Screening for ATTR amyloidosis in the clinic: overlapping disorders, misdiagnosis, and multiorgan awareness

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Accepted: 26 January 2021 / Published online: 20 February 2021
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Abstract
Amyloid transthyretin (ATTR) amyloidosis is a clinically heterogeneous and fatal disease that results from deposition of insoluble amyloid fibrils in various organs and tissues, causing progressive loss of function. The objective of this review is to increase awareness and diagnosis of ATTR amyloidosis by improving recognition of its overlapping conditions, misdiagnosis, and multiorgan presentation. Cardiac manifestations include heart failure, atrial fibrillation, intolerance to previously prescribed antihypertensives, sinus node dysfunction, and atrioventricular block, resulting in the need for permanent pacing. Neurologic manifestations include progressive sensorimotor neuropathy (e.g., pain, weakness) and autonomic dysfunction (e.g., erectile dysfunction, chronic diarrhea, orthostatic hypotension). Non-cardiac red flags often precede the diagnosis of ATTR amyloidosis and include musculoskeletal manifestations (e.g., carpal tunnel syndrome, lumbar spinal stenosis, spontaneous rupture of the distal tendon biceps, shoulder and knee surgery). Awareness and recognition of the constellation of symptoms, including cardiac, neurologic, and musculoskeletal manifestations, will help with early diagnosis of ATTR amyloidosis and faster access to therapies, thereby slowing the progression of this debilitating disease.

Keywords Amyloidosis · ATTRv · hATTR · Cardiomyopathy · Transthyretin amyloidosis

Introduction
Amyloid transthyretin (ATTR) amyloidosis is a progressively debilitating, clinically heterogeneous, and fatal disease caused by the buildup of transthyretin (TTR) amyloid fibrils in various organs and tissues, resulting in multisystem dysfunction particularly in the heart, along with the peripheral and autonomic nervous systems [1–3]. The diagnosis of ATTR amyloidosis has been increasing over the last decade, and many patients have had musculoskeletal manifestations, such as carpal tunnel syndrome, distal biceps tendon rupture, idiopathic trigger finger, or spinal stenosis, any or all of which can precede by several years the cardiac or neurologic manifestations [3–8]. Disease progression in patients with ATTR amyloidosis is remarkably fast, resulting in significant impairment of function and irretrievable loss of quality of life [9–13]. With therapies available to slow disease progression, early recognition and diagnosis of patients with ATTR amyloidosis are important to facilitate early treatment. The aim of this review is to increase awareness of the constellation of symptoms in patients with ATTR amyloidosis—especially the non-cardiac symptoms that cardiologists and others may not traditionally associate with ATTR amyloidosis but that are key for identifying patients with this progressive, fatal disease.

Wild-type vs hereditary ATTR amyloidosis symptoms
There are two forms of ATTR amyloidosis: wild type (ATTRwt) and hereditary (ATTRv [variant]). In ATTRwt amyloidosis, which was previously termed senile cardiac amyloidosis, a native non-mutated TTR protein misfolds into amyloid fibrils, primarily resulting in dysfunction of the
heart that is characterized by restrictive cardiomyopathy; this is predominantly seen in males aged > 60 years [14–16]. Although ATTRwt amyloidosis typically manifests as cardiac symptoms, patients may also have signs and symptoms of sensorimotor neuropathy and autonomic neuropathy [14, 15], along with a clinical history of carpal tunnel syndrome, spinal stenosis, and other musculoskeletal manifestations [7]. ATTRv amyloidosis, originally called familial amyloidotic polyneuropathy, is caused by a single amino acid substitution produced by a point mutation in the TTR gene. More than 130 mutations have been identified to date, with some mutations more often associated with either predominant polyneuropathy or cardiomyopathy; however, most patients experience a mixed phenotype with both neuropathic and cardiac symptoms [14, 15, 17–19]. The mechanisms by which mutations influence TTR aggregation or fibril morphology leading to organ dysfunction with such variable clinical presentations are poorly understood [20, 21]. In addition, phenotypic expression can be highly variable among individuals with a specific mutation, even within the same family [14].

Overlapping conditions and misdiagnosis of ATTR amyloidosis

ATTR amyloidosis is often overlooked or misdiagnosed in patients, at least early in its course, due to the non-specific, heterogeneous, multisystem presentation of the disease [3]. As the disease progresses, the symptoms and clinical manifestations of ATTR amyloidosis often mimic those of other more common diseases, further complicating and delaying diagnosis [22–24]. Thus, patients with ATTR amyloidosis could receive inappropriate treatments, such as chemotherapy for light-chain amyloidosis and intravenous immunoglobulins or steroids for immune polyneuropathies [3, 25, 26].

The signs and symptoms that should raise suspicion of ATTR amyloidosis with cardiomyopathy (ATTR-CM) often overlap with other more commonly recognized cardiovascular diseases, such as heart failure with preserved ejection fraction, hypertensive cardiomyopathy, aortic stenosis, hypertrophic cardiomyopathy, and light chain amyloidosis (Table 1) [25, 27–29]. Given that the life expectancy of a patient with ATTR-CM is 2 to 5 years after diagnosis, early and accurate diagnosis is key to forestalling disease progression. Recognizing the disease’s signs and symptoms, which affect multiple systems, may aid cardologists in avoiding misdiagnosis.

Recognizing a constellation of ATTR amyloidosis symptoms

Early suspicion and recognition of ATTR amyloidosis can lead to an earlier diagnosis and treatment; there is evidence to suggest that a delay in treatment leads to irretrievable loss of quality of life and progression of the polyneuropathic and cardiac manifestations for most patients [3, 9–13]. Recognition of a constellation of symptoms may raise suspicion of amyloidosis early in its course (Fig. 1). Although patients may present with predominant symptoms of cardiomyopathy or progressive polyneuropathy, there can be substantial overlap, with many individuals presenting with a combination of both, as well as other abnormalities, such as musculoskeletal symptoms, orthostatic hypotension, erectile dysfunction, gastrointestinal abnormalities, and unexplained weight loss (Fig. 2) [14, 15]. Patients may also present with ocular manifestations and symptoms of nephropathy, which are discussed in other reviews [3, 30]. This phenotypic variability poses a considerable diagnostic challenge. ATTR amyloidosis should be considered in patients with signs and symptoms associated with cardiac, neurologic, or musculoskeletal manifestations, particularly when the constellation of those symptoms suggests that multiple organs are affected [3, 31].

| Cardiac [27–29] | Neurologic [3, 24, 25] |
|-----------------|------------------------|
| • Heart failure with preserved ejection fraction | • Chronic inflammatory demyelinating polyneuropathy |
| • Hypertensive cardiomyopathy | • Paraproteinemic peripheral neuropathy (e.g., monoclonal gammopathy-associated) |
| • Aortic stenosis | • Toxic peripheral neuropathy |
| • Hypertrophic cardiomyopathy | • Vasculitic peripheral neuropathy |
| • Light chain amyloidosis with cardiac involvement | • Idiopathic axonal polyneuropathy |
| • Idiopathic restrictive cardiomyopathy | • Paraneoplastic neuropathy |
| • Iron overload | • Diabetic neuropathy |
| • Other infiltrative cardiomyopathies (e.g., Fabry disease) | • Alcoholic neuropathy |
| | • Motor neuron disease (e.g., amyotrophic lateral sclerosis) |
| | • Fibromyalgia |
| | • Light chain amyloidosis |

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Cardiovascular symptoms of ATTR amyloidosis

ATTR-CM is characterized by increased ventricular wall thickness, increased valve thickness, and interatrial and interventricular septum thickness that present as restrictive cardiomyopathy and progress to heart failure—initially in the setting of preserved ejection fraction, conduction system disturbances, and arrhythmias—with resulting impaired functional capacity, syncope, or palpitations [14, 15, 17, 32–34]. The signs and symptoms that should raise suspicion of ATTR-CM include a history of right-sided heart failure; heart failure with preserved ejection fraction (especially in men); intolerance to angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, angiotensin receptor neprilysin inhibitors (ARNi), or beta-blockers; or atrial arrhythmias, conduction system disease, or need for a pacemaker (Table 2) [28, 29, 35, 36]. Additionally, heart failure in patients with ATTR amyloidosis progressively worsens over time, with patients experiencing decline in diastolic dysfunction, decrease in left ventricular ejection fraction (~3% every 6 months), increased restrictive filling, and decline in functional capacity (~26 m decrease in 6-min walk distance every 6 months) [15, 27, 33, 37–39]. In patients with ATTRwt and ATTRv amyloidosis, troponin levels or N-terminal pro-B-type natriuretic peptide (NT-proBNP) levels are elevated and increase over time; this is an indicator of clinical progression of heart failure [33, 36].

Neurologic symptoms of ATTR amyloidosis

Patients with amyloid polyneuropathy, such as ATTR amyloidosis, are frequently misdiagnosed with chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) [24, 25, 40]. Other neuropathies confused with ATTR amyloidosis include paraproteinemic peripheral neuropathy, toxic peripheral neuropathy, vasculitic peripheral neuropathy, idiopathic axonal polyneuropathy, diabetic polyneuropathy, alcoholic neuropathy, paraneoplastic neuropathy, monoclonal gammopathy—associated neuropathy, and, more rarely, motor neuropathy and amyotrophic lateral sclerosis (Table 1) [24, 25, 40]. Recently published guidelines review in greater detail the misleading features that often lead to these...
misdiagnoses [24]. Two key features of ATTR amyloidosis with polyneuropathy (ATTR-PN) distinguish it from the more common diabetic polyneuropathy: its progressive nature and, frequently, distal limb weakness. Diabetic polyneuropathy is typically a slow, progressive, and distal sensory neuropathy without much limb weakness (Table 3).

ATTR-PN is characterized by symmetrical length-dependent peripheral neuropathy; depending on the TTR mutation in the case of ATTRv amyloidosis, distal and occasionally proximal limb weakness may be prominent [3, 19]. As the disease progresses through each stage, the pattern of progression and class of nerve fiber impacted is reflected through heterogeneous clinical manifestations experienced by the patient with ATTR-PN [19, 41–43]. Early symptoms of ATTR-PN include burning pain, especially in younger patients; older patients experience burning pain, numbness, and loss of pain and temperature sensation, whereas the ability to perceive touch pressure and joint position is relatively preserved [3, 41]. Examination of nerve fiber involvement at this stage demonstrates degeneration of unmyelinated and small myelinated nerve fibers more than large myelinated fibers [41]. As ATTR-PN progresses, muscle weakness increases, especially in the lower limbs; patients with ATTR-PN suffer from progressive lower limb numbness, weakness, and gait imbalance [15, 43–45].

**Fig. 2** Symptoms of ATTR amyloidosis. Patients with ATTR amyloidosis may present with clinical signs or symptoms of cardiomyopathy or progressive polyneuropathy along with musculoskeletal symptoms and signs of autonomic dysfunction. ATTR amyloidosis should be considered for patients with cardiac, neurologic, or musculoskeletal manifestations, particularly when those symptoms suggest multiple organs are affected. *ATTR* amyloid transthyretin

**Table 2** Signs and symptoms that should raise suspicion of ATTR amyloidosis with cardiomyopathy

| Signs/symptoms                                                                 | 
|-------------------------------------------------------------------------------|
| Heart failure with predominant right-sided symptoms (e.g., distended jugular veins, anorexia, gastrointestinal upset, dependent edema, weight gain) |
| HFpEF, especially in men                                                       |
| Intolerance to ACE inhibitors, angiotensin receptor blockers, ARNi, or beta-blockers |
| Unexplained atrial arrhythmias, conduction system disease, or need for a pacemaker |
| History of musculoskeletal syndromes or procedures: CTS; lumbar spinal stenosis; spontaneous distal bicep tendon rupture; or shoulder, knee, or hip surgery |

*ACE* angiotensin-converting enzyme, *ARNi* angiotensin receptor-neprilysin inhibitors, *ATTR* amyloid transthyretin, *CTS* carpal tunnel syndrome, *HFpEF* heart failure with preserved ejection fraction
In addition to signs and symptoms of sensorimotor neuropathy, autonomic dysfunction is observed early in the course of ATTR amyloidosis and can precede motor impairment, but it often goes unrecognized [41, 46, 47]. Furthermore, in cases of severe autonomic dysfunction with reduced sympathetic function, the signs and symptoms of heart failure can be masked [48]. Autonomic neuropathy can manifest as orthostatic hypotension, recurrent urinary tract infection, erectile dysfunction, and/or gastrointestinal disturbances [3, 14, 15, 49]. Orthostatic hypotension, which is commonly reported as a symptom of ATTR amyloidosis, may manifest as dizziness or fainting when standing up, blurred vision, confusion, or light-headedness [15, 17, 46]. Meanwhile, gastrointestinal disturbances may include nausea, vomiting, constipation, diarrhea (possibly alternating with constipation), or fecal incontinence and unintentional weight loss [3, 14, 15, 49].

**Musculoskeletal manifestations of ATTR amyloidosis**

Patients with ATTR amyloidosis may develop musculoskeletal manifestations 5 to 15 years prior to other symptoms (Fig. 3) [4, 7, 50, 51]. Numerous studies have reported the presence of ATTR amyloid in tissue removed during orthopedic surgeries, including the flexor tenosynovium, rotator cuff tendons, and ligamentum flavum [52, 53]. Rotator cuff surgery has been predominately reported in patients with ATTRwt

| Feature                  | ATTR polyneuropathy                                      | Diabetic polyneuropathy | References |
|-------------------------|----------------------------------------------------------|--------------------------|------------|
| Pain                    | Mild, moderate, or severe                                 | Mild                     | [61–64]    |
| Motor weakness          | Common                                                   | Uncommon                 | [14, 15, 43, 44, 63, 64] |
| Muscle loss             | Common                                                   | Uncommon                 | [15, 43, 44, 63, 64] |
| Progression             | Months                                                   | Years                    | [44, 62]   |
| Distribution            | Distal and occasionally proximal                         | Distal                   | [61–64]    |

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**Table 3** Comparison of neuropathies related to ATTR amyloidosis and diabetes

| Feature                  | ATTR polyneuropathy                                      | Diabetic polyneuropathy | References |
|-------------------------|----------------------------------------------------------|--------------------------|------------|
| Pain                    | Mild, moderate, or severe                                 | Mild                     | [61–64]    |
| Motor weakness          | Common                                                   | Uncommon                 | [14, 15, 43, 44, 63, 64] |
| Muscle loss             | Common                                                   | Uncommon                 | [15, 43, 44, 63, 64] |
| Progression             | Months                                                   | Years                    | [44, 62]   |
| Distribution            | Distal and occasionally proximal                         | Distal                   | [61–64]    |
amyloidosis [53]. Carpal tunnel syndrome, the most common non-cardiac manifestation in patients with ATTR-CM, often presents years before a diagnosis of ATTRwt or ATTRv amyloidosis [4, 15, 37, 51, 54]. Carpal tunnel syndrome is caused by median nerve compression resulting in numbness, tingling sensations, or hand weakness. A recent study found that 10.2% of patients with bilateral carpal tunnel syndrome tested positive for amyloid deposits [6]. Of the 10 patients identified in the study, five were diagnosed with ATTRwt amyloidosis and two with ATTRv amyloidosis, and several also had a clinical history of trigger finger, lumbar spinal stenosis, or biceps tendon rupture [6]. Trigger finger due to amyloidosis is thought to occur when amyloid fibrils deposit in connective tissue, causing restricted movement of the flexor tendon, which then results in the finger being stuck in a bent position. The coexistence of trigger finger and carpal tunnel syndrome was also reported in members of a Japanese family with ATTRv amyloidosis [8]. In addition, a clinical history of lumbar spinal stenosis has been reported by several studies in patients with ATTRwt and ATTRv amyloidosis [5, 6, 53, 55]. Similarly, rupture of the distal biceps tendon (also known as Popeye sign) can be an early sign of amyloidosis; in patients aged >50 years, Popeye sign should raise suspicion of ATTR amyloidosis [56].

Orthopedic surgery is significantly more common in patients with ATTR-CM compared with the general population [57]. Arthroplasty typically occurs over 6 to 8 years before diagnosis of ATTR amyloidosis [57]. One study found that 25.9% (28/108) and 18.8% (12/64) of patients with ATTRwt and ATTRv amyloidosis with cardiomyopathy, respectively, underwent hip or knee arthroplasty [57]. In addition, rotator cuff repair occurred in 9.9% of patients with ATTR amyloidosis [53, 57]. A history of a constellation of these musculoskeletal syndromes and surgeries in a patient along with cardiac or neurologic symptoms should raise clinical suspicion and prompt physicians to screen for ATTR amyloidosis [7].

**Implementation of screening for ATTR amyloidosis in clinical practice**

Cardiologists should screen for ATTR amyloidosis in patients with clinical signs and symptoms suggestive of multisystem involvement, particularly those with the constellation of cardiac, neurologic, and musculoskeletal manifestations described in this review. Given the multisystemic nature of ATTR amyloidosis, a multidisciplinary approach to

![Fig. 4 Constellation of symptoms checklist for cardiac ATTR amyloidosis. Healthcare practitioners should evaluate patients with heart failure with preserved ejection fraction for a clinical history of carpal tunnel syndrome or lumbar spinal stenosis, along with progressive neuropathy or autonomic dysfunction. Clustering of these clinical signs and symptoms should prompt screening for cardiac amyloidosis and trigger referral to a multidisciplinary team at an amyloidosis expert center. ATTR amyloid transthyretin](image)
assessment, diagnosis, and management of patients is recommended by the guidelines [24, 28]. The assessment of patients with cardiac symptoms should include noninvasive or invasive procedures, as described elsewhere [28, 30, 58, 59].

It can be challenging to identify ATTR amyloidosis given the diversity of diagnostic clues that can manifest in a patient over time (across many years). As cardiac amyloidosis is present in 10% to 15% of patients with heart failure with preserved ejection fraction [27, 33, 58, 60], the addition of screening questions and a check of multiple symptoms could help to identify patients with ATTR amyloidosis (Fig. 4).

Conclusion

Awareness of the non-cardiac symptoms that cluster with cardiac and neurologic symptoms can unmask a diagnosis of ATTR amyloidosis and prompt referral to a center with expertise in this disease (Fig. 4) [3, 24, 28]. Because ATTR amyloidosis is now a treatable disease, recognizing the constellation of associated signs and symptoms, including those that are neurologic and musculoskeletal, is important because early treatment will make a meaningful impact on a patient’s quality of life, autonomy, and physical function [9–13].

Acknowledgements

Medical writing support was provided by Monique N. O’Leary, PhD, of ApotheCom (San Francisco, CA, USA).

Author contribution

All the authors met the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this manuscript and take responsibility for the integrity of the work as a whole. All the authors contributed substantial intellectual content to drafts of the manuscript and have read and approved the final manuscript.

Funding

Medical writing support was funded by Akcea Therapeutics.

Declarations

Conflict of interest

Jose N. Nativi-Nicolau reports funding for clinical trials from Pfizer, Akcea Therapeutics, and Eidos; educational grants from Pfizer; and consulting fees from Pfizer, Eidos, Akcea Therapeutics, and Alnylam. Chafic Karam reports consulting/educational activities for Akcea Therapeutics, Alexion, Alnylam, Argenx, Biogen, CSL Behring, Medscape, and Sanofi Genzyme; and has received research grants from Sanofi Genzyme and Akcea Therapeutics. Sami Khella reports honoraria from Akcea Therapeutics and Alnylam. Mathew S. Maurer reports grants from Pfizer and Alnylam; and personal fees from Pfizer, Eidos, Akcea Therapeutics and Ionis.

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