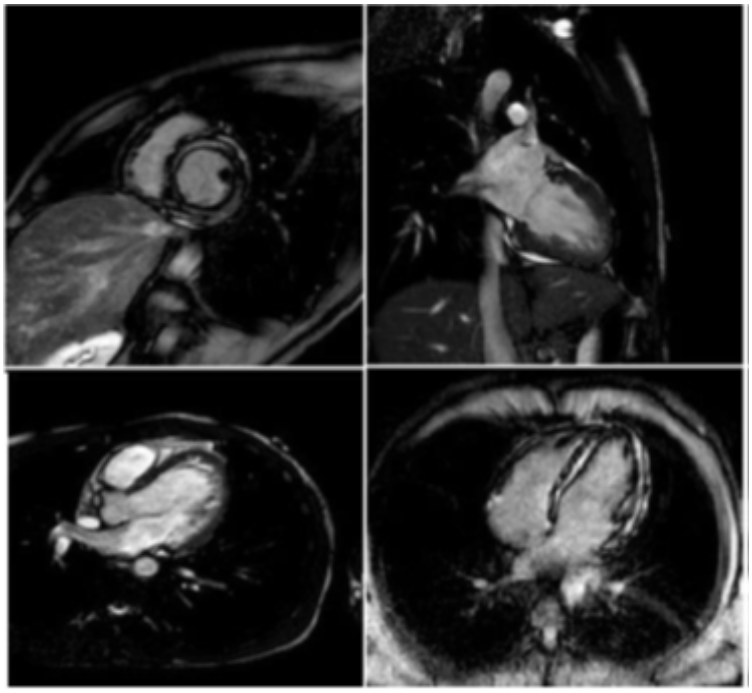

Figure 3 – *Cardiac magnetic resonance of the younger sibling.*

characterized by myocardial fibrosis and inflammation. The authors found LV involvement in 79% of patients (systolic dysfunction and LGE on CMR), and an important susceptibility to ventricular arryhtmias.[1] These clinical features are consistent with the sibling's disease, as summarized in Table 1.

The DSP gene variant Met1299Gly A>AGGTC of this case series has already been described.[10] The clinical phenotype of the disease in question is broad. Our sample of three cases from the same family follows a previously described cohort with a predominance of left ventricular involvement.[10] The

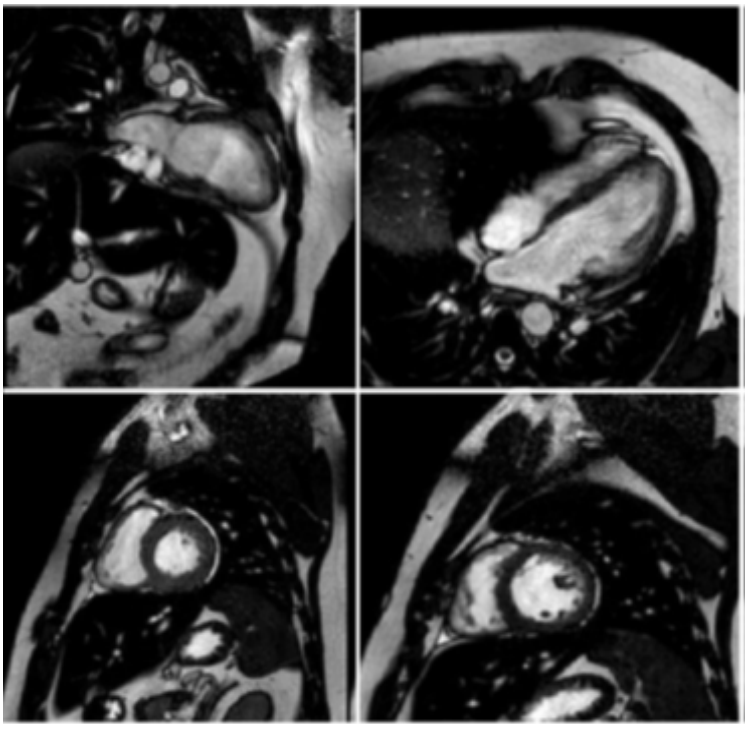

Figure 4 – *Cardiac magnetic resonance of the older sibling.*

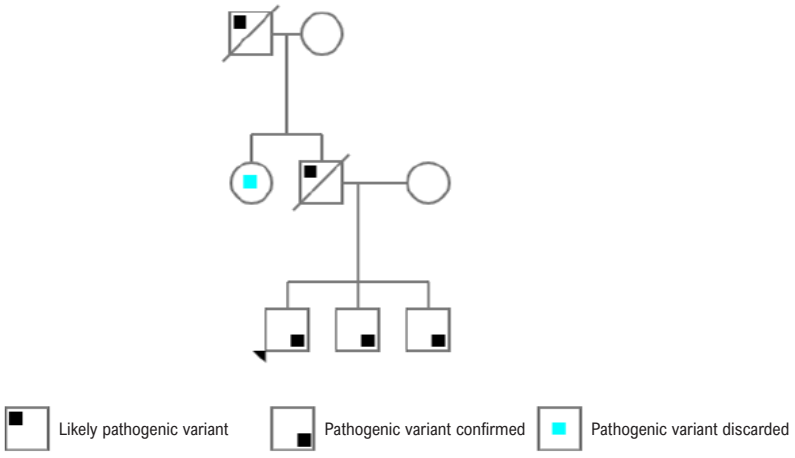

Figure 5 – *Familiar pedigree illustrating the cases.*

heterogeneity of expressivity and clinical penetrance among DSP gene variants is another key feature of DSP cardiomyopathy.[1,11] Smith et al.[1] compared DSP cardiomyopathy probands to genotype-positive family members and found a penetrance of 57% in the non-proband group. Our report, similarly to other,[10-12] demonstrated the variability of clinical expression and the extension of the intra-variant disease since the pathological aspects such as clinical presentation, LGE extension, and LVEF differ amongst the siblings.

The genetic architecture of cardiomyopathies is marked by a notable heterogeneity, in which many variants in many other genes can cause the same phenotype. Not all individuals carrying a causative variant manifest the disease, and among those who do, there is great variability in age of onset and disease severity.[2] However, the genetic test performed on the siblings helped for a precise diagnosis, once it classified the variant as definitely pathogenic. Indeed, some goals were reached, such as diagnosis confirmation, informed prognosis,

Table 1 – Summary of the cases

	Index Case	Younger sibling	Older sibling
Chest pain	Yes	No	No
EKG	Early ventricular repolarization	Ventricular repolarization abnormalities	First-degree AVB
First Echocardiogram	LVEF 63%, mitral valve prolapse	LVEF 44%, diffuse LV hypokinesia	LVEF 50%, diffuse LV hypokinesia
Holter	992 PVCs	1418 PVCs	2 PVCs
CMR	Diffuse epicardial LV LGE. No systolic diastolic dysfunction	Diffuse epicardial LV LGE. Mild systolic disfunction	Diffuse epicardial LV LGE. Mild systolic disfunction
Follow up			
Medical Therapy	Bisoprolol 10mg Ramipril 10 mg	Bisoprolol 10mg Ramipril 10 mg	Bisoprolol 5mg Ramipril 10 mg
ICD Therapy	No	No	No
LVEF	0.56	0.51	0.5

EKG: electrocardiogram; AVB: atrioventricular block; LV: left ventricle; LVEF: left ventricle ejection fraction; LGE: late gadolinium enhancement; PVC: premature ventricular contraction; CMR: cardiac magnetic resonance; ICD: implantable cardioverter-defibrillator.

treatment selection, and even reproductive management, since the patients were young.

The index case presented with episodes of myocarditis, which has been reported previously on DSP gene mutation,[11,13,14] and postulated to be a "hot phase" of the disease. Acute myocardial injury was found in 15% of overall DSP patients in Smith *et al.*[1] cohort although the authors acknowledge that the strict criteria (troponin elevation with normal coronary angiography in patients with chest pain) might have underestimated the real prevalence. Furthermore, 40% of DSP patients had LV LGE, which may indicate clinically silent episodes of myocardial injury. Episodes of clinically suspected myocarditis are another point that deserves attention.[15] It was also described in 15% of a cohort of 73 patients,[10] and it was the initial symptom of the index patient, with two episodes of recurrence.

None of the siblings met the 2010 ARVC Task Force Criteria,[16] which reaffirms the difficulty of diagnosing rare cardiomyopathies such as DSP LDAC. These criteria have performed poorly on patients with DSP mutations,[1,11,14] due to a lack of LV involvement markers criteria. Piriou *et al.*[11] propose acute myocarditis as a diagnostic criterion of DSP LDAC, especially to consider genetic workup when a patient presents with acute myocarditis or recurrent myocarditis and a positive family history of SCD or cardiomyopathy.

The risk stratification for ventricular arrhythmias and SCD was a major difficulty for DSP variants. Regarding the indication for ICD implantation, Carrick et al. have proposed a current tool. According to the authors, the main independent predictors of arrhythmic risk in DSP gene variant carrier patients were female sex, history of non-sustained ventricular tachycardia, EF below 50%, moderate to severe right ventricular systolic dysfunction and 24h- premature ventricular contraction burden.[17] At the time of patient evaluation, the independent factors associated with arrhythmic risk were unknown. Indeed, the implantation of the devices was based on the primary prophylaxis of young and active patients and on the fact that SCD may be the first manifestation of the disease, especially amongst truncating mutation holders.[18]

Conclusion

DSP cardiomyopathy is a rare arrhythmogenic disorder with notable heterogeneity and is probably underdiagnosed. Acute myocarditis, particularly if recurrent, in patients with significant family history and epicardial LGE on CMR should raise the concern for genetic assessment, a relevant tool for straight diagnosis, prognosis, and counseling. Larger multicenter cohorts are urgently needed to delineate better clinical features, risk stratification, and prognosis, as well as interventional and translational studies to evaluate possible therapies.

Author Contributions

Conception and design of the research and Critical revision of the manuscript for content: Gâmbaro GA, Felicio ML, Andrade LGM, Garcia LR, Brito FS; Acquisition of data: Gâmbaro GA, Garcia LR; Analysis and interpretation of the data: Gâmbaro GA, Felicio ML, Garcia LR; Writing of the manuscript: Gâmbaro GA, Garcia LR, Brito FS.

Potential conflict of interest

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Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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