Transcript Details
This is a transcript of an educational program. Details about the program and additional media formats for the program are accessible by visiting: https://reachmd.com/programs/on-the-frontlines-of-attr-cm/managing-genotype-positive-patients-in-hereditary-attr-cm/39316/

ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

Managing Genotype-Positive Patients in Hereditary ATTR-CM

Announcer:
You're listening to *On the Frontlines of ATTR-CM* on ReachMD. Here's your host, Dr. Shelina Ramnarine.

Dr. Ramnarine:
This is *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Shelina Ramnarine, and I'm joined today by Dr. Naveen Pereira. He's a Professor of Medicine, Associate Professor of Pharmacology, and Consultant for the Department of Cardiovascular Diseases at the Mayo Clinic College of Medicine in Rochester, Minnesota. We'll be discussing his recent research on genotype-positive family members of patients with hereditary transthyretin amyloid cardiomyopathy, or ATTRv-CM. Dr. Pereira, welcome to the program.

Dr. Pereira:
Thank you very much for having me. It's my pleasure.

Dr. Ramnarine:
So let's start with some background, Dr. Pereira. Could you tell us why you decided to focus on this particular patient population? What did you aim to understand during the study?

Dr. Pereira:
So hereditary amyloidosis is not uncommon as a disease process, and until recently, there weren't any disease-altering therapies, and now there are. These therapies are very expensive but can really help patients. And so a large part of these patients are diagnosed when they present with heart or neurological problems, but as we are diagnosing these patients, since it's hereditary—that means there's a genetic transmission—it's possible that their first-degree relatives may also carry the gene that caused this disease. And there is a big unknown as to what to do with these relatives who now know that they have a family member with the disease and carry the gene that predisposes them to developing a disease. And the question is whether these newer therapies can be given to these patients and at what point should they receive it.

Dr. Ramnarine:
That makes sense. So, when you assessed the patients at baseline, what did you learn from their initial clinical assessment, especially when you compared those findings to their genetic profiles?

Dr. Pereira:
Right. So now we are just talking about these family members who really did not have a diagnosis of hereditary amyloidosis, but they came to our attention because they are family members of those who did and are gene positive now. And so what we discovered is, as you would expect, many of them are young. So in fact, the average age of these patients was in their late 40s, and there was a pretty good distribution of males and females, but what was striking was that there was almost a 16 to 18 percent prevalence of peripheral neuropathy and carpal tunnel syndrome. So these patients had, perhaps, disease, but weren't diagnosed. They were diagnosed with the neurological symptoms but probably didn't have the diagnosis of amyloidosis until they were known to be gene positive. So that's the general presentation, but in this particular cohort, none of them really had heart problems.

Dr. Ramnarine:
Interesting. So let's talk about that a little further. Let's talk about the follow-up data. After about seven years, what forms of disease progression were most common, and were there any unexpected results?

Dr. Pereira:

Right. So this is one of those few, what we call, longitudinal studies, where you have a diagnosis and then we follow them, as you mentioned, for seven years, to see what happens when you're gene positive. And what we found is that a significant proportion of these patients developed peripheral neuropathy. The incidence of new neurological symptoms was high, up to 25 to 26 percent. However, we did not see any of these patients develop cardiac symptoms such as heart failure, which is typical of hereditary amyloidosis when it affects the heart. And it was a fairly substantial follow-up. What was unique about this study is that we had imaging results available, so we could see what their heart looked like at the time they were known to be gene positive, and then we could see what their heart looked like several years down the line. And what we found is that there was some reduction in heart function and some increase of thickening of the heart, which is characteristic of amyloidosis, but we have certain criteria to diagnose cardiac amyloidosis, and only 10 to 11 percent of these patients had at least two of such abnormal echocardiographic criteria. So almost 90 percent of patients did not have these characteristic echocardiographic findings. So our conclusion was, really, that these patients will develop neurological symptoms, but the cardiac course seems to be a little less aggressive in terms of development.

Dr. Ramnarine:
For those just tuning in, you're listening to *On the Frontlines of ATTR-CM* on ReachMD. I'm Dr. Shelina Ramnarine, and I'm speaking with Dr. Naveen Pereira about the clinical characteristics and outcomes of previously undiagnosed individuals with transthyretin variants.

So, Dr. Pereira, with the results of the study in mind, as you were just mentioning, let's talk about how we can apply this knowledge in clinical practice. What recommendations do you have for clinicians monitoring genotype-positive patients, especially in terms of how often to screen and what imaging strategies to consider?

Dr. Pereira:
Right. So when you first see a patient who is gene positive, I think the question is, do they have amyloid? And at least when we started the study—this was several years ago—PYP scans were not being used commonly. This is used to image the presence of amyloid in the heart. So there's consensus statement saying that if you want to make a diagnosis of amyloid, you really should do PYP scanning in patients with hereditary amyloidosis, so ATTR amyloidosis. And whether you do a heart biopsy is controversial, because if the patient has no symptoms at all and no features from a heart perspective of amyloid, I would not do a heart biopsy. But certainly, PYP scanning would be the first initial.

Now the question is, okay, you have amyloid by PYP scanning, but you have no symptoms suggestive of heart failure, or you have no echocardiographic or structural changes that suggest that there's amyloid. And for those patients, I think you should just follow them by echocardiography on a periodic basis. Generally, I would do at least an echo within a year just to see what the rate of progression is, and if everything looks rock steady stable, then do it at intermittent levels every two to three years.

Patients, obviously, who are symptomatic and have some structural changes suggestive of amyloid could be treated as you would treat any other amyloid patient. And, of course, as you saw in our study, patients had peripheral neuropathy and carpal tunnel. So if they had peripheral neuropathy, the chances that the neuropathy could be due to amyloid is fairly high. And so if appropriate neurological referral and diagnosis of amyloid is made as the cause of neuropathy, then those patients should also be treated. So I think knowing a gene positive can explain conditions like neuropathy. As you can see, it was present in about 16 to 18 percent of our patients, and they didn't know that they had amyloid. And then during follow-up, keeping a close watch for heart failure symptoms or echocardiographic changes of amyloid is important.

Dr. Ramnarine:
Now, from a patient perspective, testing positive for a TTR gene variant can raise a lot of anxiety, even in the absence of symptoms. How do you think clinicians should approach counseling and reassuring patients?

Dr. Pereira:
It's a very good question. I think all these patients who are diagnosed with being positive for a gene for ATTR amyloid should undergo genetic counseling. And so they should meet with a certified genetics counselor, and that counselor can explain to them the uncertain nature of disease progression in these genetic conditions. There is uncertainty in terms of penetrance of disease, meaning when that disease will manifest, and there's uncertainty in terms of expression: whether it will manifest as a neuropathy or cardiac issues like heart failure. So having appropriate counseling with a certified genetic counselor is highly recommended.

Dr. Ramnarine:
So before we wrap up our program, Dr. Pereira, do you have any closing thoughts you'd like to share with the audience?

Dr. Pereira:
Yeah. There is a clinical trial called ACT-EARLY that's targeting these patients who are gene positive and have amyloid present, and

they will get therapy versus placebo, and we'll see what the outcomes of this trial are. And I think you should keep a close watch for the results to understand whether it's appropriate to treat patients who are gene positive and may not necessarily have symptoms suggestive of amyloidosis.

Dr. Ramnarine:
So as those final insights bring us to the end of our program, I'd like to thank my guest, Dr. Naveen Pereira, for joining me to discuss his research on previously undiagnosed ATTRv patient family members. Dr. Pereira, it was great having you on the program.

Dr. Pereira:
Thank you for having me.

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