

**Wild Type Transthyretin
Amyloidosis
ATTRwt
An Overview**



INTRO

Wild-type ATTR is also referred to as ATTRwt. It is not hereditary. This disease used to be called SSA, which stood for Senile Systemic Amyloidosis, which is now an outdated term.

Deposits of TTR amyloid can be found throughout the body, so it is a systemic amyloidosis disease, with significant clinical involvement most commonly found in the heart. Wild-type ATTR is also common in 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. As research continues, wild-type ATTR 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.

It is called wild-type ATTR because the misfolding and depositing amyloid protein comes from transthyretin protein without a genetic mutation, referred to as "wild-type" because it is the natural form of this protein. These deposits can interfere with the heart's normal function, causing heart rhythm problems and heart failure.

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 electri-

cal 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 wild-type ATTR. To a lesser extent, wild-type ATTR 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 wild-type ATTR. 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 wild-type ATTR and many other amyloidosis diseases can cause cardiomyopathy in this older male age group, it is extremely important to identify the type of amyloid. A patient with AL (light chain) Amyloidosis who shows cardiomyopathy symptoms will often be treated with chemotherapy – and this is not the right treatment for wild-type ATTR patients with cardiomyopathy. For this reason, medical investigation is needed and the diagnosis of the type of amyloid must be correct.

For wild-type ATTR, 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 wild-

type ATTR are ongoing and may replace the need for heart 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 run a protein sequence analysis test to see which type of protein is affected. If this test shows that the transthyretin (TTR) protein is involved, then a simple 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 wild-type ATTR 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 wild-type ATTR. The cardiac biomarkers 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 medicine 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 wild-type ATTR is underdiagnosed.

TREATMENT

Many of the same treatments used for other ATTR diseases that involve cardiomyopathy can be applied to wild-type ATTR. Trial drugs for ATTR, such as tafamidis and diflunisal, are sometimes considered for wild-type ATTR patients. There have been advances in research that are studying the 'silencing' of gene expression through the addition of stranded RNA. This is called RNAi (meaning RNA interference). New medications are in development that include RNAi therapy, targeting transthyretin (TTR). Eventually some of these new medications may be options for patients with wild-type ATTR.

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.

Since it is common for there to be no other major organ involvement other than the heart with wild-type ATTR, a heart transplant is a treatment option if severe cardiac involvement is present.

Small studies have been looking at a component of green tea to slow progression of the TTR-related diseases that involve the heart. Curcumin, a component of the spice turmeric, has shown some promise in decreasing TTR deposition. In addition, studies continue with "genistein," which is a component of soy. Research may continue in these areas. Always consult with your doctor before considering any dietary changes.

FAQ

What does TTR mean?

Since systemic amyloidoses 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 “wild-type ATTR” and “ATTR” are two different diseases. Wild-type ATTR is not hereditary, while ATTR 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 Wild-type ATTR Amyloidosis?

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

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

Wild-type ATTR (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 as a result of genetic mutations. Wild-type ATTR 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 of these subunits of TTR is to carry the thyroid hormone and vitamin A (retinol) within the bloodstream.

What causes Wild-type ATTR?

Wild-type ATTR is not considered to be a hereditary disease. Specialists state that this disease occurs because of malfunctions in "normal" wild-type transthyretin, instead of mutations in inherited DNA sequences that cause the TTR protein to malfunction.

Even though it is not considered to run in families, it is not known if this disease is caused by an "epigenetic" factor. Epigenetic means that someone can inherit changes in their gene function, but it does not involve changes in their DNA sequence. Research continues in this area.

Wild-type ATTR is not contagious.

How common is Wild-type ATTR Amyloidosis?

Medical statistics vary, but it is thought that wild-type ATTR 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. In order 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 wild-type ATTR 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 wild-type ATTR?

When amyloid deposits cause cardiomyopathy in wild-type ATTR, 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 from a tissue or organ biopsy, 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, including:

1. Proteomics (the study of proteins) by mass spectrometry. LMDMS = "Laser microdissection by mass spectrometer." LMD ("laser microdissection") uses lasers for a contact- and contamination- free way to cut biopsy tissue samples into very small sections. These sections can then be broken down further for analysis. The MS ("mass spectrometer") is a device that separates a small biopsy section through a multi-step process, turning them into beams of particles and bending them with electricity and magnetism to make a kind of spectrum. Then the device can tally and identify the molecules in that tissue sample. This allows the amyloid to be further broken down and chemically tested, so the exact type of amyloid protein can be identified. This technique is usually very precise, however, it is not available in all labs and is currently an expensive testing technique.

2. Immunohistochemistry is a common and more affordable testing technique that is used to identify the types of proteins in tissues by the use of markers, like fluorescent dyes or enzymes. The biopsy sample is viewed with electron microscopy, which magnifies very small details using a beam of electrons to separate the elements. Or, it is viewed with light microscopy, which uses light wavelengths to probe and separate the sample. The electron microscopy technique can be focused onto the sample with a better resolution (and better depth of vision) than is possible with light microscopes. Immunohistochemistry works well for wild-type ATTR heart biopsies, however it still needs to be coupled with DNA analysis to confirm the identity of wild-type ATTR versus hereditary ATTR.

3. Extraction of proteins with electrophoresis. This amyloid typing test uses the motion of charged particles in a fluid through an electric field. This provides a break down of the amyloid protein, allowing for more lab analysis and typing. Further DNA analysis is then recommended for clarification.

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

The accuracy of each form of typing depends upon the technique itself, but also on the ability and experience of the laboratory performing them. It is best to have typing done in a reference laboratory at an experienced center, and the typing should agree with the clinical features of the patient's disease. Unfortunately, costs of typing are not always covered by insurance, but it is very important to have correct typing before any treatment is initiated.

What heart tests are helpful for diagnosis and monitoring of wild-type ATTR?

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 any damage, and then can be used regularly to monitor any future problems. Two troponin tests can be done — cardiac serum troponin T and serum troponin I. The other important biomarker is N-terminal pro-brain natriuretic peptide (NT-proBNP) or brain natriuretic peptide (BNP). Different laboratories use one versus another.

- Cardiac troponins T (cTnT) and I (cTnI) are released when the heart muscle has had some injury. In general, the more damage there is to the heart, the greater the amount of troponin T and I there will be in the blood.
- NT-proBNP is another "biomarker" that should be performed, especially if a person has symptoms such as swelling in the legs (edema), difficulty breathing, shortness of breath, and fatigue. It is used to detect heart stress or strain. This blood test can be useful in distin-

guishing fluid in the lungs due to congestive heart failure (in which it would be elevated) or from lung or pleural disease (in which case it should be normal or near normal). The pleurae are the linings of the lung, and can be involved with amyloid.

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 down 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:



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