Afro-Caribbean Heart Failure in the UK: Etiology, Outcomes and ATTR V122I Cardiac Amyloidosis

Short title: Dungu UK Afro-Caribbean Heart Failure & ATTR V122I

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Word count: 6901

Subject codes: Race and ethnicity, cardiomyopathy, heart failure, echocardiography, mortality/survival

ABSTRACT

Background

It has been reported that subjects of African descent present with heart failure at a younger age and due to different etiologies than Caucasians. We present contemporary data from UK Afro-Caribbean patients in London.

Methods and Results

All heart failure patients presenting to St George's Hospital Heart Failure clinic between 2005 and 2012 were included (n=1392). Patients were predominantly Caucasian (71%) and male (67%), median age at presentation73 years (range 18-100). In 211 Afro-Caribbean patients, the commonest cause of heart failure was non-ischemic dilated cardiomyopathy (DCM) in 27.5% (Caucasians 19.9%, $p<0.001$). Lower rates of ischemic cardiomyopathy (ICM) were observed (13% vs. 41%, $p<0.001$). The 4th commonest cause of heart failure in Afro-Caribbeans was cardiac amyloidosis (11.4%). The prevalence may have been even higher as not all patients were tested for amyloidosis. Patients with ATTR V122I had the worst prognosis compared to other causes of Afro-Caribbean heart failure and Caucasian patients.

To better understand this condition, we analyzed data from the largest international cohort of ATTR V122I patients, followed at the UK National Amyloidosis Centre (n=72). Patients presented with cardiac failure (median age of 75, range 59-90 years). Median survival was 2.6 years from diagnosis.

Conclusions

In London, the etiology of heart failure varies depending on ethnicity and affects age of presentation and outcomes. In Afro-Caribbean patients, ATTR V122I is an underappreciated cause of heart failure, and cardiomyopathy is often misattributed to hypertension. As

promising TTR therapies are in development, increased awareness and proactive detection is needed.

Key words:

Ethnicity, heart failure, amyloid, prognosis

INTRODUCTION

Most large heart failure studies in the United Kingdom population fail to include specific data on Afro-Caribbean patients because ethnic minority groups form a relatively small proportion nationwide.[1] However, more than one million people of Afro-Caribbean ethnicity live in the Greater London area (2011 census data) forming a significant proportion of the city's population (13.3%).[2] There are few studies focusing on ethnic differences in heart failure in UK populations. Previous studies in African American subjects suggest that heart failure is less likely to be due to coronary artery disease and frequently due to hypertensive heart disease.[3] The limited reports in the UK Afro-Caribbean population suggest this cohort often present in heart failure with preserved ejection fraction (HFpEF) which may be related to hypertensive cardiomyopathy.[4]

The role of Afro-Caribbean ethnicity in cardiovascular risk is still not fully understood. A higher prevalence of hypertension, elevated body mass index (BMI) and diabetes is recognized.[5] We have identified a rapidly progressive form of heart failure in elderly Afro-Caribbean patients in increasing numbers over recent years due to cardiac amyloidosis.[6] Variant transthyretin V122I has been estimated to be carried by 3.43% of African Americans and is inherited in autosomal dominant fashion.[7] Transthyretin amyloidosis (ATTR) V122I is associated with isolated cardiac involvement in patients over the age of 60 years affecting males to females in a ratio of 6:1.[6] Survival in ATTR V122I is reported to be poor [8] but the prevalence of the clinical phenotype in the British Afro-Caribbean population is unknown.

The clinical features and natural history of ATTR V122I amyloidosis have been little studied. The Transthyretin Amyloidosis Cardiac Study (TRACS) reported only 11 patients with ATTR V122I subtype [8] and the Transthyretin Amyloidosis Outcomes Survey (THAOS),

which is a multicenter, observational study that has reported 957 ATTR amyloidosis patients from 30 centers, included only 39 individuals with the V122I variant.[9]

This study aims to: 1) compare and contrast clinical presentations and outcomes of heart failure patients depending on Caucasian or Afro-Caribbean ethnicity in the UK setting; 2) evaluate the prevalence of ATTR V122I as a cause of heart failure in Afro-Caribbean patients in London; and 3) describe the clinical phenotype of the disease for ATTR V122I patients with histologically proven amyloidosis.

METHODS

Patient identification in the general heart failure clinic (SGH)

St George's Hospital (SGH) is a regional cardiac center and local general hospital for a large catchment area of South West London of approximately 1.5 million people. All patients referred to the clinic with heart failure between September 2005 and November

2012 were eligible for inclusion in this analysis. Clinic patients were referred from local primary care clinicians following a suspected diagnosis of heart failure or by the medical teams following an in-patient admission with decompensated heart failure. The diagnosis was defined according to history and examination, echocardiographic findings and, when clinically indicated, supported by non-invasive ischemia testing, invasive cardiac catheterization in the setting of regional wall motion abnormalities, positive stress testing or angina, cardiovascular magnetic resonance (CMR), serology, genetic testing and endomyocardial biopsy if indicated. The etiologies listed are deemed the primary cause of heart failure symptoms and were determined at initial assessment and verified at the time of analysis following thorough review of patient records and any subsequent investigations or findings. Ischemic cardiomyopathy was diagnosed in the context of coronary artery disease and regional wall motion abnormalities on cardiac imaging or positive ischemia testing;

dilated cardiomyopathy in the absence of obstructive coronary artery disease or known causes of ventricular dilatation; hypertensive heart disease in the context of documented systemic hypertension at presentation with left ventricular hypertrophy and no other cause for heart failure determined through cardiac imaging, with cardiac biopsy to rule out amyloidosis if diffuse late gadolinium enhancement on CMR was found. Patient ethnicity was determined via self-reported forms completed at the time of registration, according to Office of National Statistics (ONS) classifications.

The term "Caucasian" has been used in reference to all white ethnicities and "Afro-Caribbean" for all black ethnicities. Prospective collection of data has been made over the years with corresponding census of survival. Completions were made by interrogating the Electronic Patient Records, namely updating mortality dates, latest hospital discharges, visits for imaging studies, or latest biochemistry results and cross confirmation with the NHS Strategic Tracing Service.

Specialist referral clinic (NAC)

In order to understand this condition further, we collaborated with the UK National Amyloidosis Centre (NAC) to describe the clinical phenotype, including patients identified at SGH. Only patients possessing the amyloidogenic gene mutation producing variant TTR V122I and a positive biopsy to confirm systemic amyloidosis were included in the analyses. Ethnicity was derived from self-reported questionnaires. Mortality data were obtained from the Office of National Statistics.

Investigations

Low voltage amplitude on ECG was defined as: mean limb lead (I, II, III, aVL, and aVF) QRS amplitude <0.5 mV; and sum of S wave in V1 and mean of the R wave in V5 and V6

<1.5 mV.[10] Cornell criteria [11] defined left ventricular hypertrophy (LVH), reported to have higher specificity in Afro-Caribbean patients.[12]

Echocardiography was performed using a GE system (Vivid 7 since 2005). British Society of Echocardiography defined criteria for left and right ventricular (LV/RV) wall thickening and LV diastolic dysfunction were used. LV ejection fraction (EF) was assessed with biplane Simpson's method.[13] LV mass was calculated with the corrected American Society of Echocardiography simplified cubed equation. [14]

Cardiovascular magnetic resonance (CMR) studies from referring centers were analyzed [15] using dedicated software (CMRtools 2012, Cardiovascular Imaging Solutions, London) and reported according to international guidelines.[16] Gadolinium contrast was used in each CMR study. 99mTc-3,3-diphos- phono-1,2-propanodicarboxylic acid (DPD) scintigraphy was performed using two General Electric (GE) hybrid SPECT-CT gamma cameras (Infinia Hawkeye 4 and Discovery 670). Patients received 700 MBq 99mTc DPD, and planar whole body images were acquired after 3 hours, along with cardiac SPECT-CT. Myocardial uptake was allocated a Perugini score grade 0-3. [17]

All patients undergoing genetic testing received counseling before and after blood samples were taken. DNA was extracted from whole blood and the coding regions of the transthyretin gene were amplified by polymerase-chain-reaction assay; exons 2, 3 and 4 were sequenced.[18,19]

The presence of amyloid was confirmed by staining with Congo red and apple-green birefringence in cross-polarized light.[20] Immunohistochemical staining was subsequently performed using the peroxidase anti-peroxidase method to confirm amyloid fibril type, using

monospecific antibodies reactive with serum amyloid A protein (SAA), transthyretin (TTR) and kappa and lambda immunoglobulin light chains.[21]

Statistics

Statistical analysis was performed using SPSS 21. Normally distributed data are presented as mean ± 1 standard deviation (SD). Non-normally distributed data are presented as median (25^{th} and 75^{th} percentiles). Categorical data are presented as frequencies and percentages. Dichotomous and categorical data for compared using Chi-square Test or Fisher's Exact Test; with calculation of odds ratios when appropriate. The distribution of continuous variables was assessed for normality with Shapiro-Wilk Test or W-statistic and groups were compared using the Independent Samples T Test for normally distributed data and Mann-Whitney or Wilcoxon tests for non- normally distributed data.

We used Kaplan-Meier survival analysis to compare survival between Afro-Caribbean and Caucasian patients, then the impact of diagnosis on long-term survival among Afro-Caribbean patients only. We used the Gehan-Breslow test to compare curves and the Holm-Sidak method to account for multiple comparisons. Data regarding NYHA class was missing for some SGH patients and thus analysis was performed on 968 Caucasian and 197 Afro-Caribbean patients.

The study was approved by the Ethics Committee of the Royal Free Hospital.

RESULTS

Heart failure was confirmed in 1392 patients in the heart failure clinic at SGH during the 7-year study period. The median age at presentation was 73 years (range 18-100) with Caucasian (71%) and male (67%) predominance. Asian patients (14%) were predominantly of South Asian origin (originating from India, Pakistan, and Bangladesh); we have excluded these patients from subsequent analyses for clarity.

A total of 211 Afro-Caribbean patients (15%), 68 female and 143 male, presented during this time period - Black Caribbean 118 (55%); Black African 88 (41%); Mixed black and white ethnicity 9 (4%). Afro-Caribbean patients were significantly younger (71 years, 25^{th} - 75^{th} percentiles 54-77) than Caucasians (74 years, 25^{th} - 75^{th} percentiles 64-82, $p<0.001$) with a smaller proportion presenting aged 80 years and over (19% vs. 33%, $p<0.001$). Black Caribbean patients (median 73 years, 25^{th} - 75^{th} percentiles 58-78) were significantly older than Black African patients (median 65 years, 25^{th} - 75^{th} percentiles 47-74, $p = 0.007$). Hypertension was significantly more prevalent in Afro-Caribbean patients (71% vs. 54% in Caucasians, $p < 0.001$). History of cerebrovascular accident (CVA) was similar in Caucasian and Afro-Caribbean patients (13% vs. 14%, $p = 0.69$). Investigation rates differed in Afro-Caribbean patients, with higher rates of CMR (41% vs. 21% for Caucasian patients, $p <0.001$) and cardiac biopsy (14% vs. 3% for Caucasian patients, $p<0.001$). Coronary intervention and biventricular pacemaker implantation (CRT) were performed less frequently in Afro-Caribbean patients, compared to Caucasian patients (8% vs. 20%, $p < 0.001$ and 26% vs. 17%, $p = 0.006$ respectively).

Etiology of heart failure

Table 1 compares Afro-Caribbean and Caucasian patients with both heart failure and preserved ejection fraction (HFpEF) or heart failure with reduced ejection fraction. A total of 352 Caucasian patients had heart failure with ejection fraction ≥50% (36%) compared to 77 Afro-Caribbean patients (36%, $p = 0.97$). Overall ejection fraction was no different between groups (both 40%, $p = 0.93$). No significant difference in the presence of poor LV systolic function <35% was demonstrated between the 2 groups (Caucasian patients 32% vs. Afro-Caribbean patients 38%, $p = 0.60$). Left ventricular (LV) wall thickness was significantly higher in Afro-Caribbean patients ($p<0.001$). Ischemic cardiomyopathy was much less common in Afro-Caribbean patients (13%) than Caucasians (41%, $p < 0.001$). No difference

in NT-prohormone brain natriuretic peptide (NT-pro BNP) was observed between groups (Caucasian patients 2459 ng/L (848-6525) vs. Afro-Caribbean patients 2195 ng/L (654-5132), p = 0.17). Atrial fibrillation was significantly more prevalent in Caucasian than Afro-Caribbean patients (35.8% vs. 21.3%, p<0.001).

The top 5 diagnoses in Afro-Caribbean heart failure patients were: 1) Non-ischemic dilated cardiomyopathy (27%); 2) Ischemic heart disease (13%); 3) Hypertensive cardiomyopathy (12%); 4) cardiac amyloidosis (all subtypes - 11%); and 5) valvular heart disease (7%) – Supplementary Table 1.

Cardiac amyloidosis secondary to variant ATTR V122I was diagnosed in 18 of 211 Afro-Caribbean patients (8.5%). All 18 patients with ATTR V122I were aged over 65 years (range 68-84), in keeping with the reported age-related clinical phenotype.[22] Subgroup analysis revealed that 153 Afro-Caribbean patients aged over 60 years were referred to the heart failure clinic during the study period. The prevalence of ATTR V122I in Afro-Caribbean patients aged >60 years was 11.8%. The only other ATTR subtype diagnosed in Afro-Caribbean patients was non-hereditary senile cardiac amyloidosis due to wild-type TTR (4 patients, 1.9%). AL amyloidosis was diagnosed in only 2 Afro-Caribbean patients (0.95%). Of note, for all ethnicities, ATTR amyloidosis was found more frequently than AL type, an opposite finding to all other previous reports from specialist amyloidosis centers.

Heart failure admissions

Patients were followed up in the general heart failure clinic for a median of 2.9 years (Caucasian patients 2.9 years, 25^{th} - 75^{th} percentiles 1-5, Afro-Caribbean patients 3.2 years, 25^{th} - 75^{th} percentiles 2-6, p = 0.02). During the follow-up period, the median hospitalization rate of all causes during follow-up in both Caucasian and Afro-Caribbean heart failure patients was 2 (range 0-64, 25^{th} - 75^{th} percentiles 0 - 4 vs. 0 - 5 respectively, p = 0.069).

Survival

Survival differed significantly according to etiology and ethnicity overall (median survival in Caucasian 4.7 years vs. Afro-Caribbean 5.9 years, p = 0.031). 579 deaths occurred during follow up (486 Caucasians and 93 Afro-Caribbeans). No significant difference in survival was observed according to ethnicity in patients with ischemic cardiomyopathy (p = 0.25) or dilated cardiomyopathy (p = 0.71).

Kaplan-Meier survival curves for the top 5 diagnoses in Afro-Caribbean heart failure patients are presented in Figure 1. No significant difference in median survival was observed between Afro-Caribbean patients with non-ischemic dilated cardiomyopathy and hypertensive cardiomyopathy (DCM 7.41 years, HTCM 7.32 years, p = 0.88) and patients with ATTR V122I had the poorest survival (ATTR V122I 2.33 years vs. DCM p<0.001 and vs. HTCM p=0.002). No significant difference in survival was observed between ATTR V122I and ICM (p = 0.11) or VHD (p = 0.19) in Afro-Caribbean patients. It should be noted that the age at presentation differed according to etiology. Afro-Caribbean patients with ATTR V122I presented at a relatively old age - median 76 years, interquartile range 74-78 – compared to Afro-Caribbean patients with DCM (68 years, 25^{th} - 75^{th} percentiles 51-75, p = 0.001) and HTCM (61 years, 25^{th} - 75^{th} percentiles 47-72, p = 0.001). The median age of Afro-Caribbean patients with ICM (76 years, 25^{th} - 75^{th} percentiles 71-81, p = 0.74) and valvular heart disease (81 years, 25^{th} - 75^{th} percentiles 74-85, p = 0.23) was similar to ATTR V122I. The median age of presentation was similar in Caucasians for each of these etiologies (67 years for DCM, p = 0.27; 82 years for VHD, p=0.54; and 75 years for ICM), except HTCM (79 years, p < 0.001).

The clinical features of biopsy-proven ATTR V122I amyloidosis

A total of 72 ATTR V122I patients with histological corroboration were reviewed at the UK National Amyloidosis Centre between January 1995 and March 2013, including the 18 SGH patients (Table 2). Cardiac biopsies were obtained in 39 patients (54%) and non-cardiac biopsies in 33 patients (46%, rectum n=12, fat pad n=10, stomach n=4, bone marrow n=3, prostate n=2, liver n=1 and carpal tunnel n=1).

The median age at presentation was 74 years (range 59-90, 25^{th} - 75^{th} percentiles 70-80). Male predominance was observed (84.7%). The majority (85%) were referred from London centers. Black African or Caribbean ancestry was declared in 89%, including 2 patients of mixed ethnicity. The cohort included 8 patients of white ethnicity (8%), 1 Asian patient and 1 patient of Arabic descent. With regards to country of origin, 47% originated from Jamaica 18% from Nigeria, 15% from Ghana and less than 20% from other countries.

Sixty-eight patients were heterozygous for the TTR V122I allele and 4 patients were homozygotes. All homozygous patients were male and presented at a younger age (65 ± 3 years) compared to heterozygotes (74 ± 7 years, $p = 0.004$).

The majority of V122I ATTR patients were in New York Heart Failure Association (NYHA) class II and III (92%) at first review. Almost half (46%) had a history of carpal tunnel syndrome. A history of hypertension was common (47%). Median duration of symptoms prior to referral was 1.06 years (25^{th} - 75^{th} percentiles 0.68-2.41). Fluid overload was present in 60% of patients despite diuretic therapy. None of the patients exhibited macroglossia or peripheral neuropathy.

Median serum Creatinine was 131 (25^{th} - 75^{th} percentiles 113-164) µmol/L and glomerular filtration rate (GFR) was 48 (25^{th} - 75^{th} percentiles 39-61) ml/min. Renal impairment (estimated GFR <60 ml/min, corrected for ethnicity) was present in 79.4%. NT-pro brain

natriuretic peptide (NT-pro BNP) was >100 pMol/L in 96% (median 435 pMol/L; 25^{th} - 75^{th} percentiles 269-644).

ECG showed low voltage complexes in 38% and 17% had criteria for LVH (Table 3). Concentric LV wall thickening (>12mm) was evident on echocardiography in all patients, (median 17mm, 25^{th} - 75^{th} percentiles 15-19 vs. 17mm, 25^{th} - 75^{th} percentiles 16-18, p = 0.47). Diastolic dysfunction was present in every case, and was categorized as severe (grade 3 or 4) in 43%. LV ejection fraction was moderately impaired overall (mean 39 ± 11 %, range 19-69%). A small (<1.5cm) pericardial effusion was evident in 49% (Table 3).

Thirty-nine patients (54%) underwent cardiovascular magnetic resonance (CMR) prior to referral. Mean LV end diastolic volume 140 ± 36 ml, mean LV end systolic volume 75 ± 33 ml and mean LV stroke volume 66 ± 19 ml. Mean LV ejection fraction 48 ± 14 %. Mean LV mass 230 g (25^{th} - 75^{th} percentiles 214-248) was hugely increased (mean 144 g and upper limit of normal 183 g for males aged >70 years). Extensive late gadolinium enhancement (LGE) was present in all. ^{99m}Tc-DPD scintigraphy was acquired in 27 patients (38%). All DPD scans were strongly positive with Perugini Grade 2 myocardial uptake in 15 patients (56%) and Grade 3 in 12 patients (44%).

Survival in ATTR V122I

During the follow-up period, 38 patients died (52.8%). Median (range) age at death was 77 years (64-91). The median survival from the date of diagnosis was 2.62 years. Median survival in Afro-Caribbean patients was 2.92 years compared to 1.45 years in Caucasian ATTR V122I patients. Of the 24 patients in whom mode of death details were available, 2 (8%) had a sudden cardiac death (neither had a pacing device and both died in their sleep), one patient died from a CVA after the implanted ICD converted previously undetected atrial fibrillation with fast ventricular rate to sinus rhythm and the rest (88%) died of progressive

heart failure. No significant difference in survival was observed between NAC and SGH ATTR V122I patients (p = 0.36).

DISCUSSION

We report a study of Afro-Caribbean heart failure patients attending a general cardiology clinic and a description of the clinical phenotype for an important, as yet underappreciated, cause of heart failure ATTR V122I amyloidosis.

Afro-Caribbean patients are frequently diagnosed with hypertensive heart failure and our data confirm that hypertensive cardiomyopathy is a relatively common cause of morbidity in this cohort (12%). Despite normal blood pressure at presentation, hypertension may be the etiology for many more of the non-ischemic dilated cardiomyopathy cohort, as 63% had a history of hypertension and many more had no regular BP checks prior to presentation. Survival in hypertensive cardiomyopathy and non-ischemic dilated cardiomyopathy was better than other causes of heart failure in Afro-Caribbean patients but the age at presentation for these diagnoses was significantly lower. Although heart failure seems different between races, when we compared heart failure by etiology the differences disappeared; once a patient has heart failure secondary to ischemic or dilated cardiomyopathy the survival is very similar regardless of ethnicity. Etiology also has an influence on apparent differences in the age of heart failure patients according to ethnicity. Age at presentation will contribute to poor survival in cardiac amyloidosis whereas hypertensive Afro-Caribbean patients present at a young age, from the age of 30 years.[23] Afro-Caribbean heart failure patients with hypertensive cardiomyopathy presented at a median 61 years of age in this study, significantly lowering the overall Afro-Caribbean heart failure age. Afro-Caribbean patients

with hypertensive cardiomyopathy also presented significantly younger than Caucasians, reinforcing the need to treat a condition prevalent in this ethnic group aggressively.[24]

The high prevalence of cardiac amyloidosis and specifically the transthyretin subtype is striking. Cardiac ATTR V122I amyloidosis was a relatively common cause of heart failure in Afro-Caribbean patients presenting to the general heart failure clinic.

The typical clinical picture in ATTR V122I amyloidosis is presentation with heart failure symptoms in the seventh decade and beyond, with fluid overload despite use of diuretics. The prognosis is poor, with a median survival of 2.6 years after confirmation of diagnosis. Survival compares poorly to other causes of heart failure in UK Afro-Caribbeans. Cardiac investigations revealed elevated serum biomarkers, increased LV wall thickness and impaired systolic and diastolic function. Almost half of patients had a history of carpal tunnel syndrome, which should be considered a red flag for this disease among older Afro-Caribbean heart failure patients. Despite autosomal dominant inheritance of the genetic variant, there was significant male predominance (85%). As we reported previously, the ECG may be misleading.[25] Nearly one-fifth of patients had voltage criteria for LVH that is liable to be interpreted as an indication of hypertensive cardiomyopathy in the Afro-Caribbean population. CMR with gadolinium enhancement is more sensitive than echocardiography for identifying ATTR amyloidosis, as increased wall thickness and diastolic impairment are also found in hypertensive cardiomyopathy. [6,15]

The allele frequency of ATTR V122I, an autosomal dominant condition, has been reported to be carried by 3.4% in African-Americans [7] but the gene frequency in the UK population is unknown. The penetrance of TTR gene mutations is also unknown but reported to be variable. Our study reports that 12% of all Afro-Caribbean patients aged > 60 years at SGH were diagnosed with ATTR V122I, a figure with important implications. Specialist

amyloidosis investigation was reserved for patients with high clinical suspicion of the disease so the prevalence of ATTR V122I may have been even higher as not all heart failure patients at SGH were referred to the UK NAC for further characterization.

The prevalence of ATTR amyloidosis in the general cardiology clinic is significantly higher than would be expected from the recent study of UK death certificate data.[26] Retrospective review of death certificates reveals an annual incidence of systemic amyloidosis (all types) of 0.8 per 100,000 UK population, with predominantly Caucasian ethnicity (4.5% black African, black Caribbean or mixed black and other ethnicity nationwide). The low absolute numbers in the wider population likely represents combined underdiagnosis and possible low penetrance of the gene, given the expected allele frequency. The recently reported longitudinal Atherosclerosis Risk in Communities study failed to demonstrate a significant difference in mortality between 124 V122I TTR variant carriers (3%) and 3732 noncarriers, but the incidence of heart failure was higher in allele carriers and median age of carriers at final follow-up is younger than the median age of presentation for ATTR V122I and low proportions of males were included or followed to visit 5.[27] Wild-type ATTR amyloidosis is reported to be an increasingly important cause of heart failure with preserved ejection fraction (HFpEF) and has been shown to be the primary etiology in up to 13% of patients of all ethnicities. [28]

The geographic origins of the ATTR V122I patients reported here is consistent with a founder mutation in West Africa.[29] During the Atlantic slave trade, from the 16th through to 19th centuries, subjects were transported from West Africa to the Americas and Caribbean. Migration of Caribbeans to the UK, predominantly to London, began following World War II. The latest 2011 UK Census reports that Black African and Caribbean subjects comprised 4.5% of the British population (13.3% of London population), and in the age cohort >70

years, 80% originate from the Caribbean. The lack of a positive family history in the majority of patients suggests that the V122I variant cannot reliably indicate a low penetrance for this disease. Under diagnosis is a likely contributing factor. Worldwide distribution of family members is another factor, and the late onset may contribute to the absence of a family history due to a shorter life expectancy in previous generations and in parts of West Africa.

Under-recognition of ATTR V122I amyloidosis is suggested by the observed referral patterns in this study, noting that 25% of the known UK cohort were referred in just 7 years from a single south London center with routine on-site CMR coupled with growing awareness of this disease. A substantial and progressive increase in referrals generally during the past 5 years can be attributed to increased access to CMR elsewhere in the UK.[6] Factors that are likely impeding diagnosis are lack of awareness of this condition, and limited investigation of Afro-Caribbeans with heart failure reported previously.[3] The combination of LVH on ECG and a history of hypertension in half of patients had frequently led to initial misdiagnosis of hypertensive cardiomyopathy. We propose a simple diagnostic algorithm to aid detection of cardiac amyloid in Afro-Caribbean patients who may otherwise be inaccurately labeled as having hypertensive heart disease or non-ischemic DCM (Figure 2). We do not propose use of the algorithm to detect ATTR V122I in Caucasian patients since the relative prevalence is very small. The NHLBI GO Exome Variant Project has not detected the mutation in 8,600 European Americans, indicating that the mutation is effectively nonexistent in Caucasians, contrary to our data. The landmark study by Jacobson et al [30] failed to demonstrate the gene mutation in any Caucasian patients and only a few individual cases of Caucasian patients with ATTR V122I have been reported.

Novel Treatment Options and Implications for Genetic Screening

Several new pharmacological treatments for ATTR amyloidosis are now in development, comprising RNA inhibitors that suppress TTR production in the liver, and drugs bound by circulating TTR protein that promote its normal soluble non-amyloid conformation. [31] The siRNA agent ALN-TTRSC (Alnylam Pharmaceuticals) has been shown to suppress TTR production profoundly in ATTR patients and healthy volunteers [32] and a phase 3 clinical trial in familial amyloid cardiomyopathy is in progress. A Phase 3 clinical trials of Tafamadis (Vyndaqel™), a TTR stabiliser,[33] in cardiac ATTR amyloidosis is also in progress. A potential cure for amyloidosis using the immunotherapeutic approach of combining the compound CPHPC ((R)-1-[6-[(R)-2-carboxy-pyrrolidin-1-yl]-6-oxo-hexanoyl]pyrrolidine-2-carboxylic acid) to clear circulating serum amyloid P component, present in all types of amyloid, and anti-SAP-antibodies has been shown to be safe in a phase 1 trial in man.[34] The role of this strategy in cardiac involvement is not yet known.

The V122I allele is inherited in an autosomal dominant fashion. To date, genetic screening for carriers had been discouraged at this center due to the lack of available treatments. However, screening for early disease in family members and non-invasive surveillance programs will need to be considered as effective treatments emerge for all ATTR subtypes.[35]

LIMITATIONS

We acknowledge potential selection bias exists for patients presenting to the heart failure clinic. Although we have a robust system for detecting and monitoring patients with an index admission with heart failure, some patients may not have been included in this study and others may not be referred by colleagues in the general medical teams treating heart failure. Despite this, we believe we have identified a relatively large and representative cohort of

patients in our catchment area. Etiology of heart failure was determined by the heart failure clinician at the time of diagnosis and reviewed at the time of data collection; this introduces bias but, in our opinion, more accurately classifies patients by diagnosis. Afro-Caribbean patients were less frequently investigated with coronary angiography, based on clinical assessment, thus the low rates of ischemic cardiomyopathy may have been influenced by the index of suspicion. A significant selection bias relating to genetic testing of overt amyloidosis patients only is appreciated but any additional positive results would result in a higher proportion of V122I cases.

Survival is reported from the date of diagnosis; whilst we have assessed the duration of symptoms prior to diagnosis, the lag from disease onset to symptoms may be influenced by recall bias.

CONCLUSION

Consideration of race in the approach to a patient with heart failure is important for the most personalized management. In London, the etiology of heart failure varies depending on ethnicity and affects age of presentation and outcomes. Non-ischemic DCM, often with preceding history of hypertension and concomitant LVH, is the commonest cause of heart failure in Afro-Caribbeans. For the first time we report the high prevalence of ATTR V122I in the Afro-Caribbean UK heart failure population. The genetically variant allele is carried by up to 4% of African Americans. Penetrance is as yet unknown.

We describe the clinical phenotype of patients with ATTR V122I amyloidosis. ATTR V122I amyloidosis does not respond to standard heart failure medications and progresses to death in 2.6 years with intractable heart failure. Phase 3 trials of three separate TTR specific disease modifying agents are in progress, underscoring the importance of awareness and early

diagnosis of this otherwise overlooked and rapidly fatal condition. For patients of African descent who present with heart failure and left ventricular wall thickening, regardless of any history of hypertension, ATTR V122I should be considered and actively investigated.

Acknowledgements

We would like to thank the UK National Amyloidosis Centre for confirming the cardiac amyloidosis diagnosis in patients through genetic testing and histological confirmation.

Funding sources

J.N.D. was supported by a British Heart Foundation Clinical Research Training Fellowship grant no. FS/09/063/28026

Disclosures: None

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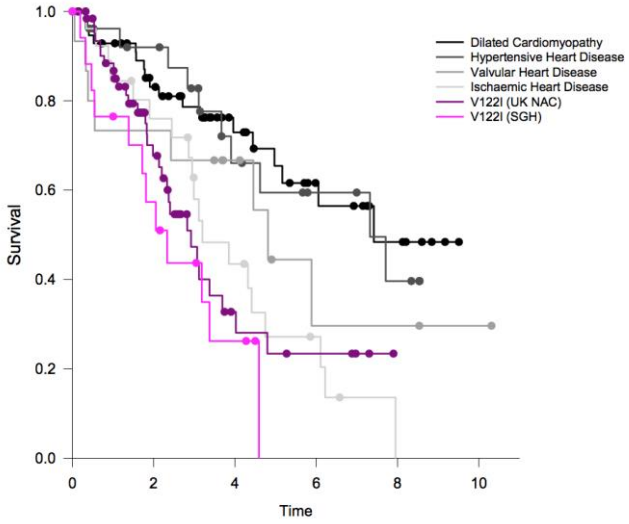
Figure legends

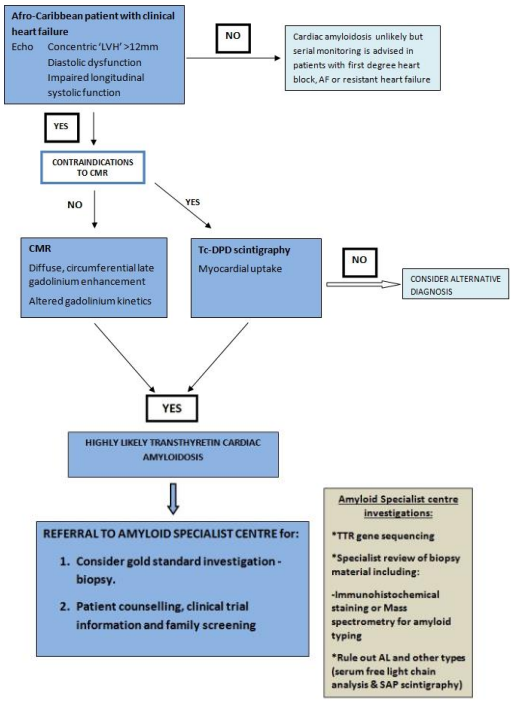
Figure 1 - Kaplan-Meier survival curves demonstrating the difference in survival according to the top 5 causes of heart failure in Afro-Caribbean patients attending the general heart failure clinic and 64 Afro-Caribbean patients with ATTR V122I (UK NAC).
Median survival (years): DCM 7.4; HTCM 7.3; VHD 4.8; Ischemic 3.2; ATTR V122I (SGH) 2.3; ATTR V122I (NAC) 2.9



Number at Risk

Years	0	1	2	3	4	5	6	7	8
DCM	58	53	42	34	23	18	17	12	7
HHD	26	26	23	19	12	10	10	10	5
VHD	15	12	12	11	11	5	3		
IHD	28	22	19	13	10	6	3	1	
V122I NAC	64	54	29	14	10	6			
V122I SGH	18	14	10	7	4	0			

Figure 2 - A proposed diagnostic algorithm to detect cases of ATTR amyloidosis in Afro-Caribbean patients



TABLES

Table 1
Comparison of heart failure patients at St George's hospital according to ethnicity

	Caucasian patients (N = 984)	**Afro-Caribbean patients (N = 211)**	**P value***
Age (range)	74 (64-82)	71 (54-77)	**<0.001**
Aged >80 years	325 (33%)	40 (19%)	**<0.001**
Male gender	656 (68%)	143 (68%)	0.76
Hypertension	532 (54%)	150 (71%)	**<0.001**
CVA	131 (13%)	30 (14%)	0.69
NYHA class**			
I	340 (35%)	84 (43%)	
II	402 (42%)	70 (36%)	0.24
III	213 (22%)	40 (20%)	
IV	13 (1%)	3 (1%)	
Ischemic cardiomyopathy	405 (41%)	28 (13%)	
			<0.001
Non-ischemic	579 (59%)	183 (87%)	
Cardiac amyloidosis (all types)	16 (1.6%)	24 (11.4%)	**<0.001**
ATTR V122I	3 (0.3%)	18 (8.5%)	**<0.001**
Dilated cardiomyopathy	196 (19.9%)	58(27.5%)	**<0.001**
Hypertensive cardiomyopathy	22 (2.2%)	26 (12.3%)	**<0.001**
Invasive coronary angiography	477 (48%)	120 (57%)	0.16
Patients <80 years	*365 (56%)*	*106 (62%)*	*0.082*
Patients >80 years	*112 (34%)*	*14(34%)*	*0.54*
Echocardiography	984 (100%)	211 (100%)	**NS**
CMR performed	210 (21%)	87 (41%)	**<0.001**
CRT device therapy	257 (26%)	36 (17%)	**0.006**
Endomyocardial biopsy	31 (3.2%)	29 (13.7%)	**<0.001**
Sinus rhythm	596 (60.6%)	159 (75.4%)	
Atrial fibrillation	352 (35.8%)	45 (21.3%)	**<0.001**
Paced rhythm	36 (3.7%)	7 (3.3%)	
LV septal wall thickness, mm (echo)	10 (9-12)	11 (10-14)	**<0.001**
LVEF, % (echo)	40 (30-54)	40 (30-55)	0.93
LVEF <35%, N	315 (32%)	80 (38%)	0.60
Creatinine µmol/L	101 (80-130)	107 (88-138)	**0.008**
Troponin µg/L	0.03 (0-0.09)	0.04 (0-0.12)	0.30
NT-pro BNP (ng/L)	2459 (848-6525)	2195 (654-5132)	0.17

*Compared to Caucasian patients
**Caucasian N=968; Afro-Caribbean N = 197
CVA – cerebrovascular accident; LVEF – left ventricular ejection fraction; CRT – cardiac resynchronization therapy

Table 2

Clinical characteristics of patients with biopsy-proven ATTR V122I amyloidosis (NAC)

	ATTR V122I (N = 72)
Age (years)	74 ± 6.9
Male gender	61 (84.7%)
Black African/Caribbean ethnicity	64 (89%)
NYHA Class	
I	3 (4.2%)
II	35 (48.6%)
III	31 (43.1%)
IV	3 (4.2%)
Duration of symptoms before diagnosis (years)	1.06 (0.68-2.41)
Fluid overload at presentation	43 (59.7%)
Hypertension	34 (47.2%)
Type 2 diabetes	13 (18.1%)
History of CVA	6 (8.3%)

MGUS	17 (23.6%)
Creatinine (µmol/L)	131 (113-164)
eGFR ml/min	48 (39-61)

*N = 42; NYHA – New York heart Association; CVA – cerebrovascular accident; MGUS – monoclonal gammopathy of uncertain significance detected on serum light chains; ACE – angiotensin converting enzyme; ARB – Angiotensin receptor blocker; eGFR – estimated glomerular filtration rate (correct for ethnicity); NT-pro BNP – N terminal brain natriuretic peptide

Table 3

ECG and echocardiographic characteristics of patients with biopsy-proven ATTR V122I amyloidosis

ECG	**ATTR V122I (N=72)**
Rate (beats per minute)	74 (66-85)
Rhythm	
Sinus	42 (58%)
Atrial fibrillation/flutter	22 (31%)
Paced	8 (11%)
*Axis**	
Normal	17 (26.6%)
Left axis deviation	40 (62.5%)
Right axis deviation	7 (10.9%)
PR interval (ms)†	198 (174-226)
First degree heart block†	21 (50%)
Low voltage criteria*	24 (38%)
Left ventricular hypertrophy criteria*	11 (17%)
Interventricular septum thickness (mm)	17 ± 2
Posterior wall thickness (mm)	17 ± 2

End diastolic diameter (mm)	43 ± 6
End systolic diameter (mm)	34 ± 7
Left ventricular mass (g)	299 (260-354)
Left atrial diameter (mm)	46 ± 6
Left ventricular ejection fraction (%)	39 ± 11
Diastolic function	
Normal	0 (0%)
Grade 1-2 dysfunction	41 (57%)
Grade 3-4 dysfunction	31 (43 %)
E/A ratio†	2.5 ± 0.9
E/E' ratio	16 (14-19)
Pericardial effusion	35 (49%)

*Only for 64 non-paced ECGs

†Only for 42 patients in sinus