Transthyretin Amyloidosis

Information for **Patients** and **Family**

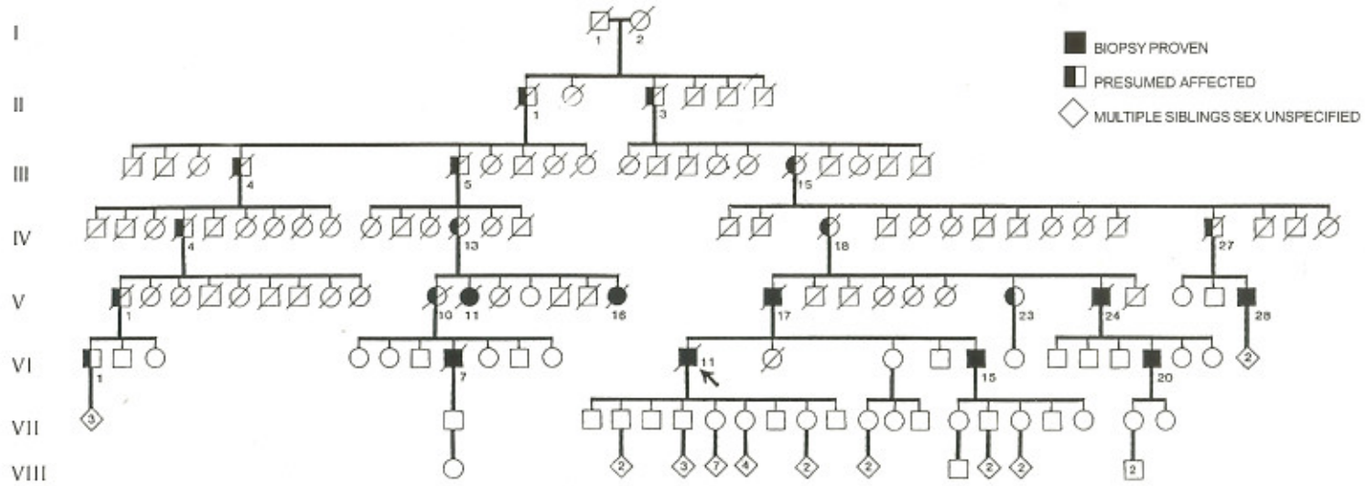
TYPES OF FAMILIAL SYSTEMIC AMYLOIDOSIS

TYPE	DISTINGUISHING FEATURES	USUAL CLINICAL FEATURES
Transthyretin	Most common, worldwide	Neuropathy, Heart failure Diarrhea, Kidney failure
Fibrinogen	United States, Europe	Hypertension, Kidney failure
Apolipoprotein AI	United States, Europe	Kidney failure
Lysozyme	Europe, Canada	Kidney failure, Liver failure
Gelsolin	Finland	Corneal changes (eye), Occasionally heart and kidney disease
Cystatin C	Iceland	Intracranial hemorrhage
Apolipoprotein AII	United States, Russia	Kidney failure

TYPES OF SYSTEMIC AMYLOIDOSIS

TYPE	DISTINGUISHING FEATURES	CHEMICAL NATURE OF AMYLOID
Primary / Immunoglobulin	Sporadic occurrence No predisposing factors	Immunoglobulin (Antibody protein)
Secondary / Reactive	Occurs with chronic inflammatory diseases (Rheumatoid arthritis, Crohn's disease)	Liver protein made during inflammation
Hereditary / Familial	Occurs in families with certain gene mutations.	Genetically abnormal proteins

Typical Family Tree of a Family With Hereditary Amyloidosis



What is transthyretin amyloidosis?

Transthyretin (TTR) amyloidosis is a disease caused by the abnormal accumulation of protein molecules in body tissues. These protein accumulations or "amyloid deposits" are made from a blood protein, TTR, which normally transports thyroid hormone and vitamin A to the body tissues. When an inherited defect in the TTR protein occurs, this abnormal form of TTR has the tendency to accumulate in tissues such as the heart, kidneys, nerves, and intestine. The presence of these deposits interferes with the normal functions of the organs, and as the deposits enlarge more tissue damage occurs and the disease (TTR amyloidosis) worsens.

What is transthyretin?

TTR is a normal blood protein. Its function is to carry thyroid hormone and vitamin A to tissues where they are needed for normal metabolism. Like all proteins TTR is made from the 20 different amino acids which are linked end to end to make large molecules. Each protein is identified by the arrangement of the amino acids in the protein chain and this arrangement is determined (coded) by a specific gene. In the case of TTR a single gene located on chromosome 18 codes for the amino acid alignment (sequence) which is characteristic of this protein and distinguishes it from all other proteins.

What causes transthyretin amyloidosis?

TTR amyloidosis is caused by mutations in the protein. A mutation occurs when the position of one amino acid in the protein chain is replaced by a different amino acid. This causes a structural change in the protein molecule, and the protein then has a tendency to deposit in the tissues. The protein that actually deposits in the tissues has changed its structure so that aggregation of many protein molecules makes fibrils (β-fibrils) which are very resistant to being dissolved or degraded by normal body functions. Greater than 80 TTR mutations have been discovered.

Who gets transthyretin amyloidosis?

TTR amyloidosis is an hereditary disease. A mutation in the gene for TTR protein is passed from one generation to another. It is an autosomal dominant disease which means that both men and women get the disease and that only one copy of the mutated gene is required to cause the disease. An individual with a mutant form of TTR may have obtained the genetic trait from either their mother or father and they in turn are capable of passing the mutant gene on to their children. Each child has an equal chance (50/50) of inheriting the mutant gene instead of the normal gene. TTR amyloidosis almost always occurs after age 20 and in most individuals the disease begins after age 50. By that time most individuals with mutated TTR genes have had the opportunity to raise families and, therefore, have passed the gene on to their children before they themselves develop the clinical disease.

What happens in transthyretin amyloidosis?

While TTR amyloid deposits may occur in any organ, they most commonly affect the peripheral nerves, heart, intestine, and the kidney. For any one individual it is difficult to predict which organ will be involved to the greatest extent and, therefore, cause disease symptoms that will be recognized by the patient and their physician. Amyloid involvement of the peripheral nerves most commonly causes numbness or tingling in the feet or hands at the beginning and then may progress to cause difficulties in walking or performing fine hand movements. Involvement of the heart often causes congestive heart failure with tiredness, weakness, and swelling of the feet from water retention. Involvement of the intestine may cause constipation, or diarrhea, or alternating constipation and diarrhea. In some patients with specific forms of TTR amyloidosis, deposits of the protein occur in the eye and obstruct vision. A few individuals developed deposits of amyloid in the linings around the brain and this may cause headache and stroke-like symptoms.

Diagnosis

The diagnosis of TTR amyloidosis can only be firmly established by tissue biopsy. Biopsy of an affected organ such as peripheral nerve, intestine, heart, or kidney allows the demonstration of amyloid deposits with special stains on microscopic sections of the tissue. First, however, it is necessary for the physician to suspect the diagnosis of amyloidosis so that a biopsy will be done. For many individuals a family history will suggest that TTR amyloidosis diagnosis should be considered. If an affected individual reports that their mother or father had a similar illness or was found to have amyloidosis when they died this will raise the likely diagnosis of amyloidosis. The same is true if an affected person has a brother or sister who has the disease. Now we have the ability to test the DNA of individuals suspected of having TTR amyloidosis and determine if they have one of the mutant genes which causes this disease. By isolating DNA from a sample of blood, tests can be done to detect the genetic mutation associated with TTR amyloidosis. In addition DNA tests can be done for any person who wants to know if they have a TTR gene mutation that can cause the disease before they develop any signs. This will allow that person to seek medical advice and counseling without being subjected to extensive medical tests for other diseases which might be suspected if the results of DNA analysis were not known.

Prognosis

TTR amyloidosis is a progressive disease which usually causes increasing organ dysfunction over a time of several years. The rate of progression varies considerably depending on which TTR mutation causes the disease. Major causes of disability include bowel dysfunction with severe diarrhea and weight loss, congestive heart failure with generalized weakness and difficulties breathing from fluid retention. A smaller number of individuals develop kidney failure and require dialysis treatments. It is not unusual for affected individuals to live 5, 10, 15, or sometimes even 20 years after the first signs of disease.

Treatment

The only specific treatment for TTR amyloidosis is liver transplantation. TTR is made in the liver and if an individual receives a transplanted liver they no longer make the abnormal protein. This procedure has been done for several hundred subjects. Many have benefitted from liver transplantation and are able to live a relatively normal life, although the degree of organ impairment that occurred before the liver transplantation does not usually reverse. Unfortunately, some individuals continue to have progression of their disease after liver transplantation. It is felt that after TTR amyloid deposits have started to occur in various organs, normal TTR protein may continue to be deposited even though the mutant form of the protein is no longer present.

Research

The fact that liver transplantation is not available to many individuals, especially those at older age when TTR amyloidosis very often occurs, and the fact that liver transplantation is not curative for some individuals, it is important that we continue medical research to discover new ways of treating or preventing this disease. At the present time studies are ongoing to develop therapeutic agents which might interfere with the formation of amyloid tissue deposits. Other studies are aimed at methods to suppress the manufacture of abnormal TTR by the liver. These studies are aided by the availability of transgenic animals (mice) that have been given the human TTR gene so that controlled studies can be done to test new types of treatment. If these new treatments are effective in the animal models, then they may be applied to the treatment of the disease in humans. No such naturally occurring model of TTR amyloidosis has been found in any animal species except humans, and, therefore, the use of laboratory animals to find a treatment for this disease is absolutely essential.

For more information...

Amyloid Center website:

Indiana University School of Medicine, Indianapolis, Indiana
http://www.iupui.edu/~amyloid

Information website for the doctor:

American College of Physicians
http://pier.acponline.org/pierindex.html/hp

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13