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CASE REPORT

Pathogenic *BAG3* Variant in Peripartum Cardiomyopathy and Significant Family History of Sudden Death

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Abstract

The *BAG3* gene encodes the BAG3 protein, a multifunctional chaperone involved in proteostasis and protection of cardiomyocytes. Pathogenic *BAG3* variants have previously been associated with dilated cardiomyopathy (DCM), including peripartum cardiomyopathy (PPCM). We present the case of a woman who complained of palpitations during the late postpartum period and was diagnosed with left ventricular dysfunction; genetic testing revealed a pathogenic variant of the *BAG3* gene. Several cases of sudden death were noted in her family history. After 3 years of follow-up, ventricular function was significantly improved with regular cardiovascular medication, and no symptoms were reported. We emphasize the role of genetic testing in this case.

Introduction

Genetic cardiomyopathies represent an important cause of heart failure in young people.[1] The *BAG3* gene, located in locus 10q26.11, has 4 exons and encodes the BAG3 protein, which acts as chaperone involved in complex quality system control including proteostasis, as well as sarcomeric integrity and viability.[2] Pathogenic *BAG3* variants have been associated with dilated cardiomyopathy (DCM) and peripartum cardiomyopathy (PPCM).[3]

Keywords

Dilated Cardiomyopathy; Peripartum Period; Sudden Death

Case report

A 36-year-old Black female was referred to the University Hospital for cardiologic evaluation due to previous diagnosis of DCM/PPCM associated with family history of sudden cardiac death (SCD). She had been diagnosed with type 1 diabetes at the age of 22 and treated with insulin for 16 years, with no record of heart disease. She became pregnant at the age of 32 and presented at gestational week 34 with gestational hypertension. Her daughter was born by cesarean section, and both mother and newborn were discharged from the hospital after 48 hours. Two weeks later, the patient presented with palpitations and was admitted to the emergency room. The electrocardiogram (ECG) revealed sinus rhythm and ventricular repolarization changes in the anterior wall, including a notable inversion of the T waves. Denying other symptoms, she discharged against medical advice and was referred for further investigation. Cardiac magnetic resonance imaging (MRI) performed 2 weeks after the incident showed enlargement of the left ventricle (LV) with reduced left ventricular ejection fraction (LVEF) (29%) and transmural late gadolinium enhancement (LGE) in the anterolateral wall. She was treated with enalapril 10 mg twice daily, rosuvastatin 20 mg once daily, and metoprolol succinate 25 mg once daily, with improvement in symptoms. Despite the cardiac MRI findings, other etiologies (e.g., coronary artery disease) were not pursued, and she was diagnosed with PPCM at that time.

At our first examination, she was asymptomatic. Physical examination was unremarkable apart from overweight. She was in New York Heart Association functional class I. ECG showed sinus rhythm, with no

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abnormalities detected at that time. A two-dimensional echocardiogram was performed, confirming signs of DCM with enlargement of the end-systolic and end-diastolic diameters, LVEF of 49% (Simpson's method), and diffuse LV hypokinesis. Considering the diagnosis of diabetes and the previously reported results, coronary computed tomography angiography was initially performed, which showed no coronary calcification, atherosclerosis, or obstructive lesions (calcium score = 0).

Her family history was remarkable. She is the daughter of non-consanguineous couple, and her father, brother, and paternal half-brother died of SCD at the ages of 42, 28, and 26, respectively. With this background strongly suggesting an autosomal dominant disease, we decided to further investigate a possible hereditary cardiomyopathy. Therefore, she was offered a genetic test, which revealed a heterozygous pathogenic variant in the *BAG3* gene (NM_004281.3: c.824del; p.Ser275Thrfs*32). The genetic test included all genes recommended by the ClinGen Expert Panel as associated with the DCM phenotype.[4] The adult at-risk relatives were all deceased, and the children were either very young or unavailable for testing (Figure 1).

We continued the clinical treatment previously started in the emergency room with enalapril 10 mg twice daily, rosuvastatin 20 mg once daily, and metoprolol succinate 25 mg once daily. Three years after delivery, a repeat MRI of the heart showed a remarkable improvement in LV function compared to the previous examination (Figure 2). Due to the risk of SCD, an evaluation for an implantable cardioverter defibrillator was considered. However, myocardial findings, including LGE, were significantly reduced, and there were no symptoms or ventricular arrhythmias and good tolerance to pharmacotherapy.

Discussion

This patient's clinical presentation is suggestive of DCM that initially presented as PPCM. The incidence of PPCM varies according to geographic regions. In Haiti, the incidence is approximately 1 in 300 live births, whereas, in the USA, it ranges from 1 in 1,000 to 1 in 4,000.[5] The reasons for this distinct epidemiological distribution remain unknown, although ethnic factors may contribute as potential risk factors. In a cohort study, truncating variants in the *TTN* gene were found to be the most prevalent (10%) among PPCM cases. Additionally, variants in *DSP* (1%), *FLNC* (0.8%), and *BAG3* (0.2%) genes have also been identified in PPCM.[3]

Hereditary DCM may initially manifest as PPCM, and both have phenotypic and genetic similarities, including cases associated with a genetic variant in *BAG3*.[2] Hereditary DCM is usually inherited in an autosomal dominant manner, and *BAG3* is one of the causes.[6,7] In this report, the presence of cardiomyopathy in the family is a strong indication of a genetic etiology. However, a negative family history should not preclude testing, as the variants may be *de novo*.[8]

The *BAG3* gene encodes a multifunctional chaperone that is highly expressed in cardiac muscle. This protein is involved in the quality control system and in the maintenance of proteostasis.[2] Dysfunction of the BAG3 protein leads to disruption of the Z-lineage in the sarcomere, increases the susceptibility of cardiomyocytes to apoptosis, aggregates disordered proteins, and alters myofibrillar architecture. In addition, male sex has been associated with a higher incidence of cardiomyopathy and a worse prognosis, suggesting a non-genetic factor, such as the cardioprotective effect of estrogen. It should be noted that reverse remodeling in DCM can occur in more than 40% of cases, predicting excellent prognosis.[9] Despite reverse remodeling, follow-up is recommended.[10] Optimal medical therapy with angiotensin-converting enzyme inhibitors, beta-blockers, and aldosterone antagonists is useful in postpartum patients with DCM/PPCM to reduce the risk of SCD and progressive heart failure.[6,11]

It is noteworthy that, in this case, other differential diagnoses could not be completely excluded, such as myocardial infarction with non-obstructive coronary arteries or spontaneous coronary artery dissection, which are well recognized as possible etiologies of heart disease in women, especially during the peripartum period.[12]

Conclusion

The etiology of PPCM remains uncertain, but there is robust evidence about the association between genetic susceptibility, including *BAG3* gene variants, and DCM/PPCM. In this case, we illustrate the identification of a pathogenic *BAG3* variant related to PPCM and a family history of sudden death.

This report also emphasizes the importance of family history in the proper investigation of DCM/PPCM. Identification of the gene variant is important to understand the disease, possible treatments, and prognosis. It is worth

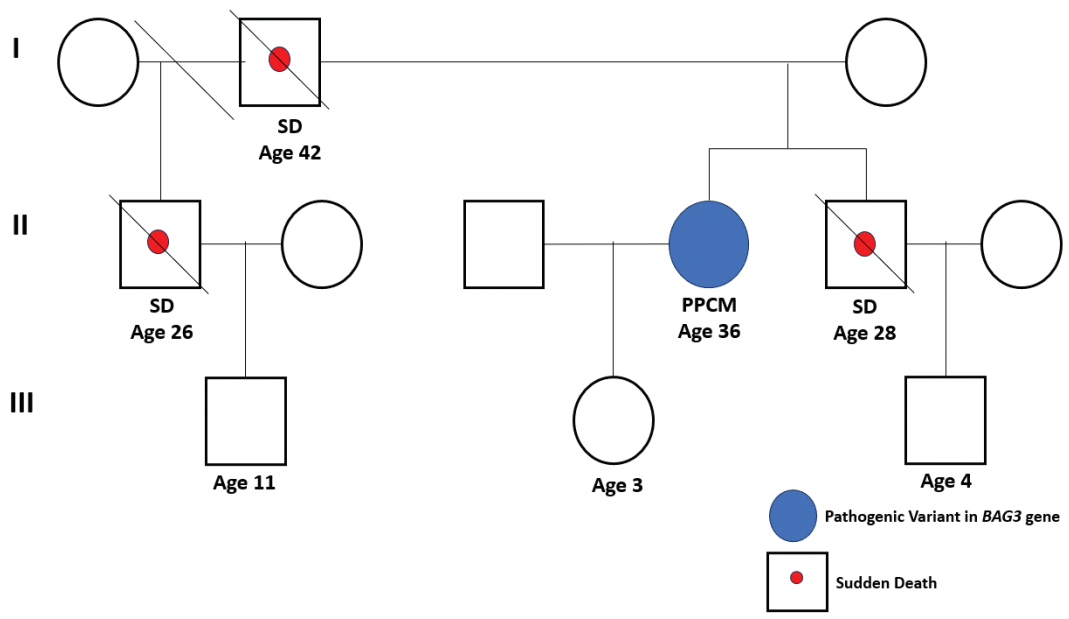

Figure 1 – The patient's pedigree.
PPCM: peripartum cardiomyopathy; SD: sudden death.

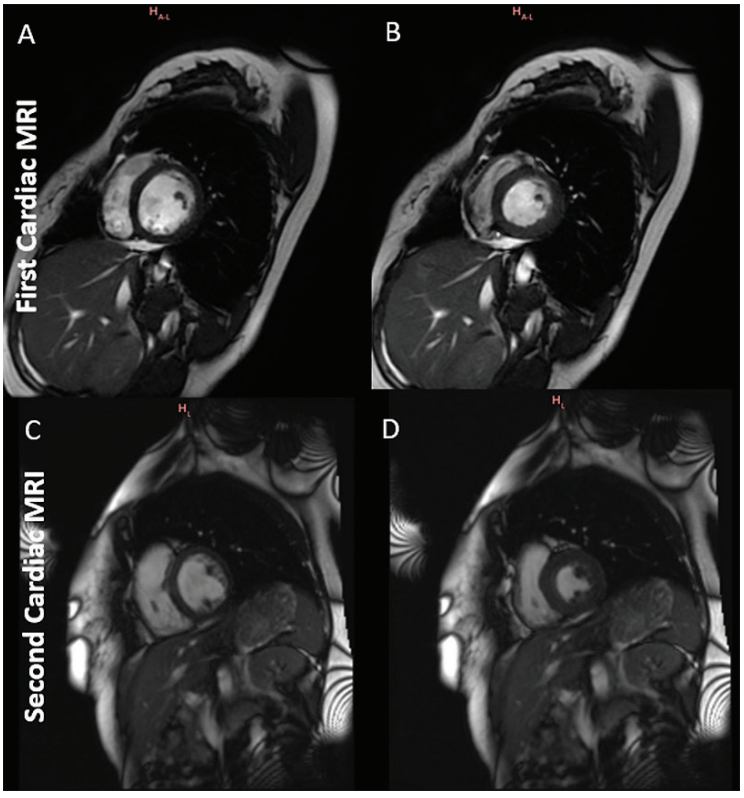

Figure 2 – Cardiac cine MRI (short axis) showing improvement in left ventricular enlargement and LVEF after 3 years.
A and C) maximum diastolic LV; B and D) maximum systolic LV.

noting that genetic counseling can not only improve outcomes in cardiomyopathy, but also prevent and minimize morbimortality in probands and their families.

Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, statistical analysis, obtaining financing, writing of the manuscript, critical revision of the manuscript for intellectual content: Pereira APLC, Rodrigues EV, Tassi EM, Lima MAFD, Souza F.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

This study is not associated with any thesis or dissertation work.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of the HUGG-UNIRIO/EBSERH under the protocol number 42416621.3.0000.5258. All the procedures in this study were in accordance with the 1975 Helsinki Declaration, updated in 2013. Informed consent was obtained from all participants included in the study.

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