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Best Practices for Identifying, Diagnosing and Treating Transthyretin Amyloidosis (ATTR-PN and ATTR-CM)

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Welcome to CME on ReachMD. This activity titled, "Best Practices for Identifying, Diagnosing and Treating Transthyretin Amyloidosis (ATTR-PN and ATTR-CM)" is provided by Voxmedia.

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Dr. Russell:
This is CME on ReachMD and I'm Dr. John Russell. Joining me to share best practices for identifying, diagnosing and treating transthyretin amyloidosis are Dr. Sammy Khella and Noel Dasgupta.

Dr. Khella is a Professor of Clinical Neurology and Chief of the Department of Neurology at Penn Presbyterian Medical Center in Philadelphia.

And Dr. Dasgupta is an Associate Professor of Clinical Medicine, Clinical Pathology and Laboratory Medicine at Indiana University in Indianapolis.

Dr. Khella, Dr. Dasgupta, welcome to you both.

Dr. Khella:
Thank you very much. It's nice to see you all.

Dr. Dasgupta:
Thank you so much for having us today. It's always exciting to talk to Sammy about amyloidosis

Dr. Russell:
So, why don't we get started?, Why don't we start with you, Dr. Khella. Can you give us some background on amyloidosis and how it's classified?

Dr. Khella:
Yes, Dr. Russell, there are a number of different types of amyloidosis. The kind we're talking about today is a systemic amyloidosis, not really cerebral amyloidosis as occurs in Alzheimer and other neurodegenerative disorders. And the type we're talking about today is hereditary transthyretin amyloidosis. Of course, we have to mention light chain amyloidosis. Now, hereditary amyloid transthyretin amyloidosis is a disorder of the TTR, or the transthyretin protein, and it is hereditary, as the name implies. However, there is also a wild-type form where there is no genetic variant in the amino acid sequence of the TTR protein. Light chain amyloidosis is a product of a clone of cells that is making either the Kappa, or more frequently the Lambda light chains, this is a malignancy that is treated in a separate and different way than hereditary amyloidosis.

For the hereditary amyloid type, it presents as either a cardiomyopathy or a peripheral neuropathy, or a combination of the two. And the

peripheral neuropathy is usually an axonal form that is fiber length dependent. And if you remember, nothing else from this talk, remember that this is a progressive neuropathy that is occurring because the TTR gene is making a protein that is misfolding and then depositing in the various tissues that I mentioned.

Dr. Russell:
So, with that background in mind, let's zero in on the two forms of hereditary ATTR amyloidosis. Sticking with you for just another moment, Dr. Khella, what are the signs and symptoms of ATTR polyneuropathy?

Dr. Khella:
This is really a multi-systemic illness and I will talk about the neurologic forms of this disease, and then I will defer to Dr. Dasgupta to discuss the cardiac abnormalities. For the neuropathy that develops, it's as I said, an axonal fiber length-dependent process that occurs initially as a small fiber neuropathy in the feet and toes and it may be very painful, or it may not be painful, and it progresses up into the proximal portions of the lower extremities. And of course, it causes also a carpal tunnel syndrome as well as a systemic neuropathy, or peripheral neuropathy, affecting the fingertips. And again, it that progresses up the arms.

In addition, this illness, both the hereditary form and sometimes a little bit in the wild-type form, people get gastrointestinal symptoms caused by dysautonomia. The gastrointestinal symptoms can be an alternating diarrhea with constipation, and orthostatic hypotension with lightheadedness, and sometimes even syncope. There are also tendinopathies that can be associated with this. Biceps tendon rupture is a classic form, as well as carpal tunnel syndrome.

And I will turn it to Dr. Dasgupta to discuss the cardiomyopathy form.

Dr. Russell:
So, along those lines, Dr. Dasgupta, what are the signs and symptoms of patients with ATTR cardiomyopathy?

Dr. Dasgupta:
Yes. Patients often present with heart failure. So, signs and symptoms of heart failure can include things like shortness of breath, swelling, feeling like you're out of breath when you're walking. Often, the heart function is initially normal, but the heart walls are stiff, so the heart relaxes slowly, and this can cause a diastolic type of heart failure. Further in the disease, the heart muscle can actually get weak, and you can get heart failure with reduced function of the heart.

One of the things we often see in this condition is that the walls of the heart are thicker than we would expect. Sometimes we can have other causes of wall thickening, like hypertension, but in patients with amyloidosis where protein is deposited in the heart, they have unexplained thickening of the heart walls.

So, we may see this as a discrepancy between the amount of electrical conduction we see on the EKG because this amyloid protein doesn't conduct electricity compared to the thickness of the walls on cardiac imaging. Patients might also have problems with the conduction disease, or with the conduction system of the heart. The amyloid can deposit in the conduction system and lead to heart arrhythmias, heart block. Commonly, patients present with things like atrial fibrillation. Sometimes the heart valves are affected, and we can see things like aortic stenosis, where the aortic valve, the valve that pumps blood to the body, is thickened and narrowed. And this is especially common when we see a form where the heart size is normal, but the walls of the heart are thick, so the stroke volume is reduced results in low flow, low gradient aortic stenosis.

This is often a multi-system disease, so in addition to seeing cardiac features, we also see nerve involvement. And as Dr. Khella said, we can see other symptoms like diarrhea and constipation, so it's really important to talk to other specialists.

Dr. Russell:
So, given those cardiac symptoms, let's focus on diagnostic approaches. Coming back to ATTR polyneuropathy, Dr. Khella, what tests are used to diagnose patients who primarily have neurologic symptoms, but maybe even have some cardiac symptoms as well?

Dr. Khella:
When I see a patient with a progressive neuropathy that is either just sensory progression, or sensory and motor progression, especially if the patient has proximal weakness. That is one of the tip offs that occurs in this disease as the motor symptoms progress. I do a number of things, and sometimes I do them all at once, depending on how advanced the patient is. I do genetic testing, and if the patient does not have a genetic variant, and I've done a biopsy either of skin or fat aspirate, nerve, salivary gland, or I would defer to my cardiology colleagues if the patient has had a heart biopsy. All of those tissues can be done to stain them for Congo red and then do mass spectroscopy to identify the protein if there is a Congo red stain. If there is no Congo red stain, and the genetic testing is negative, then the patient doesn't have amyloidosis. If the genetic testing is negative but the Congo red stain is positive, then the patient has wild-type amyloidosis and as I said, the Congo red staining tissue needs to be typed. The protein needs to be typed, either by mass

spectroscopy or less sensitively, by immunohistochemistry.

Now, if the genetic testing is positive for a pathogenic variant, and you know there are now more than 130 identified pathogenic variants. But in the United States, the most common ones are the V122I T60 and the V30M variants. Those are the most common. If a patient has one of those or any of the others that have been identified, and the biopsy is negative, then the patient doesn't have the disease amyloidosis, the patient is a carrier and needs to be followed, probably lifelong because some carriers may then go on to have symptomatic disease.

On the other hand, if the genetic testing is positive and the patient has a positive Congo red staining tissue that is identified as TTR, then they have the disease H-ATTR, hereditary ATTR amyloidosis. And that is my paradigm for evaluating a patient who I suspect has amyloid neuropathy.

Dr. Russell:
OK, so how about ATTR cardiomyopathy, Dr. Dasgupta? What tests are used to diagnose patients who have predominantly cardiac symptoms, and how might that approach change if they also would have some of these neurologic symptoms?

Dr. Dasgupta:
Well, the first thing is to recognize patients that might be at risk for ATTR cardiomyopathy. Those tend to be older adults. We know in the United States, the V122I mutation affects 3 to 4% of African Americans, and we know that this is more commonly diagnosed to date in men. So, looking at older patients, potentially African American, and identifying if they have anything, like unexplained thickening of the heart walls would be one thing to first think about. How we actually approach the patient once we have a high clinical suspicion is to look at the EKG. And again, as I mentioned previously, the amyloid protein doesn't conduct electricity, so the voltage on the EKG will seem low relative to the amount of wall thickness we see on imaging. One of the things is to first notice a discrepancy between the EKG voltage and the LV wall thickness on cardiac imaging.

In terms of cardiac imaging, the two techniques that are often used to first screen for cardiac amyloidosis are echocardiography, first noting thick walls, and often, the ejection fraction is preserved. We can also do a special technique called strain, where we're actually looking at the mechanical deformation of the heart, and what we notice is that the deformation is normal in the apex compared to the other segments, and this is considered an apical sparing pattern. Seeing an apical sparring pattern is one clue that the patient might have amyloidosis.

Cardiac MRI is also done frequently, and we may see diffuse late gadolinium enhancement and increased extracellular volume.

Now, these techniques are all very helpful to identify a patient with potential cardiac amyloidosis. Once you have a high suspicion from one of these tests, and after you've excluded light chain amyloidosis by checking serum free light chains, serum immunofixation, and urine immunofixation, you want to do a test to definitively diagnose cardiac amyloidosis. So, you can choose either a biopsy diagnosis or a non-biopsy diagnosis.

For a biopsy diagnosis, you can biopsy any organ that you think is affected. Most commonly for cardiologists, we biopsy the heart, but other sites could be chosen.If you do a biopsy and you find amyloid deposition, then you can type the amyloid protein to determine what type of amyloid is seen in the heart or other organ. Alternatively, if you do not want to perform a biopsy diagnosis, you can use bone imaging techniques to try to noninvasively identify cardiac amyloidosis. What we found is that tracers previously used for bone scintigraphy take up in high quantity in transthyretin amyloidosis. We utilize this technique to help diagnose transthyretin amyloidosis after we've excluded that the patient does not have light chain amyloidosis.

After you confirm the patient has amyloidosis either by doing a biopsy with typing or by seeing a nuclear test in the United States, we usually use pyrophosphate that shows high uptake resistant with transthyretin amyloidosis. We then go ahead and do genetic testing to determine if it's wild-type or hereditary, as Dr. Khella discussed.

If there is evidence of both cardiac and neurologic involvement, it can be more tricky to treat the patients and we have to consider what other systems are involved as well. For example, if the patient is having diarrhea and also having heart failure, we have to determine if we need to adjust their diuretics in response to how much diarrhea they're having. We have to look at things like if their blood pressure falls when they stand. So, it's more complicated when patients have multi-system disease because any treatment you give could affect another organ. It's also important to consult with a neurologist or other specialists.

We also know that currently, specific treatments are approved for neurologic disease only. If a patient has hereditary disease with neurologic involvement, they may be a candidate for additional therapies. Having a good neurologist and other specialists is always very important.

Other things that I didn't mention before in terms of labs would be elevated troponin and NT-proBNP that are unexplained.

Dr. Russell:
For those just joining us, this is CME on ReachMD. I'm Dr. John Russell, and I'm talking about the management of ATTR amyloidosis with Dr. Sammy Khella and Noel Dasgupta.

Dr. Khella, once a patient is diagnosed with ATTR polyneuropathy, what is their typical prognosis?

Dr. Khella:
Well, the prognosis depends on where they are in their force. Patients with very early disease who are treated early can have a stable, prolonged course of peripheral neuropathy with the therapies that we will discuss in a minute. However, as the patient continues to advance, and as I said, this is a progressive neuropathy, their survival may be significantly diminished. Now, most of these patients who have illness that is causing that's going to cause them to die, they usually die of heart failure and other cardiac abnormalities. They don't typically die of the peripheral neuropathy, except for patients who present with very early and severe early in their life. In other words, in their 30s or 40s, and a severe form of the polyneuropathy that can be deadly.

The problem that patients have in terms of survival is really the delay in diagnosis. It takes a number of Dr. visits, sometimes a number of years. In one study, it took more than 6 years from the onset of symptoms for patients to be diagnosed. So, it's not unusual for a patient to go for several years before being diagnosed with H-ATTR.

In terms of survival, we don't really know the new figures, given the therapies that we have available. The time to survival in the pre-therapeutic era for hereditary ATTR was about 8 to 10 years. Commonly these patients are misdiagnosed because the neuropathy is confused most often with chronic inflammatory demyelinating polyneuropathy, that's a mouthful. Otherwise known as CIDP. And CIDP is a demyelinating neuropathy, whereas amyloid neuropathy is axonal. And CIDP is very responsive to immunotherapy, whereas amyloid neuropathy does not respond to immunotherapy. They do look a little bit alike in that both amyloid neuropathy and CIDP neuropathy cause proximal muscle weakness, unlike most of the other neuropathies like diabetic neuropathy or alcoholic neuropathy or nutritional neuropathy or chemotherapy-induced neuropathy. I could go on and on. But all of those other neuropathies, they usually cause just a distal weakness, whereas CIDP and amyloid cause proximal and distal weakness.

Finally, the patients are misdiagnosed because they are treated for CIDP and it takes a year or two years of getting IV Ig and not responding and continuing to progress until somebody realizes that this may be the wrong diagnosis.

For the cardiomyopathy, I would defer to Dr. Dasgupta to discuss the diagnosis, and especially the prognosis and survival.

Dr. Russell:
Along those lines, and speaking of prognosis, Dr. Dasgupta, can you tell us about the prognosis for patients with ATTR cardiomyopathy, and how that prognosis differs for patients that have ATTR polyneuropathy with cardiac involvement?

Dr. Dasgupta:
This is a disease of older individuals in general. For patients with a known family history, they may have had genetic testing where they're able to identify the disease earlier than patients without a genetic mutation that is known.

For hereditary or variant ATTR cardiomyopathy, the patients are typically over age 40 when they develop symptoms. For the wild-type form, where there is no mutation, but the disease seems to occur more with aging, they tend to be over 50 years old, but more commonly in the 60s or older.

In both cases, the majority of patients are men that are diagnosed. However, we know that there are probably more women that have the disease that we have not been diagnosing, and these may be under diagnosed. For patients who have cardiomyopathy, they may see multiple specialists. Often it takes two or three years at least before they are diagnosed with amyloidosis, and the life expectancy for a patient with variant ATTR with just cardiomyopathy is estimated to be about 2 to 5 years based on prior data, and with wild-type 4 years. And with patients who have variant ATTR with predominantly cardiomyopathy, it's estimated that the life expectancy after diagnosis is 8 to 10 years. lHowever, we don't really know what the life expectancy is today because these figures are based on patients that weren't treated. Now we have new therapies that actually work and can stabilize the disease, so patients are living longer and have improved quality of life.

Dr. Russell:
How about we switch gears and move off the prognosis and move towards focusing on treatment? Dr. Khella, can you briefly review current and emergent therapies for ATTR polyneuropathy?

Dr. Khella:
Yes. Well, as we alluded to in the beginning of the talk, TTR has made primarily in the liver. It's made in other parts of the body, but the

current therapies target production of liver. From that organ, TTR secreted into the bloodstream, and it's made in the liver as a monomer, and in the bloodstream, it circulates as a tetramer, as a homotetramer. It is most stable in its homotetrameric form when it is normal. However, in wild-type disease and in hereditary ATTR, the misplaced amino acid in the case of the hereditary form, and for reasons that are not entirely clear in the wild-type form, the tetramer falls apart, if you will, and becomes a misfolded monomer. These misfolded monomers then aggregate into these small oligomers that finally deposit in the tissues as toxic amyloid fibrils that are not very well removed from the tissues and end up causing destruction of the tissue

The therapies have been targeted to either reduce the amount of TTR that's being produced from the liver, and/ or the tetramer is stabilized so it stays as a tetramer rather than falling apart and misfolding as a misfolded monomer. The drugs that are FDA approved in the United States for lowering TTR production in the liver are patisiran, inotersen, which is really not going to be produced anymore and has been replaced by eplontersen, vutrisiran, are the FDA-approved drugs. These are used and FDA approved for the treatment of polyneuropathy. The TTR tetramer stabilizers are tafamidis and diflunisal.

Tafamidis is FDA approved. Diflunisal is the old nonsteroidal that's not used anymore as a nonsteroidal to treat the arthritic pain and so forth. So, diflunisal and tafamidis are the drugs that currently are used to stabilize the tetramer. These are used either in early polyneuropathy where diflunisal has been shown to reduce the progression of the neuropathy compared to placebo. And tafamidis as well, although tafamidis is not approved in the United States for neuropathy, it's only approved for cardiomyopathy. And going to the FDA for approval is acormadis, which is also known also known as AG10.

There are currently trials to try to remove the fibrils once they've deposited in the tissue, but these trials are currently in progress, and we don't have public data for their efficacy.

Dr. Russell:
Along those same lines, Dr. Dasgupta, what does the therapeutic landscape look like for ATTR cardiomyopathy?

Dr. Dasgupta:
Well, first, as Sammy mentioned, we try to work on this disease by attacking different parts of the pathway. As you recall, the transpiration protein is made by the liver and comes as a tetramer, or four pieces bonded together. And something may happen where that tetramer becomes unstable, and it can misfold into monomers that can go to different organs and tissues and cause end-organ dysfunction. The stabilizers are medications that bind to the tetramer and prevent it from breaking down.

Tafamidis is the only therapy that is approved currently for cardiomyopathy, and it is a TTR stabilizer. It showed a decrease in all-cause mortality in hospitalization and there was less decline in the 6-minute walk and quality of life scores than placebo. That's our only therapy right now that's approved.

Acormadis is another stabilizer that recently completed a trial and showed a win ratio of decreased mortality and cardiovascular hospitalization than NT-ProBNP and 6-minute walk. That’s another stabilizer that may be approved in the future if it's approved by the FDA.

The next type of drugs that we're looking at are what are known as silencers. These are drugs go to the liver and prevent the liver from synthesizing most of the protein. These include drugs that are small interfering RNAs, or antisense oligonucleotides. The HELIOS-B trial just released its results using vutrisiran. Vutrisiran is a small interfering RNA that is injected subcutaneously every 3 months, and it was found to have decreased mortality and cardiovascular hospitalization. And again, there was less decline in the 6-minute walk and quality of life compared to placebo. So, that has not yet been reviewed by the FDA.

Another trial that's ongoing is using eplontersen, which is an antisense oligonucleotide that's injected every month, and we're still awaiting those results.

Other therapies that are currently in trial include CRISPR gene editing. Those trials are currently being done for cardiomyopathy. We're also exploring antibodies that will actually go to the heart and deplete or remove amyloid from the heart. And those trials are underway, currently.

Dr. Russell:
With those treatment options in mind, I'd like to open up the floor to both of you. How would the two of you collaborate on a patient who had both neurologic and cardiac involvement? And does one of the organ systems take precedence over the other in a treatment plan?

Dr. Khella:
Well, for a patient with a mixed phenotype, of course we have to collaborate very carefully with our neurology colleagues.

There is to date no good data to suggest that using both a silencer and a stabilizer is effective. There is some published data to suggest

that it's probably not harmful, and I usually depend on my cardiology colleagues to tell me how severe and how progressive the heart failure is. And if the patient has a predominant neuropathic phenotype and minimal cardiac disease, than I prefer to use a silencer since that's what's approved by the FDA for the treatment of a polyneuropathy.

Noel, what is your take on this?

Dr Dasgupta:
This is complicated because right now, only certain drugs are approved for neuropathy and certain drugs for cardiomyopathy, although in the future, some of the same drugs might be approved for both. I first consider what the FDA approved therapies are. Right now if the patient has hereditary disease, they might be a candidate for gene silencer. And since many of these patients also have cardiac disease if they have hereditary disease, that might be an appropriate treatment.

When I'm deciding on treatment, if they do have hereditary disease, I always talk to the patient and see if they are willing to try a subcutaneous drug. Some of the nuances of the gene silencers are some can either be only given by a healthcare practitioner, or some can be given at home. So, it's up to the patient if they feel like they are able to do that. In some cases where they have predominantly cardiomyopathy and only want to use an oral form of treatment, I may choose to do tafamidis. But again, this is largely based on patient preferences and what's available currently, and this may change in the near future.

Dr. Russell:
We've certainly covered a lot of information today. Before we close, I'd like to hear some take-home messages from both of you.

Dr. Khella, could you start us off?

Dr. Khella:
Sure. I would test for amyloid and think about that disease in a patient with a progressive neuropathy that looks like they have a systemic illness. If they have GI symptoms, they have orthostasis, they have early erectile dysfunction in a young man, those are the things that make me think of amyloid. And especially if they have not been responding to treatments such as CIDP. Progression and progressive neuropathy, and progressive symptoms are the hallmark features of this illness.

Dr. Russell:
Thank you so much, Dr. Khella. And turning to you, Dr. Dasgupta, what would be your final words on this topic?

Dr. Dasgupta:
First, I want people to realize that amyloidosis is more common than we previously thought and to always consider amyloidosis in patients that are older, in African Americans, in patients with heart failure with preserved ejection fraction and in patients with unexplained left ventricular hypertrophy. I want people to remember that it's possible to make a non-biopsy diagnosis of amyloidosis using bone scintigraphy. But if you are not able to make a diagnosis using bone scintigraphy, biopsy is still important. And before you do any noninvasive diagnosis with bone scintigraphy, you should rule out light chain amyloidosis.

I want people to realize that there are new therapies that can significantly improve prognosis and quality of life. These therapies work best if they're started earlier, so the earlier you identify a patient, the earlier they will get treated and have a better quality of life. And I want people to realize that the field of treatment is rapidly advancing and we're seeing new therapies such as gene editing and antibodies to remove amyloid deposits, and these are really exciting for the future of patients with amyloidosis.

Dr. Russell:
So, with those key take-home messages in mind, I want to thank my guests, Dr. Sammy Khella and Dr. Noel Dasgupta, for sharing diagnostic and treatment strategies for transthyretin amyloidosis. Dr. Khella, Dr. Dasgupta, it was great speaking with you both today.

Dr. Khella:
Thank you, John. This is really a lot of fun and I'm hoping that we get the message across that this is a very treatable disease at this time.

Dr. Dasgupta:
Thank you so much for having me. It was a great discussion. And again, this is an exciting time for both doctors and patients when we're seeing such rapid advances in treatment for amyloidosis. And it's really amazing to see patients improve on therapy, and it's been a pleasure to be part of this journey.

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