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Review Article

Role of Multimodality Imaging in the Diagnostic work-up for Cardiac Amyloidosis

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Abstract:

Cardiac amyloidosis is caused by the deposition of transthyretin or light-chain fibrils into the myocardium, leading to restrictive cardiomyopathy, and eventually death if untreated. The improvement in diagnostic modalities has seen a recent surge in the number of patients being diagnosed with cardiac amyloidosis, particularly transthyretin amyloidosis. The diagnostic workup often starts with echocardiogram, followed by cardiac magnetic resonance and finally pyrophosphate scintigraphy. It is important to know that while transthyretin amyloidosis is often diagnosed non-invasively with technetium pyrophosphate scan in the contemporary practice, the diagnosis of light-chain amyloidosis still needs tissue confirmation.

Key words: access; barriers; cancer; detection; diagnosis; enablers; yemen; health system; screening

Introduction

Cardiac amyloidosis (CA) is caused by infiltration of myocardial interstitium with either transthyretin (ATTR) or light-chain (AL) amyloid fibrils [1,2]. TTR is a hepatically-produced tetramer that undergoes dissociation and eventually attains the configuration of insoluble amyloid fibril either sporadically due to unknown mechanisms (called wild type ATTR) or due to mutation in the TTR gene (called hereditary ATTR) [3,4,5]. On the other hand, AL is derived from light-chain immunoglobulin produced by clonal plasma cells in the bone marrow and hence is a blood disorder.

Better understanding of clinical manifestations of CA, as well as addition of more sophisticated imaging modalities in the diagnostic armamentarium has sparked renewed interest in the field of CA [6.7]. In the current era, not only CA can be diagnosed in timely manner, but advancements in the therapeutic landscape have helped mitigate symptoms and reduce mortality. The multimodality imaging used to diagnose CA comprises primarily of echocardiography, cardiac magnetic resonance (CMR) and technetium pyrophosphate scintigraphy (Tc-PYP).

1.Transthoracic echocardiogram

Echocardiography is often the first test which, although has low sensitivity and specificity to diagnose CA, can provide multiple clues that can raise suspicion for CA [8,9]. CA patients have disproportionately thickened left ventricle, and discrepancy seen with left ventricular 'hypertrophy' on echocardiography and low-voltage criteria demonstrated on EKG provides an important information [10]. This discrepancy is a result of poor electrical conduction through the amyloid fibrils as opposed to myocardial cells. In addition, there are other features that are often seen on echocardiogram of a CA patient including bi-atrial enlargement and trivial pericardial effusion [11,12,13]. The most important clue on speckled-tracking echocardiography for CA that often warrants further investigation is the abnormal longitudinal strain and apical sparing pattern with 'cherry-on-the-top' appearance [14]. The abnormal longitudinal strain is a measure of longitudinal deformation, with values nearing 0% indicate akinesis, positive values indicate dyskinesis, and negative values indicate shortening/contraction. The underlying mechanism for this pattern is poorly understood but is thought to be related to disproportionate amyloid burden in the different segments in the basal compared with apical segments of the myocardium.

2. Cardiac Magnetic Resonance

Cardiac magnetic resonance (CMR) has a high sensitivity and specificity for the detection of CA when compared with echocardiography; however, it cannot definitively diagnose CA [15,16]. It cannot reliably differentiate between ATTR and AL. Amyloid infiltration results in abnormal gadolinium kinetics, seen on post-gadolinium T1 inversion recovery imaging, whereby the gadolinium and the blood null at the same time. Extracellular space expands due to amyloid infiltration, which is accurately visualized using the administration of gadolinium-based contrast agent [17,18,19]. The gadolinium passively distributes in the expanded extracellular space created by amyloid fibrils, producing typical pattern of diffuse, subendocardial and/or transmural late gadolinium

enhancement (LGE) on CMR that is pathognomonic for CA. LGE pattern also predicts prognosis, as transmural enhancement represents advanced cardiac amyloidosis and has been associated with a poorer prognosis [20]. The only problem with gadolinium-based contrast agents is the risk of developing nephrogenic systemic fibrosis in patients with a glomerular filtration rate of less than 30 mL/min/1.73 m^2. In addition, native T1 (T1 time before the administration of contrast) is a quantifiable and sensitive marker of CA, and native T1 mapping can not only help in the diagnosis of CA, but used to monitor disease progression [21,22,23]. A pre-contrast T1 time > 1044 ms for AL and > 1077 ms for ATTR have been associated with a poor prognosis. T1 mapping can estimate myocardial extracellular volume fraction which is used as a surrogate in quantification of myocardial amyloid burden, and has demonstrated correlation with disease severity in CA

3.Tc-pyrophosphate scintigraphy

Nuclear scintigraphy using Tc-99m pyrophosphate (PYP) tracer is the only test that can obviate the need for biopsy in the diagnosis of ATTR in majority of cases [24]. The interpretation of Tc-99m PYP is based on the acquisition of planar images initially. The first step is semi-quantitative measurement of myocardial tracer uptake using visual grading, ranging from 0 to 3. It is worth noting that Tc-99m PYP is a bone-avid tracer that is readily absorbed by ribs at all times. Therefore, the degree of myocardial tracer uptake is assessed by comparing it with uptake in the ribs (Table). Patients with positive Tc-PYP scan have a grade ≥ 2 tracer uptake in the myocardium and a heart to contralateral lung (H/CL) ratio of ≥ 1.5, which is further confirmed on SPECT to establish the diagnosis of ATTR [25]. It is important to remember that patients with AL can also potentially have some myocardial tracer uptake and therefore, concomitant blood test for paraproteinemia is mandatory for accurate interpretation of the Tc-PYP result to rule out AL [26,27,28]. It is important that there are some exceptions in ATTR patients who may not exhibit classic myocardial tracer uptake, such as those with Ser77Tyr and P64L variants, and tissue diagnosis becomes the definitive method to establish diagnosis of ATTR in these patients [29,30,31,32].

Visual Grade on Planar Image	Tracer Uptake
0	No myocardial uptake
1	Myocardial uptake< rib uptake
2	Myocardial uptake= rib uptake
3	Myocardial uptake> rib uptake

Conclusions

The advancements in imaging modalities has revolutionized the field of CA, helping in timely diagnosis of CA. While echocardiography can raise suspicion for CA, CMR can predict presence of CA with high sensitivity and specificity, and finally Tc-PYP can establish the diagnosis of ATTR.

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