Transthyretin Cardiac Amyloidoses in Older North Americans

Kumar Dharmarajan, MD, MBA, and Mathew S. Maurer, MD

The amyloidoses are a group of hereditary or acquired disorders caused by the extracellular deposition of insoluble protein fibrils that impair tissue structure and function. All amyloidoses result from protein misfolding, a common mechanism for disorders in older persons, including Alzheimer's disease and Parkinson's disease. Abnormalities in the protein transthyretin (TTR), a serum transporter of thyroxine and retinol, is the most common cause of cardiac amyloidoses in elderly adults. Mutations in TTR can result in familial amyloidotic cardiomyopathy, and wild-type TTR can result in senile cardiac amyloidosis. These underdiagnosed disorders are much more common than previously thought. The resulting restrictive cardiomyopathy can cause congestive heart failure, arrhythmias, and advanced conduction system disease. Although historically difficult to make, the diagnosis of TTR cardiac amyloidosis has become easier in recent years with advances in cardiac imaging and more widespread use of genetic analysis. Although therapy has largely involved supportive medical care, avoidance of potentially toxic agents, and rarely organ transplantation, the near future brings the possibility of targeted pharmacotherapies designed to prevent TTR misfolding and amyloid deposition. Because these disease-modifying agents are designed to prevent disease progression, it has become increasingly important that older persons with TTR amyloidosis be expeditiously identified and considered for enrollment in clinical registries and trials. **J Am Geriatr Soc 60:765–774, 2012.**

Key words: amyloidosis; transthyretin; cardiomyopathy; heart failure; aging

CASE PRESENTATION

A 75-year-old African-American man presents with congestive heart failure. Over the past 18 months, he has noted increased fatigue, early satiety, and worsening lower extremity swelling. Although he has a history of hypertension, he has recently required much less pharmacotherapy because of symptomatic hypotension. He has no other medical problems. He lives independently and tries to restrict sodium intake, although he is often unsuccessful. Your examination is notable for a blood pressure of 98/70 mmHg, regular heart rate of 90 beats per minute, marked jugular venous distention, bibasilar lung crackles, pulsatile liver three finger breaths below the costal margin and 16 cm in span, and 2+ lower extremity edema.

He is symptomatically managed with diuretics. Initial diagnostic testing includes a 12-lead electrocardiogram (ECG) and standard two-dimensional transthoracic echocardiogram (2D TTE). The ECG demonstrates low limb-lead voltage and precordial Q waves, and the 2D TTE shows significant thickening of the right ventricular free wall, interventricular septum, and left ventricular posterior wall. Because cardiac amyloidosis could produce this presentation, genetic sequencing is performed of the transthyretin gene. A mutation is found whereby isoleucine is substituted for valine in codon 122 (Val122Ile), and the diagnosis is made of cardiac transthyretin amyloidosis. The patient enters a clinical trial testing a transthyretin stabilizer to prevent further amyloid formation.

BACKGROUND

The German botanist Matthias Schleiden coined the word *amyloid* in 1834 to describe the waxy starch in plants.[1] Today, the amyloidoses refer to a large group of hereditary or acquired disorders caused by the extracellular deposition of insoluble protein fibrils that impair tissue structure and function. These deposits are easily seen with light microscopy using hematoxylin and eosin, sulfated Alcian blue, or Congo red staining.[2] More than 20 precursor proteins are known to form amyloid fibrils in vivo.[3] The resulting disorder is classified according to the protein composition of the fibrils and the clinical features of the disease.[4] Although almost every amyloidogenic protein may involve the heart, predilection for the myocardium varies considerably, because some rarely involve this organ, whereas others do so almost exclusively. When cardiac involvement is present, resulting myocardial dysfunction is a frequent cause of disability, hospitalization, and death.[5–7]

From the Division of Cardiology, Columbia University Medical Center, New York, New York.

Address correspondence to Mathew S. Maurer, Clinical Cardiovascular Research Laboratory for the Elderly, Columbia University Medical Center, Allen Pavilion of New York Presbyterian Hospital, 5141 Broadway, 3 Field West, Room 035, New York, NY 10034. E-mail: msm10@columbia.edu

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From a pathobiological perspective, all amyloidoses result from abnormal protein folding and metabolism.[8] Normally, after biosynthesis, the majority of proteins must be converted into tightly folded three-dimensional structures to function appropriately. The protein's primary structure, the order of amino acids that contribute to a unique polypeptide chain, determine proper folding in part, as do auxiliary proteins within the cell, including folding catalysts and molecular chaperones such as heat shock proteins. Catalysts accelerate steps in the folding process that would otherwise occur extremely slowly, and chaperones bind vulnerable nascent polypeptides to prevent their inappropriate binding with other intracellular molecules.[9] When folding occurs unsuccessfully despite these supportive measures, intracellular proteolysis intentionally degrades the nascent polypeptide. In the great majority of cases, proteins easily acquire their intended three-dimensional structure, which is the most energetically favorable conformation.[8]

This process of normal protein folding and conformational maintenance is subverted in the amyloidoses. Initial misfolding may result from genetic mutations that alter the primary structure of a polypeptide or the function of important auxiliary proteins, as well as from multiple potential epigenetic factors.[10] Insufficient quality-control mechanisms in intracellular and extracellular environments are unable to properly refold the misfolded protein, shield it to prevent aggregation, or target it for degradation.[10] These misfolded proteins ultimately aggregate and organize into thread-like amyloid fibrils that deposit in tissues and become highly resistant to degradation. These fibrils, as well as their prefibrillar precursors, can provoke oxidative stress, cellular dysfunction, and apoptosis in cardiac myocytes.[11,12]

This mechanism of protein misfolding with subsequent amyloid formation is a common disease pathway that injures postmitotic cells in older persons. For example, accumulation of amyloid proteins is thought to contribute to common neurodegenerative diseases associated with aging, including Alzheimer's disease and Parkinson's disease.[8,10] In Alzheimer's disease, cleavage of the amyloid precursor protein by gamma secretases results in multiple polypeptide fragments, once of which is named Aβ. Fibrillar and prefibrillar aggregates of the Aβ protein have been implicated in disease pathogenesis.[13] Similarly, in Parkinson's disease, significant alpha synuclein deposition within the dopaminergic neurons of the substantia nigra alongside dysfunction of the ubiquitin-proteasome system has been linked with neurotoxicity.[10] The mechanisms driving the greater prevalence of amyloidoses in older persons are unclear, but may relate to microenvironmental changes associated with aging, including alterations in pH and protein concentration, high oxidative stress, proteasome dysfunction, and impairments in mechanisms that assist in extracellular aggregate clearance, such as immune system pathways.[9,14,15] As with neurons, cardiac myocytes are postmitotic and may be particularly susceptible to the above age-related alterations.

The systemic amyloidoses that affect cardiac function are listed in Table 1. The subtypes shown to have clinically meaningful effect predominantly in older persons are the familial amyloidoses, most often due to mutations in the transthyretin protein, and senile cardiac amyloidosis, due to deposition of wild type (nonmutated) transthyretin. Cardiac AL amyloidosis (previously called primary amyloidosis), in contrast, although clearly associated with severe cardiac dysfunction and poor clinical prognosis, is not unique to older persons and can result from any plasma cell dyscrasia at any age.[2,5] Other forms of systemic amyloidoses such as AA amyloidosis (previously called secondary amyloidosis) resulting from deposition of proteolytic fragments of serum amyloid A and hemodialysis-related amyloidosis due to β2-microglobulin deposition only rarely affect the heart.[2]

TRANSTHYRETIN CARDIAC AMYLOIDOSES IN OLDER NORTH AMERICANS

Pathobiology and Epidemiology

Transthyretin (TTR) is a 127 amino-acid transport protein primarily synthesized in the liver that functions as a tertiary carrier of thyroxine and the retinol-retinol binding complex.[3] TTR was formerly called prealbumin because it migrates closer to the anode than does albumin on serum protein electrophoresis. Because of its short half-life in plasma, TTR has been used as a nutritional marker in some settings when combined with clinical, anthropometric, and other laboratory measurements, although despite its name and use in nutritional assessment, TTR is not a precursor to albumin.[3] TTR is an unrelated protein that circulates in its native state as a tetrameric complex composed of four single-chain TTR monomers. Cardiac transthyretin amyloidosis occurs when the TTR protein misfolds, dissociates from its tetrameric form into four structurally abnormal monomers, oligomerizes (aggregates), and ultimately deposits in cardiac tissue as insoluble amyloid fibrils (Figure 1).

There are two distinct forms of cardiac TTR amyloidosis. The first occurs because of a mutation in the TTR gene. More than 100 TTR mutations have been identified, the great majority of which are amyloidogenic. Most persons with TTR amyloidoses are heterozygous carriers of mutations in TTR and express normal and variant TTR to differing degrees.[3,5] In these individuals, deposition of large amounts of fibrillar TTR as amyloid can subvert the architecture of normal body tissues and consequently cause organ dysfunction. Some TTR mutations lead predominantly to noncardiac disability, including debilitating polyneuropathy, autonomic dysfunction, vitreous opacities, and ultimately, death at a young age.[3] These persons are said to have familial amyloidotic polyneuropathy (FAP) and are predominantly of European or Japanese descent, although sporadic mutations occur worldwide. In North America, TTR mutation much more frequently causes cardiac disease that is inherited in an autosomal-dominant fashion. This condition is referred to as a familial amyloidotic cardiomyopathy. Examples include Thr60Ala (Appalachia mutation), Ser77Tyr (FAP II), and Ile84Ser (Indiana mutation), the last two of which are rare.[3] The most common mutation causing cardiomyopathy is Val122Ile, whereby isoleucine is substituted for valine in codon 122. Pooled data on African Americans from multiple epidemiological studies indicate that approximately 3.0% to 3.9%

Table 1. Systemic Amyloidoses Affecting Cardiac Function

Characteristic	Familial Amyloidoses	Senile Cardiac Amyloidosis	Light Chain Amyloidosis (Primary Amyloidosis)
Nomenclature[4]	Mutant transthyretin amyloidosis	Wild-type transthyretin amyloidosis, senile cardiac amyloidosis, senile systemic amyloidosis	AL amyloidosis
Precursor protein	Variant transthyretin most commonly (>100 known mutations)[3] Very rarely mutations in apolipoprotein A-1, fibrinogen, and gelsolin[2,5]	Wild-type transthyretin[2]	Monoclonal lambda or kappa immunoglobulin light chain[1]
Epidemiology	~3–3.9% of African Americans in United States with Val122Ile mutation (up to 150,00 older African Americans in United States carry mutation)[16,17] Uncertain population prevalence of other mutations	~25% of Finnish study population aged ≥ 85[23] ~30% of Minnesota study population with CHF and preserved ejection fraction aged ≥ 75[24] >90% men[19]	2,000–2,500 people per year in United States[5]
Cardiac manifestations	Variable by specific mutation; CHF, atrial and ventricular arrhythmia, bradycardia, advanced heart block with Val122Ile mutation[3,28,31]	CHF, atrial and ventricular arrhythmia, bradycardia, advanced heart block[2,5,19,24]	CHF, atrial and ventricular arrhythmia, bradycardia, advanced heart block[2,5]
Extracardiac manifestations	Variable by specific mutation; can include polyneuropathy, autonomic neuropathy, ophthalmological abnormalities[3]	Carpal tunnel syndrome[21]	Renal failure, proteinuria, polyneuropathy, autonomic neuropathy, gastrointestinal symptoms[1,2,5]
Definitive diagnosis	Genomic mutational analysis, endomyocardial biopsy[18,45]	Endomyocardial biopsy[45]	Serum-free light chain assay, urine protein electrophoresis, endomyocardial biopsy, fat pad biopsy[1,2,5]
Treatment	Supportive care, including avoidance of potential toxic therapies, orthotopic heart transplant, combined heart and liver transplantation in younger adults, investigational therapy[46,48–52,54–60]	Supportive care, including avoidance of potential toxic therapies, orthotopic heart transplant, investigational therapy[46,48–54,56–60]	Supportive care, including avoidance of potential toxic therapies, treatment of underlying malignancy, combined heart and bone marrow transplantation in younger adults[2,5,46,48–52,54]

CHF = congestive heart failure.

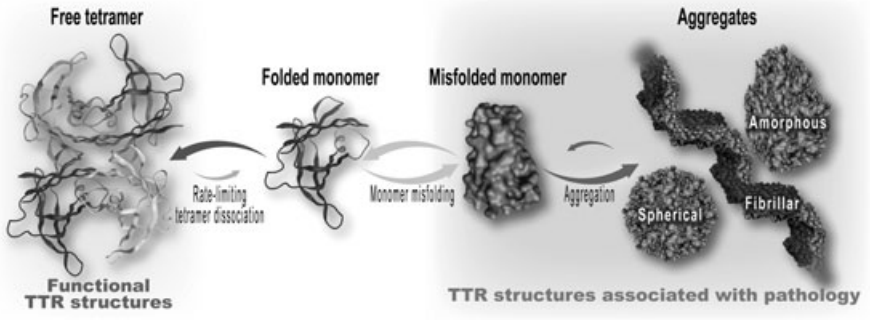

Figure 1. Prevailing theory of pathogenesis of transthyretin amyloidosis. The tetrameric transthyretin molecule dissociates into four monomers (only one shown for simplicity). The monomer misfolds, aggregates with like molecules, and ultimately organizes into thread-like amyloid fibrils that are resistant to degradation and deposit in tissues. Image courtesy of Jeffery W. Kelly, PhD.

are heterozygous carriers of the Val122Ile mutation.[16,17] Given this allele frequency, it is estimated that approximately 750,000 to 1,200,000 African Americans in the United States alone are carriers. Based on recent census data and in light of the age-dependent penetrance of this condition, it is estimated that 100,000 to 150,000 older African Americans have the disease. Homozygosity for the Val122Ile mutation is much more uncommon and is not required for cardiac amyloid deposition; heterozygosity is sufficient. Val122Ile is therefore the most common mutation associated with cardiac transthyretin amyloidosis worldwide despite its limitation to African Americans and certain West African populations in which up to 5% of people carry the mutation.[18]

The second distinct pathway of cardiac TTR amyloidosis is through wild-type TTR deposition, previously called senile cardiac amyloidosis. In contrast to cases of familial TTR deposition, TTR in senile cardiac amyloidosis

has a normal primary structure and has no known risk of familial inheritance.[2,5] Although deposition also occurs to some degree in the aorta, brain, pancreas, liver, lung, and kidney, leading some to advocate the nomenclature senile systemic amyloidosis, the presentation of senile cardiac amyloidosis is always primarily as a cardiomyopathy.[2] Wild-type TTR deposition has a clear association with sex and aging and is almost exclusively seen in men aged 65 and older.[19–22] For example, more than 98% of persons with cardiomyopathy from wild-type disease in an international registry of transthyretin amyloidosis were men; the mean age was 71.[19] One-quarter of a Finnish population aged 85 and older had amyloid deposition in the heart on postmortem examination.[23] Almost 25% of this group had moderate or severe intramyocardial amyloidosis, and the extent of deposition was greater with older age and male sex. Additional data showed that, in a U.S. community-based sample, approximately 30% of subjects aged 75 and older with congestive heart failure and a preserved ejection fraction had cardiac deposits of wild-type TTR.[24] In contrast, only 5% of subjects younger than 75 with heart failure and a preserved ejection fraction had cardiac amyloid deposits. It is unclear why this striking age and sex association exists with senile cardiac amyloidosis. It is possible that posttranslational modification of the TTR protein changes with aging, because cardiac TTR deposits in senile cardiac amyloidosis are composed of a combination of intact TTR and carboxy-terminal TTR fragments. This contrasts with certain forms of familial TTR cardiomyopathy in which cardiac biopsy almost exclusively shows intact TTR protein.[25] Wild-type TTR deposition may also be related to age-related changes in chaperone and proteasome function, among other causes.[26] The reasons for the association between senile cardiac amyloidosis and male sex are even more poorly understood, although they may relate to sex hormone function.[27]

Clinical Features and Prognosis

Familial TTR amyloidosis and senile cardiac amyloidosis cause a restrictive cardiomyopathy characterized by thick, stiff ventricles that result in small increases in chamber volume despite large rises in ventricular pressure. TTR amyloid can infiltrate any cardiac structure, including the atrial and ventricular myocardium, electrical conduction system, valvular tissue, and small and large arteries.[1,5] The myocardial deposits cause poorer ventricular compliance and relaxation abnormalities, with ensuing diastolic dysfunction. Eventual myocyte necrosis and fibrosis produce systolic dysfunction.[1] The resultant heart failure syndrome is a product of biventricular involvement and often includes elements of left and right heart failure, including fatigue, hypotension, dyspnea on exertion, orthopnea, paroxysmal nocturnal dyspnea, hepatomegaly, ascites, early satiety, nausea, and lower extremity edema.

The cardiac conduction system is also frequently compromised and may result in rhythm disturbances, including symptomatic bradycardia, atrial fibrillation, and complex ventricular arrhythmias. In series of 18 individuals with senile cardiac amyloidosis and heart failure, 56% had first degree atrioventricular (AV) block, 21% had left bundle branch block, 71% had left anterior fascicular block, 50% had right bundle branch block, and more than one-third were not in sinus rhythm.[21] These findings may result from direct fibril deposition in specialized conduction tissue but may also result from localized ischemia of conduction pathways due to microvascular amyloid deposits.[1,5] Although a common outcome, it is unknown what percentage of individuals with cardiac TTR amyloidosis will ultimately require a permanent pacemaker, although more than 20% had paced cardiac rhythms by ECG in a recent analysis of persons with TTR cardiomyopathy in an international amyloidosis registry.[19] In addition, atrial involvement frequently results in the development of common atrial arrhythmias, such as atrial fibrillation and atrial flutter, with their associated sequelae, including palpitations, chest discomfort, and cardioembolic stroke. Intra-atrial thrombus was common and far exceeded what would be expected in a matched control group without cardiac amyloidosis.[28] Last, complex ventricular arrhythmias, such as multiform ventricular ectopy and nonsustained ventricular tachycardia, are also common and have been noted in up to half this population.[29] Although such arrhythmias may be a harbinger of subsequent sudden cardiac death, electromechanical dissociation is more often the cause of cardiac arrest in these persons. As a result, much uncertainty exists about the role of automated implanted cardioverter defibrillators in these individuals, because these devices primarily treat "shockable" rhythms such as ventricular tachycardia and ventricular fibrillation.

A unique feature of senile cardiac amyloidosis is the common association with bilateral carpal tunnel syndrome. A small series has shown that approximately 40% of people with senile amyloidosis and heart failure have concomitant carpal tunnel syndrome.[21] Carpal tunnel syndrome often precedes the diagnosis of congestive heart failure by 3 to 5 years and can be a useful diagnostic clue to the underlying pathology.[5]

The natural history of familial cardiac amyloidosis from the Val122Ile mutation and senile systemic amyloidosis has not been well characterized, with current reports in only small, single-center patient samples. For example, in a study of African Americans with cardiomyopathy referred for systemic amyloidosis to the Boston Medical Center Amyloid clinic, those with the Val122Ile mutation had an average life expectancy of 27 months.[30] Data from Columbia University Medical Center suggest an even worse life expectancy once cardiomyopathy is apparent, with 50% survival of only 11 months.[31] Most of these individuals with the Val122Ile mutation experience hospitalization for cardiovascular decompensation in the months preceding death.

The diagnosis of senile cardiac amyloidosis appears to have a significantly better prognosis than that of familial amyloidotic cardiomyopathy due to the Val122Ile mutation, the reasons for which are unknown. A Mayo Clinic retrospective review of patients with senile cardiac amyloidosis and heart failure found a median survival of 5 years with a median age at diagnosis of 72.[32] A second small series found a similar average life expectancy of approximately 6 years.[21] Data from Columbia University Medical Center are concordant with these findings.[31] It may be that senile cardiac amyloidosis is truly a more benign entity than is cardiac amyloidosis from the Val122Ile mutation, although

it may also be that individuals with wild-type cardiac amyloidosis are being diagnosed earlier in their disease course than are persons with the Val122Ile mutation. In support of this, wild-type TTR has constituted an increasing percentage of biopsy-proven diagnoses of cardiac amyloidosis as the population has aged and clinical suspicion for the disease entity has increased with time.[33]

Ultimately, prognosis for individuals with cardiac amyloidosis must incorporate functional status at the time of diagnosis. Few data on the effect of functional status exist for individuals with the TTR amyloidoses. Extrapolating from individuals with AL amyloidosis and cardiomyopathy, functional class is a significant predictor of overall mortality, with greater potency than multiple diagnostic and imaging modalities, including ECG, standard two-dimensional echocardiography, and cardiac magnetic resonance imaging, when each is used in isolation.[34]

Diagnosis

The diagnosis of cardiac TTR amyloidosis is difficult to make on clinical grounds alone because congestive heart failure, atrial arrhythmia, and conduction abnormalities are all nonspecific disease manifestations and are otherwise common in older persons, but a few presentations are more suggestive of the underlying restrictive physiology, including that of marked right-sided heart failure with increasing abdominal girth, early satiety, and lower extremity edema, as well as the development of relative hypotension in a person with longstanding hypertension. These findings are especially notable in an individual of African-American descent or with a history of idiopathic bilateral carpal tunnel syndrome (Table 2).

Additional diagnostic testing is always required. The most commonly ordered studies are the ECG and two-dimensional transthoracic echocardiogram (2D TTE).

Table 2. Findings Suggestive of Cardiac Amyloidosis

1. Historical and physical findings
Heart failure with a normal or preserved ejection fraction in the absence of hypertension, particularly in men
Hypotension in a person with previous hypertension
Evidence of right-sided heart failure, including loss of appetite, hepatomegaly, ascites, and lower extremity edema
Intolerance of commonly used cardiovascular medications, including digoxin, calcium channel blockers, angiotensin converting enzyme inhibitors, angiotensin receptor blockers, and beta blockers
Bilateral carpal tunnel syndrome
2. Imaging findings
Low QRS voltage or pseudo-infarction pattern on ECG
Progressive diminution in QRS voltage on serial ECGs over time
Thick interventricular septum and refractile myocardium (granular sparkling) on standard 2D TTE
Low voltage on ECG and thick interventricular septum on 2D TTE or CMRI (low voltage to mass ratio)
Low tissue Doppler velocities, strain, or strain rate using more-advanced echocardiographic techniques
Subendocardial late gadolinium enhancement on CMRI

ECG = electrocardiogram; 2D TTE = two-dimensional echocardiogram; CMRI = cardiac magnetic resonance imaging.

Classic ECG findings in individuals with cardiac amyloidosis include low QRS voltage, pseudo-infarction patterns, conduction abnormalities including bundle branch block and hemi-block, and rhythm disturbances such as atrial fibrillation. Figure 2 is a composite of four ECGs, each of which illustrates common findings in persons with cardiac TTR amyloidosis.[22,30,32] The ECG can be particularly helpful when serial cardiograms show progressive diminution in voltage over time,[5] although ultimately, electrocardiographic findings lack sensitivity and specificity for persons with biopsy-proven cardiac amyloidosis. The combination of low voltage and pseudo-infarction is seen in only a minority of individuals.[35] In addition, low voltage is seen in many other conditions, including obesity, chronic obstructive pulmonary disease, pericardial effusion, and hypothyroidism.

As with the ECG, classic echocardiographic patterns of cardiac amyloidosis exist but are neither sensitive nor specific. Persons with all cardiac amyloidoses are more likely to have thickened ventricular walls and refractile myocardium (Figure 3A and B). According to the American Society of Echocardiography, the thickness of the normal left ventricular posterior wall and interventricular septum ranges between 6 and 11 mm. Persons with cardiac TTR amyloidosis of all etiologies may average wall thicknesses of 17 to 18 mm, with concentric left ventricular hypertrophy.[21,32] They are also more likely to have echogenic myocardium that appears granular or "sparkling" on standard ultrasound assessment,[36] although in the early phases of the disease, many persons with amyloid will have normal or just slightly high echocardiographic wall thickness, and only a minority will have characteristic granular echogenicity.[35,36] Higher degrees of accuracy can therefore be achieved when ECG and 2D TTE are used in combination, especially when suspicion of cardiac amyloidosis is high. For example, the presence of low voltage in limb and precordial ECG leads plus an interventricular septal thickness greater than 1.98 cm had a 79% positive predictive value for cardiac amyloidosis in a sample referred for cardiac biopsy.[36] Sensitivity and specificity in this population were 72% and 91%, respectively, and the negative predictive value was 88%. The predictive power of voltage-to-mass ratio as a continuous variable has not been reliably demonstrated.

Additional modalities can be used to further increase diagnostic accuracy. More-advanced echocardiographic techniques, such as tissue Doppler imaging, and strain and strain rate measurements can be helpful. Normal 2D TTE measures cardiac systolic function predominantly by assessing contraction of the heart along its short axis, although subendocardial myocytes are longitudinally oriented and are particularly susceptible to damage in amyloidosis, resulting in early impairment in longitudinal contraction not appreciated on standard 2D TTE.[5,37] In contrast, strain and strain rate techniques can be used to measure cardiac systolic and diastolic deformation in longitudinal, radial, and circumferential directions. Characteristic impairments can lead to the early diagnosis of cardiac amyloidosis and help differentiate it from other more-common conditions that cause thickened ventricular chambers and diastolic relaxation abnormalities such as longstanding hypertension.[35,38]

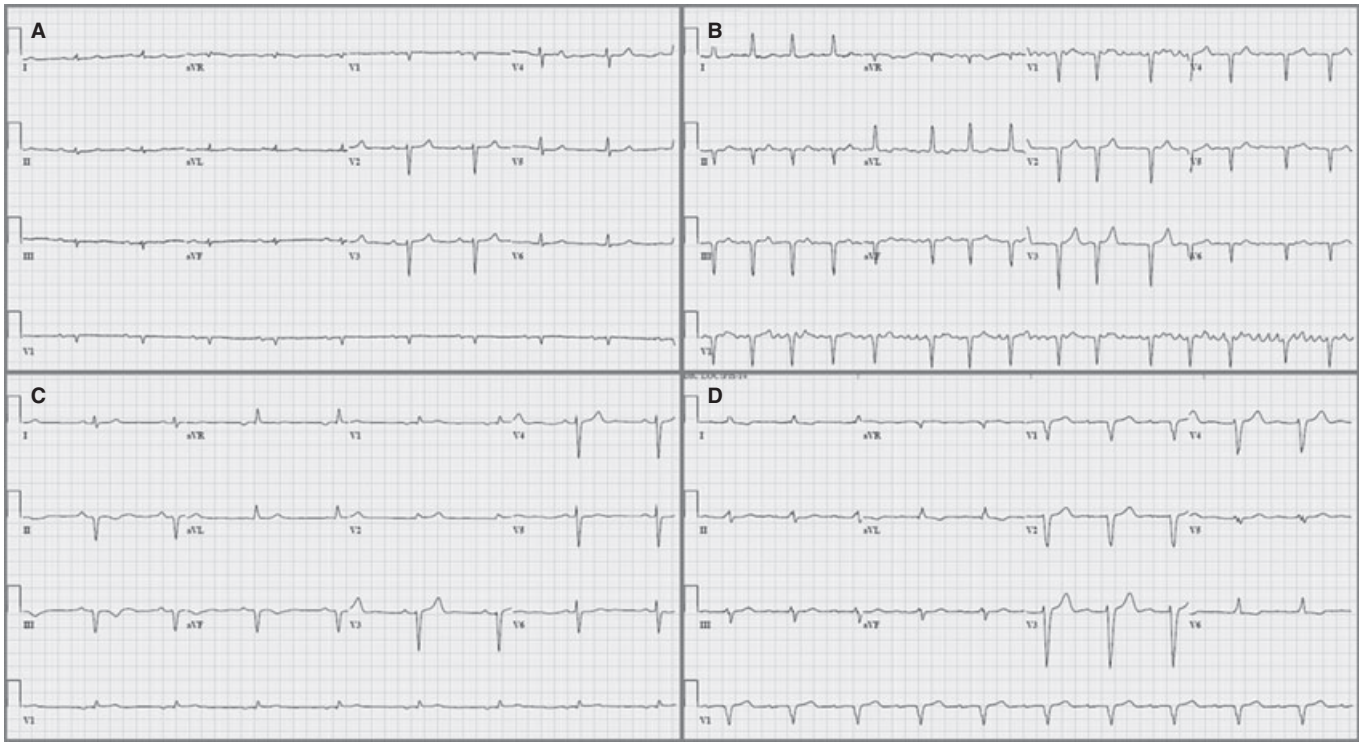

Figure 2. Representative electrocardiograms from individuals with familial amyloidotic cardiomyopathy due to the Val122Ile mutation. (**A**) Sinus bradycardia with first-degree atrioventricular (AV) block, low limb lead QRS voltage, poor precordial R-wave progression (cannot exclude anterior myocardial infarction); (**B**) atrial fibrillation, anterolateral and inferior infarcts (pseudo-infarcts); (**C**) marked sinus bradycardia, inferior infarct (pseudo-infarct); (**D**) sinus rhythm with marked first-degree AV block, low limb lead QRS voltage, left bundle branch block.

Cardiac magnetic resonance imaging (CMRI) can also be used to increase diagnostic sensitivity. Intravenous gadolinium contrast accumulates within amyloid infiltrated myocardium. The combination of myocardial late gadolinium enhancement and altered gadolinium blood pool kinetics can identify the presence of amyloid and locate it within the heart (Figure 3C and D).[39] Sensitivity can be as high as 90% with more-diffuse late gadolinium enhancement, which is associated with greater interstitial amyloid infiltration on endomyocardial biopsy and worse contractile impairment.[40,41] Reported specificity, positive predictive value, and negative predictive value of diffuse gadolinium enhancement ranges between 88% and 90%.[41] In contrast, individuals with longstanding hypertension may have ventricular walls on echocardiography that are similarly thick as those of persons with cardiac amyloidosis but do not have late gadolinium enhancement unless there is prior history of myocardial infarction or other rare infiltrative diseases.[39]

Last, noninvasive scintigraphic imaging with technetium may be able to specifically identify cardiac amyloidosis from TTR as opposed to other precursor proteins. Two recent studies found that use of a particular technetium isotope (^{99m}Tc-DPD) accurately differentiated between cardiac amyloidosis due to monoclonal immunoglobulin light-chain deposition (AL amyloidosis) and that due to TTR deposition. Sensitivity and specificity were high.[42,43] It has also been demonstrated that technetium pyrophosphate can be used to differentiate individuals with heart failure and a preserved ejection fraction or AL amyloidosis from those with cardiac TTR amyloidosis (Figure 3E–G). The ratio of cardiac to whole body technetium uptake has also been shown to identify individuals at higher risk for major cardiac adverse events and was an independent predictor of outcomes in these individuals alone or in combination with left ventricular wall thickness.[44] Thus, with the appropriate radiotracer, scintigraphy may more accurately diagnose TTR cardiac amyloidosis than do echocardiography and CMRI, both of which identify only nonspecific patterns associated with all forms of cardiac amyloid deposition. Further confirmatory studies are needed to validate the utility of this modality.

Until such time that specific radiotracers become widely available, definite diagnosis of cardiac TTR amyloidosis can be achieved through endomyocardial biopsy. This technique is well suited for diagnosing cardiac amyloidosis, because amyloid deposits are usually deposited diffusely throughout the subendocardium.[45] Once amyloid deposits are found, the precursor protein can be identified using histochemical and sequence analysis. At this time, endomyocardial biopsy is the only way to definitively diagnose senile cardiac amyloidosis through demonstration of cardiac TTR deposits in the absence of an amyloidogenic TTR mutation. In contrast, familial TTR amyloidosis can be diagnosed without cardiac tissue in cases in which clinical suspicion is high and imaging results support the diagnosis. These individuals can have their TTR gene sequenced with close to 100% accuracy for less than $500, with results returned in 6 to 8 weeks. Medicare covers sequence analysis. For evaluation of

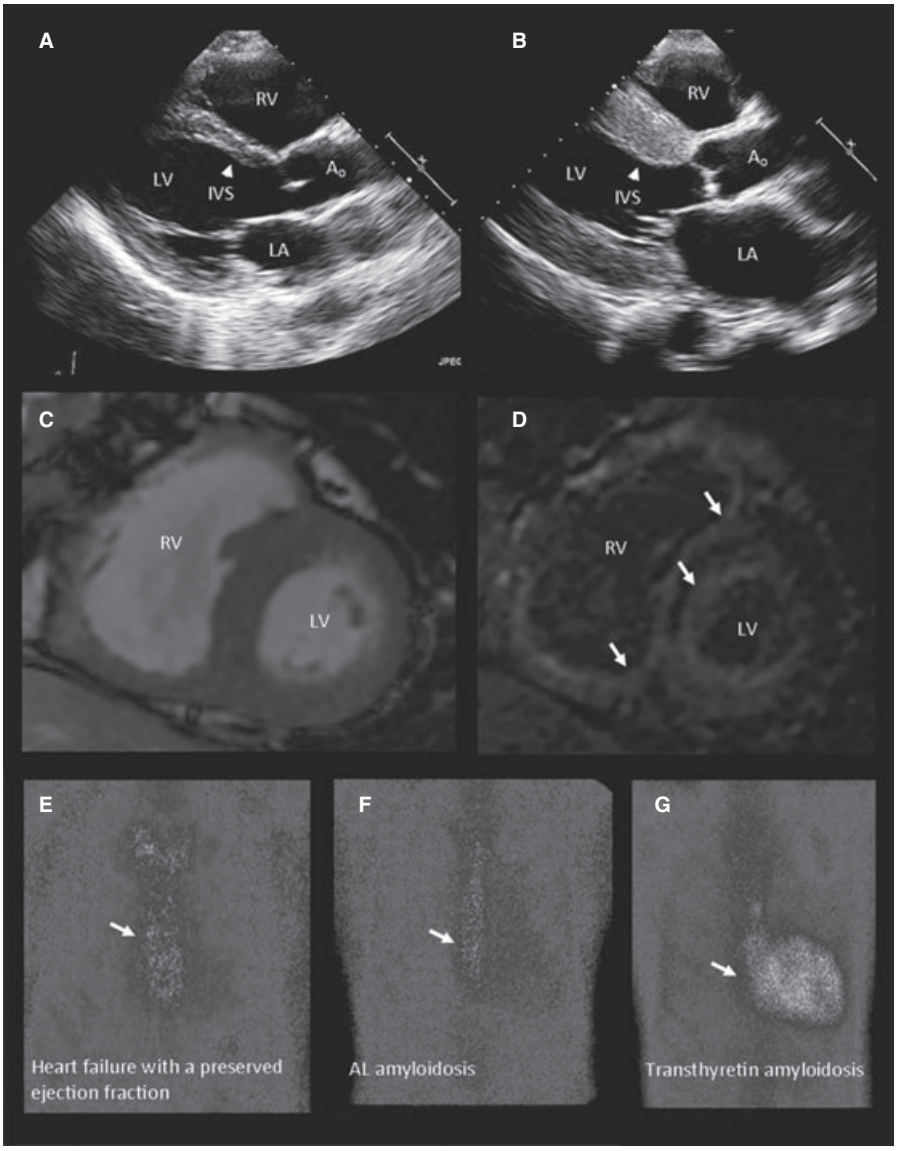

Figure 3. Characteristic imaging findings in patients with cardiac transthyretin amyloidosis. (**A**) Echocardiogram in individual without cardiac disease. Interventricular septum (IVS) (arrowhead) is normal in thickness. (**B**) Echocardiogram in individual with familial amyloidotic cardiomyopathy due to Val122Ile mutation demonstrates markedly thickened IVS. (**C**) Cardiac magnetic resonance imaging scan in individual with transthyretin amyloidosis showing short axis of heart. (**D**) Identical short axis view from the same individual demonstrates diffuse subendocardial late gadolinium enhancement of both ventricles characteristic of amyloid deposition. Differences in cardiac retention of a technetium-pyrophosphate-99 radiotracer in individuals with heart failure and a preserved ejection fraction in hypertension (**E**) and AL amyloid (**F**) demonstrating no cardiac tracer retention compared with the individual with cardiac transthyretin amyloidosis (**G**). LA = left atrium; LV = left ventricle; RV = right ventricle; A_o = aorta.

family members, testing for a specific mutant allele can be performed at lower cost and is available within 2 to 4 weeks from most laboratories. The names and contact information for specific international laboratories offering TTR sequencing for clinical use can be found at www.genetests.org.

Treatment

Until recently, treatment for cardiac amyloidosis has almost exclusively been supportive care. The most important of these interventions has been the combination of salt restriction and diuretic use to reduce high intracardiac filling pressures and improve New York Heart Association functional class. The use of torsemide or bumetanide may be preferable to the more commonly used furosemide, because these two loop diuretics have greater oral bioavailability and potency.[46] This higher oral bioavailability may be particularly important in individuals with cardiac amyloidosis and right heart failure who have impaired drug absorption due to bowel wall edema. Moreover, the use of long-acting diuretics from other classes, including thiazide, thiazide-like, and aldosterone antagonists, can provide additional receptor blockade within the nephron and greater natriuresis. When increasing diuretic dosage and optimizing volume status in individuals with restrictive cardiomyopathy, care must be taken to avoid excessive volume depletion given the preload-dependent nature of

cardiac amyloidosis. Careful follow-up of serum electrolytes and fastidious checking of daily weights by the individual or caregiver can help avoid complications and achieve fluid balance.

Supportive care includes a number of other interventions. For individuals with atrial fibrillation, a rhythm control strategy using an agent such as amiodarone may be helpful because it can reestablish AV synchrony and manage excessive ventricular rates that further worsen diastolic filling, although this approach has not been validated in clinical trials and will require regular monitoring for known potential complications of amiodarone use such as thyroid, ophthalmological, liver, and lung toxicities. In addition, in individuals with advanced restrictive heart disease, atrial transit may contribute only minimally to ventricular filling.[47] For individuals with significant bradycardia or advanced conduction system disease and symptoms, a permanent pacemaker should be strongly considered. Because isolated right ventricular pacing may result in ventricular dyssynchrony with further decline in stroke volume than is already present, biventricular pacing may be beneficial, although this awaits further study to support widespread recommendation.[48] Progressive worsening of cardiac conduction is common, and autonomic neuropathy may add to the effects of bradycardia to create significant hemodynamic instability. Finally, in individuals with significant orthostasis, regular use of support stockings and counter-pressure maneuvers may help avoid falls. Fludrocortisone should be avoided in this population because it may cause significant volume retention. Pseudoephedrine may be proarrhythmogenic, and midodrine, although purported to be beneficial, is of questionable efficacy based on a recent Food and Drug Administration review.[49,50]

Special consideration must be made in the general care of individuals with cardiac amyloidosis, including early anticoagulation for those in atrial fibrillation and avoidance of potentially toxic therapies commonly used in individuals with heart failure. Anticoagulation should be the rule in those with atrial fibrillation even if traditional stroke risk factors enumerated in validated risk-prediction models such as the CHADS2 and CHA2DS2-VASc scores are not elevated. A retrospective analysis has shown that persons with cardiac TTR amyloidosis have an almost 20% prevalence of intracardiac thrombus. Atrial fibrillation and diastolic relaxation abnormalities are associated with thrombus formation, and anticoagulation with warfarin appears protective.[28] At this time, there is insufficient evidence to evaluate the safety and efficacy of novel oral anticoagulants such as dabigatran and apixaban in this population.

Care must be taken to avoid potentially harmful therapies commonly used in individuals with atrial fibrillation and congestive heart failure, such as digoxin, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, and beta blockers. Digoxin binds to amyloid fibrils and exerts unpredictable local effects, with subsequent risk of arrhythmogenesis.[51] Serum digoxin levels are an inaccurate estimate of tissue effects. Similarly, dihydropyridine calcium channel blockers also bind amyloid fibrils and can exert potentially deleterious negative inotropic effects and result in high-degree AV block.[52] Neither digoxin nor calcium channel blockers should be used in individuals with cardiac amyloidosis. In contrast, ACE inhibitors, angiotensin receptor blockers, and beta blockers can be used, albeit with extreme caution. ACE inhibitors and angiotensin receptor blockers may induce hypotension, because angiotensin blockade can significantly reduce vascular tone in the setting of concomitant sympathetic dysfunction due to TTR deposition.[5] Beta blockers may have undesirable negative inotropic and chronotropic effects. Because individuals with cardiac amyloidosis have restrictive cardiomyopathy with a relatively fixed stroke volume, augmentation of cardiac output relies disproportionately on faster heart rate. This normal heart rate response is frequently impaired with normal aging and may be further exacerbated by beta blockade.

Disease-modifying treatments have until recently been limited to organ transplantation in highly selected older persons up to the age of 77.[53] Orthotopic heart transplant has rarely been performed for familial or senile cardiac amyloidosis, often with the use of extended donor criteria.[54] Posttransplantation life expectancy is longer than in nontransplanted controls with amyloidosis but is shorter than the average life expectancy of all heart transplant recipients. Although not an immediate complication, amyloidosis can theoretically recur in transplanted grafts. This is not surprising because the liver is the site of synthesis for mutated TTR and continues to produce the abnormal protein. The combination of orthotopic heart and liver transplants has therefore been used in highly selected younger individuals.

Given the obvious limitations of organ transplantation, it is exciting that a number of new pharmacotherapies specifically designed to reduce amyloid burden are on the horizon. These agents are designed to decrease production of the amyloidogenic protein or increase its clearance from the body. For example, a number of small molecules and pharmacological agents have been shown to increase TTR's native-state stability and kinetic barrier to misfolding and aggregation.[1,5,55] Two of these compounds with the most robust clinical data are diflunisal and tafamidis. Diflunisal is a nonsteroidal anti-inflammatory drug (NSAID) that binds to unoccupied thyroxine binding sites on TTR and reduces tetramer dissociation.[56] Unpublished data from Columbia University Medical Center demonstrate that, when given for 1 year to a small group of elderly persons with cardiac TTR amyloidosis, diflunisal was associated with echocardiographic stabilization of cardiac structure and function and worse glomerular filtration rate and platelet count. Expected side effects of NSAIDs such as renal impairment, gastritis, peptic ulcer disease, and fluid retention may therefore limit prolonged use of the agent in older persons.

In contrast, tafamidis is a first-in-class small molecule that stabilizes the TTR tetramer and prevents its dissociation without the side effects expected of NSAIDs. Tafamidis has had favorable results in phase II and III trials in individuals with familial TTR polyneuropathy and was well tolerated.[5,57] Preliminary data from an open label trial also suggest efficacy in persons with familial TTR cardiomyopathy,[58] although randomized trials in persons with the Val122Ile mutation or wild-type disease have not been performed.

Active clinical research programs are also testing strategies of ribonucleic acid (RNA) interference through the use of small interfering RNAs (siRNAs) and antisense nucleotides to silence the TTR gene. RNA interference is a natural cellular process within many eukaryotic cells that controls gene activity. In this process, a short segment of double-stranded RNA called an siRNA unwinds into a single-stranded RNA and ultimately pairs with a complementary strand of messenger RNA (mRNA). This binding prevents the mRNA from being translated into a protein product. In this manner, siRNAs are being produced to selectively target the mutant TTR gene.[59] Similarly, antisense nucleotides have been designed that specifically bind to mRNA transcripts of the TTR gene.[60] Using these new technologies, Phase I clinical studies are ongoing to test drug safety and tolerability in individuals with transthyretin amyloidosis. As with tafamidis, none of these studies specifically test drug effects in persons with cardiac amyloidosis from the Val122Ile mutation or wild-type disease.

CONCLUSION

A significant portion of older North Americans with heart failure and a preserved ejection fraction have significant transthyretin cardiac amyloidosis. As new targeted therapeutics become available, it will be increasingly important that these persons be identified. As shown in Table 2, historical clues such as intolerance to commonly used cardiovascular medications can be combined with characteristic findings on physical examination and imaging studies to select individuals with a high likelihood of disease. These individuals can undergo endomyocardial biopsy and genetic testing to confirm or exclude the diagnosis. Those with cardiac TTR should be given the appropriate supportive care to improve functional status and avoid the most undesirable disease complications such as acute decompensated heart failure, syncope, and cardioembolic stroke. Where appropriate, individuals should be given access to clinical trials testing potential disease-modifying agents.

Knowledge of the clinical syndromes due to the TTR amyloidoses is incomplete. The natural history of disease, including its variable penetrance and progression, links between genotype and phenotype, and the response to supportive and more-specific therapies, must be better understood. One manner in which this is being done is through the Transthyretin Amyloidosis Outcomes Survey (THAOS, listed on clinicaltrials.gov), a multicenter longitudinal, observational survey open to all individuals with transthyretin amyloidosis. THAOS is an open-ended registry with hopes of enrolling several thousand people with TTR amyloidosis at more than 50 worldwide sites over a 10-year period. Pfizer, who is responsible for site identification, initiation, and support, will perform registry management and operations.

The individual described in the clinical vignette is typical for someone with cardiac TTR amyloidosis from the Val122Ile mutation. In his case, the diagnosis of cardiac TTR was delayed approximately 18 months after the first manifestation of congestive heart failure, but once considered, the final diagnosis required only the 2 weeks necessary for targeted genetic sequencing of the mutant allele. The individual is currently participating in an open-label trial of a transthyretin stabilizer. It is hoped that this novel agent will slow disease progression and improve quality of life for what has hitherto been a relentlessly progressive myopathic process.

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