ATTR Amyloidosis Backgrounder

Disease Overview

Transthyretin (ATTR) amyloidosis is an underdiagnosed, rapidly progressive, debilitating and fatal disease caused by toxic misfolded transthyretin (TTR) proteins. The toxic misfolded TTR proteins collect as amyloid deposits throughout the body, including the nerves, heart and digestive system, resulting in progressive organ damage. There are two different types of ATTR – hereditary ATTR (hATTR), which is caused by an inherited variant, or change, in the TTR gene, and wild-type ATTR (wtATTR), which occurs without a TTR gene variant.[1-4]

Worldwide, there are ~50,000 patients with hATTR[2] and ~200,000 to 300,000 patients with wtATTR.[i]

hATTR

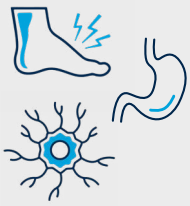
hATTR is an inherited autosomal dominant disease, meaning each child of a parent with the gene has a 50% chance of inheriting the genetic variant that causes the condition.[4,5] Though, inheriting the variant does not necessarily mean a person will develop symptoms of hATTR.[4,5] Although anyone may be at risk for this disease, it is more common among certain ethnicities, including those of African, Brazilian, French, Irish, Japanese, Portuguese and Swedish descent.[4,6,7] Without treatment, median survival from diagnosis is 4.7 years, and 3.4 years for patients presenting with cardiomyopathy.[7-10]

wtATTR

Unlike the hereditary version of the disease, wtATTR is associated with aging and is not passed down in the family.[1] It most commonly affects men who are age 60 or older, but it can also affect women.[11-13] Without treatment, median survival following diagnosis is 2.5 to 5.5 years. wtATTR is the most common form of the disease which is often misdiagnosed and almost always characterized by cardiomyopathy. [14-20]

Symptoms

ATTR is a multisystem disease that may present with symptoms related to cardiomyopathy, sensory-motor neuropathy, autonomic neuropathy, musculoskeletal involvement and other symptoms.[1,3,21,22]



Polyneuropathy refers to nerve damage that affects sensation, movement, strength, the digestive system and other bodily functions.[3,5,21]

Cardiomyopathy is a disease of the heart muscle that makes it difficult for the heart to pump blood to other parts of the body, which can lead to heart failure.[23]

[i] Information based on Alnylam modeling data.

Common symptoms associated with ATTR include:[3,4,21,22,24,25,26,27]

Cardiomyopathy:
Abnormal heart rhythms (arrhythmias)
Leg swelling (edema)
Fainting
Shortness of breath

Sensory-motor neuropathy:
Difficulty walking
Weakness
Tingling, pain and numbness
Loss of sensitivity to temperature

Autonomic neuropathy:
Sudden falls
Recurrent urinary tract infections (UTIs)
Diarrhea, constipation, nausea, vomiting
Unintentional weight loss
Sexual dysfunction

Musculoskeletal symptoms:
Bilateral carpal tunnel syndrome
Biceps tendon rupture
Lumbar spinal stenosis
Osteoarthritis
Trigger finger

Other symptoms:
Glaucoma
Blurred or spotty vision
Floaters in the eye

Symptoms vary from person to person,[4] often increasing in severity as the disease progresses, leading to significant disability, decreased quality of life and loss of physical function, including:[12,21,28,29]

Decreased ambulation:[3,21,30]
Inability to walk unaided
Wheelchair-bound or bedridden

Decline in daily function:[31-34]
Impairment in self-care
Impairment in ability to perform usual activities
Pain/discomfort

Social burden:[35,36]
Anxiety
Depression

Diagnosis

Timely and appropriate diagnosis of ATTR requires differentiating between hATTR and wtATTR.[3]

ATTR can be diagnosed using a variety of neurologic and cardiac assessments. These may include nerve conduction studies, laboratory tests, echocardiograms, cardiac magnetic resonance imaging (CMRI) and scintigraphy with bone tracers.[4,22] A tissue biopsy may be used to confirm the presence of TTR amyloid protein and can help establish a diagnosis.[12]

Both wtATTR and hATTR have symptoms that can be similar, so it is important to determine if someone carries a gene variant associated with the condition.[1] Genetic testing can identify the specific TTR variant and help confirm a diagnosis, which can inform whether other family members should also get tested.[4]

For more information on ATTR visit Alnylam.com or contact media@alnylam.com.

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