Transcript Details

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Understanding the Pathophysiology Behind ATTR-CM

Announcer:
You're listening to *Heart Matters* on ReachMD. On this episode, we'll hear from Dr. Frederick Ruberg, who's the Thomas J. Ryan Professor of Cardiovascular Medicine and a Professor of Radiology at Boston University Chobanian and Avedisian School of Medicine as well as the Chief of Cardiovascular Medicine at Boston Medical Center. He'll be discussing the pathophysiology and prevalence of transthyretin amyloid cardiomyopathy, or ATTR-CM. Let's hear from Dr. Ruberg now.

Dr. Ruberg:
ATTR cardiomyopathy is a term describing a protein-folding disorder where a protein—in this case TTR, or transthyretin—misfolds and aggregates as something called amyloid fibrils in different organs of the body. I'm most interested, as a cardiologist, in cardiac amyloidosis, or misfolding of TTR protein in the heart. TTR is a protein produced by the liver, and it exists as a four-subunit protein that circulates in the blood. And sometimes, subunits break apart, misfold, and then aggregate as amyloid fibrils that deposit in between the cardiac myocytes and cause symptoms of congestive heart failure, and ultimately, unfortunately, death. And part of the pathophysiology also includes the capacity of the heart to respond to deposited amyloid, and that sometimes involves injury to the heart muscle and heart cells from the amyloid deposits as well as reabsorption of the amyloid deposits that have already been deposited through restorative mechanisms in the heart—typically the reticuloendothelial system.

So ATTR cardiac amyloidosis can be subclassified into whether the TTR protein is genetically normal or genetically abnormal. Genetically normal TTR is called wild type, and wild-type ATTR cardiac amyloidosis occurs in older individuals and is probably a relatively common cause of congestive heart failure in people over the age of 70 years. Variant ATTR, where the TTR is genetically abnormal, also occurs in people of different ages.

There are over 130 different variants. These are single nucleotide switches or polymorphisms in the TTR gene that are passed on in an autosomal-dominant manner, and a large number of those can cause cardiac or peripheral amyloidosis—or both. So knowing the genetic sequence of the TTR protein is critical to understand whether or not it's hereditary or variant because the variant and the hereditary amyloidosis have different progressions of disease and ages of onset, and also, treatments are different depending upon which pharmaceutical agents target which type of amyloid.

An important variant that clinicians need to know about is the V142I or V122I variant. This common variant exists in 3.4 percent of self-identified Black individuals in the United States. It originated in West Africa, and it causes predominantly—almost exclusively—a cardiac amyloidosis phenotype. The variant exists in about 3.4 percent of individuals. That's 1.5 million carriers of V142I in the US population. We know from population studies that people who hold that variant have a higher risk of congestive heart failure and a higher risk of death as they get older, but we don't know what proportion of people who have the variant ultimately develop cardiac amyloidosis. That's a very important unknown, and that under considerable investigation, including from my research group.

Announcer:
That was Dr. Frederick Ruberg discussing the pathophysiology of transthyretin amyloid cardiomyopathy. To access this and other episodes in our series, visit *Heart Matters* on ReachMD.com, where you can Be Part of the Knowledge. Thanks for listening!