Position statement on the non-invasive diagnosis of patients with ATTR cardiac amyloidosis, endorsed by the Hellenic Society of Nuclear Cardiology, for the Nuclear Medicine practitioners

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Cardiac amyloidosis is a rare condition characterized by the accumulation of abnormal proteins called amyloids in the heart tissue [1]. These amyloids can disrupt the normal functioning of the heart and lead to a variety of symptoms and complications [2]. Some essential information about cardiac amyloidosis is as follows:

Types

There are different types of amyloidosis, but the two most common ones, that can affect the heart tissue, are AL amyloidosis and ATTR amyloidosis [3].

AL amyloidosis

This type is caused due to the abnormal production of light chains immunoglobulin by plasma cells in the bone marrow. It is also known as primary amyloidosis and can affect various organs, including the heart [4].

ATTR amyloidosis

ATTR stands for "transthyretin amyloidosis." Transthyretin (TTR or TBPA) is a transport protein in the plasma and cerebrospinal fluid, that transports the thyroid hormone thyroxine (T4) and retinol to the liver. There are two main forms of ATTR amyloidosis [5]:

Hereditary ATTR (hATTR): This form is caused by genetic mutations that lead to the production of abnormal transthyretin protein. It tends to run in families [6].

Wild-type ATTR (wtATTR): This form occurs when the normal transthyretin protein misfolds and forms amyloids that are deposited at the heart tissue. Typically affects older individuals; it is the most common variant and is not inherited [7, 8].

Symptoms

The symptoms of cardiac amyloidosis can vary but often include [2]:

- Fatigue
- Shortness of breath
- Swelling in the legs and ankles
- Irregular heart rhythms
- Chest pain
- Fainting or dizziness

Diagnosis

Cardiac amyloidosis can be challenging to diagnose, because its symptoms can mimic those of many other heart conditions [9].

Early diagnosis and management are crucial for improving the quality of life and prognosis for individuals with this condition [10].

The diagnosis of ATTR (transthyretin cardiac amyloidosis) involves a combination of clinical evaluation, laboratory tests, imaging studies, and sometimes a biopsy to confirm the presence of amyloid deposits.

The steps that lead to the diagnosis are:

Clinical evaluation:

- Cardiac Symptoms as dyspnea, poor physical condition, fatigue, ankle edema and ascites, atrial fibrillation, disturbances of impulse conductions [11, 12].

- Non cardiac symptoms as bilateral carpal syndrome, lumbar canal stenosis (also known as red flags) [13].
- Serum and urine protein electrophoresis and immunofixation should always be performed, in order to rule out other causes of protein buildup [14].

Imaging studies

Echocardiography (echo) is commonly used to assess the structure and function of the heart. It can reveal signs of thickened heart walls and reduced cardiac function [15].

Cardiac magnetic resonance imaging (MRI) is highly sensitive for detecting cardiac amyloidosis. It can visualize the amyloid deposits in the heart tissue [15].

Nuclear imaging scans, such as technetium-99m pyrophosphate scintigraphy (PYP scan) or ^{99m}Tc-DPD scintigraphy, are used to detect amyloid deposits in the heart. Nuclear Cardiac Imaging plays a pivotal role in the non-invasive diagnosis of ATTR-Cardiac Amyloidosis and in the differential diagnosis, if cell dyscrasia is excluded [15].

Genetic testing

Genetic testing may be recommended to identify mutations in the transthyretin (TTR) gene, which can confirm the hereditary form of ATTR cardiac amyloidosis [16, 17]. A special topic among genetic aspects is the pre-symptomatic testing, i.e., investigating the relatives of the already affected individuals.

In some cases, an endomyocardial biopsy (EMB) may be performed, to obtain a tissue sample from the heart for establishing the diagnosis. It is an invasive procedure and is typically reserved for cases where non-invasive testing is inconclusive [18].

It's important to note that ATTR cardiac amyloidosis can be challenging to diagnose, due to its nonspecific symptoms and the need for specialized tests. A multidisciplinary team of healthcare professionals, including cardiologists, geneticists, and pathologists, is often involved in the diagnosis making. Early diagnosis is crucial, because treatment options are nowadays available, and early intervention can improve outcome.

Treatment

The treatment of cardiac amyloidosis depends on the type and severity of the condition [15]. Options may include:

- Medications to reduce the production of amyloid proteins or manage symptoms. Currently, only Tafamidis is FDA approved and in use either in Europe and United States.
- Heart transplant in severe cases.
- Emerging therapies, such as RNA interference (RNAi) drugs like Patisiran and Inotersen for hATTR amyloidosis.

Prognosis

The prognosis for cardiac amyloidosis can vary widely. Early diagnosis and appropriate treatment can significantly improve outcomes. However, if the condition is advanced and not treated, it can lead to heart failure and a poor prognosis.

Research

There has been ongoing research into the treatment of cardiac amyloidosis, particularly for ATTR amyloidosis. New therapies are continually being developed, offering hope for better outcomes and prolonging survival.

It's important to consult with a healthcare professional if you suspect that someone may have cardiac amyloidosis. Early diagnosis and management are crucial for improving the quality of life and prognosis for individuals with this condition.

Nuclear imaging

Planar scintigraphy and single-photon emission computed tomography (SPECT or SPECT/CT) are nowadays the cornerstone modalities for distinguishing patients with TTR amyloidosis.

Radiotracers

The most common radiotracers for the diagnosis of TTR amyloidosis include ^{99m}Tc-DPD (diphosphono-1,2propanodicarboxylic acid) and ^{99m}Tc-PYP (pyrophosphate). Both the agents are used in Europe, and only ^{99m}Tc-PYP is currently FDA approved at the United States. Alternatively, during the shortage of ^{99m}Tc-PYP at the States, ^{99m}Tc-HMDP (hydroxymethylene diphosphonate) was proposed as a suitable for TTR imaging radiopharmaceutical. These three radioligands are currently considered to be specific for diagnosing TTR amyloidosis [14, 19].

The uptake mechanism of radiotracers to the myocardium has not been clarified yet. Several hypotheses have been addressed; most probably the radiopharmaceuticals bind to microcalcifications of the affected myocardium. It is actually discovered that microcalcifications are more dense in ATTR than in AL amyloidosis. However, this theory is not always valid, since in some cases, there is no or minimal uptake despite the TTR amyloid existence. The structure of amyloid fibrils may play a role, since almost all the amyloid deposits contain a mixture of C-terminal fragments and full-length TTR (type A amyloid) or only full-length TTR (type B amyloid). Recent studies using pathology proved that type A amyloid express significant ^{99m}Tc-DPD uptake, finding that was not evident in type B fibrils [20].

Planar scintigraphy using ^{99m}Tc-PYP, ^{99m}Tc-DPD, or ^{99m}Tc-HMDP can be combined by semiquantitative or simply qualitative methods. The most common qualitative method is Perugini grading scale, with four scale uptake estimation [21] (Figure 1):

- Grade 0 - no cardiac uptake
- Grade 1 -mild cardiac uptake, inferior to bone uptake
- Grade 2 -moderate cardiac uptake, equal to bone uptake
- Grade 3 -strong cardiac uptake more than bone uptake.

Score 2 or 3 carry a very high sensitivity and specificity for diagnosing TTR cardiac amyloidosis. Currently, in all patients suspected for TTR cardiac amyloidosis, SPECT or preferably SPECT/CT should always be performed to assess myocardial radiotracer distribution and exclude the blood pool interference. Recent studies showed that ^{99m}Tc-PYP, ^{99m}Tc-DPD and

^{99m}Tc-HMDP SPECT have a sensitivity of more than 90% for differentiating ATTR-CM [22-24]. However, cardiac uptake may also be seen in 1 in 5 patients with AL amyloidosis patients [25] (Figure 2).

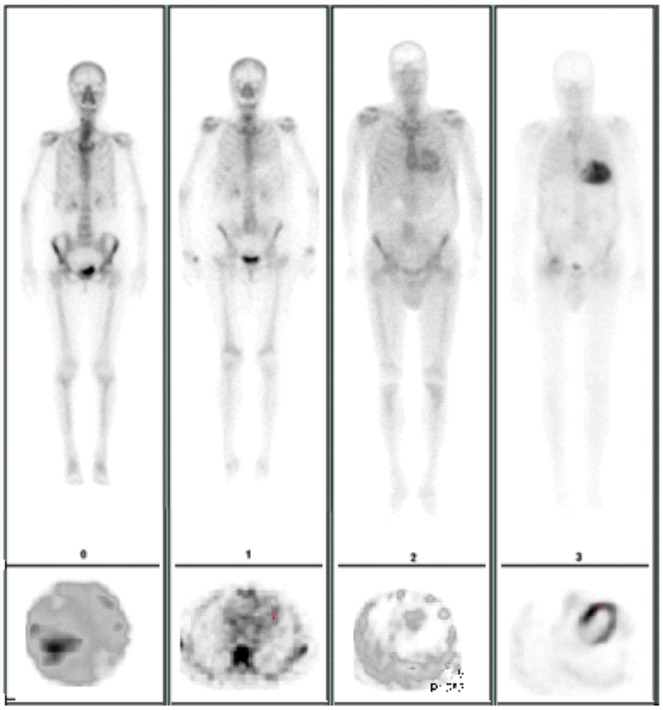

Figure 1. ^{99m}Tc-DPD scintigraphy: radiotracer uptake graded according to the Perugini score [29]. Planar and SPECT images for each corresponding Grade (source: Nuclear Medicine Laboratory, AHEPA Hospital, Greece).

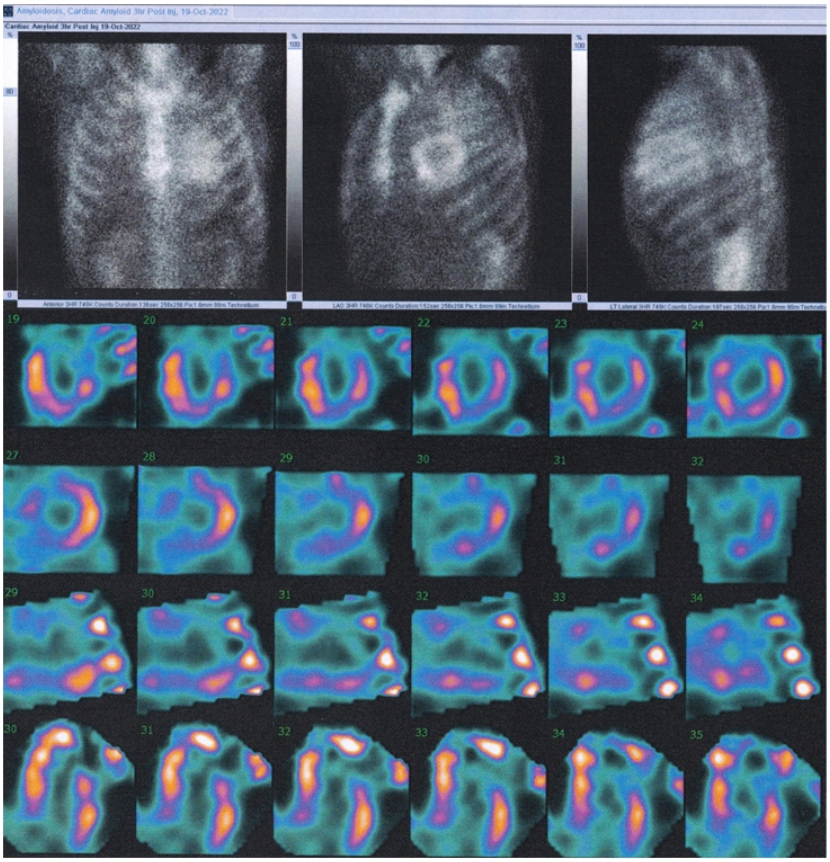

Figure 2. ^{99m}Tc-DPD scintigraphy: radiotracer uptake graded according to the Perugini score [29], Grade: III. Serum and urine-sample analysis revealed light chains, finding consisted with AL amyloidosis (source: Nuclear Medicine Department, Onassis Cardiac Surgery Cente).

In conclusion, Nuclear imaging plays a pivotal role in the diagnosis of ATTR-CM as an essential part of the diagnostic algorithm [14] (Figure 3), assessment of disease severity, and selection of appropriate treatment.

Nowadays the diagnosis of TTR cardiac amyloidosis diagnosis can be established based on the cardiac uptake of the above 3 radioisotopes (^{99m}Tc-PYP, ^{99m}Tc-DPD, and ^{99m}Tc-HMDP) without the need for histological confirmation, provided that the patient fulfills all the following criteria:

- HF with echocardiographic and/or CMR findings (red flags for amyloidosis)
- Cardiac ^{99m}TcPYP/DPD/HMDP uptake, Grade 2 or 3
- Absence of abnormal serum free light chains (FLC) levels and absence of monoclonal protein in serum and urinary protein immunofixation with electrophoresis.

Recently, American and European Societies involved at the diagnosis and management of TTR amyloidosis, suggested a standardized reporting scheme, helping the clinicians and imaging specialist to keep a uniform and easily-followed procedure (Appendix 1).

Ongoing studies indicate that the semiquantitative and qualitative amyloid assessment, as well as assessment of SUV [27], or retention index [28] on SPECT/CT may predict and evaluate treatment response.

The use of positron emission tomography (PET) with positron-emitting radionuclides for the diagnosis of CA is currently being investigated [29]. However, this method is not yet recommended for routine use in the diagnosis of CA [30].

Conclusion

Cardiac amyloidosis remains a serious infiltrative disease, due to fibrils deposition at the myocardium. This can be attributed either to rare genetic mutations in the hereditary forms or as a consequence of senility. Nowadays, advances in imaging modalities led to a non-invasivediagnosis, and the certainty that cardiac amyloidosis is not any more a rare disease as we thought some years ago. Nuclear cardiology today plays a pivotal role in the evolution of the diagnosis and management, rendering with a non-invasive, easy, cost effective and mainly very specific and sensitive method for the selection of suitable candidates for therapy. Cardiac scintigraphy using ^{99m}Tc-PYP, ^{99m}Tc-DPD, or ^{99m}Tc-HMDP is the only method today that"bridges the gap between the latest advances in the field of research and clinical practice"[31].

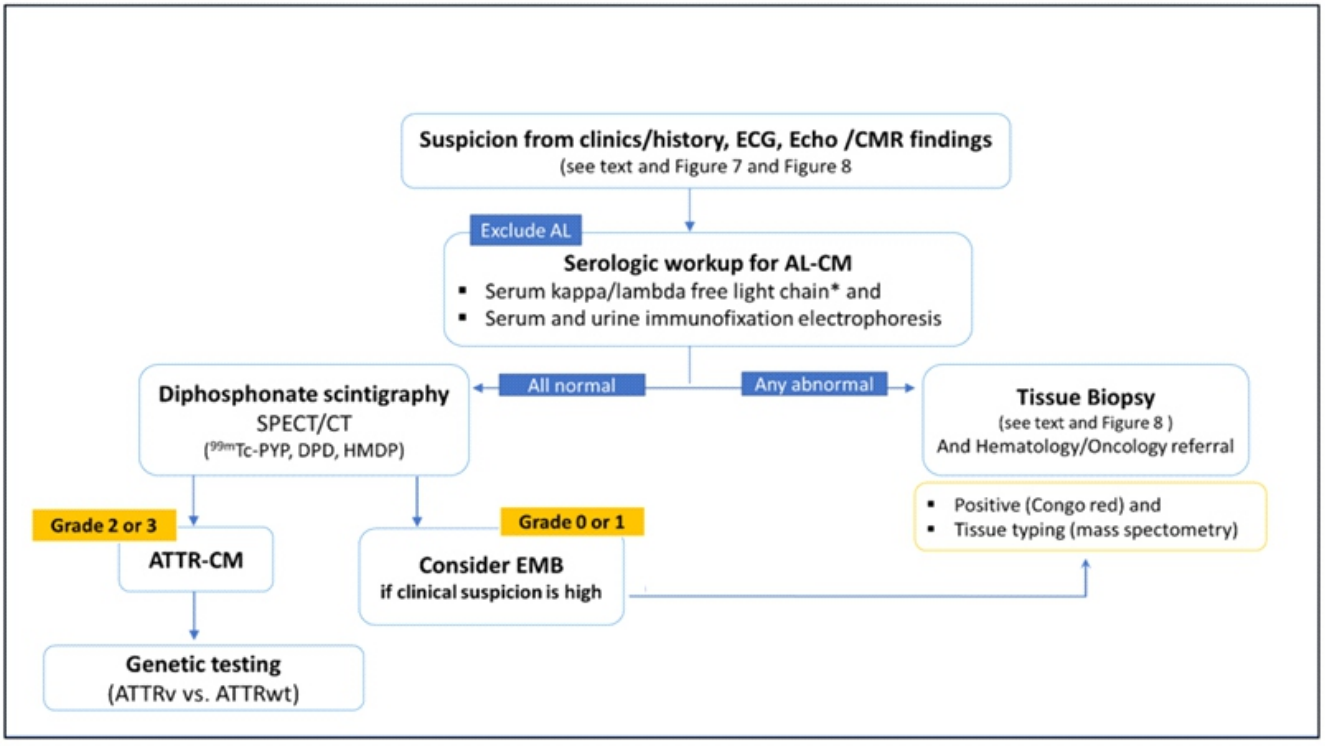

Figure 3. Diagnostic algorithm (*Adopted by: Brito et al. World Heart Federation Consensus on Transthyretin Amyloidosis Cardiomyopathy (ATTR-CM). Global Heart. 2023; 18(1): 59).*

Appendix 1. *Standardized Reporting of cardiac scintigraphy with bone seeking tracers.*

Parameters	Elements
Demographics	Patient name Date of study Age Sex Reason for test Medical history Risk factors for coronary artery disease Medication Previous imaging studies Blood test for cell dyscrasia
Acquisition protocol	Imaging technique: Whole-body, planar images (anterior, lateral), SPECT or SPECT/CT Name and dose of the radiotracer Time between injection and imaging
Findings	Image Quality Visual uptake Semi-quantitative interpretation in comparison of rib uptake (Perugini scale)
Extracardiac findings	Shoulder and hip gridles uptake Soft tissue uptake (signs of systemic ATTR amyloidosis)
Conclusions	1. Results of imaging findings a) Negative for myocardial uptake b) Positive for myocardial uptake 2. If positive, report the grade (I, II, III) according to Perugini scale. 3. If grade II or III report that the study is suggestive for ATTR- Cardiac amyloidosis if the results for light chain disease are available and are negative, if not available, 4. Recommend ruling out light chain amyloidosis by performing serum and urine immunofixation electrophoresis and quantitation of serum kappa and lambda light chains of serum kappa and lambda light chains.

Notes: *Planar imaging and semiquantitative methods like heart to contralateral hemithorax (H/CL ratio) are insufficient to diagnose ATTR-CA. Recent literature discurrage the use of the H/CL ratio (26) emphasizing that diagnosis should only be made based on the visual grade from SPECT or SPECT/CT.*

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