

HEREDITARY AMYLOIDOSIS

Q & A QUESTIONS ANSWERS



INTRODUCTION

This booklet is provided to you by the Amyloidosis Support Network to offer guidance and understanding to adults who may suspect hereditary amyloidosis. While this booklet provides some general information about amyloidosis, it centers on the hereditary form which is known scientifically as familial. Referring to it as familial may be new to you, but we believe it is important for patients to be familiar with the medical world's language to better understand the terms that are used by our physicians. Familial amyloidosis is not the most common form of the disease and all the more reason why we feel this booklet is necessary.

WHAT IS AMYLOIDOSIS?

Amyloidosis is a group of diseases, all of which have deposits of amyloid fibrils in tissues. Systemic amyloidosis has been classified into three major types that are very different from each other. Two of the three types of systemic amyloidosis are AL (sometimes referred to as primary) and AA (sometimes referred to as secondary). This booklet concentrates on the third type, which is hereditary, or, AF, the amyloid of the familial type (also sometimes referred to as FA or FAP).

To simplify matters, we refer to this third type of systemic amyloidosis as AF throughout this publication.

WHAT IS AF AMYLOIDOSIS?

AF is a disease caused by inheriting a gene mutation that produces an amyloidogenic protein. This protein can be deposited in an abnormal form in the body's tissues and organs, creating amyloid fibrils (fibril means threadlike fiber or filament). The term amyloid means "starch-like" and amyloid is not soluble. The effect is that if the amyloid fibrils build up, then this can compromise tissue or organ function. Although you are born with a gene mutation, amyloid deposits don't occur until adulthood.

There are 2 main classifications of AF: TTR and non-TTR. There are over 100 different variations of combined TTR and non-TTR amyloidosis, and more will be discovered as research continues. Each family with AF has its own pattern of organ involvement, onset and associated symptoms. Since these variations affect individuals differently, it is important to establish which variation you have in order to identify a treatment plan that is tailored for your type of amyloidosis.

1) **Defining ATTR Amyloidosis**

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 transport protein transthyretin (TTR); so these diseases are often designated with the acronym ATTR.

In most 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 in your body. Genetic information for TTR is encoded by a single gene on chromosome 18. TTR is mainly manufactured in the liver; however a smaller portion also comes from the choroid plexus of the brain. Mutations of this TTR protein cause AF.

The most common TTR variants in the United States are: Val30Met (this is considered to be the most common worldwide); Thr60Ala; Leu58His; and Ser77Tyr. Another particular mutation, Val122Ile, is seen predominantly in the African-American population and may be associated with the propensity for cardiomyopathy.

The majority of AF variations are TTR related. The other AF variations are defined in this publication as “non-TTR.”

2) **Defining Non-TTR Amyloidosis**

These diseases are considered to be even more rare than the ATTR variations.

Non-TTR amyloidoses consist of other proteins which, when mutated, can cause certain symptoms. These proteins include: Apolipoprotein AI, Apolipoprotein AII, Gelsolin, Fibrinogen, Cystatin C, and Lysozyme.

WHAT SYMPTOMS OCCUR WITH AF?

The most common ATTR symptoms are associated with nerve or cardiac involvement. The gastrointestinal tract, eye, kidney, and carpal ligament (also known as carpal tunnel syndrome) can also be affected.

Non-TTR symptoms can vary with each mutation, some involving the kidneys, liver, and/or heart. Some mutations have symptoms that involve the brain or the eye.

Each individual can present with varied clinical symptoms. The symptoms, as well as the prognosis, depend on the tissue and organ(s) affected by the amyloid deposits. Although AF may cause serious complications for some individuals, there are carriers of AF that may not show symptoms of the disease at all. Others may have a few, more minor, health issues.

However, you should never ignore any health problem. Early detection can be important with any disease. For more specific information on symptoms and a list of AF variations, go to our website at www.amyloidosis.org.

HOW DOES SOMEONE GET AF?

AF is not contagious. It is considered to be an inherited, autosomal dominant disease. This means that to get this disease, a person needs one copy of the mutant gene – in other words, it can be inherited from one parent. Each offspring of that parent has a 50/50 chance of inheriting the gene. If an offspring is not born with the gene mutation, then they can not pass it on to their own offspring.

HOW COMMON IS AF?

AF can be found in virtually every ethnic background. Generally, AF is an uncommon condition and is considered a rare disease. There is no consensus among doctors on the incidence of AF in the United States or worldwide. Typically, families know when they have AF because of similar symptoms and causes of illness among blood relatives, so family history is a key indicator.

IS IT A FORM OF CANCER?

No. None of the types of amyloidosis diseases are considered to be cancer.

WHAT TESTS ARE GIVEN FOR THESE DISEASES?

Since amyloidosis diseases are often under diagnosed or misdiagnosed, it is extremely important to utilize the latest testing procedures to confirm your diagnosis and the sub-type of the disease if you or your physician suspect amyloidosis.

If you have symptoms

A tissue biopsy of the symptomatic site is considered the most accurate diagnostic test available. When the tissue biopsy sample is stained with Congo Red stain, it is then put under a light microscope and the amyloid deposits show up as an "apple-green" birefringence ("birefringence" means double refraction) with the polarizing microscope.

Once the Congo Red staining is done, then additional immunostaining of the biopsy specimen, using commercially available antiserum against TTR, should also be performed. However, this is not always enough. Since there are so many variations of AF, and more are discovered all the time, gene sequencing (a DNA test) is also recommended because immunostaining may not identify a certain variant that is not within the more well known TTR types.

DNA testing

Genes are pieces of DNA, and most genes contain the information for making a specific protein. Some genes tell the body how to make a protein, for example, the TTR (transthyretin) gene tells the liver how to make the TTR protein. Sometimes there are differences, for whatever reason, in the coding of the gene so the body gets told to make a slightly different protein. This change is called a mutation in the genetic code of the DNA. This test is mainly used for people who have a family history of AF. DNA is isolated from a sample of blood, then gene sequencing can be performed to see if you carry the genetic mutation for a particular variation of AF.

If you don't have symptoms

- a) Your doctor will help you decide if you need a tissue biopsy in the absence of clinical symptoms.
- b) If you have a parent with one of the AF types, you can be tested to see if you've inherited the same amyloid gene. This DNA test is done by a blood sample. This testing is for adults, it is not recommended that children be tested.
- c) If you suspect your parent has (or had) AF, but no definite diagnosis was ever made for this parent, you should try to speak to your parent's doctor, or one of the doctors at the amyloid centers, to try to determine if testing is necessary. Go to www.amyloidosis.org for a listing of worldwide amyloidosis centers.

It is important to understand that carrying the gene mutation does not always mean that you will have symptoms later on, or that this disease will seriously affect you.

SHOULD I GET TESTED?

If you have a family history of AF, then consult with your doctor. Seeking genetic counseling may be recommended, if you are an adult. Since genetic testing may contain emotional and physical significance for you and your family, this is a decision that, ultimately, you need to make for yourself. With a genetic counselor, once you have discussed the variety of issues surrounding the results of these types of tests, you can make an informed decision on whether to proceed with the testing process. Some people want to know if they carry a genetic mutation, so they can more carefully watch their health or understand the issues surrounding family planning.

However, it should be noted that most genetic counselors are not knowledgeable in the AF diseases, so your consultations with a qualified genetic counselor may only center on the broader issues of being tested for a genetically inherited disease.

Regardless of your decision to be tested, some professionals recommend that you acquaint yourself with the amyloid mutation that is identified within your family and know how to recognize the symptoms that generally accompany your AF variation.

Finding these problems early and treating them promptly might prevent future health complications, thus leading to improved survivability and quality of life.

WHAT SHOULD I CONSIDER BEFORE HAVING A GENETIC TEST?

There are a number of personal, ethical, legal and social issues to think about. Apart from questions that are of a very personal nature, here are only some of the questions that you should ask a qualified genetic counselor, should you decide to see one: Who will have access to the information from the test results? How will that information be used? Who owns the genetic information stored in each individual's DNA? Could testing lead to discrimination by employers or insurance companies, or to privacy and disclosure disputes? What is genetic discrimination? What are the ways that the results might change my life?

IF I KNOW THAT I CARRY THE GENE MUTATION, WHAT CHANCES DO I HAVE OF EVER SHOWING SIGNS OF THE DISEASE?

Most AF symptoms, if they develop, occur in adulthood. Although genetic tests can identify a particular problem gene, they cannot predict how severely that gene will affect the person who carries it. It is known that inflammation and oxidative stress are triggered in most AF families, but the actual clinical disease does not manifest itself until amyloid fibrillation occurs. At that time, symptoms can range from none, to mild, to very severe.

If you are familiar with the common symptoms associated with your AF variant, you might be better able to keep a watchful eye on your health. For instance, you may not know that for some variations, carpal tunnel syndrome can occur years before other symptoms develop. You could experience early signs of the clinical disease and not realize that there was a connection. Having a genetic mutation is only a part of the story, because many illnesses develop from a mix of high-risk genes, environmental factors and/or unhealthy lifestyle (such as a smoker with a family history of familial cardiac amyloidosis). Keep in touch with your doctor.

WHAT KIND OF DOCTOR SHOULD I SEE?

The Amyloidosis Support Network recommends that you consult with a specialist in the field of amyloidosis. You can go www.amyloidosis.org or other amyloidosis websites on the internet that recommend top treatment centers for

amyloidosis worldwide. Once your diagnosis is confirmed, then a treatment plan can be laid out for your individual case. Depending on your symptoms, your local hematologist, neurologist, cardiologist, nephrologist, and/or general physician can then work with you and consult with your amyloidosis specialist to gain maximum concentration on your health needs.

IS IT CURABLE?

Today's treatment plans consist of stopping, or slowing, the overproduction of the amyloid protein in your body and treating the symptoms. Reversing any damage to the organs and other parts of the body is difficult to achieve, thus, early detection is essential.

For some TTR and other variants of AF, a liver transplant is considered curative. However, the statistics vary as to who can benefit from these transplants. It is not known if the previously-formed amyloid deposits completely disappear after transplantation, but studies continue in this area.

It is possible that AF can cause serious health complications, so it should not be taken lightly. However, do not assume that disability or an untimely death is stamped on your future. There are treatments available and research continues. Advances in treatment are likely, with new studies and clinical trials in view.

HOW MANY TYPES ARE THERE?

With over 100 noted variations, and more being discovered, the answer to this becomes very complex. This is why it is recommended that you seek an amyloidosis specialist who can help you determine your exact AF variation.

For a list of most known TTR and non-TTR variants of AF, please refer to www.amyloidosis.org on the internet. The list will show the amyloid protein type or variant and its associated geographic/ethnic origins and the organs that are usually involved.

WHAT ARE THE TREATMENT OPTIONS?

Since there are many variations of AF, there are several differing treatment plans, so consult with your doctor on what is available for your type of AF.

Treatment for ATTR

For most ATTR variations, the amyloid malfunction occurs primarily in the liver. And, although the liver is the main source of amyloid production, it is often not affected by the disease. The amyloid burden can cause damage in other parts of the

body. Your doctor has two assignments when focusing on your health:

- Supportive treatment - treating your symptoms and organ damage; and,
- Source treatment - slowing down, or stopping, the overproduction of amyloid at the source of the disease.

Supportive treatment is helpful for various symptoms, including peripheral neuropathy, autonomic neuropathy, and cardiac, and can change the quality of life for many people.

To address the source of the disease, for some ATTR variations and since the transthyretin protein is primarily made in the liver, replacing this organ removes most of the source of the mutant protein production. The outcome of liver transplantation is largely dependent on the mutation that exists in the patient.

Age is the main risk factor regarding the development of cardiomyopathy. Regardless of age, consideration must also be given if a patient is treated while in a later stage of clinical disease. It is overwhelmingly believed that if treatment begins during early onset of clinical symptoms that the overall success rate rises.

Treatment for Non-TTR

Supportive treatment (referring to the organ damage and/or other symptoms) is a vital focus for all amyloidosis diseases, so careful monitoring of all symptoms must be maintained.

Support treatment can vary with each mutation of the non-TTR diseases, however, many of them present with heart and/or kidney damage, so organ transplantation has been used in these cases with success. Although not a cure, and even if production of the variant amyloid protein continues, an organ transplant can slow the progression of the disease, improve quality of life and prolong survival significantly.

Liver transplants are even less of a source treatment option for most of the non-TTR diseases. But, the fibrinogen variation has amyloid production occurring solely in the liver, so a liver transplant (often occurring with a kidney transplant) can be an important and successful treatment in this variation.

Lysozyme, apolipoprotein A-I, along with the other non-TTR variations, are so varied that you should consult with a specialist at an amyloid center to recommend a treatment for your individual needs. It is possible that your treatment regimen can then be carried out by your local physician(s).

IS RESEARCH BEING DONE?

Studies are being conducted all over the world. Research can take years of hard work before the results are analyzed and can be turned around to be used in clinical trials on humans. Likewise, it could take years of clinical trials before the treatment (if successful) is available to the general public. There are many medical journal articles available discussing the current research, and most amyloidosis websites have these articles available for your review.

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. A diet low in protein and/or sodium may be necessary when the kidneys are involved. Consult with your physician on any dietary changes, and report any vitamins or other supplements that you take. Remember, you are a part of the team of people who must keep in communication with each other about your health.

WHAT ARE THE INSURANCE IMPLICATIONS?

When discussing private insurance in the United States, the term “pre-existing condition” might be an issue. Group medical plans offer a waiver of the pre-existing condition clause if you have previous uninterrupted coverage. If you know that you are at risk for any hereditary health condition, and you live in the U.S., it is recommended that you never let your insurance lapse. Maintaining continuous coverage will assure that the insurance company cannot deny benefits. Also, it might be a good idea to take out supplemental insurance at the appropriate time. This covers such things as travel expenses, food and lodging for you and a caregiver. With a rare condition like amyloidosis, traveling to get experienced health care can be necessary.

If your insurance has been interrupted, it is important to honestly disclose any pre-existing conditions to your insurer. Failure to do so allows an insurance company the right to rescind your policy at a later date and you may be liable for reimbursed claims.

Regarding disability, if you start experiencing symptoms, and you live in the U.S., the ASN strongly suggests that you immediately file for social security disability (SSDI) whether or not you're entitled to receive such benefits. The application also includes a test for SSI eligibility, which is a special program for lower income persons that have not worked enough to earn social security benefits.

WHAT IF I HAVE MORE QUESTIONS?

Please call on us if you have more questions about AF. We will do what we can to point you in the right direction, by recommending a medical specialist or medical journal article. Your family and its history can provide you with a blueprint for your health. Now you are building from that blueprint. So keep asking questions!

“Learn from yesterday, live for today, hope for tomorrow. The important thing is to not stop questioning.”

--Albert Einstein

The Amyloidosis Support Network, Inc. (ASN), a nonprofit organization founded in 2004, produced this booklet. The ASN was established to improve survivability and quality of life by:

1. Promoting disease awareness in the medical community so it can be recognized earlier and appropriately treated.
2. Providing patient education, advocacy and support resources.
3. Supporting high-value research projects through our partnerships.

For a list of major amyloidosis treatment centers, patient support resources, and other important information on amyloidosis, go to our website at www.amyloidosis.org.

Information on how to contact the ASN is provided on the back cover of this booklet. Tax-deductible contributions are welcomed and very much appreciated.

Special appreciation is extended to Dr. Merrill Benson, as well as other amyloidosis specialists on our Medical Advisory Board, for their input and counsel on this booklet.



DEDICATION

“Edward J Derbyshire was a man who brought a light into every life he met. With his vivacious ways and loving heart, he was a great father, husband and man.

This booklet was made possible by the fundraising efforts of the family & friends of Edward Derbyshire who passed away on October 12th 2004 due to familial amyloidosis. This booklet is dedicated to his memory and the valiant 6 year fight he fought. “

Anne Derbyshire, daughter of Edward

**OUR CORE MISSION IS
MEDICAL COMMUNITY
AND PUBLIC AWARENESS.
IN ADDITION, WE ARE
COMMITTED TO:**

- Patient education & advocacy programs
- High-value research programs through our partnerships



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