Dr. Louis Kuritzky (00:08):

Hello, I'd like to welcome you to the American Heart Association, ATTR, closing the knowledge gaps in transthyretin cardiomyopathy podcast series. My name is Louis Kuritzky and I'll be leading the discussion today on the episode titled Pathophysiology and Clinical Features of TTR Cardiac Amyloidosis, No Longer a Rare Disease and Still Underdiagnosed. I am joined by two colleagues, Dr. Singh and Dr. Nativi who will introduce themselves further in a moment. This series is intended to increase the ability of healthcare clinicians to recognize and provide for the early identifications of patients with transthyretin amyloid cardiomyopathy that we'll probably, in our discussion, call ATTR and to ensure both an accurate and timely diagnosis, offering patients appropriate treatment before the onset of irreversible cardiac dysfunction. Being able to make the correct ATTR diagnosis and devise a treatment plan is firmly grounded in understanding the life-threatening pathophysiologic changes of cardiac amyloidosis and being able to engage in appropriate evaluation strategies to enable early detection.

(01:31):

Let's review our learning objectives for this next half hour or so that we will spend together. Number one, we want to briefly summarize the epidemiology, pathophysiology and diagnostic strategies appropriate to ATTR. Number two, recognize that there are recent and clinically evolving guidelines specifically on this topic as recent as 2022 and 23 that our colleagues can avail for further knowledge on the topic. We'll provide the very basics of a diagnostic approach and the potential role of primary care clinicians in the early identification of ATTR. And then we'll mention some aspects of the genetics where we'll separate a little bit out wild type from hereditary ATTR. As far as introductions. Dr. Nativi will you start by introducing yourself and giving us a brief bio.

Dr. Jose Nativi (02:26):

Hi, my name is Jose Nativi. I'm a heart failure and transplant cardiologist at Mayo Clinic, Florida and a member of the multidisciplinary amyloidosis program here at Mayo. I would like to thank the American Heart Association for organizing this podcast on a topic that I'm very passionate about, that is patients with cardiac amyloidosis. Thank you for the invitation.

Dr. Louis Kuritzky (02:52):

Well thank you and welcome and Dr. Singh, yourself please.

Dr. Vasvi Singh (02:56):

Well, hello everybody. I'm Vasvi Singh, I'm an advanced imaging cardiologist. I am also the director of the Cardiac Amyloidosis Program of the Cardiac NRI program and I co-direct the cardiac CT and cardiac PET programs and Midwest Part Vascular Specialist at HCA Midwest Health in Kansas City. And I would truly like to thank the program committee for the kind invitation.

Dr. Louis Kuritzky (03:20):

Well welcome to both of you for audience members. I am a family medicine physician. Currently on the faculty of the UCFHCA Family Medicine Residency Program in Gainesville, Florida. So hopefully our combined discussions will help our target audience, which should hopefully involve numerous primary care clinicians to better address this problem. And I'd like to start out with what might seem a very simplistic approach and that is simply to talk about the word transthyretin. Many of you in the audience might be too young to remember that transthyretin through the 1970s was actually called prealbumin. It was a marker for nutritional status and nobody knocked on my door to tell me personally, Hey Lou, the name has changed to transthyretin and here's why.

(04:08):

Well, here is the why about this. The name is very simple. Transthyretin is a four component molecule that carries both thyroid hormone and retinol. Hence the name transthyretin, a transport protein for carrying to some degree some of the necessary thyroid hormone and some of the retinol to various target tissues in the body. Transthyretin itself is not toxic. It is a normal substance. It is when altered physiology of the management of transthyretin comes into play that we end up with downstream consequences. So Dr. Singh, can you give us a bit of history about why we now are focusing on a disease that many of my colleagues probably never heard of or think it's incredibly rare?

Dr. Vasvi Singh (04:57):

Sure. So like you said, cardiac amyloidosis simply put is a disorder caused by amyloid [inaudible 00:05:05] in the extracellular space of the heart and ATTR or transthyretin cardiac amyloidosis is perhaps the most common form of cardiac amyloidosis. You're right, once considered a rare disease and an elusive diagnosis that was considered to be untreatable, it is now gaining increased attention primarily due to advances in multimodality imaging techniques and targeted breakthrough therapies. And like you said in ATTR, the pathogenesis involves the transporter of thyroid hormone thyroxin and that of retinol, which is vitamin A and therefore the name transthyretin that is derived from liver. It becomes unstable, dissociates as monomers, it misfolds and deposits as fibrils in the heart. Another name for it that you all know is prealbumin like you said. So the pathogenesis of this disease is the result of either due to gene mutation that is leading to a variant TTR protein known as mutant or hereditary ATTR or much more commonly the native TTR protein that may misfold with just the aging process known as wild-type ATTR or previously known as systemic senile amyloidosis.

Dr. Louis Kuritzky (06:27):

Thank you. So the normal metabolism of transthyretin includes its job to drop off its target hormones and then either donate amino acids to the amino acid pool or go back and be regenerated in the liver. The problem, as I understand it, and please help me if our colleagues need further clarification, is that misfolded transthyretin doesn't happen normal metabolic pathway available to it. And so our body ends up dealing with the debris of this misfolded transthyretin in a pathway that produces potentially pathogenic fibrils that we call amyloid.

(07:05):

And I think the only common disorder that my colleagues know of amyloid is in the brain, but it's important that they know we're going to talk about cardiac amyloidosis. Amyloidosis can be involved in tissue compartments all over the body. So Dr. Nativi, what's being done? Do you think that's helping our colleagues both in primary care and cardiology be more aware? Do you think when I send a patient to the cardiologist for consultation for heart failure, you think my local cardiologist is likely to be one that's going to have ATTR on the top of his list of consideration? Or are both of our communities, primary care and cardiology in need of reinvigoration on this topic?

Dr. Jose Nativi (07:46):

There's room for improvement in both. I think it's getting better. There are several educational efforts about early diagnosis of amyloidosis, but we are not there yet. There's still a lot of patients that are not diagnosed and some of them have still with delayed presence with delayed diagnosis. So strategies, to answer your question, what strategies we are doing now to create more awareness during our educational session? I can mention three of them. One is educating that amyloidosis is not rare. When I was on training, we were diagnosing one case per year and always triggered at grand rounds and

everybody was reading about it. That has changed a lot. We are diagnosing much more patients in the last years and keeps growing every year. Every program is diagnosing more than the previous years.

Dr. Louis Kuritzky (08:43):

Well before you leave that Doctor Nativi, ATTR is not getting more common is it? Isn't it just that now we're wise enough to start looking for it? It was always there, right? And because people are living older, it has nothing to do with the change in the pathology, does it?

Dr. Jose Nativi (08:58):

The epidemiology hasn't changed. It's just that we are, and I think that to summarize it, I can say that two milestones had happened that they creating more awareness is that now we can do non-invasive diagnosis. Before it was very, very challenging. You needed invasive biopsies on older adults. And second, now we have options of therapies that prolong life and improve quality of life. So those two together is promoting that interest in looking and diagnosing this condition. And then to mention the other two factors that we are doing during our educational sessions about awareness is to explain to all of them that all of us have patients with amyloidosis in our clinics, all of us. So if we go through the data, any paper that you read about heart failure with preserved ejection fraction just to put one of the cohorts of patients, the papers range from a prevalence on that population.

(10:01):

Anything from 11% to 16%. If you study a cohort of patients with heart failure with preserved ejection fraction, you're going to find it and it's a matter of maybe during a cardiology practice, you're going to have higher prevalence because you are going to have more patients with heart failure, with preserved ejection fraction, and you're enough family practice, internal medicine practice, you're still going to have patients with heart failure with preserved ejection fraction, maybe not at the same amount of cardiologists, but still you're going to have them. So I think these patients are in our clinics. And the other important factor is that these patients, they already enter the medical system. If we look, there's some studies, there was a paper that we published this year that we looked three years before the diagnosis of amyloidosis. All these patients have an ICD code of something, either cardiovascular, musculoskeletal, you name it.

(11:01):

So these patients are already on the healthcare system. You don't have to go and look for them in their houses. They already enter the healthcare system. So it's an opportunity for us to find them. And then the last point that we do in education in order to increase awareness is that we are teaching, especially our fellows in training. But what everyone that is, there's a suspicion of amyloidosis that's a medical emergency. For example, when you get a CT scan reading and there's a mass, that radiologist is going to call that doctor who ordered that test immediately, right? Because there's a serious concerns if there's a mass or a tumor, right? Same happened with amyloidosis.

(11:46):

I tell my fellows, if you are going to put in your echocardiogram reading infiltrative cardiomyopathy or suspicious of infiltrative cardiomyopathy or in the MRI, your responsibility is to call that doctor that ordered that echocardiogram and that MRI and tell them that the differential diagnosis of an infiltrative cardiomyopathy goes from TTR amyloidosis. It could be light chain amyloidosis that has a very poor survival without treatment. It's around 20, 25%, the survival of patients with light chain amyloidosis untreated in one year, or it could be something more serious as multiple myeloma with even worsening survival. That's your differential of an infiltrative echocardiogram or of an infiltrative MRI. So those are

kind of some of the, and they're others, but these are where we are educating, creating awareness that is not rare. These patients are already in your clinic and is a medical emergency when you raised a suspicion.

Dr. Louis Kuritzky (12:56):

Well, I'm glad to hear you point out the frequency because to think that perhaps as many as one out of six of my HFpEF patients could be victims of this disorder. That's not something that I can push aside and say, well, it's not that much. It's really a very important disorder. And especially because I see that oftentimes primary care clinicians are somewhat passive about HFpEF, because at the current time, the only drug we have approved is an SGLT2 inhibitor. And many of our patients who are lesser socioeconomically privileged individuals simply can't afford that. Do we have any other doors to knock on that could possibly help them? And I think you're right to overlook this is really a grave concern, which in addition to this signal for cardiomyopathy that should be stimulated both cardiologists and primary care physicians to look further. I think I've seen publications of yours where you are trying to remind us there are a number of triggers.

Dr. Jose Nativi (13:53):

There's several way to name them either triggers, if you read papers, they call it red flags. We're calling it lately a constellation of symptoms that can raise that suspicion to order that ultrasound, that echocardiogram. And on the last 2023 American College of Cardiology expert consensus document, there's a big emphasis on the multidisciplinary care of these patients. Because amyloidosis affects several organs, multiple organs, it can affect the musculoskeletal system with carpal tunnel back pain, spinal stenosis, cervical stenosis, trigger finger. It can affect the heart as we know with heart failure, atrial fibrillation, sick sinus syndrome requiring pacemakers. It can affect the neurological system affecting the sensory part, but as a difference compared to diabetics. It also affects the motor part of the nervous system affecting ambulation. And it can also cause autonomic dysfunction with orthostatic hypotension or erectile dysfunction. So it's a constellation of symptoms. So how do we put this together?

(15:12):

Well, some practices are doing checklists. They're doing a checklist. If you have a patient with heart failure with preserved ejection fraction, and if you have musculoskeletal symptoms or neuropathy symptoms or autonomic dysfunction symptoms, then you go and expand and start an amyloidosis workup. People sometimes tell me, Dr. Nativi for me it's hard to remember that list. And I say, okay, how about we remember just two to start just to start. If you want to do amyloidosis clinic, then you go through the whole list. But if you want to start something practical in your clinic, just remember the carpal tunnel and the spinal stenosis. So what we are teaching is if you have a patient with heart failure, with preserved ejection fraction or any heart failure, just expand your review systems on the clinical practice. It really takes less than 10 seconds to add to your review system.

(16:11):

The reason that I know is because I measure it, but we're not used to that. Cardiologists, we're not used to that. So we need to add about carpal tunnel, spinal stenosis and just adding those two, your pretest probability is going to be higher to unmask these patients. So that's kind of the way that we are unmasking a lot of patients. We had spent a lot of time educating providers about the EKG diagnosis, the echocardiographic diagnosis, the cardiac MRI diagnosis. But at the end of the day, something has to start that screening and it starts at the bedside. It takes 10 seconds. I start personally in our practice, it doesn't matter how the echocardiogram looks or the MRI looks, if you come to my clinic and you have

heart failure with preserved ejection fraction, you have bilateral carpal tunnel, you are going to go through the amyloidosis evaluation.

(17:06):

It doesn't matter how the rest of the things, because sometimes we tend to wait for the MRI or wait for the echo. I don't wait. I just order everything, the echo, the pyrophosphate and the diagnostic algorithm and go from there. And the last thing that I want to mention about the constellation of symptoms is something that we learned on the last, I will say probably around five to seven years. That is the musculoskeletal symptoms. They happen five to 15 years before you see it on the echo. So that's where we can have an impact on this delayed diagnosis that these patients are having. That's when we can say, okay, we combine these two symptoms, the carpal tunnel, the spinal stenosis, and then five, 10 years the patient developed heart failure. That's a very high pretest probability that this patient is going to be amyloidosis. And we are doing a lot of emphasis. And as you mentioned, we're trying to publish in this area of the musculoskeletal symptoms because they happen first.

Dr. Louis Kuritzky (18:10):

That certainly gives an open door to many of our primary care colleagues because certainly we see carpal tunnel, spinal stenosis, and all the distant tissue compartments that are affected by amyloidosis as well as the heart. And maybe we have to think about this upside down as you are explaining to us now, when you see that person with carpal tunnel and then they're developing heart failure, you need to think about amyloidosis now. And I think one other thing that was off-putting previously, when I heard that the diagnostic path included myocardial biopsy, it was easy for me to walk away from that.

(18:45):

So Dr. Singh, let's say that our colleagues hear Dr. Nativi's message clearly and they start thinking, darn it, there's a whole bunch more amyloidosis out there than I've ever looked for, and I'm going to be willing to pull the diagnostic trigger when I see a patient with HFpEF and spinal stenosis or HFpEF and carpal tunnel syndrome. What next steps would you want my primary care colleagues to know or cardiology colleagues also to know about in the diagnostic process? What should we be doing next? Maybe we'll just want to send the patient off to cardiology, but in the event we do want to participate, what participation should we do?

Dr. Vasvi Singh (19:23):

Yeah, absolutely. So as has been alluded to earlier, ATTR patients may demonstrate multi-organ involvement including cardiac and non-cardiac symptoms. And therefore maintaining a high index of suspicion in order to trigger a diagnostic pathway is extremely important in terms of testing to start with basic tests, those demonstrating low QRS voltage relative to the LV mass on ECG and echocardiography respectively should raise your suspicion. Maybe this is amyloid. And even though you know low QRS voltage has commonly been described in amyloidosis, it is a finding of a late stage disease and therefore a disproportionately lower QRS voltage in the presence of increased LV wall thickness should raise your suspicion about the disease even if the QRS voltage is normal. Other echo findings, especially concentrically increased LV wall thickness, diastolic dysfunction, I mean we've all heard the 555 signs where all the tissue velocities they reduced to less than five centimeter per second atrial enlargement, a myocardial speckling pattern.

(20:35):

They have been described on transthoracic echocardiography that individually they're neither sensitive nor specific for this disease. Now, apical sparing strain pattern on speckled tracking echocardiography, it

does carry a higher accuracy for cardiac amyloidosis. However, the specificity has been shown to be reduced in patients who have concomitant chronic kidney disease. So again, something to be aware of the limitations of each of these initial imaging tests. Now the recommended protocol would be in a patient that in clinically suspect of the disease is based on in addition to the ECG echo findings, you will look at if a patient had cardiac MRI, did they have morphological findings of amyloidosis, which would include not only increase LV wall thickness, thickness of the atrial ventricular walls, maybe increased RV thickness, thickening of the biatrial walls, but specifically on T1 mapping technique, they have significantly elevated extracellular volume, typically described more than 40% for both diagnostic and prognostic purposes.

(21:50):

And then they have certain pattern of almost diffused fibrosis on late gadolinium enhancement imaging. Once you have echo and MR morphological features and the patient may have a combination of one or both depending on what diagnostic testing they had initially. Now you then go down to find out if the findings that you're seeing on morphological imaging are they amyloid or not. The first step that we have to do is to rule out light chain amyloidosis because like we mentioned, that is a hematological emergency. And the recommended testing that is performed for ruling out light chain amyloidosis is serum and urine immunofixation and serum free light chain assay. Now if all of these three tests are negative, then we move ahead by ruling out a AL amyloidosis and order bone scintigraphy testing, which in the United States can be performed by technician 99 and pyrophosphate or HDP scan.

(22:48):

Now one caution that has been advised in several publications is that whenever we are employing bone scintigraphy testing with [inaudible 00:22:56] or HDP, we have to perform spec imaging in addition to planar in order to avoid false positive tests. Because on a planar anti posterior image, the heart may look like positive, but that may be due to radio tracer activity in the LV blood pool. Whereas if you looked at an axial SPECT image, you can clearly see if the positive uptake seen on planar, is it LV myocardial diffuse uptake or is it only blood pool activity? So HDP or PYP scan has to be with SPECT imaging. Now if your pyrophosphate or HDP scan is strongly positive, then in the absence of light chain amyloidosis, cardiac amyloidosis is diagnosed with high certainty. Now that we know that it is ATTR, we have to do genetic testing to know if it is either wild type or hereditary ATTR. So following is the diagnostic algorithm that is recommended by consensus statements and guidelines.

Dr. Louis Kuritzky (23:59):

That's very helpful. I want to get your reemphasis on two things if I could. The first thing is when I first read about bone scintigraphy, I said, what does bone have to do with pickup in the myocardium? So I want to make sure our listeners know that you did not make an error when you said bone scintigraphy. Was it just by accident that it was discovered that bone scintigraphy got highlighted in the myocardium to pick up extra scintographic signal in that method because they're going to otherwise feel funny about doing that?

(24:30):

And then the other thing I'd like you to comment on just briefly again, when we see a patient with back pain in primary care, every primary care doctor knows, prove and make sure this person does not have cauda equina. There's lots of back pain. Cauda equina is rare, but if you miss it's a dreadful error. It's unacceptable. And if I'm hearing you correctly, you're also saying amyloidosis is more common than we thought. There's plenty of amyloidosis, but unless you make sure they don't have a light chain disease, a light chain amyloidosis, that's a similar dreadful error. Am I putting that in the right perspective?

Dr. Vasvi Singh (25:06):

Absolutely. So to answer the first part of the question, yes, you know bone scintography radio tracers are very well known to especially nuclear cardiologists because in the 1970s they were used for acute myocardial infarction imaging. And then later in some biopsy studies, they realized that there are increased micro falsifications within amyloid hearts. And then several subsequent studies have postulated different hypothesis on why these radio tracers go and bind to amyloid. But that is one of the mechanisms described. So definitely there is a pathological overlap between them and therefore we saw the resurgence of these radio tracers that were used for myocardial infraction imaging in the acute setting now for cardiac amyloidosis imaging.

(25:54):

And to answer your second question, light chain amyloidosis absolutely needs to be ruled out first because that has a very dismal prognosis up to even six months when heart is involved without treatment. So number one, we need to send an urgent referral to a hematology oncology colleagues who would then initiate appropriate targeted therapy including chemotherapy in these patients. But then also the most common cause of false positive pyro phosphate scans is light chain amyloidosis.

Dr. Louis Kuritzky (26:26):

Wow.

Dr. Vasvi Singh (26:26):

So when we are working up for transthyretin cardiac amyloidosis, only when we rule out AL amyloidosis that we can say, ah-ha. Okay, now using non-invasive techniques, we know it is ATTR.

Dr. Louis Kuritzky (26:39):

Thank you for that clarification. Dr. Nativi, thank you for your contributions to our discussion so far. What are the two things you'd like to have our colleagues take home with them from this discussion we've shared?

Dr. Jose Nativi (26:52):

Well, thank you. I want to say that amyloidosis is not rare. We all have patients with amyloidosis in our clinic and we have ways to make these diagnosis with imaging and with laboratories. And all of you now can go back to your clinics and make a diagnosis of amyloidosis. And when you make that diagnosis, then you can tell the patient and their families that there's hope because now we have ways to treat them in a way to prolong their lives and improve their quality of lives.

Dr. Louis Kuritzky (27:26):

Thank you very much. I concur completely. Dr. Singh, two takeaways, please.

Dr. Vasvi Singh (27:31):

I agree with Dr. Nativi that a key takeaway that I would also mention is that ATTR cardiomyopathy is a prevalent disease and it is hidden in plain sight in the patients that we see every day. And therefore a very high clinical suspicion needs to be maintained by establishing a diagnosis of this disease. And then secondly, always remember that current advances in multimodality advanced cardiac imaging has enabled the diagnosis of this disease non-invasively in a majority of your patients. And therefore, pursuing a diagnostic pathway should be encouraged in the vast majority of your patients.

Dr. Louis Kuritzky (28:12):

Great, thank you. So my points to my colleagues are, don't forget what one of my colleagues coined the term myoelectric gap. When you see an echocardiogram, the reports ventricular wall thickness, they're looking at mass, not voltage. So you should be questioning if they showed LVH on the echo, why am I not seeing LVH or good degree of voltage on the EKG? That's a place to think of amyloidosis because the mass increases from simple infiltration of the amyloid fibrils into the tissue. And the second thing is this is not just for your new patients. We all have a huge group of patients who have heart failure and they have probably only a tiny minority of them ever been investigated for the possibility of amyloidosis. So even if you've had a patient for a long term and they seem to be doing fine, that's good, but especially if they have HFpEF, it's never too late to look for this contributory pathology and potentially have a major impact on the outcome of their disease.

(29:16):

We haven't touched on therapy in this particular session, but that is covered in other podcasts. So this concludes our discussion for today. I appreciate the contributions of Dr. Nativi and Dr. Singh and their willingness to share this information that will be valuable to clinicians of all endeavor. There are a total of six podcasts on this topic that will be completed sometime between now and June of 2023, and we hope that you'll be willing to join us for one or more of the remainder of this series called ATTR: Closing the Knowledge Gaps in Transthyretin Cardiomyopathy. It's important to recognize that this activity is supported by an independent medical education grant by Pfizer. The views and opinions in this activity are those of we the speakers, and reflect the synthesis of science that we have shared with you. The content should not be considered as the official policy of the American Heart Association. To get additional information, please visit learn.heart.org for more education. Thank you. Thanks to my colleagues and we hope you have a great day.