Dr. Ahmad (00:00):

Welcome, and thank you for joining this podcast on Hypertrophic Cardiomyopathy: Recognition, Diagnosis, and Differentiation from Other Types of Left Ventricular Hypertrophy or Phenocopies. The purpose of the American Heart Association Hypertrophic Cardiomyopathy podcast is to educate healthcare professionals on hypertrophic cardiomyopathy and to improve the care of affected patients through early central recognition diagnosis and treatment. The American Heart Association's Hypertrophic Cardiomyopathy Initiative is sponsored by MyoKardia Incorporated.

Dr. Ahmad (00:35):

I'm Dr. Ferhaan I am an associate professor at the University of Iowa Carver College of Medicine, and I'm the Director of the Hypertrophic Cardiomyopathy Center here at the University of Iowa. I'm joined today by Dr. Vlad Zaha who is an assistant professor at the University of Texas Southwestern Medical Center, and he is a specialist in multi-modality imaging as a focus on cardiomyopathies.

Dr. Ahmad (01:01):

Last podcast, we had a great opportunity to get an overview of hypertrophic cardiomyopathy. And this time we're really going to get into the details of how we make a diagnosis of hypertrophic cardiomyopathy and how we distinguish it from other disorders that can look like hypertrophic cardiomyopathy. And sometimes that distinction can be quite challenging. As we have discussed in the past, genetic underpinnings of hypertrophic cardiomyopathy have become pretty well recognized, and it turns out that variants in genes that encode proteins involved in the sarcomere or in the Z-disk are generally the ones that are associated with hypertrophic cardiomyopathy.

Dr. Ahmad (01:46):

And in particular, two genes, myosin heavy chain 7 and myosin-binding protein c3 are the most commonly involved genes. And while we still don't fully understand how the genetic variant or the genotype leads to the phenotype of hypertrophic cardiomyopathy, it does appear that many of these variants, and perhaps the majority of these genetic variants, are causing a kind of a gain of function where the sarcomere is overactive and the crossbridge cycling rate is elevated. And somehow this then leads to the phenotype of cardiac hypertrophy. And even the phenotype of cardiac hypertrophy is quite variable, even in patients with the same variant from the same family.

Dr. Ahmad (02:31):

And Vlad, you see this as an imaging specialist. I'm sure that you are very familiar with all the different variations that you can see in terms of the pattern of cardiac hypertrophy.

Dr. Zaha (02:41):

Yes Ahmad, this is really an interesting part of the diagnosis where imaging can provide convincing information about the manifestations of the phenotype. And there are important parts of the diagnostic imaging that involves structural and functional characterization of the myocardium, as well as, more recently, characterization of the myocardial tissue. In terms of the specific patterns, most of the time, hypertrophic cardiomyopathy involves the interventricular septum, but there are variants where the hypertrophy can be concentric, or can be manifested by an abnormal thickening of a certain area of the myocardium. One of them specifically is the apical variant that can be complicated even in a larger proportion of patients with apical scar formation, apical aneurysm, which has an association then with malignant arrhythmias. One area that is of particular interest is the differentiation of the hypertrophic

cardiomyopathy from other types of hypertrophic heart disease, as we call them, phenocopies of hypertrophic cardiomyopathy. So Ferhaan, I would like you to introduce the main genetic abnormalities that are of interest from the perspective of specialists in hypertrophic cardiomyopathy that are allowing us to differentiate phenocopies or other manifestations of hypertrophic ventricular disease that are not hypertrophic cardiomyopathy.

Dr. Ahmad (04:19):

Well Vlad, they're both sort of genetic theologies for cardiac hypertrophy that are not hypertrophic cardiomyopathy, as well as acquired non-genetic ideologies. We could start by discussing some of the genetic causes. And it's really important to distinguish these non-hypertrophic cardiomyopathy phenocopies because many of them actually have very distinctive therapies, and actually emerging therapies now for some of these diseases which are completely distinct from the usual hypertrophic cardiomyopathy therapy. And in fact, if you miss these diagnoses, ultimately, we do the patient a disservice because they do not get the benefit of therapies that are specific for their particular disorders.

Dr. Ahmad (05:00):

In particular, a couple of disorders that I'll mention right away, because we do have different therapies for them available, and this includes Fabry disease, which is due to a variant in alpha-galactosidase. That's an x linked disorder, but whereas men usually get a more severe phenotype, actually women can also get a phenotype, usually with an older age. Actually, for the past decade and a half probably, there's enzyme replacement therapy available for these patients that is quite effective. And therefore, you definitely do not want to miss this diagnosis. And actually, if you get genetic testing about 1% of patients that are tested for hypertrophic cardiomyopathy actually have Fabry disease.

Dr. Ahmad (05:39):

Another one that you don't want to miss is amyloid cardiomyopathy. There are a variety of both genetic and non-genetic causes for amyloidosis, but you can have variants in the transthyretin gene, TTR, which can cause a pattern of cardiac hypertrophy that might look like hypertrophic cardiomyopathy. But again, we now have some FDA approved therapies for amyloid cardiomyopathy, especially Tafamidis, which is now approved and quite effective in many patients in arresting the amyloid process and actually improving outcomes in patients that have TTR amyloidosis.

Dr. Ahmad (06:15):

And there's some also new investigational drugs that are currently in trials. And so again, you do not want to miss this diagnosis because there are actually distinctive therapies available for these phenocopies. And there's other genetic causes too. So there's variants in PRKG2 which causes a kind of a gain of function of an enzyme called AMPK and causes glycogen storage within the heart that again, might look superficially like hypertrophic cardiomyopathy, but is a completely distinct disorder. Danon disease due to variants in LAMP2, and also give you severe cardiac hypertrophy. Both of these disorders, PRKG2 and LAMP2 variants are associated quite often with ventricular preexcitation or conduction system disease as well. And then you have a number of other genetic etiologies, like the Noonan syndrome, which is due to variants in a variety of genes associated with the MAP kinase signaling pathway. Friedreich's ataxia, and then various myocardial myopathies. Many of these disorders can also get associated with peripheral or neuromuscular manifestations as well. And again, some of the treatments are similar to hypertrophic cardiomyopathy, but they're still distinct disorders.

Dr. Ahmad (07:23):

But besides these various genetic etiologies, there's a variety of acquired forms of hypertrophy that we need to distinguish from hypertrophic cardiomyopathy. And I think this again, is that an area that you have to deal with a great deal, Vlad, in terms of using imaging to try to distinguish these different ideologies.

Dr. Zaha (07:40):

Thank you Ferhaan. It is definitely one area where the referrals are coming from community, often for differentiating patterns of cardiac hypertrophy that may be relevant for patients due to the inherent risks associated with hypertrophic cardiomyopathy evolution. Specifically, what is important is to realize the prevalence of hypertension as a really common disease that can manifest in its natural course as a concentric hypertrophy of the left ventricle, which needs to be differentiated in some patients from hypertrophic cardiomyopathy. And there have been studies looking at the complexity of the pattern of hypertrophy and identifying criteria of heterogeneity of segmental hypertrophy. There is a specific role for a more advanced and more detailed imaging diagnosis to capture all these parameters and the complimentary role for ubiquitously available echocardiography and more specialized cardiac MRI protocols.

Dr. Zaha (08:52):

Another area that is important in differentiating in some patients is valvular heart diseases, and especially involving the mitral valve due to the overlapping phenotyping. Some patients' hypertrophic cardiomyopathy is associated with progressive mitral dysfunction.

Dr. Ahmad (9:09):

When we face a patient that's coming in- Vlad, how do you approach the patient in terms of seeing them in the clinic?

Dr. Zaha (9:15):

So this is the group of patients that has, I would say, an interesting evolution from the perspective of progression from the genetic abnormality towards the phenotype and the presence of symptoms that would then trigger a cardiac evaluation. In many instances, the patients remain asymptomatic and they would present with an episode of maybe chest pain, maybe dyspnea. They may have an episode of syncope or presyncope. So relatively discreet and general symptoms that would need them to be placed in context, and to understand what is the relationship between those symptoms and exertion. And the evaluation being a general cardiac evaluation has probably some specific features that would need to be on the front end of the providers who consider the potential for hypertrophic cardiomyopathy, specifically regarding the physical examination.

Dr. Zaha (10:19):

The classic finding is that a systolic murmur or fourth heart sound suggesting the diastolic dysfunction or an abnormal palpation of the chest, where there is increased impact like a left ventricular lift. If we focus then on the electrical activity of the heart, abnormalities on the electrocardiogram are quite frequent in these patients. It's almost all these patients will have an abnormal electrocardiogram. There are necessarily typical findings that would be pathognomonic for hypertrophy cardiomyopathy. So that's something just to keep in mind as a normality. Where the disease is suspected, probably the first imaging step to take is a resting echocardiogram that has the potential to provide further information

regarding cardiac structure, and would present the presence of hypertrophy of left ventricular outflow obstruction and abnormalities in the mitral valve function with a well-described systolic, anterior motion of the anterior mitral valve leaflet. As well as diastolic dysfunction in patients otherwise, and I would say in unexpected diastolic dysfunction in younger patients.

Dr. Zaha (11:40):

It is important to realize that echocardiography has its limitations by the presence of difficult ultrasound windows in some patients. And therefore, all patients that are referred to a specialized center undergo a more detailed evaluation with cardiac MRI for evaluation of the entire myocardium, or interrogating the presence of functional changes in the flow across the left ventricle or outflow tract, and abnormalities in the mitral valve. Another parameter that we are investigating is the exercise response, and specifically the dynamic left ventricle or outflow obstruction during exercise with echocardiographic visualization. There is a full set of evaluations that can be performed directly and the patients can have comprehensive myocardial phenotyping assessment that would present, at the end, a conclusion regarding their myocardial structure, the presence of any risk factors or hemodynamic instability, such as left ventricular outflow obstruction with dynamic pattern. As well as risk factors that make them more prone to malignant arrhythmias, specifically the presence of myocardial scar.

Dr. Zaha (13:07):

These all imaging studies would then be complemented by a specific interrogation of the genes as you were mentioning, Ferhaan. So I would like to bring back the focus on the genetic investigation in patients who have undergone a comprehensive imaging and functional evaluation. So if you'd like to comment further specifically about testing for individual genes or testing for panels of genes in these patients. As well as what is the role of genetic counseling and how has the interpretation of genetic panels performed?

Dr. Ahmad (13:51):

That's right. And I'm glad you mentioned genetic counseling because, in fact, that's a critical component of any hypertrophic cardiomyopathy clinical care team. I actually had the privilege of setting up two hypertrophic cardiomyopathy centers over the years in two different institutions, and genetic counseling is certainly an integral part of that.

Dr. Ahmad (14:09):

So, in terms of genetic testing, the most common tests that we do are basic panels that are offered by various commercial clinical testing laboratories. And sometimes they're done in- house by institutions. And they will have basically a list of anywhere between a dozen to 20, 25 genes that they sequence. And they will sequence the coding sequences of the genes. So that's the exons and the adjacent intronic sequences. The genes that make up these panels are chosen based on the evidence that they're associated with HCM. And so we do have very strong evidence that about a dozen genes can be associated with hypertrophic cardiomyopathy.

Dr. Ahmad (14:53):

And then you have probably another somewhere between 12 and 20 other genes that have weaker levels of evidence that they're truly associated with hypertrophic cardiomyopathy. And various laboratories will choose to include or not to include these other genes. And it really becomes a bit of a judgment call. Now, while you do have at least a dozen genes that you're pretty confident are associated

with hypertrophic cardiomyopathy, as I mentioned earlier, there's a couple genes that are most commonly associated with hypertrophic cardiomyopathy. And again, those are myosin heavy chain 7 and myosin-binding protein C3. And actually, if you do find a pathogenic variant in the patient, 80% of the time it will be in one of those two genes. Unfortunately, overall, genetic testing is successful only between say 30 to 50% of the time in identifying a pathogenic variant. The numbers are a little bit higher if you have a clear family history that's positive for hypertrophic cardiomyopathy, and it's a little bit lower if it's an isolated case of hypertrophic cardiomyopathy without a clear family history.

Dr. Ahmad (15:55):

The rest of the time, you will either find no variant or you may find a variant of uncertain significance. Which basically means that there is a change, some sort of genetic variant that exists that's different from the population control, but it's not clear that it's actually pathogenic or cause any change in function, or the structure, or the expression of the protein product. And therefore it's unclear whether that is an innocent bystander or it's truly pathogenic. Now, if it turns out that you do a genetic panel to not identify a pathogenic variant, there are some other possibilities that you can explore. You can do something called whole exome sequencing, which is basically using next generation sequencing to sequence all 20,000 genes in the genome. Or even do a whole genome sequencing, which is not yet clinically available, but will soon be available, where you just basically sequence the entire genome of these patients.

Dr. Ahmad (16:53):

Now, for both of these technologies, you really do need more than just your individual patient. Because if you do these broad spectrum sequencing analyses, you will identify hundreds of thousands of variants or more because we all do have a large number of the nine variants that exist in our respective exomes and genomes. So, what you really need to do is then also perform a similar test in other individuals in the tree who are also affected. And preferably, individuals who are pretty far in the family tree or family pedigree so that if you do end up identifying a variant that you think is disease causing, you're pretty confident. If they're pretty far apart in the family tree, it's more likely that variant is disease causing and that they have inherited just by chance alone because they're related.

Dr. Ahmad (17:39):

And we have a pipeline, ways that analyze these variant data. Obviously, we look at what's shared between individuals in the family that are affected. And you also look to see whether these variants have been identified just in the general normal population. You also look to see if in silico or competitional analysis suggests that these variants are actually damaging to the poaching product. So there's a variety of things you do. So the analyses that you perform to, you hope, identify a pathogenic variant in that patient and in that family.

Dr. Ahmad (18:10):

And you also have to remember that you can still be led astray, because sometimes you will find a variant that has not been described in your reference population, but your reference population may not be the right one for your patient. So it's been quite well-documented now, for example, in African American patients, in the past, a number of them have been told that they have a pathogen variant because the reference population was a Caucasian population.

Dr. Ahmad (18:35):

But if you actually ended up sequencing an appropriate reference population, i.e. an African American cohort and see that those variants are actually quite common in just the normal general population amongst African Americans. And so, it can be a very, very tricky process. And there are a lot of caveats involved in making a diagnosis, especially when you use one of these large-scale genome or exome sequencing technologies.

Dr. Ahmad (18:59):

Having said all that, obviously there's a number of benefits to doing genetic testing. If you were successful in identifying a pathogenic variant, it could help in diagnosis. We talked a little bit about phenocopies, certainly if there's other genetic disorders that mimic hypertrophic cardiomyopathy you might pick them up by genetic testing. Or if you have again, an athlete, and you're not quite sure whether this is a physiological hypertrophy, or is it really hypertrophic cardiomyopathy, a genetic diagnosis can be helpful.

Dr. Ahmad (19:26):

There is also some emerging evidence now that gene type can sometimes give you some information about the phenotype and the prognosis. It's not very granular yet, but on a large scale, for example, the SHaRe registry that was published a couple of years ago in Circulation showed that individuals or cohorts that are identified to have a pathogenic variant in a sarcomere gene have a poorer prognosis than individuals who do not have a variant identifiable by genetic testing. Again, this is a level of large cohorts. Can you translate that into individual patients? I'm not sure that you really have that kind of granular date and ability yet, but perhaps in the future we will. Also, of course, it's very, very helpful in screening families. So if you identify a pathogenic variant in your patient, then it's a simple matter, relatively simple matter, nothing's simple in genetics, but it's a relatively simple matter to then do a simple blood test in relatives within that family to see if they also have the same pathogen branch. And if they do, then they're of course at risk of either having or developing hypertrophic cardiomyopathy in the future. And if they don't have the variant, their risk of developing hypertrophic cardiomyopathy is quite low. It's probably the same as the general population.

Dr. Ahmad (20:44):

So, a number of potential benefits. We talked a little bit about some of the drawbacks. Certainly, we can have these variants of uncertain significance that can be tough to ascertain whether they're really linked to the pathogenesis of the disease and the family. Sometimes we end up just doing traditional clinical screening of family members by imaging, for example. And if you identify other members of the family that do have the same phenotype, then we can see if they also have inherited that variant of uncertain significance. And that increases the likelihood that this is truly a genetic variant. But unfortunately, sometimes when we face these results in generic testing, then can't really use that information directly, or at least immediately.

Dr. Ahmad (21:24):

There's also the issue, and patients always are concerned about how a genetic diagnosis can affect them from a socioeconomic standpoint. So for example, will it affect their ability to get certain jobs? Will it affect their insurability? We do have the Genetic Information Nondiscrimination Act that was passed more than 10 years ago now in 2008, which prohibits discrimination on the basis of genetic information, for the purposes of most employment and for the purposes of health insurance. However, it doesn't prevent the use of that information for other purposes, like life insurance and disability insurance. So

sometimes we advise patients to perhaps take care of some of their financial issues before they get genetic testing, just so that hopefully they will minimize their economic risks by having genetic testing done.

Dr. Ahmad (22:12):

What's your experience been, Vlad, translating genetic results to your patient population?

Dr. Zaha (22:17):

Definitely genetic information at least is informative, especially for the genes that have been defined as pathogenic. Where it becomes even more interesting is thinking about the next generation. And in many of these families, that's where there is potential value in the future. Thinking about the evolution of the science in the last decade with gene editing and the possibility of identifying defects that may be then treated by specific gene editing technology.

Dr. Zaha (23:00):

The other paradigm that is important is the fact that once the genetic diagnosis is made, it is fixed in place, right? So, it's not evolving, but there is this genotype to phenotype gap that needs to be acknowledged. And that's where the longitudinal follow-up with imaging studies and also offering those imaging studies for the patient's families, for their screening, is an important factor to consider. As well as considering nowadays using potentially wearable devices as a replacement for our, I would say, classic ambulatory EKG monitoring that can be done in these patients due to an increased risk of atrial fibrillation in this patient population.

Dr. Ahmad (23:46):

So, I think more knowledge is useful. There are definitely ethical concentrations and societal considerations as far as what is happening with the information available. But considering that this is a lifespan disease, the earlier the diagnosis, the more options the patients have to consider. And they may be under the radar for specialized centers that can consult them on the long-term and improve their health and survival overall.

Dr. Zaha (24:17):

You know, it's amazing that hypertrophic cardiomyopathy was first recognized many decades ago, and yet we're still learning so much about this. So many exciting avenues for the investigation, and eventually translation to therapy, I think.

Dr. Ahmad (24:32):

Well, thanks so much. I've learned so much. Thank you for joining us for the hypertrophic cardiomyopathy podcast. This podcast was entitled Recognition, Diagnosis and Differentiation from Other Types of Left Ventricular Hypertrophy. Please continue to visit our website for future episodes in this podcast series.

Dr. Zaha (24:50):

Thank you for listening.