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Understanding hypertrophic cardiomyopathy and recent guidelines

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Dr. Arbelo:
Hello. My name is **Elena Arbelo**, and I am the coordinator of the Cardiomyopathy and Southern Cardiac Death Clinic at Hospital Clinic, Barcelona, Spain.
Very happy to be here to talk about understanding hypertrophic cardiomyopathy and discuss the recent guidelines. These are my disclosures.

What is hypertrophic cardiomyopathy? Hypertrophic cardiomyopathy is characterized by left ventricular hypertrophy, which is normally higher or more evident in the septum. There should be no other cause to justify this level of hypertrophy sufficiently. In order to diagnose this, the ESC guidelines proposed a 15-millimeter threshold. Those that have more than 15 millimeters, a maximal and diastolic left ventricular wall thickness should be considered they have hypertrophic cardiomyopathy. If this is a family with hypertrophic cardiomyopathy or a person with a mutation in a sarcomeric gene, then the threshold should be 13 millimeters. In case of children, we have to adjust for body size and therefore we use z-scores. The ESC guidelines recommend diagnosing hypertrophic cardiomyopathy in case of a z-score above two.

This is what hypertrophic cardiomyopathy looks like. Basically, the heart is thick, and in this figure, you can see how the septum is even thicker. In the histological cuts, what you see is bundle disarray hyperchromatic nuclei of the cardiomyocytes and the presence of increased collagen in between the fibers. Why is it important? It's important because hypertrophic cardiomyopathy increases the risk of sudden cardiac death, induces progressive functional limitation, atrial fibrillation, heart failure, and increases the risk of stroke. It is a disease that is present in about one in 500 individuals, and it's normally inherited with an autosomal dominant pattern. However, women are usually diagnosed less and much later in life and have worse outcomes, so it's important that we suspect the disease.

These are the documents that we have nowadays to guide diagnosis and management of this cardiomyopathy. The 2023 ESC guidelines was a guideline encompassing all cardiomyopathy subtypes and the 2024 US guidelines focusing on hypertrophic cardiomyopathy. I will focus on the ESC guidelines. Basically, the first step that we need to take into consideration is that cardiomyopathies need to be managed in multidisciplinary teams. We need to have cardiomyopathy experts, but we need the participation of other experts like imaging, electrophysiology, heart failure, geneticists, genetic counseling, et cetera. Very important. Also, the role of the cardiac surgeon. The other thing we need to ensure is the adequate coordination and transition between adult and pediatric services. The cardiomyopathies can be diagnosed at an early age. Also, when we have adults with a diagnosis of cardiomyopathy, we need to screen the family, and this may include children.

This is the central figure of the ESC guidelines. Basically, the important change that we need to achieve is to have a cardiomyopathy mindset. We must suspect cardiomyopathy from different conditions and then we need to undergo a systematic multiparametric

approach to characterize that cardiomyopathy. This care, as I said, needs to be multidisciplinary coordinated, and needs to be centered in the patient but also in the family. As I said, these are inherited diseases, and the family, on one hand, will help to characterize better the phenotype in the family. On the other hand, when we diagnose a patient with cardiomyopathy, we necessarily need to screen first-degree relatives. This is how it happens. First, we suspect cardiomyopathy. Any patient with any kind of symptoms in the cardiovascular system could potentially have cardiomyopathy. Either be dyspnea, chest pain, palpitations, syncope, sudden cardiac arrest, or they may be an incidental finding after a murmur or an abnormal ECG, or the detection of an arrhythmia. We may suspect cardiomyopathy during family screening. In any case, the first step that we need

to do is to characterize the suspected cardiomyopathy in terms of ventricular morphology and function. So hypertrophy, dilatation, and systolic diastolic function. Also, and this is important because the CMR has a very important role, we need to identify the presence of ventricular scar or fatty replacement. With that, we come up with five different phenotypes. I insist, it's phenotypes. You may have a thick heart, the hypertrophic cardiomyopathy. You may have a dilated one, a non-dilated left ventricular cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, or restrictive.

The important thing is that this is not a diagnosis. It's just a phenotype. Very importantly, once you see a thick heart, and without another cause sufficient to justify the level of hypertrophy, you need to look at different features, to go beyond and understand what's the underlying etiology. For instance, age will help us suspect what type of hypertrophic cardiomyopathy or the other. For instance, amyloidosis or Fabry usually are diagnosed later in life while Pompe or Danon disease is diagnosed earlier.

With the phenotypes, very important, always, always, always do this multi-parametric approach that includes the family history, pedigree analysis, evaluating the signs and symptoms, and especially, the extracardiac involvement. The presence of arrhythmias, the genetic testing, and other laboratory markers, and in some cases, pathology, because we're going to go from the phenotype to a phenotype-based but integrated etiological diagnosis.

The guidelines show different tables where you can see by phenotype the different characteristics that will lead you to suspect one etiology or the other. For instance, in case of family history inheritant patterns, most sarcomeric hypertrophic cardiomyopathy has an autosomal disease. If you see an X-linked or a matrilineal inheritance pattern, then you need to suspect other etiologies, underlying etiologies, that will have different management pathways. Age we discussed already but same happens with extracardiac signs and symptoms. For instance, if you have a hypertrophic cardiomyopathy phenotype, and you have learning difficulties or developmental delay, you may suspect mitochondrial disease, Danon disease, or Noonan, for instance. The ECG may also give you hints, red flags for specific diagnosis. Short PR is very typical, for instance, of Danon disease. AV block, you may have it in amyloidosis, in Fabry, in Danon disease, or sarcoidosis, et cetera. The same happens with lab tests. Elevated CKs leads you to think, for instance, in mitochondrial disease, glycogenosis or Danon disease.

The importance of the ECG goes beyond suspecting hypertrophy. We need to look at the ECG because with that we're going to have some hints on the distribution of the hypertrophy, the presence and locations of fibrosis, and it will help us in the early diagnosis of relatives or identify possible underlying etiologies. These are two examples. We have the echo image of a hypertrophic heart. With the echo, you cannot distinguish beyond the hypertrophic phenotype, but when you look at the ECG, you have two very different ECGs. On the left, you see atrial fibrillation, low QRS voltages and cellular necrosis, while on the right, you have short PR, high QRS voltages, and repolarization abnormalities. Same phenotype, different ECG. These are two different diseases that have different prognosis and different management.

Another very important test in cardiomyopathy is the genetic test. In the case of hypertrophic cardiomyopathy, we identify a sarcomeric protein gene mutation, so pathogenic variant, or likely pathogenic, in 40% to 60% of individuals. Then in a small subgroup of 5% to 10%, we may have other genetic and non-genetic causes that have specific management. Remember, the typical sarcomeric hypertrophic cardiomyopathy has an autosomal dominant inheritance, but it has genetic heterogeneity, incomplete penetrance, and variable sparsity. It's very important, it's a class I in the guidelines, to do a genetic test in any index case of a patient or newly diagnosed patient with cardiomyopathy because it will help diagnosis, it will guide prognosis, therapy, and it will allow reproductive advice.

Then multimodality imaging. Probably multimodality imaging and genetic testing are the key things that the new guidelines have highlighted, and it's important to take into account that this is the first step. First step, we need to, when we suspect cardiomyopathy, we need to do a comprehensive evaluation of the cardiac dimensions on the left and right ventricular systolic and diastolic function, and this is usually done initially with the echo. Then we also need to assess the presence of scar, and we may need CMR. The cardiomagnetic resonance is crucial at baseline diagnosis of patients with hypertrophic cardiomyopathy as it will allow to evaluate the morphology and some specific characteristics, and may even suggest specific underlying etiology. For instance, the typical sarcomeric hypertrophic cardiomyopathy will show fibrosis in areas where you have hypertrophy usually being patchy and in the mid-wall. Then in the follow-up, the magnetic resonance is indicated with a two-way recommendation both for establishing prognosis and for following up a therapeutic

response in specific underlying etiologies. The role of imaging in hypertrophic cardiomyopathy, as I'm saying, it's crucial. Diagnosis, distinguishing between the healthy and the pathological heart, phenotyping the specific etiology, explaining symptoms, and allowing family screening and guiding genetic testing. It's important to guide treatment, heart failure patient, left ventricular obstruction with myosin inhibitors, myectomy, alcohol septal ablation, and treating other causes. Then imaging is crucial also for establishing prognosis. It helps with the sudden cardiac risk prediction, and it helps monitor effects of treatments and disease progression.

Concentrating on hypertrophic cardiomyopathy in the assessment of left ventricular obstruction, the first step, as always, is the 3D echo and the Doppler echocardiography. This needs to be done at rest, but it has to be repeated with Valsalva and maybe sitting and/or standing. It's very important to also talk to the patient. Some patients have more symptoms right after eating, so what we do is we echo after a very heavy meal, so this way, we unmask possible left ventricular obstruction that we may not detect at rest. The important thing is that we see obstruction of 50 or more millimeters of mercury, then it has specific management pathway. If there is not obstruction, but the patient is still symptomatic despite these maneuvers, we may need to do an exercise test, and this would be a class I indication. If the patient does not have obstruction and is asymptomatic, it's only recommended to repeat echocardiography every year.

What do we do in the case of heart failure symptoms? First thing, atrial fibrillation. The atrial fibrillation is a very complex arrhythmia in patients with hypertrophic cardiomyopathy because it provokes symptoms and then it has high risk of stroke and heart failure decompensation. The first step, always assess if there's atrial fibrillation. If there's atrial fibrillation, anticoagulation is mandatory irrespective of the CHA_2DS_2-VASc. Then it's preferred that you restore sinus rhythm, it's usually better tolerated, but if you cannot, at least make sure that the rate is adequately controlled. If you don't have atrial fibrillation or if everything is managed properly in the case of atrial fibrillation, and the patient is symptomatic, you evaluate if there's obstruction of the left ventricular outflow tract. If there is, there is a specific management pathway that I will talk about just after. If not, you need to manage the patient with the usual heart failure recommendations based on the presence of left ventricular dysfunction or not,

which I want to highlight now. In hypertrophic cardiomyopathy, we consider dysfunction or significant dysfunction if the ejection fraction is below 50. What about management of left ventricular outflow tract obstruction? First step, is to treat with beta-blockers, that's the class I, and if the patient does not tolerate them or if they're still symptomatic, you may consider channel calcium blockers. The real innovation is the second line treatment because we now finally have a specific treatment which are the cardiac myosin inhibitors to treat this patient. Phase 3 pivotal trials at the time of the guidelines, we only had mavacamten, and after aficamten has also shown positive results, have shown that these types of drugs allow improvement of the peak VO 2, reduce the gradients both at rest and Valsalva, and improve echo biomarkers like BNP, TnT, and also quality of life and NYHA functional class. This would be the second-line treatment. At the time of our guideline, this would be a IIa indication. Maybe if we were to review the guidelines, we may consider, with longer-term data, that this could be a class I. Then if the patient is still symptomatic despite this treatment, we may consider septal reduction therapies.

Regarding septal reduction therapy, I will only highlight a couple of things. It's important that septal myectomy rather than alcohol septal ablation is done in children or if there's other surgical indication. For instance, the presence of abnormalities of the mitral valve. The other thing to consider is that we may send the patient for a septal reduction therapy in expert centers at the earlier stage. Rather than class III, IV, do it in class II, but it needs to be center with high expertise, low complications, and there needs to be other indications. For instance, the presence of moderate to severe, SAM-related mitral regurgitation or atrial fibrillation.

The other thing that we need to do in hypertrophic cardiomyopathy is evaluate the risk of sudden cardiac death to decide whether a patient needs an ICD or not. In secondary prevention, of course, this indication is class I, but in primary prevention, what we recommend is that you use the HCM sudden cardiac death risk calculator to predict the number of events at five years. If you are in what we consider the high-risk group, so more than 6%, equal or more to 6% of risk at five years, the ICD should be considered. Then the other two groups, what you need is shared decision-making. Intermediate group and low-risk group, you may still consider the implantation of an ICD considering together with the patient all the evidence, the presence of competing risks, and the patient's culture, beliefs, preference, et cetera. Importantly, there is now a validated risk score for children that we also recommend in the guideline.

What about these other clinical markers that may lead us to consider ICD implantation in the low-risk group? Well, this is the calculator. The left ventricular apical aneurysms per se are not a reason to implant an ICD based on the ESC guidelines. What the guidelines say is that this should be done together with the HCM sudden cardiac risk score, and that, if the risk is high, is when you should consider implanting an ICD. This is because the presence of apical aneurysms is rarely in isolation. Usually, patients with apical aneurysms have more left ventricular dysfunction and have more ventricular tachycardia or prior ventricular fibrillation. Therefore, the risk score per se already identifies the patients at risk. Another thing that we need to consider and should take into account, especially in the low-risk group, is the presence of fibrosis of an extensive late gadolinium enhancement equal or more of 15%.That is a class IIb, so it could be used or may be used to guide decisions on ICD implantation. This is because many observational studies and several meta-analyses of

these studies have shown that late gadolinium enhancement is associated with a higher incidence of sudden cardiac death in the follow-up of these patients. The only question that remains is whether this is an independent predictor or this is not independent of the HCM sudden cardiac risk score. When we look at the data, it suggests that the best threshold to guide the decision is probably around 15% using the six standard deviation technique. Finally, patients with left ventricular dysfunction, that is ejection fraction below 50% that are in the low-risk category, may be implanted an ICD

because these patients have a much higher rate of sudden cardiac death and need for transplant and all-cause mortality.

With this, I would like to conclude. Diagnosis and managing patients with hypertrophic cardiomyopathy requires a multidisciplinary, patient-centered, and family-centered approach, and that this needs to be a multiparametric evaluation of the family history, signs and symptoms, ECG, lab results, multimodality imaging, genetic testing, and holter to go from a phenotype to a phenotype-based integrated etiological diagnosis that will allow us a more personalized management of these patients.

Thank you.

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