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TRANSTHYRETIN AMYLOIDOSIS - SYMPTOMS, DIAGNOSIS, TREATMENT - A SYSTEMIC REVIEW

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ABSTRACT

Background: Transthyretin amyloidosis (ATTR) is a rare, progressive systemic disorder caused by extracellular deposition of misfolded transthyretin, most commonly affecting the heart and peripheral nervous system. Because early manifestations are nonspecific, the disease is often under-recognised and diagnosed late, when organ damage is advanced.
Methods: We performed a narrative review of the literature using PubMed and Google Scholar, searching for clinical and translational studies on transthyretin amyloidosis, with particular focus on symptoms, diagnostic pathways, and currently available as well as emerging treatments. Additional references were identified from the reference lists of key articles.
Results: ATTR may present with a broad spectrum of cardiac, neurologic, gastrointestinal, musculoskeletal, and autonomic symptoms. Red-flag features include unexplained heart failure with preserved ejection fraction, increased ventricular wall thickness with low QRS voltages, bilateral carpal tunnel syndrome, lumbar spinal stenosis, and biceps tendon rupture. Diagnosis relies on a combination of clinical assessment, biomarkers, advanced imaging, and tissue biopsy when required, together with exclusion of light-chain amyloidosis. Disease-modifying therapies, particularly transthyretin stabilisers and gene-silencing agents, have significantly improved prognosis, especially when initiated early in the disease course.
Conclusions: Clinicians should maintain a high index of suspicion for ATTR in patients with compatible multi-system features. Timely recognition and appropriate use of non-invasive diagnostic algorithms allow earlier initiation of targeted therapy, which is crucial for improving survival and quality of life in transthyretin amyloidosis.

KEYWORDS

Transthyretin Amyloidosis, Cardiac Amyloidosis, ATTR, Amyloidosis, Transthyretin, Tafamidis

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Introduction

Amyloidosis comprises a heterogeneous group of systemic diseases characterized by extracellular deposition of misfolded protein fibrils in various organs, ultimately leading to progressive organ dysfunction and failure. The most common systemic forms include light-chain amyloidosis (AL) [1], related to a clonal plasma-cell disorder, and secondary amyloidosis (AA), which develops in the setting of chronic inflammatory conditions. In recent years, increasing attention has been directed towards transthyretin amyloidosis (ATTR).

Despite growing awareness, transthyretin amyloidosis remains challenging to diagnose owing to its nonspecific and often multisystem clinical presentation. For many years treatment was limited to symptomatic management, and prognosis was poor. However, the introduction of transthyretin stabilisers and gene-silencing therapies has markedly changed the therapeutic landscape, making early and accurate diagnosis more important than ever.

The aim of this narrative review is to summarise current knowledge on transthyretin amyloidosis, with particular emphasis on its pathogenesis, clinical manifestations, diagnostic pathways, and available as well as emerging treatment options, in order to facilitate earlier recognition and improved management of affected patients. and secondary amyloidosis following a chronic inflammatory process (AA), another form, known as transthyretin amyloidosis (ATTR), typically affects the heart.

Methodology

Literature review in Pubmed and Google Scholar databases, with particular emphasis on guidelines and expert opinions published by cardiology societies dedicated to this issue, including the guidelines of the Polish Cardiac Society and the European Society of Cardiology. Most of the literature included in the work was published in the years 2015-2025, except particularly important works published in earlier years. Keywords search terms included: "Transthyretin amyloidosis", "ATTR amyloidosis", "Cardiac Amyloidosis", Amyloidosis ATTR symptoms", Amyloidosis ATTR diagnosis" Amyloidosis ATTR treatment". To ensure the quality of the included studies, publications were evaluated based on their relevance to the research topic and the robustness of their methodology.

Pathogenesis of transthyretin amyloidosis

Transthyretin amyloidosis is associated with the deposition of transthyretin which normally is present in the form of a tetramer and has transport functions for thyroxine and retinol. There are two forms of this disease - a genetic form associated with a gene variant (ATTRv - variant) and the so-called wild type (ATTRwt - wild type) [2]. In the case of the genetic variant, a defective protein with an unstable structure is formed, which leads to deposits in tissues. Patients with the normal gene can also lose the normal structure (e.g., due to age) and deposit amyloid deposits - this is the wild type [3]. Once regarded as a rare curiosity, ATTRwt is now recognised as an important and underdiagnosed cause of heart failure with preserved ejection fraction, restrictive cardiomyopathy, conduction disturbances, and peripheral or autonomic neuropathy. Epidemiological data suggest that a significant proportion of elderly patients with unexplained increased left ventricular wall thickness or bilateral carpal tunnel syndrome may in fact suffer from unrecognised ATTR cardiomyopathy. Transthyretin amyloidosis can produce nonspecific symptoms and is sometimes difficult to diagnose, especially in the younger patient population. This requires diagnostic vigilance and the cooperation of multiple specialists.

Symptoms

In the case of transthyretin amyloidosis, amyloid deposits can affect various tissues and organs. However, the primary symptoms are often related to cardiac involvement. A hallmark of ATTR is left ventricular (LV) hypertrophy, which can be observed through imaging studies, although it typically does not correlate with electrocardiogram (ECG) changes, especially in the early stages. Patients commonly experience heart failure with preserved ejection fraction (HFpEF), restrictive cardiomyopathy, and arrhythmias, particularly supraventricular arrhythmias (SVT) such as atrial fibrillation (AF) and atrioventricular conduction disturbances [4]. Episodes of hypotonia and orthostatic syncope may also occur, along with apparent improvements in disease management in individuals treated for hypertension, which can be linked to the involvement of the autonomic nervous system[5].

Extracardiac manifestations of amyloidosis frequently indicate nervous system involvement, with polyneuropathy and bilateral carpal tunnel syndrome being among the most prevalent issues. Additionally, there is an increased risk of biceps brachii muscle rupture.

Consequently, the symptoms of this disease are often nonspecific, making it essential for healthcare providers to remain vigilant and inquisitive when considering further diagnostic evaluations for their patients.

Table 1. Symptoms of transthyretin amyloidosis[5]

ATTR cardiac symptoms	Extracardiac symptoms of ATTR
• Symptoms of heart failure • Orthostatic hypotonia • Atrial fibrillation • Supraventricular arrhythmias • Atrioventricular conduction disturbances • Myocardial thickening on imaging • Left ventricular diastolic dysfunction	• Bilateral carpal tunnel syndrome • Rupture of the tendon of the biceps arm muscle • Muscle weakness • Family history of polyneuropathy

Diagnostics

Diagnosis of transthyretin amyloidosis is a complex process that requires multiple tests including endomyocardial biopsy in some situations. Currently, when cardiac amyloidosis (CA) is suspected, the first diagnostic step should be to exclude light chain (AL) amyloidosis. To do this, laboratory tests are performed. This is done through laboratory tests, primarily:

- Serum free light chains (FLC),
- Serum protein immunofixation with electrophoresis (SPIE),
- Urine protein immunofixation with electrophoresis (UPIE).

If the results of all three tests are negative, there is a very high probability that light chain amyloidosis can be ruled out [6].

Currently, there are no laboratory tests specific for ATTR amyloidosis, despite ongoing research to develop them. The use of markers typical in heart failure such as brain natriuretic peptide (BNP) and cardiac troponins may be of some interest. Their elevated levels can be significantly elevated even early in the disease, often much more so than imaging studies performed would suggest.

Echocardiography is the primary imaging study used due to its availability. In the initial stages of the disease, echocardiographic changes can be subtle and nonspecific. The most frequently observed changes include an increase in left ventricular muscle thickness accompanied by impaired systolic function, atrial hypertrophy, and elevated filling pressures linked to impaired diastolic function. Less common clinical manifestations may include right ventricular hypertrophy, intracardiac thrombus, thickening of the atrial septum and valves, and pericardial effusion [7]

Table 2. Echocardiographic features of cardiac amyloidosis [4]

<table>
<tr><th colspan="2">Unexplained LV thickness (at least 12mm) and at least one of the following conditions:</th></tr>
<tr><th>Characteristic echocardiography findings at least 2 of:</th><th>Multiparametric echocardiographic score at least 8 points</th></tr>
<tr><td>Grade 2 or worse diastolic dysfunction</td><td>Relative LV wall thickness (IVS + PWT)/LVEDD greater than 0.6
- 3 points</td></tr>
<tr><td>Reduced wave velocities s', e', a' 5 cm/sec.</td><td>E/e' wave ratio greater than 11
- 1 point</td></tr>
<tr><td rowspan="3">Decreased global longitudinal left ventricular strain less than - 15%</td><td>TAPSE 19 mm or less
- 2 points</td></tr>
<tr><td>Absolute value of global LV longitudinal strain 13% or less
- 1 point</td></tr>
<tr><td>Peak systolic-to-basal longitudinal strain ratio greater than 2.9
- 3 points</td></tr>
</table>

An imaging test that provides significantly higher quality imaging is magnetic resonance imaging (MRI). This method, even though it has been used in cardiology for a relatively short time, allows very accurate imaging and visualization of even very subtle changes, impossible to observe, for example, in echocardiography. The most common changes on MRI are analogous to those seen on echocardiography, typically left ventricular hypertrophy and thickening of the atrial septum and valves. Earlier studies suggested that this hypertrophy was concentric, but thanks in part to the introduction of MRI imaging, newer studies report that asymmetric LV muscle hypertrophy is more common, most often within the interventricular septum. With the progression of the disease and accumulation of amyloid, left ventricular systolic function, which may be preserved in the early stages of the disease, also deteriorates. Late gadolinium enhancement (LGE) imaging is a hallmark of myocardial amyloidosis and includes transmural or subendocardial global post-contrast enhancement. Studies have shown the importance of this imaging modality in assessing the prognosis of patients with myocardial amyloidosis. It has been observed that myocardial changes in the course of these diseases are a kind of continuum, and as more amyloid is deposited, cardiac function changes [8]. Patients with transmural LGE have a much more severe prognosis than patients without LGE features or with subendocardial LGE. However, it is important to note that MRI does not allow differentiation between light chain amyloidosis and ATTR and other, rarer types of amyloidosis. Since in both cases, the study shows deposits with features

of amyloidosis. In this case, it is important to have the previously mentioned laboratory tests that allow to exclude some of the potential differential diagnoses [9]

Table 3. features of cardiac amyloidosis on cardiac magnetic resonance imaging [4]

Characteristic CMR findings the first two must be present
Diffuse subendocardial or transmural LGE
Abnormal gadolinium kinetics
ECV>_0.40% (strongly supportive, but not essential/diagnostic)

Isotope-based tests such as Single Photon Emission Computed Tomography (SPECT) have become a mainstay in the non-invasive diagnosis of ATTR amyloidosis in recent years. Currently used markers are: 99mTcDPD (3,3-diphosphonate-1,2- -propanedicarboxylic acid, 99mTc HMDP (hydroxymethylene diphosphonate,) and 99mTcPYP (pyrophosphate), now recognized as specific ATTR-related cardiomyopathy. It is worth noting, however, that despite the high specificity of these tests are not 100% sensitive, in some patients with a confirmed diagnosis of ATTR these tests give a false negative result. 99mTc-methylene diphosphate (MDP) has also been used in the past for ATTR testing. However, later studies have shown that this radionuclide, compared to others, is far less sensitive and specific [10]. The utility of radioisotope testing in diagnosing ATTR amyloidosis was highlighted in a study conducted by Perugini et al. in 2005. This research involved 25 patients with confirmed cardiac amyloidosis -15 with ATTR and 10 with AL - alongside 10 healthy individuals. The study showed significant uptake of 99mTc-3,3-Diphosphono-1,2-Propanodicarboxylic in all patients with ATTR, while no uptake was observed in the AL patients or the healthy subjects. This investigation proposed a visual assessment scale for tracer uptake, which remains in use today and is commonly referred to as the Perugini scale. The scale evaluates tracer uptake in both the bone and the heart. The specific components of this scale can be found in Table 4 [11]. A meta-analysis of 6 papers on the subject by Treglia et al. which included 529 patients evaluated the sensitivity and specificity of radioisotopic testing using technetium for the diagnosis of ATTR amyloidosis. This work showed a very high specificity of 95.4% and a sensitivity of 92.2% for this method. The authors also noted the significant heterogeneity between the various tests. This was due to the different study protocols, techniques, populations included in these studies, and some subjectivity in the visual assessment of the Perugini scale [12]. Studies are currently underway to evaluate the utility of 18F-sodium fluoride positron emission tomography (18F-NaF PET/CT) as an alternative to SPECT. One of the first such studies was conducted by Zhang et al. Twelve patients with ATTR-CA and five healthy patients were included in the study. The patients underwent 18F-NaF PET/CT with imaging one hour and three hours after administration of the radiolabel and then compared the results with a previously performed SPECT study. It turned out that despite the high specificity and lack of false-positive results after PET, the sensitivity was well below that of SPECT and was only 25% at 1 hour and 30% when assessed at 3 hours after administration of the tracer [13].

Table 4. Perugini scale

Scale score	**Comparison of uptake by heart and bone**
0	absent cardiac uptake and normal bone uptake
1	mild cardiac uptake, inferior to bone uptake
2	moderate cardiac uptake accompanied by attenuated bone uptake
3	strong cardiac uptake with mild/absent bone uptake

Despite significant advances in the development of non-invasive techniques, still, the test that allows definitive confirmation of transthyretin amyloidosis is histopathological examination. It is possible to evaluate the fragment of various organs however, the sensitivity varies considerably. The test with the highest reliability is the histopathological examination of a fragment of myocardium taken by endomyocardial biopsy. However, the collection of such a slice is fraught with the risk of serious complications, so sometimes samples of other organs are taken.

Table 5. Sensitivity of organ biopsies in the diagnosis of ATTR wild-type amyloidosis and ATTR associated with genetic variant

Type of biopsy	Sensitivity in the detection of ATTRv	Sensitivity in the detection of ATTRwt
Endomiocardial biopsy	99%	99%
Subcutaneous tissue biopsy	73%	25%
Gastrointestinal biopsy	74%	57%
Combination biopsy of subcutaneous tissue and gastrointestinal tract	94%	66%

The stain used to evaluate amyloid deposits by optical microscopy is Congo red. It is possible to see extracellular deposits stained red or pink. A characteristic of amyloid is birefringence under polarized light in which deposits were typically described as apple-green. However, recent guidelines from the International Society of Amyloidosis have highlighted that the color of amyloid deposits under polarized light can also be different, red, yellow, and green. This variability depends on the spatial distribution and orientation of amyloid fibrils within the tissue [14]. Other methods that make it possible to evaluate histopathological material for amyloidosis are mass spectrometry and immunohistochemical (IHC) studies. Spectrometry is currently considered the best method to diagnose CA, but it is not available at every site due to the availability of the required equipment and the high price. For this reason, results based on immunohistochemistry are also accepted if performed in experienced centers. Immunoelectron microscopy (IEM) is another method that can diagnose CA with the highest sensitivity and specificity of more than 99%. This technique combines elements of IHC and electron microscopy. This method, despite its very high sensitivity, is virtually unused in clinical practice due to poor availability and high price [15].

Table 6. Comparison of histopathological methods in CA

Method	Sensitivity	Comments
Immunohistochemistry (IHC)	76%	A method widely available and relatively inexpensive. It is a subjective method, the risk of false positives or false negatives. Lower quality in non-expert centers
Immunofluorescence (IF)	85%	For some types of amyloidosis, greater sensitivity. Requires frozen samples, less availability than IHC. interpretation may still be subjective
Laser Capture Microdissection with Mass Spectrometry (LCM-MS)	94-100%	Currently the gold standard. High sensitivity and specificity. Expensive method, requires highly specialized equipment and personnel. Less available than IF and IHC
Immunoelectron Microscopy (IEM)	>99%	Highest sensitivity. Time-consuming, technically demanding, expensive method. Very limited availability. Used in research and when other methods are inconclusive

Given the potential genetic basis of the disease, sequencing of the TTR gene remains an important part of diagnosis. This is a test that is of particular importance in cases:

- ATTR-related cardiomyopathy
- Familial amyloid polyneuropathy
- In 1st-degree relatives of individuals with a confirmed diagnosis of the genetic form of ATTR

Genetic testing plays a crucial role in distinguishing between the genetic variant-related form of ATTR (ATTRv) and the wild type. These diagnoses are particularly important for the relatives of patients, as they may be able to detect the disease in themselves before symptoms appear. Siblings of patients diagnosed with

ATTRv can especially benefit from genetic testing, as it allows for the potential identification of the disease at a stage when symptoms are still nonspecific.

For the offspring of affected patients, identifying a pathological variant of the TTR gene can occur even before any clinical symptoms develop. In such cases, it is advisable to assess the patient's clinical symptoms approximately 10 years prior to the expected onset of symptoms.

It is important to note that the presence of a gene variant of uncertain significance does not automatically indicate a diagnosis of ATTRv. Consequently, genetic testing should not be performed on the relatives of patients with such a variant.

Treatment

In the treatment of myocardial amyloidosis, we distinguish two directions: symptomatic treatment - in particular, the symptoms of heart failure, and causal treatment aimed at stopping the progression of the disease.

Currently, the only drug registered for the causal treatment of the cardiac form is Tafamidis. This medication operates by stabilizing the structure of transthyretin, effectively preventing the formation of protein monomers that accumulate in tissues. While Tafamidis slows disease progression, it does not reverse existing changes. Therefore, it is particularly important to quickly and effectively diagnose this disease. The drug is the mainstay of treatment of transthyretin amyloidosis according to the guidelines of the European Society of Cardiology and is mentioned by the Expert Position of the Polish Cardiac Society on the diagnosis and treatment of cardiac transthyretin amyloidosis [5,6]. A study by Maurer et al that included 441 patients with transthyretin amyloidosis showed the drug's effectiveness in reducing all-cause mortality among patients compared to placebo. At 30-month follow-up, mortality was 78 of 264 (29.5%) among patients using Tafamidis vs. 76 of 177 (42.9%) among patients in the placebo group. Less deterioration in the 6-minute walk test was also observed in the group using Tafamidis. The incidence of side effects was similar in both groups, demonstrating the safety of this drug [16].

For the form of the disease associated with the genetic variant in the course of which polyneuropathy is present, drugs with a different mechanism of action - gene silencing drugs such as patisiran or inotersen - have been used. These drugs affect the production of the defective protein in the liver through small interfering RNA (siRNA) which leads to the degradation of the RNA responsible for TTR production. These drugs are currently registered for the treatment of polyneuropathy in the course of ATTRv however, some studies show their potential effect also on cardiomyopathy in the course of ATTR [17]. The Apollo-B study evaluated the efficacy of ATTR cardiomyopathy Patisiran for both ATTRv and ATTRwt forms. The study enrolled 360 patients, who were randomly assigned to receive either patisiran (181 patients) or a placebo (179 patients). Patients were followed up for 12 months. After this period, they were reevaluated. Statistically significant differences were observed in the decrease in the distance in the 6-minute walk test: -8.15m for Patisiran vs -21.35m in the placebo group p=0.02, and in the Kansas City Cardiomyopathy Questionnaire - Overall Summary (KCCQ-OS) score for assessing the quality of life: increased by 0.3 in the Patisiran group and decreased by 3.4 in the placebo group, (p=0.04). There were 5 deaths (3%) in the patisiran group and 8 (4%) in the placebo group, a difference that was not statistically significant. Furthermore, the incidence of side effects was similar between both groups, indicating the safety profile of Patisiran [18]. Currently, only drugs whose mechanism is to reduce amyloid accumulation are available, but they do not affect already formed deposits. Clinical trials are underway to develop drugs that could lead to the removal of already formed lesions. Such treatment would be highly applicable to patients whose disease is already at an advanced stage. The possibility of immunotherapy seems particularly promising in this regard. In the case of ATTR, high hopes are pinned on PRX004, which is in the early stages of clinical trials [19].

The phase 1 study of this monoclonal antibody included 21 patients with ATTRv. Patients had a gradual dose increase every 28 days (0.1, 0.3, 1, 3, 10 or 30 mg/kg) followed by Long-Term Extension of up to 15 additional doses in some patients. All patients successfully completed the dose escalation phase without reaching the Maximum Tolerated Dose (MTD) or dose-limiting toxicities (DLT). After a minimum of 9 months, myocardial function assessed by Global Longitudinal Strain (GLS) and neuropathy by Neuropathy Impairment Score (NIS) were also evaluated, observing improvement in 7 patients. No grade 4 or 5 adverse effects were observed. Due to its safety and potential efficacy, the drug was referred to phase 2 clinical trials [[20]].

Symptomatic treatment of patients with ATTR cardiomyopathy is a complex problem due to the severe symptoms of the disease and the limitations associated with the safety of many drugs in the course of this disease. An important example of these complications is the treatment of heart failure in patients with CA. It

is one of the most common manifestations of the disease but its treatment is significantly more difficult compared to patients with HF without amyloidosis. Angiotensin-converting enzyme inhibitors (ACEIs), angiotensin II receptor antagonists (ARBs), angiotensin receptor-neprilysin inhibitor (ARNI) and B-receptor antagonists are discouraged or should be used with extreme caution because of the risk of exacerbating hypotension due to autonomic neuropathy. On the other hand, calcium channel blockers are absolutely contraindicated because they irreversibly bind to amyloid fibrils. In the case of digoxin, the situation is similar - this drug can bind to amyloid fibers and accumulate, leading to increased toxicity. However, in the case of digoxin, it is possible to use this drug, but with extreme caution and only in carefully selected patients [21].

It is important to recognize that cardiac amyloidosis is a highly prothrombotic condition. Increased thromboembolic risk is present in patients even when sinus rhythm is maintained [22]. Typical thromboembolic risk assessment scales should not be used in cases of atrial fibrillation. It has been shown that thrombi in the left atrial appendage can also occur in patients with a low CHADS-VASc score. For patients with CA, it is worth considering transesophageal echocardiography before planned cardioversion, regardless of the risk assessment using the scales [23].

Another important component of symptomatic treatment in patients with CA is the evaluation of indications and possible implantation of cardiac implantable devices (CIED). Patients with ATTR may have indications for both pacemaker (PM) implantation for atrioventricular conduction disturbances and implantable cardioverter defibrillator (ICD) implantation for secondary prevention due to ventricular arrhythmias.

Conclusions

Transthyretin amyloidosis is a challenging and often underdiagnosed disease that presents with many non-specific symptoms. Early referral for appropriate diagnostic tests is crucial for effective diagnosis. Raising awareness among physicians of the disease's symptoms is essential, as it can lead to an earlier diagnosis and allow for the initiation of disease-modifying treatments before serious complications arise. Diagnosis of this disease is a complex process that requires knowledge of the available tests and their limitations and the cooperation of many specialists: cardiologists, radiologists, pathologists, and others. This knowledge is especially important for physicians early in their careers. Special attention should be paid to imparting this knowledge to medical students in clinical classes during their studies. The recent introduction of causal treatment in the form of Tafamidis was a turning point in the treatment of patients with transthyretin amyloidosis. Before the introduction of this drug, only symptomatic medications were available. Work is currently underway to introduce even more effective drugs.

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