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Recognizing ATTR-CM in High-Risk Populations

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

Dr. Jackson:
This is *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Steve Jackson, and joining me to discuss the prevalence and recognition of transthyretin cardiac amyloidosis, or ATTR-CM, among older Black and Hispanic patients is Dr. Frederick Ruberg. He's the Chief of Cardiovascular Medicine at Boston Medical Center, as well as the Thomas J. Ryan Professor of Cardiovascular Medicine at Boston University Chobanian & Avedisian School of Medicine.

Dr. Ruberg, thanks for being here today.

Dr. Ruberg:
Thank you so much for having me. It's my pleasure.

Dr. Jackson:
To start our conversation, Dr. Ruberg, can you provide some background on what ATTR-CM is and why awareness of it has grown in recent years?

Dr. Ruberg:
ATTR-CM, or ATTR cardiac amyloidosis, is a problem of misfolded protein. So in amyloidosis, protein misfolds and then deposits amyloid protein aggregates in organs. And in cardiomyopathy, ATTR amyloidosis results from misfolded TTR protein. TTR is also called transthyretin, and that leads to deposition of amyloid deposits in between the heart cells, causing a restrictive cardiomyopathy. Transthyretin is a plasma-circulating protein that binds to thyroid hormones and retinol binding protein. And it was discovered that in conditions that relate to aging or in conditions that relate to inherited genetic variants in the TTR gene, this protein can be prone to misfolding and aggregating as amyloid, resulting in ATTR-CM, or ATTR amyloid cardiomyopathy.

Awareness has grown over recent years for a number of reasons. First of all, there has been a concerted effort, and successful effort I might add, to develop medications that slow and halt the deposition of amyloid protein in ATTR cardiomyopathy. We now have three available FDA-approved therapies for ATTR cardiomyopathy. And so in the context of developing the therapies and testing them, and the clinical trials and the publications thereof, the disease became more widely known.

And the other reason is because there was a quantum shift in the capacity to diagnose amyloidosis by the development of non-invasive imaging. Before 2017 or so, diagnosis of ATTR cardiac amyloidosis required a heart biopsy to make the diagnosis. And after about 2017, owing to the publication of an important report in *Circulation* by a number of people around the world, myself included, we were able to establish that amyloid cardiomyopathy could be diagnosed with imaging and blood testing alone. And if everything lined up, then you could avoid a heart biopsy. So by putting the diagnosis in the hands of doctors who could order imaging and blood testing and relieving the doctors and patients from having to do a procedure that carries risk, we are able to increase awareness and also increase diagnosis.

Dr. Jackson:
So let's look specifically at older Black and Hispanic patients. What do we currently know about the prevalence of ATTR-CM in these communities?

Dr. Ruberg:

Well, for the longest time, we really knew very little. And that's partially because these are populations of patients that have been relatively understudied and underrepresented in clinical research, both in terms of observational clinical research and clinical trial research.

One of the inherited genetic variants called V142I is disproportionately represented in the self-identified Black population in the United States, and its prevalence actually is around three and a quarter or three and a half percent. And so this means that there's a lot of people, maybe a million to a million and a half people, who actually have this variant and are at risk for developing ATTR amyloidosis. But for the longest time, we didn't really know whether or not the prevalence of this allele necessarily was associated with increased prevalence of ATTR amyloidosis as a result of that. Population studies tantalizingly suggested that this was an important question to answer. A number of population studies demonstrated that the carriage of the allele increased the risk of important outcomes like death and hospitalization for heart failure compared to patients who didn't have the risk allele. But none of those studies were able to look phenotypically and deeply to understand which patients who had the allele could develop cardiac amyloidosis. And again, I'm talking about primarily patients who identify as Black in the United States.

So recently, my colleagues and I completed a study where we actively screened about 650 older Black and Caribbean Hispanic patients —I'll explain why in just a moment—for ATTR amyloidosis using that sensitive imaging testing that I described earlier. And with that, we were able to identify that, not surprisingly, the prevalence of cardiac amyloidosis in this population increased with age, and it was also much more common in men than in women. And in fact, when you looked at older Black men over age 75 with heart failure, the prevalence of ATTR cardiac amyloidosis was more than 15 percent. It actually approached almost 20 percent. This is a lot. This is almost one in five people, obviously, which means that it's not something that is a zebra diagnosis that we may have learned about in medical school. This is a real and potentially common problem that needs to be thought about and screened for in common clinical practice.

We were particularly interested in understanding about the Afro-Caribbean and Caribbean Hispanic populations because of potentially common ancestry. And interestingly, we found that the patients who identified as Afro-Caribbean, say from Haiti or people who self-identified as Black from Dominican Republic, had different prevalence of cardiac amyloidosis compared to those who did not identify as Black. This has to do with the prevalence of the V142I allele in people who trace their origin to West Africa.

As I said, for the longest time, we really didn't know until recently the importance of ATTR cardiac amyloidosis in these populations, and now we understand it to be a potentially relatively common and now treatable cause of heart failure.

Dr. Jackson:
So you briefly touched on this point, but I'll ask it a little more specifically. Why has ATTR-CM historically been either underdiagnosed or diagnosed much later in these populations?

Dr. Ruberg:
So there are a number of reasons why ATTR-CM has been historically underdiagnosed and diagnosed later in populations who identify as Black or Hispanic. Part of it has to do, I believe, with access to care and the capacity of these populations to avail themselves of the medical system that potentially could help them.

The other reason, I think, is that doctors frequently think about cardiac amyloidosis secondarily and typically would misattribute symptoms that could be cardiac amyloidosis to other diseases and chronic diseases that are potentially more common in these populations. I'll give you a specific example. So hypertension or high blood pressure is one of the most common chronic conditions, if not the most common chronic condition, in the United States. It happens to be disproportionately higher in people who identify as Black. And so it would not be surprising to me that a doctor would attribute a patient's symptoms of heart failure or echocardiographic features that might actually be attributable to amyloidosis to a patient's high blood pressure because it existed beforehand.

This speaks to doctors also not getting anchored on specific diagnoses and maintaining an open mind as they approach their patients, because it's possible that cardiac amyloidosis can develop, and it typically does in the context of a background of hypertension. So it's critical that doctors think about amyloidosis and, as I said, particularly in populations where they might not otherwise have paid attention to this particular diagnosis.

Dr. Jackson:
For those just joining us, this is *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Steve Jackson, and I'm speaking with Dr. Frederick Ruberg about ATTR-CM prevalence and management in older Black and Hispanic patients.

So with these disparities in mind, what red flags should prompt clinicians to consider ATTR-CM in these patient populations?

Dr. Ruberg:

So I think this is a super important question, and I appreciate you asking. Part of the challenge in making the diagnosis of cardiac amyloidosis is that, as I mentioned, one can't get anchored on a prior diagnosis and has to maintain an open mind. And that open mind is to consider what might be changes in a patient's appearance, either clinically or echocardiographically, for example, or to also integrate non-cardiac features that are associated with cardiac amyloidosis.

I'll start with the cardiac features. So any patient who has increased wall thickness by echocardiography above the upper limit of normal but no explanation or no satisfactory explanation should prompt the consideration. As wall thickness increases, typically, electrocardiographic voltage increases. One of the features of cardiac amyloidosis is discordance between the echocardiographic wall thickness and the electrocardiographic voltage. So as the voltage gets lower and the wall thickness gets higher, that's a red flag. We call that the voltage-to-mass or the voltage-to-wall thickness ratio. Anybody who has an elevated injury marker of cardiac troponin that is out of proportion to what you'd expect is also potentially a red flag for cardiac amyloidosis. We've found that troponin can be a really good discriminator, on top of some classic features, that can help raise the likelihood that amyloidosis is present.

And then for the non-cardiac clinical cues, one thinks about things like carpal tunnel syndrome. There's strong evidence that bilateral carpal tunnel syndrome may precede the development of cardiac amyloidosis in many patients by 10 or 15 years. So the presence of bilateral carpal tunnel syndrome and heart failure should raise red flags. Similarly, lumbar spinal stenosis—my colleagues and I are exploring right now whether or not lumbar spinal stenosis can intercede the development of cardiac amyloidosis. Again, carpal tunnel and spinal stenosis are common problems. But when you start putting that together with heart failure, that should raise the likelihood that this patient might have cardiac amyloidosis.

Dr. Jackson:
And beyond increasing awareness, how can clinicians improve the screening and care pathways for patients who may be at higher risk for ATTR-CM?

Dr. Ruberg:
Besides keeping an open mind, which obviously is the first and foremost requirement to make a diagnosis of cardiac amyloidosis, I think clinicians can think about utilization of validated clinical risk scores that can help identify patients who might be at higher risk. One great risk score that's been published and validated is the Mayo risk score for ATTR. It used to be called the Transthyretin and Cardiac Amyloidosis score, or TCAS score. This score utilizes simple demographics like sex and age, and comorbidities like blood pressure, basic echocardiographic features like wall thickness and relative wall thickness, and ejection fraction to provide a risk score. And if that score is a six or higher, then that patient has a higher likelihood of having cardiac amyloidosis. The score tends to be more sensitive than specific, but one can use that as a means to identify a population you might want to send for follow-on testing, say, with sensitive nuclear imaging for cardiac amyloidosis.

Another thing one can do is to use echocardiographic risk scores that have been validated. One of them is called the IWT or Boldrini score that uses a number of different echocardiographic variables, including strain and strain-rate ratios, tissue Doppler velocities, and diastolic function to raise or lower the likelihood of amyloidosis.

And finally, at the cusp of more broad implementation are automated interpretation or artificial intelligence tools. The listeners probably know there's been an explosion of AI tools now in diagnosis in amyloid cardiomyopathy. They include ECG AI tools and echocardiographic AI tools. These tools can be implemented in line in the echocardiographic interpretation or implemented into the EHR to provide a risk threshold that, when exceeded, raises the likelihood pretty substantially of amyloid cardiomyopathy, and again, can trigger follow-on testing. And I'd also point out that low scores or negative adjudications for these ECG tools are also very good at ruling out cardiac amyloidosis. So I think we're just on the cusp of understanding as a system how we use these tools to really identify more patients and identify patients more accurately.

Dr. Jackson:
And with that in mind, I want to thank my guest, Dr. Frederick Ruberg, for joining me to discuss his approach to ATTR-CM management among older Black and Hispanic patients. Dr. Ruberg, it was great having you on the program.

Dr. Ruberg:
Thank you so much for the time today. It was my pleasure.

Announcer:
You've been listening to *On the Frontlines of ATTR-CM* on ReachMD. To access this and other episodes in our series, visit *On the Frontlines of ATTR-CM* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!