

Patient Information

AA Amyloidosis



Introduction

AA amyloidosis was previously known as secondary amyloidosis, or reactive systemic amyloidosis. It occurs in patients who have suffered from prolonged, chronic inflammatory or infectious diseases for many years.

Most patients with AA amyloidosis have amyloid deposits in their kidneys which disrupt the kidney structure and cause problems with kidney function, most commonly protein in the urine. There are always amyloid deposits in the spleen, which may be enlarged. There may also be amyloid deposits in other parts of the body, which usually do not cause symptoms.

The fibrils found in the amyloid deposits are formed from a protein called amyloid A protein which is derived from a normal blood protein of unknown function, called serum amyloid A protein (SAA). SAA, which is produced in the liver, is found in very small quantities (less than 5 mg per litre) in the blood of all healthy people. But in response to many kinds of inflammation, infection or injury in the body, SAA production increases greatly, along with the production of another normal trace protein called C-reactive protein (CRP). Production of some other blood proteins also increases, although to a much smaller extent, as part of this normal reaction to disease, which is called the acute phase response. The concentration of SAA increases more dramatically than that of any other protein and may exceed 2,000 mg per litre.

What are the symptoms of AA amyloidosis?



The most common symptoms of AA amyloidosis are caused by amyloid deposits in the kidneys. At first the deposits cause abnormal kidney function, and over time may lead to end stage kidney failure. Symptoms of kidney disease may include:

- proteinuria (protein in the urine) – detected on urine testing
- swollen ankles (oedema)
- weight loss and poor appetite
- breathlessness
- nausea and vomiting
- itchy skin
- increased need to pass urine at early stages
- reduced quantity of urine at late stages

If end stage kidney failure develops (kidneys stop functioning altogether), dialysis or a kidney transplant is needed in order for the patient to survive.

AA amyloidosis usually causes an enlarged spleen, which often does not cause any symptoms, but may be detected on examination by a doctor, or on imaging tests.

Rarely:

- AA amyloid deposits in the thyroid gland may cause a goiter.
- AA amyloid deposits in the liver may cause an enlarged liver.
- There may be AA amyloid deposits in the gut and the adrenals. These usually do not cause any symptoms but in occasional rare patients they may have severe effects.
- AA amyloid in the heart very rarely has clinically significant effects.

If there is recovery from whatever disease or injury caused the acute phase response, then SAA values drop rapidly. However, if the disease persists, SAA concentrations remain high. In up to 10% of patients with sustained high concentrations of SAA persisting for several years, the SAA forms amyloid A fibrils in the tissues and these amyloid deposits cause AA amyloidosis.

The longer that inflammation persists, the greater the chances that AA amyloidosis will appear. The average duration of chronic inflammatory disease before AA amyloidosis appears is about 20 years. However, some patients develop AA amyloidosis after just a few years.

Before 1994, AA amyloidosis was the diagnosis in almost 1 in 3 of the patients seen at the NAC. Since then it has progressively become far less common in the UK and other developed countries. In 2012, only around 5% of patients newly diagnosed with amyloidosis at the NAC had AA amyloidosis. This is believed to be a result of the greatly improved therapies available for many of the associated inflammatory diseases, such as rheumatoid arthritis and Crohn's disease. These therapies can be very effective in lowering SAA production, thereby preventing development of amyloidosis.

Conditions that may lead to AA amyloidosis

Diseases in which chronic inflammation may eventually lead to AA amyloidosis are listed here:

Arthritis

Most commonly:

- Rheumatoid arthritis
- Juvenile (childhood) inflammatory arthritis

Up to 10% of patients with these conditions may develop AA amyloidosis if they suffer prolonged disease without control by modern treatments that suppress SAA production.

Less commonly:

- Ankylosing spondylitis
- Psoriasis and psoriatic arthropathy
- Reiter's syndrome
- Adult Still's disease
- Behçet's syndrome

Crohn's disease

Hereditary periodic fever syndromes

Familial Mediterranean fever (FMF)

Patients may develop AA amyloidosis if SAA levels are not controlled by long term colchicine treatment.

TNF receptor associated periodic syndrome (TRAPS)

Long term anakinra treatment may reduce the chances of development of AA amyloidosis.

Mevalonate kinase deficiency (MKD), also known as hyperimmunoglobulin D syndrome and periodic fever syndrome (HIDS)

Long term anakinra or etanercept treatment may reduce the chances of development of AA amyloidosis.

Cryopyrin-associated periodic syndrome (CAPS)

Patients may develop AA amyloidosis if SAA levels are not controlled by long term canakinumab treatment.

Deficiency of the IL-1 receptor antagonist (DIRA)

Long term anakinra treatment may reduce the chances of development of AA amyloidosis.

Pyogenic sterile arthritis, pyoderma gangrenosum and acne (PAPA) syndrome

Long term anakinra or etanercept treatment may reduce the chances of development of AA amyloidosis.

Chronic infections - may be local (limited to one organ) or systemic (throughout the body)

Most commonly:

- Bronchiectasis
- Chronic infections in intravenous drug users
- Chronic pyelonephritis (kidney infection) or infected pressure sores in paraplegic patients

Less commonly:

- Tuberculosis
- Leprosy
- Chronically infected burns
- Chronic leg ulcers
- Chronic osteomyelitis (infection inside the bone)
- Whipple's disease

Cancer

Most commonly:

- Hodgkin's disease
- Kidney cancer
- Castleman's disease (a rare lymph node tumour that secretes cytokines causing inflammation)

Less commonly:

- Cancer of the gut, lung, urogenital tract
- Basal cell carcinoma (BCC)
- Hairy cell leukaemia

Very rarely

- Some other connective tissue disorders
- People with no detectable underlying inflammatory disorder – sometimes these people have inherited periodic fever syndrome genes

Unknown cause (in around 6% of patients with AA amyloidosis, no underlying inflammatory disease is detected)

Is AA amyloidosis inherited?

AA amyloidosis itself is never inherited. However, the inflammatory diseases that are associated with AA amyloidosis do tend to run in families. The hereditary fever syndromes in particular have a very clear genetic basis.

Is it possible to predict who will get AA amyloidosis?

Some patients may be exposed to chronic inflammation and high SAA values for decades yet may never develop AA amyloidosis. Others develop AA amyloidosis after just a few years of chronic inflammation. For example, children with familial Mediterranean fever may develop rapidly progressive kidney failure due to AA amyloidosis, even before the FMF is diagnosed and colchicine treatment is established.

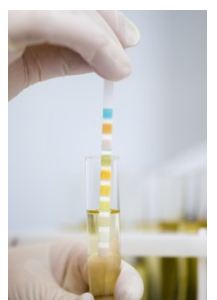
The reason for this is unclear. There is some evidence that genetic factors related to variations within the gene for SAA may play a part in determining the likelihood

that high concentrations of SAA will form amyloid deposits. It is not possible at present to predict which patients with chronic inflammation will develop AA amyloidosis if the inflammation is not treated successfully and which will not.

However, it is clear that successful treatment of inflammatory conditions, with suppression of SAA production, does prevent the development of AA amyloidosis. It is therefore very important that patients are always careful about taking all their pills.

Diagnosis of AA amyloidosis

Patients with AA amyloidosis usually come to medical attention because of abnormalities in kidney function. In over 90% of cases, proteinuria (protein in the urine) is the first sign. AA amyloid may be widely distributed in the body without causing other symptoms. There are always deposits in the spleen, which may be enlarged.



So doctors may suspect AA amyloidosis if a patient with a longstanding inflammatory condition develops symptoms of kidney disease, especially if there is also an enlarged spleen. Other signs of kidney disease in AA amyloidosis may include:

- Nephrotic syndrome:
 - large amounts of protein in the urine (> 3.5 g/day)
 - low albumin in the blood
 - peripheral oedema – swollen ankles.
- End stage kidney failure: the kidneys stop functioning altogether and the patient needs either dialysis or a kidney transplant in order to survive.
- Rarely:
 - haematuria (blood in the urine)
 - renal tubular defects
 - nephrogenic diabetes insipidus
 - renal calcification (calcium deposits in the kidneys).

The diagnosis of amyloidosis may be confirmed (or may be eliminated) by taking a biopsy from the kidney, and/or undergoing an SAP scan.

- Biopsy is a procedure where a small sample of tissue is obtained, processed and examined under the microscope to see whether amyloid deposits are present.
- SAP scanning shows the distribution and amount of amyloid in the organs throughout the body. SAP scanning has revolutionised understanding of the natural course of amyloidosis and its response to treatment.

Biopsies can show microscopic traces of amyloid in small tissue samples but cannot provide a whole body overview. SAP scanning is the only way to obtain a full



picture of the extent of disease. In AA amyloidosis, repeated serial SAP scanning can be very helpful in showing that amyloid deposits are regressing (shrinking) when the underlying inflammatory disease is effectively treated.

The image on the left shows a patient undergoing SAP scanning at the NAC.

Blood tests

In AA amyloidosis, blood tests may show that the kidneys are not functioning well.

The concentrations in the blood of proteins which are produced in increased amounts in response to inflammation, SAA (serum amyloid A protein) and CRP (C-reactive protein), are usually raised in AA amyloidosis. The aim of treatment of AA amyloidosis is to control the underlying inflammatory disease and thereby reduce SAA production and thus its concentration in the blood.

Doctors at the NAC recommend monthly monitoring of SAA concentration in the blood in order to guide treatment. When necessary, patients are provided with blood test bottles so their local doctors can draw blood monthly, and the patient can then send the samples to the NAC by post for laboratory testing.

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.

SAP scans in thousands of patients with various forms of amyloidosis have shown that 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.

A sink analogy

It may be helpful to envisage amyloid deposits blocking up the organs as somewhat similar to the everyday situation of a blocked sink.



Water running from the tap at full blast represents the uncontrolled production and large quantity of precursor proteins capable of forming amyloid fibrils. The small sink outlet represents the body's limited capacity to clear amyloid deposits away from the organs. If the tap is turned on fully so that the rate of running water far exceeds the drainage rate, water builds up in the basin despite some drainage. If the tap is turned down sufficiently, the water can drain away slowly.

In AA amyloidosis, if the rate of production of amyloid forming SAA due to underlying inflammatory disease can be reduced sufficiently, amyloid stops accumulating in the tissues. Amyloid deposits may even be cleared away faster than they are produced. Kidney function may then stop deteriorating and it often improves when the underlying inflammation is well controlled.

Goal of treatment

The goal of treatment of AA amyloidosis is to control the associated inflammatory disease, leading to a damping down of the acute phase response and reduced production of SAA.

When the SAA concentration is reduced, formation of new amyloid deposits is slowed down and often halted completely. There is frequently regression of existing deposits if the SAA value is maintained close to normal (less than 10 mg per litre). There is then a good chance of improvement in kidney function, overall health and length of survival.

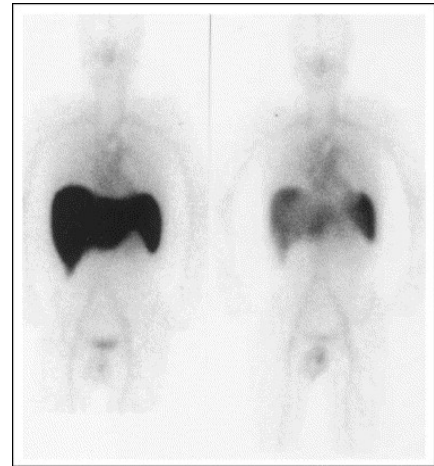
The precise treatment given depends on which chronic inflammatory disease is present.

In recent years the outlook for patients with AA amyloidosis has improved dramatically with the introduction of several new and effective drugs that control inflammation and lower SAA values in the common chronic inflammatory diseases associated with AA amyloidosis such as rheumatoid arthritis and Crohn's disease.

These drugs include new injectable, biological drugs for arthritis and Crohn's disease, such as:

- anti-TNF drugs such as
 - infliximab
 - etanercept
 - adalimumab
- anti-IL-1 drugs such as
 - anakinra
 - canakinumab

The following image shows whole body SAP scans with amyloid in the liver and spleen (dark black areas in left panel) and significant amyloid regression between the initial scan and follow-up two years later (right panel – black colour much fainter). These images were obtained from a man with rheumatoid arthritis complicated by AA amyloidosis whose amyloidosis entirely remitted (amyloid deposits shrank) following treatment with infliximab for the rheumatoid arthritis.



There are specific treatments for some inflammatory diseases which suppress the acute phase response and SAA production very effectively. This makes development of AA amyloidosis very unlikely **as long as patients are careful about taking their medicines as prescribed.**

These treatments include:

- lifelong colchicine for familial Mediterranean fever (FMF). Crucially, colchicine controls SAA production effectively, and thereby prevents amyloidosis, even if it does not completely relieve all the symptoms of FMF.
- anakinra for some other periodic fever syndromes, such as TRAPS, MKD and DIRA.
- canakinumab for CAPS.
- appropriate antibiotic drugs for tuberculosis.

Occasionally it may not be possible to identify an underlying inflammatory condition in patients with AA amyloidosis. These patients may improve with empirical treatment with anti-inflammatory drugs, guided by frequent SAA measurements.

Surgery

Surgical treatment may occasionally be helpful to patients with AA amyloidosis caused by Castleman's tumour (a rare cause of AA amyloidosis).

This lymph node tumour secretes substances called cytokines that cause inflammation and increase SAA production. Surgical excision of this tumour leads to regression of AA amyloid deposits.

How long does it take for kidney function to improve?

When inflammation is successfully controlled by effective anti-inflammatory therapy, and SAA values are kept low, ideally below 4 mg per litre, kidney function usually stabilises and often improves. This improvement occurs gradually and may take months to years.

The stabilisation or improvement of kidney function usually reflects stabilisation or regression (shrinkage) of the AA amyloid deposits in the kidneys.

If there is recurrence of inflammation and SAA concentrations rise, even after many years of good inflammation control, AA amyloid deposits can build up again quite fast, and kidney function can then worsen. It is therefore important for patients to continue to monitor monthly SAA values, even if inflammatory disease has been well controlled for years.

Monitoring during treatment

We usually recommend monthly measurement of the SAA concentration in the blood in order to determine whether treatment is controlling inflammation adequately.

Patients may sometimes be symptom free, despite on-going inflammation. SAA values rather than subjective symptoms should be used to guide treatment decisions. Patients visiting the NAC may be provided with a special kit for sending monthly blood samples in the post. NAC doctors can then recommend appropriate adjustment in treatment dosages, or changes in drug regimes based on the SAA results. SAA results may be sent directly to patients to encourage their understanding of their progress and involvement in their own management.



Continued monitoring of SAA is important even after therapy has led to adequate control of SAA production. There may be sudden resurgences of inflammation even after a relatively long period of stable disease and improved kidney function.

An SAP scintigraphy scan is usually recommended about once a year to quantify the amyloid deposits in the organs. Serial scans can show how effectively amyloid deposits are being cleared and give an indication of the level of inflammation that is acceptable in any particular patient.

Sometimes it is necessary to try various different treatments before SAA production is effectively controlled. Occasionally low dose chemotherapy drugs may be used to suppress inflammation when other drugs fail.

Treatment of kidney disease in AA amyloidosis

Kidney disease is often the most serious health problem for patients with AA amyloidosis. In some patients, kidney function improves once SAA values are lowered, even if amyloid deposits just stabilise but do not regress. All patients with AA amyloidosis affecting their kidney function should be seen regularly by a nephrologist who is expert in amyloidosis.

Important principles include:

- careful monitoring and maintenance of fluid balance
- regular testing of kidney function with blood and urine tests
- use of diuretics when required.

Abnormal kidney function due to AA amyloidosis may affect the ability of the kidneys to produce urine. This means that the body is unable to cope well with excess fluids. Patients with fluid overload may develop swelling in the legs (oedema) or difficulty breathing due to heart failure and build-up of fluid in the lungs.

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

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

1. **D**iet:

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 added to the food from the salt shaker, 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.



2. Diuretics:

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

Doctors will often prescribe diuretics (water tablets) which help the body to lose excess salt and water. Taking these drugs is not a substitute for avoidance of excessive dietary salt and water. Removal of excess body fluid reduces ankle swelling and breathlessness. Furosemide is usually prescribed first. Other diuretics such as spironolactone may be added later. Since diuretics increase the amount of urine produced, they should usually be taken in the morning sometimes with another dose at lunchtime.

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 excess. 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.

Dialysis and kidney transplantation

In patients who have already developed kidney failure before their AA amyloidosis was controlled, dialysis may become necessary. Kidney transplantation may be successful and it is rare for AA amyloid to significantly affect a transplanted kidney.

Outlook for patients with AA amyloidosis

If not effectively treated, AA amyloidosis leads inevitably to kidney failure, necessitating dialysis or kidney transplantation. But over the past 10 years the outlook for patients with AA amyloidosis has brightened considerably.



Most patients can be treated with drugs that suppress inflammation and lower SAA values. This slows down, halts or reverses the deposition of AA amyloid. Many patients survive with a good quality of life for decades after diagnosis of AA amyloidosis.

AA amyloidosis has also become far less common in developed countries such as the UK over the last 10 years. This is believed to be a consequence of the widespread use of the new powerful drugs that combat inflammation for diseases such as rheumatoid arthritis. When the inflammation is controlled by these drugs, patients are not exposed to prolonged high SAA concentrations. So amyloidosis develops far less frequently than it did in the past. In contrast, in developing countries where these drugs are not widely available, AA amyloidosis remains more common.

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