Hereditary ATTR Amyloidosis

**Introduction**

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 safely going away. About 30 different proteins are known to form amyloid deposits in humans. These amyloid forming (‘amyloidogenic’) 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 blood protein called transthyretin (TTR) is the amyloid precursor protein that forms the amyloid deposits. ATTR amyloidosis can be either hereditary or acquired (non-hereditary, known as wild-type ATTR amyloidosis).

**Transthyretin (TTR)**

Transthyretin (TTR) is a normal blood protein, 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’. All the TTR in the blood is produced by the liver. TTR in the brain and the eye is made separately by a structure called the choroid plexus, which is located within the brain and produces the cerebrospinal fluid that bathes the brain and spinal cord.

People who are born with inherited mutations (alterations) in the TTR gene produce abnormal, (‘variant’) TTR throughout their lives. The variant TTR protein is amyloidogenic (amyloid forming). Over the course of several decades, usually after the age of 30 and often much later, people with inherited TTR gene mutations may develop symptoms of disease caused by the build-up of amyloid deposits.

More than 100 different mutations in the TTR gene have been observed. Many of these can cause hereditary ATTR amyloidosis in which amyloid deposits containing variant TTR affect the nerves and/or the heart, and sometimes also the kidneys and eyes. Some people without any mutations in the TTR gene develop wild-type ATTR amyloidosis with advancing age in which amyloid deposits containing normal wild type TTR mainly affect the heart and very often preceding carpal tunnel syndrome.
Hereditary ATTR amyloidosis is the most commonly recognised form of hereditary systemic amyloidosis worldwide. Hereditary ATTR amyloidosis 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.

**How common is hereditary ATTR amyloidosis?**

Hereditary ATTR amyloidosis is the most commonly recognised form of hereditary systemic amyloidosis (‘systemic’ describing amyloid deposits that are not restricted to one organ or type of tissue). In overall terms it is nevertheless a very rare disease.

We do not know exactly how many people around the world have hereditary ATTR amyloidosis. More than 130 amyloid-forming variants (mutations) of TTR have been observed and different mutations may cause different disease manifestations. The commonest type, associated with a particular mutation of the TTR gene (called Val30Met or V30M), is believed to affect about 10,000 people worldwide.

Despite being extremely rare in most parts of the world, hereditary ATTR amyloidosis is common in some very localised parts of Portugal, Sweden and Japan. It may also be common, but under-diagnosed in several other regions including Spain, France, Brazil, Argentina, Cyprus and Bulgaria.

**Who gets hereditary ATTR amyloidosis?**

Hereditary ATTR amyloidosis runs in families. It may be inherited either from the patient’s mother or from the patient’s father. People with hereditary ATTR amyloidosis are born with a mutation (alteration) in the TTR gene that causes the condition, although they usually only begin to experience symptoms in middle age. People with a mutation in the TTR gene may pass the condition on to their children. Some people with TTR gene mutations may never experience symptoms at all.

Hereditary ATTR amyloidosis was first described in 1952 in a number of families in Portugal. Since then it has been diagnosed in families from Japan, Sweden and County Donegal in North-West Ireland. Worldwide, most people with hereditary ATTR amyloidosis have ancestors originating in one of these regions. In the UK, hereditary ATTR amyloidosis is most common in people with Irish ancestry. It is estimated that 1% of the people in County Donegal have a TTR gene mutation. It may also be common, but under-diagnosed in several other regions including Spain, France, Brazil, Argentina, Cyprus and Bulgaria.

**What causes hereditary ATTR amyloidosis?**

The symptoms of hereditary ATTR amyloidosis are caused by ATTR amyloid deposits inside body tissues, mainly in the nerves, heart, kidneys and eyes. People with mutations (alterations) in the TTR gene produce abnormal, variant TTR protein, throughout their lives. The variant TTR is amyloidogenic. This means that it has a tendency to misfold and form ATTR amyloid deposits which build up slowly and damage the affected organs.

**When do hereditary ATTR amyloidosis symptoms appear?**

Symptoms of hereditary ATTR amyloidosis may appear as early as age 20, or as late as age 80. Age of onset is usually quite consistent within families.

The TTR gene mutation that most commonly causes hereditary ATTR amyloidosis in the UK results in production of the Thr60Ala (T60A) variant TTR protein. Thr60Ala-associated hereditary ATTR amyloidosis is often seen in people with Irish ancestry. Symptoms tend to start relatively late, between ages 45 to 78, most often after age 60.

The TTR gene mutation that most commonly causes hereditary ATTR amyloidosis worldwide results in production of the Val30Met (V30M) variant TTR protein. Most patients with the Val30Met-associated hereditary ATTR amyloidosis first experience symptoms in their 30s.
Symptoms of hereditary ATTR amyloidosis

Symptoms of hereditary ATTR amyloidosis may include:

- **Peripheral neuropathy**: limb weakness and pain, loss of sensation, usually starting in the feet.
- **Autonomic neuropathy**: disturbances of bowel, bladder and blood pressure and sexual dysfunction.
- **Heart failure**: symptoms result from stiffening of the heart due to amyloid deposits (restrictive cardiomyopathy). They may include:
  - shortness of breath, sometimes just after mild exertion
  - palpitations and abnormal heart rhythms, most frequently atrial fibrillation/flutter
  - ankle swelling (oedema)
  - fatigue
  - dizziness or fainting, which may occur after exertion, or after eating
  - angina (chest pain)
  - weight loss
  - nausea
  - disrupted sleep.
- **Disease due to amyloid deposits in the**:
  - eye
  - kidneys
  - thyroid gland
  - adrenal glands
  - blood vessels.

Different types of hereditary ATTR amyloidosis

More than 100 different mutations in the TTR gene have been reported. Different mutations may cause a wide variety of different clinical symptoms. But there is often little correlation between the underlying mutation and the clinical disease features in hereditary ATTR amyloidosis. Within families the pattern may be reasonably consistent for:

- age of onset
- rate of disease progression
- involvement of different body systems.

In some families all affected members have just neuropathy, while in other families all affected members have both neuropathy and cardiac disease. In a few cases certain mutations have been associated with either particularly severe disease or with relatively limited disease.

The most common TTR mutations which cause amyloid in the UK are the Thr60Ala (T60A), often seen in people with Irish ancestry, and the Val122Ile (V122I) mutation, found in people with African ancestry. People with the T60A mutation often start to experience symptoms between age 50-75, most often after age 60. The heart is almost always affected and most patients also have neuropathy. Symptoms of autonomic neuropathy such as erectile dysfunction (in males), diarrhoea and/or constipation, weight loss, and low blood pressure on standing are very common.

The V122I mutation has been found in 1 in 25 African Americans and is associated with late onset (over age 60) hereditary ATTR amyloidosis mainly affecting the heart, often also causing carpal tunnel syndrome and sometimes causing peripheral neuropathy. V122I-associated hereditary ATTR amyloidosis has only been recognised in recent years and usually affects people of African ancestry aged over 60. Although the disease is believed to be underdiagnosed, it is thought to have low penetrance, meaning that most people carrying this mutation do not ever develop disease.

The most common TTR mutation worldwide leads to production of the Val30Met (V30M) TTR protein variant. People with this mutation often start to experience symptoms in their 30s. Peripheral and autonomic neuropathy are the main symptoms and heart problems are rare. Curiously, most British patients with this mutation develop symptoms later in life and do have cardiac involvement.

People carrying a mutation in the TTR gene do not always develop disease. Some cases have been reported where people over age 60 have no disease despite having two copies (one inherited from each parent) of the TTR mutation which results in production of the Val30Met TTR protein variant. About 1 in 500 people in northern Portugal carry a Val30Met TTR mutation, and 80% of them develop disease. About 1 in 25 people in northern Sweden carry this same mutation but only 11% of them develop disease. The reason for this geographic variation is unclear.

Sometimes people diagnosed with hereditary ATTR amyloidosis are not aware of anyone else in the family with the condition. This may be because the mutation first arose in that person, or because other family members were not diagnosed, or did not develop the disease despite having the mutation.
In a recent NAC study of 60 patients with hereditary ATTR amyloidosis Thr60Ala, less than 40% had a definite family history of amyloidosis.

**Diagnosis**

Doctors may suspect hereditary ATTR amyloidosis on the basis of patients’ symptoms, findings on physical examination and sometimes family history. The diagnosis can be confirmed by tests including:

- Tissue biopsy
- Genetic testing
- Imaging studies

All patients in the UK with suspected or diagnosed ATTR amyloidosis should be referred to the NAC.

The ‘gold standard’ test (the best available method) for diagnosing hereditary ATTR amyloidosis is a combination of detection of ATTR amyloid on heart, gastrointestinal tract or nerve biopsy, together with genetic testing showing a TTR gene mutation.

**Tissue biopsy**

In this procedure, a small sample of tissue is removed from the body with a needle and examined in the laboratory. The tissue sample is often obtained from under the skin in the stomach area (abdominal fat biopsy). The procedure is simple, quick, safe and relatively painless. This 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.

Alternatively, when ATTR amyloidosis is suspected, the biopsy sample may be taken from the heart, a nerve in the arm or leg, or the bowel, depending on the clinical features of the patient. Since hospitals usually preserve biopsy tissue, it is recommended that material suspected of containing amyloid is sent to the NAC for review and further staining.

In the laboratory, the tissue sample is examined using specific techniques to identify amyloid fibrils, including staining of the tissue with a dye called Congo red. Positive Congo red staining can identify amyloid. Then immunohistochemistry and proteomics testing can identify TTR fibrils and determine which type of ATTR amyloidosis is present, by distinguishing between variant ATTR in hereditary ATTR amyloidosis and wild-type ATTR in senile systemic amyloidosis.

**Genetic testing**

Genetic testing involves examination of the DNA from the patient’s cells. These tests are usually performed on a blood sample.

These techniques can identify amyloidogenic mutations (abnormalities) in the TTR gene. There are over 100 known mutations in the TTR gene, and different mutations lead to different types of disease. The precise mutation identified may provide information about the likely clinical course. For example, amyloid deposits usually involve just the nerves and not the heart in younger patients with the Val30Met mutation and, in contrast, the Val122Ile mutation usually leads to amyloid deposits predominantly in the heart, and only occasionally affects the nerves. The Thr60Ala mutation, typically found in people with Irish heritage, typically leads to disease affecting the nerves and the heart.

In wild-type ATTR amyloidosis (senile systemic amyloidosis), amyloid fibril analysis detects wild-type ATTR protein and genetic testing will not detect any abnormalities in the TTR gene.

Genetic testing in a healthy person without symptoms can provide information on whether the mutation is present, but cannot predict whether the person will go on to develop amyloidosis.

People who are at risk of having inherited a potentially amyloid-causing mutation may choose to undergo genetic testing after counselling with a physician at the NAC. For enquiries please contact Professor Julian Gillmore at julian.gillmore@nhs.net.

**Imaging studies of the heart**

ECG, echocardiogram, DPD scanning and cardiac magnetic resonance (CMR) scanning all provide helpful information.

DPD scanning and CMR are very sensitive for detecting ATTR amyloid deposits in the heart. A DPD scan, in combination with a series of blood and urine tests, are sufficient to diagnose cardiac ATTR amyloidosis without a need for demonstration of amyloid within a tissue (heart, fat or nerve) biopsy in the majority of patients. SAP scans cannot identify amyloid deposits in the heart or nerves.
Treatment

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

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

When amyloid precursor protein supply is control:

1. Existing amyloid deposits often regress (become smaller).
2. New amyloid deposits stop appearing.
3. Organ function is often preserved and may also recover.

Reducing variant TTR supply

Genetic-based therapies

- Small interfering RNA
- Antisense oligonucleotides

These two approaches aim to ‘switch off’ the gene for TTR in the liver cells, so that TTR (both mutant and wild-type) 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 and has been shown to reverse neuropathy in a majority of patients who participated in a phase 3 study called the APOLLO trial. This trial 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 fared 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 function. Once this was observed, all patients receiving inotersen were monitored with regular blood tests.

Since 2019 patisiran and inotersen have been approved by the regulatory authorities, including NICE and NHS England, for treating neuropathy caused by hereditary ATTR amyloidosis.

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 formally assessed and patients with wild-type ATTR amyloidosis were not included in the drug trials.

Tafamidis

Tafamidis was developed as a specific drug for ATTR amyloidosis. It is bound by TTR in the blood. This binding is thought to stabilise the TTR and makes it less amyloidogenic. The pivotal trial of tafamidis included 441 patients, some of whom had wild-type ATTR amyloidosis, while others 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 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). These drugs are in common use as pain killers for conditions such as arthritis. Diflunisal is bound by TTR in the blood. This binding is presumed to make the TTR less amyloidogenic. Trials are currently underway to assess the effect of diflunisal on the progression of neuropathy and cardiomyopathy in patients
with hereditary ATTR amyloidosis. Results from the first study report were encouraging, but the numbers of patients involved was small and the extent of benefit was modest. The trial involved 130 patients with hereditary ATTR amyloidosis affecting the nerves, 64 of whom received diflunisal for two 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
- worsening of heart failure

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

The NAC can now offer patients with ATTR amyloidosis, subject to various eligibility criteria demanded by the pharmaceutical companies, various opportunities for treatment with the new drugs or for participation in clinical trials.

Liver transplantation

All the TTR in the blood, which forms the amyloid deposits everywhere except in the eye and the blood vessels around the brain, is made in the liver. In the past, liver transplantation was a treatment option for some patients with hereditary ATTR amyloidosis, although almost exclusively younger patients with the Val30Met mutation. Since the advent of the new drugs, liver transplantation is rarely recommended in the UK.

Heart transplantation

For hereditary ATTR amyloidosis, a combined heart and liver transplant has been performed in a few dozen cases around the world. This operation is only an option for a very small minority of patients, and it carries significant risks.

Supporting amyloidotic organ function

In all types of amyloidosis it is important that treatment should support the function of organs containing amyloid.

In ATTR amyloidosis this may include:

**Heart disease treatment**

ATTR amyloid deposits in the heart cause the heart to stiffen which can lead to symptoms of heart failure. Patients can benefit from supportive treatment measures for heart failure. However many standard medications used for heart failure can sometimes worsen symptoms. Careful attention to fluid balance is important.

**Fluid balance**

The most important principle of treatment for cardiac amyloidosis is strict fluid balance control. Specialist heart failure nurse involvement may help patients to achieve this. Many patients with ATTR cardiac amyloidosis should limit their fluid intake. This advice is extremely important, but is often overlooked.

When there is cardiac amyloidosis, the heart may be too stiff to pump the blood efficiently around the body. This can 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.

Fluid excess can be avoided by careful attention to the three Ds:

1. **Diet**
2. **Diuretics**
3. **Daily weights**

1. **Diet:**

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

Salt intake should be limited. This includes attention not just to salt deliberately added to the food during cooking or at the table but also to ready prepared foods with high salt content such as processed foods, crisps, bacon, canned meats, sausages, canned soups and smoked fish. Apart from that, a balanced, healthy diet is always advisable. It can be very helpful to meet with a dietician for precise and personalised dietary advice.
2. Diuretics:
Doctors will often prescribe diuretics (water tablets) which increase the amount of urine produced and help the body to lose excess salt and water in the urine. This can help to reduce ankle swelling and breathlessness. Diuretics prescribed may include furosemide and spironolactone. Taking these drugs is not a substitute for avoidance of excessive dietary salt and water.

Patients should follow their doctor’s advice carefully regarding the dose of diuretic and the time of day when the tablet should be taken.

3. Daily weights:
Some patients benefit from recording their weight regularly, usually daily or weekly. It is important that weight should be measured consistently - using the same scales, at the same time of day. This is usually best done first thing in the morning after passing urine, just wearing underclothes. Several litres of fluid can accumulate in the body without it being very noticeable. An increase in weight can be an early sign of fluid overload. The doctor or nurse can then recommend appropriate measures such as increased diuretic dose, before the patient even feels unwell because of the fluid overload.

Neuropathy

Treatment of peripheral neuropathy symptoms
Medications that may help to alleviate neuropathic pain include gabapentin, pregabalin and duloxetine. Medical staff can give advice regarding appropriate foot care and footwear. This is important in order to prevent painless ulcers at pressure points and to protect areas of the foot that lack sensation.

Treatment of autonomic neuropathy symptoms
If there is orthostatic hypotension (drops in blood pressure and faintness on standing up from sitting or lying positions), elastic stockings may be recommended. Patients may benefit from instruction in how to change position carefully from lying to sitting, sitting to standing and standing to walking. Drug treatment with midodrine or fludrocortisone may also be helpful to maintain blood pressure and allow higher diuretic doses. Care should be taken to avoid dehydration if there is vomiting and diarrhoea. Intravenous fluids and anti-nausea drugs may be necessary, but it is important to avoid fluid overload if there is heart disease. There are drugs that can help to control diarrhoea and constipation, and others that can help to combat erectile dysfunction.

Questions or enquiries:

Specialist heart failure nurses are well qualified to guide you with day to day heart failure management. They can often be consulted by telephone, and can help both with heart failure symptoms and with anxiety and stress related to disease. GPs and hospital specialists can also be helpful.

The doctors and nurses at the National Amyloidosis Centre can be contacted between 08:00 – 17:30 Monday to Friday at +44 (0)20 7433 2738.
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 2 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.

Hereditary ATTR 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.

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 father.
- Each child has a 50% (1 in 2) chance of receiving a normal copy of the gene from the father.
- 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, in the case of the hereditary systemic amyloidosis, 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 systemic 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.

**Electrocardiogram (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. 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 adequate information about body organs that are moving. The heart is in constant motion, so SAP scanning is not of use for assessment of amyloid deposits 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 National Amyloidosis Centre 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 size of ATTR amyloid deposits. Asymptomatic ‘early stage’ ATTR amyloid deposits can be detected in the heart by DPD scans when other heart tests appear normal.

The DPD scan is made in 3D by a method called single photon emission computed 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 may be minor discomfort when the tracer is injected, but the tests are otherwise painless. There is only slight exposure to radiation from the tracer and the CT scan.

**Heart biopsy**
Heart muscle biopsy involves removal of a small sample of heart muscle which is then examined in 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.
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