the BRIDGE
hATTR amyloidosis

Your health
and hereditary
ATTR amyloidosis

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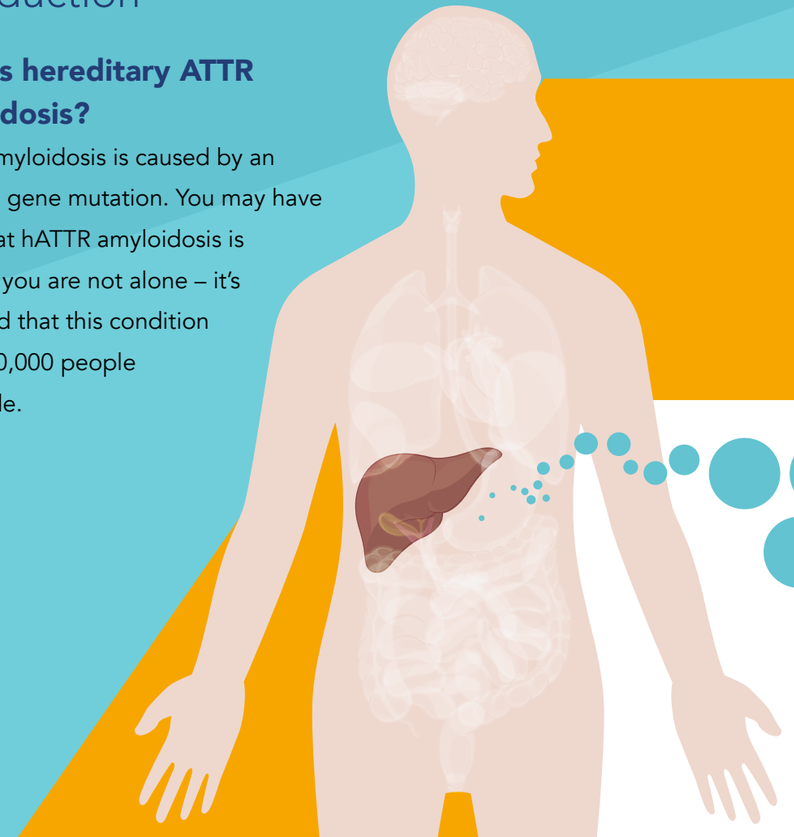
If you have just found out hereditary ATTR (hATTR) amyloidosis affects you, it might feel like there's a lot of information to take in. Perhaps there's a family history with the condition, or you may have never heard of it before – either way, it can feel overwhelming.

This leaflet is designed to help give you an introduction to hATTR amyloidosis.

Introduction

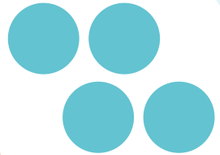
What is hereditary ATTR amyloidosis?

hATTR amyloidosis is caused by an inherited gene mutation. You may have heard that hATTR amyloidosis is rare, but you are not alone – it's estimated that this condition affects 50,000 people worldwide.



What happens in the body?

Your liver produces a protein called TTR or transthyretin, which helps carry substances in the blood. If you have hATTR amyloidosis, a gene mutation can cause this protein to change shape and 'misfold'. The new shape means the protein gathers together in structures known as 'amyloid fibrils' (see the Glossary on page 26 for more details), which build up in various parts of the body. This can result in a variety of symptoms.



TTR

A protein called TTR (or transthyretin) is made in the liver.

Misfolded amyloid fibrils

The TTR protein misfolds (this means it takes on an abnormal shape).

The change in shape causes the protein to gather in amyloid fibrils.

Amyloid deposits

The amyloid fibrils build up throughout the body and form deposits, which is what causes symptoms.

Symptoms

Which parts of the body can hATTR amyloidosis affect?

Symptoms can appear in various areas and systems of the body, and sometimes can seem unrelated. Here are some key symptom groups to know about and look out for.

"The first symptom was weight loss. I also started to have feet and hand problems…loss of sensation, pain and pricking. Then came digestive problems"

Catilena. *Living with hATTR amyloidosis*

Peripheral nerve-related ('polyneuropathy')

Our peripheral nervous system is made up of nerves which branch from the brain and spinal cord into the arms and legs, and it's these nerves that are responsible for motor function or movement. When this system is affected, a person could experience symptoms like numbness, pain or tingling.

Heart-related ('cardiomyopathy')

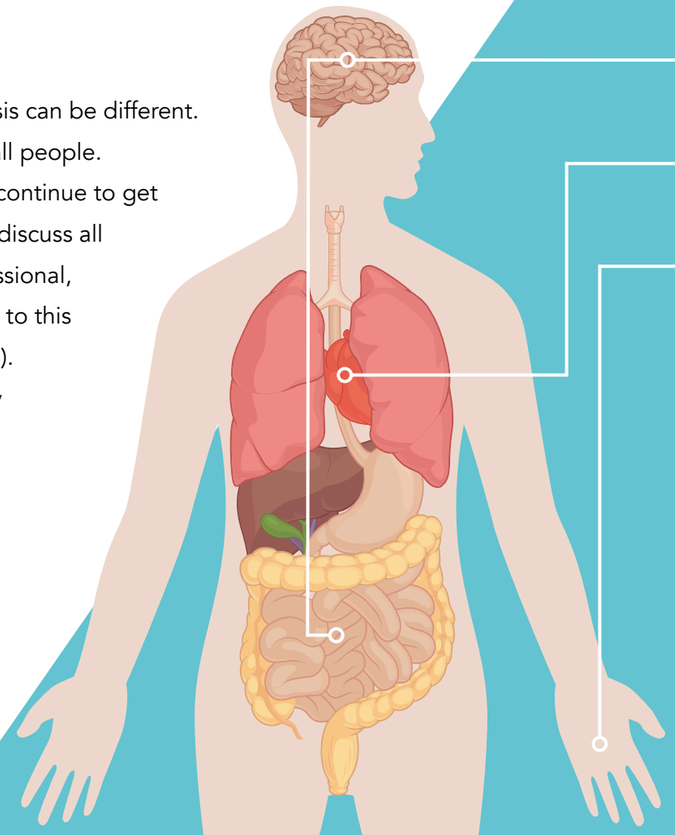
This is the most common type of hATTR amyloidosis. It affects the heart, which can include symptoms like shortness of breath or chest pain.

Autonomic nerve-related ('autonomic dysfunction')

hATTR amyloidosis can also affect the autonomic nervous system, which helps control bodily or organ functions like digestion. Symptoms to look out for can be digestive in nature – such as nausea, constipation or weight loss – but they can also involve urinary tract infections, sexual dysfunction or excessive sweating.

What are the symptoms?

Everyone's experience of hATTR amyloidosis can be different. Symptoms vary and not all of them affect all people. The symptoms of hATTR amyloidosis may continue to get worse over time, so it's really important to discuss all your symptoms with your healthcare professional, even if you think they might not be related to this specific condition (e.g. erectile dysfunction). And the more you tell them, the more they may be able to help.



Peripheral nerve-related (polyneuropathy) symptoms

- Tingling
- Numbness
- Carpal tunnel syndrome*
- Burning pain
- Loss of sensitivity to temperature
- Weakness

Heart-related (cardiomyopathy) symptoms

- Increasing fatigue
- Dizziness
- Shortness of breath
- Leg swelling (edema)
- Palpitations and abnormal heart rhythms (atrial fibrillation)
- Chest pain

Autonomic nerve-related symptoms

- Urinary tract infections
- Excessive sweating
- Dizziness upon standing
- Sexual dysfunction
- Nausea and vomiting
- Diarrhoea
- Severe constipation
- Unintentional weight loss

Other symptoms

- Glaucoma
- Blurred or spotty vision
- Abnormalities of the pupil or blood vessels on the white of the eye
- Detached retina
- Progressive dementia
- Headache
- Loss of movement control
- Seizures
- Weakness
- Stroke-like episodes
- Kidney dysfunction

**Carpal tunnel syndrome is a condition in which a nerve in your wrist is under pressure. This causes pain, tingling or numbness, mainly in your hand and fingers.*

Who am I likely to see at my medical consultations?

Your primary care physician will most likely refer you to one or more specialists including neurologists, cardiologists, gastroenterologists and ophthalmologists.

This is because hATTR amyloidosis is a multi-system disease which can affect multiple organs.

How do you test for hATTR amyloidosis?

Healthcare professionals will use a combination of tests to diagnose hATTR amyloidosis. These may include:

"In terms of examinations it took a long while. We got after 3 ½ - 4 years to the point where all examinations were complete. It's easy to get a wrong diagnosis"

Roland. *Living with hATTR amyloidosis*

Genetic testing

This simple blood test will tell you if you carry a mutation in the TTR gene associated with hATTR. Genetic counsellors may be available to help you understand the issues related to genetic testing – including the medical, social and psychological consequences of a positive result – and can help you decide if the test is right for you.

Tissue biopsy

By removing a small sample of tissue for lab examination, your doctors can confirm the presence of amyloid deposits.

Other tests

These can include nerve tests, muscle tests, echocardiogram, MRI and other types of scans. They can determine the impact of amyloid deposits on the heart, nerves and other organs.

Why can it take years to diagnose hATTR amyloidosis?

As symptoms vary between individuals and some of the symptoms may be similar to those of common diseases or mimic the ageing process, hATTR amyloidosis can take some time to diagnose. You may end up visiting multiple doctors and specialists to confirm the diagnosis. That's why it's important to tell your doctor about a family history of hATTR amyloidosis and other chronic conditions – it could help speed-up the process.

Why is it so important to get an early diagnosis?

As the symptoms of hATTR amyloidosis are likely to continue to progress over time, early diagnosis and treatment are important. Once diagnosed, your doctor can find you the most appropriate treatment which might potentially delay the worsening of the disease, manage your symptoms and maintain your daily activities. If left untreated, your symptoms could change, and you may experience increasing loss of mobility as the disease progresses.

I'm finding my diagnosis difficult. Where can I find some support?

Receiving a diagnosis of hATTR can result in a range of emotions, from shock and anger to anxiety and fear. Talk to your doctor or healthcare professional about how you are feeling. They can help you plan an approach that's tailored to you. You can also find support in loved ones, patient groups and others in the same situation. There are some places you can contact for advice at the back of this leaflet.

"I got in touch with the hospital and the association straight away… The disease evolves very rapidly, creates irreversible damage"

Jean-Christophe. *Living with hATTR amyloidosis*

What causes hATTR amyloidosis?

This condition is inherited, passing down through family members affected by hATTR amyloidosis. This means there's nothing you could have done to prevent getting the condition. Inherited conditions are not contagious.

"…there are sixteen nephews, grandchildren that could have the gene. In the world, it's called a rare disease. In our family, it's more like an epidemic"

David. *Living with hATTR amyloidosis*

Is hATTR amyloidosis genetic?

Yes. Our genes are units of inheritance and we get two copies of each, one from our mother and one from our father. Each gene codes for a particular protein, but mutations that occur in genes can lead to the production of a protein that causes a condition or disease. This is the case with hATTR amyloidosis.

- **Chromosomes** are long coils of DNA in our cells. We have 23 pairs.
- **DNA** is a chemical complex carrying genes.
- **Genes** are sections of DNA responsible for a particular protein, like TTR. A mutation can occur here and be passed on to future generations.

How is hATTR amyloidosis passed on to future generations?

A person only needs to inherit one copy of the gene mutation from one parent in order to develop the disease risk. This is known as an 'autosomal dominant inheritance' pattern.

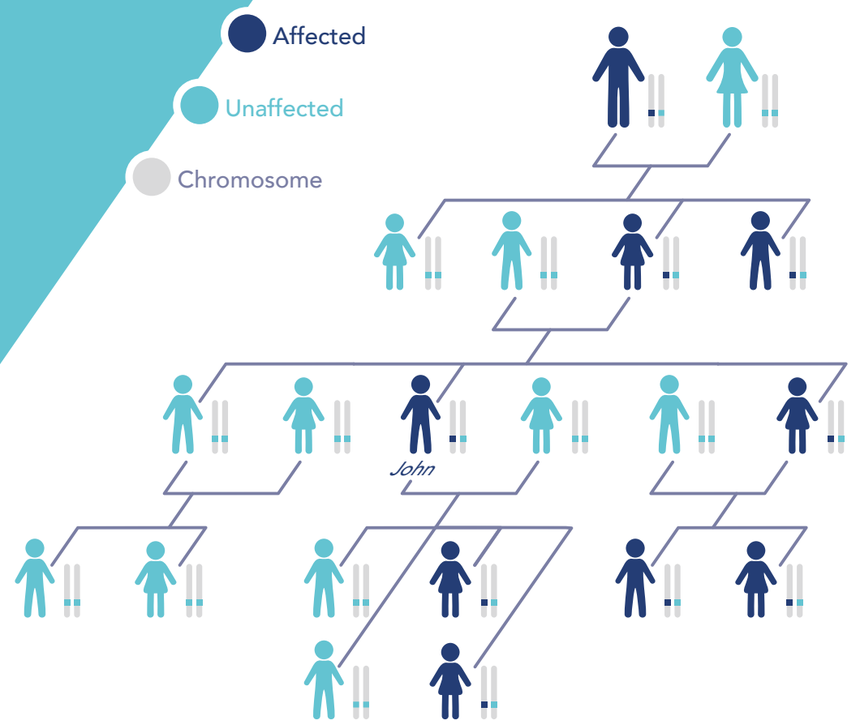
Could members of my family be at risk too?

When one parent carries the gene mutation responsible for hATTR amyloidosis, each child has a 50% chance of inheriting the gene. It's important to know that not all individuals with the gene mutation will develop signs and symptoms of the disease, and the age of onset and symptoms can vary. It can be upsetting to hear that your relatives may be at risk, and you should discuss this with your healthcare professional.

The family tree opposite shows a possible pattern of hATTR amyloidosis inheritance.

In this example, John is living with hATTR amyloidosis. He inherited the gene from his mother, who inherited it from her father. As John's grandfather carries the gene mutation, other relatives are also affected by hATTR amyloidosis, although some are not symptomatic.

John also has four children. In this example, two of John's children have inherited the gene, but it could have been all of them or none at all.



This family tree example shows a possible pattern of hATTR amyloidosis inheritance.

An "unaffected" person does not carry the gene and so won't have hATTR amyloidosis. An "affected" person carries the gene for hATTR amyloidosis, but may not show symptoms and may not develop the disease.

Treating the disease

Is there a specific treatment for hATTR amyloidosis?

Until recently, there were very few treatment options for hATTR amyloidosis including a liver transplant. This is because the TTR protein is mostly made by the liver and a transplant will mean you produce less of the abnormal TTR protein.

Medicine is advancing quickly so it's important that you keep talking to your doctor about the best treatment options for you. Right now, treatments are available, or currently under development to:

- Stabilise the TTR protein – TTR stabilisers stop TTR protein from forming amyloid deposits
- Remove amyloid deposits
- Stop production of TTR protein – blocking the TTR gene through "gene silencing" stops the TTR protein from being produced

"Today's generations can get earlier diagnosis; they have more treatment options and I believe there is a promising future"

Catilena. *Living with hATTR amyloidosis*

Managing symptoms

What type of treatment(s) should I expect to take?

hATTR amyloidosis can be associated with a variety of symptoms – for which treatments are available. As well as tackling the underlying cause of the disease, treatments are also available to help alleviate symptoms and improve your quality of life. If treatment is started during the early onset of symptoms, the overall success rate is higher – so early detection is essential.

For example, several medications can be prescribed for peripheral nerve related symptoms like tingling, or a burning sensation in some parts of the body. These medications can help with pain relief and nerve damage.

Doctors may also prescribe medications to treat gastrointestinal symptoms like diarrhoea, severe constipation, nausea and vomiting. These can lessen the pain and reduce the impact they have on your daily life.

Next steps

What are my next steps?

It may feel like there is a lot to think about, so here are some things that could help when you're planning your next medical appointment.

- List all your symptoms and include any new ones that you haven't covered with your doctor yet, no matter how trivial they may seem.
- Decide on the questions you might like to ask your doctor. Writing them down will help you remember.
- Think about the questions your doctor might be likely to ask you.
- Take a friend or family member along for support, to ask questions on your behalf or to take notes that you can refer to afterwards.
- If you are aware of a family history of the condition, consider talking to other affected family members to better understand their experiences.
- Think about widening your support network or connecting with other people with the condition.
- Review the information available via other resources to see if this prompts any other topics for discussion with your doctor.

Symptoms checklist

It's important to speak to your doctor about your symptoms. You are unlikely to experience all of the symptoms listed here and symptoms can vary between individuals.
You may also have experienced a particular symptom and not realised it could be related to your amyloidosis.

That's why it's a good idea to record any symptoms in this list that you do experience to show to your healthcare team. If you've spoken to your doctor about symptoms in the past, make notes on how they may have changed since your last appointment.

Heart-related
Cardiomyopathy

- [ ] Increasing fatigue
- [ ] Dizziness
- [ ] Shortness of breath
- [ ] Leg swelling
- [ ] Palpitation and abnormal heart rhythms
- [ ] Chest pain

Autonomic nerve-related
Autonomic dysfunction

- [ ] Dizziness upon standing
- [ ] Nausea and vomiting
- [ ] Diarrhoea
- [ ] Severe constipation
- [ ] Unintentional weight loss

And also

- [ ] Sexual dysfunction
- [ ] Urinary tract infections
- [ ] Excessive sweating

Peripheral nerve-related
Polyneuropathy

- [ ] Tingling
- [ ] Numbness
- [ ] Carpal tunnel syndrome*
- [ ] Burning pain
- [ ] Loss of sensitivity to temperature
- [ ] Weakness

Other

- [ ] Glaucoma
- [ ] Blurred or spotty vision
- [ ] Abnormalities of the pupil or blood vessels on the white of the eye
- [ ] Detached retina
- [ ] Progressive dementia
- [ ] Headache
- [ ] Loss of movement control
- [ ] Seizures
- [ ] Weakness
- [ ] Stroke-like episodes
- [ ] Kidney dysfunction

**Carpal tunnel syndrome is a condition in which a nerve in your wrist is under pressure. This causes pain, tingling or numbness, mainly in your hand and fingers.*

FAQs

Here are some questions you may want to ask your doctor or healthcare professional.

My health

- Is there anything I can do to help maintain my health?
- How should I change / manage my diet or eating habits?

Help and support

- Are there any support groups that I can contact?
- Is there any other help I can receive?

My condition

- Why do I have this condition?
- How might my condition change over time?
- Are my symptoms common for this condition?

Prognosis

- How will this impact me in the long term?
- How might it affect my work or home life?
- How are my symptoms likely to change over time?

Family

- How should I speak to my family members about my diagnosis?
- Could other family members be similarly affected?
- How was this condition passed on in my family?

Treatment

- What treatments are currently available?
- What happens next?

It's likely that you will have many more questions for your doctor and will want further information and support in the coming days and weeks. So, you can find out more using the contacts and resources opposite.

Sources of support

the BRIDGE
hATTR amyloidos

https://www.hattrbridge.eu
The Bridge™ is a website developed and produced by Alnylam Pharmaceuticals; it is designed to help raise awareness of hereditary ATTR (hATTR) amyloidosis and promote education on the condition for patients and their families.

AMYLOIDOSIS ALLIANCE
THE VOICE OF PATIENTS

Amyloidosis Alliance is an international umbrella patient advocacy organisation, aiming to raise awareness and improve the quality of care of amyloidosis patients.

ATTR AMYLOIDOSIS ALL IRELAND SUPPORT GROUP
amymattrs@gmail.com
ATTR Amyloidosis All Ireland Support Group offers support to patients affected by Hereditary ATTR Amyloidosis or Wild Type ATTR Amyloidosis. We are committed to raising awareness to ensure people are diagnosed and have access to available treatments at the earliest opportunity.

UKATPA
ATTR AMYLOIDOSIS PATIENTS' ASSOCIATION

info@UKATPA.org
https://www.ukatpa.com
UK ATTR Amyloidosis Patients' Association acts to provide extensive patient information and support.

Glossary

You're likely to come across many new words, descriptions and biological and medical terms that you're unfamiliar with when discussing your condition with your doctor. Be sure to ask them to clarify if you do not understand what they are explaining to you. As an extra help here is a list of some terms your doctor may use plus some other useful definitions.

Amyloid fibrils Amyloid fibrils are formed by normally soluble proteins, which assemble to form insoluble fibres that cannot be degraded.

Autosomal dominant inheritance Autosomal dominant is one of several ways that a trait or disorder can be passed down through families. In an autosomal dominant disease, if you inherit the abnormal gene from only one parent, you can get the disease.

Cardiomyopathy Chronic disease of the heart muscle.

Chromosomes Carriers of genetic information which are passed down through families.

Chronic A health condition or disease that is persistent or long-lasting in its effects.

DNA DNA stands for deoxyribonucleic acid. It's the genetic code to produce proteins (the building blocks of the body) which determine all characteristics of a living thing.

Familial Relating to or occurring in a family or its members.

Gene Genes contain a particular set of instructions, usually coding for a particular protein or for a particular function.

Gene mutation A gene mutation results from errors during DNA replication.

hATTR amyloidosis Hereditary ATTR (hATTR) amyloidosis is an inherited, rapidly progressive, life-threatening disease.

Polyneuropathy The simultaneous malfunction of the peripheral nerves throughout the body.

Prevalence How widespread or common a condition is.

Transthyretin Transthyretin (or TTR) is a protein that transports vitamin A and a hormone called thyroxin throughout the body.

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