Transthyretin amyloidosis

Transthyretin amyloidosis is a slowly progressive condition characterized by the buildup of abnormal deposits of a protein called amyloid (amyloidosis) in the body's organs and tissues. These protein deposits most frequently occur in the peripheral nervous system, which is made up of nerves connecting the brain and spinal cord to muscles and sensory cells that detect sensations such as touch, pain, heat, and sound. Protein deposits in these nerves result in a loss of sensation in the extremities (peripheral neuropathy). The autonomic nervous system, which controls involuntary body functions such as blood pressure, heart rate, and digestion, may also be affected by amyloidosis. In some cases, the brain and spinal cord (central nervous system) are affected. Other areas of amyloidosis include the heart, kidneys, eyes, and gastrointestinal tract. The age at which symptoms begin to develop varies widely among individuals with this condition, and is typically between ages 20 and 70.

There are three major forms of transthyretin amyloidosis, which are distinguished by their symptoms and the body systems they affect.

The neuropathic form of transthyretin amyloidosis primarily affects the peripheral and autonomic nervous systems, resulting in peripheral neuropathy and difficulty controlling bodily functions. Impairments in bodily functions can include sexual impotence, diarrhea, constipation, problems with urination, and a sharp drop in blood pressure upon standing (orthostatic hypotension). Some people experience heart and kidney problems as well. Various eye problems may occur, such as cloudiness of the clear gel that fills the eyeball (vitreous opacity), dry eyes, increased pressure in the eyes (glaucoma), or pupils with an irregular or "scalloped" appearance. Some people with this form of transthyretin amyloidosis develop carpal tunnel syndrome, which is characterized by numbness, tingling, and weakness in the hands and fingers.

The leptomeningeal form of transthyretin amyloidosis primarily affects the central nervous system. In people with this form, amyloidosis occurs in the leptomeninges, which are two thin layers of tissue that cover the brain and spinal cord. A buildup of protein in this tissue can cause stroke and bleeding in the brain, an accumulation of fluid in the brain (hydrocephalus), difficulty coordinating movements (ataxia), muscle stiffness and weakness (spastic paralysis), seizures, and loss of intellectual function (dementia). Eye problems similar to those in the neuropathic form may also occur. When people with leptomeningeal transthyretin amyloidosis have associated eye problems, they are said to have the oculoleptomeningeal form.

The cardiac form of transthyretin amyloidosis affects the heart. People with cardiac amyloidosis may have an abnormal heartbeat (arrhythmia), an enlarged heart (cardiomegaly), or orthostatic hypertension. These abnormalities can lead to
progressive heart failure and death. Occasionally, people with the cardiac form of transthyretin amyloidosis have mild peripheral neuropathy.

**Frequency**

The exact incidence of transthyretin amyloidosis is unknown. In northern Portugal, the incidence of this condition is thought to be one in 538 people. Transthyretin amyloidosis is less common among Americans of European descent, where it is estimated to affect one in 100,000 people. The cardiac form of transthyretin amyloidosis is more common among people with African ancestry. It is estimated that this form affects between 3 percent and 3.9 percent of African Americans and approximately 5 percent of people in some areas of West Africa.

**Causes**

Mutations in the *TTR* gene cause transthyretin amyloidosis. The *TTR* gene provides instructions for producing a protein called transthyretin. Transthyretin transports vitamin A (retinol) and a hormone called thyroxine throughout the body. To transport retinol and thyroxine, four transthyretin proteins must be attached (bound) to each other to form a four-protein unit (tetramer). Transthyretin is produced primarily in the liver. A small amount of this protein is produced in an area of the brain called the choroid plexus and in the light-sensitive tissue that lines the back of the eye (the retina).

*TTR* gene mutations are thought to alter the structure of transthyretin, impairing its ability to bind to other transthyretin proteins and altering its normal function.

**Inheritance Pattern**

This condition is inherited in an autosomal dominant pattern, which means one copy of the altered gene in each cell is sufficient to cause the disorder.

In most cases, an affected person inherits the mutation from one affected parent. Rarely, cases result from new mutations in the gene and occur in people with no history of the disorder in their family. Not all people who have a *TTR* gene mutation will develop transthyretin amyloidosis.

**Other Names for This Condition**

- Portuguese polyneuritic amyloidosis
- Portuguese type familial amyloid neuropathy
- Swiss type amyloid polyneuropathy
- type I familial amyloid polyneuropathy
- type II familial amyloid polyneuropathy
Diagnosis & Management

Genetic Testing Information

• What is genetic testing?
   /primer/testing/genetictesting

• Genetic Testing Registry: Amyloidogenic transthyretin amyloidosis

Research Studies from ClinicalTrials.gov

• ClinicalTrials.gov
  https://clinicaltrials.gov/ct2/results?cond=%22transthyretin+amyloidosis%22

Other Diagnosis and Management Resources

• Boston University: Amyloid Treatment & Research Program
  http://www.bu.edu/amyloid/

• GeneReview: Hereditary Transthyretin Amyloidosis
  https://www.ncbi.nlm.nih.gov/books/NBK1194

• MedlinePlus Encyclopedia: Autonomic neuropathy
  https://medlineplus.gov/ency/article/000776.htm

Additional Information & Resources

Health Information from MedlinePlus

• Encyclopedia: Autonomic neuropathy
  https://medlineplus.gov/ency/article/000776.htm

• Health Topic: Amyloidosis
  https://medlineplus.gov/amyloidosis.html

• Health Topic: Arrhythmia
  https://medlineplus.gov/arrhythmia.html

• Health Topic: Autonomic Nervous System Disorders
  https://medlineplus.gov/autonomicnervoussystemdisorders.html

• Health Topic: Eye Diseases
  https://medlineplus.gov/eyediseases.html

• Health Topic: Peripheral Nerve Disorders
  https://medlineplus.gov/peripheralnervedisorders.html
Genetic and Rare Diseases Information Center

- Familial transthyretin amyloidosis
  https://rarediseases.info.nih.gov/diseases/656/familial-transthyretin-amyloidosis
- Hereditary amyloidosis
  https://rarediseases.info.nih.gov/diseases/6611/hereditary-amyloidosis

Additional NIH Resources

- National Institute of Neurological Disorders and Stroke: Orthostatic Hypotension Information Page
  https://www.ninds.nih.gov/Disorders/All-Disorders/Orthostatic-hypotension-Information-Page

Educational Resources

- MalaCards: amyloidosis, hereditary, transthyretin-related
  https://www.malacards.org/card/amyloidosis_hereditary_transthyretin_related
- Merck Manual Home Edition for Patients and Caregivers: Amyloidosis
  https://www.merckmanuals.com/home/hormonal-and-metabolic-disorders/amyloidosis/amyloidosis
- Neuromuscular Disease Center, Washington University
  https://neuromuscular.wustl.edu/nother/amyloid.htm#transthyretin
- Orphanet: ATTRV30M amyloidosis
  https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=EN&Expert=85447

Patient Support and Advocacy Resources

- Amyloidosis Foundation
  http://amyloidosis.org/
- Amyloidosis Support Groups
  https://www.amyloidosissupport.org/
- Family Caregiver Alliance
  https://www.caregiver.org/
- Metabolic Support UK
  https://www.metabolicsupportuk.org/
- National Organization for Rare Disorders (NORD): Amyloidosis
  https://rarediseases.org/rare-diseases/amyloidosis/
- The Foundation for Peripheral Neuropathy
  https://www.foundationforpn.org/
Clinical Information from GeneReviews
• Hereditary Transthyretin Amyloidosis
  https://www.ncbi.nlm.nih.gov/books/NBK1194

Scientific Articles on PubMed
• PubMed
  https://www.ncbi.nlm.nih.gov/pubmed?term=%28%28transthyretin+amyloidosis%5BTIAB%5D%29%29+OR+%28familial+amyloid+polyneuropathy%5BTIAB%5D%29%29+AND+english%5Bla%5D+AND+human%5Bmh%5D+AND+%22last+1440+days%22%5Bdp%5D

Catalog of Genes and Diseases from OMIM
• AMYLOIDOSIS, HEREDITARY, TRANSTHYRETIN-RELATED
  http://omim.org/entry/105210

Medical Genetics Database from MedGen
• Amyloidogenic transthyretin amyloidosis

Sources for This Summary

Reprinted from Genetics Home Reference:
https://ghr.nlm.nih.gov/condition/transthyretin-amyloidosis