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RESEARCH

Extending the reach of expert amyloidosis care: A feasibility study exploring the staged implementation of a UK amyloidosis network☆

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ABSTRACT

There has been an exponential increase in the diagnosis of transthyretin amyloid cardiomyopathy (ATTR-CA). In response, the Midlands Amyloidosis Service was launched with the aim of providing patients with a timely diagnosis, remote expertise from the National Amyloidosis Centre and access to emerging transthyretin (TTR)-directed therapies. This was a descriptive study of a pilot hub-and-spoke model of delivering specialist amyloidosis care. Patients with suspected amyloidosis were referred from the wider Midlands region, and seen in a consultant-led multidisciplinary clinic. The diagnosis of ATTR-CA was established according to either the validated non-biopsy criteria or histological confirmation of ATTR deposits with imaging evidence of amyloid. Study endpoints were the volume of service provision and the time to diagnosis from the receipt of referral. Patients (n=173, age 75±2 years; male 72 %) were referred between 2019 and 2021. Eighty patients (46 %) were found to have cardiac amyloidosis, of whom 68 (85 %) had ATTR-CA. The median time from referral to diagnosis was 43 days. By removing the need for patients to travel to London, an average of 187 patient-miles was saved. Fifteen (9 %) patients with wild-type ATTR-CA received tafamidis under the Early Access to Medicine scheme; 10 (6 %) were enrolled into phase 3 clinical trials of RNA interference or antisense oligonucleotide therapies. Our results suggest that implementing a UK amyloidosis network appears feasible and would enhance equity of access to specialised amyloidosis healthcare for the increasing numbers of older patients found to have ATTR-CA.

Summary box

What is known?

The incidence of transthyretin amyloid cardiomyopathy is increasing because of improved diagnoses and has recently overtaken light-chain amyloidosis as the most common manifestation of amyloidosis worldwide.

What is the question?

Can lessons be learnt about the feasibility of delivering multi-centre specialist amyloidosis care using a hub-and-spoke model?

What was found?

Not all UK patients with cardiac amyloidosis are willing to travel long distances to access expert care, but it is feasible to deliver highly specialised healthcare via a network supported by a central hub.

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What is the implication for practice now?

This study highlights a growing need to implement a UK amyloidosis network to avoid inequalities in the access to, and quality of, specialised healthcare.

Introduction

Although cardiac amyloidosis (CA) is rare, it is one of the leading causes of restrictive cardiomyopathy, characterised by extracellular deposition of misfolded protein fibrils throughout the heart. The amyloid fibrils can be detected by demonstrating apple-green birefringence in polarised light when stained with Congo Red.[1–3] Most cases of CA can be attributed to two amyloid fibril subtypes: transthyretin (ATTR) and light chain (AL) amyloidosis.[1,3] ATTR-CA is further subdivided depending on transthyretin gene sequencing into: (i) wild-type ATTR-CA (ATTRwt-CA), a condition with a normal TTR sequence and that typically affects older men; or (ii) hereditary or variant ATTR-CA (ATTRv-CA), which is associated with over 130 different pathogenic variants in the gene encoding ATTR.[2,4,5] The most common variants in the UK and Ireland responsible for ATTRv-CA are V122I, which is present in ~4 % of African-Caribbeans, and T60A, which is estimated to affect 1 % of the population in North-West Ireland.[6]

Irrespective of the underlying aetiology of amyloid production, cardiac dysfunction is the leading cause of morbidity and mortality in patients with amyloidosis.[2] Without access to TTR-targeted pharmacotherapy, median survival from the time of diagnosis of ATTRwt-CA is estimated at 5 years, but those with advanced UK National Amyloidosis Centre (NAC) stage III disease (defined as N-terminal pro-B-type natriuretic peptide (NT-proBNP) >3,000 ng/L and estimated glomerular filtration rate (eGFR) <45 mL/min/1.73m^2), have a median survival of only 2 years.[6] Myocardial infiltration into the interstitium causes increased biventricular wall thickness (pseudohypertrophy) resulting in restrictive physiology associated with bi-atrial dilatation and a low cardiac output.[2] Patients with CA also frequently experience heart rhythm disturbances, such as atrial fibrillation (AF) and atrioventricular conduction delay.[2,4,7] The combination of significant diastolic dysfunction and loss of the atrial contribution to ventricular filling in patients with ATTR-CA with concurrent AF is often poorly tolerated, resulting in clinical deterioration and recurrent hospital admissions with congestive heart failure.[4]

Since 1999, the UK NAC has been commissioned by the UK NHS to deliver a diagnostic and treatment advisory service that is available free of charge at the point of delivery to patients with suspected or proven amyloidosis.[8,9] Currently, it is the world's largest amyloidosis practice, with a referral rate of 1,400 new patients per annum from the UK and internationally.[8] Improvements in cardiac imaging techniques and the development of novel anti-amyloid agents, coupled with validation of a non-biopsy algorithm, have led to an exponential surge in the diagnosis of ATTR-CA over the past decade.[5,6] In response to this heightened demand, the Midlands Amyloidosis Service (MAS) was launched at University Hospitals Birmingham (UHB) NHS Foundation Trust in August 2019, with the aim of providing patients with a timely diagnosis, remote multidisciplinary expertise from the NAC, access to targeted novel therapies and participation in phase 3 clinical trials. We herein report our first 2 years of experience at the MAS.

Methodology

Local context: establishment of a 'hub-and-spoke' model

Since its establishment in 2019, the MAS has served as the 'hub' to which primary care service providers and cardiology centres from surrounding hospitals, or 'spokes', referred patients in whom a diagnosis of CA was suspected. These spokes cover a large geographical catchment area, with a population of ~6 million, and comprise the following regions: Birmingham (City and Sandwell NHS Foundation Trust, and UHB NHS Foundation Trust), Wolverhampton (Royal Wolverhampton NHS Foundation Trust), Worcester (Worcestershire Acute Hospitals NHS Trust), Cheltenham and Gloucester (Gloucestershire Hospitals NHS Foundation Trust), Coventry and Warwick (University Hospitals Coventry and Warwickshire NHS Trust), Walsall (Walsall Manor Hospital), Dudley (Russells Hall Hospital), Hereford (Hereford County Hospital), Nuneaton (George Eliot Hospital), and Shropshire and Telford (Shrewsbury and Telford NHS Trust) (Fig. 1). During this pilot phase (2019–21), patients could still be referred to the NAC at the discretion of their local clinician. Referrals made directly to the NAC were not redirected to the MAS.

Ethical considerations

The conduct and reporting of this study were in line with the principles of the Declaration of Helsinki and guided by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[10] According to the policy activities that constitute research locally, this work met criteria for operational improvement activities and, therefore, formal ethical approval was not required. The study was approved by the UHB NHS Divisional Clinical Quality Group (CARMS-17907).

Patients

Consecutive patients with suspected CA who were referred to the MAS for assessment between 1 August 2019 and 30 September 2021 were retrospectively identified from the UHB electronic database.

Setting and intervention

All patients referred to the MAS were reviewed in a 'one-stop' multidisciplinary clinic that comprised specialist consultants from the cardiology, nephrology and neurology departments (minimum of three consultant physicians per clinic, with an average of six clinics per year). Patients underwent a comprehensive consultation, which included: a detailed review of the patient's presentation and family history; full physical examination; 12-lead electrocardiography (ECG); and serological testing, including full blood count, liver, bone and renal function profiles, high-sensitivity Troponin I (hsTnI), and NT-proBNP. Serum and urine protein electrophoresis and immunofixation were performed to exclude monoclonal dyscrasia. Imaging assessments were made using transthoracic echocardiography (TTE), cardiovascular magnetic resonance (CMR) and ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD) scintigraphy. In those cases where patients had already undergone ^{99m}Tc-DPD scintigraphy or CMR locally, on receipt the referral imaging was transferred via the Radiology Picture Archiving and Communication System (PACS) and reviewed before attendance at the MAS clinic and in subsequent video multidisciplinary team (MDT) meetings with NAC clinicians. To avoid the need for repeated tests, cardiac imaging was not routinely repeated if it had been performed within 6 months of the date of referral and was deemed to be of diagnostic quality. The diagnosis of ATTR-CA was established according to either validated non-biopsy criteria or histological confirmation of cardiac ATTR amyloid deposits with imaging evidence of amyloid cardiomyopathy by echocardiography and/or CMR.[1]

All patients with a confirmed diagnosis of CA were discussed at a remote MDT meeting between specialists at MAS and two experts from the NAC. Clinicians from the 'spokes' were also invited to attend this meeting. The bimonthly MDT would decide which individuals required an onward referral to the NAC. More complex patients (eg those with rare hereditary variants and/or those with suspected ATTRwt-CA that did not fulfil non-biopsy criteria) were also offered review at the NAC.

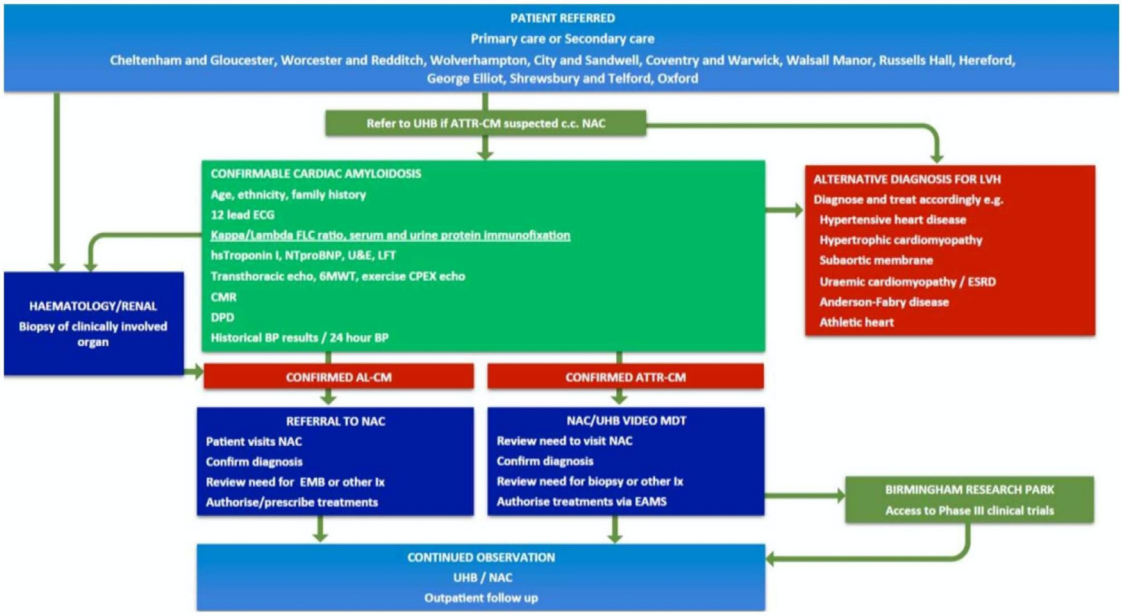

Fig. 1. 'Hub-and-spoke' model referral pathway to the Midlands Amyloidosis Service. Abbreviations: AL-CM, light chain amyloid cardiomyopathy; ATTR-CM, transthyretin amyloid cardiomyopathy; EAMS, early access to medicines scheme; ECG, electrocardiogram; EMB, enodmyocardial biopsy; ESRD, end-stage renal disease; FLC, free light chains; hs Troponin I; high sensitivity Troponin I; LFT, liver function tests; LVH, left ventricular hypertrophy; NAC, National Amyloidosis Centre; NTproBNP, N-terminal pro b-type natriuretic peptide; U&E, urea and electrolytes; UHB, University Hospitals Birmingham NHS Foundation Trust.

When amyloid tissue typing was needed, histology samples were forwarded to the NAC.

Echocardiography

Echocardiography (on a PHILIPS EPIQ 7 ultrasound machine) was updated at baseline at the MAS. Images were obtained and analysed by British Society of Echocardiography-accredited cardiac sonographers in accordance with the updated joint guidance from the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[11]

Cardiovascular magnetic resonance

CMR was performed in-house using a Siemens MAGNETOM® Avanto 1.5T scanner. Within a standard clinical scan, late gadolinium enhancement (LGE) imaging was obtained with magnitude-only inversion recovery (MG-IR) and phase-sensitive inversion recovery (PSIR) sequence reconstructions. T1 mapping was initially conducted using the modified look-locker inversion (MOLLI) recovery sequence, and repeated 15 min after an infusion of 0.1 mmol/kg of gadobutrol (Gadovist®) to produce extracellular volume (ECV) measurements.[12]

Bone scintigraphy

Patients were administered 700 MBq of ^{99m}Tc-DPD intravenously before whole-body planar images were obtained 3 h later using a single-photon emission computed tomography-computed tomography (SPECT/CT) scanner (UHB scanner: Siemens Symbia T16 16-slice). The intensity of myocardial uptake on all ^{99m}Tc-DPD scintigraphy was graded from 0 to 3 according to the Perugini grading system.[13]

Histology

All biopsies were formalin fixed, paraffin embedded and stained with Congo Red. Monospecific antibodies reactive to various amyloid fibril subtypes were used in immunohistochemical staining of all amyloid deposits.[1]

Genotyping

Patients with confirmed ATTR-CA and those eligible for presymptomatic genetic cascade screening underwent TTR gene sequencing after informed written consent. Genomic DNA was isolated from whole blood and amplified by polymerase chain reaction, and the entire coding region of the transthyretin gene was sequenced by Sanger method.[1,14]

Amyloid-specific treatment

MAS clinicians were responsible for the authorisation of TTR stabiliser therapy (tafamadis) under the Early Access to Medicine Scheme (EAMS) following MDT discussion with the NAC. MAS clinicians were also responsible for coordinating local heart failure, specialist neurology and genetics reviews. Specialists at the NAC were responsible for facilitating enrolment into phase 3 trials at local research sites for eligible patients with ATTR-CA. Patients with AL-CA received chemotherapy via their designated haematologist locally, with input from the specialists at the NAC.

Measures of improvement

There were no baseline metrics of quality improvement for comparison because there was no dedicated regional service provision before intervention. The study endpoints were chosen *a priori* as the volume of service provision and the time to diagnosis from the receipt of referral.

Historical comparator

The NAC electronic database was retrospectively interrogated to identify the total number of referrals made from the same catchment area for patients with suspected amyloidosis (using postcode data) during the 2019–21 study period and for historical comparison, the number

Fig. 2. Catchment of referrals to the newly established Midlands Amyloidosis Service.

of referrals made over an equivalent 2-year period from 1 August 2016 to 30 September 2018.

Results

Referral cohort

In total, 173 patients were referred to the MAS between August 2019 and September 2021. Their median age was 75 years and most were male (72 %). More than three-quarters of patients referred for assessment were White (138/173, 79 %), with the remainder being of African-Caribbean (30/173, 17 %), British Asian (4/173, 2 %) or Hispanic (1/173, 0.6 %) ethnicity. Fig. 2 depicts the geographical distribution of patients referred.

The median time from receipt of referral to diagnosis was 43 days. Of the 149 patients seen, 80 found to have CA: 68 (85 %) had ATTR-CA, nine (13 %) had AL-CA, two (1 %) had hereditary apolipoprotein A-1 Arg173Pro variant-associated amyloidosis, and one (<1 %) had Glu526Val fibrinogen α-chain amyloidosis (Fig. 3). Conversely, there was no evidence of cardiac involvement in two (1 %) patients who were found to have systemic AL amyloidosis. Of those patients found to have CA, 95 % (76/80) were formally discussed in video MDT with the NAC. Thirteen subjects discussed in MDT had previously declined travel to London; all were above the age of 80 years. By removing the necessity for all patients to travel to London, a total of 32,346 patient miles was saved (187 ± 7 miles per patient).

Baseline characteristics of all patients found to have CA following referral to the MAS are detailed in Table 1. Of the 68 patients with ATTR-CA, 12 (18 %) were diagnosed as hereditary variant (ATTRv-CA) after Sanger TTR gene sequencing: V122I (n=9), T60A (n=2), Val30Met (n=1). As expected, most patients found to have ATTRwt-CA (n=56) were older (median age 82 years), male (47/56; 84 %), and of White origin (52/56; 93 %). Similarly, most patients found to have non-V122I-associated ATTRv amyloidosis and AL-CA were White, although the majority of the subjects in both these subgroups were female. Patients found to have V122I-associated ATTRv-CA were mostly of African-Caribbean origin (8/9, 89 %).

CA was ruled out in 34 % (59/173) of patients following ^{99m}Tc-DPD and CMR imaging where alternative causes of left ventricular hypertrophy (LVH) were identified (Figs. 3 and 4). Alternative diagnoses for the aetiology of cardiomyopathy were made based on the consensus opinion of at least two consultant physicians (W.E.M., R.P.S., M.F., J.D.G.). In these patients, all testing was performed locally in the West Midlands, and patients returned to their referring hospitals with alternative confirmed diagnoses, thereby reducing the referral burden on the NAC.

Non-attendance/loss to follow-up

Twenty-four (14 %) patients declined to attend their regional MAS appointment, citing frailty as the main reason for this decision (mean age 84 years; 58 % New York Heart Association (NYHA) Class III–IV). All but three of these patients (21/24) lived in the West Midlands region. One patient who had moved abroad to Belgium was lost to follow-up.

Collaborative shared care

No referrals to the MAS were rejected or sent directly to the NAC. Twenty-six patients (15 % of all referrals) received hybrid care. These patients were initially discussed in video MDT with the NAC, before undergoing a remote telephone review with the NAC before being discharged and receiving ongoing follow-up at the MAS.

Twenty-nine patients (17 % of all referrals) still received a face-to-face review at the NAC following their face-to-face review at the MAS. These included patients with ATTRv-CA with an indication for small interfering (si)RNA therapy (patisiran; n=5), those patients whom it was felt would benefit from further diagnostic work-up with a serum amyloid P component (SAP) scan (n=1) or those with rare amyloid types or rarer TTR variants (n=11).

Ninety-four (54 % of all referrals) received local care only. These patients could be classified into four groups: (1) those in whom a diagnosis of amyloidosis was excluded based on the history, echocardiography, CMR and ^{99m}Tc-DPD results (n=59); (2) older patients with ATTRwt-CA (n=14) and ATTRv-CA V122I (n=2) in end-stage heart failure deemed unlikely to benefit from potential access to TTR-modifying therapies; (3) those who declined to travel to London (n=13); and (4) a proportion of patients with AL-CA who were deemed too unwell to travel to London (n=6).

Symptoms

The majority of patients (63/80, 79 %) diagnosed with ATTR-CA were in New York Heart Association (NYHA) class II-III, while all patients with AL-CA were in NYHA class III-IV.

Biomarkers

Median baseline NT-proBNP in both the AL- and ATTR-CA subgroups exceeded 3000 ng/L, whereas median estimated glomerular filtration rate (eGFR) was ≤ 45 mL/min/1.73 m^2 in both the V122I-associated ATTRv-CA and AL-CA cohorts. By contrast, median eGFR in both the ATTRwt-CA and T60A-associated ATTRv-CA groups was 60 and 70 mL/min/1.73 m^2, respectively.

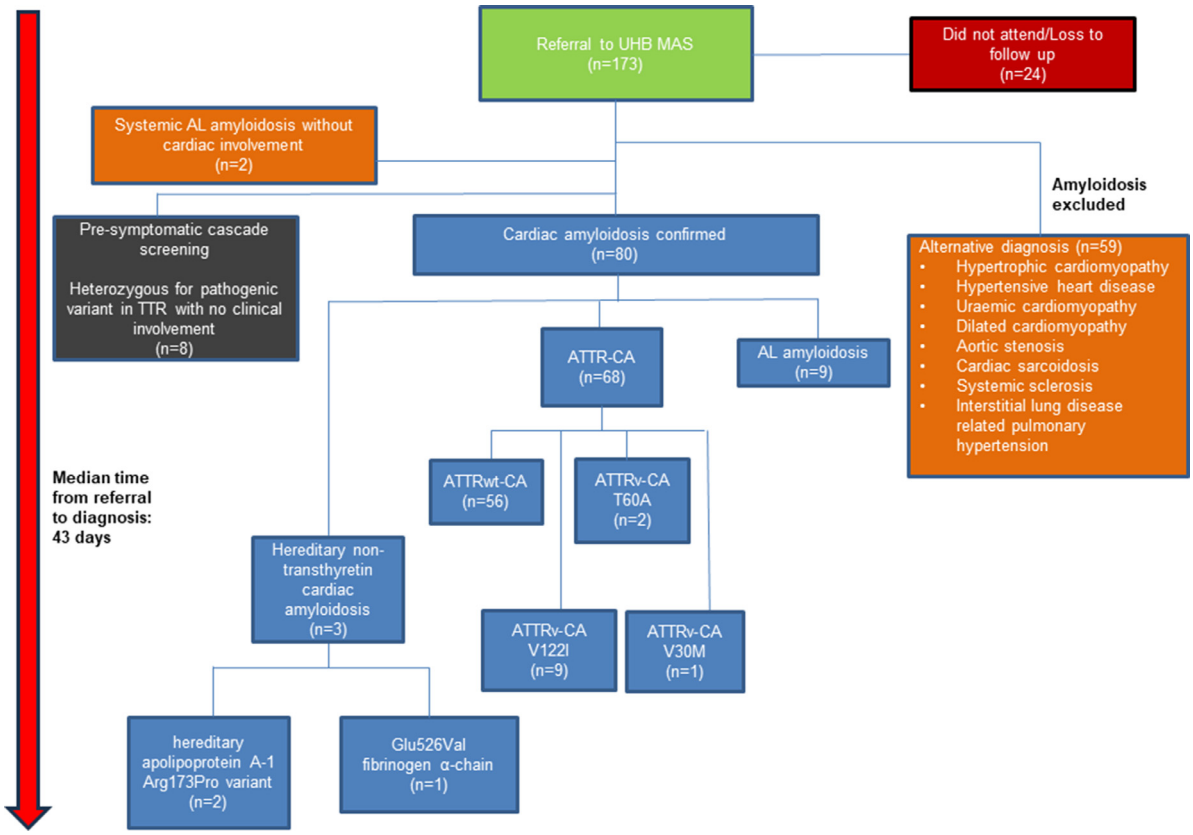

Fig. 3. Diagnostic pathway for all patients referred to the Midlands Amyloidosis Service. Abbreviations: AL, light chain; ATTR-CA, transthyretin cardiac amyloidosis; ATTRwt-CA, wild type transthyretin cardiac amyloidosis; ATTRv-CA, variant transthyretin amyloid cardiomyopathy; TTR transthyretin; MAS, Midlands Amyloidosis Service; UHB, University Hospitals Birmingham NHS Foundation Trust.

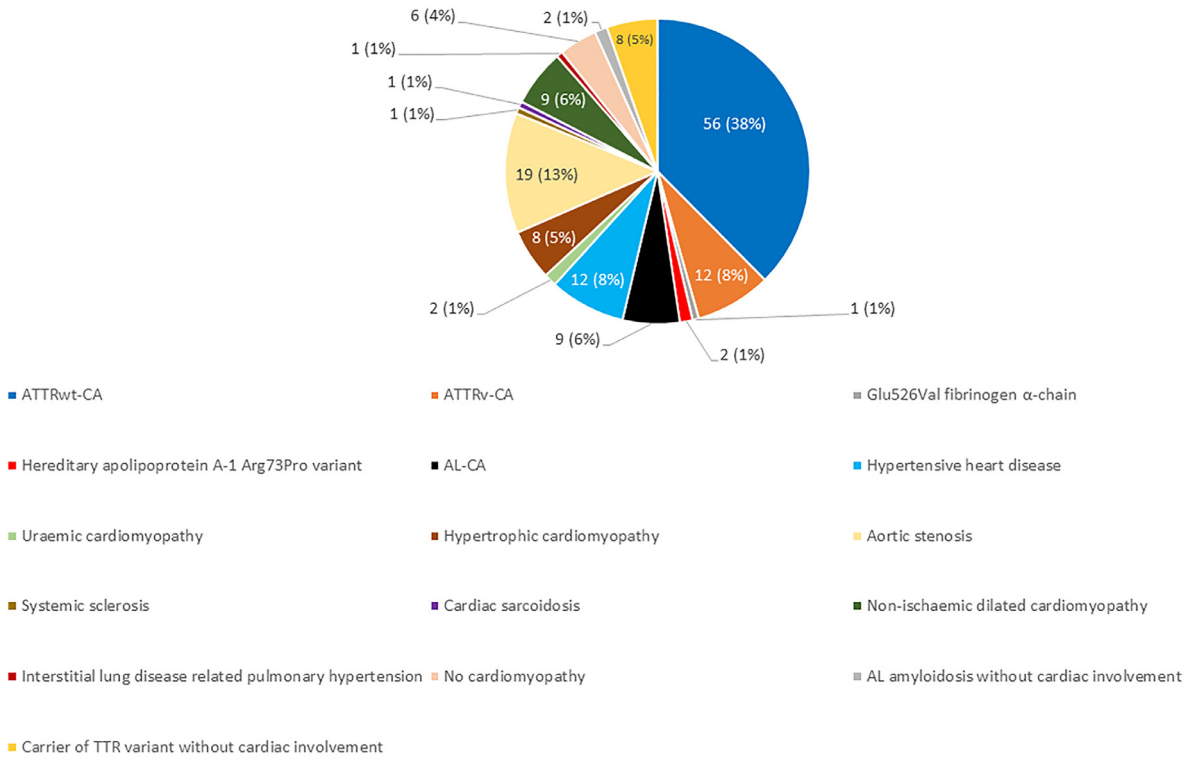

Fig. 4. Overall distribution of diagnoses made at the Midlands Amyloidosis Service (n=149). Abbreviations: AL, light chain; ATTR-CA, transthyretin cardiac amyloidosis; ATTRwt-CA, wild type transthyretin cardiac amyloidosis; ATTRv-CA, variant transthyretin amyloid cardiomyopathy; TTR transthyretin; MAS, Midlands Amyloidosis Service; UHB, University Hospitals Birmingham NHS Foundation Trust.

Table 1
Characteristics of patients found to have cardiac amyloidosis after referral to the Midlands Amyloidosis Service (n=80).

Characteristic	ATTRwt-CA (n=56)	ATTRv-CA V122I (n=9)	ATTRv-CA T60A (n=2)	Others: ATTRv-CA/apolipoprotein A1/fibrinogen[a] (n=4)	AL-CA (n=9)
Age at diagnosis Median (range)	82 (61–90)	77 (54–82)	67.5 (64–71)	68.5 (50–72)	72 (51–82)
Sex, n (%)					
Male	47 (84 %)	5 (56 %)	0 (0 %)	2 (50 %)	3 (33 %)
Ethnicity					
White	52	0	2	4	8
Asian	0	1	0	0	1
African-Caribbean	4	8	0	0	0
Left ventricular ejection fraction (LVEF, %); median (range)	50 (10–75)	52 (22–60)	44 (35–53)	58 (38–63)	43 (36–65)
Missing data	0	1	0	0	0
Interventricular septal end-diastole diameter (mm); median (range)	17 (8–25)	17 (12–19)	13.5 (12–15)	14 (13–20)	14 (11–19)
Missing data	0	1	0	0	0
NYHA class, (n)					
I	4	0	0	1	0
II	27	5	2	1	0
III	25	4	0	1	8
IV	0	0	0	1	1
NT-proBNP (ng/L), median (range)	3,571 (271–12,443)	4,443 (1,370–14,434)	3,980 (1,266–6,694)	4,398 (57–13,839)	7,124 (2,072–35,000)
NT-proBNP ≤2000 (n)	17	1	1	1	1
NT-proBNP 2001–2999 (n)	6	1	0	0	8
NT-proBNP ≥3000 (n)	30	5	1	3	0
Missing data	3	2	0	0	
eGFR (mL/min), median (range)	60 (26–90)	45 (19–72)	70	43 (7–78)	42 (25–82)
>90 (n)	5	0	0	0	0
60–89 (n)	22	2	2	2	3
45–59 (n)	17	2	0	0	0
30–44 (n)	9	1	0	0	5
15–29 (n)	1	2	0	1	1
<15 (n)	0	0	0	1	0
Missing data	2	2	0	0	0
HS Troponin I (ng/L); median (range)	73 (12–373)	214 (24–1,599)	26 (24–27)	99 (17–195)	143 (57–767)
Missing data	3	2	0	0	0
Heart rhythm (n)					
Sinus rhythm	17	7	1	2	6
AF	38	1	1	2	3
Missing data	1	1	0	0	0
Lumbar spinal stenosis (n)					
Yes	6	1	0	0	0
Carpal tunnel syndrome (n)					
Yes	24	4	2	1	3
DPD uptake (n)					
Perugini grade 0	0	0	0	0	4
Perugini grade 1	2	0	0	3	1
Perugini grade 2	32	5	1	0	0
Perugini grade 3	21	3	1	0	0
Not performed	0	1	0	1	4
Unspecified	1	0	0	0	0
Biopsy locally (*n*)					
None	51	9	1	3	1
EMB	2	0	0	0	1
Renal	0	0	0	1	0
Bone marrow	2	0	0	0	6
Fat	1	0	0	0	0
Colonic	0	0	1	0	1
Device (*n*)					
none	43	7	1	4	8
VVI/dual chamber	9	1	0	0	1
CRT	3	0	1	0	0
ICD	1	0	0	0	0
ILR	0	1	0	0	0

(*continued on next page*)

Table 1 (*continued*)

Characteristic	ATTRwt-CA (n=56)	ATTRv-CA V122I (n=9)	ATTRv-CA T60A (n=2)	Others: ATTRv-CA/apolipoprotein A1/fibrinogen[a] (n=4)	AL-CA (n=9)
Medications, *n* (%)					
Anticoagulant	42 (75 %)	3 (33 %)	1 (50 %)	2 (50 %)	5 (56 %)
Beta-blocker	25 (45 %)	3 (33 %)	0	2 (50 %)	1 (11 %)
ACE inhibitor	39 (70 %)	2 (22 %)	0	1 (25 %)	4 (44 %)
MRA	24 (43 %)	3 (33 %)	1 (50 %)	0	3 (33 %)
Digoxin	10 (18 %)	1 (11 %)	0	0	2 (22 %)
Diuretic	49 (88 %)	8 (89 %)	1 (50 %)	2 (50 %)	8 (89 %)
No treatment	1 (2 %)	0	1 (50 %)	1 (25 %)	0
Missing data	0	1 (10 %)	0	0	0
Amyloidosis disease specific treatment, n (%)	24 (43 %)				
		2 (22 %)	2 (100 %)	0	7 (78 %)
Phase III trial, n (%)	10 (18 %)	1 (11 %)	1 (50 %)	0	0

AF = atrial fibrillation; AL-CA = light chain amyloid cardiomyopathy; ATTRwt-CA = wild-type transthyretin amyloid cardiomyopathy; eGFR = estimated glomerular filtration rate; EMB = endomyocardial biopsy; MRA = mineralocorticoid receptor antagonist; T60A = Thr60Ala variant transthyretin cardiac amyloidosis; V1221 = Val122Ile variant transthyretin cardiac amyloidosis.

[a] Others include the following: Val30Met variant transthyretin, amyloidosis, p.A101V (A81V) TTR variant, hereditary lysozyme amyloid – D67H variant, hereditary apolipoprotein A-1 Arg173Pro variant, and Glu526Val fibrinogen α-chain.

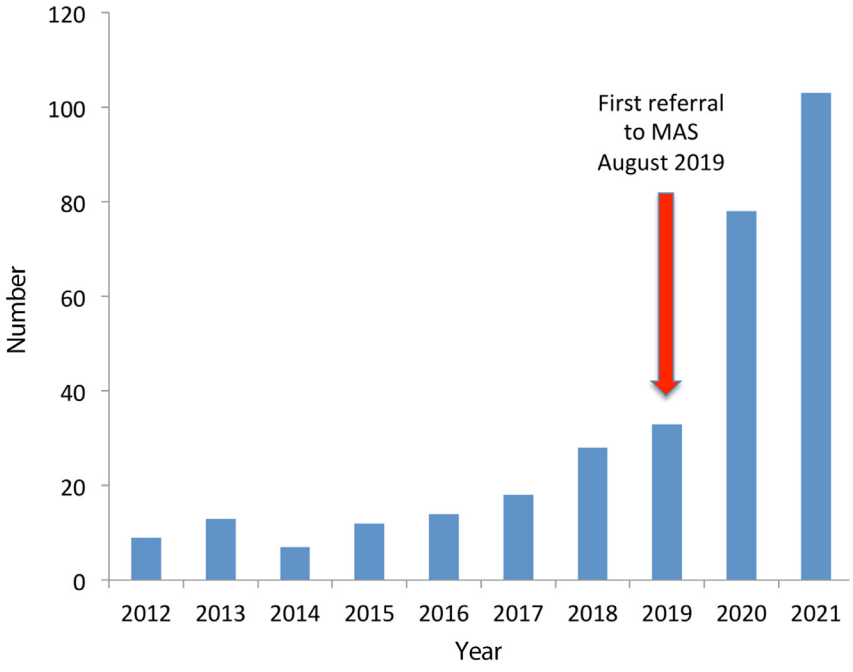

Fig. 5. MAS = Midlands Amyloidosis Service.

Diagnostic imaging

All patients had undergone an echocardiography referral to the MAS. Nearly one-third of patients (29/105, 28 %) had undergone CMR before referral to the MAS; the remainder (72 %) underwent CMR at the MAS. CMR was performed at the MAS either in cases of diagnostic uncertainty, or where baseline ECV calculation was felt to be helpful before the patient potentially receiving disease-modifying therapy.

Only 13 % (19/142) of patients had undergone ^{99m}Tc-DPD imaging at their local hospital before referral for assessment. An increase in capacity for ^{99m}Tc-DPD scintigraphy formed an integral part of the MAS service development. A total of 209 ^{99m}Tc-DPD scans were performed over the 24-month period, although not all patients were formally referred for assessment (Fig. 5). Of the 56 patients found to have ATTRwt-CA, 53 (95 %) had grade 2 or 3 cardiac uptake of ^{99m}Tc-DPD during scintigraphy. Scintigraphy was performed in almost all patients (92 %; 11/12) subsequently found to have ATTRv-CA. One older, bedbound African-Caribbean patient with end-stage heart failure (NYHA Class IV) was considered too frail to undergo ^{99m}Tc-DPD scintigraphy, but was regarded as having ATTRv-CA after demonstrating the pathogenic V122I variant on TTR Sanger sequencing following a characteristic echocardiogram in the absence of a monoclonal dyscrasia. Another patient with Glu526Val fibrinogen α-chain amyloidosis had a CMR that was characteristic for CA, but did not require ^{99m}Tc-DPD imaging. In the AL-CA cohort, ^{99m}Tc-DPD scintigraphy was performed in 56 % (5/9) of patients, four of whom tested negative for any myocardial tracer uptake. Likewise, there was no myocardial ^{99m}Tc-DPD uptake in a patient with hereditary lysozyme amyloidosis (D67H), who had a live donor renal transplant in 2009 after developing end-stage renal failure. Following this episode, the patient underwent scintigraphy using purified human serum amyloid P labelled with radioactive iodine, which revealed further splenic and hepatic involvement. To-date, the renal allograft remains unaffected by amyloidosis.

Tissue biopsy

Two (4 %) patients with concomitant paraproteinaemia required an endomyocardial biopsy before a diagnosis of ATTRwt-CA was reached. All nine patients found to have AL-CA underwent a bone marrow biopsy

Table 2
Characteristics of patients referred for genetic and clinical screening after a diagnosis of hereditary cardiac amyloidosis in a first-degree relative.

Patient	Sex	Ethnicity	Amyloidosis variant	Age at diagnosis (years)	DPD uptake (Perugini grade)	NT-proBNP (ng/L)	eGFR (mL/min)	HS Troponin I (ng/L)	Heart rhythm	LVEF (%)	IVSd (mm)
1[a]	M	Asian	Wild-type	33	Not performed	49	76	<5	Sinus rhythm	60	9
2[b]	M	African-Caribbean	V122I	42	0	1734	52	43	Sinus rhythm	50	26
3	M	African-Caribbean	V122I	55	0	No results	71	No results	Not performed	Nil	Nil
4	M	White	T60A	65	0	55	>90	No results	AF	60	9.8
5	F	White	Val30Met	53	0	36	64	<5	Sinus rhythm	64	8
6	M	Brazilian	A81V/A101V	46	0	51	>90	<5	Not performed	Nil	Nil
7	M	White	p.Ile88leu	66	0	89	>90	<5	Sinus rhythm	80	11
8	F	White	D67H lysozyme	74	0	1221	66	8	Sinus rhythm	63	19

AF = atrial fibrillation; DPD = ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid; eGFR = estimated glomerular filtration rate; F = female; HS Troponin I = high sensitivity troponin I; LVEF = left ventricular ejection fraction; IVSd = Interventricular septal end diastole; M = male.

[a] This patient underwent presymptomatic genetic cascade screening.

[b] This patient had apical variant hypertrophic cardiomyopathy with a pathogenic variant in MYBPC3, which, in the absence of any ^{99m}Tc-DPD tracer uptake, was deemed to be the cause of left ventricular hypertrophy.

(6/9) and/or a renal biopsy (3/9) in combination with a CMR that was characteristic for CA.

Neuropathy

In the ATTR-CA cohort, nearly half (46 %) had a previous history of carpal tunnel syndrome, but only 10 % (7/68) had a history of lumbar spinal stenosis. The latter was absent in the AL-CA cohort, although one-third (3/9) had a preceding diagnosis of carpal tunnel syndrome.

Arrhythmia and devices

Atrial fibrillation was detected in 68 % (38/56) of patients with ATTRwt-CA at baseline. The incidence of AF was much less frequent in other amyloidosis subgroups. Twelve patients with ATTRwt-CA subsequently developed atrioventricular conduction delays sufficient to require implantation of a pacemaker (dual chamber pacemaker, n=9; cardiac resynchronisation therapy, n=3). Only one patient (ATTRwt) received an implantable cardioverter defibrillator and one (V122I ATTRv) an implantable loop recorder.

Disease-modifying therapy

Fifteen (9 %) patients with ATTRwt-CA received tafamidis, a transthyretin stabiliser, under the Early Access to Medicine Scheme (EAMS). A further ten (6 %) patients with ATTRwt-CA were successfully enrolled into phase III clinical trials of gene-silencing RNA therapy,[15,16] or antisense oligonucleotide inhibitor therapy.[17] Two (1 %) patients with ATTRv-CA also received novel TTR-directed therapy facilitated via the NAC, having undergone diagnostics at the MAS. Conversely, seven (4 %) patients with AL-CA received chemotherapy comprising cyclophosphamide, bortezomib and dexamethasone.

Screening

The characteristics of patients referred for genetic and clinical screening following a diagnosis of ATTRv-CA in a first-degree relative are detailed in Table 2. Eight patients (75 % male) were referred for presymptomatic cascade genetic screening following a diagnosis of ATTRv-CA within a first-degree relative, seven of whom were found to have a pathogenic *TTR* variant. There was a wide age range (median age 54 years, IQR: 44–66 years) among individuals who decided to pursue presymptomatic cascade genotyping following appropriate genetic counselling. None of these patients have yet to manifest any clinical signs of CA following a comprehensive clinical screening assessment tailored to the particular *TTR* variant. One male patient of African-Caribbean origin with MYBPC3-associated hypertrophic cardiomyopathy (HCM) had an incidental finding of a pathogenic mutation in V122I as part of genotyping. Nonetheless, the absence of any myocardial ^{99m}Tc-DPD tracer uptake on bone scintigraphy excluded an ATTR-CA phenotype.

Historical comparator

During the study period (1 August 2019–30 September 2021), a total of 310 patients with suspected CA were referred to either the MAS or NAC for assessment. The number of patient referrals with suspected CA that the NAC received from 1 August 2016 to 30 September 2018 and from 1 August 2019 to 30 September 2021 was 205 and 192, respectively.

Discussion

This study demonstrates that, with the availability of remote expert input from the NAC, there is feasibility to develop a regional service, which can facilitate an accurate and timely diagnosis in patients with suspected amyloidosis and avoid the need for long-distance travel. To our knowledge, our centre is the first UK regional unit outside of London to offer a dedicated amyloidosis service. Recent published guidance by the European Society of Cardiology emphasised the importance of collaboration between centres and establishment of a network to allow patients to be referred to regional or national referral centres for complex diagnostic procedures and decision making.[18] Our analysis supports the notion that ATTRwt-CA is now the more commonly diagnosed form of CA ahead of AL-CA. In keeping with prior reports,[6] there was a strong male predominance among patients with ATTRwt-CA and most were older. It is notable that most patients (96 %) with ATTR-CA were non-invasively diagnosed according to the validated non-biopsy diagnostic criteria, although a small but important minority still required endomyocardial biopsy.[1] These data also highlight a key role for regional centres identifying patients eligible to receive novel TTR disease-modifying treatments, such as tafamidis under EAMS, or improving access to phase 3 clinical trials of TTR-specific RNA interference or antisense oligonucleotide therapies. Finally, our work demonstrates the importance of being able to provide local genetic counselling and cascade testing, which permits timely diagnosis of ATTRv-CA among at-risk relatives, as supported by a recent UK consensus statement.[19]

The integration of telemedicine within the service through virtual MDTs is integral to the delivery of care for our patients with amyloidosis. The establishment of the MAS coincided with the advent of the Coronavirus 2019 (COVID-19) pandemic, during and following which

there has been a drive to reduce face-to-face consultations and implement the use of telemedicine.[20,21] Cases were discussed with amyloidosis specialists at the NAC remotely to ensure that patients received expert multidisciplinary input regarding their care, and those suitable for enrolment into phase 3 trials could be identified. It is noteworthy that older patients with ATTR-CA are limited by extracardiac manifestations of ATTR-CA, which impairs their mobility and functional capacity, thus contributing to the frailty of these patients.[22] Our centre enabled such patients to receive specialist advice regarding their condition without the need to travel to the NAC and reducing exposure to COVID-19. A further advantage of the model used by the MAS was the provision of a timely diagnosis in patients referred with suspected CA. The median time from receipt of referral to confirmation of diagnosis in patients referred to the MAS was 43 days for both the AL and ATTR subgroups. Although no data relating to time from symptom onset to diagnosis are available in the current study, these findings suggest that this model of care will help avoid lengthy diagnostic delays, which has been a notable issue based on historical reports.[23,24]

Until recently, AL amyloidosis was perceived as the most commonly diagnosed form of systemic amyloidosis. An epidemiological study by Pinney et al. of all patients found to have systemic amyloidosis at the NAC between 2000 and 2008 revealed an estimated minimum incidence of 0.3 cases per 100,000 population for AL amyloidosis compared with that of TTR-related amyloidosis, where the estimated incidence was 0.03 cases per 100,000 population.[9] By contrast, the higher incidence of ATTR-CA compared with AL-CA based on our 2-year experience supports the concept that TTR-CA is the most common form of amyloidosis, although its true prevalence remains unknown. Lopez-Sainz et al. reported similar findings, whereby 64 % of 180 patients with amyloidosis treated at their centre were found to have ATTR-CA. AL-CA was less frequently diagnosed in their cohort of patients (64/180; 36 %).[25] Winburn et al. attempted to estimate the prevalence of ATTR-CA within a Japanese cohort across a 9-year period (January 2010 to September 2018) by retrospectively analysing the hospital-based Japan Medical Data Vision database, and demonstrated a higher prevalence of this disease compared with that of AL-CA (70.3–86.1 per million versus 2.4–2.9 per million patients). However, this report was limited by the lack of data on endomyocardial biopsy or bone scintigraphy result in most patients with a diagnosis of ATTRwt-CA.[26] It is likely that the increased awareness of clinicians of ATTR amyloidosis, coupled with the validation of a non-biopsy diagnostic algorithm, improvements in advanced imaging techniques, and the on-going development of novel disease-modifying therapies, are all factors that will contribute to the ever-increasing number of diagnoses.[5,6,25]

The MAS provided pre-symptomatic cascade genetic and clinical screening for first-degree relatives of index patients already found to have ATTRv-CA. Disease onset and organ involvement varies according to the particular pathogenic *TTR* variant, but patients with ATTRv predominantly present after the age of 40 years. Patients often present with symptoms related to peripheral neuropathy or autonomic dysfunction, which can precede cardiac involvement by 10–15 years.[2] In a 3-year longitudinal study of 65 asymptomatic carriers of ATTRv amyloidosis, 60 % (39/65) transitioned to symptomatic status with primarily neurological symptoms (familial amyloid polyneuropathy (FAP) stage 1) and were subsequently treated with tafamidis.[27] Our centre has so far performed clinical screening in eight patients. These patients (and those referred beyond the 2-year study period) will be closely monitored and referred to the NAC for disease-modifying therapy if and when symptoms develop.

The combined number of referrals made to the NAC and the MAS in between 2019 and 2021 was much greater than the number made from the same geographical catchment area to the NAC for an equivalent period from 2016 to 2018, before the establishment of the MAS. These data suggest that there is a need to develop regional services as part of a network, to support the ongoing work at the NAC because of increasing demand, rather than formally decentralising care. A common way to coordinate and integrate care for patients and populations with specific conditions has been to establish care pathways and networks. These networks do not necessarily require the creation of new organisational entities or physical facilities, but rather seek to broker care across providers for patients with a particular condition in a form of virtual integration.[28] Clinical networks have already been shown to improve outcomes in the provision of specialist care, such as stroke services,[29] but further evaluation of any proposed reconfiguration of the amyloidosis healthcare model will be needed. Healthcare networks are best understood as learning systems to generate collaborative knowledge used to inform the best possible care. Establishing networks provides a framework to set standards of practice and formalise pathways of care, which helps avoid duplication of work and diagnostic testing in an already overburdened healthcare system.[19,30] The effectiveness of the UHB/NAC partnership was driven by active collaborative leadership and the development of mutual trust between both centres. Although the founding principle of this clinical network has been voluntary contributions by its members, as members gain experience, status and personal growth through their participation, adequate investment and resourcing from commissioners will be needed for the network to flourish and extend its inclusion to more UK centres.

A very important offshoot from this MAS/NAC clinical partnership has been the improvement in patient access to phase 3 randomised controlled trials. An early example of the introduction of a clinical network facilitating better access to research in rare disease is the program of NHS Highly Specialised Services (HSS) for rare mitochondrial disorders.[31] Further collaborative work is required to help ensure clinicians are able to offer patients with amyloidosis the opportunity to enrol in registries such as the European Rare Disease Network or the TRANSCEND study. Collection of this important 'real-world' observational data will improve our collective understanding of the natural history of ATTR amyloidosis and its response to treatment. For this to work, there will need to be adequate investment in IT infrastructure and data administrators.

Limitations

The findings from this study are limited by its retrospective, observational design. Therefore, the study will have been subject to selection bias; it is notable that a proportion of patients declined to attend the MAS despite referral from their local hospital, largely because of frailty. As a result, the cohort likely reflects a significant underestimation of the actual number of patients living in the Midlands with a diagnosis of ATTR-CA. Despite Birmingham being classed as one of the first 'super-diverse' cities in the UK, where citizens from ethnic minorities comprise more than half the population, only one-fifth (21 %) of patients referred to the MAS were non-White. Recent data suggest that V122I-associated ATTRv-CA is often overlooked as a cause of heart failure among African-Caribbean patients.[32] Hypertension is common in this population, and can frequently coexist with ATTR-CA,[33] but the presence of left ventricular hypertrophy on ECG and a history of hypertension can result in patients being wrongly labelled with hypertensive cardiomyopathy.[32,34] Further prospective studies exploring the barriers to such patients being referred and attending specialised healthcare clinics are needed.[22]

Conclusion

These data suggest that the staged implementation of a UK amyloidosis network is feasible and would ensure equity of access to specialised amyloidosis healthcare for the increasing numbers of older patients found to have ATTR-CA. Much work is still required to increase the awareness of CA among clinicians, so that patients are diagnosed promptly to facilitate early access to appropriate disease-specific treatments.

Conflicts of interest

WEM has received advisory board fees from Alnylam, Ionis Pharmaceuticals (formerly Akcea) and Pfizer.

CRediT authorship contribution statement

Chern Hsiang Choy: Writing – original draft, Data curation, Formal analysis, Writing – review & editing. **Richard P. Steeds:** Methodology, Project administration, Writing – review & editing. **Jennifer Pinney:** Methodology, Project administration, Writing – review & editing. **Shanat Baig:** Data curation, Writing – review & editing. **Lauren Turvey-Haigh:** Writing – review & editing. **Yasmin Wahid:** Data curation, Writing – review & editing. **Helen Cox:** Writing – review & editing. **Alex Zaphiriou:** Writing – review & editing. **Venkataramanan Srinivasan:** Writing – review & editing. **David Wilson:** Writing – review & editing. **John Fryearson:** Writing – review & editing. **Mubarak Ahamed:** Writing – review & editing. **Sern Lim:** Writing – review & editing. **Colin Chue:** Writing – review & editing. **Guy Pratt:** Writing – review & editing. **Marianna Fontana:** Methodology, Project administration, Writing – review & editing. **Julian D. Gillmore:** Methodology, Project administration, Writing – review & editing. **William E. Moody:** Data curation, Formal analysis, Supervision, Methodology, Project administration, Writing – review & editing.

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