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CLINICAL CASE CHALLENGES

Phenotypic Spectrum of Transthyretin Cardiac Amyloidosis in a Family

Impact of Mutation Zygosity and Sex

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The amyloidoses are a family of disorders in which protein misfolding results in insoluble fibril formation and aggregation. Amyloid deposits disrupt tissue architecture and organ function (1,2). Over 27 different precursor proteins have been identified as being amyloidogenic (1,2). The 2 most clinically significant proteins associated with cardiac amyloidosis are immunoglobulin light chain and transthyretin (TTR) (1,2). Cardiac TTR amyloidosis (ATTR) can be hereditary (hATTR) or wild-type ATTR. Hereditary ATTR occurs due to a pathogenic mutation in the TTR gene, which occurs either spontaneously or as a result of an autosomal dominant inherited mutation. Conversely, wild-type ATTR involves no mutation of the TTR gene and typically occurs due to aging and is most often identified in patients after the age of 70 years (1,2).

There are over 100 confirmed pathogenic point mutations in the TTR gene that cause hATTR (2). In the United States, the most common variant involves a substitution of valine for isoleucine at position 122 (V122I) (1-4). This variant is almost exclusively identified in those of African descent, with nearly 3%-4% of all African Americans showing genopositivity (1-4). Studies have shown variation in severity of presentation based on hereditary pattern and sex (2,5,6). We fully characterized 3 sibling carriers of the V122I mutation to illustrate the phenotypic spectrum of disease presentation highlighting challenges and unanswered questions for surveillance and treatment for asymptomatic carriers (**Table 1**).

CASE 1: MR. C—THE HOMOZYGOUS MALE

Mr. C is a 62-year-old Black American male referred for evaluation of heart failure. The patient reported shortness of breath with climbing 1 flight of stairs, lower extremity pitting edema, and orthopnea over the course of the prior year. During this period, the patient had multiple hospital admissions for recurring pleural effusion and cough. He had a history of hypertension and a neuropathic history of bilateral carpel tunnel syndrome at age 49 years and sciatica at age 56. A transthoracic echocardiogram (TTE) revealed increased left ventricular wall thickness with a septal wall diameter of 2.1 cm and severe diastolic dysfunction with a restrictive filling pattern. Using 2-dimensional speckle-tracking echocardiography, we observed relative apical sparing of longitudinal strain. Cardiac magnetic resonance imaging (CMR) demonstrated diffusely elevated native T1 values, and we noted an abnormal nulling pattern on post-contrast inversion time (TI) scout sequences. Post-contrast delayed imaging also exhibited diffuse subendocardial enhancement in a pattern consistent with amyloidosis. Serum and urine immunofixation and free light chain assays showed no evidence of a monoclonal gammopathy. Technetium-99m pyrophosphate (PYP) with single-photon emission computed tomography (SPECT) imaging revealed increased uptake in the myocardium with a heart to contralateral lung uptake (HCL) ratio of 1.8 and a visual cardiac uptake grade of 3. On serum laboratory analysis, his serum troponin I and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentrations were elevated. Genetic testing revealed a homozygous V122I mutation, establishing the diagnosis of hATTR cardiac amyloidosis. Mr. C initiated disease-modifying therapy with tafamidis; however, his heart failure continued to advance, and he

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underwent isolated heart transplantation 2 years later. Treatment with tafamidis was continued after transplantation.

CASE 2: MR. L—THE HETEROZYGOUS MALE

Mr. L is a 68-year-old Black American male and brother of Mr. C who was referred for screening for hATTR. Genetic testing revealed the patient to be heterozygous for a V122I mutation. The patient reported occasional mild shortness of breath, but denied any notable activity-limiting symptoms. He had a medical history of hypertension and a neuropathic history of erectile dysfunction at age 58 years, and bilateral carpal tunnel syndrome and bilateral foot paresthesia at age 65. A TTE revealed an increased left ventricular wall thickness with a septal wall diameter of 1.4 cm and mild diastolic dysfunction. Imaging with CMR demonstrated normal native T1 values, and we noted a normal nulling pattern on post-contrast TI scout sequences. However, subtle delayed gadolinium enhancement was observed along the subendocardial surfaces of the basal inferior, inferoseptal, and inferolateral walls. Serum and urine immunofixation and free light chain assays showed no evidence of a monoclonal gammopathy. PYP with SPECT imaging was performed with quantitative assessment of the HCL ratio, which measured 1.8, and a visual uptake score of 3. He had normal serum troponin and NT-proBNP concentrations on laboratory analysis. Mr. L could not afford therapy with tafamidis and enrolled in a clinical trial for a novel TTR stabilizer. He continues to have minimal cardiovascular symptoms 3 years after diagnosis.

ABBREVIATIONS AND ACRONYMS

ATTR = transthyretin amyloidosis

CMR = cardiac magnetic resonance imaging

hATTR = hereditary transthyretin amyloidosis

HCL = heart to contralateral lung (uptake ratio for PYP scan)

NT-proBNP = N-terminal pro–B-type natriuretic peptide

PYP = technetium-99m pyrophosphate (scan)

SPECT = single-photon emission computed tomography

TTE = transthoracic echocardiogram

TTR = transthyretin

V122I = valine substitution for isoleucine at position 122

CASE 3: MS. T—THE HOMOZYGOUS FEMALE

Ms. T is a 64-year-old Black American female and sister to Mr. C and Mr. L. She presented for clinical screening after her brothers were diagnosed with hATTR. Ms. T was found to be homozygous for the V122I mutation. The patient reported mild shortness of breath with exertion, but denied any marked activity-limiting symptoms. She had a medical history of diabetes mellitus, hypertension, and renal carcinoma status post-nephrectomy, and a neuropathic history of bilateral carpal tunnel syndrome at age 62 years and bilateral foot paresthesia at age 64. Her ventricular myocardial wall thickness was minimally increased at 1 cm (septal and posterior wall) with normal left ventricular diastolic parameter on TTEs. Longitudinal strain using 2-dimensional speckle-tracking echocardiography showed normal patterns throughout. A CMR demonstrated normal native T1 and T2 values, a normal nulling pattern on post-contrast TI scout sequences, and no evidence of late gadolinium enhancement. Her PYP with SPECT imaging revealed a calculated HCL ratio of 1.3 and a visual uptake score was 1. On laboratory analysis, her troponin I and proBNP concentrations were normal. Due to the lack of objective evidence of TTR cardiac amyloidosis, Ms. T was not started on prophylactic treatment. She is monitored annually with cardiovascular biomarkers and electrocardiography.

DISCUSSION

The V122I gene mutation is highly prevalent among Black Americans, and the phenotypic penetrance is variable. In this report, we characterized 3 siblings who typified the varying clinical presentation of V122I hATTR, with a focus on the mutation zygosity and patient sex.

Hereditary ATTR is an autosomal dominant condition where homozygous patients may present with earlier onset and more severe symptoms than their heterozygous counterparts. Reddi et al (6) observed that this disease develops nearly a decade earlier in homozygous patients (62 ± 6 years vs 72 ± 8 years). Mr. C (homozygous) developed New York Heart Association (NYHA) functional class III symptoms at 61 years of age and required repeated hospitalizations. His clinical presentation contrasted with his heterozygous brother, who developed NYHA functional class I-II symptoms at age 66 years. Multimodality imaging and laboratory measurements confirmed more severe, later stage cardiac disease in the homozygous sibling. Both brothers complained of neuropathic symptoms, which are a typical early clinical finding that precedes cardiac involvement (7).

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TABLE 1 Patient Comparisons

	Case 1—Mr. C	Case 2—Mr. L	Case 3—Ms. T
Sex/age, y	Male/62	Male/68	Female/64
Inheritance	Homozygous V122I	Heterozygous V122I	Homozygous V122I
Age of onset of cardiac symptoms, y	61	66	62
NYHA functional class	III	I-II	I-II
Age of onset neuropathy, y	49	58	62
Peripheral neuropathy, age at diagnosis, y	Carpal tunnel (49) Sciatica (56)	Carpal tunnel (60) Feet numbness (65)	Carpal tunnel (62) Feet numbness (64)
Autonomic neuropathy, age at diagnosis, y	None	Erectile dysfunction (58)	None
Intolerance to beta-blockers	Yes	Yes	N/A
Labs			
Troponin, ng/mL	0.20	<0.03	<0.03
NT-proBNP, pg/mL	5739	175	85
Prealbumin, mg/dL	<5	19	17
GFR, mL/min	65	69	41
Immunofixation	No evidence of monoclonal gammopathy	No evidence of monoclonal gammopathy	N/A
ECG			
Pattern	Low voltage, pseudoinfarction pattern	Left ventricular hypertrophy	Normal
TTE			
Diastolic dysfunction	Severe	Mild	Normal
Septal/posterior wall thickness, cm	2.1/1.7	1.4/1.2	1.0/1.0
Global longitudinal strain	Reduction global with apical sparing—5.5%	Unavailable	Normal—22.3%
Relative regional strain ratio	0.94	Unavailable	0.73
CMR			
Late gadolinium enhancement	Abnormal uptake Diffuse subendocardial enhancement	Abnormal uptake Subtle diffuse subendocardial enhancement	Normal
T1 values, max	Abnormal	Normal	Normal
Gadolinium kinetics	Abnormal	Normal	Normal
PYP scan			
Visual uptake score	3	3	1
HCL ratio	1.8	1.8	1.3
Treatment/outcomes	Tafamidis, progressive heart failure now status post-heart transplantation	AG-10 clinical trial, stable cardiomyopathy	No treatment, asymptomatic

CMR = cardiac resonance imaging; ECG = electrocardiogram; GFR = glomerular filtration rate; HCL ratio = heart to contralateral lung ratio (uptake ratio for PYP scan); N/A = not applicable; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PYP scan = technetium-99m pyrophosphate; TTE = transthoracic echocardiogram; V122I = valine substitution for isoleucine at codon 122.

This family exemplifies how sex can affect the penetrance of hereditary cardiac amyloidosis. Females (regardless of zygosity) typically exhibit a later onset of disease and a lesser severity of symptoms when compared with males. Although there is 1:1 genotypic distribution in males to females, there has been an observed 3:1 phenotypic expression in males to females concerning cardiac symptoms (2). In the present case, Ms. T had much less severe disease presentation than her 2 brothers. At 63 years of age, Ms. T reported minimal symptoms. Her TTE showed normal diastolic function and global longitudinal strain patterning. In addition, her CMR showed no objective evidence of cardiac infiltration that could be attributed to hATTR. Lastly, her NT-proBNP and troponin I concentrations were in the normal range. Although her HCL ratio on PYP imaging was intermediate (1.3), the patient had no other corroborating imaging or biomarker evidence for TTR cardiac deposition that would have prompted consideration for invasive diagnosis. We continue to follow her closely with serial imaging and biomarker surveillance.

The variable phenotypic penetrance, whether due to inheritance pattern or sex, muddies the water for defining surveillance or treatment initiation for asymptomatic genotype-positive patients. As we continue to better understand the natural history of this highly prevalent genetic variant, evolving screening protocols could be influenced by inheritance pattern and sex with stratification of patients into highest (homozygous male) and lowest (heterozygous female) intensity of monitoring. Furthermore, timing for initiation of therapy for genotype-positive family members is unclear. Should family members with foreshadowing conditions (ie, carpel tunnel syndrome, spinal stenosis, biceps tendon rupture, intermediate findings on PYP imaging)

consider treatment, especially when considering earlier intervention is associated with superior outcomes (8)? In patients with these potential harbingers of future cardiac disease, should we consider early introduction of diflunisal before development of significant heart failure. Diflunisal is a nonsteroidal anti-inflammatory drug with potent TTR stabilizing properties that is an inexpensive alternative to tafamidis. It has been effective in carefully select patients with TTR cardiac amyloidosis; however, it may predispose patients to congestive heart failure, chronic kidney disease, or gastrointestinal mucosal irritation/bleeding (9). Or, perhaps we should consider promising over-the-counter therapy with turmeric or epigallocatechin-3-gallate (green tea), although these have yet to be proven in clinical trials.

This family demonstrates the differences in disease severity and phenotypic penetrance for V122I hATTR based on mutation zygosity and patient sex. Considering the high prevalence of the mutation among Black Americans, it is imperative that clinicians be cognizant of subtle and more overt clinical findings for early diagnosis and treatment because the average weighted mean and median delay in diagnosis from symptom onset is 5.7 and 2.6 years, respectively (10). Many questions remain for surveillance, disease prevention, and treatment initiation for asymptomatic genotype-positive family members.

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Dr Shah has been a consultant for Akcea Pharmaceuticals and Alnylam Pharmaceuticals; and has served on a medical steering committee for Eidos Therapeutics. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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