Experts' opinion

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The scintigraphic diagnosis of cardiac amyloidosis. An expert opinion endorsed by the Section of Nuclear Medicine of the Polish Cardiac Society and the Polish Nuclear Medicine Society

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Abstract

Amyloid transthyretin cardiomyopathy is a progressive disease that confers significant mortality. While it is relatively rare, the frequency of diagnoses has risen with the increased contribution of novel diagnostic approach over the last decade. Traditionally tissue biopsy was considered to be a gold standard for amyloidosis diagnosis. However, there are significant limitations in the wide application of this approach. A noninvasive imaging-based diagnostic algorithm has been substantially developed in recent years. Establishing radionuclide imaging standards may translate into a further enhancement of disease detection and improving prognosis in the group of patients. Therefore we present in the following document current evidence on the scintigraphic diagnosis of cardiac transthyretin amyloidosis. Moreover, we present standardized protocol for the acquisition and interpretation criteria in the scintigraphic evaluation of cardiac amyloidosis.

KEY words: transthyretin amyloidosis; cardiomyopathy; scintigraphy

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Transthyretin amyloidosis as an underdiagnosed cause of heart failure

Amyloid cardiomyopathy (CA) is relatively rare, however, the frequency of diagnoses has risen with the increased contribution of novel diagnostic approach over the last decade [1]. There are numerous pathogenic proteins that may cause the disease. Two subtypes account for more than 90% of CA cases — light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) [2]. Distinguishing between AL and ATTR is critical as these diseases have different pathogenesis and are treated differently by cardiologists (ATTR) and hematologists (AL). Importantly, two main subtypes of ATTR exist wild-type ATTR (wtATTR) and hereditary ATTR (hATTR). In the case of wtATTR, the transthyretin (TTR) protein gradually deposits in form of amyloid fibers over a period of time. In contrast, patients with hATTR are born with a pathologic TTR genetic variant, leading to accelerated amyloid deposition. The mechanism of the disease includes destabilization of the TTR tetramer structure, the misfolded protein then assembles in a highly ordered

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fashion to form fibrils that accumulate in the interstitial space. In 70% of ATTR cases, amyloid deposits occur in the heart, leading to the development of CA [3]. For both types of ATTR, the pathomorphological signs include thickened cardiac muscle with alterations of the valves structure, developing as a result of amyloid fibers replacing cardiac tissues. Moreover, common extracardiac sites of involvement and associated manifestations include the kidneys, liver, gastro-intestine tract, tongue, and the nerves of both the autonomous and peripheral nervous systems [4].

The clinical presentation of ATTR CA includes heart failure with preserved ejection fraction (HFpEF), hypertrophic (HCM) ,and restrictive cardiomyopathies (RCM). Despite being considered a rare disease, ATTR amyloidosis may be more prevalent than suspected, particularly in the elderly population. Amyloidosis is often disguised as HCM presenting with increased myocardial thickness, mass, or altered structure of valves. It is essential that cardiologists are aware of this disease because, in most patients, the presentation of the disease is mainly cardiological (HCM/RCM and/or HFpEF). HCM is a complex and relatively common myocardial disorder characterized by primary left ventricular hypertrophy. The guidelines include recommendations for HCM diagnosis, especially the use of bone scintigraphy with 3,3-diphosphono-1,2,-propanodicarboxylic acid (DPD) in patients with symptoms or who have non-invasive test results suggesting ATTR [5]. The degree of heart involvement determines the prognosis of the disease, and thus the earlier it is diagnosed, the better the survival rates for the patients [6].

The history of ATTR CA shows that while it is a rare, progressive disease, it is more common than previously thought. According to recent studies, 13% of hospitalized HFpEF patients had wtATTR [7], 5% of patients diagnosed with HCM had hATTR [8], and 5% of patients with severe low flow aortic stenosis had wtATTR [9]. The prevalence of the disease was also investigated by a population-based study of HFpEF patients and resulted in the diagnosis of ATTR in 7% of patients diagnosed with active isotope screening [10]. Another study revealed that the incidence of wtATTR and hATTR was 155–190 per million and 5 per million, respectively [11]. Until now, all forms of the disease may have been underdiagnosed due to the lack of targeted treatment available, although new therapies that improve survival may change this situation. [12].

In our opinion, it is necessary to further enhance ATTR detection, mainly by raising awareness of the occurrence of the disease. The diagnostic difficulties are a result of the lack of characteristic symptoms in the early phase of the disease that might be called "a great pretender". Symptoms are non-specific, similar to CHF (congestive heart failure). Some factors that serve as clinical guidelines for the diagnosis are referred to as "red flags". The main red flags for wtATTR are cardiological symptoms such as HFpEF, left ventricle hypertrophy, lack of hypertrophy in electrocardiogram (ECG), and cardiac arrhythmias [13]. A vast number of patients present with carpal tunnel syndrome. Most patients suffer from progressive intolerance to standard CHF therapy. Furthermore, there is a disproportion between QRS in ECG and the degree of hypertrophy in echocardiographic examination. Additionally, autonomic nervous system dysfunction appears in the late stage of the disease. To sum up, there should remain a high index of suspicion and diagnostic vigilance during initial diagnosis, patients who present with red flags specific to the disease should be referred for further radioisotope testing. Diagnostic process involves cooperation between cardiologists, hematologists, nephrologists, nuclear medicine specialists, and other specialties. As the nature of the disease is complex, the screening of patients who are genetically burdened or have a family history of amyloidosis is of great significance.

There is significant progress in treatment, as disease-modifying therapies are now available [13]. Tafamidis, a transthyretin stabilizing agent, has been shown to reduce mortality in patients with ATTR cardiomyopathy [12]. The treatment is especially effective if used in the early stage of the disease when the heart has not yet suffered irreversible damage. Hence, early diagnosis is a vital factor. Tafamidis is currently the only drug that has shown efficacy in a randomized trial in patients with ATTR cardiomyopathy, and is recommended in this group of patients in both the hATTR and wtATTR [12, 13]. In selected patients with isolated polyneuropathy tafamidis or gene silencers (patisiran, inotersen) may be considered as treatment options according to current guidelines [13]. Moreover, multiple therapies are currently investigated for ATTR patients [13].

Diagnostic algorithm for ATTR cardiomyopathy

While biomarkers are not included in the diagnostic recommendations, the majority of patients have them checked at the beginning of the diagnostic route. Echocardiography examination is of great importance [13]. Echocardiography may provide incremental information on the current stage of the disease, and show typical lesion associated with CA — increased echogenicity of the heart muscle, thickening of valves and ventricle walls, and impairment of diastolic function [14]. Generally, all echocardiographic abnormalities suggesting cardiac amyloidosis should be the starting point for further research. The most pathognomonic symptom of ATTR visible on echocardiography is the "apical sparing" pattern delivered from the evaluation of the global longitudinal strain (GLS) [15]. Nevertheless, this examination requires high levels of experience. Equally, cardiovascular magnetic resonance imaging (CMR) may be helpful as it enables differentiation between amyloidosis, HCM, and hypertrophy in the course of other diseases [13].

Traditionally tissue biopsy was considered to be a gold standard for amyloidosis diagnosis [16]. However, there are significant limitations in the wide application of this approach — the limited experience of pathologists regarding ATTR, underdiagnoses derived from adipose tissue sampling, the difficulty of immunohistochemical typing, and the low availability of mass spectrometry. In most patients, the presentation of ATTR is including cardiac involvement. Thus, advances in cardiac multimodality imaging were an impetus for the early diagnosis of ATTR. Importantly, there is a new strategy for noninvasive diagnostics [17]. It entails echocardiographic examination, CMR (late gadolinium enhancement, T1-mapping), and radionuclide bone scintigraphy.

Both invasive and non-invasive diagnostic criteria have been proposed. Invasive diagnostic criteria apply to all forms of cardiac amyloidosis, whereas non-invasive criteria are accepted only for ATTR and AL [18]. The distinction is important because testing positive for amyloid deposits does not determine the exact type of cardiac amyloidosis, and hence an array of tests should be performed according to the diagnostic algorithm. In terms of invasive

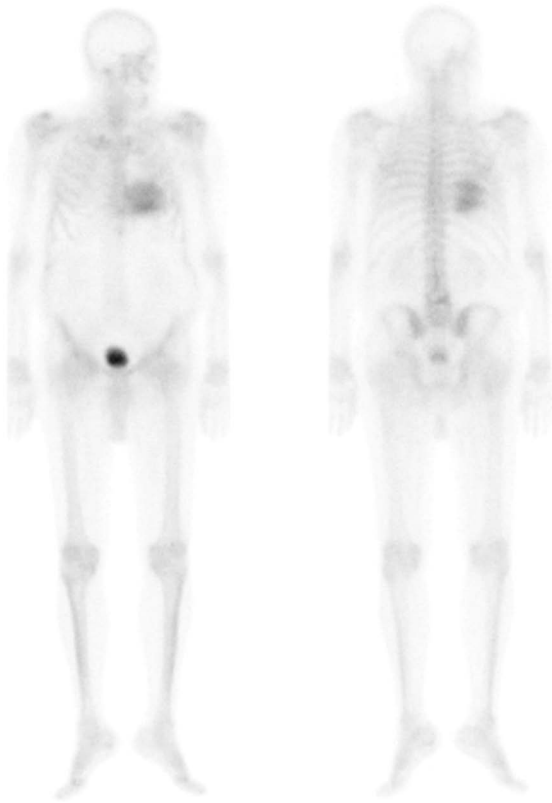

Figure 1. Results of planar whole-body scintigraphy with [^{99m}Tc]Tc-DPD consistent with cardiac amyloidosis (grade 3) in a patient with wtATTR; John Paul II Hospital, Department of Nuclear Medicine, Krakow, Poland

methods, the diagnosis can be confirmed by cardiac biopsy or if amyloid deposits within the tissue from an extracardiac biopsy are accompanied either by the characteristic features of CA by echocardiography or CMR [13]. For the non-invasive methods, ATTR can be confirmed with scintigraphy, serum-free light chain (FLC) assay, serum (SPIE), and urine (UPIE) protein immunofixation. Currently, positive scintigraphy indicates a high probability of ATTR [19]. Regardless, it is always necessary to perform biochemical diagnostics: the evaluation of FLC assay, SPIE and UPIE. Evaluation of those is necessary to differentiate between ATTR (negative results for monoclonal proteins in blood and urine) and AL. However, it is necessary to refer all patients with positive FLC assay, SPIE or UPIE results for hematological evaluation, in order to differentiate MGUS (monoclonal gammopathy of undetermined significance) or AL amyloidosis.

Patients who present with either clinical symptoms or CMR or echocardiography results suggestive of amyloidosis should be referred for scintigraphy with bone-seeking tracers labelled with [^{99m}Tc]Tc. Cardiac scintigraphy with [^{99m}Tc]Tc-PYP (pyrophosphate)/DPD (3.3-diphosphono-1.2-propanodicarboxylic acid)/HMDP (hydroxymethylene diphosphonate) ought to be considered in all patients with unexplained LV hypertrophy, HFpEF, familial amyloid polyneuropathy, family history of amyloidosis and an elderly patient's history of low-grade aortic stenosis. Myocardial imaging with [^{99m}Tc]Tc-PYP/DPD/HMDP is a very sensitive and specific test for the diagnosis of ATTR cardiac involvement and may help in its early detection [13, 18]. Since the uptake of radiotracers is different in normal myocardium and myocardium affected by amyloid, this diagnostic method is highly accurate, especially for ATTR. The Perugini grading scale is a widely recommended method of scoring the tracer uptake (Fig. 1) [20, 21]. Despite the fact that myocardial [^{99m}Tc]Tc-PYP/DPD/HMDP uptake correlates with left ventricle wall thickness and cardiac biomarkers, the visual grading scale has not been shown to be an independent predictor of outcomes [18, 22]. The results scintigraphy test can be assessed according to Perugini grading scale while imaging with [^{99m}Tc]Tc-PYP/DPD/HMDP or heart/contralateral lung (H/CL) uptake ratio for [^{99m}Tc]Tc-PYP, defined as the fraction of heart region of interest (ROI) mean counts to contralateral lung ROI mean counts. Interpretation of the examination may be positive (scale ≥ 2 or H/CL ≥ 1.5 with obligatory SPECT confirmation), neutral (scale 1 with H/CL 1–1.5), or negative (0 with H/L< 1) [18]. In the absence of light chains, heart uptake ≥ 2 eliminates the need for an endomyocardial biopsy and ATTR diagnosis can be confirmed. To distinguish hereditary from wild-type amyloidosis a genetic test should be performed. If there is no cardiac uptake in scintigraphy and monoclonal protein is detected, AL amyloidosis should be ruled out. Otherwise, beyond these two clinical scenarios, an endomyocardial biopsy may be performed for diagnosis confirmation in histopathological tests.

Importantly, pyrophosphate has a high affinity to calcium accumulates in the cells that have been impacted by necrosis. Thus, elevated myocardial tracer uptake can be seen in various conditions of myocardial injury, including pericarditis. Additionally, a regional radiopharmaceutical uptake can be seen in the case of muscle damage induced by commonly used chemotherapy agents, or general drug toxicity, and hence the results might be questionable [18].

It has been shown that [^{123}I]MIBG can detect cardiac denervation in patients with cardiac ATTR amyloidosis [18]. Multiple positron emission tomography (PET) tracers have also been investigated in terms of the possibility of their application in the diagnosis of amyloidosis. Carried studies have confirmed their diagnostic value, although the results are not specific for the type of amyloid [18]. They are not currently recommended to be used in the basic diagnostic algorithm. However, several recent studies suggest a promising role for amyloid PET radiopharmaceuticals to image CA, and several PET tracers are now tested for in vivo detection of amyloid deposits.

Image acquisition and interpretation

Recommendations on the used activities are in line with the guidelines of the American Society of Nuclear Cardiology (ASNC) and the European Association of Nuclear Medicine (EANM) (Tab. 1) [18, 20]. Various activities are recommended by different scientific bodies, with the lowest being 370 MBq and the highest 740 MBq. The guidelines allow that individual centers modify imaging procedures based on local conditions and expertise. The time between injection and acquisition is 2–3 hours, after which a planar whole-body and the SPECT or SPECT/CT is performed (Fig. 2). The specific planar whole-body imaging should be mandatory as it is especially useful for the visual interpretation and quantification of the degree of myocardial uptake. We would like

Table 1. Recommendations for standardized acquisition for scintigraphy with [^{99m}Tc]Tc-PYP/DPD/HMDP for cardiac amyloidosis

Imaging procedures	Recommendation
Preparation	No fasting required
Scan type	Rest scan
Activity of ^{99m}Tc	370–740 MBq (10–20 mCi) intravenously
Time between injection and acquisition: ^{99m}Tc-PYP/DPD/HMDP	2–3 h
Position	Supine
Energy window	140 keV, 15–20%
Collimators	Low energy, high resolution
Whole-body planar imaging	
Views	Anterior (or anterior-and-posterior)
Image duration	Maximum 20 cm per minute
Matrix size	256 × 1024
Planar imaging	
Number of views	Anterior and lateral
Detector configuration	90°
Image duration (count based)	750,000 counts
Matrix size	256 × 256
SPECT imaging	
Angular range/detector configuration	180°/90° or 360°/180°
Number of views/detector	minimum 32
Matrix size	128 × 128
Time per stop	20 s/25 s (may be corrected according to the administered activity)

DPD — 3.3-diphosphono-1.2-propanodicarboxylic acid; h — hour; HMDP — hydroxymethylene diphosphonate; keV — kiloelectronvolt, MBq — megabecquerel; mCi — millicurie; PYP — pyrophosphate; s — second; SPECT — single-photon emission computed tomography

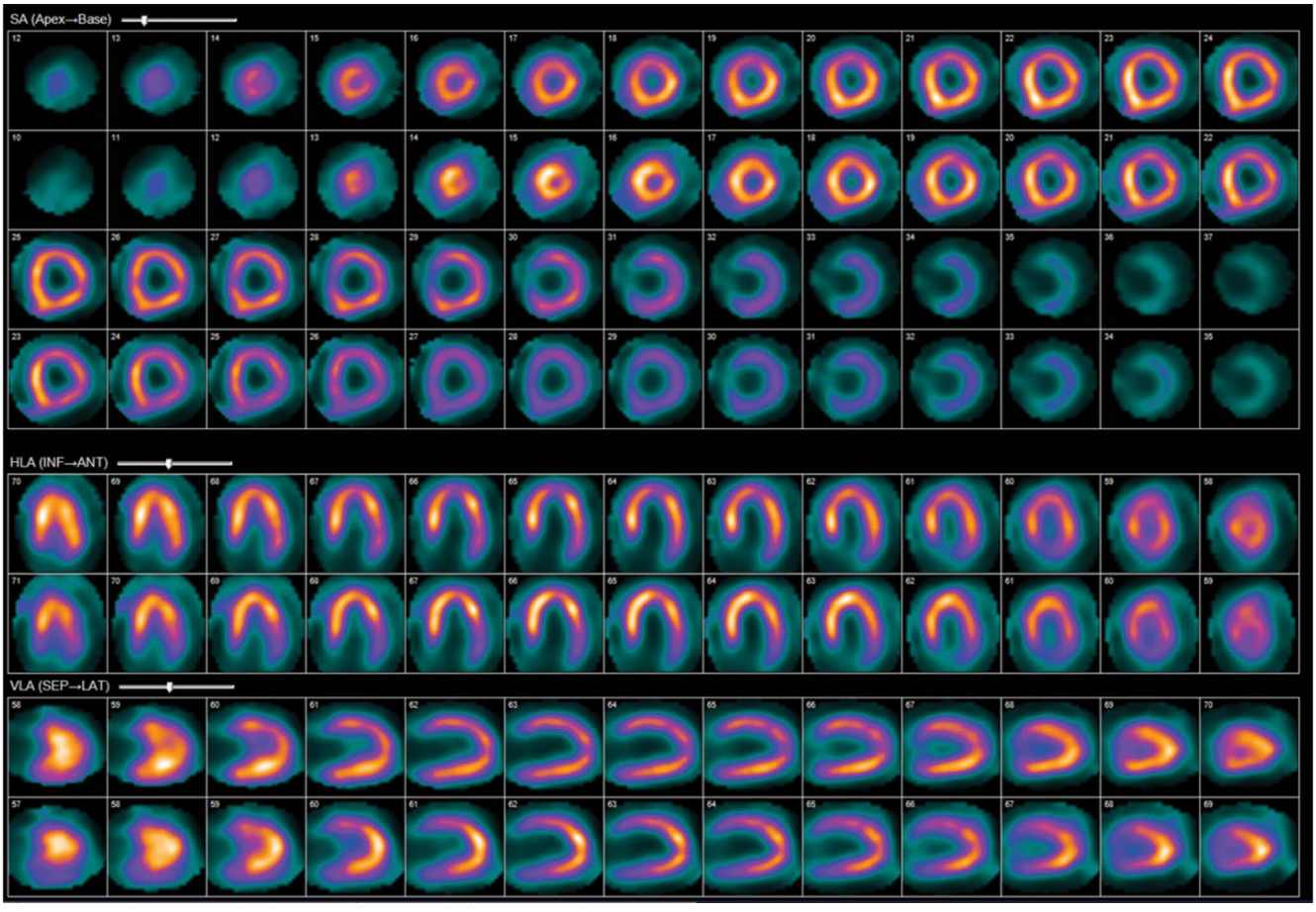

Figure 2. Results of SPECT imaging with [^{99m}Tc]Tc-DPD consistent with cardiac amyloidosis in a patient with hATTR (the upper rows in a given series are shown without attenuation correction, and the lower ones present results after attenuation correction); John Paul II Hospital, Department of Nuclear Medicine, Krakow, Poland

Table 2. Recommendations for interpretation of scintigraphy with [^{99m}Tc]Tc-PYP/DPD/HMDP for cardiac amyloidosis

[^{99m}Tc]Tc-PYP/DPD/HMDP uptake grading	
Grade 0	No myocardial uptake and normal bone uptake
Grade 1	Myocardial uptake less than rib uptake
Grade 2	Myocardial uptake equal to rib uptake
Grade 3	Myocardial uptake greater than rib uptake with mild/absent rib uptake
Heart/contralateral lung (H/CL) uptake ratio (the fraction of heart ROI mean counts to contralateral lung ROI mean counts) assessment for [^{99m}Tc]Tc-PYP	
H/CL ≥ 1.5	Positive (with SPECT confirmation)
H/CL 1–1.5	Neutral
H/L < 1	Negative

DPD — 3.3-diphosphono-1.2-propanodicarboxylic acid; H/CL — heart/contralateral lung; HMDP — hydroxymethylene diphosphonate; ROI — region of interest; SPECT — single-photon emission computed tomography; PYP — pyrophosphate

to stress the importance of including the description of the scintigraphy changes in soft tissues and bone structures while reporting the whole-body and planar images.

The procedure may be performed with the application of the following markers [^{99m}Tc]Tc-PYP/DPD/HMDP. According to the diagnostic algorithm of the nonbiopsy diagnosis of cardiac transthyretin amyloidosis, the results of bone scintigraphy with [^{99m}Tc]Tc-PYP/DPD/HMDP classify patients into 4 grades (0, 1, 2 and 3). The interpretation of the results is shown in Table 2. In patients suspected of CA the grade 2 or 3 [^{99m}Tc]Tc-PYP/DPD/HMDP uptake (in the absence of free immunoglobulin light chains in blood and urine) is highly specific for ATTR and the patient does not require a tissue biopsy to confirm the diagnosis. Importantly, the SPECT or SPECT/ CT scans enable a better assessment of amyloid deposits in cardiac region.

Experience and future directions

Lack of standardized procedure constitutes a barrier to disease detection in local setting. The problem may be solved by implementing the recommendations for performing scintigraphy for amyloidosis, which could be used in both hospitalized patients and during outpatient visits. It is crucial to include planar whole-body and SPECT or SPECT/CT scans, in line with the nuclear imaging guidelines. Another critical action that might positively contribute to accessing scintigraphy is raising awareness among medical professionals of the diagnostic procedures by cooperation between nuclear medics and other specialists. There is a need for cross-departmental cooperation, that would lead to a proper referral for scintigraphy, based on pretest probability assessment, including biomarkers and imaging results. Overall, establishing radionuclide imaging guidelines will translate into further enhancement of disease detection and improving prognosis in the group of patients with suspicion of CA.

Conflict of interest

The authors have no conflicts of interest to disclose.

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