CONDITION

Transthyretin familial amyloid polyneuropathy

An inherited condition in which abnormal transthyretin protein damages nerves and sometimes the heart.

WHAT IT IS
Inherited amyloid condition damaging peripheral and autonomic nerves

BODY SYSTEM
Nervous system, heart and circulation, and digestive system

MAIN SYMPTOMS
Foot numbness, burning pain, bowel changes, dizziness on standing

WHAT CAUSES IT
An inherited harmful change in the TTR gene

HOW IT IS DIAGNOSED
TTR genetic testing plus clinical or biopsy evidence

MAIN TREATMENT
TTR-targeted medicines, symptom support, and sometimes transplantation

CAN IT BE CURED?
No - treatment can slow further damage

IS IT AN EMERGENCY?
Sometimes - fainting or severe breathing difficulty

LONG-TERM OUTLOOK
Progressive, though earlier treatment can preserve function longer

Overview

Transthyretin familial amyloid polyneuropathy is an inherited condition that mainly damages nerves outside the brain and spinal cord. It is often called hereditary transthyretin amyloidosis with polyneuropathy, or hereditary ATTR amyloidosis.

The liver normally makes a protein called transthyretin, or TTR. In this condition, a change in the `TTR` gene makes the protein unstable. The protein can break apart and form abnormal deposits called amyloid. These deposits build up in nerves and other tissues.

"Polyneuropathy" means that many nerves are affected. Damage often begins in the small nerves that sense pain and temperature in the feet. It can later affect balance, muscle strength, digestion, blood pressure, bladder function, and sexual function.

Amyloid may also collect in the heart, making its walls stiff or interfering with its rhythm. Some people have mostly nerve symptoms, while others have a mixture of nerve and heart problems.

The condition matters because nerve damage can become permanent. However, treatments that reduce or stabilize TTR can slow further damage. Recognizing the condition early may help preserve movement, independence, and organ function.

Symptoms

Symptoms differ according to the genetic change involved, age at onset, and which organs contain amyloid. They may begin in early adulthood or much later in life.

Nerve symptoms usually start in both feet and move gradually upward. Possible symptoms include:

Amyloid can also damage autonomic nerves. These control automatic functions such as blood pressure, digestion, sweating, and bladder emptying.

Autonomic symptoms may include dizziness or faintness when standing, constipation, diarrhea, nausea, feeling full after small meals, or alternating constipation and diarrhea. Some people lose weight without intending to because digestive symptoms make eating difficult.

Other symptoms can include reduced or excessive sweating, difficulty emptying the bladder, erectile difficulties, or other changes in sexual function.

Carpal tunnel syndrome may cause hand tingling, pain, or weakness. It can occur years before more widespread nerve symptoms, especially when both wrists are affected.

Heart involvement may cause breathlessness, ankle swelling, tiredness, palpitations, or fainting. These symptoms have many possible causes, so tests are needed to find out whether amyloid is responsible.

- Burning, tingling, stabbing pain, or unusual sensitivity in the feet
- Reduced ability to feel pain, heat, cold, or touch
- Poor balance, frequent tripping, or weakness in the feet and legs
- Numbness or weakness in the hands as the condition advances

Causes and risk factors

The condition is caused by a harmful change, also called a pathogenic variant, in the `TTR` gene. It follows an autosomal dominant inheritance pattern. This means each child of a person

with the variant has a 1 in 2 chance of inheriting it.

Inheriting the variant does not always mean that symptoms will develop. This is called reduced penetrance. The likelihood and usual age of symptoms differ among `TTR` variants and families.

A person can inherit the variant from a parent who has symptoms, from a parent whose symptoms are mild or unrecognized, or from a parent who never develops symptoms. For this reason, the absence of an obvious family history does not exclude the condition.

More than one type of TTR amyloidosis exists. Wild-type transthyretin amyloidosis is not caused by an inherited `TTR` variant and usually affects the heart in older adults. Genetic testing distinguishes hereditary ATTR from the wild-type form.

Diagnosis

Diagnosis can take time because early symptoms may resemble diabetes-related nerve damage, vitamin deficiency, spinal conditions, or other types of neuropathy.

A clinician may examine sensation, reflexes, strength, balance, blood pressure while lying and standing, and signs of heart involvement. Tests are then chosen according to your symptoms.

Genetic testing can identify a harmful `TTR` variant. A positive result must be interpreted together with symptoms and other findings because some people carry a variant without having active amyloid-related damage.

Other tests may include:

A biopsy may use fat, salivary gland, nerve, heart, or another affected tissue. A negative biopsy from one site does not always exclude amyloidosis.

Special nuclear medicine scans can help diagnose ATTR amyloid in the heart in certain circumstances. Before interpreting these scans, blood and urine tests are used to look for abnormal antibody proteins associated with light-chain, or AL, amyloidosis. AL amyloidosis is a different condition and requires different treatment.

Genetic counselling can help you understand what a test may mean for you and your relatives. Testing an adult relative who has no symptoms is usually arranged through a genetics or amyloidosis service so that the person can consider the medical, emotional, and family implications.

- Nerve conduction studies and electromyography to assess larger nerves and muscles
- Tests of small-nerve or autonomic function

- An electrocardiogram, heart ultrasound, blood tests, or cardiac MRI
- A tissue biopsy examined with Congo red stain, which makes amyloid visible
- Protein analysis, often using mass spectrometry, to identify the amyloid type

Treatment and management

Treatment aims to slow new amyloid formation, manage symptoms, and protect affected organs. It cannot reliably repair nerve damage that has already occurred, which is one reason timely diagnosis matters.

TTR-silencing medicines reduce the liver's production of transthyretin. Examples include patisiran, vutrisiran, and eplontersen. The medicines available and their approved uses differ by country. They are given by injection or infusion and require planned follow-up.

TTR stabilizers help keep the protein from breaking apart. Tafamidis is used for ATTR-related heart muscle involvement in many countries. Its approved use for polyneuropathy differs between regions.

Treatment choice is based on the main organs affected, the stage of nerve or heart involvement, other medical conditions, and local availability. Follow-up may include blood tests, nerve assessments, walking tests, heart imaging, and reviews of nutrition and daily function.

Supportive care remains important even when you receive a TTR-targeted treatment. It may include:

Some treatments for common heart conditions may be poorly tolerated when cardiac amyloidosis is present. Medication changes should therefore be made with the clinicians overseeing your heart and amyloidosis care.

Liver transplantation greatly reduces production of variant TTR and was once a main treatment, particularly for selected people with certain variants and early symptoms. It is now used less often because TTR-targeted medicines are available. It does not remove existing deposits, and heart amyloid can still progress in some people. Combined organ transplantation is considered only in selected circumstances.

- Medicines and practical measures for nerve pain
- Physiotherapy, exercise planning, braces, or mobility aids
- Treatment for constipation, diarrhea, nausea, or low blood pressure
- Foot care when sensation is reduced
- Nutrition support for weight loss or difficulty eating

- Cardiology care for fluid retention, rhythm problems, or heart failure

Complications

Ongoing nerve damage can cause difficulty walking, falls, loss of hand function, or reduced independence. Loss of protective sensation also raises the risk of unnoticed burns, pressure injuries, and foot wounds.

Autonomic nerve damage can lead to repeated fainting, dehydration from severe diarrhea, poor nutrition, bladder problems, or sexual difficulties. Digestive symptoms and unplanned weight loss can have a major effect on strength and quality of life.

Cardiac amyloid may lead to heart failure, in which the heart cannot fill or pump effectively. It may also cause an abnormal heart rhythm or problems with the heart's electrical signals.

Eye and kidney problems occur with some `TTR` variants. Amyloid made within the eye or central nervous system may continue to cause problems even after treatments that mainly reduce TTR production by the liver.

Prevention

The inherited `TTR` variant cannot be prevented through diet, exercise, or lifestyle changes. A person who carries it did not cause the condition.

Relatives who may have inherited the family variant can choose whether to have genetic counselling and testing. For carriers without symptoms, planned monitoring may identify early nerve or heart changes. Monitoring does not prevent amyloid formation, but it may allow treatment to begin before substantial damage has developed.

People planning a family can discuss reproductive options with a genetics service. These may include testing during pregnancy or in vitro fertilization with testing of embryos. These are personal choices, not requirements.

For people with reduced sensation, regular foot checks and well-fitting footwear can help prevent complications from unnoticed injuries. These measures do not prevent the underlying condition.

Living with it and what to expect

Hereditary ATTR polyneuropathy usually progresses over years, but its pace is not the same

for everyone. The specific genetic variant, age when symptoms begin, organs affected, and response to treatment all influence the course.

Symptoms that come from established nerve loss may not fully improve. The main goal of current TTR treatments is often to slow or stabilize further decline. Some people have improvement in selected symptoms, but this cannot be promised.

Regular follow-up usually looks for changes in sensation, strength, walking, blood pressure, nutrition, digestion, and heart function. New symptoms should be reported rather than saved for a distant annual review, because they may change the monitoring or support you need.

Practical adjustments can help you remain active. Physiotherapy, pacing, hand or ankle supports, mobility aids, workplace changes, and help with driving decisions may become useful at different stages. Using an aid is a safety measure, not a sign that treatment has failed.

The condition can affect family plans and relationships because it is inherited. Genetic counsellors, specialist nurses, mental health professionals, and amyloidosis support organizations can help with these concerns. Many people continue working, caring for others, travelling, and taking part in valued activities, although adaptations may be needed as symptoms change.

When to get medical help

Arrange a routine appointment if you develop persistent numbness, burning pain, bowel changes, dizziness on standing, unexplained weight loss, or worsening balance. This is especially important if a relative has a known `TTR` variant or ATTR amyloidosis.

Contact your care team promptly for a new foot wound, repeated falls, worsening ankle swelling, increasing breathlessness, new palpitations, reduced urine output, or difficulty eating and drinking. These symptoms may need assessment before your next scheduled follow-up.

Seek emergency help for severe breathing difficulty, chest pain, fainting with slow recovery, or signs of a stroke such as sudden facial weakness, arm weakness, or difficulty speaking. Emergency assessment is also appropriate for a serious injury after a fall or severe vomiting or diarrhea that leaves you unable to keep fluids down.

Common questions

Is transthyretin familial amyloid polyneuropathy the same as amyloidosis?

It is one form of amyloidosis. "Amyloidosis" describes a group of conditions involving abnormal

protein deposits. In this form, the protein is transthyretin, the cause is inherited, and peripheral or autonomic nerves are affected.

If I have the gene change, will I definitely develop symptoms?

No. Some carriers never develop symptoms, while others become unwell at different ages. Risk is influenced by the specific variant, family pattern, age, and possibly other factors that are not fully understood.

Can the nerve damage be reversed?

Established nerve loss is often permanent. TTR-targeted treatment may slow further damage, and some people experience improvement in certain symptoms or function. Pain control, physiotherapy, nutrition support, and treatment of autonomic symptoms can also improve daily life.

Can it skip a generation?

The variant itself does not skip generations if it is inherited, but the condition may appear to do so. A parent may carry the variant without symptoms or may have had mild symptoms that were not recognized. Each child of a carrier has a 1 in 2 chance of inheriting the variant.

Is this condition always inherited from a parent?

Usually, a harmful `TTR` variant is inherited from a parent. A family history may not be known because relatives were never tested or did not develop clear symptoms. A new variant arising for the first time is possible but uncommon.

Does a negative biopsy rule it out?

Not always. Amyloid may be unevenly distributed, so one tissue sample can miss it. The meaning of a negative biopsy depends on the tissue tested, the testing method, genetic findings, symptoms, and other organ assessments.

Sources

- GeneReviews: Hereditary Transthyretin Amyloidosis , University of Washington and NCBI Bookshelf
- Adams D, Ando Y, Beirão JM, et al. Expert consensus recommendations to improve diagnosis of ATTR amyloidosis with polyneuropathy , Journal of Neurology , 2021
- Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians , Orphanet Journal of Rare Diseases , 2013



- 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
- US Food and Drug Administration: ONPATTRO prescribing information , patisiran
- US Food and Drug Administration: AMVUTTRA prescribing information , vutrisiran
- US Food and Drug Administration: WAINUA prescribing information , eplontersen