Patient Information

Hereditary ATTR Val122Ile Amyloidosis

Introduction

Hereditary ATTR amyloidosis is an inherited genetic disease in which there is thickening and stiffening of the heart muscle, due to a build-up of abnormal protein. This abnormal protein may also build up in the carpal tunnels in the wrists and in the lower back known as the lumbar canal. Most patients are at least 60 years of age. This condition is more common in men than in women, and is particularly common in people of Afro-Caribbean or African American ancestry, about one in twenty of whom possess the gene that predisposes them to developing this condition.

Until recently many people with ATTR amyloid affecting the heart were misdiagnosed as having heart disease due to other more common causes, such as high blood pressure or ischaemic heart disease.

Hereditary ATTR amyloidosis (the most commonly recognised form of hereditary systemic amyloidosis worldwide) was traditionally referred to as familial amyloid polyneuropathy (FAP), when disease mainly affected the nerves, or familial amyloid cardiomyopathy (FAC), when disease mainly affected the heart. However, it is now understood that in clinical practice there is significant overlap in disease manifestations, not only between patients with different mutations, but also among those with the same mutation. Most TTR mutations can cause amyloid deposits in both the nerves and the heart. The International Society of Amyloidosis has therefore recommended the use of the term hereditary ATTR amyloidosis to describe disease caused by ATTR amyloid deposits in all patients with TTR gene mutations.

What causes ATTR Val122Ile amyloidosis?

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This condition is caused by a mutation in the TTR gene which results in the production of an abnormal ('variant') TTR protein called Val122Ile, sometimes called V122I. A mutation is a permanent change in the sequence of DNA which makes up the genes in all cells in the body. The DNA acts like a blueprint or recipe for building the proteins that make up the body. The proteins are made up of strings of amino acids, assembled in a precise order. The DNA determines the order in which amino acids are assembled. In people with the Val122Ile mutation, an amino acid called valine is replaced by an amino acid called isoleucine at position number 122 in the TTR molecule. Thus, every TTR molecule produced in the body is slightly different to normal, 'wild-type' TTR. This different, 'variant' TTR is more amyloidogenic than the normal 'wild-type' TTR, meaning that it has a greater tendency to form amyloid fibrils which deposit in the tissues of the heart, causing heart stiffening, and sometimes in the wrist, causing carpal tunnel syndrome.

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www.ucl.ac.uk/amyloidosis (more detailed information is available at www.amyloidosis.org.uk)
Visit the NAC online support forum at www.ucl.amyloidosis.org.uk/forum
A place where patients, family members and carers can connect, communicate and help each other
This information sheet has been reviewed by members of the UK Amyloidosis Advisory Group (UKAAG)

Recent development of new, sophisticated heart scans (cardiac MRI and DPD scans, discussed in Appendix 2 at the end of this information leaflet) has helped doctors to diagnose amyloid in the heart to manage patients appropriately. Since these new scans have been available doctors have realised that ATTR amyloidosis affecting the heart is more common than was previously believed. But nobody knows just how common this condition is, and how frequently patients are still misdiagnosed.

Doctors at the National Amyloidosis Centre (NAC) at the Royal Free Hospital in Hampstead, London pioneered the use of these scans for diagnosing amyloidosis in the heart. All patients in the UK with a diagnosis of amyloidosis should be referred to the NAC for an assessment. This will allow patients to benefit from specialist expertise, and help with ongoing investigations to determine how common the condition really is.

If you or your relative have suspected or diagnosed amyloidosis, you can ask for a referral to the National Amyloidosis Centre at the Royal Free Hospital. The consultants at the NAC also welcome enquiries from relatives of patients with hereditary ATTR amyloidosis. Please contact Professor Julian Gillmore by email at julian.gillmore@nhs.net.

What is ATTR amyloidosis?

Amyloidosis is a rare disease caused by abnormal deposition and accumulation of proteins in the tissues of the body. Amyloid deposits are primarily made up of protein fibres known as amyloid fibrils. These amyloid fibrils are formed when normally soluble body proteins aggregate (clump together) and then remain in the tissues instead of being safely cleared away. About 30 different proteins are known to form amyloid deposits in humans. These amyloid forming proteins are known as 'precursor proteins.' Amyloid deposits cause disease by gradually accumulating within organs and thereby disrupting the structure and damaging the function of the affected tissues.

Different types of amyloidosis are named according to the precursor proteins which form the amyloid fibrils. All have the initial 'A' denoting amyloidosis and letter(s) identifying the particular precursor protein which forms amyloid fibrils within the amyloid deposits.

In ATTR amyloidosis, a protein called transthyretin (TTR) is the amyloid precursor protein that forms the amyloid deposits. Transthyretin (TTR) is a normal blood protein, mostly made in the liver and present in everybody. In healthy people, normal, so-called 'wild-type' TTR functions as a transporter of thyroid hormone and vitamin A (retinol) within the bloodstream, hence the name: 'trans-thy-retin'.

ATTR amyloidosis can be either hereditary or acquired (non-hereditary, known as wild-type ATTR amyloidosis).

The hereditary types of ATTR amyloidosis affect people with genetic alterations (mutations) in the TTR gene. People with these mutations have structurally abnormal, amyloid-forming (amyloidogenic), 'variant' TTR in their blood, which clumps together and forms amyloid deposits in tissues.

People with wild-type ATTR amyloidosis have only the normal, 'wild-type' TTR in their blood, and do not have any abnormal 'variant' TTR. In this condition the normal, 'wild-type' TTR proteins clump together and form amyloid deposits.

This information leaflet is focused on a particular type of hereditary amyloidosis called variant ATTR Val122Ile amyloidosis. Other information leaflets available from the National Amyloidosis Centre discuss the other types of ATTR amyloidosis.

Who gets variant ATTR Val122Ile amyloidosis?

The Val122Ile variant was first identified in 1988 in amyloid fibrils from a 68 year old African American who died of cardiac amyloidosis. He had no known family history of amyloidosis. DNA analysis found that he carried the Val122Ile mutation. Subsequent research found that the Val122Ile mutation was present in nearly 4% of African Americans. This means that about 1.3 million people in the US are at risk of developing this condition. The Val122Ile mutation has also been found in 23% of African Americans with a diagnosis of cardiac amyloidosis.

There is less precise data available for the UK population but it is believed that this mutation is probably also common in people in the UK of Afro-Caribbean ancestry. In these people, ATTR Val122Ile amyloidosis is probably an underdiagnosed cause of heart failure.

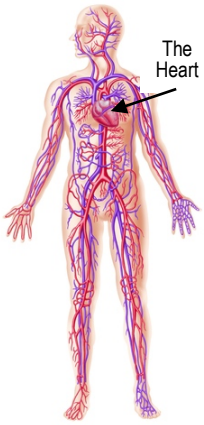
The Val122Ile mutation has variable penetrance. This means that carrying the Val122Ile gene mutation does not guarantee that a person will develop amyloidosis. Some people carry the mutation all their lives but do not develop symptomatic amyloid deposits. Genetic testing in a healthy person without symptoms can provide information on whether the Val122Ile mutation is present, but cannot predict whether the person will go on to develop amyloidosis. For more information on genetics, see Appendix 1 at the end of this information leaflet.

How can you help us understand this condition better?

Many aspects of this condition are not fully understood, including its prevalence in the UK. If you are of Afro-Caribbean ancestry and you or your family member have heart disease which is suspected to be amyloidosis, please contact Professor Julian Gillmore by email at julian.gillmore@nhs.net to discuss the possibility of genetic testing. Genetic testing is performed using blood samples taken from a vein. Your involvement is critical to help us to learn more about the disease, so that we may be better able to treat patients.

Symptoms of hereditary ATTR amyloidosis

ATTR amyloid deposits in the heart muscle may cause no symptoms at all if they are small. But when amyloid deposits in the heart are large, they can lead to stiffening of the heart muscle. This is called a 'restrictive cardiomyopathy'. When the heart muscle is stiff, the heart is unable to pump the blood around the body as efficiently as usual.



Symptoms of heart failure may then appear, including:

- shortness of breath, sometimes just after mild exertion
- palpitations and abnormal heart rhythms, most frequently atrial fibrillation or atrial flutter
- leg swelling (oedema)
- weight loss
- nausea
- fatigue and muscle weakness
- dizziness and collapse (syncope or fainting), which may occur after exertion, or after eating
- disrupted sleep
- angina (chest pain)

Breathlessness may be worse during exercise or when lying flat at night. Patients may feel more comfortable at night propped up with several pillows.

Some patients may experience carpal tunnel syndrome – tingling and pain in the wrists, pins and needles in the hands. Carpal tunnel syndrome is caused by amyloid deposits in the nerves and often appears 3-10 years before the symptoms of heart disease.

Diagnosis

The majority of patients diagnosed with ATTR amyloidosis affecting the heart at the NAC are referred by cardiologists. Cardiologists may first suspect this diagnosis when a patient experiences symptoms of heart failure, as described above, and ECG, echocardiogram and sometimes CMR findings are suggestive of amyloid deposits in the heart.

Genetic tests can identify patients with ATTR amyloid in the heart due to hereditary ATTR Val122Ile amyloidosis. Genetic testing is performed on blood samples taken from the patient's vein.

A heart biopsy may be recommended to confirm the presence of amyloid and distinguish between hereditary ATTR amyloidosis and AL amyloidosis affecting the heart. The distinction is very important, as treatment for these conditions is completely different.

The 'gold standard' test (the best available method) for diagnosing hereditary ATTR amyloidosis is a combination of detection of ATTR amyloid on heart biopsy and genetic testing showing that there is a mutation in the TTR gene.

Biopsies from other parts of the body, such as abdominal fat or the rectum, are often used to diagnose other types of amyloidosis. In hereditary ATTR amyloidosis these tests can be useful if they do show amyloid. But in many patients with this condition these tests are negative despite the presence of amyloid deposits in the heart.

DPD scans, which are performed at the NAC, are very helpful for confirming the presence of amyloid deposits in the heart and the 'pattern of uptake' may strongly suggest ATTR type amyloidosis. DPD scanning is exquisitely sensitive for detecting ATTR amyloid deposits in the heart. A DPD scan, in combination with a series of blood and urine tests, may be sufficient to diagnose cardiac ATTR amyloidosis without a need for demonstration of amyloid within a tissue (heart, fat or nerve) biopsy. Cardiac MRI (CMR) scanning, also available at the NAC, can give additional important information. Recent advances in CMR imaging technology have led to a dramatic increase in the frequency of detection of amyloid deposits in the heart.

The SAP scan, which identifies amyloid deposits in many parts of the body, cannot detect amyloid in moving organs such as the heart. Patients with hereditary amyloid cardiomyopathy do not have any amyloid detectable on SAP scans.

Specialist blood tests called cardiac biomarkers are frequently raised in hereditary ATTR amyloidosis affecting the heart. For more information, see Appendix 2 at the end of this information leaflet.

Which tests can help to diagnose amyloid cardiomyopathy?

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ECG
Echocardiogram
Cardiac magnetic resonance (CMR) scan
Radionuclide imaging (DPD scan)
Blood tests: 'cardiac biomarkers'
(NT-proBNP and troponin)
Genetic tests
Heart biopsy
Abdominal fat biopsy / rectal biopsy

For more details on each of these tests, see Appendix 2 at the end of this information sheet

Treatment

Treatment of all types of amyloidosis is currently based on the following principles:

- Reducing the supply of amyloid forming precursor proteins.
- Supporting the function of organs containing amyloid.

When amyloid precursor protein supply is controlled:

- existing amyloid deposits often regress (become smaller)
- new amyloid deposits stop appearing
- organ function is often preserved and may also recover.

The new drugs, discussed on page 6, can help patients with ATTR Val122Ile amyloidosis by reducing the supply of amyloid forming TTR. The genetic based therapies, patisiran and inotersen, do this by reducing TTR production. Tafamidis and diflunisal work by stabilising TTR, which may make it less likely to form amyloid deposits.

Most patients also benefit from symptomatic, supportive treatment. Many standard medications used for heart failure are not of proven efficacy in patients with amyloid deposits in the heart, but the following measures can be very helpful:

Fluid balance

Patients with cardiac amyloidosis should limit their fluid intake.

The most important principle of treatment for cardiac amyloidosis is strict fluid balance control. Specialist heart failure nurse involvement may be valuable.

When there is cardiac amyloidosis, the heart is often too stiff to pump the blood efficiently. This may lead to fluid build-up, causing leg swelling (oedema) and breathlessness due to fluid in the lungs. This problem is exacerbated if the patient drinks too much fluid.

There may be episodes of worsening symptoms if there is even a small fluid excess. It is preferable to catch and treat heart failure symptoms at an early stage, before they become overwhelming.

Fluid excess can be avoided by careful attention to the 3 **D**s:

1. **D**iet
2. **D**iuretics
3. **D**aily weights

1. Diet:

Fluid intake should be *steady* and should usually not exceed *1.5 litres per day*.

Salt intake should be strictly limited. Salt should not be added to food. In addition, this includes attention not just to salt added to the food from the salt pot, but also to food with high salt content such as crisps, bacon, canned meats, sausages, canned soups and smoked fish. It can be very helpful to meet with a dietician for precise and personalised dietary advice.

If salt and fluid intake is too high, the benefits of diuretic drugs can be completely lost.

2. Diuretics:

Doctors may prescribe diuretics (water tablets) which help the body to clear excess salt and water via the urine.

Taking these drugs is not a substitute for avoidance of excessive dietary salt and water. If patients consume too much salt and drink too much fluid, the benefits of diuretics may be lost.

Removal of excess fluid from the body leads to reduced ankle swelling and breathlessness. The first diuretic prescribed is often furosemide. Other diuretics such as spironolactone may be added later to increase the effect. Diuretics lead to increased amounts of urine and should be taken first thing in the morning, sometimes with an additional lunchtime dose. It is important to follow the doctor's advice carefully regarding diuretic dose and the time of day when the tablet should be taken.

3. Daily weights:

Patients should monitor and record their weight daily. Weight should be measured consistently, using the same scales, at the same time of day, usually first thing in the morning after passing urine, just wearing underclothes. Each litre of excess fluid weighs one kilogram. Several litres of fluid can accumulate in the body without it being very noticeable. But an increase in weight can be an early warning sign of fluid retention.

Variations from week to week or even from day to day of about ± 1-2 kilograms are normal. If there is greater variation in weight, the doctor or nurse treating the patient can recommend appropriate measures. These may include increasing or reducing the diuretic dose. Some patients learn over time how to make appropriate small adjustments to the diuretic dose according to their weight fluctuations.

The aim is to detect and treat any excess fluid, before the patient feels unwell because of the fluid overload.

Support stockings can be helpful for patients with leg oedema (swelling in ankles and lower legs).

Monitor your weight and blood pressure daily. It is helpful if you record them in a chart that you can show your local heart failure team during regular reviews. It is important for your local cardiology/haematology teams to agree to an exact, pre-determined plan for monitoring your fluid balance and adjusting diuretic doses in the event of unexpected fluid retention.

Medications

Many standard heart failure medications reduce the already low blood pressure in patients with cardiac amyloidosis, and can sometimes worsen symptoms.

The following drugs should be used with caution:

- calcium channel blockers
- digoxin
- beta blockers
- angiotensin converting enzyme (ACE) inhibitors
- angiotensin receptor blockers

Follow your doctor's advice carefully and take the medicines your doctor prescribes for you.

Under certain circumstances some other treatments may be helpful. For example:

- Alpha agonist drugs such as midodrine may help to maintain blood pressure and allow higher diuretic doses.
- In some cases anticoagulation may be recommended.
- A pacemaker may be recommended if there is a slow or irregular heart rate.
- Implantable cardiac defibrillators (ICDs) may occasionally be recommended if there is an abnormally fast heart rate leading to dizziness or loss of consciousness.

Heart transplantation

Most patients with hereditary ATTR amyloidosis are too elderly to undergo a heart transplant. The risk of complications from this major operation is high with advanced age. Heart transplantation may very rarely be an option for a patient who presents at an unusually young age (before 60 years) with the disease.

Liver transplantation

Most TTR in the body is produced in the liver, and liver transplantation has been helpful in some patients with hereditary ATTR amyloidosis mainly affecting the nerves. However, liver transplantation does not prevent the progression of cardiac ATTR amyloid deposits, so it is not effective for patients with hereditary ATTR Val122Ile amyloidosis.

Exercise

It is believed that limited, light exercise is beneficial for the general well-being of patients with amyloid in the heart. However, it is important to be careful, and to exercise within limits, to avoid exhaustion. If there are symptoms on exercise, patients should not push themselves.

Drug interactions

It is very important that patients tell their doctors about any drugs they may be taking, including complementary or alternative medications or supplements. Some drugs may interact inside the body and lead either to toxicity due to raised drug levels, or lack of effect due to reduced drug levels.

If patients with amyloidosis become ill or require any treatment for a different condition it is important to inform the treating doctors so that, if necessary, the NAC doctors can be informed, in order to maintain co-ordinated care.

Surgery and anaesthesia

It is generally advisable for patients with amyloidosis to avoid undergoing surgery, anaesthesia and other invasive procedures.

If such procedures are necessary, patients should request that the surgeons, anaesthetists and other doctors involved contact the NAC doctors beforehand, to discuss any special considerations. For example, it is very important that great care is taken to monitor and maintain blood pressure and fluid balance throughout such procedures. Care should also be taken because of the tendency of tissues with amyloid in them to bleed and to heal poorly.

Outlook

Hereditary amyloid cardiomyopathy is a disease which progresses slowly. Patients with this condition survive longer than those with AL amyloidosis in the heart. Most patients with hereditary ATTR Val122Ile cardiac amyloidosis survive for over 7 years after symptoms start. Furthermore, a number of new drugs for ATTR amyloidosis are in various stages of development. These drugs are not yet available, but they do offer hope for the future.

New drugs in development for ATTR amyloidosis

Genetic based therapies

- small interfering RNA
- antisense oligonucleotides

These two approaches aim to 'switch off' the gene for TTR in liver cells, so that TTR is simply not produced. Recent clinical trials of these drugs in patients with hereditary ATTR amyloidosis and symptomatic neuropathy had very encouraging results, serving as a landmark in the field of amyloidosis treatment.

A drug called patisiran belongs to the small interfering RNA drug class. The APOLLO trial was a phase 3 study which enrolled 225 patients with hereditary ATTR amyloidosis and randomised them to receive either patisiran or placebo by intravenous injection every three weeks for 18 months. Patients who received patisiran did significantly better than those who received placebo, in terms of neuropathy symptoms, quality of life, daily activities and disability. According to standardised neuropathy scores, neuropathy symptoms actually improved with patisiran. Patisiran was safe and well tolerated.

Another drug called inotersen belongs to the antisense oligonucleotide drug class. The NEURO-TTR trial was a phase 3 study which enrolled 172 patients with hereditary ATTR amyloidosis and randomised them to receive either inotersen or placebo for 15 months. Patients who received inotersen did significantly better than those who received placebo, in terms of neuropathy symptoms, quality of life, daily activities and disability. A few patients receiving inotersen experienced drops in platelet counts and abnormal kidney functions. Once this was observed, all patients receiving inotersen were monitored with regular blood tests.

In 2019 patisiran and inotersen were approved by the regulatory authorities in the EU and the US, and subsequently by NICE and NHS England, for treating neuropathy in patients with hereditary ATTR amyloidosis. Since then, the NAC doctors have been able to prescribe these drugs for suitable patients.

So far trials have only assessed the impact of these drugs on nerve damage caused by ATTR amyloidosis. Effects on cardiac ATTR amyloidosis have not been assessed and patients with wild-type ATTR amyloidosis were not included in the drug trials. However, the next generation of interfering RNA drugs and antisense oligonucleotide drugs are due to be tested in patients with cardiac ATTR amyloidosis.

Tafamidis

Tafamidis was developed as a specific drug for ATTR amyloidosis. It is bound by TTR in the blood. This binding stabilises the TTR and makes it less amyloidogenic. The pivotal trial of tafamidis included 441 patients, most of whom had wild-type ATTR amyloidosis, while some had hereditary ATTR amyloidosis. Patients who received the active drug had better outcomes than those who received placebo, including fewer hospitalisations for heart disease, a 30% reduction in death over a period of 2.5 years, reduced decline in functional capacity and improved quality of life. Tafamidis appears to slow progression. Its benefit in hereditary ATTR amyloidosis (as opposed to wild-type ATTR amyloidosis) remains unproven.

Tafamidis is approved in Europe for treatment of hereditary ATTR amyloidosis patients with stage 1 symptomatic polyneuropathy, to delay neurological impairment and before liver transplantation, but it is not currently available within the NHS. The US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have approved tafamidis for cardiomyopathy caused by ATTR amyloidosis, although it is not approved in the US for ATTR polyneuropathy. It will need to be evaluated by NICE before it can become available within the NHS.

Diflunisal

This belongs to a class of drugs called 'non-steroidal anti-inflammatory drugs' (NSAIDs). Drugs from this class are in common use as pain killers, for conditions such as arthritis. Diflunisal is bound by TTR in the blood. This binding is thought to make TTR less amyloidogenic.

Trials are currently underway to assess the effect of diflunisal on the progression of neuropathy and cardiomyopathy in patients with familial amyloid polyneuropathy and familial amyloid cardiomyopathy. The first study report was recently published, with an encouraging result, but the numbers of patients involved was small and the extent of benefit was modest. The trial involved 130 patients with familial amyloid polyneuropathy (hereditary ATTR amyloidosis which affects the nerves), 64 of whom received diflunisal for 2 years while 66 received placebo (dummy pills). The rate of progression of neuropathy was slower in the patients who received diflunisal than in those who did not. Results of trials of diflunisal in cardiac ATTR amyloidosis are not yet available.

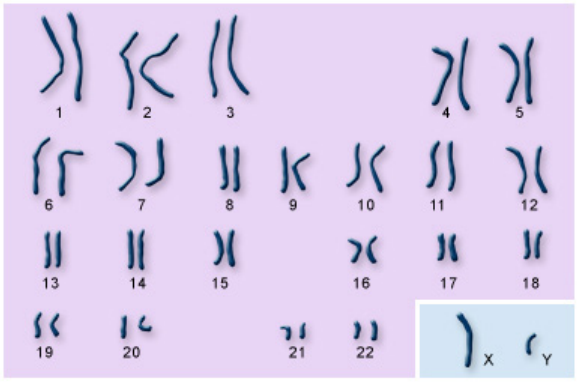
It is important to note that NSAIDs such as diflunisal may have serious side effects, which may be especially dangerous in patients who are already unwell with amyloidosis. These side effects include bleeding from the stomach and gut, worsening of kidney function and worsening of heart failure.

Diflunisal use for ATTR amyloidosis is an 'off-label' indication, and only amyloidosis specialists should prescribe it.

Appendix 1

Basic genetics - understanding inheritance

The human body is made up of millions of tiny cells, each of which contains identical copies of the genes which we inherit from our parents. These genes function like an instruction manual, or a recipe book, for the cells to construct the proteins and other substances which make up the body. Human cells each contain about 25,000 different genes.



Each cell contains two copies of each gene, one from each of our parents. Within each cell, the genes are arranged into forty six long strings, called chromosomes. Twenty three chromosomes come from the father and twenty three from the mother. Complicated interactions between the two copies of each gene determine how the body is composed, inside and out. External traits, like hair colour, eye colour and height and internal traits like blood group are all a consequence of which genes we inherit from our parents. The sex chromosomes determine whether a person is a man or a woman. Women have two X chromosomes and men have one X and one Y chromosome in every cell of their bodies. The illustration above shows the chromosomes from the cell of a man.

When a gene is located within one of the sex chromosomes, the way in which it is inherited is called 'sex-linked'. Diseases that result from a mutation (abnormality) in a gene within a sex chromosome may be passed from parent to child by 'sex-linked' inheritance.

All the other 44 chromosomes apart from the X and Y chromosomes are referred to as 'autosomes'. Diseases that result from mutations in genes within the autosomes may be passed on from parent to child by 'autosomal dominant' inheritance or by 'autosomal recessive' inheritance.

Hereditary ATTR Val122Ile amyloidosis is inherited by autosomal dominant inheritance, discussed below.

How do mutations cause amyloidosis?

The genes act like an instruction manual or a recipe for protein production inside every cell of the body. Sometimes an alteration or error may arise within a gene. This is called a mutation.

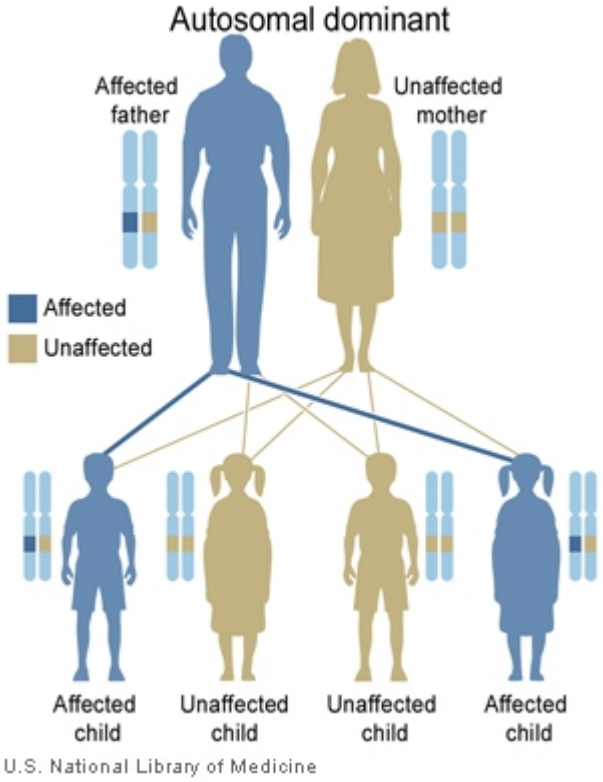
Anyone who has ever baked a cake knows that a single error in the recipe may have a number of different effects on the final product. It may lead to complete disaster, for example if you put in salt instead of sugar, or forgot the baking powder. Alternatively, there may be little effect on the final product, for example if you used margarine instead of butter.

Similarly, a mutation in a gene may have a number of different effects. Some mutations have minimal effects or no effects either on the proteins produced or on the person's health. Other mutations may lead to abnormal protein production, causing a wide variety of diseases.

The mutated genes that cause hereditary systemic amyloidosis have important effects on the abnormal so called 'variant' proteins whose production they determine. The differences in structure between the normal and the amyloidogenic variant proteins are usually extremely small but nonetheless they have very important effects on the behaviour of the variant proteins. In all cases the variants have an increased tendency to clump together and form amyloid fibrils. Thus even a very small change in a gene can lead to serious disease.

Autosomal dominant inheritance

Complex rules control the inheritance of many characteristics, and of many diseases. Hereditary systemic amyloidosis syndromes are inherited in a fashion known as autosomal dominant. This means that the presence of just one copy of a mutated gene can cause the disease.



Autosomal dominant inheritance is illustrated in the figure. The yellow box represents an unaffected gene and the blue box represents an affected gene, carrying a mutation. The two columns next to each person in the figure represent two identical chromosomes (strings of genes) each person inherits, one from each parent.

In the figure, the father has one copy of a mutated gene, and one copy of a normal gene. He therefore suffers from the disease, since, as mentioned above, in this type of disorder, just one copy of a mutated gene is enough to cause disease. The mother, like the vast majority of the population, has two normal genes and is healthy. Each child gets one copy of each gene from their mother, and one from their father.

When there is simple autosomal dominant inheritance of a condition:

- Each child has a 50% (1 in 2) chance of receiving a mutated copy of the gene from the affected parent.
- Each child has a 50% (1 in 2) chance of receiving a normal copy of the gene from the affected parent.
- Half of the children have a mutated gene and develop the disease. They can then pass the mutated gene and the disease on to half of their children.
- Half of the children have two copies of the normal gene. They are healthy and they cannot pass the disease on to their children.
- Brothers and sisters of people with the disease have a 50% (1 in 2) chance of having the mutated gene and developing disease.
- Men and women have equal chances of receiving the mutated gene and of developing disease.

Incomplete penetrance

For many of the diseases that are passed on by autosomal dominant inheritance, all people with a mutation in the gene develop disease. However, for variant ATTR Val122Ile amyloid cardiomyopathy this is not the case. An additional genetic principle called incomplete penetrance operates, making the situation more complicated.

Incomplete penetrance means that:

- Some people who inherit a mutated copy of the gene do not develop any amyloid at all.
- Some people who inherit a mutated copy of the gene develop only a small amount of amyloid and do not suffer from any clinical problems.
- Some patients diagnosed with hereditary ATTR Val122Ile amyloidosis have no family history of the disease.

Information about a particular family is important for evaluation of the likelihood that a young healthy person with a mutation will develop disease.

Appendix 2

Tests that help to diagnose amyloid in the heart

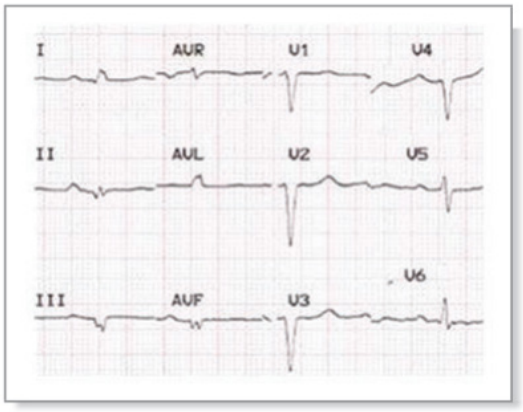
Tests that can help doctors to detect amyloid deposits in the heart include:

Blood tests: cardiac biomarkers

When heart muscle is damaged by amyloid deposits, blood tests may detect raised levels of NT-proBNP (*N*-terminal fragment of brain natriuretic peptide) and high sensitivity troponin. These are known as 'cardiac biomarkers'. Patients with ATTR amyloid in the heart may have cardiac biomarker levels that are higher than normal.

ECG

The ECG test is a safe, rapid, painless method whereby the electrical impulses controlling the heart's contractions can be detected, measured and represented as a tracing on graph paper.



Typical ECG of a patient with cardiac amyloidosis
(Image from Banypersad S et al, J Am Heart Assoc, 2012)

Some ECG appearances are suggestive of amyloidosis in the heart.

Echocardiogram

Echocardiography is an ultrasound test. It is safe and painless and does not involve any exposure to radiation. This test is routinely performed when patients visit the NAC. When amyloidosis in the heart is advanced, it is usually clearly visible on the echocardiogram. However, the findings may be less clear at the early stages of amyloid heart disease.

Cardiac magnetic resonance (CMR)

CMR is a method whereby a magnetic field and radio waves are used to obtain detailed pictures of the heart. It is safe and painless, and does not involve any exposure to radiation.

CMR provides very detailed information on the structure of the heart. CMR has been available at the NAC since our new, state of the art CMR unit opened in early 2016. In some patients, echocardiography may not be able to determine whether heart wall thickening is due to amyloidosis or to another cause such as high blood pressure (hypertension). In such patients, CMR imaging can help to distinguish between these different causes of heart wall thickening.

When doctors analyse CMR scans, they can often clearly visualise the amyloid deposits within the heart walls, between the heart cells. It is expected that in the future it may be possible to use CMR to accurately measure the quantity of amyloid within the heart wall. Such measurements could then be repeated to follow the build-up of amyloid deposits and their regression with treatment.

Radionuclide imaging (DPD scan)

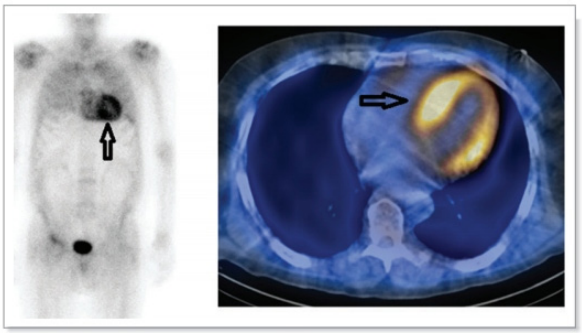
SAP scanning does not provide information about amyloid in the heart.

A different radioactive marker that does home in on amyloid in the heart is called 99mTc-DPD, or just DPD. DPD scans are routinely undertaken at the NAC in patients with suspected ATTR amyloid in the heart.

DPD scans are most useful when the deposits are of TTR type, and the amount of DPD taken up by the heart correlates with the amount of ATTR amyloid present. Asymptomatic, 'early stage' ATTR amyloid deposits in the heart can sometimes be detected by DPD scan, when other heart tests appear normal.

The DPD scan is obtained in 3D by a method called single photon emission computerised tomography (SPECT), and is combined with a standard CT scan. The doctors can then assess both the structure of the heart and the extent of amyloid deposits.

DPD scanning and SPECT are safe tests. There is only slight exposure to radiation from the tracer and the CT scan.



Left: DPD scan. *Right*: fused CT/SPECT scan.
Both scans show TTR cardiac amyloidosis.
The arrows point at the amyloid deposits in the heart.
(Image from Banypersad S et al, J Am Heart Assoc, 2012)

Biopsy

Heart biopsy

Heart muscle biopsy involves removal of a small sample of heart muscle which is then examined under the microscope to detect amyloid deposits. It is the 'gold standard' for diagnosing amyloid deposits in the heart. This means that it is the best available test, against which all other tests are measured. This test is performed by cardiologists or cardiothoracic surgeons.

Patients are usually sedated during the biopsy, which usually takes less than an hour. During the procedure, the doctor numbs a small area of skin in the neck, then inserts a long, narrow tube called a catheter into a blood vessel and threads it through to the heart. X-rays are performed to ensure that the catheter tip is positioned next to the heart wall. Then a grasping device at the end of the catheter is used to remove a tiny sample of heart tissue. The catheter is then withdrawn, bringing the heart tissue with it. The tissue is sent to the laboratory for analysis. The procedure is usually safe and painless, and does not require admission to hospital.

Abdominal fat biopsy

Frequently, a small piece of fat tissue is taken from the skin of the stomach area (abdominal fat biopsy). The procedure is simple, quick, safe and relatively painless.

It proceeds as follows:

1. A small area of the skin in the stomach area is numbed with local anaesthetic.
2. A needle is inserted into the numb area to take out some fat cells from underneath the skin.
3. The fat cells are preserved and sent to the laboratory for analysis.

Examination of biopsy tissue

In the laboratory a special staining technique using a dye called 'Congo red' is used to identify amyloid deposits in the tissue sample. Then further stains are used to determine the protein composition of the amyloid fibrils. If amyloid fibrils composed of TTR are present along with the Val122Ile mutation, then ATTR Val122Ile amyloidosis is diagnosed.

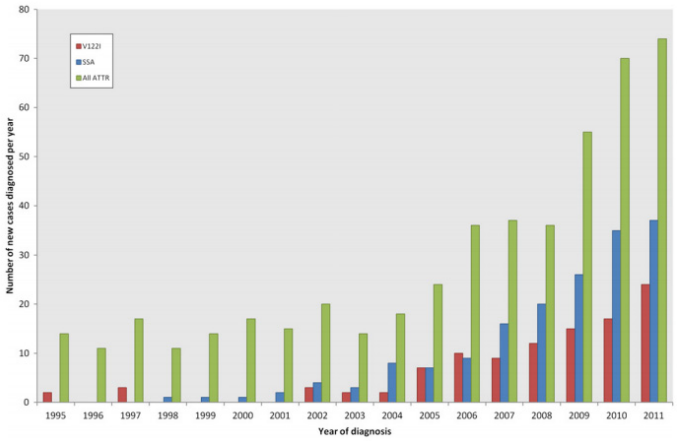


Chart showing how ATTR amyloidosis has been diagnosed far more frequently at the NAC in recent years than it was in the past. The red boxes represent the number of patients with Val122Ile amyloidosis. The blue boxes represent the number of patients with wild-type ATTR amyloidosis, a type of ATTR amyloidosis that is not inherited. The green boxes represent the total number of patients with ATTR amyloidosis.

Funded by a bequest
from
Laura Lock

The Amyloidosis Awareness Programme of the NAC is generously supported by:
Akcea Therapeutics ◆ Alnylam Pharmaceuticals ◆ The Tufton Charitable Trust