

**Wild Type
Transthyretin Amyloidosis
ATTRwt**

An Overview

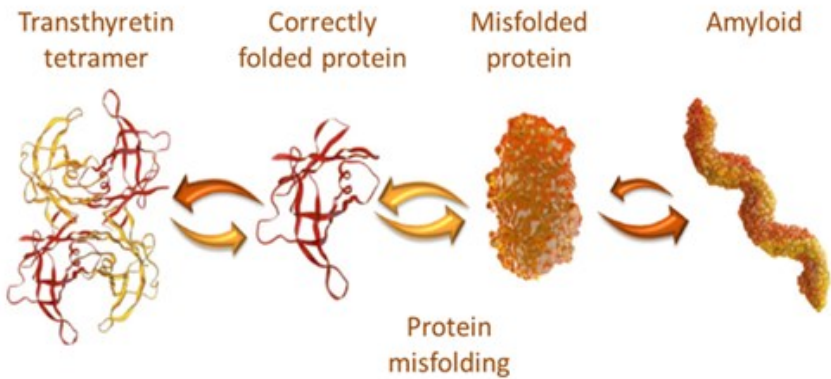


Amyloidosis was first discovered 150 years ago by the well know German pathologist, Dr. Rudolf Virchow. Although the disease has been recognized for many years, treatments have only been widely available for the past 25 years. Amyloidosis is a very complicated disease that is often difficult for doctors to diagnose. This, in part, accounts for why it has taken so long to develop effective treatments.

INTRODUCTION

Wild-type ATTR is also referred to as ATTRwt. It is a disease that occurs during the aging process and is not hereditary (a genetic test is needed to make a more accurate diagnosis). ATTRwt occurs when your liver delivers proteins, specifically transthyretin proteins, that misfold and form fibrils. These fibrils harden and build up in your heart wall, causing it to thicken and lead to heart disease.

Deposits of TTR amyloid can be found in other parts of the body, so it is a systemic amyloidosis disease, and while there is significant clinical involvement most found in the heart, ATTRwt is also common in bilateral carpal tunnel, which can be the first (early) symptom.



This is a disease that is almost exclusively a disease of men, originally reported in those age of 80 and over. However, as research continues, ATTRwt has been increasingly found in individuals in their early 60s. It is often overlooked as an amyloidosis disease because so many people experience heart problems in their later years.

SYMPTOMS

Cardiomyopathy means a disorder or disease of the heart muscle. Congestive heart failure, and an irregular heart rhythm called atrial fibrillation, are the most common symptoms.

Amyloid deposits in the heart can make the heart unable to function efficiently. This may result in shortness of breath, dizziness, or edema (swelling, especially in the legs). Some symptoms may occur with only minor activity. Amyloid can also affect the electrical system of the heart, causing the normal heartbeat to speed up or slow down. This is known as arrhythmia. During atrial fibrillation, the abnormal heart rhythm usually causes rapid and irregular beating.

For some older men, a history of carpal tunnel syndrome (especially without a clear cause), along with heart problems, is a signal to the doctor to consider testing for ATTRwt. To a lesser extent, ATTRwt has shown amyloid deposits in the lungs, bladder, and bowel, often with no, or minor, symptoms for the patient; although some patients have extensive bladder involvement that can lead to hematuria (blood in the urine).

In addition, peripheral neuropathy symptoms are present in a small number of patients, and spinal stenosis has also been found to be related to ATTRwt. Spinal stenosis narrows the spaces in the backbone and puts pressure on the spinal cord and nerves. Symptoms are caused by the pressure on the nerve root, causing pain that occurs mainly along the back of the leg.

DIAGNOSIS

Since ATTRwt and many other amyloidosis diseases can cause cardiomyopathy in the older male age group, is it extremely im-

portant to identify the type of amyloid. A patient with AL (light chain) Amyloidosis who shows cardiomyopathy symptoms will be treated with chemotherapy – and this is not the right treatment for patients with ATTRwt or cardiomyopathy. For this reason, medical investigation such as urine or blood testes is needed to ensure that the diagnosis of ATTRwt is correct.

For ATTRwt, it is difficult to get a positive diagnosis for amyloid deposits in tissues other than the heart. If a patient's echocardiogram results (heart test) show signs of complications, then, in many cases, a biopsy of the heart tissue is needed to get an accurate diagnosis. However, studies of newer heart scans for ATTRwt are ongoing and may replace the need for biopsy in the future.

If a biopsy of the heart tissue is obtained, then this biopsy tissue is sent to a lab for Congo-red staining. The lab will stain the biopsy and, if it turns an apple green color under a 'polarizing' microscope, then amyloidosis is confirmed. The lab will also take the biopsy tissue and a protein sequence analysis test to see which type of protein is affected. If this test shows that the transthyretin (TTR) protein is, then a blood sample is sent to a lab and experts do a genetic sequencing test to examine the DNA chains.

If this TTR genetic sequencing test produces no identifiable mutations, then ATTRwt is the resulting diagnosis. So, you can see that it takes several steps, and a doctor must continue testing until an accurate diagnosis is achieved.

These heart tests can help with diagnosing and monitoring heart stress or damage, as well as response to treatment:

Blood tests to look for stress and strain on the heart are useful in many forms of heart disease, including ATTRwt. The cardiac bi-

omarkers that are used include troponin T or troponin I, and NT-proBNP (which stands for N-terminal pro-brain natriuretic peptide) or BNP (brain natriuretic peptide). Different laboratories use one versus the other.

The echocardiogram (also called echo”) is an ultrasound of the heart. A doctor can look at the size and shape of the heart, and whether it is relaxing normally in between heartbeats. Amyloid cannot be seen directly, but it does make the heart larger and stiffer than normal.

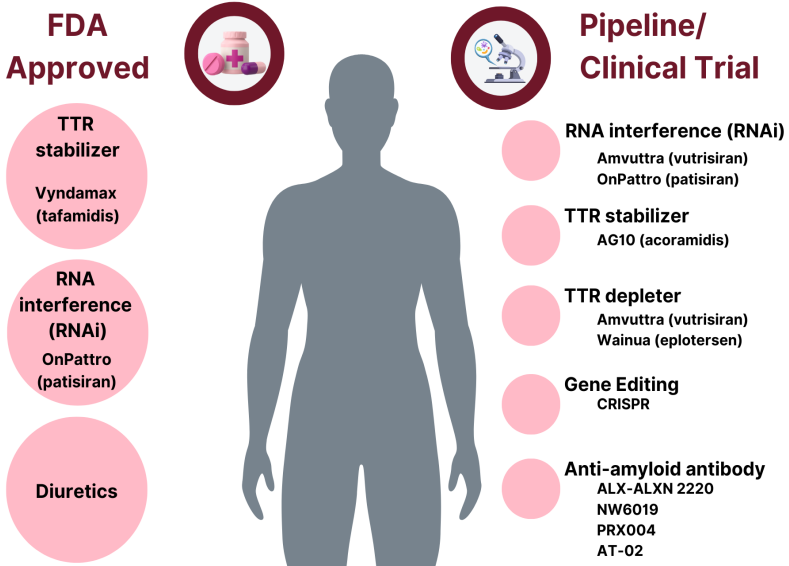
Recently, other imaging tests for the heart have also shown to be useful. One test is the MRI (magnetic resonance imaging), and, in this instance, is also referred to as CMR (for cardiac magnetic resonance). Pyrophosphate scanning, a nuclear test, is also used to evaluate whether an unusual type of abnormality of heart muscle function (“cardiomyopathy”) is present. Current data suggests this scan may be useful in distinguishing different types of amyloid heart disease. Many experts agree that ATTRwt is underdiagnosed.

TREATMENT

While there is currently no cure, there are many clinical trials ongoing for future treatments. One currently approved treatment, Vyndamax (tafamadis) has been approved by the FDA for ATTRwt. In addition, Onpattro (Patisiran) has recently been approved for ATTR cardiac involvement. There have also been advances in research that are studying the ‘silencing’ of gene expression through the addition of stranded RNA. This is called RNAi (meaning RNA). New medications are in development that include RNAi therapy, targeting transthyretin (TTR).

Typically, for heart problems, diuretics can be prescribed to increase urination, which helps to decrease fluid retention in the body. As with all amyloidosis diseases, the use of diuretics for an amyloid heart condition must be carefully controlled by your doctor.

ATTRwt, ATTRv cardiac treatment & development of additional therapies



FAQ

What does TTR mean?

Since systemic amyloidosis are referred to with a capital A (for amyloid) followed by an abbreviation for the fibril protein, ATTR amyloidosis stands for the protein transthyretin (TTR); so these diseases are often designated with the acronym ATTR.

Note that ATTRwt and ATTRv are two different diseases. ATTRwt is not hereditary, while ATTRv is hereditary. However, both diseases involve “TTR,” which stands for “transthyretin.”

In medical texts, transthyretin (formerly called prealbumin) is defined as a normal protein in the blood. In simpler terms, transthyretin helps to move the thyroid hormone and vitamin A (retinol) in your body. Thus, the name Transthyretin, which means that it TRANSpports THYroxine and RETINol.

What is the difference between ATTR and ATTRwt?

Transthyretin (TTR) has subunits in the TTR blood protein that can produce two forms of systemic amyloidosis: they are the hereditary TTR and wild-type TTR amyloid diseases.

ATTRv– Variet TTR: This is the hereditary form and is also referred to as the ‘variant’ form of TTR amyloid diseases because the protein is misfolded because of mutations in a patient’s inherited genetic code.

ATTRwt (or ATTRwt) – Normal TTR: This is the non-hereditary form and is often referred to as the ‘normal’ TTR amyloid disease because it does not exist because of genetic mutations. ATTRwt is a collection of misfolded amyloid proteins that travel into the organs and are only from the normal wild-type transthyretin.

The regular function of both subunits of TTR is to carry the thyroid hormone and vitamin A (retinol) within the bloodstream.

How common is ATTRwt?

Medical statistics vary, but it is thought that ATTRwt is present in around 80% of males over 80 years of age. However, it is also

believed that only 25% of this same age group experience symptoms.

Some medical experts think that this disease is underdiagnosed and not as rare as the statistics show. These are just some of the reasons that exist for this theory:

- Heart problems are common in older patients. To accurately diagnose the patient, a series of cardiac tests may be necessary. These tests are not always performed, especially if there is a financial concern and/or a lack of insurance coverage.
- Since ATTRwt is thought to be rare, it is not considered as a potential diagnosis even when more cardiac tests are completed.
- There may be a fear of complications from a heart biopsy with older patients. If the biopsy is not performed, it can result in an incomplete diagnosis.

More awareness of this disease within the medical community, and the public at large, is needed.

What are the symptoms of heart involvement with ATTRwt?

When amyloid deposits cause cardiomyopathy in ATTRwt, it can result in a stiffening of the heart. Some patients may experience:

- Nausea
- Weight loss
- Inability to sleep
- Increasing fatigue

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

Congestive heart failure and atrial fibrillation are the most common symptoms. The term “arrhythmia” refers to changes in the normal electrical impulses that cause the heart to beat. The result is a heart that can beat too fast, too slow or erratically. Atrial fibrillation (or a-fib for short) is one of many forms of arrhythmia. During a-fib, the heart’s two small upper chambers cause an abnormal heart rhythm, usually rapid and irregular beating. This may result in increased heart damage, stroke or heart failure.

How do they diagnose the TYPE of amyloidosis?

If any lab test results in a positive diagnosis for amyloidosis, then identifying the type of amyloid protein is the next crucial step. Treatments can differ and should be tailored to the patient and the exact type of amyloidosis that they have.

Typing can be done by a variety of lab techniques.

In all cases, after any lab technique is used to determine the type of amyloidosis, further DNA analysis should be performed to differentiate ATTRwt from hereditary ATTR amyloidosis. Treatments differ for these two diseases, so it is important to be certain and get a correct diagnosis.

What heart tests are helpful for diagnosis and monitoring of ATTRwt?

If heart involvement is suspected, then blood tests for heart biomarkers can aid in determining if a patient has signs of heart tissue strain or damage in their blood. The results of these tests can be used as “markers” (or “biomarkers”) to first determine the extent of damage, and then can be used regularly to monitor any future problems.

These biomarker blood tests can be affected by changes in kidney function, drugs, and other causes. They should be interpreted in the context of other tests of cardiac function, such as an echocardiogram or cardiac magnetic resonance imaging.

The echocardiogram (also called “echo”) is an ultrasound of the heart. A doctor can look at the size and shape of the heart, and whether it is relaxing normally in between heartbeats. Amyloid cannot be seen directly, but it does make the heart larger and stiffer than normal.

Other imaging tests for the heart have also shown to be useful. One test is the MRI (magnetic resonance imaging), and, in this instance, is also referred to as CMR (for cardiac magnetic resonance). CMR with a contrast agent called “gadolinium”, given by vein at the time of the scan, is a way to detect amyloid deposits in the heart.

Pyrophosphate scanning, a nuclear medicine test, is also used to evaluate whether an unusual type of abnormality of heart muscle function (“cardiomyopathy”) is present. An intravenous injection of pyrophosphate is made while the patient is at rest, followed about an hour later by a set of images that are taken while

the patient lies under a camera. The images take about 15 minutes. These images are recorded on a computer for analysis, and recent data suggests this scan may be useful in distinguishing different types of amyloid heart disease.

What is the difference between DNA and RNA?

In simple terms, our DNA stores and transfers genetic information. A gene tells a cell how to make a specific protein.

Proteins are formed inside our cells, and it is our DNA that holds the “recipe” for making proteins. DNA and RNA work together and they both carry genetic information to make up the many different proteins we need. However, they perform different functions for this task.

The RNA helps to move the DNA “code” from storage to where it can be used. RNA is converted (or “translated”) into a sequence of amino acids that makes up a protein.

In basic biological terms: Transcription = DNA → RNA Translation = RNA → protein

The collections of proteins within a cell are essential for our body’s health and function, and they work in a variety of ways, serving activity inside the cell as well as interaction outside the cell – in virtually every process within the cell.

How can the new RNAi research help with TTR amyloidosis diseases?

RNAi is short for “RNA interference.” By putting “silencing RNA” into cells that make an abnormal TTR, the translation of RNA to protein is stopped. This means that the production of the abnormal TTR that causes amyloid can be dramatically reduced. RNA

interference technology is underway and shows promise. Whether it will change the course of patients with TTR amyloid is under active investigation now.

What kind of doctor should be consulted?

It is strongly recommended that you consult with a specialist in the field of amyloidosis. The Amyloidosis Foundation provides a list of amyloidosis treatment centers under “Patient Resources” on this website. Once your diagnosis is confirmed, then a treatment plan can be laid out for your individual case. Depending on your symptoms, you will be seeing a local hematologist (blood), oncologist (cancer), neurologist (nerves), cardiologist (heart), nephrologist (kidney), gastroenterologist (GI tract), internist and/or general physician. These doctors should coordinate your care with the amyloidosis specialist to develop the best treatment program.

Is there a special diet that I can follow?

Eating a well-balanced, heart-healthy and nutritious diet is always recommended. Although amyloid is an abnormal protein, the amount of protein in the diet does not affect the onset of the disease. Consult with your physician on any dietary changes and report any vitamins or other supplements that you take. You are a part of the team of people who must keep in communication with each other about your health.

NOTES:

**To Locate an Amyloidosis Clinic, please visit the
Resources page on our website:**



www.amyloidosis.org



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