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Hypertrophic Cardiomyopathy: The 3 Things You Need to Know

Annoucer:
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Dr. Masri:
How well do we really know hypertrophic cardiomyopathy, its pathophysiology, and treatment?

This is CME on ReachMD, and I’m Dr. Ahmad Masri. I’m here with Dr. Steve Ommen, and together we’ll explore the top 3 things you need to know about HCM. Welcome, Steve.

Dr. Ommen:
Thank you, Ahmad. I’m pleased to be here and happy to have this conversation with you.

Dr. Masri:
All right, let’s get started. So the first thing we need to know about HCM is that it’s common – more common than most people realize. And it also has a pathophysiology that complicates current treatment. So what is our current understanding of HCM, Steve?

Dr. Ommen:
Yeah, that’s a really great question, and a perfect place to start. First of all, that it is relatively common – anywhere from 1 in 500 to 1 in 200 people around the world are diagnosed with HCM without any geographic or ethnic hot spots or cold spots. That the disease can be completely compatible with normal longevity and excellent quality of life if we follow modern management recommendations. We need to tell our patients that it can be genetic. Many patients have mutations in the cardiac sarcomere proteins that can result in familial patterns of HCM, usually in an autosomal dominant pattern. We also have to talk to our patients about the fact that while most people can achieve normal longevity, that sudden cardiac arrest is possible and occurs in about 0.8% of patients with HCM on an annual basis. And then lastly, most of our therapies are designed to help patients feel better in their daily lives and to lead a more normal quality of life that we hope for them.

Now, you also asked about the pathophysiology, and I think there’s 2 ways to look at the pathophysiology. There’s the macro pathophysiology that we’ve been dealing with for years, which is the phenomenon of a thick heart muscle which can lead to diastolic dysfunction of various degrees, and then dynamic outflow tract obstruction, which alters the way blood flows through and out of the heart, which can cause patients to be highly symptomatic. More recently, there’s been a lot of focus on the cellular pathophysiology of disease, where there is enhanced myosin and actin interactions, which has now become the target for new, novel agents that are being investigated.

So, Ahmad, with that in mind, that brings us to the second thing I think that we agreed we’d talk about, and can you talk us through how we diagnose HCM? What are the standard tests and things that you want to look for when you are suspecting hypertrophic

cardiomyopathy in a patient?

Dr. Masri:
Absolutely, thank you Steve. The really classical presentation of HCM centers around having unexplained left ventricular hypertrophy. That's after somebody comes and complains of symptoms of shortness of breath, chest pain, having other symptoms of heart failure as we discussed earlier. But the cardinal finding on echocardiography, for example, is having unexplained left ventricular wall hypertrophy or thickness, and in general, the guidelines use thresholds of 15 millimeter LV wall thickness or 13 millimeter in the presence of family history. What's interesting is one can, in their daily routine practice, just implement a strategy of simply explaining all cases of left ventricular hypertrophy they see, and this way, they hopefully can pick up HCM as well as other diseases that can mimic hypertrophic cardiomyopathy.

In terms of the obstructive phenotype, having a dynamic murmur on exam is very important. I think clinicians should get into the habit of asking people to Valsalva, or even, if they're more comfortable, asking them to stand while they're auscultating them if they hear a systolic murmur. That can be really a good clue that there's a dynamic murmur present there on exam. And it doesn't really take much to do that.

Family history is extremely important, and as you mentioned, some of these cases come without evidence of family history, but a lot of them do. And obtaining this detailed family history going back a couple of generations really is vital because the things that people tell you sometimes surprise you and can give you a clue that there is something more going on with this patient, even, for example, if they have hypertension or if they have other causes that could lead, in theory, to increase the ventricular hypertrophy.

In terms of the other diagnostic methods, you know, we start almost always in a cardiology clinic evaluation with an EKG. And it can range from being really dramatic, showing left ventricular hypertrophy as strain pattern and catching the eye, essentially, to really being very unremarkable looking. There is a couple of specific patterns, one probably important one to mention is in the case of apical hypertrophic cardiomyopathy, where you would have deep inverted T waves in the presence of high voltage, and this is what's known as Yamaguchi pattern on electrocardiograms.

Echocardiography still plays the essential role in the diagnosis of HCM. It provides, really, a wealth of information in terms of assessing the degree of LV wall thickness, the distribution of the thickness. It's really not a binary yes or no. One has to think about how this distribution of thickness looks – asymmetric or symmetric – and where the thickest segment is, as well as assessing the exact HCM phenotype. We can also assess LV function, show the presence of systolic anterior motion of the mitral valve, which is the hallmark of obstructive hypertrophic cardiomyopathy, and then look at the degree of mitral regurgitation as well as the complications that arise because of that, including diastolic function assessment, pulmonary hypertension, or pulmonary pressure in direct assessment of them.

And then we really have to talk to our stenographers to make them aware that anytime you see SAM [systolic anterior motion] or you see left ventricular outflow track gradient, even if it's not crossing the threshold of 30 mmHg, which defines obstruction, to ask patients to perform different maneuvers. The most common one we do routinely in the echo lab is Valsalva maneuver.

We do also use exercise testing, with or without cardiopulmonary exercise, testing for peak VO2 measurement as well as other wealth of information. That gives us an idea on patients' exercise capacity, blood pressure response to exercise, as well as the degree of LVOT obstruction with exercise as another provocative maneuver to try and understand their symptom burden.

And then, in general, people always talk about cardiac catheterization and coronary angiography in patients who are symptomatic. Really, we are typically able to diagnose hypertrophic cardiomyopathy without specifically doing coronary angiography or cardiac catheterization, and we typically would reserve it in complicated cases or in the case we need, really, coronary assessment to understand suitability for alcohol septal ablation.

There are a couple of other tests and concepts that we go after. For example, cardiac MRI has really an important role nowadays. It can help differentiate the types of left ventricular hypertrophy, help provide detailed anatomy of the mitral valve, sub-mitral valve apparatus, as well as the distribution of thickness.

But perhaps the most important aspect, which is currently present also in the guidelines that Dr. Ommen chaired and authored, is that that presence, burden, and distribution of enhancement on late gadolinium enhancement imaging, this represents the amount and degree of myocardial fibrosis that is considered to be a risk factor for sudden death that has to be taken into account with other risk factors.

For those just tuning in, you're listening to CME on ReachMD. I'm Dr. Ahmad Masri, and here with me today is Dr. Steve Ommen. We're discussing hypertrophic cardiomyopathy, and what makes this condition so challenging, to both diagnose and treat.

So let's move on to our third topic that we need to know and discuss in regard to HCM, which is the first question, is there a deficit in

how we currently manage and treat hypertrophic cardiomyopathy? And this really might be a complicated and loaded question, as much as the diagnosis, where you do have couple of options of treatment and some of them are very effective. But most of the data we have is observational data, and we do generally lack large, randomized, controlled trials in the current standard of care therapies in hypertrophic cardiomyopathy.

What do you think about that, Steve? And can you take us through some of the current management approaches in HCM?

Dr. Ommen:
Yeah, absolutely. Those are very important points. So, largely, as we mentioned earlier on, the pharmacologic or invasive management of patients with HCM is really directed at relief of symptoms. So we'll talk only about symptomatic patients at this point, and I think we'll limit our discussion today, as well, to those patients who have obstructive physiology.

So it's important to point out that it's very rare for patients with HCM to have class 4 symptoms or symptoms at rest. And that's in part because that macro pathophysiology that we talked about before is something that is minimized when a patient is at rest or sitting down, but as soon as a patient tries to walk across the room or walk up a flight of stairs, their contractility goes up, and their preload and afterload go down, all of which promote their outflow tract obstruction getting worse. So to date, all of the primary therapies had been focused on relieving those macro phenomenon – keeping contractility in check, making sure afterload and preload are maintained, all in ways to decrease the impact of that outflow tract obstruction.

As we pointed out, that would include beta-blockers and the nondihydropyridine class calcium channel blockers as first-line therapy, as well as getting rid of any agents that might be provoking those phenomenons, such as pure vasodilators or high-dose diuretics. If patients aren't responsive to those medications, and the patient's symptom status is the response we're looking for – it's not something we measure in the echo lab but is how is the patient doing – then they can move on to the more advanced therapies. It is true that many patients are asymptomatic. A lot of patients have kind of mild to moderate symptoms, kind of in the class 2 range, and then some do get more advanced symptoms in class 3. And traditionally, the class 3 patients who are unresponsive to the pharmacologic therapy are the patients for whom we consider septal reduction therapy.

So when you talk about the gaps, or ask about the gaps we have, there's a couple of things here. One of them is for patients who have only mild to moderate symptoms and yet are having side effects from the standard therapies. That's a gap. Do you really want to take someone all the way to an invasive procedure? In some cases, the patients may opt for that, but there are many patients who don't feel that their lifestyle is impacted enough that they want to pursue an invasive operation or invasive catheter-based procedure when their symptoms are only mild or moderate. They just want to feel a little bit better. And then the other big gap, of course, is there are robust data that show that both surgical myectomy and catheter-based alcohol septal ablation have much better outcomes when they're performed in high-volume comprehensive centers for HCM, which means it's not as easy for many patients, logistically, to get to centers that can do that. So there are a lot of patients in the class 2 to 3 range who potentially could benefit from therapies, short of invasive therapies, knowing that there is somewhat of a limited supply of those procedures available.

And I think we can get into the discussion here, the newer investigational therapies are now not focusing primarily on those macro phenomena, but on the cellular level – actin-myosin interactions – in a way to impact the outflow tract obstruction in patients' symptoms at a cellular level rather than a macro hemodynamic level.

Dr. Masri:
That was beautifully laid out, and as you mentioned, the cardiac myosin inhibitors, which are this new class of medications that work at the cellular level, they do represent the first class of medications that, you know, is trying to directly and specifically address some of the abnormalities that we have, such as excessive myosin and actin interactions. The aim is to decrease the number of myosin hits which are available for engagement with actin, which is counteracting that hypercontractility. There are really some exciting things about this new class of medications. They're currently under investigation or under regulatory review, and there's a lot more to learn about them as time goes, especially from these open-label studies that are going for 5 years or so.

So far, we know that they do make patients feel better. They improve exercise capacity, but perhaps, at least myself, what I'm looking for in long-term extension studies is to see that how do they address the structure and function of the heart? How do they address the underlying disease so that we go beyond only discussing symptom relief and management of symptomatic patients? What do you think?

Dr. Ommen:
Yeah, I think that's really important. We in the HCM community are very excited that we have drug companies focused on HCM specifically, rather than trying to adopt medications from other diseases for our purposes. And I think there's a lot of promise that these agents will have an important role going forward.

To your point, we do want to see a lot of long-term data. Can it change the course of disease? We haven't had long enough studies to

know whether it alters hypertrophy in the long term, whether it can prevent hypertrophy in otherwise genotype-positive individuals who don't yet have phenotype – lots of unknown questions. And then there's also some safety questions that remain to be completely answered, and that is for some patients, these agents act as such a potent negative inotropic agent that it suppresses myocardial function to lower the normal levels, which in every other cardiac condition is associated with worse outcomes. So we do want to see some safety data come forward, but we are excited to see a number of agents being investigated. And then it'll be, you know, upon us as HCM specialists to help define the optimal place and role for these new agents to help those patients right now who aren't optimally managed.

Dr. Masri:
Well, very well said. Thank you for your thoughts on that. This has been a fascinating conversation, but before we wrap up, Steve, can you share your one take-home message with our audience?

Dr. Ommen:
Thank you for that. I only get one, huh? All right, I'll try to be concise. What I would say is that with appropriate application of our current therapies attacking both the macro pathophysiology and the potential of new agents to attack the cellular pathophysiology, HCM patients can expect the opportunity to have a great quality of life and normal or near normal longevity.

Dr. Masri:
Great, and I would add for myself is that we really cannot treat HCM effectively if we don't recognize it. Keep it in your mind in your routine daily practice and truly always try to explain all cases of left ventricular hypertrophy that you encounter in your practice.

Unfortunately, that's all the time we have today. Please look for our other activity, titled "Emerging Therapies in HCM: The Potential Role of Cardiac Myosin Inhibition," for a more in-depth review of the mechanism of action of these medications and where do they fit in the treatment plan for our patients.

And so with that, I want to thank our audience for listening in and thank you, Dr. Steve Ommen, for joining me and for sharing all of your valuable insights. It was great speaking with you today.

Dr. Ommen:
Thank you, Ahmad. It was a great conversation, and good-bye.

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