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EDITORIAL

Decreasing Door-to-Diagnosis Time in Cardiac Amyloidosis: A Simple "One-Stop Shop" Approach

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Cardiac amyloidosis (CA) remains a challenging disease to detect and to diagnose. Recent advancements in treatment necessitate more rapid diagnosis so that treatment can be initiated as early as possible. In this issue of *Mayo Clinic Proceedings*, Bézard et al[1] report on the real-life evaluation of an algorithm for the diagnosis of CA. The authors propose a "one-stop shop" approach to the diagnosis of CA by performing 4 tests simultaneously at the first day of a visit: serum and urine screening for monoclonal protein (MCP), nuclear cardiac scintigraphy, salivary gland biopsy, and DNA TTR testing. Additional tests are performed as necessary. Bézard et al reported that of the 1222 patients referred to their center who met the retrospective criteria for this approach, three-fourths received a definitive diagnosis without additional testing. Of those who underwent additional tests, almost one-quarter had a cardiac biopsy performed. There was a high prevalence of amyloidosis at 68% for the entire cohort. Those diagnosed with CA included 50% wild-type transthyretin amyloid (ATTRwt), 26% light chain (AL), and 20% hereditary ATTR. Seventy-one percent of the ATTRwt patients were diagnosed with the simplified 1-day testing protocol. The authors found that AL can be excluded if the screening result for monoclonal gammopathy is negative, consistent with reports that the absence of MCP has a negative predictive value approaching 99% in AL. However, this study did highlight important caveats about diagnosis using nuclear cardiac imaging. The data demonstrated false-negative nuclear cardiac scintigraphy results in patients with endomyocardial biopsy–proven ATTR CA because of earlier stage disease or specific ATTR mutations.

The work by Bézard et al highlights that a simplified approach to the diagnostic algorithm for CA is feasible and can be accomplished with 1 day of testing in most patients, especially those with the most common form of CA, ATTRwt. Today, there are considerable delays in the diagnosis of CA, often 3 to 4 years, with visits to multiple subspecialists often needed.[2,3] Why is that the case? Diagnostic algorithms for CA often start with a clinical suspicion or abnormal cardiac imaging findings and proceed in a sequential fashion to testing for MCP followed by either nuclear cardiac scintigraphy (MCP negative) or a tissue diagnosis (MCP positive). Whereas amyloid experts readily understand these algorithms, they are often daunting to other providers. The requirement for stepwise testing leads to the risk that providers and patients will not complete all diagnostic tests.

The most serious mistake in the diagnosis of CA in the era of nuclear cardiac scintigraphy is inadequate testing for MCP. Poterucha at al[4] demonstrated that only 40% of patients undergoing technetium Tc 99m pyrophosphate (^{99m}Tc-PYP) scans at their quaternary center had complete MCP testing performed. It is well recognized that even grade 2 or grade 3 ^{99m}Tc-PYP uptake may occur in AL, and thus MCP testing is critical. Unfortunately, we see patients with AL CA who are misdiagnosed with ATTR on the basis of an abnormality on ^{99m}Tc-PYP scan without adequate MCP screening. One of the most common mistakes is the use of serum protein electrophoresis (SPEP) without immunofixation electrophoresis (IFE).[5] An additional hurdle for clinicians is that many laboratories perform IFE only if SPEP is abnormal, even if serum IFE is ordered. This "reflex" testing strategy does not fulfill the

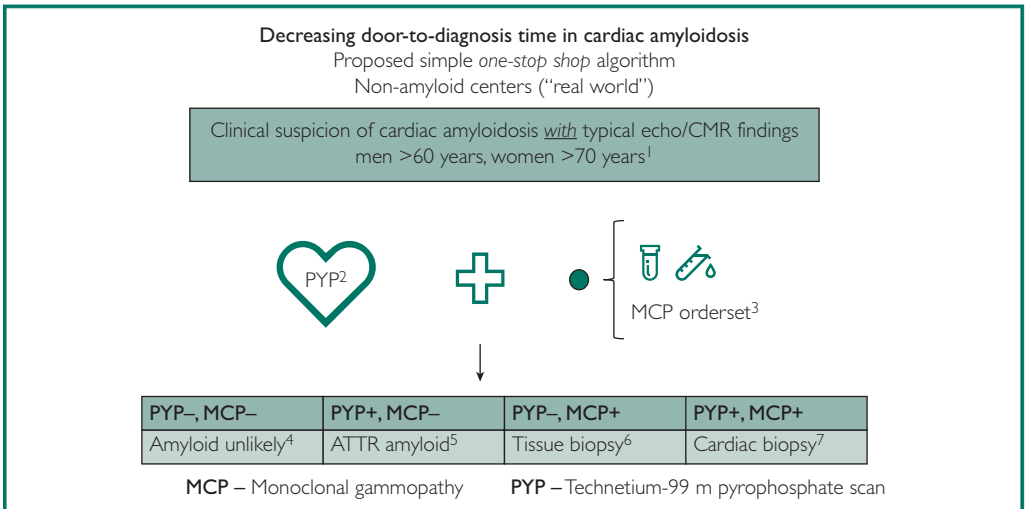

FIGURE. Decreasing door-to-diagnosis time in cardiac amyloidosis: proposed simple one-stop shop algorithm for non-amyloid centers.[1] Technetium Tc 99m pyrophosphate (^{99m}Tc-PYP) scan is often not indicated in younger patients and those with findings typical of AL (nephrotic syndrome, hepatomegaly, macroglossia, periorbital purpura); note that tissue biopsy is mandatory to confirm AL. CMR, cardiac magnetic resonance.[2] Imaging with ^{99m}Tc-PYP or other accepted bone-avid nuclear cardiac tracer (^{99m}Tc-DPD, ^{99m}Tc-HDMP).[3] "Hot-button" order set required with PYP order: serum and urine monoclonal protein (MCP) testing (immunofixation or mass fixation, *not* serum protein electrophoresis with reflex immunofixation).[4] If strong clinical suspicion persists, proceed with cardiac biopsy.[5] DNA TTR sequence.[6] With suspicion for AL amyloid, hematology referral and noncardiac or cardiac biopsy, including fat aspirate/fat pad biopsy, lip/salivary gland biopsy, and bone marrow, depending on clinical findings and availability.[7] Cardiac biopsy preferred, hematology referral.

criteria necessary to evaluate for AL. Unfortunately, the misdiagnosis of amyloid type due to inadequate MCP testing may lead to life-threatening delays in treatment as well as administration of ineffective and costly therapy.

Whereas the availability of nuclear cardiac scintigraphy (^{99m}Tc-PYP, DPD, HDMP) for the diagnosis of ATTR CA has been a major advance,[6] this is a test in evolution. In addition to misdiagnosis of AL as ATTR, we see patients diagnosed with ATTR who do not have amyloidosis at all. False-positive scans are most commonly due to tracer activity in the cardiac chambers (blood pool) rather than in the myocardium. Current guidelines strongly support single-photon emission computed tomography imaging to confirm myocardial uptake, and many experts prefer imaging at 2 to 3 hours rather than at 1 hour to reduce false-positive results.[4] The study of Bézard et al, along with most studies reported to date, included patients with a high pretest probability of CA. As nuclear cardiac scintigraphy for CA is employed more widely, especially in individuals without typical echocardiographic or imaging findings, the diagnostic accuracy is expected to be less robust. As patients are diagnosed earlier in their clinical course, the potential for false-negative results increases. Despite the potential for early detection, at the current time, caution is advised in the use of nuclear cardiac scintigraphy alone to diagnose ATTR CA in patients not fitting the original nonbiopsy consensus guidelines. New imaging agents and techniques may allow earlier and more accurate diagnosis in the future.

We propose a simplified version of the "one-stop shop" algorithm for use in non-amyloid centers (Figure) where patients will increasingly be seen. This algorithm focuses on men older than 60 years and women older than 70 years, the group most likely to have ATTRwt. ^{99m}Tc-PYP scanning

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is usually not needed or indicated in younger patients and those with findings typical of AL (nephrotic syndrome, hepatomegaly, macroglossia, periorbital purpura). In such patients, urgent comprehensive screening for MCP with referral to a hematologist experienced in amyloidosis is crucial. The proposed algorithm includes ^{99m}Tc-PYP scanning with simultaneous MCP testing in the same order set to ensure that adequate testing is performed. The goal is to establish the presence or absence of amyloid within a week of the initial suspicion. Although cardiac magnetic resonance imaging is a valuable tool in evaluation of CA, it is not as widely available as other imaging tests, and we did not include it as a routine test in this algorithm designed for non-amyloid centers. A key requirement of the proposed algorithm is accurate ^{99m}Tc-PYP scanning using current guidelines. We note that our proposed strategy of performing simultaneous MCP testing with ^{99m}Tc-PYP scanning does not align with current appropriate use criteria published by the multisociety guidelines for imaging in CA.[7] However, because of the challenges in adequate screening for MCP, we agree with Poterucha et al that simultaneous testing provides the safest and most expedient means of affording a timely and accurate diagnosis. We did not include fat aspirate or salivary gland biopsy as these are not readily available outside of amyloid centers and did not recommend up-front TTR DNA testing as this is necessary only if ATTR is confirmed. It is expected that a network of local, regional, and national experts will assist providers in ensuring an accurate diagnosis, with continued referral of AL patients and complex ATTR patients to amyloid centers.

Key points for the non-amyloid specialist include the following:

1. A positive ^{99m}Tc-PYP scan alone does not establish the diagnosis of ATTR amyloid.
   a. Guidelines require typical echocardiography/cardiac magnetic resonance findings and the absence of MCP.
   b. Recent myocardial infarction and other conditions may cause ^{99m}Tc-PYP uptake.
2. MCP testing requires serum free light-chain assay or immunofixation electrophoresis of serum and urine (or mass fixation). SPEP with reflex immunofixation is not adequate to exclude AL.
3. Perform single-photon emission computed tomography to confirm myocardial uptake of ^{99m}Tc-PYP; imaging at 2 to 3 hours is preferred.
4. Endomyocardial biopsy is recommended if testing is inconclusive and clinical suspicion persists.

We believe the paper by Bézard et al highlights the need for focused, expedited screening using appropriate diagnostic tools when there is a clinical suspicion for CA. Time to diagnosis matters as a more rapid diagnosis can lead to quicker treatment initiation. Time from presentation to diagnosis is critical to measure and improve in CA, just as it has been in the initial reperfusion strategies with acute myocardial infarction. We also believe that a focused, expedited evaluation algorithm will prove cost-effective and superior overall for those facing a diagnosis of CA.

POTENTIAL COMPETING INTERESTS

Dr Martha Grogan, Editorial Board member, and Dr R. Scott Wright, associate editor of the journal, had no role in the editorial review or decision to publish this article.

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