

Hereditary ATTR Amyloidosis (hATTR amyloidosis) Backgrounder

Disease Overview

Hereditary ATTR amyloidosis (hATTR amyloidosis) is an inherited, rapidly progressive, life-threatening disease. It is caused by a mutation in the transthyretin (TTR) gene that results in misfolded TTR proteins accumulating as amyloid fibrils in multiple sites, including the nerves, heart, and gastrointestinal track.¹ TTR protein is produced primarily in the liver and is normally a carrier for retinol binding protein – one of the vehicles used to transport vitamin A around the body. hATTR amyloidosis involves many systems in the body and can result in a wide variety of symptoms, including sensory and motor, autonomic (e.g., diarrhea, hypotension, erectile dysfunction) and cardiac symptoms.

The disease continuum of hATTR amyloidosis includes patients who present with predominantly polyneuropathy symptoms (involving the nerves), historically known as familial amyloidotic polyneuropathy (FAP), as well as patients who present with predominant cardiomyopathy symptoms (involving the heart), historically known as familial amyloidotic cardiomyopathy (FAC). However, many patients experience polyneuropathy, cardiomyopathy and gastrointestinal symptoms.

hATTR amyloidosis represents a major unmet medical need, affecting approximately 50,000 people worldwide.² The condition has a progressive course and can lead to morbidity, disability and can potentially lead to mortality within two to 15 years.¹ hATTR amyloidosis is often underdiagnosed or misdiagnosed and there remains a significant unmet medical need for therapies that can treat the underlying cause of the disease.²

Cause

hATTR amyloidosis is caused by a mutation in the TTR gene. hATTR amyloidosis is an inherited, autosomal dominant disease, meaning a person needs only one copy of the mutant gene to manifest the disease and therefore it can be inherited from one parent. The mutation causes the TTR protein to misfold and to accumulate as amyloid fibrils in multiple organs. hATTR amyloidosis is associated with more than 120 different known mutations in the TTR gene. The most common mutation associated with polyneuropathy is V30M, which is responsible for approximately 50 percent of mutations presenting predominantly with polyneuropathy.³

Symptoms

The degree and severity of hATTR amyloidosis symptoms and onset vary from person to person depending on the degree to which their organ function is compromised.

Commonly reported sensory and motor symptoms are:^{4,5}

- Neuropathic pain
- Altered sensation (i.e., change in sensitivity to pain and temperature)
- Numbness and tingling
- Muscle weakness
- Impaired balance
- Difficulty walking

Commonly reported autonomic symptoms are:^{4,6}

- Nausea and vomiting
- Changes in gastrointestinal motility (i.e., diarrhea, constipation, gastroparesis, early satiety)
- Orthostatic hypotension (i.e., dizziness and fainting upon standing)
- Bladder dysfunction
- Erectile dysfunction

Commonly reported cardiac symptoms are:⁷

- Shortness of breath
- Edema
- Palpitations and arrhythmias

Other commonly reported symptoms:^{4,6}

- Carpel tunnel syndrome
- Generalized fatigue
- Unintentional weight loss
- Ocular changes (i.e. blurred vision, blindness)

Diagnosis

Patients with hATTR amyloidosis require an early and accurate diagnosis due to the rapid natural progression of the disease. Because hATTR amyloidosis is often misdiagnosed due to its constellation of symptoms, which may overlap with other more common diseases, multiple specialists are often seen prior to diagnosis. Since the etiology of hATTR amyloidosis is different from that of other diseases with polyneuropathy and cardiomyopathy, a misdiagnosis could lead to ineffective or possibly detrimental treatment.⁸ hATTR amyloidosis should be considered in patients with progressive neuropathy or cardiomyopathy with multisystemic involvement, especially in those with a family history of amyloidosis.

hATTR amyloidosis is diagnosed in a variety of ways; however, blood tests and biopsy are commonly used to confirm the presence of TTR amyloid protein. Genetic testing may also be used to identify the specific TTR mutation. Other diagnostic tests for hATTR amyloidosis with polyneuropathy may include nerve conduction studies and/or renal function tests.⁹ Echocardiograms, cardiac magnetic resonance imaging (MRI), and scintigraphy with bone tracers can also be used to help diagnose those presenting with predominant cardiomyopathy symptoms.⁵

Treatments

Despite currently available treatments some patients may experience progressive and severe disease-related morbidities. Patients may work with an amyloidosis specialist to select an individualized treatment plan. Based on symptoms and TTR mutation, a patient's care team may include a primary care physician, hematologist, oncologist, neurologist, cardiologist, nephrologist, as well as other health care professionals. Current treatments for hATTR amyloidosis either manage symptoms (supportive treatment) or aim to stabilize the protein. Orthotopic liver transplantation may be a treatment option in select patients. Disease progression may occur with current treatments.

Clinical studies are ongoing to develop new treatments for hATTR amyloidosis.

For more information on hATTR amyloidosis, please contact media@alnylam.com or visit alnylam.com.

- ¹. Suanprasert N, et al. *J Neurol Sci*. 2014;344:121-128. 19.
- ². Hawkins PN, et al. Evolving landscape in the management of transthyretin amyloidosis. *Annals of Medicine*. 2015;47(8):625-638.
- ³. Ruberg and Berk. *Circulation*. 2012;126:1286-300.
- ⁴. Coelho T, et al. Safety and efficacy of RNAi therapy for transthyretin amyloidosis. *N Engl J Med*. 2013;369(9): 819-829.
- ⁵. Ando et al. *Orphanet J Rare Dis*. 2013;8:31.
- ⁶. Coelho et al. *Curr Med Res Opin*. 2013;29(1):63-76.
- ⁷. Shin et al. *Mt Sinai J Med*. 2012;79(6):733-748.
- ⁸. Dzungu et al. *Heart*. 2012;98(21):1546-1554.
- ⁹. Conceição et al. *Journal of the Peripheral Nervous System*. 2016;21:5-9.
- ¹⁰. Adams D, Suhr OB, Hund E, Obici L, Tournev I, Campistol JM, Slama MS, Hazenberg BP, Coelho T; European Network for TTRFAP (ATTReuNET). First European consensus for diagnosis, management, and treatment of transthyretin familial amyloid polyneuropathy. *Curr Opin Neurol*. 2016 Feb;29 Suppl 1:S14-26.