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Genetic Mutation Screening Revealed a Rare MYBPC3 Mutation in a Case with Complex Arrhythmogenic Right Ventricular Cardiomyopathy

*Boneva T[1], Karamfiloff K[1], Ivanova R[1], Zlatancheva G[1], Shumkova M[1], Stoyanova K[1], Yaneva-Sirakova T[1], Vassilev D[2] and Dimova I[3]**

[1]Department of Cardiology, Alexandrovska University Hospital, Bulgaria

[2]Department of Cardiology, SBALK "Medica COR" Rousse, Bulgaria

[3]Department of Medical Genetics, Medical University Sofia, Bulgaria

Abstract

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) is characterized by progressive fat or fibrofatty replacement of the Right Ventricular (RV) myocardium. The cause of ARVD/C is not yet clear, but recent studies suggest it is most often related to genetic mutations. Left Ventricular (LV) or biventricular involvements are increasingly identified in ARVD/C patients. The genetic background of cardiomyopathies could shed light on the mechanism of their development, clinical presentations and new treatment options.

We describe here a patient affected by arrhythmogenic right ventricular cardiomyopathy with left ventricular involvement, with the presence of coronary artery anomalies. There were aneurisms of coronary arteries and Left Circumflex Artery (LCx) arises from right coronary sinus. Physiological, imaging and invasive study was performed in details. In addition, genetic analysis by Next Generation Sequencing (NGS), using panel of genes for hereditary cardiomyopathy, was done. We detected a missense mutation in MYBPC3 gene (c.1316G>A, p.Gly439Asp), classified as variant of unknown significance. We discuss myosin-related mutations in different kinds of cardiomyopathy with dosage-dependent effects of MYBPC3 on myosin that occurs across the cardiac cycle.

The association of the found MYBPC3 mutation with the development of that complex cardiomyopathy is worthy to be investigated, since it could have an important impact on the application of new treatment, using specific myosin targeted agents.

Keywords: Arrhythmogenic cardiomyopathy; Next generations sequencing; MYBPC3 mutation

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Correspondence:
Ivanka Dimova, Department of Medical Genetics, Medical University Sofia, Zdrave str. 2, Sofia 1431, Bulgaria, Tel +359-2-9172268; E-mail: ivanka.i.dimova@gmail.com

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Abbreviations

ACM: Arrhythmogenic Cardiomyopathy; ARVD/C: Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy; CMR: Cardiac Magnetic Resonance; CRT-D: Cardiac Resynchronization Therapy- Defibrillator; DCM: Dilated Cardiomyopathy; ECG: Electrocardiogram; EDV: End-Diastolic Volume; EF: Ejection Fraction; ESV: End-Systolic Volume; FAC: Fractional Area Change; HCM: Hypertrophic Cardiomyopathy; HR: Heart Rate; LCx: Left Circumflex Artery; LGE: Late Gadolinium Enhancement; LV: Left Ventricle; LVEF: Left Ventricle Ejection Fraction; MR: Mitral Regurgitation; NGS: Next Generation Sequencing; PAP: Pulmonary Artery Pressure; RA: Right Atrium; RAP: Right Atrial Pressure; RV: Right Ventricle; RVOT: Right Ventricular Outflow Tract; RVP: Right Ventricular Pressure; SCD: Sudden Cardiac Death; TAPSE: Tricuspid Annular Plane Systolic Excursion; TR: Tricuspid Regurgitation

Introduction

Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy (ARVD/C) is a hereditary cardiomyopathy characterized by progressive fat or fibrofatty replacement of the Right Ventricular (RV) myocardium, which is a common cause of Sudden Cardiac Death (SCD) in the young men and athletes [1]. The cause of ARVD/C is not yet clear, but recent studies suggest it is most often related to desmosomal abnormalities [2,3]. ARVD/C is not a simple RV disease. Left Ventricular (LV) or biventricular involvement is increasingly identified in ARVD/C patients [4]. Cardiac Magnetic Resonance (CMR) is a valuable diagnostic tool for ARVD/C due to the high negative

predictive value, which can identify LV impairment and thus has a significant impact on clinical decision-making [5,6]. Most of the ARVD/C patients had CMR evidence of LV involvement, of which Late Gadolinium Enhancement (LGE) and Left Ventricular Ejection Fraction (LVEF) were the most sensitive indicators. Biventricular and left-dominant disease variants have been identified and have led some to use the term 'Arrhythmogenic Cardiomyopathy' (ACM) to define the broader spectrum of the disease phenotypic expressions. LV involvement can be considered a late manifestation of advanced disease; however, recent studies at the level of genetic characterization have hypothesized that potential LV involvement may develop ahead of significant RV dysfunction in patients with ARVD/C. CMR evidence of LV involvement is a strong independent predictor of hard cardiac events [7]. Additionally, the presence of LV dysfunction plays an incremental role in predicting adverse cardiac events compared to RV dysfunction alone.

Case Presentation

Patient presentation

A 73 years old patient was admitted in our clinic with symptoms and signs of decompensated right and left sided heart failure. There were the following concomitant diseases: optimally treated arterial hypertension and atrial fibrillation, known for 4 months before hospitalization. The treatment included Acenocoumarol and beta blocker - Bisoprolol 5 mg/daily.

Physical examination

The following symptoms were observed: elevated jugular venous pressure with positive venous pulse and hepatojugular reflux; vesicular breathing with basal crackles; Heart Rate (HR) 80/min, systolic murmur in the 4th left intercostal space, louder in inspiration; hepatomegaly, peripheral oedema.

Electrocardiogram (ECG): on admission-atrial fibrillation, HR 80/min.

Holter ECG - Atrial fibrillation, heart rate 60/min, premature ventricular beats, non-sustained wide complex tachycardia (Figure 1A).

Echocardiography demonstrated dilated cardiac chambers, predominantly right sided, mildly reduced left ventricular ejection fraction - 42%; right ventricular dysfunction, Fractional Area Change (FAC) - 28%; Tricuspid Annular Plane Systolic Excursion (TAPSE) - 12 m/sec, Moderate Mitral Regurgitation (MR), severe Tricuspid Regurgitation (TR), with Pulmonary Artery Pressure (PAP) - 37 mmHg (Figure 1B).

Invasive study: coronary arteriography reveals no stenosis but dilation and aneurisms of coronary arteries, Left Circumflex Artery (LCx) arises from right coronary sinus. Right heart catheterization: high Right Atrial Pressure (RAP) - 25/30/21 mmHg with severe tricuspid regurgitation and Ventricularization of Right Atrium (RA), mild pulmonary hypertension PAP - 35/20 mmHg; Right Ventricular Pressure (RVP) - 37/9/17 mmHg. Regarding diagnostics of unknown cardiomyopathy CMR was performed - cardiomegaly with RV and RA dilation (RA - 75/67 mm), apical trabeculation of RV, dilated inferior v. cava - 30 mm, desynchrony in RV Outflow Tract (RVOT), hypokinesis of the apical and septoapical segments of the RV and LV, jet of significant tricuspid regurgitation with incomplete coaptation of the valve leaflets. Late Gadolinium Enhancement (LGE) in RV free wall to RVOT and LV apical and septoapical zone. The RVEF was 36.5% and LVEF - 45%, with moderately increased End-Diastolic Volume (EDV) and End-Systolic Volume (ESV) of LV (Figures 1C-1E). Due to the wide complex tachycardia, CRT-D (Cardiac Resynchronization Therapy-Defibrillator) was implanted followed by no dynamics in echo-parameters, clinically stable, no sustained wide complex tachycardia on Holter ECG.

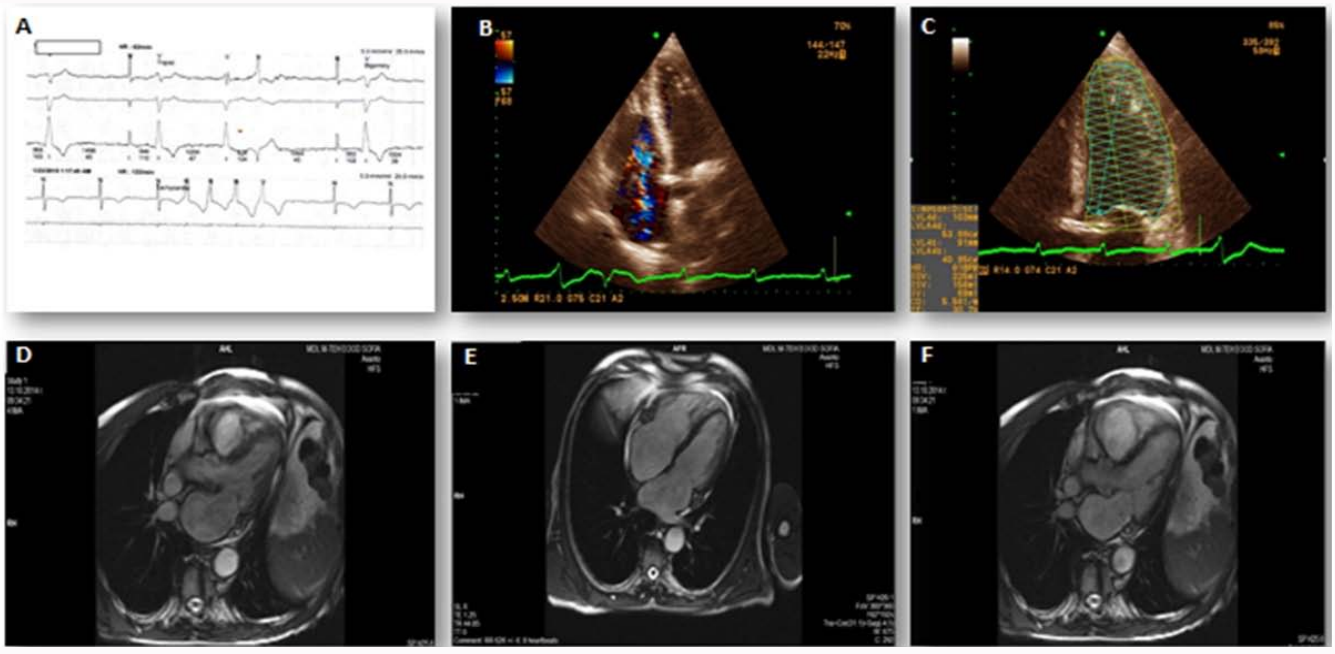

Figure 1: A) Holter ECG. B, C) Echocardiography on 1st day. Severe tricuspid regurgitation, ejection fraction 32%. D-F) Cardiac magnetic resonance image shows cardiomegaly due to RV and RA dilation (RA - 75/67 mm), apical trabeculation of RV, dilated inferior v. cava - 30 mm, desynchrony in RVOT, hypokinesis of apical and septoapical part of LV, jet phenomenon proximal of tricuspid valve during systole with incomplete coaptaion of valve leaflets. LGE in RV free wall to RVOT and LV apical and septoapical zone. RVEF – 36.5% and LVEF - 42% with moderate increasing of EDV and ESV of LV.

Genetic testing

Genetic testing was offered to the patient and performed after signing an Informed consent. Using Next Generation Sequencing (NGS) of genes' panel for hereditary cardiomyopathy, the following genetic variant was detected: NM_000256.3 (MYBPC3): c.1316G>A (p.Gly439Asp). This sequence change replaces glycine with aspartic acid at codon 439 of the MYBPC3 protein (p.Gly439Asp). The glycine residue is highly conserved and there is a moderate physicochemical difference between glycine and aspartic acid. This variant is present in population databases at an extremely low frequency (rs763045718, ExAC 0.01%). ClinVar contains an entry for this variant in a patient with cardiomyopathy (Variation ID: 628463). Algorithms developed to predict the effect of missense changes on protein structure and function are either unavailable or do not agree on the potential impact of this missense change (SIFT: Deleterious; PolyPhen-2: Benign; Align-GVGD: Class C1). In summary, the available evidence is currently insufficient to determine the role of this variant in disease. Therefore, it has been classified as a Variant of Uncertain Significance.

Discussion

Abnormalities in cardiac Myosin Binding Protein C (MyBP-C, encoded by MYBPC3) are the most common cause of Hypertrophic Cardiomyopathy (HCM) – mutations are detected in about 30% of HCM cases. Most MYBPC3 mutations in HCM result in premature termination codons that cause RNA degradation and a reduction of MyBP-C in the heart [8]. Pathogenic or likely pathogenic variants (mostly missense and splicing mutations) in MYBPC3 were reported in about 5% of cases with Dilated Cardiomyopathy (DCM) as well [9]. It is an interesting observation how different mutations in a same gene could make different myosin dysfunctions. It was demonstrated that stepwise loss of MyBP-C resulted in reciprocal augmentation of myosin contractility. Direct attenuation of myosin function, *via* a damaging missense variant (F764L) that causes Dilated Cardiomyopathy (DCM), normalized the increased contractility from MyBP-C depletion [10]. Another therapeutic agent MYK-461, a pharmacologic inhibitor of myosin ATPase, rescued relaxation deficits and restored normal contractility in HCM cardiomyocytes with MYBPC3 mutations. These data define dosage-dependent effects of MyBP-C on myosin that occur across the cardiac cycle. Therapeutic strategies to MyBP-C activity may rescue depressed cardiac contractility in patients with DCM, whereas inhibiting myosin by MYK-461 should benefit the substantial proportion of HCM patients with MYBPC3 mutations.

Conclusion

We presented here detailed clinical symptoms of a patient with quite complex arrhythmogenic cardiomyopathy, with left ventricle involvement and anomalies in coronary arteries, whereby genetic testing revealed an extremely rare genetic missense variant in MYBPC3 gene. The genetic change in the exon 14 of the gene causes aminoacidic change Glycine/Aspartic acid with a moderate physicochemical difference in the protein. The association of this mutation with the development of that complex cardiomyopathy is worthy to be investigated, since it could have an important impact on the application of new treatment, using specific agents, connected to myosin activity.

References

1. Jain A, Tandri H, Calkis H, Bluemke DA. Role of cardiovascular magnetic resonance imaging in arrhythmogenic right ventricular dysplasia. J Cardiovasc Magn Reson. 2008;10(1):32.
2. Vimalanathan AK, Ehler E, Gehmlich K. Genetics of and pathogenic mechanisms in arrhythmogenic right ventricular cardiomyopathy. Biophys Rev. 2018;10:973-82.
3. Hoorntje ET, Te Rijdt WP, James CA, Pilichou K, Basso C, Judge DP, et al. Arrhythmogenic cardiomyopathy: Pathology, genetics, and concepts in pathogenesis. Cardiovasc Res. 2017;113(12):1521-31.
4. Berte B, Denis A, Amraoui S, Yamashita S, Komatsu Y, Pillois X, et al. Characterization of the left-sided substrate in arrhythmogenic right ventricular cardiomyopathy. Circ Arrhythmia Electrophysiol. 2015;8(6):1403-12.
5. Chellamuthu S. Is cardiac MRI an effective test for arrhythmogenic right ventricular cardiomyopathy diagnosis? World J Cardiol. 2014;6(7):675.
6. Motevali M, Siahi Z, Mohammadzadeh A, Sangi A. Cardiac Magnetic Resonance Imaging (MRI) findings in Arrhythmogenic Right Ventricular Dysplasia (ARVD) compared with echocardiography. Med Sci. 2018;6(3):80.
7. Aquaro GD, Pingitore A, Di Bella G, Piaggi P, Gaeta R, Grigoratos C, et al. Prognostic role of cardiac magnetic resonance in arrhythmogenic right ventricular cardiomyopathy. Am J Cardiol. 2018;122(10):1745-53.
8. Helms AS, Tang VT, O'Leary TS, Friedline S, Wauchope M, Arora A, et al. Effects of MYBPC3 loss-of-function mutations preceding hypertrophic cardiomyopathy. JCI Insight. 2020;5(2):e133782.
9. Hershberger RE, Norton N, Morales A, Li D, Siegfried JD, Gonzalez-Quintana J. Coding sequence rare variants identified in MYBPC3, MYH6, TPM1, TNNC1 and TNNI3 from 312 patients with familial or idiopathic dilated cardiomyopathy. Circ Cardiovasc Genet. 2010;3(2):155-61.
10. Toepfer CN, Wakimoto H, Garfinkel AC, McDonough B, Liao D, Jiang J, et al. Hypertrophic cardiomyopathy mutations in MYBPC3 dysregulate myosin. Sci Transl Med. 2019;11(476):eaat1199.