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Breaking Down ATTR Pathophysiology

Announcer:

Welcome to ReachMD. This medical industry feature, titled “Breaking Down ATTR Pathophysiology,” is sponsored by AstraZeneca. And now, here’s Dr Marcus Anthony Urey.

Dr Urey:

Hi, I’m Dr Marcus Anthony Urey, Director of Cardiac Amyloidosis and Heart Transplantation at the University of California San Diego. Today, I’ll be discussing the pathophysiology of transthyretin-mediated amyloidosis, otherwise known as ATTR amyloidosis.

ATTR amyloidosis is a protein misfolding disorder of the transthyretin protein.¹ To better understand the pathophysiology of this disease, let’s take a step back to review the structure and function of transthyretin within the healthy body.

Transthyretin is a tetramer largely synthesized in the liver, which produces over 95 percent of it.²⁻⁴ It’s then secreted into the bloodstream to transport thyroxine and retinol throughout the body.¹⁻³ Now that we’ve characterized regular transthyretin, let’s explore the mechanism that drives its misfolding, which leads to ATTR amyloidosis.¹ There are two forms of the disease, one that is age-related called wild-type ATTR amyloidosis, seen in older individuals, and a second form called hereditary ATTR amyloidosis, seen in those with a mutation in the gene encoding transthyretin.⁴⁻⁷ The hereditary form is autosomal dominant, meaning there’s a 50% chance of a child inheriting the pathogenic variant.⁸⁻¹⁰

In both cases, the tetrameric structure of transthyretin becomes unstable due to weakened molecular bonds between the monomers, leading to their dissociation.⁴⁻⁷ The instability of the transthyretin subunits can result in misfolded amyloidogenic monomers.⁴⁻⁷ These monomers can then aggregate into insoluble amyloid fibrils and deposit in tissue and organs causing irreversible and debilitating damage.^{1,4-6,11-14} An important point here is that amyloid deposits into various organs and tissues, meaning it’s a multisystem disorder with diverse clinical manifestations.^{1,11-14} For example, amyloid fibrils can deposit in the musculoskeletal system, and result in a nerve compression or impingement neuropathy such as carpal tunnel syndrome and lumbar spinal stenosis. Although less common another important musculoskeletal symptom includes a ruptured biceps tendon.^{1,11-14}

Additionally, polyneuropathy can occur as a result of fibril deposition within the nerve. Patients may experience symptoms such as muscle weakness, difficulty walking, pain in the hands and feet, as well as autonomic dysfunction, such as orthostatic hypotension, chronic diarrhea or constipation, and erectile dysfunction.^{1,11-14} Other symptoms can include heart failure, atrial fibrillation, and bradyarrhythmia due to amyloid deposition in the heart.^{1,11-14} And so that’s why it’s important to recognize that ATTR amyloidosis is a protein misfolding disorder that manifests as a multi-system disease with symptoms that can be mistaken for those of other diseases.^{1,11-14}

Announcer:

This medical industry feature was sponsored by AstraZeneca. If you missed any part of this discussion or to find others in this series, visit Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

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