

Transthyretin Amyloidosis (ATTR-CM)

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Transthyretin cardiac amyloidosis (ATTR-CM) is an underdiagnosed, life-threatening disease linked to heart failure.

Transthyretin amyloidosis also goes by these names:

- Cardiac amyloidosis.
- Amyloidosis ATTR.
- Transthyretin amyloid cardiomyopathy (ATTR-CM).
- Transthyretin cardiac amyloidosis (ATTR-CM).
- TTR amyloidosis.

What really happens to the organization when a case has ATTR-CM?

First of all, TRANSTYRETIN (TTR), is a natural transport protein that becomes unstable.

TRANS-(TRANSPORTS)-THY(THYROXINE)-RENTIN(RETINOL).

That unstable TTR protein folds abnormally and forms aggregations of amyloid fibrous, which can deposit in the heart and other areas of the body. The Accumulation of that protein causes the progressive stiffness of the myocardium which leads to Heart Failure.

The two types of transthyretin amyloidosis (ATTR-CM) include:

Familial (Hereditary) ATTR-CM: An inherited change (mutation) in the TTR gene causes amyloids to build up in your heart, nervous system, or both. It can also affect the kidneys. Different TTR mutations cause ATTR-CM in various races and ethnicities around the world. In the United States, people who are Black are more likely to develop familial transthyretin amyloidosis. It usually affects men over 60 years of age.

Wild-type ATTR-CM: This type occurs for no known reason. It most commonly affects your heart and nervous system. It is caused by a mutation in the gene that produces the protein transthyretin. It affects men and women, while the onset of symptoms can occur as early as the age of 50-60. People who carry the genetic mutation may never develop symptoms.

The first step in suspecting ATTR-CM is to watch for the following signs and symptoms. Because of the way it affects the heart, ATTR-CM often presents with symptoms of heart failure, such as fatigue, shortness of breath, and peripheral edema, but it can also cause other symptoms, related to the build-up of amyloid fibrils throughout the body.

Common signs and symptoms of ATTR-CM are:

- Fatigue.
- Leg, ankle, or abdominal swelling.
- Shortness of breath with activity.
- Sudden drop in blood pressure upon standing.
- Trouble breathing when lying down.
- Irregular heartbeat (arrhythmia).
- Eye problems (e.g., glaucoma, Eye Floaters)
- Gastrointestinal problems (such as diarrhea, constipation, nausea), etc.

We may order the following tests to evaluate your heart's function and check for any signs of ATTR-CM:

1)Electrocardiogram (EcG) and Cardiac ultrasound or Positron Emission Tomography (PET scan)

Echocardiogram findings help determine the speed and direction of blood flow in the heart.

Ultrasound findings associated with ATTR-CM include but are not limited to, an irregular heartbeat or bundle branch block that prevents electrical impulses from effectively delivering the heartbeat. Findings associated with ATTR-CM include, among others, heart failure with preserved ejection fraction, or HFpEF, which is related to the amount of blood that passes through the heart with each beat.

2)Cardiac MRI

Cardiac MRI is a painless but sensitive and specific diagnostic tool that helps detect transthyretin-related amyloidosis and light chain amyloidosis. However, it is currently unknown whether MRI has the ability to distinguish the type of amyloid.

These tests are not typically used to confirm a diagnosis of ATTR-CM, but they do help us to get a better picture of the heart and determine whether ATTR-CM may be the cause of symptoms.

Symptoms of ATTR-CM may include:

- Unexplained weight loss
- Pain or numbness in the lower back or legs
- Carpal tube syndrome diagnosed

Delayed diagnosis is because the symptoms of ATTR-CM are the same as other common causes of heart failure.

Early diagnosis is important for the proper treatment of ATTR-CM

Other types of Amyloidosis which also “damage” the heart should be excluded. This is an important step, as immunoglobulin light chain amyloidosis (known as AL amyloidosis) and cardiac transthyretin amyloidosis are treated differently.

Special blood and urine tests are necessary to rule out AL amyloidosis:

- Scintigraphy (SPECT test)

This is a non-invasive imaging test that can be used to detect ATTR-CM. During the test, images are taken by a γ -camera. These images can help us know if transthyretin (TTR) amyloid fibrils are present in your heart.

- Myocardial biopsy

During this particular operation, some small samples of myocardial tissue are taken for examination. The biopsy is performed by a cardiologist while you are awake, using local anesthesia. If amyloid fibrils are found in the removed tissue, it is sent to a lab to determine whether it is transthyretin amyloid fibrils or a different type of cardiac amyloidosis. A biopsy can be taken from other parts of the body, but it is less accurate in detecting ATTR-CM.

- Genetic testing

Once ATTR-CM is diagnosed, genetic testing and counseling are recommended. Genetic testing can confirm or rule out the inherited form of ATTR-CM (HATTR).

Can we prevent transthyretin amyloidosis (ATTR-CM)?

If you have the TTR gene mutation that causes familial ATTR-CM, there's a 50% chance of passing it to each

of your children. Not every child who inherits this gene mutation develops ATTR-CM.

Before having children, you may want to meet with a genetic counselor. This specialist can discuss options like preimplantation genetic diagnosis (PGD). This technique may lower the risk of passing the changed gene to your child. With PGD, healthcare providers select embryos that don't have the faulty gene. They then implant these embryos into your uterus using in vitro fertilization (IVF).

Treatment of ATTR Amyloidosis includes stabilizers of the Transthyretin tetramer and drugs that stop the production of Transthyretin by destroying its mRNA before it makes it to the ribosomes. In specific cases of hereditary ATTR alone (eg, age <60 years, without significant cardiac or renal involvement) orthotopic liver transplantation may be performed.

For Transthyretin Amyloidosis, until today, a stabilizer of the Transthyretin tetramer, Tafamidis, is used. (This is not given to asymptomatic carriers. Diflunisal, a non-steroidal anti-inflammatory, can be used as a stabilizer of the Transthyretin tetramer.

- Tafamidis (VYNDALCEL, VYNDAMAX) has been tested in both types of ATTR Amyloidosis with very good results.
- Diflunisal (ANALERIC) at a low dose of 250 mg 2 times a day helps mainly in neurological manifestations of Transthyretin Amyloidosis.
- (AG10 or Acoramidis is similar to Tafamidis, under investigation)

Therapies that reduce translation of Transthyretin mRNA into Transthyretin protein (normal and mutant). These are currently approved for polyneuropathy from hereditary transthyretin amyloidosis (ATTRh amyloidosis).

- Patisiran (Onpattro) and Vutrisiran (Amvuttra) are siRNA therapeutic agents that act on mRNA so that the protein Transthyretin is not made.
- Inotersen (Tegsedi, AKCEA-TTR-LRx) is a complementary oligonucleotide ASO that acts on mRNA to prevent the protein Transthyretin from being made.
- (Eplontersen is similar to Inotersen, under investigation)

Treatments that break up Transthyretin amyloid fibrils:

- The combination of Doxycycline (antibiotic) and ursodiol (tauroursodeoxycholic acid) is being tried.

- An antibody is also tested to neutralize the abnormally folded Transthyretin.
- In addition, the catechin Epigallocatechin 3-gallate found in green tea is tested.

Conclusion:

It is important to get an accurate diagnosis as soon as possible, because treatments may be more successful if started early.

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