Hereditary ATTR (hATTR) Amyloidosis Backgrounder

Disease Overview

Hereditary transthyretin-mediated (hATTR) amyloidosis is a rare, underdiagnosed, inherited, rapidly progressive, debilitating, and often fatal type of ATTR. The condition is caused by variants (i.e., mutations) in the transthyretin (TTR) gene.[1,2,3] TTR protein is produced primarily in the liver and is normally a carrier of vitamin A.[4] The variant results in misfolded TTR proteins that accumulate as amyloid deposits in multiple tissues, including the nerves, heart and gastrointestinal (GI) tract.[1,2,3] The condition can have a debilitating impact on a patient's life and may lead to premature death within 4.7 years following diagnosis.[5] It is estimated that there are approximately 50,000 patients with hATTR amyloidosis worldwide.[6]

Cause

hATTR amyloidosis is an autosomal dominant disease caused by a variant in the TTR gene, meaning a person needs only one copy of the variant gene to manifest the disease, therefore, it can be inherited from one parent.[7,4] More than 120 different TTR gene variants have been identified, with predominant symptom presentation varying by genotype.[8] The most common variants in the US are V122I, T60A and V30M.[9] Some variants are more common in certain populations, including those of Portuguese, Swedish, Japanese, African, and Irish descent.[7,10]

Symptoms

hATTR amyloidosis is a multisystem disease with heterogeneous symptom presentation, meaning the types and severity of symptoms and onset vary from person to person.[3] Some common symptoms include:[2]

Peripheral sensory-motor neuropathy:
Neuropathic pain
Paresthesia
Weakness

Autonomic dysfunction:
Orthostatic hypotension
Recurrent urinary tract infections

GI manifestations:
Diarrhea
Nausea
Vomiting

Cardiovascular manifestations:
Conduction abnormalities
Arrhythmias
Heart failure

CNS manifestations:
Progressive dementia
Headache
Ataxia (impaired balance and coordination)

Ocular manifestations:
Glaucoma
Other eye vessel and pupil abnormalities, as well as vitreous opacities (floaters)

Symptoms of hATTR amyloidosis can progress quickly, leading to significant disability and dysfunction, including:[7,11]

Decreased ambulation:[12]	Decline in daily function:[13,14,15]	Social burden:[16]
Inability to walk unaided	Impairment in self-care	Anxiety
Wheelchair-bound or bedridden	Impairment in ability to perform usual activities	Depression
	Pain/discomfort	

Diagnosis

Accurate diagnosis of hATTR amyloidosis is often delayed for years due to its constellation of symptoms, which may overlap with other more common diseases.[7] 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.[17] hATTR amyloidosis should be considered in patients with progressive polyneuropathy or cardiomyopathy, especially in those with a family history of hATTR amyloidosis.

hATTR amyloidosis is diagnosed using a variety of tests. These may include nerve conduction studies, renal function tests, echocardiograms, cardiac magnetic resonance imaging (MRI), and scintigraphy with bone tracers. Biopsies are used to confirm the presence of TTR amyloid protein and can establish a diagnosis. However, genetic testing can identify the specific TTR variant and can help confirm a diagnosis.[18]

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

[1] Adams D, Coelho T, Obici L, et al, *Neurology*. 2015;85(8):675-682.
[2] Conceicao, et al, *Journal of the Peripheral Nervous System*. 2016;21:5-9.
[3] Shin, et al, *Mt Sinai J Med*. 2012;79(6):733-748.
[4] National Institutes of Health: Department of Health and Human Services. Genetics Home Reference. Transthyretin amyloidosis. https://ghr.nlm.nih.gov/condition/transthyretin-amyloidosis#inheritance. Accessed January 24, 2018.
[5] Swiecicki P, Zhen D, Mauermann M, et al, *Amyloid* 2015;22(2):123-131.
[6] Gertz MA. *Am J Manag Care*. 2017;23 Suppl 7:S107-S112
[7] Ando, et al, *Orphanet J Rare Dis*. 2013;8:31.
[8] Rowcenzio, et al, *Human Mutation*. 2014;35:2403-2412.
[9] Ruberg F, Berk J, et al, *Circulation*. 2012;126(10):1286-1300.
[10] Reilly M, Staunton H, Harding AE. *Journal of Neurology, Neurosurgery and Psychiatry* 1995;59:45-49.
[11] Dharmarajan K, Mauer M, *J Am Geriatr Soc*.2012;604(4):765-774.
[12] Coutinho, et al, *Excerpta Medica*. 1980;497:92-94.
[13] Vinik, et al, *J Periph Nerv Syst*. 2014;19:104-114.
[14] Vinik E, Hayes R, Oglesby A, et al, *Diabetes Technology & Therapeutics* 2015;7(3):497-508.
[15] Pruppers M, Merkies I, Faber C, et al, *Journal of Peripheral Nervous System* 2015;20:319-327.
[16] Lopes A, Sousa A, Fonseca I, et al, *J Community Genet* 2018:9:93-99.
[17] Dungu, et al, *Heart*. 2012;98(21):1546-1554.
[18] Adams D, Suhr OB, Hund E, Obici L, et al, *Curr Opin Neurol*. 2016 Feb;29 Suppl 1:S14-26.