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Early Detection of ATTR-CM: Clinical Clues and Imaging Approaches

Announcer:
You're listening to *On the Frontlines of ATTR-CM* on ReachMD. And now, here's your host, Dr. Shelina Ramnarine.

Dr. Ramnarine:
This is *On the Frontlines of ATTR-CM* on ReachMD, and I'm Dr. Shelina Ramnarine. Joining me to explore the evolving diagnostic landscape in transthyretin amyloid cardiomyopathy, or ATTR-CM, is Dr. Valmiki Maharaj. He's the Director of the Heart Failure Clinic, the Cardiac Amyloidosis Clinic, and the Cardiovascular Disease Fellowship Program at the University of Minnesota Medical School.

Dr. Maharaj, welcome to the program.

Dr. Maharaj:
Thanks for having me.

Dr. Ramnarine:
So, let's start with some context. Dr. Maharaj, we know that ATTR-CM has historically been underdiagnosed. From your perspective, what clinical scenarios should prompt us to consider this diagnosis earlier in the disease course?

Dr. Maharaj:
I think ATTR-CM or cardiac amyloidosis should be considered anytime heart failure seems out of proportion to what we expect. We see a lot of heart failure patients in the clinic, and about half of our heart failure population is patients with heart failure with preserved ejection fraction. And those patients who have significant wall thickening that we think may not be due to hypertension and other non-cardiac risk factors or red flags should be worked up—why do they have congestive heart failure? I think our community and healthcare providers do a great job of working up why patients have heart failure with reduced ejection fraction, but I do think patients with heart failure with preserved ejection fraction don't get the same amount of evaluation as they should.

I also consider patients who have progressive heart failure who don't seem to be responding as expected to standard therapies. So typically, we try to start what we consider guideline-directed medical therapy medications for these patients, such as, beta blockers, renin-angiotensin-aldosterone antagonists, or even mineralocorticoid receptor antagonists or SGLT2 inhibitors. If they don't seem to be thriving or responding the way we would think with this treatment, that should be a clinical clue. And then we classically learn in medical school that people who have unexplained hypertrophy, but then low voltage on the ECG— although I would say low voltage is a relatively late presenting sign—people who have what we perceive to be low voltage to mass ratio are the patients we should consider for ATTR-CM.

Dr. Ramnarine:
And beyond symptoms of heart failure, what extracardiac features or historical cues tend to be most helpful in identifying ATTR-CM?

Dr. Maharaj:
A lot of non-cardiac features actually occur often years prior to when the cardiac diagnosis is made. Often, when I'm going through a patient's problem list and I'm trying to consider working up for ATTR-CM, I'll look at their problem list and look for a different constellation of symptoms. Commonly, I'll break it down into musculoskeletal or orthopedic, neuropathic, and symptoms of autonomic dysfunction.

I think that orthopedic and musculoskeletal symptoms are the easiest to probably screen for, with the big ones being bilateral carpal tunnel syndrome requiring bilateral carpal tunnel release. Often, this can occur between five and 15 years prior to the diagnosis of cardiac manifestations. Other orthopedic conditions include lumbar spine stenosis, bicep tendon rupture, and other needs for, early

knee or hip replacement or other joint replacements.

I do look at peripheral neuropathy. Sometimes, I do wonder—for example, a lot of patients come in with type 2 diabetes as a competing condition, and I look at their blood sugar and their hemoglobin A1C—how well controlled is their diabetes? Do they have any other manifestations of diabetic and organ disease? And if I find those things look pretty well controlled or I don't see other issues, such as nephropathy or retinopathy, it makes me wonder, could their neuropathy that was initially deemed to be diabetic in nature actually be from some other condition? So that also clues me in to workup for cardiac amyloidosis.

Autonomic symptoms can be a little bit more difficult to screen for. Typically, I'll look for orthostatic hypotension and gastrointestinal disturbances like early satiety, nausea, vomiting, gastroparesis issues with an irritable bowel syndrome-type picture where you have alternating diarrhea and constipation.

And then I'll do a quick family history as well, looking for history of neuropathy and cardiomyopathy. I think that the cardiac conditions are somewhat well attuned to most cardiologists, but I think it's very important to try and look for these extracardiac features, which is sometimes a little bit more difficult to ascertain.

Dr. Ramnarine:
So, once ATTR-CM is suspected, how do you approach initial diagnostic testing with echocardiography and cardiac MRI?

Dr. Maharaj:
Typically, an ECG and echocardiography are our first initial tests. ECG of course, often patients can have atrial fibrillation, although most of them will be in sinus rhythm. low voltage is classically taught as a medical school board exam question, but I'll tell you, most patients actually do not have low voltage on ECG, and they may even have less ventricular hypertrophy on ECG.

I think what's important is when you compare the voltage of the QRS complex on your ECG, how does that compare to the wall thickness on your echocardiogram? In the echocardiogram, we do look for increased wall thickness and signs of high feeling pressures and restrictive cardiomyopathy. So, this could include signs of diastolic dysfunction, low Doppler velocities across the mitral and tricuspid valve being biatrial enlargement, which can be consistent with other restrictive cardiomyopathies. And then in particular, strain imaging. We do strain mapping and look at global longitudinal strain. And the classic dogma that we learn about is seeing apical sparing on the global longitudinal strain map. So, this is a classic finding. It's not universal, and you won't see it in every amyloid patient, but it can be present on certain patients when we have them undergo echocardiography.

Regarding the MRI, I think it adds great tissue characterization that sometimes you can't get on an echocardiogram. So, on an MRI, we might get more precise wall thickness and chamber size compared to an echocardiogram. An MRI does add the characteristics of the cardiac tissue, so we can look at late gadolinium enhancements, and the typical pattern that we see on a patient with cardiac amyloidosis is diffuse late gadolinium enhancement or fibrosis in the subendocardium of the myocardium.

Dr. Ramnarine:
For those just tuning in, you're listening to *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Shelina Ramnarine and I'm speaking with Dr. Valmiki Maharaj about advances in identifying transthyretin amyloid cardiomyopathy or ATTR-CM.

So, Dr. Maharaj, let's continue down the diagnostic pathway by talking about nuclear scintigraphy. How does it work and are there any considerations to keep in mind when doing it?

Dr. Maharaj:
Nuclear scintigraphy has really changed the landscape or diagnosis of cardiac amyloidosis. Nuclear scintigraphy has been around for a long time, but really in the last five to 10 years, it has really helped increase awareness and diagnostic rates of cardiac amyloidosis.

Prior to this, many patients had to undergo tissue biopsy, which carries some extra risk, especially if you're trying to look at biopsying the heart and doing an endomyocardial biopsy. But nuclear scintigraphy uses a technetium-labeled radiotracer. And while we don't know the exact mechanisms, we believe that amyloid fibrils are somewhat more calcium avid, and this allows the bone radiotracer to bind to the heart. So, for the radiotracer, what's commonly used in the United States is pyrophosphate. HMDP is also another common radiotracer used in the United States. This tracer actually will bind to the amyloid deposits in the myocardium, and when we see significant cardiac uptake, particularly with absence or diminished bone uptake, we can make the diagnosis of ATTR-CM.

What's very important when we're using nuclear scintigraphy is that we have to make sure we have ruled out AL amyloid first. About 10 percent of patients with AL amyloidosis can also have uptake on the nuclear scintigraphy PYP scan. So, if you see uptake on the PYP, you have to make sure, did you check your serum and urine studies to exclude a monoclonal process? I think this is a very important workup in the evaluation of cardiac amyloidosis because the treatment of AL amyloid is vastly different than TTR amyloid. So the most important test that you need to order to exclude AL amyloid in the monoclonal process is your serum and urine immunofixation coupled

with your serum and urine Kappa Lambda light chains, if you are able to exclude AL amyloid with a normal, no monoclonal protein within that patient, and you get significant uptake in the myocardium on a nuclear scintigraphy scan, you can essentially make the diagnosis non-invasively of ATTR-CM.

Dr. Ramnarine:
After confirming ATTR-CM, how do biomarkers, staging systems, and genetic testing refine diagnosis and guide next steps?

Dr. Maharaj:
Yeah, that's a very good question and something actually a lot of patients will ask about- what stage are they at? What is their prognosis? Right now, we utilize two different staging systems. There's the revised Mayo Clinic staging guidelines and the National Amyloid Center from the United Kingdom staging guidelines. They're roughly similar. Essentially, we use cardiac biomarkers such as natriuretic peptide levels and NT-proBNP and high sensitivity troponin to stage the disease. The UK group also uses your estimated glomerular filtration rate, or EGFR, to stage the disease. And people who have higher levels of these biomarkers are essentially presenting later on in their disease severity.

Now, even though patients may be presenting in what we consider either stage one or stage two or stage three disease, we still consider treating them regardless of what stage they're at, because we find that patients at all stages can actually benefit from treatment. Now, to determine if this is a wild-type or hereditary ATTR-CM, you have to do genetic testing. There is no other means of actually trying to determine if this patient has wild type versus hereditary or variant amyloidosis, where patients can have an inherited mutation. There are approximately 120 mutations that currently exist within the TTR protein, and certain mutations are more prevalent in different areas of the country, different ethnicities, and different racial backgrounds. So, I do offer genetic testing to all my patients I see regardless of their presenting signs or symptoms and regardless of age.

I think that it's helpful to know, could a hereditary mutation be present? And could this have implications not just for treatment, but also for prognosis for that patient? But also, for their family and their first-degree family relatives, in hereditary cases, I do advise cascade testing if the index person I'm seeing does actually have a mutation. Cascade family testing can allow for earlier detection and potentially earlier intervention in the affected family members.

Dr. Ramnarine:
I'd like to thank my guest, Dr. Valmiki Maharaj, for joining me to discuss current perspectives on the diagnosis of patients with transthyretin amyloid cardiomyopathy. Dr. Maharaj, it was great having you on the program.

Dr. Maharaj:
Thank you. I enjoyed it.

Announcer:
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