CONDITION

Appalachian type amyloidosis

Learn how Appalachian type amyloidosis affects the heart and nerves, how it is inherited and diagnosed, and what treatment and follow-up may involve.

WHAT IT IS
Rare inherited transthyretin amyloidosis

BODY SYSTEM
Heart and circulation, nervous system

MAIN SYMPTOMS
Shortness of breath, swelling, numbness or tingling, dizziness or fainting

WHAT CAUSES IT
Inherited TTR gene variant

HOW IT IS DIAGNOSED
Tissue biopsy with protein analysis, TTR genetic testing

MAIN TREATMENT
Disease-modifying medicines and supportive care

CAN IT BE CURED?
No, treatment generally only slows progression

IS IT AN EMERGENCY?
Sometimes, with severe difficulty breathing

LONG-TERM OUTLOOK
Variable progression with possible lasting organ damage

Overview

Appalachian type amyloidosis is a rare inherited form of transthyretin amyloidosis, also called hereditary ATTR amyloidosis or hATTR. It is caused by a particular change in the TTR gene. This change is often written as p.Thr80Ala using current naming or Thr60Ala using older naming.

The condition received its regional name because it was identified in families living in the Appalachian region of the United States. The same genetic change has also been found in people with ancestry from northwestern Ireland. A person does not need to live in Appalachia or have known Irish ancestry to be affected.

The TTR gene provides instructions for making transthyretin, a protein produced mainly by the liver. Transthyretin normally carries thyroid hormone and vitamin A-related proteins through

the blood. In hereditary ATTR amyloidosis, an altered form of transthyretin can become unstable. The protein may separate, misfold, and collect in tissues as amyloid deposits.

In Appalachian type amyloidosis, deposits most often affect the heart and the peripheral or autonomic nerves. Peripheral nerves carry signals between the brain, spinal cord, and limbs. Autonomic nerves control automatic functions such as blood pressure, digestion, bladder function, and sweating.

Amyloid buildup can gradually interfere with how affected organs work. Symptoms generally begin in adulthood, but the age of onset and pattern of illness vary. Some people with the genetic change never develop clear symptoms.

Recognizing the condition matters because treatments are available that can slow additional amyloid formation. An accurate diagnosis also helps relatives make informed decisions about genetic counseling and testing.

Symptoms

Symptoms usually develop gradually and can resemble more common heart, nerve, or digestive conditions. One person may mainly have heart problems, while another may have a combination of heart and nerve symptoms.

Possible heart-related symptoms include:

Amyloid can make the heart muscle thick and stiff. The heart may then have trouble relaxing and filling with blood. This is called amyloid cardiomyopathy. Amyloid may also affect the heart's electrical system, leading to an abnormal rhythm or a heartbeat that is too slow.

Peripheral nerve involvement may cause numbness, tingling, burning pain, or reduced awareness of temperature. Symptoms often begin in the feet and later move upward. Muscle weakness, balance problems, or difficulty with fine hand movements can develop. Carpal tunnel syndrome, which causes hand numbness or pain from pressure on a wrist nerve, may occur before other symptoms.

Autonomic nerve involvement can cause lightheadedness after standing, constipation, diarrhea, early fullness after eating, nausea, abnormal sweating, bladder difficulties, or sexual dysfunction. A large blood pressure drop after standing is called orthostatic hypotension.

Unintentional weight loss may occur because of digestive symptoms, reduced appetite, or advanced illness. Kidney, eye, or other organ involvement is possible in hereditary ATTR amyloidosis, but it is less central to the typical Appalachian type pattern.

These symptoms do not by themselves establish a diagnosis. Many other medical conditions

can produce similar problems.

- Shortness of breath during activity or while lying flat
- Swelling in the feet, ankles, legs, or abdomen
- Fatigue or reduced ability to exercise
- A racing, pounding, or irregular heartbeat
- Dizziness, fainting, or near-fainting
- Unexplained weight gain from fluid retention

Causes and risk factors

Appalachian type amyloidosis results from a disease-causing variant in one copy of the TTR gene. It follows an autosomal dominant inheritance pattern. This means each child of a person with the variant has a 50% chance of inheriting it, regardless of sex.

Inheriting the variant does not guarantee that symptoms will develop. This is known as reduced or age-related penetrance. The age at which illness appears, the organs involved, and the rate of progression can differ even among close relatives.

The main risk factor is having the TTR p.Thr80Ala variant. A family history of unexplained heart failure, thickened heart muscle, rhythm problems, neuropathy, carpal tunnel syndrome, or amyloidosis may provide an important clue. However, a family history may be absent because relatives were not tested, received another diagnosis, died before symptoms developed, or carried the variant without becoming ill.

The term "Appalachian type" describes the history of the variant, not a risk created by living in a particular location. Lifestyle choices do not cause the genetic change. People should not assume they do or do not carry it based only on ancestry.

A genetic counselor can explain inheritance, testing options, possible insurance or privacy considerations, and what results may mean for relatives.

Diagnosis

Diagnosis usually requires several steps. The goals are to determine whether amyloid is present, identify the amyloid protein, assess which organs are affected, and confirm whether the condition is inherited.

A clinician may begin with a medical and family history and a physical examination. Blood and

urine tests can check kidney, liver, thyroid, and heart function. Tests for abnormal immune-system proteins are especially important because another condition, light-chain or AL amyloidosis, requires different treatment.

An electrocardiogram records the heart's electrical activity. An echocardiogram uses ultrasound to examine heart structure, wall thickness, filling, and pumping. Cardiac magnetic resonance imaging may provide more detail about heart tissue.

A nuclear medicine heart scan uses a small amount of a bone-seeking tracer. In the correct clinical setting, strong tracer uptake in the heart can support a diagnosis of ATTR cardiac amyloidosis without a heart biopsy. Before relying on this approach, clinicians must evaluate for abnormal monoclonal proteins because AL amyloidosis can sometimes produce similar findings.

A tissue biopsy may be needed when scan results are uncertain or another amyloid type remains possible. A sample may come from abdominal fat, bone marrow, another affected tissue, or occasionally the heart. Congo red staining identifies amyloid under a microscope. Specialized protein analysis, often mass spectrometry, can determine the amyloid type.

Genetic testing of the TTR gene confirms hereditary ATTR and identifies the specific variant. Finding p.Thr80Ala, also called Thr60Ala, supports the Appalachian type diagnosis. Genetic testing alone shows that a person carries the variant; it does not prove that current symptoms are caused by amyloid.

Nerve conduction studies, autonomic testing, walking assessments, or neurologic examinations may help measure nerve involvement. Additional testing is guided by the person's symptoms and organs at risk.

Treatment and management

Care is often coordinated by specialists in amyloidosis, cardiology, neurology, genetics, and other affected areas. Treatment depends on whether the heart, nerves, or both are involved, as well as the person's overall health and disease stage.

Disease-modifying medicines work in two main ways. Transthyretin stabilizers help keep the protein from separating and forming additional amyloid. Gene-silencing medicines reduce the liver's production of transthyretin. Available medicines, approved uses, method of administration, and monitoring requirements differ. Some are intended for ATTR cardiomyopathy, while others are approved for hereditary ATTR with polyneuropathy.

These treatments generally aim to slow progression. They may not remove existing deposits or fully reverse established heart or nerve damage. A specialist can explain whether a

particular therapy fits the person's type of organ involvement and local regulatory approval.

Heart-related management may include medicines that help the body remove extra salt and water. These can reduce swelling and shortness of breath. Blood pressure and kidney function need monitoring because people with amyloid cardiomyopathy may be sensitive to changes in fluid balance.

Some medicines commonly used for other forms of heart failure may be poorly tolerated when amyloidosis causes low blood pressure or autonomic dysfunction. Treatment should therefore be individualized rather than changed without medical guidance.

Abnormal heart rhythms may require medication, anticoagulation to reduce stroke risk, cardioversion, or an implanted device such as a pacemaker. The best approach depends on the rhythm and the person's overall heart function.

Management of nerve symptoms may include pain treatment, physical or occupational therapy, balance support, and regular foot care. Measures for orthostatic hypotension, digestive problems, bladder symptoms, and nutrition should be tailored to the specific problem. Supportive care can improve safety and daily function even when disease-modifying treatment is being used.

Because most transthyretin is produced in the liver, liver transplantation was historically used for selected forms of hereditary ATTR amyloidosis. It is now less common because of drug therapy and because heart disease can continue after transplantation. Heart or combined-organ transplantation may still be considered for carefully selected people with advanced disease.

Complications

Possible complications depend on where amyloid accumulates and how far the condition has progressed.

Heart complications can include heart failure, atrial fibrillation or other abnormal rhythms, electrical conduction block, blood clots, stroke, and reduced blood flow to major organs. Low blood pressure may limit treatment options or increase the risk of falls.

Progressive neuropathy can interfere with walking, balance, hand function, and the ability to sense injuries. Loss of sensation in the feet raises the risk of unnoticed wounds. Autonomic neuropathy may lead to fainting, severe digestive symptoms, dehydration, bladder problems, or sexual dysfunction.

Poor appetite, diarrhea, constipation, and early fullness can contribute to weight loss or inadequate nutrition. Advanced illness may reduce independence and place stress on family

members or caregivers.

Early identification and regular monitoring can help clinicians address complications before they cause greater loss of function.

Follow up

Routine follow-up usually includes review of breathing, swelling, weight, heart rhythm symptoms, blood pressure, walking, sensation, digestion, and daily function. Depending on organ involvement, clinicians may repeat blood tests, electrocardiograms, heart imaging, rhythm monitoring, or neurologic assessments.

People taking disease-modifying therapy need monitoring appropriate to the medicine. Follow-up also helps the care team decide whether symptoms reflect amyloidosis, treatment effects, or another condition.

Relatives who carry the variant but do not have symptoms may be offered planned surveillance. The timing and tests should be based on age, family history, the specific variant, and specialist advice. Predictive genetic testing is best arranged through genetic counseling, particularly when the person being tested is healthy.

Contact a clinician promptly for a clear increase in swelling, rapid weight gain, worsening shortness of breath, repeated dizziness, new palpitations, persistent vomiting or diarrhea, or a foot wound that is not healing.

Seek emergency care for severe difficulty breathing, fainting, chest pain, sudden weakness or numbness on one side, trouble speaking, a new severe loss of balance, or another possible sign of stroke. These symptoms require urgent assessment and should not wait for a routine amyloidosis appointment.

Sources

- GeneReviews®. Hereditary Transthyretin Amyloidosis. University of Washington, Seattle.
- Adams D, Koike H, Slama M, Coelho T. Hereditary transthyretin amyloidosis: a model of medical progress for a fatal disease. Nature Reviews Neurology. 2019;15:387-404.
- Kittleson MM, Ruberg FL, Ambardekar AV, et al. 2023 ACC Expert Consensus Decision Pathway on Comprehensive Multidisciplinary Care for the Patient With Cardiac Amyloidosis. Journal of the American College of Cardiology. 2023;81(11):1076-1126.

- Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. European Heart Journal. 2021;42(16):1554-1568.
- Conceição I, Damy T, Romero M, et al. Early diagnosis of ATTR amyloidosis through targeted follow-up of identified carriers of TTR gene mutations. Amyloid. 2019;26(1):3-9.
- Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. New England Journal of Medicine. 2018;379:1007-1016.