





Patient Information

Localised 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 misfold and aggregate (clump together), and then remain in the tissues instead of safely going away. The protein which misfolds and forms amyloid fibrils is known as a 'precursor protein.' About 30 different precursor proteins are known to form amyloid deposits in humans.

Amyloidosis is usually a systemic disease. This means that many body organs and systems may be affected. Amyloidosis may also be 'local' or 'localised' which means that just a single organ or part of the body is affected. About 12% of all newly diagnosed amyloidosis patients at the National Amyloidosis Centre have localised amyloidosis.

Different types of amyloidosis are named with an 'A' to signify amyloid and other letters to signify the precursor protein which forms the amyloid fibrils. Systemic amyloidosis may be AL amyloidosis (precursor protein: immunoglobulin Light chains), AA amyloidosis (precursor protein: serum amyloid A protein), ATTR amyloidosis (hereditary or non-hereditary; precursor protein: transthyretin (TTR)) or non-ATTR hereditary amyloidosis (several different precursor proteins in different hereditary amyloidosis syndromes).

A study of patients with localised amyloidosis Reassuring results

A recent study of all patients diagnosed with localised amyloidosis at the National Amyloidosis Centre between 1980 and 2011 confirmed the excellent outlook for this condition. During this period, 606 patients were diagnosed with localised amyloidosis (12% of all newly diagnosed amyloidosis patients). Most were aged between 48 and 68 years and equal numbers of men and women were affected. Symptoms had usually been present for around seven months before localised amyloidosis was diagnosed. In most of the cases where the type of amyloid was identified, it was AL type. Serum monoclonal protein (paraprotein) was detected in around 1 in 10 of these patients. This finding is generally characteristic either of systemic AL amyloidosis or of a benign condition called monoclonal gammopathy of uncertain significance (MGUS), which is not associated with disease and only requires medical follow up but no treatment.

The most reassuring result of this large study was that of all 606 patients only one progressed to development of systemic amyloidosis five years after localised amyloid was first detected in chest lymph nodes. None of the other patients developed systemic amyloidosis and no patients died from progressive amyloidosis.

National Amyloidosis Centre, UCL Division of Medicine, Royal Free Hospital, Rowland Hill Street, London NW3 2PF, UK 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)

Localised AL amyloidosis

Localised amyloidosis is usually of AL type and is a very different disease from systemic amyloidosis. Localised amyloidosis may require no treatment or may be completely curable, for example by surgical excision of the amyloid deposits. Localised amyloidosis almost never progresses to systemic amyloidosis.



Each normal antibody consists of four protein chains. The red chains in this illustration are called the 'light chains' and the grey chains are called the 'heavy chains'.

In AL amyloidosis there is overproduction of amyloidogenic (amyloid forming) proteins called light chains. The letter 'L' in the name AL amyloidosis stands for 'light chain.' Light chains are parts of antibodies, also known ลร immunoglobulins. They are produced by cells called plasma cells which normally are mostly

located in the bone marrow. In healthy people, different plasma cells produce many different types of antibodies, usually in order to fight disease-causing pathogens. In AL amyloidosis a single line, or clone, of identical abnormal plasma cells continuously produces a large quantity of identical amyloid-forming (amyloidogenic) light chains or light chain fragments. The light chains or light chain fragments form amyloid deposits in the tissues. In systemic AL amyloidosis, the abnormal plasma cells producing the amyloidogenic light chains are usually located in the bone marrow. The identical amyloidogenic antibodies or antibody fragments are secreted into the bloodstream and can be detected in blood tests (serum monoclonal protein or paraprotein) and sometimes also in urine tests. The AL amyloid deposits accumulate in several body organs.

In localised AL amyloidosis, local foci of abnormal plasma cells producing AL amyloid deposits limited to just one place may be present in the:

- skin
- upper airways and respiratory tract
- genital and urinary system
- eye (usually affecting the conjunctiva)
- lymph nodes (rare)
- gastrointestinal tract (rare)

Localised AL amyloidosis is not usually associated with detection of a serum monoclonal protein/paraprotein in blood tests.

should lt be noted that serum monoclonal protein/paraprotein may sometimes be detected in patients with myeloma or in a benign condition called 'monoclonal gammopathy of uncertain significance' (MGUS), which is not associated with disease and does not require any treatment. Around 3% of people aged over 50 and 5% of those aged over 70 have MGUS, so some people may just coincidentally have both localised AL amyloidosis and MGUS at the same time. It is important that full investigation is performed to definitely rule out systemic AL amyloidosis in these people.

See below for a more detailed discussion of localised amyloid in each of the sites listed above.

Investigations

Localised amyloid is diagnosed by biopsy of the affected In this procedure, a small tissue sample is tissue. obtained, processed and examined under the microscope. When systemic amyloidosis is present, biopsy samples may be obtained either from the affected organs, or from other, easily accessible sites, such as the fat under the skin of the abdomen, or the rectum. However, as localised amyloidosis only affects a single site, the biopsy specimen must be obtained from that site itself. This may be simple if the site affected is easily accessible, such as the skin, or more complex if the site is difficult to access, for example the lungs. Specialist assistance (for example bronchoscopic biopsy of lung lesions) may then be necessary in order to obtain biopsy specimens.

SAP scintigraphy scanning at the National Amyloidosis Centre identifies amyloid deposits in some body organs, notably the liver, kidneys and spleen. However, it is not so useful in identifying amyloid deposits in other sites, including those most frequently affected by localised amyloid.

When localised amyloid deposits are detected in a single site, doctors need to rule out systemic amyloidosis by assessing functions of all the vital organs (heart, liver, kidney and nerves). This assessment includes blood and urine tests to evaluate organ functions, bone marrow biopsy and further investigations to evaluate any disease symptoms. All patients seen at the National Amyloidosis Centre also undergo SAP scintigraphy scanning. This detects amyloid deposits in many body organs, but not in the heart. Tests such as ECG, echocardiography and cardiac MRI may be used to evaluate heart function and to assess the heart for amyloid deposits. If the SAP scan shows no amyloid deposits and if the other test results also do not show any evidence of amyloid, then localised amyloidosis can be diagnosed.

In addition, further tests and consultations with relevant specialists may be recommended to assess the extent of the localised amyloid deposits and to plan treatment strategies.

Management

Types of localised amyloidosis

Localised amyloid in the skin

Around 14% of patients diagnosed with localised amyloidosis at the National Amyloidosis Centre have amyloid deposits affecting the skin. Localised amyloidosis in the skin may be macular (flat lesions), papular (raised lesions under 5 mm in diameter sometimes known as lichen amyloidosis), or nodular (raised lesions over 5 mm in diameter). The condition may appear in adults of any age, most commonly in people aged around 60. It is equally common in men and women. Skin of the head and neck region is commonly affected and there may be several skin lesions in different locations. Lichen amyloidosis often affects the shins, thighs and forearms. In some patients, local friction from nylon brushes, towels and other rough materials may contribute to the production of macular and lichenoid lesions.

Localised amyloid deposits in the skin are most frequently of AL type. Other types of localised amyloid that may affect the skin include:

 Macular cutaneous amyloidosis: amyloid fibrils are derived from a skin protein called galactin. There is an itchy rash, with scaly, brownish lesions that may be flat or raised (macules or papules). It is most common in people with dark skin. Hereditary cutaneous amyloid: rare, with unknown fibril type, sometimes with an associated disease affecting many body systems.

Patients with localised amyloidosis affecting the skin should be treated by a dermatologist and surgical excision may be helpful in some cases.

Localised amyloid in the respiratory tract

Localised amyloid in the respiratory tract is usually of AL type. Amyloid in the larynx is more frequent in older people but occasionally affects young adults. This may cause hoarseness or a sensation of 'fullness' in the throat, choking and shortness of breath on exertion. This condition is usually quite benign but sometimes it may be progressive.

Tracheobronchial amyloid affects the airways below the throat and above the lungs. It is very rare, and usually affects people aged over 50. There may be shortness of breath and cough. They may cough up blood and there may be recurrent pneumonia.

The lung tissue itself is the most common site for localised respiratory amyloid deposits. The deposits usually appear as nodules on chest X-ray. The nodules may grow slowly and often there are few symptoms. Frequently the diagnosis is made after nodules are detected incidentally on a chest X-ray.

Occasionally, local amyloid deposits may be detected in enlarged lymph nodes within the chest. These often cause no symptoms and can only be detected by chest imaging, for example a chest X-ray or CT. They may be an incidental finding on chest X-ray.

Patients with localised amyloid in the respiratory tract should have CT scans of the chest, and should be seen by a respiratory specialist and sometimes an ear, nose and throat (ENT) specialist. Laryngoscopy and/or bronchoscopy are often necessary in order to obtain biopsy specimens and to evaluate the extent of the disease. Respiratory function tests may be recommended.

Treatment may not be required if the local amyloid deposits cause few or no symptoms. If there are

troublesome symptoms, then the local amyloid deposits may be removed, either by surgery of by laser therapy.

Localised amyloid in the genito-urinary tract

Localised amyloid deposits may be found in the bladder or genital tract. They are usually of AL type but occasionally may be of ATTR type. There may be no symptoms, or there may be irritation or burning on passing urine, or blood in the urine. When patients undergo urological investigation with cystoscopy, the amyloid deposits may at first be mistaken for tumours, before biopsy examination shows localised amyloid. These deposits can usually be treated by surgical removal (resection).

Many men aged 50 and over undergo prostate biopsy. This is usually performed to detect or rule out prostate cancer in men with difficulty urinating or high concentrations of prostate specific antigen (PSA) in blood tests. Local amyloid deposits in the prostate are often found incidentally in these biopsies. This type of amyloid becomes more common with increasing age and may occur in about 1 in 10 men aged over 50 and 1 in 5 men aged over 75. It is usually just a localised finding with no evidence of amyloid deposits elsewhere in the body. The precursor protein for this type of amyloid deposit is often a protein derived from semen, called semenogelin. In most cases there is no need for any further investigations or treatment. In addition, small granules called corpora amylacea are a normal finding in prostate biopsies from healthy men. These granules are believed to contain amyloid fibrils formed from several different proteins secreted by prostate gland cells. They may be seen in the prostate of men as young as age 20, and their frequency increases with increasing age. They are not known to cause any disease and are not related to systemic amyloidosis.

Localised amyloid in the eye

Local amyloid deposits may affect the cornea, the conjunctiva or the orbit of the eye. When the orbit is affected, the lesions may disrupt eye movements and the structure of the orbit. Amyloid deposits in the eye may be of AL type. Other, very rare types have been identified, with precursor proteins called lactoferrin and keratoepithelin. If these deposits are symptomatic, they may be treated with local excision.

Localised amyloid in the gastrointestinal tract

Localised amyloid deposits of AL type may, rarely, be found in the stomach, or the small or large intestine. Sometimes these do not cause symptoms and are detected incidentally when patients undergo routine gastroscopy (examination of the stomach with a flexible viewing instrument inserted via the mouth and oesophagus) or colonoscopy (examination of the inner lining of the large intestine with a flexible viewing instrument inserted into the rectum).

These localised amyloid deposits may cause symptoms such as bleeding from the gut, heartburn or constipation. Supportive care is usually recommended for these patients.

Localised amyloid in the lymph nodes

Localised amyloid deposits affecting the lymph nodes are very rare. They often cause no symptoms and require no specific treatment.

Localised amyloid in other sites

Small amyloid deposits of non-AL type are sometimes detected in the blood vessel walls, and in benign or malignant tumours of glandular tissue. Such deposits are usually detected incidentally when these tissues are biopsied for a reason unrelated to amyloidosis. They generally do not cause any disease and do not require treatment or follow up.



A graph showing diagnoses of new amyloidosis patients seen at the NAC each year from 2000-2012. Localised AL amyloidosis frequency (light blue) has remained steady over this time period.

Cerebral amyloid angiopathy

The most common form of localised amyloidosis is cerebral amyloid angiopathy (CAA). CAA is totally unrelated to all other forms of local and systemic amyloidosis and patients with this condition are treated by neurologists and stroke physicians, not by amyloidosis physicians.

The National Amyloidosis Centre does not offer a service for patients with CAA. However, there is a specialist clinic at University College Hospital, run by Dr David Werring, Consultant Neurologist, where patients with CAA can be assessed.

In CAA, amyloid fibrils composed of β -protein form A β amyloid deposits in the walls of the blood vessels in the brain. This type of amyloid deposit is also found within the brain substance in patients with Alzheimer's disease, although it remains unknown whether these amyloid deposits actually cause the disease. But in CAA the amyloid in the blood vessels of the brain is known to be a common cause of strokes (bleeds in the brain, known as intracerebral haemorrhages) and problems with memory or thinking (sometimes leading to dementia).

CAA affects elderly people, almost always aged over 60, and becomes more common with increasing age. It is estimated that CAA is present in the brain in 20-40% of

the elderly general population and in 50-60% of elderly people with dementia. Alzheimer's disease also becomes more common as people age, so elderly people may have both Alzheimer's and CAA. Apart from increasing age, and a gene called apolipoprotein E, there are no known risk factors for CAA.

Neurologists and stroke physicians can diagnose CAA on the basis of clinical data combined with information from blood-sensitive brain imaging scans, looking for areas of bleeding near the surface of the brain.



There are no specific drugs available at present for CAA, but drug pressure lowering with antihypertensive drugs in patients who have had a CAA related stroke reduces the risk of future stroke. There are also a number of new drugs in various stages of development, and an active research programme.

For more information on CAA, see:

http://jnnp.bmj.com/content/83/2/124.full http://www.ucl.ac.uk/ion/departments/repair/themes/stroke http://internationalcaaassociation.org/ http://www.angiopathy.org/index.html

Appendix

Some of the tests mentioned in this information sheet are explained below:

ECG (electrocardiogram)

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. All patients with suspected amyloidosis should have an ECG. Most patients referred to the NAC have already had an ECG. We also perform this test if required. The findings can be helpful in making the diagnosis, as some ECG appearances are suggestive of amyloidosis in the heart.

Localised amyloidosis does not affect the heart. The ECG should be normal in patients with localised amyloidosis, unless there is another, unrelated heart condition.

Echocardiogram

Echocardiography is an ultrasound test. In this type of test reflections of sound waves are used to build up a detailed picture of organs inside the body. It is safe and painless and does not involve any exposure to radiation. All patients with suspected amyloidosis should have an echocardiogram. This test is routinely performed when patients visit the NAC.

The ultrasound technician uses gel to improve skin contact on the chest with a piece of equipment called a transducer. The transducer aims sound waves in the direction of the heart and detects the waves that reflect (echo) back. The sound waves cannot be heard as they are high frequency, outside the audible range for our ears.

The ultrasound machine detects the waves echoing back and converts them into a detailed picture of the heart, which the technician views on a screen like a television screen. Doctors who know how to interpret these pictures can obtain a wide variety of detailed information about the structure and functioning of the heart.

Localised amyloidosis does not affect the heart. The echocardiogram should be normal in patients with localised amyloidosis, unless there is another, unrelated heart condition.

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 has been available at the NAC since our new, state of the art CMR unit opened in early 2016. CMR provides very detailed information on the structure of the heart. 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.

Localised amyloidosis does not affect the heart. The CMR scan should be normal in patients with localised amyloidosis, unless there is another, unrelated heart condition.

Laryngoscopy

Laryngoscopy is a method of viewing the inside of the larynx (voice box) and the throat by inserting a thin tube with a camera and bright light on the end either into the nose or into the mouth. This specialist test is not available at the NAC, and we refer patients to an ENT surgeon if it is necessary. Laryngoscopy via the nose is not usually painful, but it may be uncomfortable and may cause a sensation of wanting to be sick (gag reflex). Discomfort and the gag reflex can be reduced by application of local anaesthetic spray to the nose and throat before the procedure. Laryngoscopy via the mouth is performed under general anaesthetic.

If doctors suspect localised amyloidosis affecting the upper respiratory tract (larynx and throat), laryngoscopy may be necessary in order to directly view the lesion and to assess its progress. A tissue biopsy can be taken during the laryngoscopy procedure and examined in the laboratory in order to confirm or rule out localised amyloidosis.

Bronchoscopy

Bronchoscopy is a method of viewing the trachea (windpipe) and the bronchi (branches of the airways inside the lungs). A long thin flexible tube with a bright light on the end is inserted through the nose and down to the lungs. This test is performed under general anaesthetic. It is not available at the NAC and we refer patients to a respiratory specialist if it is necessary.

If doctors suspect localised amyloidosis affecting the lower respiratory tract (lungs), bronchoscopy may be necessary in order to directly view the lesion and to assess its progress. A tissue biopsy can be taken during the bronchoscopy procedure and examined in the laboratory in order to confirm or rule out localised 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