MARTHA GROGAN: Hello, I'm Dr. Martha Grogan, a cardiologist and director of the Cardiac Amyloid Clinic at Mayo Clinic in Rochester, Minnesota, and today, we'll be convening a roundtable review on cardiac amyloidosis. And it's my honor to be here today to discuss this topic with Dr. Angela Dispenzieri, who is a professor of medicine and laboratory of medicine and a consultant in hematology, as well as a world renowned expert in amyloidosis; and Dr. Nandan Anavekark, who's an assistant professor of medicine, a senior associate consultant in cardiology, and an expert in cardiac imaging. So welcome. Thank you for joining us.

NANDAN ANAVEKAR: Thank you.

MARTHA GROGAN: The goal of our discussion today is to discuss the fascinating disease of cardiac amyloidosis, to raise awareness in the cardiology community, and to review what are the crucial steps to establish the diagnosis and the treatment plan. So we'll get started, and actually, I think, as an introduction, one thing that I find very interesting is that patients are understandably frustrated with how long it can take to establish a diagnosis. And we see this, not only when patients are referred to us, but Angela and I participate in the support groups, and patients are sometimes two, three, four years, often seeing many cardiologists. So I think to highlight, for cardiologists, some of the important things is, patients can present not only with heart failure, but they might present with chest pain, arrhythmias, atrial fibrillation, orthostatic hypotension, or a stroke, so unexplained stroke due to cardio amyloidosis. So there are a lot of different manifestations, and so, Angela, once cardiologists at least start thinking about a little bit, what are some of the other factors that should make a cardiologist suspect cardiac amyloidosis?

ANGELA DISPENZIERI: Right, amyloid is really a great imitator, so there are a lot of other symptoms that can go along. And so if a patient also has nephrotic syndrome or adema related to that, a rise in their lipids unexpectedly, that would go with nephrotic syndrome, and so that, sometimes, is a clue. Signs of neuropathy, so whether it be carpal tunnel syndrome or just a small fiber neuropathy or a painful neuropathy, hepatomegaly. There are other signs know, that they show in the textbooks, like the periorbital purpurata.

MARTHA GROGAN: How often does that happen?

ANGELA DISPENZIERI: It's pretty rare. About 10% or less of patients will actually have the procto-purpura, and similarly, the macroglossia. Although it is pretty specific for this disease, very rare, and so one has to really have a high index of suspicion to think of the diagnosis.

MARTHA GROGAN: And once we kind of think about it, we need to kind of maybe let our audience know a little bit that there are different types of amyloid, so I think it's very confusing for cardiologists. I was happy to hear that the hemotologists even get a little confused if they're not experts in dysproteinemia. But really, for cardiologist, there's only three main types, and I like that because there's a lot of different proteins that can make amyloid, but Nandan and I don't have to worry about most of those.

So the AL type for the light chain, most cardiologists kind of know about that from their training or textbooks. That transthyretin type, or TTR, there's are rare form, the hereditary type, but that's not so rare in African-Americans. Actually up to 3% or 4% of the population are carriers. And then what we've historically called senile, and now it's more appropriate to call it wild type transthyretin, and the patients, by the way, they really like it a lot better if we call them the wild type instead of senile.

ANGELA DISPENZIERI: Or age related.

MARTHA GROGAN: Age related. So age related TTR, so those are the three types that cardiologists really need to know about. We'll go into how you diagnose and what the different types are, but I think it's also important to realize they're very different diseases. They present differently. So once we start thinking about the diagnosis, what tools do we use to try to work up a patient with suspected cardiac amyloidosis?

ANGELA DISPENZIERI: Right. So a lot of cardiologists are sort of keyed in to the AL, as you mentioned, and so they tend to go with the serum protein electrophoresis looking for a monoclonal protein or a monoclonal spike. Unfortunately, that test is going to miss it in more cases than it's going to find it because it's not a very sensitive test. So the idea is good, but they're only halfway there.

They need to not only do a serum protein electrophoresis but also an immunofixation. And there's another test called the serum immunoglobulin free light chain, which basically is just measuring those immunoglobulin light chains that are the building blocks for amyloid. And so using the serum protein electrophoresis with immunofixation and the serum free light chain, you're going to capture about 97% of AL cases. You're not going to, obviously, get anything with the transthyretin cases because they're not related to the immunoglobulin. If you throw in a 24-hour urine with an immunofixation, so a 24-hour urine protein electrophoresis with immunofixation, you're going to get up to about 99% of AL cases that will-- you'll find a protein.

MARTHA GROGAN: So if we do the immunofixation and the serum and the urine, the serum free light chains and a fat aspirate will get the majority of cases.

ANGELA DISPENZIERI: Right, so the first part is, is there a clonal disorder? The second part is, do they have amyloid? I have an index of suspicion that amyloid might be there, but do they? And it is a tissue diagnosis, and so one of the easiest tests to do is to do what we call a fat pad aspirate or fat-- some do a fat biopsy.

But if you see the amyloid there, and then you can sort of say, well, we have the monoclonal protein. Ideally, you want to type the amyloid. So as you mentioned, in the cardiology world, there's three things-- or three major types of amyloid that we think of, but there are actually more than 25 proteins that can cause amyloid disease in people. And so you want to make sure that you know that amyloid is actually AL or that it's actually TTR because the implications in terms of prognosis and therapy is going to really vary depending on that.

MARTHA GROGAN: Right, and we'll talk a little bit more about the prognosis and treatment later. One of the things, I think, that we see, and certainly the hematologist noticed, too, is that cardiologists are diagnosing amyloid more because of cardiac MRI, so it's really a tool that's helped us a lot. Echo also-- we shouldn't underestimate. Echo is fantastic screening, too, and often, the diagnosis is first suggested there.

But in some patients, it's not so obvious by echo. So, Nandan, you're really a great expert in cardiac MRI, and tell us. If I'm the referring cardiologist, what do I need to know about the MRI, and should I screen my patients for amyloid using that test?

NANDAN ANAVEKAR: Sure, I think you made a great point that imaging is fundamental to understanding whether there's cardiac involvement, and echo has been the mainstay. But I think cardiac MRIs is evolving as one of the main players in understanding cardiac involvement with amyloidosis. When one attempts to obtain a cardiac MRI, I think there are a few clinical issues that needs to be understood first. And in order to study the presence of amyloid in the heart using cardiac MRI, the patient has to receive contrast, and the contrast agent we use is a heavy element.

It's called gadolinium, and the most important thing that precludes the use of that contrast agent is renal disease. Unfortunately, only as late as 1997, there are reports of this nephrogenic systemic fibrosis, a very devastating illness, that was sort of causally related to gadolinium administered to patients with renal disease. So I think that's the number one issue that we need to clarify before we proceed with a cardiac MRI examination.

The second and third issues that are important, but not necessarily come to service, is the fact that the MRI machine, or the scanner, is a very tight space, and patients may have issues with claustrophobia. In addition, they typically have to stay in the scanner for up to an hour. That's--

MARTHA GROGAN: A long time, I mean, especially if they're very sick.

ANGELA DISPENZIERI: If they have CHL.

NANDAN ANAVEKAR: Exactly.

ANGELA DISPENZIERI: Laying flat.

MARTHA GROGAN: [INAUDIBLE] flat.

NANDAN ANAVEKAR: Exactly, and so-- and in order to do the exam properly, we need communication with the patient. They have to be able to cooperate in terms of breath holding throughout the scan, and if they have issues with back problems, issues with heart failure, which many of these patients do, it can be a very tiring experience for the patient. So all of these issues need to be sort of understood before we proceed with the examination.

MARTHA GROGAN: And how about-- and I imagine that probably a fair number in our audience are actually imagers, too, that some people that are going to be doing and interpreting cardiac MRI. So what are the technical things that the imager really needs to know to make sure that they do a proper exam?

NANDAN ANAVEKAR: Sure. So there are really two parts of the cardiac MRI examination when assessing for cardiac amyloidosis. The first part is to look at the cardiac morphology, the structure and function, and the workhorse sequence that we use is called steady state free precession.

And with that pulse sequence, we're able to look at left ventricular and right ventricular chamber size. We're able to look at wall thickness. We're also able to look at atrial wall thickness as well, so I think that's very important. With these sequence, we're also able to look at pleural and pericardial effusions, which can be important in the presentation of these patients, and we can look at the volumetric assessment of cardiac function.

The integral part of the examination, which requires that gadolinium contrast, is a part of the examination known as tissue characterization, and what that requires is that we inject an intravenous contrast agent, the gadolinium. And the gadolinium has a normal kinetic profile in normal people, but this kinetics is abnormal in the setting of amyloidosis. And you'll hear the term, and many of the cardiologists would hear the term, abnormal delayed enhancement, and that's really the sort of [INAUDIBLE] of what we find on imaging of these patients.

The hyperenhancement can be variable. Typically, it can be subintercardial or entirely diffuse. The other very important aspect of the gadolinium contrast agent is that it can also be used with delayed imaging to look for intra atrial thrombii, which can also be a complication of the disease. But the key question is, how does one determine the presence of cardiac amyloidosis versus the abnormal delayed enhancement that we've see in other non-ischemic cardiomyopathies, especially those which are also associated with increased wall thickness, such as hypertrophic cardiomyopathy?

And the key point here-- it can be a little bit confusing. There's a technical aspect, and it's referred to as abnormal myocardial nulling. What that really means is, during the examination, we use a pulse sequence that really suppresses the signal from the desired tissue, so it enhances the pathology.

So for example, if you're looking for a myocardial infarction, the normal mycardial will be dark, but the abnormal myocardial-- myocardium will really brighten up, and that will give us a sense of an infarction. There is a pattern of myocardial nulling related to the blood pool nulling, and the key in amyloidosis is that pattern is reversed. And it's something that can be graphically represented with the software that's used to study the patients using the MRI, and I think that's really the key point of our examination.

MARTHA GROGAN: And if someone-- can the abnormal nulling be missed? I mean, depending on the timing of the sequences or-- how do I know, as the referring cardiologist, that they really did the nulling sequence properly?

NANDAN ANAVEKAR: You're right. So the nulling sequence, again-- if we have that abnormality, then we are very confident of an infiltrative cardiomyopathy. If we don't have that abnormality, it doesn't exclude the diagnosis. And as you had pointed out at the very beginning of this discussion, I think the diagnosis is based on the integration of both the clinical, laboratory based, and imaging based diagnosis, and I think that really helps us tie it all together from an imaging standpoint.

MARTHA GROGAN: And there, of course, are different patterns of amyloid involvement in the heart. We've seen some unusual MRIs because it was mostly intercardial and then the imager might not think it's amyloid. So we have to be aware that, with a rare disease, there are variations in our imaging, but I must say, if I see that the nulling was abnormal, then I'm really very suspicious. If it's an abnormal pattern delayed enhancement, that could be other cardiomyopathies.

NANDAN ANAVEKAR: Right. Absolutely, and I think also the key is always pick up the phone. So I always encourage fellow cardiologists and hematologists, if there's any issue with the report, if it's unclear, just give us a call, and then we can go through the images together.

MARTHA GROGAN: Yeah, great. And another thing I think it's important for our audience to realize is that sometimes we forget about old fashioned things like the electrocardiogram. So the electrocardiogram is abnormal in the vast majority of patients with any of the types of amyloid, but it's caught-- it is very common in AL to have low voltage, but still, it's only about 45% in one of the series we did. Some are a little bit higher, a little bit lower, but generally 50% have low voltage, or they may have a pseudo infarct pattern, where there are cue waves, but no regional wall motion [INAUDIBLE] on echo.

And we do really have an increased index of suspicion when we see thick walls, low voltage due to infarct. But normal voltage doesn't exclude the diagnosis, and many cardiologists think, well, I looked at the EKG, the voltage was normal. We've even had patients-- actually about 16% in one of our AL series, that had criteria for left ventricle hypertrophy. So that's important. And then the TTR type of amyloid, low voltage is less common. Probably only about a quarter of those, so that's an important thing.

The other issue is when do we need to do an endomyocardial biopsy? Well, Angela's already talked about all the other organs that could be involved, so usually for AL, we're going to do a fat aspirate. They're going to get a bone marrow. They may get a kidney biopsy.

But if all else fails, and we still have a high index of suspicion, we'll do an endomyocardial biopsy, and with the TTRs, it's more likely that you might have to go to an endomyocardial biopsy. So if you have a lot of suspicion, cardiologist needs to know to consider that biopsy. So I'm going to move on to Angela just to help us-- tell us about the treatment options for patients who have AL amyloid when they have cardiac involvement or significant cardiac involvement.

ANGELA DISPENZIERI: Right. Well, there's a huge spectrum of therapies now, compared to what it used to be.

MARTHA GROGAN: Which is great. That's exciting. And we-- just yesterday, I heard that a cardiologist hadn't referred a patient because he thought there was no treatment. So there is treatment.

ANGELA DISPENZIERI: There are a number of treatments, and again, for the AL especially, it's sort of paralleling the treatments for multiple myeloma. So we're getting sort of hand-me-downs, but that's OK. So from pills, like old drugs like melphalan and dexamethason to newer medicines like bortezobim or Velcade, which is an injectable medicine, to pills lenalidomide and pomalidomide-- all of these medications have really shown to treat the underlying bone marrow process, which in turn, allows the heart to improve. We also do high dose chemotherapy with autologous peripheral blood stem cell transplant. We used to call that bone marrow transplant, but now we have a fancier expression for it.

MARTHA GROGAN: One tricky thing is, if you mention stem cell transplant, some people think it's cardiac stem cells. So you have to be very careful that our audience knows we're talking about autologous stem cells.

ANGELA DISPENZIERI: Autologous peripheral blood.

MARTHA GROGAN: Taking your own steam cells out and putting them back in, basically. Right?

ANGELA DISPENZIERI: Right, after high dose chemotherapy. So for the real cardiac patients-- so obviously, there's a huge spectrum of severity. There are patients-- I used to be a marathon runner, and now my mileage is down. Something's not quite right. But they still have an excellent performance status, so that's a really early cardiac obviously.

To somebody who comes in in a wheelchair and oxygen because they're so far advanced. Certainly, if it's mild cardiac involvement, we do consider the high dose chemotherapy with peripheral blood stem cell transplant as an option. The more advanced patients-- there have been studies that really show that you would do them a disservice by trying to give such intensive therapy, and in fact, in these same patients, the lower dose therapies or the easier therapies actually result in as good results, if not better.

MARTHA GROGAN: Right, I think sometimes people think they have-- their patients have to get to stem cell, but that's not--

ANGELA DISPENZIERI: No, it's definitely not necessarily true.

MARTHA GROGAN: And important for a cardiologists to recognize that most of these patients, especially with the AL type of amyloid, especially if they present with heart failure, they do not do well usually with beta blockers and ACE inhibitors, standard treatment for heart failure. And most of them, initially, have a preserved ejection fraction, although they can have low EF. But cardiologists are frustrated. They want to do something.

But the patients have very severe restrictive hemodynamics with a fixed stroke volume, and lowering their heart rate or lowering their blood pressure, many of them have autonomic insufficiency. They do not do well. It's a little different in the TTRs, but I think most cardiologists should get the message, don't try to use your standard heart failure treatment. What the hematologists do is they stop it when they come to see the dysproteinemia expert. They get them off of the carvedilol all another medications, so I think that's really important.

But how about-- Angela, how about digoxin? So that's been going way back to-- we don't want to say how long that was, but when we were residents. Never ever used degoxin, and that's gotten onto almost every board exam. But do you ever use it in your patients?

ANGELA DISPENZIERI: Yeah, definitely. Again, use it for rate control because that's the challenge. These patients may have atrial fibrillation, and if the beta blocker is going to decompensate them, you need something, so amiodarone or dig. And the dig data really-- I mean, it come from-- it's sort of an in vitro kind of thing, and then obviously, patients with amyloid are known to have sudden death. And just because they had a little dig doesn't mean that that's why they had their sudden death.

MARTHA GROGAN: So it was this theoretic binding and increased toxicity. The way I look at it is, I mean, in many patients, we have to choose the lesser of evils, and so I do often use digoxin for rate control of atrial arrhythmia, as it tends to not lower their blood pressure, but I watched the levels very closely. Because when you look at the literature, it's very weak, but because it's gotten onto all these exams, people-- even sometimes people are stopping the digoxin that we started, and that's a little frustrating. So again, I think you should have an expert involved to figure out how to use digoxin.

ANGELA DISPENZIERI: And the other thing-- some of our drugs do lower potassium levels, so you really want to kind of be very cautious in monitoring that.

MARTHA GROGAN: And actually, one of the things that Angela's a great expert in is prognosis and biomarkers. And so as cardiologists, we don't check troponins too much as an outpatient, but tell us about the prognosis for these AL patients and how it's improved over the years and how we assess that.

ANGELA DISPENZIERI: Yeah, I mean, so work that I did with Alan Jaffe and colleagues, we've really started looking at using troponin and NT-proBNP as major prognostic markers for patients with amyloid. And there's sort of been iterative staging systems to use, but the one that's most recognized right now has been just using thresholds of troponin T and NT-proBNP. And you break patients almost into groups of one third each, and you have really excellent separation of curves in terms of survival. More recently, we've added in the serum immunoglobulin free light chain to further improve that sort of staging and the separation of curves and predicting how patients do.

But the cardiac biomarkers, also-- we use them as exclusionary criteria for transplant, so the high dose chemotherapy peripheral blood stem cell transplant. We use thresholds based on our experience. We know that we can get a patient through a transplant if their troponin is less than-- troponin T is less than 0.06. Treatment related mortality is about 5%. However, if it's over that, we're talking 27% or so, and so they really do help us significantly.

Finally, the NT-proBNP work out of Italy in collaboration across the world. We've sort of been using that as a response criterion to know how our patients are doing with the chemotherapy. Obviously, that's not new to cardiologists who follow heart failure, but we do use it to very much gauge how our patients are doing, and whether they're-- we think the chemotherapy's working or not.

MARTHA GROGAN: Which is important because, actually, often the imaging doesn't help us that much in the response. The wall thickening by either echo or MRI doesn't help us as much. But, Nanden, can the walls ever be normal in cardiac amyloid?

NANDAN ANAVEKAR: Yeah, that's a good point. Ideally, we'd want the textbook case on MRI with--

MARTHA GROGAN: Those are the easy ones. Everybody can diagnosis those.

NANDAN ANAVEKAR: Exactly. But you bring up a very excellent point, and the walls can be normal or subtly increased in thickness. And they can be very difficult to use as a diagnostic-- using MRI as a diagnostic tool. But I think the other key is--

MARTHA GROGAN: But the nulling--

NANDAN ANAVEKAR: The nulling is important.

MARTHA GROGAN: [INAUDIBLE] be abnormal, and we have had patients with relatively normal wall thickness of where it was the nulling.

NANDAN ANAVEKAR: Exactly. And the other thing is that we get a good look at the right ventricle, which may not be optimal using echocardiography. And we can look at subtle increases in right ventricle wall thickness.

MARTHA GROGAN: So MRI, especially unexplained heart failure in general, but particularly amyloid, it can be really helpful. And then moving on to-- we talked a little bit about there is the more rare forms of hereditary amyloid, and that there's actually a lot of different forms of hereditary. But again for cardiologists, we like to keep things simple, and it's the transthyretin type that we need to worry about. So those can have a spectrum.

Those patients have either neuropathy or cardiomyopathy or an overlap of the two, and in general, they're rare, but not in those who are of afro-caribbean descent, so as many as 4% of the population. So if you're seeing a black patient with heart failure, many of them will have a history of hypertension, but we can't just write this off as hypertensive heart disease. Those patients tend to have thick walls, and they often will have reduced ejection fraction, but then likewise, the wild type or age related-- most cardiologists still think that that as senile-- they often have very, very thick walls but a much more indolent clinical course. And that's why, back to the ALs are the ones who might have normal wall thickness, and it's because of probably toxicity of the circulating light chains and other factors that effect the myocardial directly, not just the amyloid infiltration. So we just need to be aware, as cardiologists, that there's a lot of different manifestations of this disease.

And then I'm going to finish up with Angela telling the audience there's really some exciting work, finally, in transthyretin and the TTR type of amyloids, especially the seniles. We are seeing patients, the wild types, we are seeing patients now who, in retrospect, have had symptoms since their late 50s. These are usually men, not exclusively, but majority of those are men, but for those type of patients, it's really going to be important to diagnose them earlier. Many times, they present what [INAUDIBLE], but they're not just these 90-year-old people. So what's the exciting news there on the TTR?

ANGELA DISPENZIERI: Yeah, I mean there used to be nothing, and so as you said, it was an academic exercise. But now, it's not. So there are several drugs. One is a drug called tafamidis, which basically stabilizes the transthyretin tetramer so that you can't have little monomers breaking off and forming virals. That has sort of approval in Europe, tentative approval. It's not been approved yet in this country, but there are going to be ongoing successor trials. And then there are a couple of different molecules that are out there. One is [INAUDIBLE] and the other is [INAUDIBLE], where they actually knock down the amount of transthyretin being produced. It was-- there was-- [INAUDIBLE] was in the "New England Journal of Medicine" just recently about, not the effect yet, what it does for the heart, but that it really can knock down silencing RNA, knock down the levels of transthyretin. If you don't have-- if you don't make transthyretin, then you're not going to make transthyretin amyloid, and so that's pretty exciting. So that adds to our armamentarium of, historically, we would do occasionally liver transplant for the hereditaries and sort of pull out the manufacturing plant of the abnormal transthyretin and put in a new liver, and in theory, they shouldn't get worse. But that hasn't worked as well as one would have hoped in general. And obviously, for the age related or wild type--

MARTHA GROGAN: It's not an option.

ANGELA DISPENZIERI: It's not an option because they already have normal--

MARTHA GROGAN: Just to clarify for the audience, the wild type is actually the molecular structure of the TTR is normal, but for reasons that we don't understand-- well, people like Angela might understand it. It's a [INAUDIBLE], but it becomes misfolded and forms amyloid fibrils. And so a liver transplant won't work for that. The other thing, just for people to be aware, is that the question of cardiac transplant comes up.

Well, in the ALs, that's very controversial. You really have to make sure that there's not amyloid elsewhere, which is-- there's always going to be some. And there's just the issues with these patients of really having the plasma cell [INAUDIBLE] under control. But with the TTR amyloids, especially the wild type patients or even the familials if they don't have a lot of neuropathy, but the wild type are often otherwise very healthy patients.

But in the past, we diagnose them when they're 85 years old. But we recently have had patients who have been transplanted when they were identified early enough, but cardiologists also get confused because they think amyloid, no transplant. These are these-- all this multi-organ system failure, and that's not really the case in the age related amyloid. So I think that's just another important thing for our audience.

So thanks so much for your insight. It was great to have both of you join us today. In conclusion, we have several important myths to dispel about cardiac amyloidosis.

First of all, the absence of low voltage does not exclude cardiac amyloid. Second of all, a serum protein electrophoresis is really not a good screening test for amyloid. amyloid. MRI is really a fantastic screening tool, but if the index of suspicion is high, one needs to consider cardiac biopsy.

And really importantly, treatment exists for all types of amyloid. This is not just an academic diagnosis out there, and I think you'll really find that, if you start looking for cardiac amyloid, you will find it. So thank you all for your interesting insights on this topic, and thanks to our viewers for joining us. We hope that you'll continue to follow us on our roundtable review series on theheart.org.