Afro-Caribbean Heart Failure in the United Kingdom
Cause, Outcomes, and ATTR V122I Cardiac Amyloidosis

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Background—It has been reported that subjects of African descent present with heart failure at a younger age and because of different causes than whites. We present contemporary data from UK Afro-Caribbean patients in London.

Methods and Results—All patients with heart failure presenting to St George’s Hospital Heart Failure clinic between 2005 and 2012 were included (n=1392). Patients were predominantly white (71%) and male (67%), and median age at presentation was 73 years (range, 18–100 years). In 211 Afro-Caribbean patients, the most common cause of heart failure was nonischemic dilated cardiomyopathy in 27.5% (whites, 19.9%; P<0.001). Lower rates of ischemic cardiomyopathy were observed (13% versus 41%; P<0.001). The fourth most common 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 with other causes of Afro-Caribbean heart failure and white patients. To better understand this condition, we analyzed data from the largest international cohort of ATTR V122I patients, followed up at the UK National Amyloidosis Center (n=72). Patients presented with cardiac failure (median age, 75 [range, 59–90] years). Median survival was 2.6 years from diagnosis.

Conclusions—In London, the cause 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 are needed. (Circ Heart Fail. 2016;9:e003352. DOI: 10.1161/CIRCHEARTFAILURE.116.003352.)

Key Words: amyloid ■ blacks ■ ethnology ■ heart failure ■ prognosis

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, >1 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 black subjects suggest that heart failure is less likely to be caused by coronary artery disease and frequently caused by hypertensive heart disease.3 The limited reports in the UK Afro-Caribbean population suggest that this cohort often present in heart failure with preserved ejection fraction that may be related to hypertensive cardiomyopathy.4

See Editorial by Alexander and Falk
See Clinical Perspective

The role of Afro-Caribbean ethnicity in cardiovascular risk is still not fully understood. A higher prevalence of hypertension, elevated body mass index, and diabetes mellitus is recognized.5 We have identified a rapidly progressive form of heart failure in elderly Afro-Caribbean patients in increasing numbers over recent years because of cardiac amyloidosis.6 Variant transthyretin V122I has been estimated to be carried by 3.4% of blacks 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 men:women in a ratio of 6:1.8 Survival in ATTR V122I is reported to be poor,9 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 subtype8 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 patients with heart failure depending on white 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 (St George’s Hospital)

St George’s Hospital (SGH) is a regional cardiac center and local general hospital for a large catchment area of South West London of 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 after a suspected diagnosis of heart failure or by the medical teams after an inpatient admission with decompen-sated heart failure. The diagnosis was defined according to history and examination, echocardiographic findings and, when clinically indicated, supported by noninvasive 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 causes listed are considered the primary cause of heart failure symptoms and were determined at initial assessment and verified at the time of analysis after thorough review of patient records and any subsequent investigations or findings. Ischemic cardiomyopathy (ICM) was diagnosed in the context of coronary artery disease and regional wall motion abnormalities on cardiac imaging or positive ischemia testing; dilated cardiomyopathy (DCM) 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 (LVH) 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 classifications.

The term white 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 National Health Service Strategic Tracing Service.

Specialist Referral Clinic (National Amyloidosis Centre)

To understand this condition further, we collaborated with the UK National Amyloidosis Centre 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 of <0.5 mV and sum of S wave in V1 and mean of the R wave in V5 and V6<1.5 mV.\(^{16}\) Cornell criteria\(^{17}\) defined 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 LV and right ventricular wall thickening and LV diastolic dysfunc-tion were used. LV ejection fraction (LVEF) was assessed with bi- plane Simpson method.\(^{13}\) LV mass was calculated with the corrected American Society of Echocardiography simplified cubed equation.\(^{14}\)

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-di-phospho-1,2-propanodicarboxylic acid (99mTc-DPD) scintigraphy was performed using two General Electric (GE) hybrid, single-photon emission computed tomography 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 single-photon emission computed tomography. 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 antiperoxidase method to confirm amyloid fibril type, using monospecific antibodies reactive with serum amyloid A protein, transthyretin (TTR), and κ and λ immunoglobulin light chains.\(^ {21}\)

Statistics

Statistical analysis was performed using SPSS 21. Normally distributed data are presented as mean±1 SD. Non-normally distributed data are presented as median (25th and 75th percentiles). Categorical data are presented as frequencies and percentages. Dichotomous and categorical data for compared using \(\chi^2\) test or Fisher 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 white patients and 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–Sidák method to account for multiple comparisons. Data on New York Heart Failure Association class was missing for some SGH patients, and thus analysis was performed on 968 white 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 (range, 18–100) years with white (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 women and 143 men, 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; 25th–75th percentiles, 54–77) than whites (74 years; 25th–75th percentiles, 64–82; \(P<0.001\)) with a smaller proportion presenting aged 280 years (19% versus 33%; \(P<0.001\)). Black Caribbean patients (median, 73 years, 25th–75th percentiles, 58–78) were significantly older than Black African patients (median, 65 years; 25th–75th percentiles, 47–74; \(P=0.007\)). Hypertension was significantly
more prevalent in Afro-Caribbean patients (71% versus 54% in whites; \(P<0.001\)). History of cerebrovascular accident was similar in white and Afro-Caribbean patients (13% versus 14%; \(P=0.69\)). Investigation rates differed in Afro-Caribbean patients, with higher rates of CMR (41% versus 21% for white patients; \(P<0.001\)) and cardiac biopsy (14% versus 3% for white patients; \(P<0.001\)). Coronary intervention and biventricular pacemaker implantation (cardiac resynchronization therapy) were performed less frequently in Afro-Caribbean patients than in white patients (8% versus 20%; \(P<0.001\) and 26% versus 17%; \(P=0.006\), respectively).

**Cause of Heart Failure**

Table 1 compares Afro-Caribbean and white patients with both heart failure with preserved EF or heart failure with reduced EF. A total of 352 white patients had heart failure with EF ≥50% (36%) compared with 77 Afro-Caribbean patients (36%; \(P=0.97\). Overall, EF was no different between groups (both 40%; \(P=0.93\). No significant difference in the presence of poor LV systolic function <55% was demonstrated between the 2 groups (white patients, 32% versus Afro-Caribbean patients, 38%; \(P=0.60\). LV wall thickness was significantly higher in Afro-Caribbean patients (\(P=0.001\)).

ICM was much less common in Afro-Caribbean patients (13%) than in whites (41%; \(P<0.001\). No difference in NT-prohormone brain natriuretic peptide was observed between groups (white patients, 2459 ng/L [848–6525] versus Afro-Caribbean patients 2195 ng/L [554–5213]; \(P=0.17\). Atrial fibrillation was significantly more prevalent in white than in Afro-Caribbean patients (35.8% versus 21.3%; \(P=0.001\).

The top 5 diagnoses in Afro-Caribbean heart failure patients were as follows: (1) nonischemic DCM (27%); (2) ischemic heart disease (13%); (3) hypertensive cardiomyopathy (12%); (4) cardiac amyloidosis (all subtypes: 11%); and (5) valvular heart disease (7%; Clinical characteristics in Table 1 in the Data Supplement).

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 >65 (range, 68–84 years, in keeping with the reported age-related clinical phenotype.22 Subgroup analysis revealed that 153 Afro-Caribbean patients were as follows: (1) nonischemic DCM (27%); (2) hypertensive cardiomyopathy (12%); (4) cardiac amyloidosis (all subtypes: 11%); and (5) valvular heart disease (7%; Clinical characteristics in Table 1 in the Data Supplement).

**Heart Failure Admissions**

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

**Survival**

Survival differed significantly according to the cause and ethnicity overall (median survival in white, 4.7 years versus Afro-Caribbean, 5.9 years; \(P=0.031\). Deaths (579) occurred during follow-up (486 whites and 93 Afro-Caribbeans). No significant difference in survival was observed according to ethnicity in patients with ICM (\(P=0.25\) or DCM (\(P=0.71\)).

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 nonischemic DCM and hypertensive cardiomyopathy (DCM, 7.41 years; hypertensive cardiomyopathy [HTCM] 7.32 years; \(P=0.88\) and patients with ATTR V122I had the poorest survival (ATTR V122I 2.33 years versus DCM \(P<0.001\) and versus HTCM \(P=0.002\). No significant difference in survival was observed between ATTR V122I and ICM (\(P=0.11\) or valvular heart disease (\(P=0.19\) in Afro-Caribbean patients. It should be noted that the age at presentation differed according to the cause. Afro-Caribbean patients with ATTR V122I presented at a relatively old age—median 76 years, interquartile range 74 to 78—compared with Afro-Caribbean patients with DCM (68 years; 25th–75th percentiles, 51–75; \(P=0.001\) and HTCM (61 years; 25th–75th percentiles, 47–72; \(P=0.001\). The median age of Afro-Caribbean patients with ICM (76 years; 25th–75th percentiles, 71–81; \(P=0.74\) and valvular heart disease (81 years; 25th–75th percentiles, 74–85; \(P=0.23\) was similar to ATTR V122I. The median age of presentation was similar in whites for each of these causes (67 years for DCM; \(P=0.27\); 82 years for valvular heart disease, \(P=0.54\); and 75 years for ICM), except HTCM (79 years; \(P<0.001\).

**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 Center between January 1995 and March 2013, including the 18 SGH patients (Table 2). Cardiac biopsies were obtained in 39 patients (54%) and noncardiac 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; 25th–75th 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 <20% from other countries.

Sixty-eight patients were heterozygous for the TTR V122I allele and 4 patients were homozygotes. All homozygous patients were men and presented at a younger age (65±3 years) compared with heterozygotes (74±7 years; \(P=0.004\).

The majority of V122I ATTR patients were in New York Heart Failure Association class II and III (92%) at first review. Almost half (46%) had a history of carpal
A history of hypertension was common (47%). Median duration of symptoms before referral was 1.06 years (25th–75th 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 (25th–75th percentiles, 113–164) μmol/L and glomerular filtration rate was 48 (25th–75th percentiles, 39–61) mL/min. Renal impairment (estimated glomerular filtration rate, <60 mL/min, corrected for ethnicity) was present in 79.4%. NT-prohormone brain natriuretic peptide was >100 pMol/L in 96% (median, 435 pMol/L; 25th–75th percentiles, 269–644). ECG showed low-voltage complexes in 38% and 17% had criteria for LVH (Table 3).

Concentric LV wall thickening (>12 mm) was evident on echocardiography in all patients, (median, 17 mm; 25th–75th percentiles, 15–19 versus 17 mm; 25th–75th percentiles, 16–18; \( P=0.47 \)). Diastolic dysfunction was present in every case and was categorized as severe (grade 3 or 4) in 43%.
LVEF was moderately impaired overall (mean, 39±11%; range 19%–69%). A small (<1.5 cm) pericardial effusion was evident in 49% (Table 3).

Thirty-nine patients (54%) underwent CMR before 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 LVEF was 48±14%. Mean LV mass 230 g (25th–75th percentiles, 214–248) was hugely increased (mean, 144 g and upper limit of normal, 183 g for men aged >70 years). Extensive late gadolinium enhancement was present in all. 99mTc-DPD scintigraphy was acquired in 27 patients (38%). All 99mTc-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 (64–91) years. The median survival from the date of diagnosis was 2.62 years. Median survival in Afro-Caribbean patients was 2.92 years compared with 1.45 years in white 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), 1 patient died from a cerebrovascular accident 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 National Amyloidosis Centre and SGH ATTR V122I patients (P=0.36).

Discussion

We report a study of Afro-Caribbean patients with heart failure 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 cause for many more of the nonischemic DCM cohort, as 63% had a history of hypertension and many more had no regular BP checks before presentation. Survival in hypertensive cardiomyopathy and nonischemic DCM 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 the cause the differences disappeared; once a patient has heart failure secondary to ischemic or DCM, the survival is similar regardless of ethnicity. The cause also has an influence on apparent differences in the age of patients with heart failure 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...
The allele frequency of ATTR V122I, an autosomal dominant condition, has been reported to be carried by 3.4% in blacks,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 heart failure 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 patients with heart failure at SGH were referred to the UK National Amyloidosis Centre 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 100000 UK population, with predominantly white ethnicity (4.5% black African, black Caribbean, or mixed black and other ethnicity nationwide). The low absolute numbers in the wider population likely represent 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 men were included or followed up to visit 5.27 Wild-type ATTR amyloidosis is reported to be an increasingly important cause of heart failure with preserved EF and has been shown to be the primary cause 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 after 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. Underdiagnosis 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 because of a shorter life expectancy in previous generations and in parts of West Africa.

Underrecognition 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 onsite CMR coupled with growing awareness of this disease. A substantial and progressive increase in referrals generally

### Table 2. Clinical Characteristics of Patients With Biopsy-Proven ATTR V122I Amyloidosis (National Amyloidosis Centre)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>ATTR V122I (n=72)</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>74±6.9</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>61 (84.7)</td>
</tr>
<tr>
<td>Black African/Caribbean ethnicity, n (%)</td>
<td>64 (89)</td>
</tr>
<tr>
<td>NYHA class, n (%)</td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>3 (4.2)</td>
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<tr>
<td>II</td>
<td>35 (48.6)</td>
</tr>
<tr>
<td>III</td>
<td>31 (43.1)</td>
</tr>
<tr>
<td>IV</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>Duration of symptoms before diagnosis, y</td>
<td>1.06 (0.68–2.41)</td>
</tr>
<tr>
<td>Fluid overload at presentation, n (%)</td>
<td>43 (59.7)</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>34 (47.2)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus, n (%)</td>
<td>13 (18.1)</td>
</tr>
<tr>
<td>History of CVA, n (%)</td>
<td>6 (8.3)</td>
</tr>
<tr>
<td>MGUS, n (%)</td>
<td>17 (23.6)</td>
</tr>
<tr>
<td>Creatinine, μmol/L</td>
<td>131 (113–164)</td>
</tr>
<tr>
<td>eGFR, mL/min</td>
<td>48 (39–61)</td>
</tr>
</tbody>
</table>

CVA indicates cerebrovascular accident; eGFR, estimated glomerular filtration rate (correct for ethnicity); MGUS, monoclonal gammopathy of uncertain significance detected on serum light chains; and NYHA, New York heart Association.

*n=42.

also presented significantly younger than whites, 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 the use of diuretics. The prognosis is poor, with a median survival of 2.6 years after confirmation of diagnosis. Survival compares poorly with 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 patients with heart failure. 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
during the past 5 years can be attributed to increased access to CMR elsewhere in the United Kingdom.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.1 The combination of LVH and limited investigation of Afro-Caribbeans with likely impeding diagnosis are lack of awareness of this condition, and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previously.1 The combination of LVH and limited investigation of Afro-Caribbeans with heart failure reported previous...
Conclusion

Consideration of race in the approach to a patient with heart failure is important for the most personalized management. In London, the cause of heart failure varies depending on ethnicity and affects age of presentation and outcomes. Nonischemic DCM, often with preceding history of hypertension and concomitant LVH, is the most common 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 blacks. 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 3 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 LV wall thickening, regardless of any history of hypertension, ATTR V122I should be considered and actively investigated.

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Disclosures

None.
References


We present an article highlighting an important yet underappreciated cause of heart failure in the Afro-Caribbean community, cardiac transthyretin amyloidosis (ATTR). The first part is an analysis of heart failure cause in the UK Afro-Caribbeans attending a large center in South London. The variant ATTR V122I was found to be the biopsy-proven cause of heart failure in 11.8% of Afro-Caribbeans presenting over the age of 60 years. One quarter of all the UK cases ever seen at the National Amyloid Center have been referred from St George’s, suggesting widespread under-detection elsewhere. The second part of the article is the first comprehensive phenotypic description of ATTR V122I from the world’s largest and most systematically studied cohort at the UK National Amyloid Center. To date, ATTR V122I has been severely underrepresented in the medical literature and, like other conditions affecting ethnic minority groups, is not given the priority it deserves. About priority, significance and relevance, the genetic variant is carried by up to 4% of this ethnic minority, gene carriage has been associated with a 47% increase in heart failure, and life expectancy is < 3 years after diagnosis. This previously undetermined and fatal cardiac condition is the focus of international innovative efforts to find a treatment. Currently, 3 new agents are in international phase 3 trials with phase 2 data showing knockdown of transthyretin production by >90%. With specific ATTR amyloidosis treatments in clinical development, there is a pressing need for better education and awareness of this condition.
Afro-Caribbean Heart Failure in the United Kingdom: Cause, Outcomes, and ATTR V122I Cardiac Amyloidosis


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Clinical characteristics of Afro-Caribbean heart failure patients presenting to St George's hospital, according to the top 5 aetiologies

<table>
<thead>
<tr>
<th></th>
<th>DCM (N = 58)</th>
<th>IHD (N = 28)</th>
<th>HTCM (N = 26)</th>
<th>CA - all (N = 23)</th>
<th>VHD (N = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>65 ± 14</td>
<td>73 ± 10</td>
<td>58 ± 15</td>
<td>77 ± 6</td>
<td>79 ± 8</td>
</tr>
<tr>
<td>Age &gt;80 years</td>
<td>12%</td>
<td>25%</td>
<td>14%</td>
<td>22%</td>
<td>53%</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>72%</td>
<td>61%</td>
<td>82%</td>
<td>72%</td>
<td>53%</td>
</tr>
<tr>
<td>NYHA class 3/4</td>
<td>18%</td>
<td>27%</td>
<td>12%</td>
<td>50%</td>
<td>43%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>63%</td>
<td>82%</td>
<td>100%</td>
<td>56%</td>
<td>93%</td>
</tr>
<tr>
<td>CVA</td>
<td>19%</td>
<td>14%</td>
<td>11%</td>
<td>6%</td>
<td>13%</td>
</tr>
<tr>
<td>LV septal thickness (mm)</td>
<td>10 ± 2</td>
<td>9 ± 2</td>
<td>12 ± 4</td>
<td>16 ± 2</td>
<td>11 ± 2</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>32 ± 10</td>
<td>42 ± 10</td>
<td>43 ± 13</td>
<td>38 ± 11</td>
<td>55 ± 11</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>30%</td>
<td>14%</td>
<td>7%</td>
<td>6%</td>
<td>60%</td>
</tr>
<tr>
<td>Heart rate (min⁻¹)</td>
<td>75 ± 14</td>
<td>78 ± 15</td>
<td>75 ± 10</td>
<td>76 ± 9</td>
<td>83 ± 19</td>
</tr>
<tr>
<td>Creatinine (µmol/L)</td>
<td>107 (88-144)</td>
<td>123 (84-198)</td>
<td>118 (90-159)</td>
<td>137 (106-181)</td>
<td>116 (78-144)</td>
</tr>
<tr>
<td>GFR (ml/min)</td>
<td>54 ± 16</td>
<td>44 ± 20</td>
<td>51 ± 20</td>
<td>44 ± 18</td>
<td>49 ± 18</td>
</tr>
<tr>
<td>Troponin (µg/L)</td>
<td>0.03 (0.00-0.07)</td>
<td>0.05 (0.00-0.16)</td>
<td>0.03 (0.00-0.11)</td>
<td>0.18 (0.10-0.51)</td>
<td>0.05 (0.00-0.45)</td>
</tr>
<tr>
<td>NT-pro BNP (ng/L)</td>
<td>1547 (571-4389)</td>
<td>2266 (1347-7114)</td>
<td>1268 (2721-8284)</td>
<td>5251 (2721-8284)</td>
<td>3942 (1728-7505)</td>
</tr>
</tbody>
</table>

DCM – non-ischaemic dilated cardiomyopathy; HTCM – hypertensive cardiomyopathy; IHD – ischaemic heart disease; CA – cardiac amyloidosis (all subtypes) VHD – valvular heart disease; NYHA – New York Heart Association; LV – left ventricular; EF – ejection fraction; GFR – glomerular filtration rate (adjusted for black ethnicity); CVA – history of cerebrovascular accident