Speaker 1 (00:09):

Hello, my name is Louis Krivsky. I'm a family physician and I'm pleased to welcome you to the American Heart Association's Podcast ATTR closing the knowledge gaps in Transthyretin Cardiomyopathy. This series is intended to increase the ability of healthcare practitioners to recognize and provide for early identification of patients with Transthyretin Amyloid Cardiomyopathy commonly called ATTR-CM, and to ensure accurate diagnosis and timely initiation of the appropriate treatment therapies before the onset of cardiac dysfunction when possible.

(00:49):

Being able to make the correct diagnosis and devise a treatment plan is grounded in an understanding of the life-threatening pathophysiology of cardiac amyloidosis and engaging in evaluative strategies for early detection. Before we begin, let's review the learning objectives for this specific podcast. Number one, identify genetic variants that are pertinent to the population we serve here in the United States especially that leads to hereditary ATTR. Number two, discuss how patients and clinicians might obtain genetic testing. And number three, clarify the role for and the relative safety profile of cardiac biopsy. We're joined today by two colleagues, Dr. Maurer and Dr. Ferdinand. Will you please introduce yourselves each Dr. Maurer and Ferdinand, and tell us where you're speaking to us from.

Matt Maurer (01:45):

So it's Matt Maurer, I'm a cardiologist at Columbia University in New York where I run the cardiac amyloid program.

Keith Ferdinand (01:51):

I'm Keith Ferdinand. I'm a clinical cardiologist at Tulane University in New Orleans and a Gerald S. Berenson Chair in Preventative Cardiology.

Speaker 1 (02:02):

Well, thank you both for sharing your knowledge in these upcoming 25, 30 minutes we have together. And I'd like to start the discussion off by helping our colleagues become more aware of the prevalence of a disorder that was previously considered to be extraordinarily rare. Who would like to address that one? Maybe Dr. Maurer?

Matt Maurer (02:21):

Yeah, I'm happy to start. As you indicate TTR cardiac amyloid is one of those diseases that's considered rare or a zebra, meaning they're under 200,000 individuals in the US according to FDA rules that define a rare disease. And it probably butts up against that particular number in general. The most common form of this disease is caused not by the genetic variance, but by aging. We call that a wild type trans thyroid in cardiac amyloid or what we used to call senile cardiac amyloid because it occurred in individuals of older age and the hereditary form of the disease is also quite common. There are over 130 variants in the TTR protein that can cause the disease. In the United States, the two most common variants are the so-called Val 122 Ile variant. The nomenclature is that the number position 120 second position of the protein of valine replaces isoleucine.

(03:14):

That is quite common in people who are of West African ancestry and in fact one in 25, one in 30 individuals who self-identify as black in the US at birth carry that variant that can lead to later in life, usually over the age of 60 in men, 70 in women, the disease that we're talking about. The other

common variant in the US is called the Appalachian mutation. Historically, it affects individuals of Northern Irish descent and it's called the Thr-60-Ala variant in which Threonine Thr replaces alanine at the 60th position of the protein. And that causes both a cardiomyopathy and a neuropathy. But there are another 120 or some odd different variants that are much less common.

Keith Ferdinand (03:54):

Calling it a rare disease, I sometimes get a little bit uncomfortable because I think what happens is it's rarely diagnosed when people have it. There's a pipeline issue. If you're looking for instance of people of West African African descent. Now we know that race is a social construct, but we are talking about a region of ancestry. In this particular situation, it may be as much as 3.5 to 4% of the population have the inherited gene in a heterozygous manner. There's variable though penetrance meaning that just because you have the genetic tendency doesn't mean you're going to get it. As Matt says, it can manifest itself later in life beyond the age of 60 in men, 70 in women. But if you take 3.5 and you look at 47 million people who self-identify as black in the United States, we're talking anywhere from 1.65 to 1.7 million people are carrying the gene.

(04:45):

So it's a lot out there. The question then becomes who's going to develop disease and when they develope disease, how do you make that diagnosis? But I guess technically it's rare, but boy, there's a lot of people out there. And then with the wild type, the one that Matt was mentioning comes on with advanced age, it might be in people who are 80 years of age and older. It might be as much as 20% will have some form of amyloid deposit in the heart. Now is that a disease or is that just a degenerative process of aging? I'm not sure.

Speaker 1 (05:17):

Well, thank you for making those numbers stand out to us. When you said, Matt, that many as one in 25 to carry a genetic variant, everybody's heard of cystic fibrosis and that has a similar gene frequency, and yet so far, very few, even if they've heard of amyloidosis, have paid any attention. I think Keith is right that what's happening is the lack of awareness or the nihilism in the absence of therapy in prior generations of clinicians has made us just sort of put that on the very back burner and now that we have potentially valuable interventions, it's worth looking for this disorder. So that brings me to the next question. If we are suspecting hereditary at ATPR, how do we go about getting genetic testing? What should we do? Dr. Maurer will you approach that for us?

Matt Maurer (06:02):

Yeah, well, I think genetic testing is highly relevant and should be performed in individuals who actually confirm the diagnosis. It's not something that we advocate for a genome first approach. In part because if you suspect amyloid, even for example in individuals of West African ancestry, they can have wild type disease, and so you could do a genetic test. Look for V122I, find out it's negative and mistakenly conclude even though the phenotype is suggestive amyloid that they don't have it. So we suggest genetic testing be done concomitant with other non-invasive approaches to make the diagnosis using nuclear scintigraphy.

(06:37):

Genetic testing is very easy to do. There are several national laboratories that do it. There are also programs that are sponsored by the companies that provide products that treat amyloid. So clinicians can get access to this testing usually for no cost to patients. The testing is easily done on blood or saliva, and TTR, as I said, is a pretty small gene. The amino acids are 127 in the protein, so it's well known what

the sequence is, and there aren't any major variants of unknown significance. So either you get, there's one of the genes, if you just sequence that gene, you either get a positive or negative test. So simplistically put, it's a blood test or a saliva, it's a send out in most institutions. So some do it on site and takes a few weeks for it to return. The cost is quite minimal if sometimes non-existent for patients

Speaker 1 (07:23):

When we're trying to diagnose celiac disease, we can go and order a celiac panel, which gives us anti-transglutaminase, antigliadin, IGIA levels or you can order individual things. Should we be ordering a specific genetic variant like you mentioned as the most common, or is there such a thing as an amyloidosis genetic panel? How do we actually go about the mechanics of that because I've not done that?

Matt Maurer (07:48):

Yeah, so I think you're asking really good questions. So I would not recommend you sequence someone for a particular variant in TTR. As I said, it's a small protein. It's very simple to sequence the whole gene, and just because one's ancestry is suggestive of a particular variant doesn't mean they're going to have that. So I would sequence the entire gene. The opposite is true. We don't have a amyloid panel per se. There are other very rare variants and other proteins, ApoA-I, ApoA-IV that could cause amyloid, but the reverse is true. That is most of us recognize phenotypes.

(08:18):

The phenotype of amyloid mimics that of, if you will, hypertension or hypertrophic cardiomyopathy. So it's a thick walled heart with a non dilated left ventricle. So TTR gene is included in hypertrophic panels that are offered by national laboratories, which is quite useful. So if a doctor by mistake thinks someone has, for example, HCM, sends off an HCM panel, TTR will be in that panel and it could show a variant that may misdirect them. Therefore they'll say, oh my goodness, I thought this was hypertrophic cardiomyopathy, it turns out this person actually has a disease causing variant in TTR that's causing amyloidosis. So I hope that clarifies things.

Speaker 1 (08:55):

And Dr. Ferdinand, you and I both work with a substantial number of patients who enjoy lesser socioeconomic privilege. I work for an HQFC, and so I have many patients who have very limited resources. How can we be successful in providing best advantage to persons who may not enjoy socioeconomic advantage in tracking down this diagnosis?

Keith Ferdinand (09:18):

So that's an extremely important question. Let me answer it, but let me make the comment that I really wanted to make about testing from a genetic basis. Another reason why we have to have some caution and perhaps use it only in patients who have appropriate phenotype with family history is because although I made the point that the allele is very common, if you test everybody who self-identifies as black, then you're going to have hundreds of thousands of people, especially young people who may never manifest disease, but now they're wondering if they have this terrible future that lies ahead. And we really don't know the answers to that. The other question is, although there's been legislation to try to protect people who have genetic diseases from some of the forces related to insurance and the ability to get long care insurance, et cetera, that that really starts to become a complicated socioeconomic issue if you make a genetic diagnosis early in life. So that's the point I wanted to make.

(10:14):

Now in terms of identifying people, Matt used the term phenotype, and I agree with him. If a person has thickened heart myocardial thickness greater than 15 millimeters, 1.5 centimeters, and you see on the report, [inaudible 00:10:29] left ventricular hypertrophy, but wait a minute, this guy's blood pressure wasn't that bad, then you may have to think that there's something else going on. And I've listened to Matt speak multiple times, and I know that he even has a formula that he does in which you see it on that report. Left ventricular hypertrophy really is, and it's left wall thickness because the cardiomyocytes are not hypertrophy, it's thickened because of the amyloid deposits in the heart. Then you can relate that to the basic 12 lead ECG. You don't really see it on the ECG. The QS complexes aren't very tall, so you have a discordance there.

(11:04):

The other thing that you related to is what is traditionally called red flags. There are things that tell you that this person's enlarged heart is something else going on, and it may be anything like bilateral carpal tunnel syndrome, ruptured biceps tendon, spinal stenosis, especially lumbar spinal stenosis. So patients will have a mixture, a hodgepodge of what we call in New Orleans of gumbo of different clinical manifestations, which doesn't really fit with typical left ventricular hypertrophy that you'll see with severe sustained hypertension. The problem in the black community, of course, is that you have more hypertension, early onset, poor control hypertension, you do have more left ventricular hypertrophy. So we kind of get numb when we see these echo reports rolling across our desk with left ventricular hypertrophy.

Speaker 1 (11:54):

Thank you for that clarification. I've heard that term, the myoelectric gap, that you have a measurement on echo that you think is reflecting myometrial size and yet it's not reflected on the EKG. So certainly even our primary care community should be routinely comparing what they see on an ECHO report with what they see on an EKG and if they're discordant, if there's a gap between how much voltage you're seeing on the EKG, that's not reflecting LBH, you come to question, is that real hypertrophy or is that just an additional mass that's being picked up that's not really muscle?

(12:29):

Well, I know that in this diagnostic process, Dr. Maurer, you in particular have made it clear to me that I was being unnecessarily apprehensive about cardiac biopsy. Can you relate to us what the role of cardiac biopsy is and what it's relative toxicity is, because just at face value, having had so few patients at the primary care clinician undergo that procedure, it just felt scary to me to even think about it. Could you clarify that for me and perhaps Dr. Ferdinand your experience also with that?

Matt Maurer (12:59):

Yeah, I think your sentiments are typical. I mean, it's an invasive procedure, obviously. One done subsequent to a right heart catheterization with what's called the bi-uptone, which is a small little device that's placed into the right ventricular septal area where a piece of myocardium is removed. It actually takes about 10 or 15 minutes the whole procedure to do. The biggest risk that we're all concerned about is actually, God forbid, perforating someone, making a hole in the heart. That's actually pretty hard to do in someone with amyloid you can imagine, because as we've all just heard, the walls are much thicker than normal.

(13:31):

The risks of the procedure are under 1% in specialized centers. Biggest risks are bleeding and infection, and then there's a small risk of an arrhythmia, but perforations one in tens of thousands. The role of

biopsy has declined quite a bit, thankfully, in part because as Keith was mentioning, we have a whole host of clues in the setting of a non dilated ventricle with an increased wall thickness and what we call a high relative wall thickness on echocardiography, all those red flags, and in that setting, we can pursue a non-biopsy approach that involves excluding AL amyloid.

(14:03):

The way you exclude Al amyloid is to make sure that someone doesn't have the substrate for AL amyloid. AL amyloid is a disorder of plasma cells, analogous to what we consider in multiple myeloma in which the plasma cells are making too much of a monoclonal protein. And the way you exclude that substrate is to essentially obtain three tests, a serum protein immunofixation, not just an SPEP, but immunofixation to tell the laboratory you're looking for small free monoclonal proteins. You order a urine protein immunofixation, which could be done on a spot urine. So those two, immunofixation of the serum and urine. And then the most important test is what's called a Kappa Lambda free light chain ratio. Those tests collectively have a very high sensitivity, over 99%, for identifying someone who could have AL amyloid. If all of those tests are negative, then you basically can't have AL amyloid because you don't have the substrate to have AL amyloid.

(14:55):

And then you can go on to do scintigraphy, which is in the US done with either HMDP or PYP. Those are the bone avid isotopes that we use, and if that has a positive scan confirmed with a SPECT imaging that it's in the myocardium, not just in the blood pool inside the chamber, then you've established someone has TTR cardiac amyloid, and then the genetic testing comes in to determine whether they have variant or wild type disease. So it's really a three-step process. Exclude AL, no AL, do scintigraphy, and if the scintigraphy is positive, do genetic testing. There are patients who have the light chains being positive, they have evidence of a monoclonal protein. In those patients, you can't be a hundred percent certain based on scintigraphy. And that's where you need a biopsy. It turns out that's needed in one in five patients nowadays.

(15:38):

So 80% of patients can get away without having a biopsy, which is great, but there are patients who still require an endo myocardial biopsy. The biopsy not only confirms that there's amyloid, but then you can send the tissue off usually to a laboratory to determine what we call the precursor protein. Amyloids just protein deposits. You don't know if it's AL or TTR. And so by using mass spectrometry, which is a technique to kind of chop up the amyloid and look for the precursor protein, you can identify with quite high specificity, the gold standard through the biopsy, whether someone has AL or TTR.

(16:09):

So biopsy still has a role to play, especially in someone who has evidence of monoclonal proteins, the different disease than we're talking about today. But AL is a medical emergency and a life-threatening disease, and that's something where you need to have a little fire in your belly. You see someone who has light chain amyloid and symptoms, you need to rush and get that person evaluated quickly. When I say rush, I mean within days or weeks, these people, if they have advanced disease, will not survive many, many months unless they get treatment instituted. So you can't kind of dottle for a few weeks and try to figure things out.

Speaker 1 (16:39):

Let me ask you for a little more exploration of that, and here's my inquiry to you. Both of you work in centers that would be recognized widely as centers of excellence. I saw data, for instance, at persons with thoracic aortic aneurysms. The rate of major consequence was much different in surgical centers of

excellence than in just general community hospitals. So for this biopsy, I heard quoted the number 1% serious adverse events from biopsy. Does that never come from centers of excellence? If I live in a small town, should I be referring my patient to a center of excellence as the primary care person? Or is the procedure of low enough risk that I could just use my community, cardiologist, thoracic surgeon, or whoever does that procedure there to do it? What do you guys think?

Keith Ferdinand (17:22):

I'm going to let Matt comment on that since he is indeed one of the centers of excellence in the United States for amyloid. I think however, for most of us who are practicing in clinical settings, we are going to be able to make the diagnosis of TTR amyloidosis, the one that, as I mentioned, is more common in people of West African descent. You can see in any population, but it's more common there. Especially if you do all the steps that Matt just described. And when you do the technetium scan, I've had a nuclear lab for many years, you want to make sure that you're not just doing a semi quantitative approach, that you're actually doing what's called a spec, where you slice the heart and you make sure that you're looking at the muscle itself, that you're not just looking at a shadow saying that the person has an uptake of amyloid, fibrils and myocardium.

(18:12):

If you do that, that really increases the specificity and sensitivity of the test. And I think for most clinicians who are practicing in community clinical cardiologists, if they take that extra step, take the time to do the things that Matt described in terms of ruling out AL, in terms of making sure you're doing a spec diagnostic along with just looking at the scan that you can really get by in the TTR diagnosis without doing a biopsy. Now, in terms of the complications, I'll let Matt answer that.

Matt Maurer (18:44):

Yeah, I think you raise an important point. Like all invasive procedures, I'm not sure it's a center of excellence, it's more volume. So I think the more you do, the better you are at this. This is a procedure that is done in a native heart, so the risks are higher than in a transplanted individual. And as a result, I think you just want to be forthright with the patient, obviously, and with the provider you're referring to them to and make sure they feel comfortable doing it. If someone feels comfortable, I think it's a very safe procedure to do even in a local setting. If they don't, I think that's time to get on the horn and get some additional information. Just one other aspect of this that I think relates to biopsy a little bit, and that is as we were talking about, the PYP scan in the right setting has a very high specificity.

(19:24):

So in the study seminally that led to its kind of utilization by Julian Gilmore and others that was published in circulation, the specificity was a hundred percent in amyloid centers when you excluded. But the sensitivity was not a hundred percent, it was about 70%. So I've seen as we get more and more interested in this disease, particularly people who carry the African-American variant, the Val 122 Ile variant, they're say 55, 60 years of age, they have a workup and their PYP scan is not positive, but my suspicion remains high. And with that sensitivity, I can envision missing three out of 10 people. And because I'd hate to then invite them back a year later and say, oh, now it's positive. But there was a whole year that's gone by in which amyloid was developing in the heart. Those are individuals who we at our center have offered at times a biopsy. And I can tell you that more often than not when the walls are thick, and I thought it still could be hypertension, it turns out that they have amyloid in their heart.

(20:17):

And so a biopsy is the most sensitive approach. Food for thought, but I think there'll be newer techniques that will be even more sensitive than PYP scanning that are coming that may help identify this disease earlier in its course. And what we're seeing is, Keith mentioned this before, that one of the limitations about recommending widespread genetic testing for people is we don't know about penetrants. But I'm becoming more convinced the penetrance is higher than we previously thought. The disease is associated in large studies, Framingham and other populations [inaudible 00:20:45] with a very high risk for developing heart failure, irrespective of other risk factors. And so even though you might not see it on an echo or on a PYP scan, if it's increasing your risk of heart failure, I think it's probably penetrating, so to speak.

Keith Ferdinand (20:58):

Matt, there's two points to that I want to make about the hypertrophy issue. All of us have been practicing a while and we know that what's been called left ventricular hypertrophy on echo is more prevalent in the black community. But it also is less clearly associated with blood pressure level, but it's highly associated with an increase in mortality. If you look at some of the older studies interesting in which they were doing echoes, they would say, well, the presence of LVH has a predictive power for cardiac events and death similar to that of having three vessel coronary disease or left ventricular dysfunction.

(21:30):

We didn't know it, but I'm starting to think what we've been calling LVH most of the seventies and eighties and into the nineties perhaps was undiagnosed amyloidosis. So that might be what's happening for some of the bad outcomes we were seeing what we call LVH, it really isn't, it's increased wall thickness as we've all detailed that it's not actually hypertrophy per se. But that increased wall thickness, and one of the reasons why we were seeing such bad results was perhaps especially when it's discording with the ECG and with the severity of blood pressure, it may actually have been predictive of amyloidosis, but we weren't making the diagnosis.

Matt Maurer (22:07):

I would echo that sentiment. Just to highlight Keith, you know this, we've been conducting with NIH funds a screening study, particularly focused only in blacks and individuals who are Caribbean Hispanic in which we're trying to identify amyloid people of that background who have heart failure and increased wall thickness. And surprising to us at this point, if you're a male over 75 in our dataset, one in four, one in five actually have amyloid. We're talking 20, 25%. So we probably have been missing it quite a bit.

Keith Ferdinand (22:35):

It might not be a zebra. You mentioned zebra. It might be a zebroid. A zebroid is a horse and a ze... It's kind of rare, but not really. It's more like a horse, but not quite. So it's a zebroid.

Speaker 1 (22:49):

We will credit you with the first delineation of a new medical term. I also wanted to go back to vocabulary, though. Both of you are comfortable with the letters PYP, but I've had my colleagues in primary care say, well, I couldn't order the test because all they had was bone scintigraphy. Because they didn't realize that's the label. Is that still the label that both of your gentlemen institutions also though, when you are ordering the scintigraphy scan, it's listed as bone scintigraphy?

Matt Maurer (23:16):

At my institution it's called a cardiac amyloid scan, but you're correct. They're technician based isotopes and they have been used for 60 years to image the bones.

Keith Ferdinand (23:24):

The pyrophosphate.

Matt Maurer (23:26):

Right.

Keith Ferdinand (23:27):

Yeah.

Matt Maurer (23:27):

The key here is not to order MDP. Just to be clear, there were three isotopes in the technician space, DBD, PYP, HMDP, that all can be used to image amyloid in the heart. But MDP, which is the most common one used in nuclear medicine, does not work for amyloid. So that would be a mistake to use that isotope. It will not help.

Keith Ferdinand (23:47):

Yeah. Lou, there's another really important point I think we need to make before we close, and that is bringing to light this emphasis on amyloidosis all types, but specifically in our discussion, TTR. Don't overlook, however, garden variety heart failure, both HFrEF and HFpEF. Because what's happening is that you're having an increase now in heart failure in the United States, some of it is a downward trend in blood pressure control, increase in physical inactivity, the population is getting older. There's a bunch of reasons why. And I just don't want the clinicians to miss amyloidosis. Got that.

(24:24):

But also don't want them to miss conventional heart failure, which is becoming more prevalent. It's the number one cause of admission in the Medicare population. It's more commonly seen in the black population. Again, I don't think that's because of amyloid. I think it's just because of poor control of cardiovascular risk factors, and it is a leading cause of death. So we are talking about amyloidosis, amyloid cardiomyopathy, TTR, some of these sophisticated tests. That's true, but we need to control conventional risk factors and kind of turn down this upward trend we are seeing in conventional heart failure.

Speaker 1 (25:00):

I'm so glad you brought that up, Keith. And in closing, when I give resident lectures on heart failure, the title is heart failure, the hemodynamic malignancy, because the outcomes for literally the last 40 years still show the five year survival in patients newly diagnosed with heart failure rivals, or is worse than many cancers in America. And yet when we meet a patient or their family and we make the new diagnosis and start them with medicine, it feels so commonplace that we're somewhat casual and comfortable with something that should really be a frightening and a call to arms disorder. So I'm glad we feel the same way that this is not a diagnosis to be looked at with complacency.

(25:44):

So thank both of you for sharing your knowledge today, and I'd like to close with reminding our audience that this activity is supported by an independent medical education grant by Pfizer. The views and opinions in this activity are those of the speakers and reflect the synthesis of scientific information. Content should not be considered as the official policy of the American Heart Association. To get additional information, please visit learn.art.org for more educational information. Thank you and have a great day.