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Authors
Wang, Stephani C
Smith, Charles D
Lombardo, Dawn M
et al.

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Short communication

Characteristics of VCP mutation-associated cardiomyopathy

Stephani C. Wang[a], Charles D. Smith[b], Dawn M Lombardo[a], Virginia Kimonis[c,*]

[a] *Division of Cardiology, Department of Medicine, University of California, Irvine, CA USA*
[b] *Division of Neurology, Department of Medicine, University of Kentucky, Lexington, KY USA*
[c] *Division of Genetic and Genomic Medicine, Department of Pediatrics, University of California, Irvine, CA USA*

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Abstract

VCP associated inclusion body myopathy, Paget's disease of bone, and Frontotemporal Dementia (IBMPFD, VCP disease, or multisystem proteinopathy type 1 (MSP1)) is an autosomal dominant disease caused by missense mutations in the *VCP* gene, which plays a crucial role in ubiquitin-proteasome dependent degradation of cytosolic proteins. Those diagnosed with the disorder often suffer from cardiovascular complications in the advanced stages. We conducted an observational cross-section study to investigate echocardiographic features of asymptomatic carriers and those affected by the disease to determine the differences and potential early features of the VCP-associated cardiomyopathy. The study cohort constituted of 32 patients with *VCP* mutations including 23 affected individuals diagnosed with myopathy +/- Paget disease of bone, and 9 asymptomatic carriers. Among the affected individuals, 95.7% had myopathy, 43.5% had Paget's disease of bone, and none had frontotemporal dementia, and the carriers were asymptomatic. Not surprisingly the carriers were younger (mean age 38.4 ± 3.8 years), than the affected cohort (mean age 50.6 ± 9.1 years; $p < 0.001$). There was a 43.5% prevalence of diastolic dysfunction on echocardiogram among patients who were symptomatic from VCP disease, whereas none of the two asymptomatic carriers manifested diastolic dysfunction ($p = 0.017$). Among the 5 affected individuals who had consequential echocardiograms 2–3 years apart, three affected individuals developed diastolic dysfunction, and two already had diastolic dysfunction on the initial study. The two carriers did not develop diastolic function changes. This present study represents the largest series of echocardiograms performed in patients and asymptomatic carriers with VCP myopathy, and will pave the way for future, large-scale studies that may include other imaging modalities such as cardiac MRI and strain evaluation in patients at all stages of the disease.

Keywords: VCP mutation; Cardiomyopathy; Echocardiogram; Diastolic Dysfunction.

1. Introduction

VCP disease is a rare, autosomal dominant disorder and includes combinations of hereditary Inclusion Body Myopathy (h-IBM), Paget's Disease of Bone (PDB), Frontotemporal Dementia (FTD) and Amyotrophic Lateral Sclerosis (ALS). The disease is caused by mutations in the *VCP* gene located at 9p13 - p12 that encodes valosin-containing protein. VCP is a hexameric protein of the AAA (ATPases associated with diverse cellular activities) family that interacts with several cofactors and facilitates the degradation of polyubiquitylated substrates in the proteasome, endoplasmic reticulum or autophagy [1]. VCP is also involved in variety of activities including cell cycle, membrane fusion, and mitochondrial functions [1]. VCP disease is characterized by a variety of clinical manifestations including progressive muscle weakness mainly involving the proximal muscles with muscle atrophy in 90%, bone pain and focal deformation from PDB in approximately 42%, FTD in 30%, and approximately 10% of individuals develop classic ALS [2,3,4]. There is 90% penetrance for the myopathy, and most people are diagnosed by the 3rd or 4th decade, though expression is variable, even among family members. Eventually in advanced stages of the disease, cardiomyopathy and/or respiratory failure develop, leading to mortality, typically in the 50 s to 60 s in most cases [4]. Despite the significant mortality and morbidity associated with this devastating disease, effects on the cardiovascular system and mechanism for development of cardiomyopathy are not well understood and only described in case reports or

* Corresponding author.
E-mail address: vkimonis@uci.edu (V. Kimonis).

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series [5]. The genetic association and risk factors associated with development and progression of cardiomyopathy in VCP associated disease, and thus its contribution to mortality in significant portion of affected individuals is largely unclear. In response to this dearth of information, our study focused on characterizing echocardiographic features in a cross-section study in patients with VCP associated myopathy including asymptomatic carriers, to potentially identify early stages of cardiomyopathy in order to enhance understanding of this rare but fatal disease.

2. Methods

Study Population: We conducted an observational cross-section study consisting of 32 patients with *VCP* mutations at two major institutions. This cohort included affected individuals who had myopathy and/or PDB ($n=23$) and asymptomatic carriers with no clinical manifestations ($n=9$). The study was approved by the local Institutional review boards at UC Irvine (#2007–5832) and University of Kentucky, Lexington, KY (#44,617–020237F6G), and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all patients for the studies. Data collected included demographics, clinical evaluations for myopathy, PDB and FTD and, genetic testing if not previously obtained.

Echocardiography**:** Echocardiogram characteristics were evaluated including valvular function, left ventricular morphology and function, right ventricular function and size, and presence of diastolic dysfunction. Left Ventricular End-Diastolic (LVED) dimensions and end-diastolic thickness of the posterior and septal walls were measured using standard M-mode in parasternal long-axis views. Right ventricular size and Tricuspid Annular Plane Systolic Excursion (TAPSE) were measured in 4-chamber views. LV ejection fraction (LVEF) with the biplane Simpson method in apical 4 and 2-chamber views. Diastolic dysfunction was noted to be present if: left atrial volume index $>34\,ml/m^2$, tricuspid regurgitant systolic jet velocity $>2.8\,m/s$, average E/e' ratio >14, and septal e' velocity <7 and lateral e' velocity <10. If three or more criteria are positive, then E/A ratios was examined and stage of diastolic dysfunction diagnosed based on the guideline [6]. Diastolic dysfunction was diagnosed based on the most recent recommendations by the American Society of Echocardiography, and was determined by obtaining left atrial volume index, tricuspid velocity, E/e' ratio, and finally septal and lateral e' velocity. E/A refers to ratio of peak velocity of blood flow measured in early diastole from left ventricular relaxation (E) to the peak velocity in late diastole from atrial contraction (A). Additionally, e' refers to the mitral annular velocity during early diastole, and E/e' is another way to assess diastolic dysfunction. All echocardiograms were read by the same physician at each respective site.

Data Analysis: Continuous data are presented as mean ± standard deviation (SD) and categorical variables as percentage (%). Pearson's correlation was performed to evaluate for association between disease severity and echocardiogram features. Statistical significance was established with a probability $p < 0.05$. Statistical analysis was performed using SPSS software (Windows version 11.5, SPSS, Inc. Chicago, IL, USA).

3. Results

3.1. Study population

The study cohort constituted 23 affected individuals (71.9%) diagnosed with VCP disease and 9 asymptomatic carriers (28.1%). Males represented 37.5% of the overall study population with relatively more female patients in the carrier group (77.8 vs 56.5%; $p=0.264$). The affected individuals were older at a mean age of 50.6 ± 9.1 years compared to the carrier group whose mean age was 38.4 ± 3.8 years ($p < 0.001$). Among the affected group, 95.7% had myopathy, 43.5% had PDB. Because individuals with FTD had advanced manifestation of VCP disease and were unable to travel to the two centers, they were not represented in this study. None of the carriers by definition had any clinical features. There were no statistically significant differences in the creatinine kinase (93.5 ± 28.1 vs 161.6 ± 101.9 respectively; $p=0.066$), however the affected population had higher mean alkaline phosphatase (171.2 ± 184 vs. 80.9 ± 51.7, $p=0.17$) levels compared to the control population reflecting the associated PDB.

3.2. Left ventricle evaluation

None of the patients included in the study had moderate or severe systolic dysfunction of left ventricle (ejection fraction $\leq 40\%$). Among all patients, the mean left ventricular ejection fraction was $65\pm8.3\%$ (normal $\geq 55\%$), with a mean internal diameter (LVID) of $4.6\pm0.4\,cm$ (normal 3.4–5.7 cm) during diastole. At the end of diastole, the mean left ventricular interventricular septal (IVS) thickness was $0.9\pm0.2\,cm$ (normal 0.7–1.1 cm), and the posterior wall (LVPW) thickness was $0.9\pm0.2\,cm$ (normal 0.7–1.1 cm). After adjusting for age, there were no statistically significant differences between the two groups in IVS, LVID or LVPW values. The ejection fraction also was similar between carrier and affected cohort, $63.7\pm6.7\%$ and $65.5\pm8.8\%$ respectively. However, there was a greater incidence of diastolic dysfunction in affected group than carriers (43.5% vs 0%; $p=0.017$). In this affected group, the presence of diastolic dysfunction was greater in those with the combination of myopathy and PDB, than myopathy alone (55.6 vs 38.5%), though the difference was not statistically significant ($p=0.429$). One carrier did have mild left ventricular hypertrophy without evidence of systolic or diastolic dysfunctions. Additionally, age itself did not correlate with the presence of diastolic dysfunction in this study.

Table 1
Echocardiographic characteristics in carriers and affected individuals.

	Normative Values	Carrier ($N=12$)	Affected ($N=23$)	p-value
Left ventricular function				
Left ventricular hypertrophy (%)		88.9	78.3	0.489
IVSd (cm)	0.7–1.1	0.9 ± 0.2	0.9 ± 0.2	0.730
LVIDd (cm)	3.4–5.7	4.5 ± 0.5	4.7 ± 0.4	0.381
LVIDs (cm)		2.5 ± 0.6	2.8 ± 0.5	0.193
LVPWd (cm)	0.7–1.1	0.9 ± 0.2	0.9 ± 0.2	0.518
LA dimension (cm)	1.9–4.0	63.7 ± 6.7	65.5 ± 8.8	0.573
LA Volume Index (cm)	16–28	4.7 ± 2.3	3.5 ± 0.5	0.058
Aortic root diameter (cm)	2.4–3.7	2.9 ± 0.7	2.9 ± 0.4	0.807
Ejection Fraction (%)	> 55	23.5 ± 8.9	23.6 ± 8.3	0.985
Diastolic dysfunction (%)		0.0	43.5	0.017
Right ventricular function				
TR velocity (m/s)	≤ 2.8	2.4 ± 0.5	2.2 ± 0.5	0.639
Right atrium pressure (mm hg)	2–6	10.0	8.9 ± 2.7	0.435
RVSP (mmHg)	≤ 25	33.5 ± 9.9	29.9 ± 10.7	0.562
RV size enlargement (%)		0.0	0.0	
RV dysfunction (%)		0.0	0.0	
Dilated or non-collapsible IVC (%)		0.0	8.7	0.361
Pericardial effusion (%)		0.0	0.0	
Valvular regurgitation				
MR (%)		33.3	26.1	0.682
TR (%)		33.3	52.2	0.337
AR (%)		0.0	4.3	0.525
PR (%)		22.2	26.1	0.820

*IVSd=Interventricular septum during diastole; LVPWd=Left ventricular posterior wall during diastole; LVIDd=left ventricular internal diameter during diastole; LVIDs=left ventricular internal diameter during systole; LA=left atrium; RVSP=right ventricular systolic pressure; RV=right ventricle; MR=mitral regurgitation; TR=tricuspid regurgitation; AR=aortic regurgitation; PR=pulmonic regurgitation.

3.3. Right ventricle evaluation

Right ventricle evaluation also showed no statistically significant differences between carriers and affected cohort. Overall, both groups had similar Right Ventricular Systolic Pressures (RVSP), though carriers had a slightly higher mean value. We did not identify any individual with advanced end-stage heart failure patients with severely reduced left ventricular systolic function. No other significant differences, including valvular dysfunction were observed between the two groups (Table 1).

3.4. Evaluation of disease progression

In this cross-section study, five affected individuals and two carriers had follow-up echocardiogram 2–3 years apart. Among the five affected individuals, two already had diastolic dysfunction on the initial echo which was also reflected on the follow-up studies, and three developed diastolic dysfunctions on the following echocardiogram. Among the two carriers, there were no significant differences in the echocardiographic parameters between the baseline and follow-up studies. One of the carriers was reported to develop mildly dilated ventricles and reduced systolic function seven years later.

4. Discussion

Cardiomyopathy in VCP inclusion body myopathy is not-well understood, with very little information known regarding the symptoms and prognosis of this under-recognized component of this rare disease. In an effort to enhance our understanding of this disease process, we studied the echocardiographic characteristics in those affected by the disease process and compared the findings with asymptomatic carriers of the *VCP* mutations to investigate potential early signs of cardiac involvement and differences in the two groups. To-date this is the largest- observational study characterizing echocardiogram features of individuals diagnosed with VCP disease. Our study showed a 43.5% prevalence of diastolic dysfunction on echocardiogram in affected individuals and none in carriers. Sub-analysis based on gender did not reveal any significant differences in echocardiographic features in carriers or affected cohorts. According to literature, normal prevalence of diastolic dysfunction is 30.6% with 25.3% in stage I diastolic dysfunction among individuals 40–55 years of age in the general population [7]. It is important to note that in the affected group, all but two patients had preserved systolic function, and two had mildly reduced ejection fraction of 50–55%. Advanced cardiomyopathy with LVID dilation observed in case reports was not seen in our study population. Finally, there was a trend for a higher incidence of diastolic dysfunction in patients with PDB and myopathy compared to myopathy alone. This may be an important finding, since the multiple small arteriovenous shunts in PDB are known to be associated with a high cardiac output state [8]. Under high-cardiac output, there is also a low systemic vascular resistance

due to arteriovenous shunting, which leads to depressed systemic arterial pressure and increased cardiac filling pressures. Simultaneously, sympathetic nervous systems and renin-angiotensin-aldosterone axes are activated, leading to increased renovascular resistance and thus volume overload. It is this chronic hypervolemic state that leads to ventricular enlargement, remodeling, and eventually heart failure [9]. We therefore recommend that PDB when diagnosed should be treated with bisphosphonates in order to avoid an additional burden to the cardiovascular system.

Cardiac involvements have been described in several cases or case series. Dilated cardiomyopathy was reported by Kimonis, et al. (2000) in a 11-member family affected by VCP disease, four members of which had cardiomyopathy ranging from premature coronary artery disease to congestive heart failure [10]. There have been reports of cases of VCP-associated cardiomyopathy mostly in individuals in the terminal stages of the disease [4,11,12,13]. Miller et al. (2008) reported four members of a family with dilated cardiomyopathy following echocardiography, two of whom had mild shortness of breath on exertion. All affected members were treated with angiotensin-converting enzyme inhibitors, one patient with symptomatic improvement. Postmortem analysis of the heart in a patient with VCP disease demonstrated left ventricular dilatation and thickening of the wall, and histopathological exam showed cellular hypertrophy of myocytes and multiple small parenchymal scars in both ventricles. Immunostaining of cardiac tissue showed multiple cardiomyocytes with ubiquitin-positive cytoplasmic and single nuclear inclusions [12]. A clinical report did not report associated cardiomyopathy [14]. Because there are currently no guidelines for cardiovascular evaluation of patients with VCP disease, the true incidence of cardiomyopathy however is unknown. Treatment of VCP disease is mainly symptomatic and palliation based such as physical therapy, respiratory support, and targeted treatments based on the organ involvement. For this reason, it is even more critical to understand risk factors for disease progression and initiate appropriate early intervention.

Mechanisms responsible for cardiomyopathy in VCP-associated cardiomyopathy is unclear. Lack of understanding is due to the rarity of the disease, lack of research and lack of standardized protocols for evaluation of patients. Studies in myoblasts from individuals with *VCP* mutations manifest vacuolization, an increase in autophagic marker LC3-II, increased apoptosis and defective myotube formation [1,15]. A dysregulation in protein degradation may disrupt myosin content and lead to disordered myofibrils [16]. A recent study in heart in transgenic mice overexpressing the VCP^{K424A} (mutation of lysine at position 524 within the D2 ATPase domain of VCP to alanine) known to dramatically reduced ATPase activity and produce a dominant-negative mutant, showed an up-regulation of endoplasmic reticulum mediated degradation complexes and ubiquitinated proteins, increased nuclear envelope proteins and lamins before the onset of cardiomyopathy. Analysis of gross morphology and histology at six months of age was normal, however at nine months of age revealed cardiac enlargement and atrial dilation in the VCP^{K524A} mice only. Electron microscopy of the heart in these mice exhibited intranuclear vesicles, intranuclear membrane less regions of low electron density, and mitochondrial ultrastructural abnormalities of the cardiomyocytes. Immunoblotting revealed increased nuclear envelope proteins and lamins, and proteomics revealed increased endogenous VCP interaction with RNA-binding proteins, and aggregation of large ribosomal subunit proteins [17]. Several mechanisms may be responsible for development of cardiomyopathy, which eventually lead to long-term fibrosis and dilation of the ventricle. Although unknown yet, genetic differences from variant in other genes in different individuals and families may be responsible for higher susceptibility to developing VCP associated cardiomyopathy. Large-scale evaluation of cardiac findings at different stages of disease, including advanced cardiomyopathy, in VCP patients is needed, including assessment of their echocardiographic characteristics, strain pattern, electrocardiogram, as well as cardiac MRI.

This the largest study to date evaluating echocardiographic features of patients with VCP disease, comparing affected individuals with unaffected carriers. The limitations of this study are that this is an observational cross-section study comparing carriers and the affected cohort, with limited longitudinal data available in a few individuals. Secondly, most patients have preserved systolic function and only two had mildly reduced function, thus our recruited cohort does not include patients who have advanced cardiomyopathy with reduced systolic function, left ventricular dilatation or scarring. The selection of individuals who were able to travel to our centers is most likely responsible for the differences seen between our study and other case reports and series. The study however paves the way for a larger future comprehensive, longitudinal study at several centers with a control group for comparison.

Diastolic dysfunction may be an early sign of cardiac involvement among these patients, and vigilant management with close monitoring is warranted in this phase. Echocardiogram strain evaluation as well as cardiac Magnetic Resonance Imaging (MRI) studies may add additional value in screening and monitoring this cohort in the future. Currently, there are no optimal treatments for diastolic dysfunction, as various treatments have been investigated but no survival benefits have been detected. However, once early cardiac dysfunction is detected, more vigorous and frequent monitoring should be implemented. It is also critical to initiate more aggressive risk factor management in these patients such as control of hypertension, dyslipidemia, obstructive sleep apnea, and smoking to reduce risk for coronary artery disease, tachyarrhythmias and other cardiac disease. Although no guideline is available, it may be reasonable to initiate treatment such as beta-blockers, especially among those with family history of VCP cardiomyopathy once signs of diastolic dysfunction is detected. Further large-scale studies are needed to enhance our current understanding the mechanism of cardiomyopathy, and has the potential to

prevent cardiovascular morbidity and mortality seen among patients with VCP disease.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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