

**JOHN
JEFFERIES:**

As you know, Fabry Disease is an increasingly recognized entity, both in pediatric and adult medicine. It's particular of interest in the area of cardiovascular medicine because now cardiovascular disease is the leading cause of mortality in Fabry Disease. As such, we've tried to learn as much as we possibly can, both in the diagnosis and the treatment of the cardiovascular implications of Fabry to avoid bad outcomes whenever possible, but also to enhance quality of life, to avoid symptomatology, many of the typical things that we would do in a population that had cardiovascular disease, such as heart failure or myocardial infarction.

So over the last decade, we've become increasingly cognizant of the importance of this disease and the diagnosis. And part of that has come about because of the increasing use of genetic testing. So as you may know, many hospitals and providers employ genetic testing as a part of their diagnostic criteria or toolset. And we do the same.

So many of our patients that would come to us that perhaps had thickening of the heart muscle, what we would call left ventricular hypertrophy, we may do a genetic panel to look for traditional causes of a disease called hypertrophic cardiomyopathy, but to also ferret out other more sort of singular and rare disorders, such as Fabry. And you also probably know that many states are starting to incorporate genetic testing at the time of birth, which would allow us to at least identify the genetic trigger, or the predisposition for this disease. So cardiovascular disease is an important facet in the management of Fabry Disease.

And as you'll learn from other modules, it is a multidisciplinary approach to be completely effective. But we know there's pretty serious implications of Fabry Disease on the cardiovascular system. So one is that many patients can experience premature stroke or cerebrovascular accident.

And this is very important, and we're starting to learn more about why we think that this occurs. And many times it's been thought this is typically because of deposition and ultimate sort of problems with local blood flow within the brain. What we're starting to wonder is perhaps these patients have an underlying disorder called atrial fibrillation. And that's a very common disorder that increases in prevalence as you age in the population.

But it's well associated with cerebrovascular accidents. And we're doing more surveillance for Fabry, which I'll talk more about in other segments, to help detect atrial fibrillation and help potentially prevent some of these strokes. We also know there can be endothelial dysfunction. So the lining of the blood vessels can be deranged and not work exactly as anticipated, meaning they may not constrict or dilate as they should.

Patients are prone to having myocardial disease, so a cardiomyopathy. Typically that can be in the form of left ventricular hypertrophy, so a hypertrophy, or thickened heart muscle, typically the left-sided pumping chamber, the left ventricle. But they can also manifest as other types of cardiomyopathies. Specifically, it can manifest as dilated cardiomyopathy, where it's where the chamber's enlarged and it doesn't squeeze very well.

It can also manifest as a disease called left ventricular non-compaction cardiomyopathy, which we'll talk more about later on. So all these are important. And you need to be cared for by a clinician who appreciates all these potential phenotypes and does appropriate surveillance for them.

And lastly is an importance of arrhythmias in the population. And as a provider, someone who sees a lot of patients with Fabry, I think this is really an under-leveraged opportunity for us to understand some of the pathology, the cause of morbidity and mortality in our patients that have Fabry. So specifically, as I said, we're starting to detect atrial fibrillation, which can be a problem because of thromboembolic disease and subsequent stroke.

But it can also cause things like syncope. You can have rapid heart rates that make patients become symptomatic. You can have slow heart rates, which is a very typical finding, especially in our younger populations, to have what's called sinus bradycardia. But also it can manifest as ventricular arrhythmias, so specifically ventricular tachycardia and ventricular fibrillation.

And so just to put this in context, these are the rhythm disturbances that you would see people getting shocked for by an EMS or on television or wherever the case may be. So these are life-threatening arrhythmias. And it's very important for us to recognize them and potentially deal with them as quickly as we possibly can.

There aren't great medical therapies that are going to make a big difference in the substrate of ventricular tachycardia or ventricular fibrillation. But we can put in devices that are sort of safety nets for all of this. And that's in the form of a thing called an Implantable Cardioverter Defibrillator, or an ICD. And that is a shock box that lives internally inside the body and helps to detect these abnormal rhythms and will correct them by delivering either pacing or a shock therapy to restore sinus rhythm to the heart muscle.