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Impact of Genetic Testing in Transthyretin (ATTR) Cardiac Amyloidosis

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Abstract

Purpose of Review The review's main focus centers on the genetics of hereditary cardiac amyloidosis, highlighting the opportunities and challenges posed by the widespread availability of genetic screening and diagnostic cardiac imaging.

Recent Findings Advancements in cardiac imaging, heightened awareness of the ATTR amyloidosis diagnosis, and greater access to genetic testing have all led to an increased appreciation of the prevalence of ATTR cardiac amyloidosis. Elucidation of the TTR molecular structure and effect of mutations on TTR function have allowed for novel TTR therapy development leading to clinical implementation of transthyretin stabilizers and transthyretin gene silencers.

Summary The transthyretin amyloidoses are a diverse group of protein misfolding disorders with cardiac and peripheral/autonomic nervous system manifestations due to protein deposition. Genetic screening allows for the early identification of asymptomatic *TTR* mutation carriers. With the advent of TTR-specific therapeutics, clinical guidance is necessary for the management of individuals with mutations in the *TTR* gene without evidence of disease.

Keywords Cardiac amyloidosis · Transthyretin · Hereditary amyloidosis · Cardiomyopathy · Genetic cardiomyopathy

Introduction and Nomenclature of Amyloidosis

Amyloidosis is a broad classification for a group of diseases that are characterized by the extracellular deposition of insoluble fibrillar proteins in the form of β-pleated sheets, leading to organ dysfunction [1•]. The presence of the amyloid protein is identified by specific histological techniques employing Congo red staining [2], while the precursor protein that misfolds and forms amyloid fibrils is defined by immunohistochemistry or mass spectroscopy [1•]. The type of amyloidosis is defined by the precursor protein that misfolds. Amyloidogenic light chain (AL) amyloidosis is characterized by organ deposition of monoclonal lambda or kappa free light chains, in the context of a clonal proliferation of bone marrow-derived plasma cells. In contrast, amyloidogenic transthyretin (ATTR) amyloidosis is sub-classified by the genetic sequence of the *TTR* gene as either genetically normal (wild-type) or variant transthyretin protein. In ATTR amyloidosis, TTR protein, synthesized by the liver, misfolds into amyloid fibrils and causes a specific constellation of organ dysfunction. For the purposes of this review, focused on genetically inherited cardiac amyloidosis, we will restrict our discussion to ATTR amyloidosis with cardiomyopathy.

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Transthyretin Protein

Transthyretin (TTR) protein (formerly called prealbumin) is a 127-amino acid plasma transport protein that binds to thyroid hormone and retinol/retinol-binding protein [3], and is encoded by a single-copy gene on the long arm of chromosome 18. Transthyretin has 4 exons that each code for one of

four monomers that circulate as a homotetramer (a protein complex made up of four identical subunits that are associated but not covalently bound) [4]. Nearly all TTR is synthesized in the liver but other sites of production include the choroid plexus of the brain and the retinal pigment endothelium of eye [5••]. Despite its name, TTR is not an important contributor of circulating thyroid hormone, while it is an integral protein for transport of retinol (vitamin A).

Organ Involvement

Interestingly, misfolded TTR protein, be it in the context of wild-type or variant genetics, results in significant heterogeneity in the organ manifestations of ATTR amyloidosis. Wild-type ATTR (ATTRwt) amyloidosis most commonly affects the heart and soft tissue, resulting in carpal tunnel syndrome, spinal stenosis [6], and in some cases, spontaneous biceps tendon rupture [7]. The manifestations of hereditary ATTR (hATTR or ATTRv for variant) vary depending on the pathogenic mutation in the *TTR* gene. The most common manifestations of ATTRv amyloidosis include cardiomyopathy (ATTR-CM), sensorimotor and/or autonomic polyneuropathy, leptomeningeal (and oculoleptomeningeal), and soft tissue involvement.

Polyneuropathy

The peripheral neuropathy of ATTRv amyloidosis begins as a small fiber sensory polyneuropathy in the lower extremities with clinical manifestations as paresthesias and hyperesthesias [8]. There is progression of this sensory neuropathy to more proximal areas of the lower extremities, with eventual involvement of the fingers and hands. There is early impairment of temperature and pain sensation, followed by vibration and position sensation impairment. This sensory neuropathy is subsequently followed by a motor neuropathy resulting in foot drop, wrist drop, and loss of manual dexterity [9].

Autonomic neuropathy may exist alone or in conjunction with a sensorimotor neuropathy, and may be an early sign of the disease. Manifestations of autonomic neuropathy include orthostatic hypotension, GI disturbances including impaired gastric emptying, intractable diarrhea, impotence, anhidrosis, and urinary retention [10, 11]. Autonomic involvement often results in significant morbidity, complicating the management of ATTR-CM related congestive heart failure and may dominate the phenotypic expression of this disease.

Leptomeningeal Involvement

Leptomeningeal amyloidosis is a prominent feature of certain, relatively rare, TTR mutations (Gly47Arg) [12], Asp18Gly [13], Leu12Pro [14], among others, characterized by central nervous system amyloid deposition in the pia and arachnoid membrane and in the subarachnoid space. This results in intracranial hemorrhage, focal neurologic signs, ataxia, visual impairment, dementia, and psychosis. There may be associated vitreous deposits resulting in oculoleptomeningeal involvement [15, 16].

Ocular Involvement

The spectrum of eye involvement includes vitreous opacities, dry eyes, glaucoma, and ocular amyloid angiopathy, and may be seen in a fifth of the patients with the V30M phenotype [5••, 17]. In rare cases, ocular amyloid may be the sole manifestation of the disease [18].

Nephropathy

Renal involvement is variable, and mild renal involvement may be seen with the early-onset Portuguese variant of the V30M mutation, but severe renal dysfunction is less common [19].

Cardiovascular Manifestions of ATTR Disease

Cardiac amyloidosis is a restrictive cardiomyopathy characterized by extracellular deposition of amyloid fibrils leading to increased biventricular wall thickness and advanced diastolic dysfunction. Cardiac imaging is essential for raising suspicion of diagnosis and as such, echocardiography and cardiac MRI both reflect increased biventricular wall thickness. As amyloid deposits are extracellular, they can be indirectly visualized by imaging, as well. Extracellular amyloid fibril deposition is responsible for the characteristic pattern of late gadolinium enhancement (LGE), prolonged native T1 time, and increased extracellular volume (ECV), noted on cardiac MRI [20, 21]. While left ventricular systolic function as assessed by the left ventricular ejection fraction may appear normal in earlier stages of the disease, deformation imaging through speckle tracking echocardiography often reveals early and characteristic abnormalities in cardiac amyloidosis [22, 23]. Amyloid fibril deposition also leads to a discordance between ventricular wall thickness on cardiac imaging and QRS voltage on ECG, as patients with cardiac amyloidosis may have low QRS voltages on ECG despite increased left ventricular wall thickness [24]. Clinically, this pathophysiology leads to high filling pressures, significant fluid retention, and exercise intolerance due to an inability to augment cardiac output during exertion. Finally, nuclear imaging with bone-avid compounds has dramatically altered the diagnostic approach to ATTR amyloidosis, offering the potential for widespread screening in at-risk patients.

Diffuse atrial infiltration with amyloid fibrils leads to a high prevalence of atrial fibrillation and other atrial arrhythmias [25]. Atrial electromechanical dissociation may also be seen

even in the absence of atrial fibrillation and may result in cardioembolic events in sinus rhythm [26, 27]. Often, a diffuse infiltration of the conduction system is present leading to advanced conduction disease that may require permanent pacing [28–30]. While pulseless electrical activity is thought to be the most common proximate cause of cardiac death in cardiac amyloidosis, ventricular arrhythmias are common and ICD implantation may be reasonable in select patients for secondary prevention. The benefit of implantation for primary prevention remains less clear [31].

Current Approach to ATTR Amyloidosis Identification

There are eleven different proteins that can misfold into amyloid fibrils and infiltrate the heart [32]. With the advent of gene-silencing therapeutics in ATTRv amyloidosis, accurate typing of amyloid protein is essential for the development of appropriate therapeutic strategies. Of the cardiac-avid amyloid proteins, AL and ATTR are by far the most commonly seen in the USA. Gelsolin amyloidosis is a rare heritable disease that causes well recognized neuropathy and cardiac involvement, but is seen principally in northern Europe [33]. Other precursor proteins that are associated with cardiomyopathy, such as ApoA1, are quite rare.

In the setting of clinical suspicion of cardiac amyloidosis, four main initial tests should be considered: (1) serum free light chains (FLC); (2) serum immunofixation electrophoresis (SIFE); (3) urine immunofixation electrophoresis (UIFE); and (4) ^{99m}Tc-pyrophosphate (^{99m}Tc PYP) nuclear scan (in the USA) (Fig. 1). The laboratory testing (FLC, SIFE, and UIFE) is essential initial testing elements for AL amyloidosis screening. While bone-avid radiotracers have been applied to cardiac imaging for over 40 years, in the early 2000s, researchers described the application of a similar tracer to PYP (^{99m}Tc-3,3-diphosphono-1,2-propanedicarboxylic acid (^{99m}Tc DPD), available only in Europe) that not only detected cardiac amyloidosis but differentiated ATTR and AL cardiac amyloidosis with 100% specificity [34, 35]. In 2013, Bokhari and colleagues showed comparable high rates of sensitivity (97%) and specificity (100%) with ^{99m}Tc PYP (nuclear tracer available in the USA) in differentiating AL and ATTR cardiac amyloidosis using a heart to contralateral lung (H/CL) quantitative ratio > 1.5 [36••]. Several multicenter evaluations have validated these results with the ^{99m}Tc PYP technique and additionally showed H/CL ratio > 1.6 conferred worse survival [37, 38]. With the adoption, awareness, and growing availability of this imaging technique, ^{99m}Tc PYP with its remarkable sensitivity and specificity for the ATTR amyloidosis has nearly obviated the need for histological typing of amyloid protein to *rule in* ATTR cardiac disease. The capacity to diagnose ATTR amyloidosis without biopsy has resulted in a dramatic increase of identified cases over the past 5 years. One important caveat to the nuclear testing is the decreased specificity noted in patients with circulating monoclonal protein and AL amyloidosis; thus, it is imperative to *rule out* a monoclonal gammopathy with FLC, SIFE, and UIFE as noted above. In cases of clinical ambiguity or equivocal results, obtainment of tissue (usually via endomyocardial biopsy) for typing via immunohistochemistry or with amyloid deposits micro-dissected by laser capture with application of tandem mass spectrometry (gold standard) is recommended [39••]. Once a diagnosis of ATTR amyloidosis is established by imaging with exclusion of AL amyloidosis by serum/urine testing, genetic sequencing of *TTR* is necessary.

Genetic Overview of Hereditary ATTR Disease

There are over 140 known mutations in the transthyretin gene with the majority occurring in exon 2 and 3 [5••]. Mutations in the transthyretin protein structure lead to destabilization of tetrameric formation (the rate limiting step in amyloidogenesis) and accelerate fibril formation. The nomenclature for ATTRv disease places a 1- or 3-letter abbreviation for the normal amino acid at the mutation point followed by the substituted amino acid (e.g., ATTR V122I signifies isoleucine replacing valine at position 122 in the transthyretin amino acid sequence) [40••]. There is often confusion in contemporary genetic reports as the 20-amino acid signal sequence is often included in the numbering of residues. Hence, V122I and pV142I refer to the same substitution. As both wild-type TTR (TTR protein with normal genetic sequence) and mutated TTR can each result in amyloidogensis, non-genetic factors definitively contribute to fibril deposition [5••, 41]. ATTR amyloidosis only requires one mutant TTR allele for disease pathogenesis, thus imparting an autosomal dominant inheritance pattern (50% risk of passage to offspring). Most individuals with the disease phenotype are heterozygous for the pathogenic mutation and express both normal and mutated TTR and as such TTR amyloid fibrils isolated from heterozygous patients contain both normal and variant TTR. When tissue deposits of amyloid are analyzed, 65–75% are composed of variant TTR and the remainder normal TTR [5••].

Key Elements Contributing to Hereditary ATTR Phenotypic Heterogeneity

Type of Mutation

One of the most important determinants of cardiac phenotypic presentation in ATTRv amyloidosis is the mutation. There are five main mutations that are implicated in an exclusive, predominant, or frequently occurring cardiac phenotype

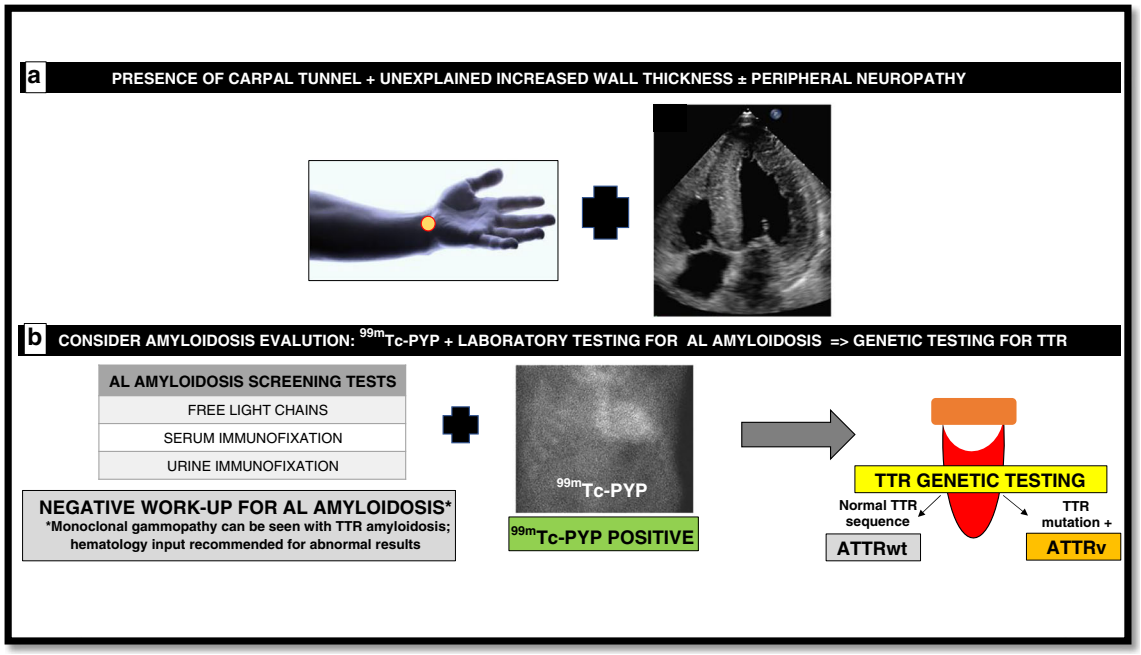

Fig. 1 **a** Key signs commonly encountered in cardiac amyloidosis; **b** Recommended studies necessary for ruling out light-chain cardiac amyloidosis and diagnosing hereditary ATTR cardiac amyloidosis

worldwide: V122I, T60A, V30M (late-onset), I68L, and L111M [42, 43•, 44, 45] (Table 1). The first three of these mutations are most commonly seen in the USA as geography is an important factor in the epidemiology and mutation prevalence for diagnosed cases of cardiac amyloidosis [46•]. V122I always exhibits a cardiac phenotype and while not classically attributed to this mutation, peripheral neuropathy can co-exist in a small proportion of patients [46•, 47]. V122I is by far the most common mutation seen in the USA with an estimated prevalence of 3.4% among African Americans [48]. T60A, a mutation with origins in the northern part of the Republic of Ireland, nearly always is associated with a cardiac phenotype but often demonstrates significant percentage of mixed disease (both cardiac and neurologic involvement) with autonomic dysfunction seen in 75% of individuals and peripheral neuropathy in 54% [45]. V30M is likely the most common mutation worldwide (outside of the USA) and has many phenotypic presentations heavily influenced by geographic location. Specifically, when evaluating patients with the mutation, outside of endemic geographical loci in specific parts of Japan, Portugal, and northern Sweden ("non-endemic"), the phenotypic presentation has low apparent penetrance that is much more age-dependent, prominently cardiac in expression with a more indolent neuropathy [49, 50].

Age

Age provides crucial effect modification between the association of *TTR* mutations and phenotypic expression. Interestingly, while *TTR* mutations are present since birth,

Table 1 Main types of hereditary TTR amyloidosis with cardiac involvement

TTR mutation	Age (years)	Male: female	Geographic origin	Cardiac phenotype	Other
V122I	> 65	1:1 (Gene+);3:1(phenotype)	USA, Caribbean, Africa	Always	PN (10%), CTS
T60A	> 45	2:1	USA (Appalachia), Ireland, Germany, Australia, England	Nearly always present	ANS (most frequent), PNS (less)
V30M (late-onset)	> 50	2:1 (variable with origin)	Sweden, France, Portugal, Japan	Age-dependent (Portugal, Japan)	All are mixed (cardiac and PNS)
I68L	> 60	Unknown	USA, Germany	Nearly always present	Predominantly cardiac < 10% PNS only
L111M	> 30	Unknown	Denmark (3 large kindreds)	Always	CTS

*PN, peripheral neuropathy; *CTS*, carpal tunnel syndrome; *ANS*, autonomic nervous system; *PNS*, peripheral nervous system

ATTR phenotypic expression does not develop until adulthood. With most mutations, penetrance rates increase with age [43•, 49, 51] suggesting that biological processes in addition to mutational considerations, related to the aging process (or environmental/lifetime exposures), over time play a role in disease presentation and timing.

Sex

Sex of the transmitting parent, as well as sex of the carrier, plays importance in phenotypic presentation in hereditary ATTR disease. Many *TTR* mutations demonstrate equal sex involvement; however, many do show higher incidence in males compared to females, such as V30M non-endemic Japanese cohorts and French V30M carriers [50–53]. However, sex appears to play a "protective" role in women with less involvement of cardiac disease, often with later onset. For those women with cardiac ATTR disease, less severe cardiac expression with reduced wall thickness and higher LV systolic function has also been observed, at least before menopausal age [54]. In addition, a validation genetic evaluation of Swedish V30M carriers showed higher rates of trait penetrance when inherited from the mother than the father [49]. The mechanism of such sex-specific effects, particularly in regard to earlier-onset disease with maternal inheritance, has not been well-elucidated although some studies have shown differences in mitochondrial DNA haplotypes in these groups [55].

Fibril Composition

There is growing data regarding the association of amyloid fibril composition with organ tropism, and therefore phenotypic presentation of ATTR amyloidosis clinical manifestations. First described by Swedish investigators among carriers of the V30M mutation using subcutaneous fat pad biopsies, full-length TTR (type B fibrils) was associated with earlier-onset disease without a cardiac phenotype with strong affinity for Congo Red and brighter green birefringence. Amyloid deposits composed of TTR fragments (type A fibrils) associated with later onset disease and cardiac involvement and with weaker Congo Red staining and birefringence [56]. Verified at autopsy, all organs displayed the same type of fibril composition in affected organs as noted in the fat pad biopsy. The same group extended this observation to a cohort of non-V30M and noted that type A fibrils were present in nearly all the investigated non-V30M (exception being two ATTR Y114C) carriers with cardiac involvement [57]. In addition, wild-type ATTR has been shown to also have the fragmented type A fibrils [58]. The clinical relevance of fibril composition may inform differential bone-avid nuclear tracer uptake as 97% of patients with type A fibrils and none of the patients with type B fibrils displayed ^{99m}Tc DPD uptake. Thus, the specificity of the ^{99m}Tc nuclear scans may be partially explained by the fibril type.

Geographic Considerations

As described above, the phenotypes of familial ATTR disease are often varied but important clinical features and characteristics are shared by kinships and individuals from a particular region or singular background, such as V30M described in specific regions in Portugal, northern Sweden, and Japan and have classically been referred to as "endemic V30M" [52, 59–61]. With advances in molecular and genetic testing, *TTR* mutations have been reported worldwide. Harnessing data from a global, multicenter, longitudinal assessment (Transthyretin Amyloidosis Outcomes Survey, (THAOS)), it was demonstrated that TTR amyloidosis type and presentation differ between the USA and the rest of the world (older, more male, more wild-type ATTR disease, with more cardiac phenotypes, V122I mutation most commonly seen in USA) [46•].

Approach to Genotype-Positive, Phenotype-Negative Individuals

With the widespread availability of genetic testing platforms and overall heightened awareness of ATTR cardiac amyloidosis, pre-symptomatic testing has become a frequent query for clinicians, usually prompted by an index patient in a family. Unfortunately, while there are no evidence-based practice guidelines established to assist in the approach to genotype-positive, phenotype negative carriers, working groups comprised of ATTR experts have convened and developed consensus documents to help guide clinicians for pre-symptomatic testing [62–64]. Establishing a monitoring approach that will be high-yield to identify early disease while simultaneously not leading to undue anxiety and increasing the cost of healthcare by unnecessary testing is critically important when considering pre-symptomatic testing. Thus, the predicted age of onset of symptomatic disease (PADO) is important to determine on an individual basis, based on the particular mutation, typical age of onset for that mutation, and onset among family members with established ATTR amyloidosis. Once the PADO has been determined for the individual at-risk, one expert consensus group has proposed monitoring to begin 10 years earlier to establish a baseline and continue annually and perhaps become more frequent as a patient nears PADO, particularly those with mutations that are known to rapidly progress [62]. Through these monitoring visits, a clinical (and not pathological) diagnosis of ATTR amyloidosis can be assumed as described in these consensus guidelines with the following scenarios (assuming comorbidities have been appropriately excluded):

1) One quantified/objective sign or symptom definitely related to onset of ATTR amyloidosis (new sensorimotor neuropathy changed from baseline, autonomic neuropathy or neurogenic/sexual dysfunction, cardiac involvement, or renal/ocular involvement), or

2) Any symptoms/sign likely related to ATTR disease in the absence of objective signs PLUS 1 abnormal test finding, or
3) Absence of symptoms PLUS 2 abnormal test findings

Current Treatment Approaches to Hereditary Cardiac ATTR Amyloidosis

Symptomatic management of heart failure is an important principle of cardiac amyloidosis therapy. Volume reduction with loop diuretics and mineralocorticoid antagonists remains the mainstay of therapy. Standard heart failure management with beta-blockers, ace-inhibitors, and angiotensin receptor blockers is often not tolerated due to worsening of heart failure symptoms and hypotension, especially in the setting of underlying autonomic dysfunction. Calcium channel blockers may be contraindicated due to direct binding of these agents to amyloid fibrils resulting in local toxicity and worsening heart failure [65, 66]. Similarly, digoxin binds irreversibly to AL amyloid fibrils in vitro, and may be associated with local digoxin toxicity in cardiac amyloidosis, although a more recent report suggests that digoxin use may be safe with cautious use in this population [67].

TTR-specific therapy has recently focused primarily on cessation of mutant TTR production by the liver or the stabilization of the TTR tetramers to slow formation of amyloid fibrils. Orthotopic liver transplant (OLT) was the first therapy to target liver production of TTR. Early experience with OLT in hereditary ATTR with the V30M mutation was promising with no evidence of disease progression at 6 months [68] and with some clinical improvement at 2 years post-transplant [69]. Long-term registry data suggested an 82% 5-year survival with OLT in ATTR V30M as compared to a 59% 5-year survival in ATTRv patients without the V30M mutation [70]. However, longer-term follow-up identified progression of ATTR cardiomyopathy even after OLT [71]. Fibril composition appears to play an important role in disease progression, as patients with type A fibrils (mixture of truncated and full-length fibrils) having a higher propensity for development or progression of cardiomyopathy after OLT [72]. Furthermore, it appears that type A fibrils are likely to complex with ATTRwt fibrils leading to progressive cardiomyopathy after OLT, despite removal of mutant protein [73, 74]. Thus, while OLT may be promising in selected patients with V30M ATTRv disease without significant cardiomyopathy, this therapy is not an optimal long-term option for all patients with ATTRv disease. Additionally, OLT will not benefit patients with wild-type ATTR amyloidosis.

The discovery of a Portuguese family who were complex heterozygotes with V30M/T119M TTR phenotype and had no manifestation of ATTRv disease led to the realization that natural TTR stabilization (in the form of a hetero tetramer in this case) could prevent disease development [75, 76]. The subsequent search for synthetic TTR stabilizers led ultimately to the repurposing of the NSAID diflunisal and the development of the novel compound tafamidis. In patients with ATTRv neuropathy, tafamidis reduces the rate of progression of neuropathy [77••] and is associated with improved survival [78]. Likewise, in a placebo-controlled randomized trial, diflunisal reduced the progression of neurologic symptoms at 2 years in patients with ATTRv peripheral and autonomic neuropathy and was associated with preserved quality of life [79••]. For ATTR-CM, TTR stabilization with diflunisal and tafamidis was also associated with improved survival in a retrospective cohort study with a mixed cohort of patients with ATTRwt and ATTRv cardiomyopathy (with most patients in the ATTRv group expressing the V122I mutation) [80]. Most recently, a randomized controlled trial of tafamidis in patients with ATTRwt and ATTRv cardiomyopathy revealed a lower rate of the primary composite outcome of all-cause mortality and cardiovascular hospitalizations in the tafamidis group compared to placebo. Tafamidis was associated with lower all-cause mortality [81••]. Based on this pivotal trial, the FDA approved tafamidis for patients with ATTR cardiomyopathy, irrespective of mutation status, in May 2019. Tafamidis is also approved for ATTR polyneuropathy in Europe, Japan, and South America.

While TTR stabilization prevents TTR tetrameric dissociation and subsequent amyloid fibrillogenesis, there is also interest in inhibiting the production of TTR by the liver through TTR gene silencing. The small interfering RNA (siRNA) agent, patisiran, improved neurologic function and quality of life in patients with ATTRv peripheral neuropathy in a randomized, placebo-controlled clinical trial [82••]. In the subgroup of patients with cardiac amyloidosis, patisiran was associated with reduced all-cause hospitalizations and mortality, with a trend towards improvement in left ventricular wall thickness, global longitudinal strain, and cardiac biomarkers [83]. Similarly, the anti-sense oligodeoxynucleotide inotersen improved neurologic outcomes and quality of life in patients with ATTRv peripheral neuropathy in another randomized trial [84••]. Each of these two gene-silencing agents was approved by US FDA for ATTR polyneuropathy in hereditary amyloidosis only. Neither of these agents is currently approved for ATTRv without neuropathy (i.e., largely excluding V122I carriers) nor approved for ATTRwt amyloidosis. While published reports primarily assessed the effect of TTR gene-silencing on neurologic outcomes, clinical trials of gene-silencing agents that include primary cardiovascular end points are ongoing.

Conclusions

Transthyretin amyloidosis can occur in the context of genetically normal or mutant TTR protein. While ATTRwt is almost exclusively a cardiac-restricted phenotype, the ATTRv amyloidoses are a group of diverse autosomal dominant disorders caused by

point mutations in the TTR gene. These diseases are characterized by varying degrees of a sensorimotor and autonomic neuropathy and a restrictive cardiomyopathy, with phenotypic expression varying by mutation, sex, and age of onset. The development of critical diagnostic tools, including Tc99m pyrophosphate cardiac imaging and genetic testing, has led to a heightened awareness of these diseases. Widespread genetic testing raises questions of penetrance and the management of patients with genotype-positive, phenotype-negative disease. While treatment with TTR gene silencers and TTR stabilizers has been effective in the management of nervous system and cardiac manifestations of this disease, further studies are needed to explore the role of these agents in preventing the onset of disease in individuals who are mutant allele carriers, as well as to assess the role of biomarkers in tracking disease progression. In addition, practice guidelines are urgently needed to guide the clinical approach and to ensure that adequate genetic considerations are entertained when treating patient with ATTRv and their family members.

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Compliance with Ethical Standards

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