Cardiac amyloidosis. Two main subtypes and diagnosis by Nuclear Medicine: SPET tracer revival

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Hellenic Journal of Nuclear Medicine 2019; 22(3): 161-164 Epub ahead of print: 7 October 2019 Published online: 30 October 2019

Cardiac amyloidosis (CA) although known since 1867 [1], has recently drawn a revived interest in medical practice. It constitutes a progressive disorder induced by autologous extracellular misfolded protein deposition, in terms of insoluble amyloid fibrils, in the myocardial tissue which causes arrhythmias and congestive heart failure, ultimately leading to precocious decease [2]. The name amyloid for this amorphous and hyaline change in tissue has been derived from the iodine-staining reaction of this material that resembles that of starch–the Greek word for starch is amylon [3]. Cardiac involvement may affect any anatomical site, including the atria and ventricles, perivascular space (most often of small vessels), as well as the valves and the conducting system, and may occur either as a localized phenomenon or within the context of a systemic disease [4]. There exist multiple pathophysiologic subtypes of myocardial amyloidosis, each with different clinical course and treatment schedules. High risk precursor molecules of CA consist of: a) light chain immunoglobulins (AL amyloidosis). This is the commonest and most severe subtype constituting 85% of all types of amyloidosis and being most often associated with cardiac damage [5, 6]. The incidence of primary AL amyloidosis is up to 9 cases in million per year [6]. b) transthyretin particles: senile systemic amyloidosis/SSA or wild-type/ wt-ATTR, which affects up to 25% of the senile population and hereditary/mutant transthyretin-related (ATTRm) form which results from a hereditary mutation of TTR protein and can affect individuals of all ages. Mutation Val30Met accounts for over 60% of the cases while mutations Val122Ile, Thr60Ala, Leu111Met, and Ile68Leu show predominantly infiltrative cardiomyopathy [4, 7]. c) serum amyloid A (secondary amyloidosis associated with chronic inflammation or SAA), which occurs in 20% of patients with rheumatoid arthritis, with decreasing incidence as management of chronic inflammation is improved. The heart is affected in 2% of the cases [2, 4]. d) atrial natriuretic peptide (isolated atrial amyloidosis or IAA) whose prevalence increases with age, reaching up to 95% in 81 to 90 year-old patients [8, 9] and impact involves disorders of the conduction system and atrial fibrillation rather than heart failure [10]. Less common precursors include mutant forms of apolipoprotein A1, fibrinogen and gelsolin [4].

We are herein focusing on two of the aforementioned subtypes, AL and ATTR, which represent the most frequent causes of CA [11]. a) In AL, the amyloid fibrils in myocardium consist of monoclonal immunoglobulin light chains associated with plasma cell dyscrasias. The estimated minimum prevalence of systemic amyloidosis in the UK is 20 per million inhabitants [12]. In most studies of patients with AL amyloidosis, the proportion of men is somewhat higher (about 1.1-1.3) than that of women [2]. Apart from the central nervous system, the toxic monoclonal light-chain proteins in AL can damage virtually all organs, most frequently the kidneys and the heart [13]. The physical and chemical attributes of subtypes of light chain immunoglobulins determine the target organ of accumulation, e.g. Vλ light chains often accumulate in the kidneys while VH, primarily in the heart [4]. Cardiac dysfunction commonly manifests as heart failure and renal involvement as nephrotic syndrome with progressive worsening of renal function. b) In ATTR, whether ATTRm or wt-ATTR, the fibrils consist of monomers or dimers of the physiologically tetrameric protein transthyretin. Familial ATTR is inherited in an autosomal dominant pattern and >100 mutations in the TTR protein have been identified so far, which result in amyloid deposition mainly in the heart and nervous system [4]. Although the TTR mutation is congenital, the first clinical manifestations of ATTRm appear between the 3nd and 6th decade of life and depend on the specific mutation in the TTR molecule. The accumulation of TTR amyloid in the myocardium is slowly progressive and may cause hypertrophic cardiomyopathy and arrhythmia. Heart failure associated with wt-ATTR may present with preserved ejection fraction [left ventricular (LV) ejection fraction (EF) ≥50% with LV hypertrophy ≥12mm] [14, 15]. In a Spanish study, wt-ATTR amyloidosis accounted for 13% of the patients above 60 years suffering from heart failure with preserved EF [16]. In a recent British study, wt-ATTR was found to affect a malefemale ratio of 8:1 [17]. The heart is the only clinically affected organ in this subtype of amyloidosis, which usually manifests itself with perimeral edema or dyspnea attributed to congestive heart failure. Interestingly, carpal tunnel syndrome induced by amyloid deposits may occur 3-5 years prior to the onset of cardiac symptoms, with associated reports of tingling and hypoesthesia in the hands [4].
Median survival of 11 and 75 months has been reported in heart failure due to AL cardiac amyloid, or to wt-ATTR, respectively [16]. The median survival of untreated patients with ATTRm is almost 10 years, although some patients may survive up to 15 years [2]. Regardless of the subtype, CA determines treatment decision-making due to its major clinical and prognostic inferences [17]. In ATTRm, cardiac involvement may limit short-term and long-term results of orthotopic liver transplantation (OLT) [18, 19] and influence decisions to perform combined heart-liver transplantation [20]. Severe cardiac involvement in AL amyloidosis can limit optimal hematologic treatments, including bone marrow transplantation [21]. Moreover, the recent clinical introduction of drugs interfering with abnormal TTR production, in particular gene “silencing” through RNA destruction, or tetrameric TTR stabilization, like patisiran and tafamidis, respectively, has completely altered the treatment and prognostic horizon, rendering early diagnosis of CA crucial.

Imaging modalities

Among various imaging modalities, echocardiography (ECHO) and cardiac magnetic resonance imaging (CMR) provide non-specific findings of amyloid concentration and thus cannot distinguish the amyloid subtype. Electrocardiographic (ECG) patterns indicating CA include low QRS voltages (56%, especially in the presence of increased LV wall thickness on ECHO, particularly in AL), pseudo-infarction (60%), supraventricular arrhythmias (mainly atrial fibrillation), atrio-ventricular or intra- and inter-ventricular conduction defects and unusual axis deviations [22, 23].

Echocardiography provides valuable information about the initial evaluation, management, and follow-up of patients with known or suspected CA [23]. Typical ECHO features suggestive of CA include the characteristic granular/sparkling appearance of the LV myocardium, increased LV wall thickness (classic feature but in advanced CA), decreased LV end-diastolic volumes, typically preserved or mildly reduced LVEF, high E/A ratio, shortened mitral E deceleration time (restrictive filling pattern), high E/e’ ratio, increased left and right atrial volumes and reduced atrial function (also imaged on CMR), impaired longitudinal strain (LS) in the LV, being worse at the base and mid ventricular regions compared to the apex, right ventricular (RV) thickening, reduced RV myocardial velocities on tissue Doppler imaging and reduced RV LS (early indicators of cardiac involvement in patients with systemic AL amyloidosis) [24, 25], valve thickening, pericardial effusion, atrial septal thickening (a characteristic feature of CA), and dynamic LV outflow tract obstruction [23]. Hence, unfortunately it is not only imperative to be vigilant for the typical ECHO findings that suggest CA but also impossible to distinguish AL from ATTR.

Cardiac MR provides the characteristic morphological features of CA/restrictive cardiomyopathy as ECHO but with better resolution images and no inherent limitation of difficult technique windows [23, 24-32]. Additional findings of CA on CMR imaging rely on tissue characterization: LV late gadolinium enhancement (LGE) which may be an early feature of cardiac involvement compared to increased wall thickness, other early features of CA, such as shortened sub-

endocardial T1 relaxation time and an expansion of the extracellular volume as well as atrial LGE and function, a characteristic feature of CA.

Currently, definitive diagnosis of CA is based on endomyocardial biopsy in conjunction with immunohistochemical parameters or, in ambiguous cases, on mass spectrometry [33]; these procedures are invasive, require specialized expert centers and also do not provide information regarding the extent of the disease.

Technetium-99m-pyrophosphate (99mTc-PYP) was first introduced in the diagnostics of CA back in 1983 [34]. Thenceforth several nuclear tracers have been tried for CA imaging by positron emission tomography (PET) as well as with traditional γ-camera. Promising PET radiopharmaceuticals are under investigation, specifically fluorine-18 (18F) fluorobetapir and carbon-11 (11C)-PiB (Pittsburgh B compound) which image amyloid fibrils, with potential quantification of the amyloid burden and detection of early cardiac involvement prior to structural changes [35].

Single-photon emission tomography (SPECT) tracers such as iodine-131-serum amyloid P component (131I-SAP) and penta- valent technetium-99m (99mTc(VI))-dimercaptosuccinic acid (DMSA) have so far yielded disappointing results due to limited signal-to-noise ratio and prolonged blood pool, respectively [23, 36]. During the last few years, two bone-seeking radiopharmaceuticals, 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) and 99mTc-PYP have been proven superior in the differential diagnosis between ATTR and AL CA and have been officially introduced into clinical practice [17, 23, 36-38]. In particular, these agents image ATTR CA, while presenting no or just a borderline cardiac uptake in AL CA. The use of 99mTc-PYP scintigraphy has been suggested for identifying ATTR, both familial and wild-type, since 99mTc-DPD is available in only certain counties. One to three hours post-injection of 555-925MBq 99mTc-PYP myocardial uptake is assessed optically for grading 0-3 (0=no myocardial uptake, 1=less than rib uptake, 2=equal to rib uptake, 3=more than rib uptake) and interpretation [17, 37]. Semi-quantitative evaluation involves drawing two regions of interest (ROI), one over the heart (H) and another over the contralateral hemithorax (CL) adjusting for background on the planar anterior projection, in order to estimate the corresponding count ratio of heart-to-contralateral (H/CL). Based on the international literature as well as on our experience, a ratio of H/CL ≥ 1.5 defines the threshold for ATTR diagnosis [36, 37]. Tomographic (SPECT) imaging follows and co-evaluation of findings establishes diagnosis with high accuracy. Diffuse intense myocardial uptake (grade 3) verified semi-quantitatively (H/CL ≥ 1.5) in the absence of monoclonal paraproteinemia is consistent with ATTR without the need for histological confirmation and allows for genotyping [38]. No myocardial tracer uptake (grade 0) contributes to AL diagnosis, especially in the context of abnormal results on serum free light chain assay or serum/urine immunofixation, and confirmation by biopsy with immunohistochemistry is warranted [39]. Faint myocardial uptake (grade 1 or 2) with H/CL ratio <1.5 may suggest a diagnosis of AL or, in a small number of cases, the ATTRm subtype, keeping in mind that certain ATTR mutations specifically in patients with early-onset bearing the V30M mutation and in patients carrying the Y114C mutation, have been linked with
amylloid fibril type B expression [40]. Patients with all other mutations or wt-ATTR express the type A amyloid fibrils [40, 41]. Thus, in case of faint uptake with H/CL <1.5, exclusion of other possible causes of cardiac uptake (myocardial infarction, hypercalcemia etc) coupled with measurement of free light chains and abdominal fat biopsy should establish the diagnosis [42].

Taking into account international reports along with our own experience, myocardial $^{99m}$Tc-PYP scan constitutes an economic and widely available modality that enables non-invasive diagnosis of ATTR with prognostic and therapeutic, including novel agents, implications as well as genetic guidance. Prognosis and genotyping have already herein been mentioned. Regarding therapeutic choices, tafamidis and patisiran, the two recently developed drugs offer alternatives to transplantation. Tafamidis binds to transthyretin, preventing tetramer dissociation and amyloidogenesis. In a recent study, tafamidis was associated with reductions in all-cause mortality and cardiovascular-related hospitalizations in ATTR patients and reduced the decline in functional capacity and quality of life as compared with placebo [43]. Patisiran targets and silences specific messenger RNA, blocking the production of transthyretin protein, enabling the clearance of transthyretin amyloid deposits in the tissues and organs and potentially can restore function [44].

Furthermore, PYP/PDP scan has been proved valuable in the setting of elderly patients with monoclonal gammopathy (MGUS), who represent a 5% of this age group and may appear with a positive biopsy for amyloid and an abnormal free light chain ratio, thus misdiagnosing the disease towards AL and receiving inappropriate chemotherapy [23].

Overall, PYP scan allows for biopsy avoidance and changes patient management. Further potential applications include screening, follow-up, and evaluation of response to treatment. Introducing $^{99m}$Tc-PYP/PDP scan in the guidelines for the diagnostic algorithm of ATTR detection has been accomplished. An ambiguous issue worth mentioning is the possibility to use other bone-seeking radiotracers considering that they might supply equal diagnostic accuracy. Several case reports and small studies mention lower sensitivity of $^{99m}$Tc-MDP compared to $^{99m}$Tc-PYP for the diagnosis of cardiac amyloidosis [45-47]. In addition, hitherto only $^{99m}$Tc-PDP and $^{99m}$Tc-PYP have been extensively studied and most importantly the underlying mechanism of uptake remains unclear [39]. Ever since the utility of $^{99m}$Tc-PYP in cardiac disorders was first reported in 1975, the mechanism of its uptake has provoked substantial ongoing research and debate. Increased calcium concentrations are still hypothetically considered and predilection for amyloid fibril type A of ATTR hearts has been recently established [40, 48-51]. Nevertheless, it has long been underlined that apart from CA, $^{99m}$Tc-PYP uptake also occurs in conditions in which calcium phosphate is present in minor amounts such as inflammatory diseases, unstable angina, cardioversion, and after radiation therapy [48, 51]. The postulation that the binding of $^{99m}$Tc-PYP in the soluble muscle proteins and enzymes in different cardiac abnormalities plays a major role coupled with a minor role of calcium phosphate has been questioned. Specifically, the uptake of $^{99m}$Tc-PYP and related phosphates in infarcted myocardium and other tissues has been long attributed to a multifactorial phenomenon resulting from complexing with various soluble and insoluble forms of tissue calcium stores, including amorphous calcium phosphate, crystalline hydroxyapatite, and calcium complexed with organic macromolecules, possibly supplemented by calcium-independent complexing with tissue constituents [48-50].

Till the mechanism of DPD/PYP cardiac uptake is elucidated, in case other bone-seeking tracers are applied, findings should be cautiously interpreted.

Bibliography
