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Prevalence of mutant ATTR cardiac amyloidosis in elderly African Americans with heart failure

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A valine to isoleucine amino acid substitution at position 122 (V122I or p.V142I) of the transthyretin (*TTR*) gene induces misfolding of this hepatic transport protein, conferring a clinical phenotype of restrictive cardiomyopathy. V122I is recognized as the world's most prevalent amyloidogenic TTR mutation with a prevalence of 3.4% in the general African American population.[1] Owing to clinical overlap with other common co-morbidities, including hypertensive heart disease, identification of V122I ATTR cardiomyopathy requires a high index of suspicion and is confirmed by specialized imaging, tissue biopsy, and/or genetic testing. Development of new ATTR-specific therapies raises the importance of accurate and timely identification of ATTR.

Despite large numbers of people carrying the V122I TTR mutation, recent data suggest that the clinical penetrance of disease in mutation carriers may be less than 10%. [2] However, no studies to-date have systematically and prospectively evaluated the role of genetic testing in identifying patients with V122I ATTR amyloidosis among high risk individuals with heart failure. We hypothesized that V122I ATTR amyloidosis constitutes an important cause of

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heart failure in elderly African Americans and that carrier status in this older population would be associated with a high degree of expression of the disease phenotype.

We prospectively and consecutively enrolled elderly African Americans over the age of 60 years with (1) an ICD-9/10 diagnosis of heart failure and (2) mean left ventricular wall thickness of at least 12 mm from November 2014 to January 2017 at Boston Medical Center (n=101). Patients with a known diagnosis of cardiac amyloidosis were excluded from the study. Genetic testing was performed from a peripheral blood sample using a two-step process as previously described. [3] Genotype positive patients were referred to the Boston University Amyloidosis Center for further evaluation to confirm the presence of cardiac amyloidosis using the currently accepted consensus diagnostic approach. [4] Demographics, biomarker, echocardiographic, and electrocardiographic information were collected from the medical record. Data collected as part of this study have been recently reported, focusing on the development and validation of diagnostic methods for cardiac amyloidosis. [3] The Boston University Medical Center institutional review board approved data collection and analyses.

Of 101 enrolled patients, two were excluded from further analysis due to insufficient blood sample for V122I identification. Genetic testing confirmed V122I genotype in n=5 patients conferring a 5.05% prevalence of the mutation in this population of elderly heart failure patients, 2.7% in the female and 6.7% in the male population (p=0.7). The characteristics of the five identified carriers with the mutant *TTR* allele are shown in Table 1. Our observed prevalence is slightly higher than the background US population. We also note that our observed prevalence is lower than that of the Afro-Caribbean UK experience [5]-- a discrepancy likely due to differences in the genetic backgrounds of the two different countries.

Notably two of five mutation carriers were confirmed to have ATTR amyloid cardiomyopathy, a third had cardiac MRI findings consistent with amyloidosis, and one carrier had a normal Tc^{99m}-pyrophosphate scan indicating the absence of ATTR cardiac amyloidosis. The last carrier was lost to follow-up and did not have confirmatory testing for ATTR amyloidosis. While the number of patients is small, this exploratory cohort suggests that screening elderly African American individuals with heart failure for the presence of mutant *TTR* may be worthwhile as carrier status is associated with clinical expression of the disease phenotype in the majority of these patients. Importantly, despite being a longstanding amyloidosis referral center, none of the patients recruited from our general cardiology or heart failure clinics had clinically suspected ATTR amyloidosis at the time of genotyping. Our data of high rates of disease expression in advanced age is consistent with the reported late onset character of this infiltrative cardiomyopathy. We have recently reported the utility of a point-of-care risk calculator as a means to screen of ATTR V122I amyloidosis. [3] Our data, although preliminary, argue that testing of at risk individuals is reasonable, and that geno-positivity identified in elderly Black heart failure patients is likely to be associated with the clinical phenotype of ATTR amyloidosis.

In summary, this small study supports the hypothesis that the prevalence of misdiagnosed V122I ATTR is high in elderly African Americans with heart failure. High clinical suspicion

and further testing of at risk patients is essential for timely diagnosis and treatment of this population.

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Table 1

Characteristics of V122I TTR gene carriers

	Carrier #1	Carrier #2	Carrier #3	Carrier #4	Carrier #5
Demographics					
Age (years)	65	66	75	77	87
Sex	Male	Male	Male	Female	Male
BMI (kg/m ²)	25.5	32.6	30.2	33.1	29.4
History of HTN	Yes	Yes	Yes	Yes	Yes
History of Diabetes	No	No	No	Yes	Yes
Biomarkers					
BNP (ng/L)	1359	568	782	358	103
Troponin I (ng/L)	0.23	0.161	0.245	0.077	0.165
Creatinine (mg/dL)	1.37	1.62	1.18	0.84	1.8
Echocardiography					
LVEF (%)	30	55	58	60	60
IVSd (mm)	12	15	18	14	16
PWD (mm)	12	15	17	14	15
LVEDD (mm)	64	49	42	43	44
Grade of diastolic dysfunction	3	2	3	1	1
Electrocardiography					
Heart rate (bpm)	64	85	61	66	70
PR interval (mm)	166	152	156	208	132
QRS interval (mm)	106	96	76	92	114
QTc interval (mm)	453	452	422	480	454
Mean limb lead QRS voltage (mm)	8	6	4	10	6
Confirmatory testing for cardiac amyloidosis					
Cardiac MRI	Heterogeneous transmural late gadolinium enhancement	NP	NP	NP	NP
Tc-99 PYP scan	NP	Positive for TTR amyloid	Positive for TTR amyloid	Negative for TTR amyloid	NP

	Carrier #1	Carrier #2	Carrier #3	Carrier #4	Carrier #5
Fat pad biopsy	NP	Positive for Congo Red staining	Negative for Congo Red staining	NP	NP
Serum immunofixation electrophoresis	NP	No monoclonal protein detected	No monoclonal protein detected	No monoclonal protein detected	No monoclonal protein detected
Kappa free light chains (mg/L)	NP	14.2	21.6	17.4	8870 *
Lambda free light chains (mg/L)	NP	10.2	13.4	10.3	4440 *
Kappa/Lambda free light chain ratio	NP	1.39	1.61	1.69	2.0 *

BMI: Body mass index, BNP: B-type natriuretic peptide, HTN: Hypertension, IVSd: Interventricular septum diameter, LVEDD: Left ventricular end diastolic diameter, LVEF: Left ventricular ejection fraction, MRI: Magnetic resonance imaging, NP: Not performed, PWd: Posterior wall diameter, Te99 PYP scan: Technetium 99 pyrophosphate scan, TTR: Transthyretin.

* Assay for total kappa and lambda light chains instead of free light chains used