Imaging cardiac amyloidosis: An opportunity for nuclear cardiology

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We completed Mr. W's dipyridamole infusion and stepped out of the PET scanner room. Suddenly, the baseline of his ECG tracing was swaying, his was bradycardic and his pulse was barely palpable; he was not responding to verbal commands. My mind was racing to understand his extreme hemodynamic response. The fact that he was a research volunteer muddled my emotional reaction to this event. Fortunately, he responded promptly to IV atropine and fluids and after a few hours of observation we felt comfortable sending him home.

Mr. W was a 52-year-old man, who had consented a few weeks ago to be a part of our research study on microvascular dysfunction in cardiac amyloidosis. He first noted shortness of breath and chest pain, while playing with his two young children, about 3 years ago. He had a coronary angiogram with insignificant disease and was told his heart was mildly thickened. He had been struggling with intermittent shortness of breath ever since. But, he was only recently diagnosed with familial cardiac amyloidosis due to a severely thickened heart. After a long conversation with me about the study, he read the 32 page consent form. He acknowledged that the study results may not help him personally. Nonetheless, he volunteered to participate in the study, in his words—to advance cardiac amyloidosis research.

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His very abnormal hemodynamic response to dipyridamole, however, was foretelling of his ultimate poor prognosis. Over the next 12 months, despite maximal medical therapy and treatment for amyloidosis, his heart failure progressed. He received a total artificial heart, but died from infectious complications before he could be transplanted.

The early diagnosis of familial cardiac amyloidosis is challenging, because amyloidosis is not often considered when the left ventricle is mildly thickened. So, his story is not unusual. Recently, there has been a surge in the clinical use of Tc-99m PYP (pyrophosphate) or Tc-99m DPD (Tc-99m 3,3-diphosphono-1,2-propanedicarboxylic acid) to diagnose cardiac amyloidosis.[1] Early imaging and institution of specific antiamyloid therapies may save future patients. I hope that perhaps Mr. W's children may benefit from this type of an early evaluation and treatment.

Cardiac amyloidosis is a rare protein misfolding disease caused by immunoglobulin light chains (AL) or transthyretin protein (ATTR expressed in the liver). Native ATTR causes senile amyloidosis—a slowly progressive disease, predominantly of men aged 65 or older and almost certainly markedly underdiagnosed, and results in death from progressive heart failure. A mutant form of TTR ($\sim$100 described mutations, Mr. W had a mutation Asparagine/Aspartic acid substitution at position 18 of TTR gene) causes familial amyloidosis—a more rapidly progressive disease. Familial cardiac amyloidosis is considered a rare disease, although almost 4% of the African-American population carries an amyloidogenic mutation and TTR amyloidosis in this population among men >70 years is believed by some to account for as much as 10% of all cases of heart failure. Also, due to the autosomal dominant mode of inheritance (in most cases), we have reasons to better diagnose this condition early, in the family members of the affected individual. We can only do that, only if we are more educated to recognize it.

Untreated cardiac amyloidosis is associated with poor outcomes, worse than some of the aggressive cancers, with a median survival of ~12 months with AL disease (with heart failure) and ~3 years with familial ATTR disease. Several promising drugs are in clinical trials: chemotherapy to suppress light chains, disease modifying agents to suppress amyloid fibril formation, decrease expression of ATTR using antisense RNA and anti transthyretin small interfering RNA molecules, disruption of amyloid.[2] Thus delays in the diagnosis of cardiac amyloidosis, while still are frequent, because of the multitude of clinical symptoms, are of increasingly pressing concern.

People like Mr. W may not diagnosed early, simply because our awareness of the disease but diagnostic tools are increasingly sophisticated and therapeutic options are on the horizon. We may be better able to identify early amyloidosis if we consider it in the differential diagnosis of patients with unexplained left ventricular hypertrophy. Endomyocardial biopsy, the definitive diagnostic tool, is invasive. Echocardiography, strain imaging, and cardiac MRI can identify amyloidosis with high certainty in the advanced stages. But, none of the patterns are pathognomonic for AL or ATTR amyloidosis, and early diagnosis remains challenging. Accumulating evidence supports radionuclide imaging with bone imaging compounds, Tc-99m DPD (Tc-99m 3,3-diphosphono-1,2-propanedicarboxylic acid) and PYP (pyrophosphate) for an accurate diagnosis of cardiac ATTR; but, a negative scan does not exclude AL disease.[3] These agents are not well known to nuclear cardiologists, but, widely available in the US and EU for over 20 years. Imaging of cardiac denervation with I-123 MIBG (metaiodobenzylguanidine) may identify early familial amyloid cardiomyopathy, but, not someone like Mr. W, who did not have neuropathy.

Amyloid imaging with PET compounds has advanced over the last decade from a preclinical development phase to clinical imaging agents. Novel amyloid binding PET radiotracers, F-18 florbetapir, F-18 flumetamol, and F-18 florbetaben have been recently FDA approved for imaging beta-amyloid in the brain for Alzheimer's disease. These novel radiotracers are fortuitous and exciting developments for cardiac amyloidosis. F-18 florbetapir[4] and C-11 PiB (Pittsburgh B compound)[5] appear to image cardiac AL and ATTR and are being evaluated by several groups. We may soon have validated PET amyloid imaging biomarkers that can be quantified and can image the two most common forms of cardiac amyloidosis: AL and ATTR.

Molecular imaging of cardiac amyloidosis, combined with tissue characterization with cardiac magnetic resonance imaging and echocardiography, may provide a greater understanding of the pathophysiology and natural history of cardiac amyloidosis than ever before. However, due to the limited evidence for cardiac imaging, the clinical translation of PET amyloid imaging from the brain to the heart may take time. Over the next few years and with support from the industry, government and foundations, we expect these agents to be validated for cardiac imaging. Until then, we can rely on Tc-99m PYP and DPD for a noninvasive diagnosis of ATTR disease.

Although, Mr. W could not benefit from amyloid specific imaging agents or therapies, his family members and children will be screened for the mutation. We hope that his gene positive relatives can be followed closely and diagnosed before they develop the overt cardiac amyloid cardiac phenotype using the existing SPECT and novel PET radionuclide techniques.

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