Dr. Brooks Cash (00:04):

Welcome to the American Heart Association, ATTR, Closing the Knowledge Gaps in Transthyretin Cardiomyopathy podcast series. I'm Dr. Brooks Cash and I will be leading the discussion today on the podcast entitled, Extra-cardiac Clues to Amyloidosis. I'm a gastroenterologist practicing at the University of Texas Health Science Center in Houston, Texas. I am joined today by my distinguished colleague, Dr. Chafic Karam, a neurologist from the University of Pennsylvania You might wonder why a podcast discussing a disorder that most commonly leads to cardiac dysfunction is being addressed by a panel that includes a gastroenterologist and a neurologist.

(00:38):

The recognition of amyloidosis has been typified by diagnostic delay. It is incumbent upon clinicians in non-cardiology specialties to consider amyloidosis in clinical presentations that range from gastrointestinal symptoms to orthostatic hypotension, and numerous considerations in between. To that end, a gastroenterologist and a neurologist will share their perspectives on amyloidosis.

(01:05):

This series is intended to enhance the ability of healthcare practitioners to recognize and provide for early identification of patients with transthyretin amyloid cardiomyopathy, commonly referred to as ATTR-CM, and to ensure the accurate diagnosis and timely initiation of the appropriate treatment therapies, before the onset of cardiac dysfunction.

(01:28):

Today's learning objectives are to highlight the gastroenterological and neurological presentations of amyloidosis. We also hope to increase awareness of currently available amyloidosis treatments and to discuss steps to enhance recognition of amyloidosis more diversely amongst non-cardiologic specialties of medicine. As I mentioned, we're joined today by my distinguished colleague, Dr. Chafic Karam. Dr. Karam, please introduce yourself.

Dr. Chafic Karam (01:58):

Yeah. Thank you, Dr. Cash, for this introduction, and thank you for having me. I'm a neurologist. I specialize in peripheral neuropathy and amyloidosis. I work at the University of Pennsylvania. I also work in a multidisciplinary clinic to treat people with amyloidosis, here at the University of Pennsylvania.

Dr. Brooks Cash (02:19):

Wonderful. And I'm Brooks Cash, Chief of Gastroenterology here at the University of Texas Health Science Center in Houston, Texas at the Texas Medical Center. I focus primarily on motility disorders in my practice of general gastroenterology, but I do see patients with amyloidosis presenting with these types of symptoms. Dr. Karam, can you give us a view of the current amyloidosis clinical landscape, from the perspective of a neurologic expert?

Dr. Chafic Karam (02:53):

Yes, of course. We're talking about TTR amyloidosis today. That's the main interest of cardiologists. As you know, there's two flavors for TTR amyloidosis. There's the wild-type and there's the hereditary amyloidosis, or TTRV, with the V standing for variant. I mainly see people with TTRVt, but I do sometimes see patients with wild-type amyloidosis. The reason I mainly see people with hereditary amyloidosis is because the neuropathy associated with this form of amyloidosis can be predominant in

those patients, especially the non V122I variant, which, in the US, is common. It can be seen in 3 to 4% of Black people, and it mainly manifests with heart failure and carpal tunnel syndrome.

(03:43):

Whereas with the other variant, a lot of time, they have neuropathy, meaning they develop numbness, tingling, burning, pain, and weakness in the feet that can affect their balance. They can also frequently have carpal tunnel syndrome. They frequently have dysautonomia, meaning that they feel lightheaded, and may pass out when they stand up. They may lso feel full early, develop severe diarrhea, and soiling, and some men may experience erectile dysfunction. There are many different manifestations of TTRV. Some patients can present with floaters in the eye that can obscure their vision, and some variants can present with central nervous system disorders such as ataxia..

(04:32):

There are many different neurological manifestations for TTRV. This is important to remember when you're seeing a patient with heart failure or cardiac dysrhythmia. As you probably know people with TTRV can have AFib and at the same time, they can have carpal tunnel syndrome, or neuropathy, or they're losing weight because of their dysautonomia. You, Dr. Cash, will tell us a little bit more about the dysmotility, so I'm not going to go into those. But if you have a combination of these symptoms, that should really raise the suspicion of amyloidosis, especially now that this is a treatable condition.

Dr. Brooks Cash (05:10):

Well, thank you so much. And you're right, that was a perfect lead into my discussion of the GI symptoms, and you did mention several of them. Perhaps the most common that we see, and we often will see this as an early symptom, is weight loss.

(05:35):

In terms of the other things that we encounter, with these patients in GI, just to put this into perspective, are a wide variety of functional GI symptoms, often mimicking those of irritable bowel syndrome, such as constipation, diarrhea, abdominal pain, bloating, and nausea. There was a really nice survey called the THAOS survey that was based on a registry database. What they found in their analysis, published about a decade ago, was that somewhere between about 56 to nearly 70% of patients with TTRV, depending on the mutation reported GI symptoms.

(06:05):

Now, we tend to see more GI symptoms with the Val30Met variant. That's the most common cause of TTRV with polyneuropathy. Those are the patients that we tend to see in a western population that are presenting with GI symptoms. In addition to weight loss, which I, as a motility expert, would consider an alarm feature, if I'm evaluating somebody for, let's say, irritable bowel syndrome, weight loss is always what we call an alarm feature that deserves additional investigation.

(06:36):

But some of the other more common symptoms are quite vague, and they fit into what we would call functional GI symptoms, meaning that these are symptoms like postprandial fullness, or early satiety, nausea, vomiting, constipation, diarrhea, alternating constipation, diarrhea, bloating. These are the most common types of symptoms we see in these patients. Unfortunately, those are also the most common types of symptoms that we see in general GI practice, especially in motility practice.

(07:05):

The concept that is that the underpinning of these symptoms is that they derive fromdisordered motility. Now disordered motility may cause symptoms in and of itself, because patients are not propelling their ingested food appropriately out of their stomach, or perhaps even their small intestine, but there may also be secondary effects. There may be small intestinal bacterial overgrowth and there may be changes in the microbiome as a result of SIBO or from altered motility. There can be changes in intestinal permeability, which lead to translocation of inflammatory cells, cytokines, and other organisms, which can then lead to inflammation and/or visceral changes with regards to sensation.

(07:52):

These are the underpinnings of the biopsychosocial theory of irritable bowel syndrome, and disorders of gut-brain interaction. In that regard, hereditary TTR is really no different. We have to have this heightened index of suspicion when we do see patients presenting with these symptoms. That's really where, I think, we have room for improvement, thinking about this condition as a potential cause.

(08:19):

Now, it's an incredibly rare condition. The prevalence of irritable bowel syndrome, or its upper GI counterpart, functional dyspepsia, in the general population, is somewhere between four to perhaps as high as 10%, depending on which clinical criteria you use. However, there's a much lower prevalence of ATTR amyloidosis. We have to keep that in mind, just in terms of our pretest probability for diagnostic testing and suspicion of the likelihood of the condition. But when we do see this admixed with other symptoms such as peripheral neuropathies, with problems with ambulation, and perhaps with the cardiovascular disorders that are common to the condition, then we really need to be thinking about ATTR as a possible etiology.

(09:02):

That's what this podcast is meant to do. To get us to be aware of this condition as a possible cause for common extra-cardiac symptoms, as well as to also to have the wherewithal to diagnose this condition. Dr. Karam, do you see a path for extending the role of primary care clinicians in the evaluation of patients for ATTR? By that I mean the role of physicians, nurse practitioners, and physician's assistants in the identification and/or referral of patients with potential amyloidosis.

(09:33):

And I'm also going to ask for an extension of that. You're an expert that focuses on this, and I have some focus on this in my practice as well, but what about our specialty colleagues? I dare say that we probably could apply the same rubric to some of our specialty colleagues, with regards to expanding the role in this condition.

Dr. Chafic Karam (09:55):

Oh, yeah, I definitely agree with you. First, with the role of the primary care clinician, whether it's a physician, nurse practitioner, physician assistant in family medicine, or internal medicine, these people are frequently the first to see these patients. Then the patient will come to them with these symptoms, and they have a challenging job. As you just mentioned, these diseases are rare, and we specialize in these disorders, so we may see things from a different lens.

(10:27):

But for the busy physician, and general practitioner, who's dealing with thousands of different diseases, what would make them think about amyloidosis? You pointed nicely to the fact that, for example, IBS is extremely more common, 100 and thousands of times more common than amyloidosis, so how do we think about this condition? This is a very challenging question that I always think about. In my opinion,

you take things as you suggested, one, which is a multi-organ involvement. If you have a patient who seems to have a multisystemic disorder, they're having neuropathy, they're having heart disease, they're having GI symptoms, so that is not just your typical IBS, or your typical distant neuropathy.

(11:18):

The other thing is that if you're trying different medication, and they keep progressing, so amyloidosis for example, neuropathy is not just going to respond to your regular treatment. It does need targeted treatment, same thing for the GI. The symptoms are frequently more severe. You mentioned weight loss, which is obviously a red flag, and not just amyloidosis, but a lot of different medical conditions. I think that, yes, there are the gatekeepers, the people who sees the patient first, and who may think about this condition, especially if you have multiple symptoms, or if you have one organ that is involved that continue to be more and more involved in refractory therapy.

(11:58):

I think at this point, and for our colleagues, same thing, if you see any red flags that we discuss frequently at amyloidosis, if you see for example, you're doing an ultrasound and you have specific sign that are suggestive on the echo of amyloidosis, if you're doing an endoscopy, and you take a biopsy, you stain it for with Congo red, and that shows amyloidosis. I do have several patients who were diagnosed that way for severe GI dysmotility, and they underwent a biopsy. That was one of the way.

(12:30):

I have a few patients who underwent carpal tunnel surgery, and they had a biopsy, and that showed amyloidosis. For my colleagues in neurology, for example, I tell them if you have a patient with a neuropathy and you've already ruled out diabetes and vitamin deficiency, but they keep getting worse, then that's worrisome. We don't call it idiopathic if it keeps progressing, and the patient now has weakness. We do have to look for other, more serious disorders, including amyloidosis. I don't know if this has been your experience, so if you have something to add on this, from a GI perspective.

Dr. Brooks Cash (13:08):

No, I think that you are spot on. There is the old adage, when you hear hoofbeats, you think of horses and not zebras, but that doesn't mean that zebras don't exist. Thinking about these patients, and identifying them, and this is really for our primary care and specialty colleagues, I think it's exactly what you said. This is true of other rare conditions aswell, such as one that I look for reasonably frequently,acute hepatic porphyria. This is a rare condition that may presentwith neurologic symptoms, pulmonary symptoms, some cardiovascular symptoms in addition to severe abdominal pain, but we rarely think about it.

(13:48):

The key is to consider these conditions when you encounter patients with the foot drop, or the limb weakness, or seizure activity, who also have perhaps some abnormal lab findings, suggesting a multisystem disease process. I also think that your point, with regards to the inherited nature of this condition, highlights the importance of taking the family history. I dare say that our primary care colleagues probably are better at this than we are. I don't know that for sure, but I think that's really important to do, because if there is a family history of amyloidosis, our suspicion for this disorder should increase.

(14:27):

We need to keep an open mind and maintain a broad differential diagnosis when we encounter patients with a plethora of what look like disparate symptoms. Ofcourse, we need to think about common things being common,bFrom a GI standpoint, our therapeutic approach to these patients is very symptom-based. We're not specifically treating the amyloidosis. We are treating their diarrhea, their constipation, their nausea. However, there are specific therapies for amyloidosis that may actually be disease modifiers, and may actually help to change the extra cardiac manifestations of the condition.

(15:08):

One of the things that I would point out, with regards to my colleagues, or other practitioners, from a GI standpoint, is that there is a relatively set algorithm that is promoted by the Rome committee for disorders of gut-brain interactions, specifically with regards to irritable bowel syndrome. We tend to recommend people be minimalists with regards to diagnostic testing, in the absence of alarm features when you suspect IBS. But if you do have patients who come in with unexplained and unintentional weight loss, or other alarm factors, then it is recommended that you do some diagnostic testing. Specifically for patients with diarrhea and abdominal pain, or bloating, or distension, we do recommend getting a fecal calprotectin.

(15:59):

Now, if that's elevated, that's actually been shown in some studies to be a marker of organic disease, that may be even associated with amyloidosis. Certainly, we think about that in context with inflammatory bowel diseases, but we should consider other disorders like TTR as well. That may lead us to do a colonoscopy, or perhaps even an upper endoscopy, and when we do, we need to take deep biopsies and send for Congo red staining. We need deep biopsies because amyloid is not in the mucosa, so we've got to get to the submucosa. That is the best way, from a GI standpoint, for us to make this diagnosis.

(16:34):

I will use clues if I look through and see if patients' echocardiogram, and they've got findings that are suggestive of amyloidosis or ifthey've got myocardial thickening, that may prompt me to do an endoscopy to obtain these deep biopsies. Theseswould be my major point, from a GI standpoint, in terms of diagnosis. Do the right test, which is a deep biops, if you're suspect amyloidosis and send that specifically for the appropriate staining. Now I'm going to move on to therapy. Chafic, while we've had a good discussion on the inherent obstacles to identifying amyloidosis, especially in specialty care what treatments are existing or on the horizon?

Dr. Chafic Karam (17:25):

Yeah, that's a great question, and it's actually one of the exciting things about hATTR , that we do have treatments available right now, and we have treatments in development. The future is really looking bright. The drugs that we currently have really alter the natural history of the disease, and not only help stop the progression, improve quality of life, but also increase survival of our patients with this condition. Not a very long time ago, the only treatment option for these patients was liver transplant for the hereditary type.

(18:06):

Then came diflunisal, which is used off-label. Then tafamidis was approved in other countries, not in the US, for over a decade, for the neuropathy. More recently, we've had a breakthrough in what we call the silencers, with first patisiran, and inotersen, and now vutrisiran, and hopefully soon eplontersen. So there are a lot of options for our patients. They're getting more and more convenient, and with less side

effects. For those with cardiac amyloidosis we have tafamidis, which also is very helpful for our patients. In the future, there'll be even more treatments.

(18:48):

They are being studied right now, and in development. It's also important to focus on the symptoms of the patient. We try to modify disease course with the amyloid-specific treatment, but we also want to relieve our patient from symptoms of neuropathy, for example. For people who have pain, we have several options that we can use to help them with their pain. For example, gabapentin is one of the most frequently used, and duloxetine is another one that can help with pain. In people with wild-type ATTR, a lot of time they have spinal stenosis, so they can be referred to surgery. They can also have biceps tendon rupture and carpal tunnel syndrome. All of these can be addressed.

(19:31):

Even the hereditary patients can suffer from those symptoms and complications and these are treatable conditions. For eople who have significant dysautonomia with the orthostatism, you can give them medication, like midodrine, to increase their blood pressure. There are other ways to help with those symptoms as well. For people with erectile dysfunction, you can target that for treatment as well. Then, obviously, one of the challenges that I personally have, and I'm really glad you're here, because it's hard for me to find GI doctors to help with, the diarrhea or the dysmotility that these patients can experience. A lot of time, I end up prescribing medication myself, but I'm glad you're here, because I would like to see what tools you use to help patient with those conditions.

Dr. Brooks Cash (20:16):

I appreciate those comments and I echo them. For the disease modifying medicines that you discussed I send those patients to an expert, because I'm not familiar with those medications in my routine practice. But for the motility disorders, and the symptoms that these patients often have,we're very comfortable dealing with these from a GI perspective. You mentioned some of them. In fact, we use a lot of the medications that you mentioned, the gabapentin and the duloxetine for pain, low dose tricyclic antidepressants as well. Those have long been used by gastroenterologists to modulate visceral hypersensitivity.

(21:02):

From a GI perspective, as I mentioned earlier, we're largely treating the symptoms. For dysmotility, especially on the slower, or more delayed side, we do have some very valuable newer therapies that have come onto the market recently. The one that I primarily use in these patients is prucalopride, which is a 5-HT4 agonist therapy.That's been approved in Europe forclose to 15 years, and in the US for the last three or four.

(21:41):

It's indicated for chronic idiopathic constipation, but it's a very specific 5-HT4 agonist that increases high amplitude propagating contractions, not only in terms of their frequency, but also their strength. There's some evidence that it can help augment not only small intestinal motility, but also gastric emptying. It is not a replacement for the traditional therapies for gastroparesis, but it can potentially have some benefit in those patients, based on some small studies done in Europe. (22:28):

We also use medications such as metoclopramide or domperidone. Domperidone is not FDA approved and needs to be obtained through a special IND But metoclopramide, commonly used for gastroparesis symptoms, is used frequently. For patients who have more of a constipation picture, in addition to

prokinetics, we can use secretagogues. Medications that bring fluid into the gut, and those include the GC-C agonists, like linaclotide, as well as plecanatide, perhaps even lubiprostone.

(23:07):

Most recently, a drug called tenapanor, a sodium-hydrogen exchanger type three inhibitor was approved for IBS with constipation. IBSrela causes retention of dietary sodium and therefore retention of other ions and fluid in the gut. That's been shown to be helpful in patients with irritable bowel syndrome with constipation. We'll use all of these medications, in addition to a multitude of over-the-counter therapies, to try to alleviate the GI symptoms that these patients have.

(23:39):

Oftentimes, it's a very iterative process. I frequently will end up treating patients with repeated courses of non-absorbed antibiotics, such as rifaximin for bacterial overgrowth. Because of their small intestinal dysmotility, they're predisposed for that condition. If they respond to that, we just simply retreat them whenever they get recurrent symptoms. There's a lot of variability with regards to approaching these patients and we have to approach them all individually. But it's important to recognize that ut there are a lot of options that we have to alleviate their symptoms. Not necessarily disease modifying therapies, but symptom modifying therapies.

(24:15):

That's really a compendium, in my mind, with regards to some of the therapies that a gastroenterologist would be able to bring to bear for these patients. I want to just wrap up, and let's just review the takeaways from today's discussion. Dr. Karam, let's start with you, and then I'll provide mine, and then we'll go ahead and close out.

Dr. Chafic Karam (24:38):

Yeah. Again, I think we need to remember there's the two main types that we deal with, the wild-type and the hereditary amyloidosis. When you have a patient with peripheral neuropathy, and common that's progressive, and you have also combination of dysautonomia, GI issues, heart disease, biceps tendon rupture, carpal tunnel syndrome, lumbar stenosis, floaters, ocular issues, et cetera. Any of those combinations, and weight loss, you should really think about amyloidosis, and consider that. Especially now that we have so many different treatments that can change the life of the patient. We do know that the earlier we use these treatments, the better the outcome.

Dr. Brooks Cash (25:25):

I agree completely with regards to my GI takeaways. It is that amyloidosis is a mimicker of disorders of gut-brain interaction. We frequently will see patients with symptoms that remind us of functional dyspepsia, or irritable bowel syndrome, chronic diarrhea, or chronic constipation. The early unintentional weight loss is a big red flag, and along with, as Dr. Karam mentioned, the other symptoms, the neurologic symptoms, the carpal tunnel. That keeps bubbling up, it's a bad prognostic sign in these patients.

(26:00):

We need to be really keeping our ears to the ground, with regards to thinking about this in our differential diagnosis when we encounter patients who have this plethora of other extra gastrointestinal symptoms, extra cardiac symptoms, and those neurologic symptoms as well. Having a high index of suspicion and knowing how to diagnose this condition with deep biopsies from the GI tract k, is important from a GI standpoint.

(26:33):

Generally, I will recommend the stomach, for these deep biopsies. Because it's thicker, you've got a little more protection to take those deep biopsies. Perhaps also the distal colon and send that tissue sample specifically for Congo red staining. Then treat the patient symptomatically, but also get them into the hands of an expert to address those other issues, with regards to their neurologic care, and their cardiac care. Those would be my major takeaways from our discussion today, as well.

(27:09):

I want to thank Dr. Chafic Karam for joining me today. 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 science. Content should not be considered as the official policy of the AHA. To get additional information, please visit learn.heart.org for more education. This concludes our discussion for today. I'm Dr. Brooks Cash, with Dr. Chafic Karam. Thank you for joining us today and have a great day.