Hereditary ATTR (hATTR) Amyloidosis Backgrounder U.S. Version

Disease Overview

Hereditary transthyretin (TTR)-mediated amyloidosis (hATTR amyloidosis) is an inherited, progressively debilitating, and often fatal disease caused by a mutation in the TTR gene. TTR protein is produced primarily in the liver and is normally a carrier of vitamin A. Mutations in TTR cause abnormal amyloid proteins to accumulate and damage body organs and tissue, such as the peripheral nerves and heart, resulting in intractable peripheral sensory neuropathy, autonomic neuropathy, and/or cardiomyopathy.[1]

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). Many patients, however, present as a mixed phenotype that includes polyneuropathy, cardiomyopathy and gastrointestinal symptoms.[2]

hATTR amyloidosis represents a major unmet medical need, affecting approximately 50,000 people worldwide.[3] The condition has a progressive course and can lead to morbidity and disability, and can potentially lead to mortality within two to 15 years.[1,4] hATTR amyloidosis is often underdiagnosed or misdiagnosed and there remains a significant need for therapies that can treat the underlying cause of the disease.[3]

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.[2,5] 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 mutations associated with polyneuropathy and cardiomyopathy are V30M and V122I, respectively.[6]

Symptoms

The degree and severity of hATTR amyloidosis symptoms and onset vary from person to person.[7]

Commonly reported sensory and motor symptoms are:[3]

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

Commonly reported cardiac symptoms are:[9]

- Shortness of breath
- Edema
- Palpitations and arrhythmias

Commonly reported autonomic symptoms are:[7,8]

- 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
- Sexual dysfunction

Other commonly reported symptoms:[7]

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

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.[2] 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, 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 and help confirm a diagnosis. Other diagnostic tests for hATTR amyloidosis with polyneuropathy may include nerve conduction studies and/or renal function tests.[10] Echocardiograms, cardiac magnetic resonance imaging (MRI), and scintigraphy with bone tracers can also be used to help diagnose those presenting with predominantly cardiomyopathy symptoms.[10]

Treatments

Due to the progressive nature of hATTR amyloidosis, managing the symptoms of the condition is an ongoing process. Physicians may prescribe medications to treat some of these symptoms and reduce the daily impact they may have.[2]

Currently, there are no approved treatments for hATTR amyloidosis in the U.S., though some patients may benefit from a liver transplant, which could substantially reduce the amount of TTR protein made in the body.[2]

Clinical studies have been conducted to evaluate new treatments for hATTR amyloidosis, which are currently under review by regulatory health agencies.

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

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