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CASE SERIES
Heart failure

Case series: clinical outcomes of the transthyretin valine-to-isoleucine mutation in a brother–sister pair

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Background Approximately 4% of the African-American population possess a valine-to-isoleucine (V122I) substitution within the transthyretin protein that results in a tendency for a normally tetrameric protein to dissociate into misfolded, monomeric subunits. These misfolded proteins can then accumulate pathologically and cause an autosomal dominant amyloid cardiomyopathy. Homozygous patients are infrequently documented in case reports, and though there are larger studies among heterozygous patients, there is a lack of studies or reports comparing disease within a family.

Case summary In this case series, we discuss a 61-year-old African-American male who succumbed to heart failure secondary to cardiac amyloidosis while awaiting orthotopic heart transplantation. We compare his case with that of his sister, a 65-year-old African-American woman with a history of recurrent supraventricular tachycardia requiring radiofrequency ablation, and intermittent chest pain with chronically elevated troponin despite no evidence of coronary artery disease. The sister in question was found to be homozygous for the transthyretin (TTR) V122I mutation with evidence of infiltrative process on cardiac magnetic resonance imaging, while clinical testing verified a heterozygous genotype in the brother. Here, we compare the clinical course and imaging data for the aforementioned brother–sister pair in the context of the amyloidogenic transthyretin V122I gene variant.

Discussion Through this familial report, we aim to highlight the variations in expression both within this family and in comparison, to the population. We also hope to emphasize the importance of genetic testing of families at risk for this specific transthyretin variant within the African-American community especially as novel therapies begin to emerge.

Keywords Homozygous transthyretin V122I • Heterozygous transthyretin V122I • Transthyretin cardiomyopathy • Amyloid cardiomyopathy • Case series

Learning points

- Disease severity can vary significantly within a family with the V122I transthyretin (TTR) variant, and it is possible that sex may be a bigger determinant of clinical outcome than zygosity.
- With new treatments in the final stages of investigation, it is essential to recognize, educate, and screen at-risk families of African descent for the V122I TTR variant.

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Introduction

Approximately 4% of the African-American population possess a single nucleotide variant resulting in a valine-to-isoleucine substitution (V122I) within the transthyretin (TTR) protein.[1] Patients possessing this amino acid substitution present clinically with an autosomal dominant amyloid cardiomyopathy with variable expression and incomplete penetrance.[2] Although there are several studies examining TTR V122I patients, no detailed description of a homozygous female patient has been reported. Moreover, there is a lack of studies comparing the disease within a family. Here, we compare the clinical course and imaging data for a brother–sister pair in the context of the amyloidogenic V122I transthyretin gene variant.

Timeline

Timeline Patient 1 (Brother)	
Age 58	Male sibling develops symptoms of exertional dyspnea. TTE shows EF 35%. Cardiac MRI suggestive of cardiac amyloidosis.
Age 59	ICD implantation for primary prevention after trial of medical therapy.
Age 60	Endomyocardial biopsy confirms cardiac amyloidosis. Mass spectroscopy confirms TTR. Genotyping studies reveal heterozygous V122I genotype.
	Patient develops acute decompensated heart failure with acute kidney injury found to be in inotrope-dependent cardiogenic shock
	Transfer to academic center for OHT evaluation
	Patient's heart replaced with total artificial heart as a bridge to transplantation.
Age 61	Post-artificial heart course complicated by cardiac tamponade, GI bleed, and renal failure requiring hemodialysis.
	Multi-organ failure. Family withdraws care and patient subsequently passed.
Timeline Patient 2 (Sister)	
Age 57	Female sibling presents with symptomatic palpitations requiring RFA of the posterior lateral free wall accessory pathway.
Age 60	Patient undergoes second ablation of a right lateral concealed accessory pathway.
Age 63	Patient develops atypical chest pain with unremarkable stress echocardiogram.
Age 65	Patient develops epigastric pain, nausea, and vomiting accompanied by chest pain. Patient with elevated troponin; left heart catheterization negative for CAD.
	Genetic tests reveal homozygous V122I TTR genotype. Cardiac MRI suggestive of cardiac amyloidosis. Family pedigree obtained.

Patient 1

Our first patient is an active, 58-year-old African-American male (at the age of symptom onset) with a prior medical history significant for hypertension initially presenting with exertional dyspnoea. Initial cardiopulmonary exam was unremarkable, though a little over a year later, he develops an elevated jugular venous pulsation, an S3, and bilateral pitting oedema. At diagnosis, his transthoracic echocardiogram revealed a reduced left ventricular ejection fraction (LVEF) of 35%. After a trial of carvedilol, olmesartan, and spironolactone, and without a significant improvement in LVEF, a dual chamber implantable cardioverter-defibrillator was placed for primary prevention. Over 2 years, he developed progressively worsening dyspnoea and lower extremity oedema culminating in recurrent hospitalizations. A repeat echocardiogram showed an LVEF of less than 20% with global hypokinesis, moderate left ventricular hypertrophy, Grade 4 diastolic dysfunction, and bi-atrial enlargement. Cardiac magnetic resonance imaging (MRI) was notable for diffuse, atypical late gadolinium enhancement in all myocardial segments (*Figure 1A,B*). Cardiac catheterization did not reveal significant coronary artery disease but demonstrated elevated filling pressures with low cardiac index (right ventricular end-diastolic pressure of 16 mmHg and a pulmonary wedge pressure of 25 mmHg). An abdominal fat pad biopsy was negative, but an endomyocardial biopsy was positive for significant amyloid deposition confirmed to be transthyretin by mass spectroscopy. Transthyretin gene sequencing revealed that the patient was heterozygous for the transthyretin V122I variant.

Despite medical interventions, his functional capacity continued to decline. During his last admission, he was found to have a serum creatinine of 4.9 mg/dL (0.6–1.3 mg/dL) and dependent on dopamine-assisted diuresis at a rate of 5 mcg/kg/min. Given inotrope-dependent cardiogenic shock, he was subsequently transferred for advanced therapies and determined to be a good candidate for orthotopic heart transplantation and mechanical circulatory support. At the time of transplant evaluation, lab results showed a peak troponin of 6.63 ng/dL (<0.04) and pro-brain natriuretic peptide (BNP) of 9700 pg/mL (0–125 pg/mL). In the subsequent weeks, the patient's heart was replaced with a total artificial heart as a bridge to heart transplantation. His post-operative course was complicated by two episodes of tamponade, gastrointestinal bleed, and renal failure requiring haemodialysis. He continued to decompensate and succumbed to his complications while awaiting transplantation at the age of 61, roughly 3 years after diagnosis.

Patient 2

Our next patient is the sister of Patient 1 (*Figure 3*), a 65-year-old African-American woman with a prior medical history of supraventricular tachycardia (SVT), hypertension, hyperlipidaemia, carpal tunnel

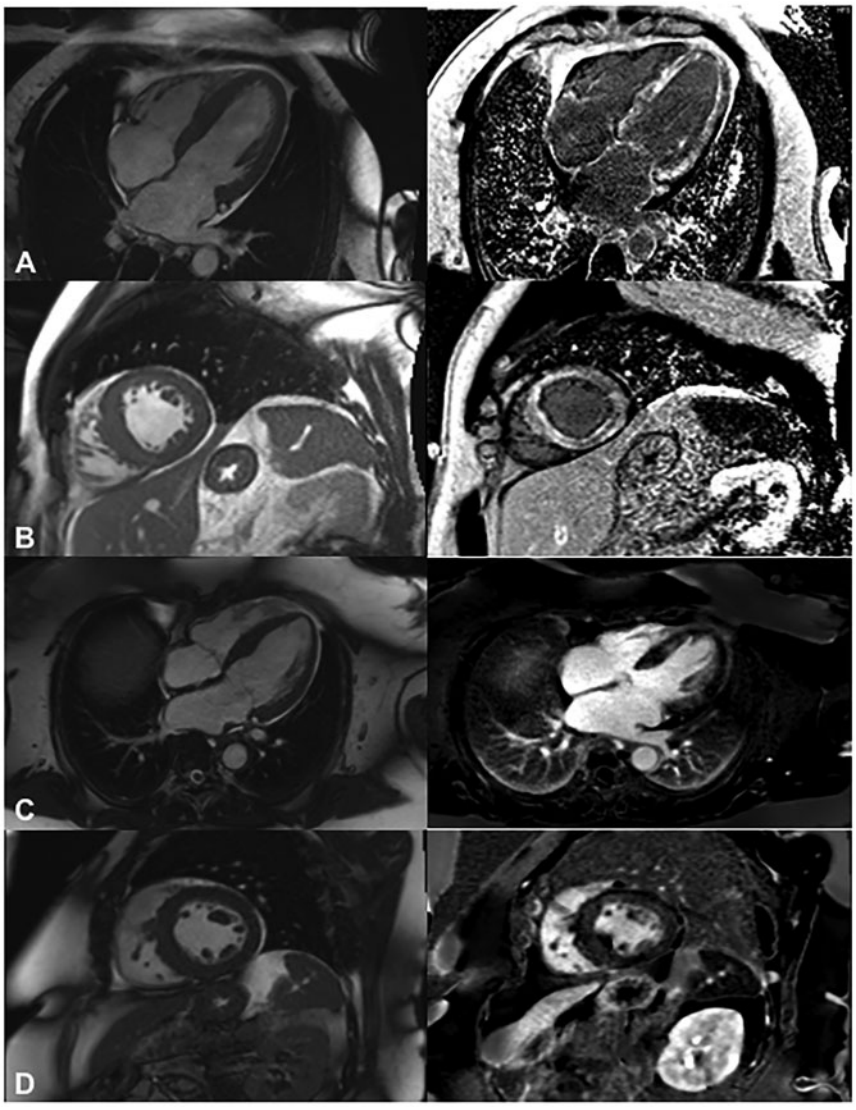

Figure 1 Cardiac magnetic resonance imaging of brother–sister pair with extensive fibrosis in a pattern suggestive of infiltrative disease. Left column cardiac magnetic resonance imaging with gadolinium, and right column with Phase-Sensitive Inversion Recovery of gadolinium-delayed hyper-enhancement. (*A*) Horizontal long axis and (*B*) mid-ventricular short axis views of the brother who is heterozygous for the transthyretin valine-to-isoleucine mutation with diffuse, atypical late gadolinium enhancement noted in all myocardial segments consistent with cardiac amyloidosis. (*C*) Horizontal long axis and (*D*) mid-ventricular short axis views of the sister who is homozygous for the transthyretin valine-to-isoleucine mutation showing patchy, abnormal delayed mid-myocardial enhancement extensively throughout the left ventricular myocardium also consistent with cardiac amyloidosis.

syndrome, and atypical chest pain with an otherwise unremarkable physical exam. With regards to her arrhythmia history, she began to experience intermittent palpitations at age 16 without significant workup at that time. At the age of 37 she went into a tachyarrhythmia during childbirth and at the age of 40, she had an ectopic atrial focus that was ablated with improvement in symptoms but intermittent palpitations. Fifteen years later, she began to experiencing worsening, and more persistent symptoms of SVT including palpitations, light-headedness, and chest pain thought secondary to a posterolateral free wall accessory pathway that was status post-radiofrequency ablation at the age of 57, and later a right lateral concealed accessory pathway after recurrence of her SVT at the age of 60. Previously the patient would develop a tight, squeezing chest pain with episodes of SVT however later developed these symptoms intermittently throughout the day. An exercise echocardiogram showed adequate functional tolerance with possible reproduction of symptoms at peak exercise, and no evidence of wall motion abnormalities. Two years later, she presented with epigastric pain and a 2–3 day history of left-sided chest pain.

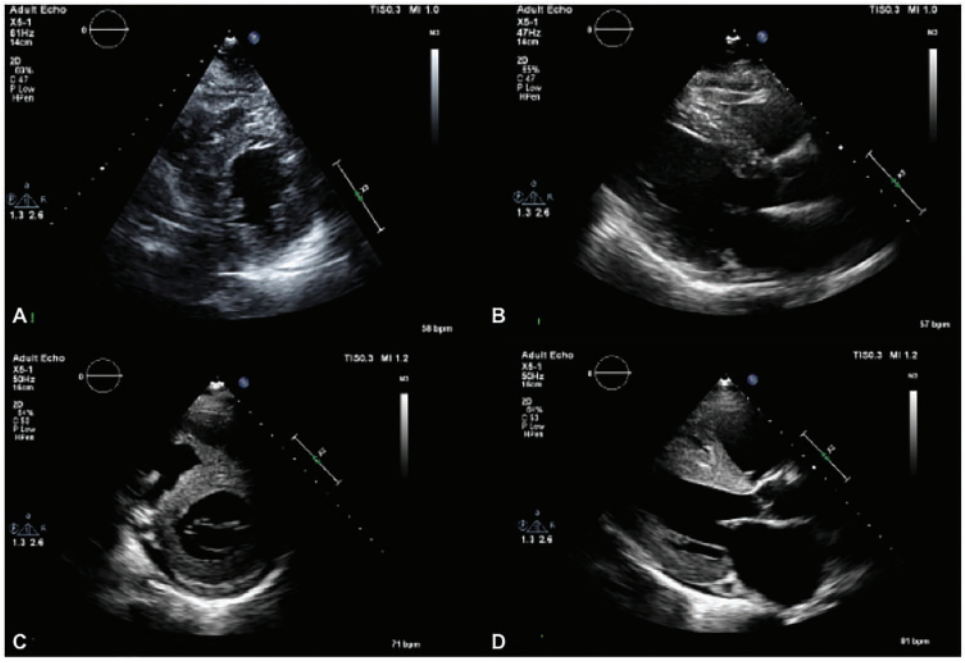

Figure 2 Transthoracic echocardiography of brother and sister pair with evidence of concentric left ventricular hypertrophy. (*A*) Parasternal short axis and (*B*) parasternal long axis views of the heterozygous transthyretin valine-to-isoleucine brother with left ventricular ejection fraction <20% and global hypokinesis with severe restrictive LV diastolic function. (*C*) Parasternal short axis and (*D*) parasternal long axis view of the homozygous transthyretin valine-to-isoleucine sister; with preserved left ventricular ejection fraction 65–70%.

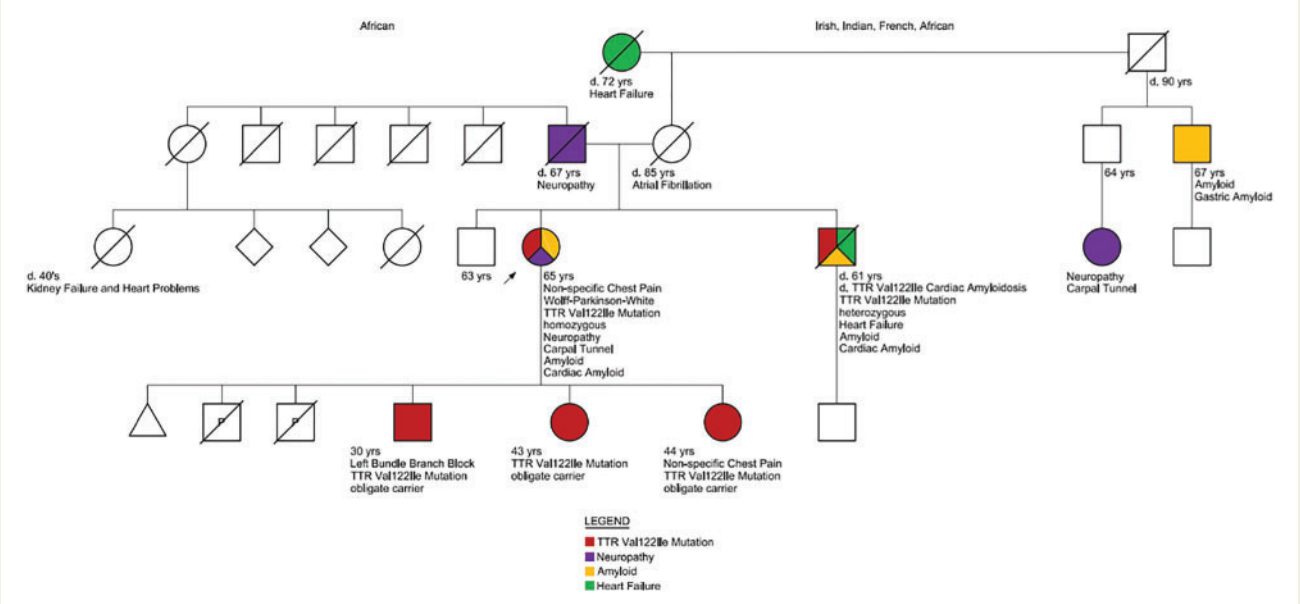

Figure 3 Family pedigree with the discussed sibling pair portrayed in the third generation.

Troponin levels were elevated [0.123 ng/mL (<0.04)], and an ECG showed new ST depressions in the inferior and precordial leads with biphasic T wave abnormalities in leads V2 and V3. A transthoracic echocardiogram again yielded normal ejection fraction and no evidence of wall motion abnormality, with only mild left ventricular diastolic dysfunction (*Figure 2C,D*). A left heart catheterization showed no obstructive coronary artery disease. A subsequent cardiac MRI displayed abnormal, patchy mid-myocardial delayed enhancement

throughout the left ventricle, consistent with an infiltrative process such as amyloidosis (*Figure 1C,D*). Given family history of amyloid cardiomyopathy, a transthyretin gene sequencing test was performed, revealing a homozygous genotype for the TTR V122I mutation.

Since her TTR amyloidosis (ATTR) diagnosis, the patient continues to complain of intermittent atypical chest pain. In recurring ER visits, she was found to have a chronically elevated troponin [range 0.09–0.21 ng/mL (<0.04)] with an otherwise baseline abnormal ECG. Clinical trials were explored, but none were available to the patient at the time.

A pedigree from genetic counselling revealed that Patients 1 and 2 have a maternal uncle who suffers from chronic, non-specific abdominal symptoms. This uncle's evaluation included an abdominal fat pad biopsy which confirmed amyloidosis, a bone marrow biopsy that was negative for light chain amyloidosis, and unexpectedly, a cardiac MRI which was negative for cardiac involvement. Patient 2 has two daughters and a son, all obligate carriers of the V122I TTR mutation (*Figure 3*). Her son was found to have a left bundle branch block diagnosed at 19, with no other symptoms of heart failure. Of her two daughters, one had non-specific chest pain during pregnancy at 35 that resolved after delivery.

Discussion

The presentation of cardiac disease in our brother–sister pair demonstrates significant variable expression in a single family with respect to disease burden. Patient 1, our male patient, developed initial symptoms at 58, followed by an unusually aggressive clinical course and death within 3 years of diagnosis. In contrast, Patient 2, our female patient, demonstrates otherwise stable cardiac function and overall functional capacity throughout her clinical course, even at an older age of 66. These findings highlight a phenotypic difference in sex that diverges from a report by Quarta *et al.*[3] among 3856 African-Americans, in which no conclusive differences according to sex were observed in V122I ATTR cardiomyopathy patients.

Patient 2's less severe course despite a homozygous genotype suggests that gender could be a determinant of clinical outcome in homozygous V122I TTR patients. This was first observed in a small cohort study of homozygous individuals which commented on a predominantly male bias.[4] Diethylstilbestrol, a synthetic oestrogen, is known to stabilize TTR, while phytoestrogens even attenuate ATTR in animal models.[5,6] The absence of a TTR stabilizing effect in males could explain the progression of amyloid disease within Patient 1. Although Patient 2 has no heart failure, her symptoms of chest pain contribute to significant morbidity.

While isolated heart and dual heart-liver transplants have resulted in successful ATTR patient outcomes,[7] no approved preventative therapy currently exists. There are however, a handful of potential therapies that are only recently emerging from Phase 3 trials. Tafamadis, a TTR stabilizer to prevent amyloid fibril build up, has demonstrated stabilization of cardiac biomarkers and echocardiographic findings among non-V30M and V122I patients.[8,9] At the end of March 2018, Pfizer Inc. announced positive results from its Phase 3 Tafamadis ATTR-ACT study, showing significant reduction in mortality and cardiovascular-related hospitalizations in a global, multicentre, double-blind, randomized, placebo-controlled study. The formal report from the ATTR-ACT study was published on August 2018.[10] And in July 2018, Alnylam published results from their APOLLO Phase 3 trial of Patisiran, an RNA interference agent inhibiting hepatic synthesis of transthyretin. While this study focused on patients with hereditary transthyretin amyloidosis with polyneuropathy, within their cardiac subpopulation they were able to demonstrate reduction in NT-proBNP levels, and favourable echocardiographic findings including improved mean left ventricular wall thickness, and longitudinal strain after 18 months.[11]

With new therapies on the horizon, outreach, and genetic TTR screening become vital in identifying V122I TTR patients within families of African descent. Variable expression and reduced penetrance within such families further emphasize this need. Just recently, the Alnylam Act™, sponsored by Alnylam Pharmaceuticals, was enacted in partnership with the Invitae genetic information company to offer TTR gene testing for at-risk patients at no monetary cost. Programs such as this can be expected to facilitate early detection of the V122I mutation, which would be paramount in providing early genetic counselling to patients, expanding their treatment options, and distributing novel preventative therapies for transthyretin cardiac amyloidosis.

Patient perspective

I was not aware of the TTR variant among African-Americans. My brother, diagnosed a few years before myself, never mentioned that the disease he was fighting was inherited. Admittedly the info was frightening and especially so without any treatments on the horizon.

My immediate concerns were for my children and my nephew. After watching my young brother suffer so tremendously and fighting so hard to live—I did not want my family to experience that pain again so soon, or to experience it themselves at a later time.

My position on genetic testing has changed drastically because a physician spent hours explaining the benefits of knowing in advance what is happening in your body. I believe my diagnosis came sooner than my brother's, which may give me different opportunities for advanced treatment. Of course, his death is saddening, but I feel I must do whatever possible to live a productive life and educate other families before they are in my brother's position.

Because the disease primarily impacts the Black Community, I am saddened that there is little information to inform people of this disease; we can't be helped when we are not part of the discussion. It's equally important that physicians know about TTR cardiac amyloidosis and its prevalence in our community, so that there is no delay in referring the patient to specialists, especially now that therapies are becoming available. Bottom line—if there's a change, offer genetic testing. Give people the opportunity to control their chances of living a healthy life.

Supplementary data

Supplementary material is available at *European Heart Journal - Case Reports* online.

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Slide sets: A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

Consent: The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

Conflict of interest: none declared.

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