AMYLOIDOSIS **DIAGNOSIS PATHWAY**

Amyloidosis is a group of rare, serious conditions caused by a build-up of an abnormal protein called amyloid in organs and tissues throughout the body. The build-up of amyloid proteins (deposits) can make it difficult for the organs and tissues to work properly.



Without treatment, this can lead to organ failure. Early diagnosis of amyloidosis is essential to minimise organ damage and improve prognosis.

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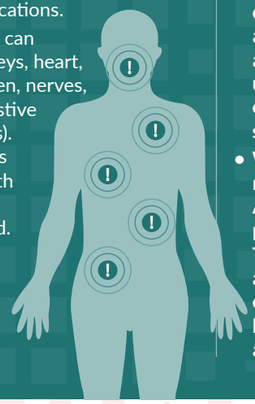
TYPES OF AMYLOIDOSIS

Whilst there are many forms of amyloidosis, the main three types are:

1 AL amyloidosis (light chain amyloidosis)

is the most common form, occurring when abnormal plasma cells in the bone marrow produce misfolded light chain proteins. These enter the blood stream and form amyloid deposits in the tissues and organs causing complications.

AL amyloidosis can affect the kidneys, heart, skin, liver, spleen, nerves, tongue or digestive system (bowels). 60% of patients will present with 2 or more organs involved.



2 ATTR amyloidosis

is caused by amyloid deposits from abnormal versions of a protein called transthyretin (TTR).

There are two types:

- **ATTRv (variant). Hereditary (familial) ATTR amyloidosis where people have an inherited mutation of the TTR gene and produce abnormal TTR proteins, which form amyloid deposits. These deposits usually affect the nerves and / or heart, although the digestive system and kidneys can be affected.**
- **Wild-type ATTR amyloidosis is non-hereditary. It is like hereditary ATTR, except the deposited TTR protein is the normal, non-mutated TTR protein. It most commonly affects the heart and can cause carpel tunnel syndrome (this may be an early symptom). This mostly affects people over the age of 60.**

3 AA amyloidosis

is very rare and occurs as a reaction to another illness, e.g., chronic inflammatory disease (such as Crohn's disease and rheumatoid arthritis), chronic or recurrent infections (such as tuberculosis) and some types of cancer (such as Hodgkin's Lymphoma).

In response to the infection or inflammation, the body produces Serum Amyloid A (SAA) protein at high levels. Where this reaction is ongoing, the SAA can form amyloid A fibrils and deposit in tissues.

The organs most commonly affected are the kidneys. Complications can occur for some patients in the liver, spleen (which may be enlarged), thyroid, digestive tract, or heart. Heart involvement is very rare.

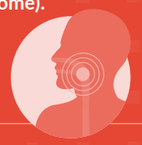
AMYLOIDOSIS SIGNS AND SYMPTOMS

If a patient presents with one, or particularly more, of the following unexplained symptoms, you should consider testing for amyloidosis:



- Severe weakness and fatigue, especially during exercise.
- Oedema (swelling in legs, abdomen or generalised swelling).
- Numbness or (painful) tingling in hands or feet (peripheral neuropathy).
- Numbness, tingling and pain in wrist, hand or fingers in both hands (carpal tunnel syndrome).
- Shortness of breath, especially during exercise.
- Foaming urine.
- Diarrhoea or constipation.
- Easy bruising.
- An enlarged tongue, which sometimes looks rippled around the edge (macroglossia).
- Difficulty swallowing or eating.
- Skin bleeding (purpura), especially spontaneous in the neck and face, and around the eyes ("racoon eyes").
- Low blood pressure, and dizziness when standing up.
- Abnormal heartbeat (i.e. symptoms of atrial fibrillation).





In most cases, the above-listed signs and symptoms are not due to amyloidosis. However, doctors treating a patient with these symptoms should carry out further investigations or refer the patient to secondary care, particularly if:

- The signs and symptoms listed above occur together without any apparent cause.
- The patient has repeatedly presented at the GP with such symptoms, without any resolution.
- Initial tests show M-proteins or free light chains detected in the blood or urine.
- There is evidence of a longstanding inflammatory disease or infection.

AMYLOIDOSIS DIAGNOSIS PATHWAY

AMYLOIDOSIS TESTS AND INVESTIGATIONS



1 Patient examination

- Measure blood pressure both sitting and standing. Check pulse frequency.
- Pay special attention to: purpura skin, tongue size, heart sounds and pulmonary symptoms (signs of pleural fluid), abdomen, bowel sounds, enlarged liver, palpable bladder, neuropathy in toes/legs and oedema in legs.

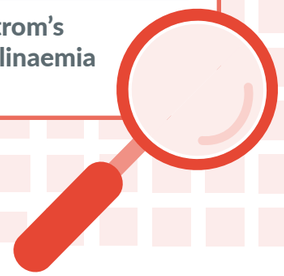
2 Blood, urine and serum protein tests

- Full blood count.
- Urine and serum protein electrophoresis.
- Serum and urine immunofixation, to check for presence of M-protein (monoclonal protein).
- Serum free light chain assay (sFLC).
- Urine tests (e.g. spot urine tests and 24-hour urine collection) for measurement of total protein and Bence Jones proteins (M-protein in the urine).
- Serum urea and electrolytes.
- Serum creatinine.
- Alkaline phosphatase or "liver function tests".
- Cardiac biomarkers (NT-proBNP or BNP).



RELATED DIAGNOSIS

- Monoclonal gammopathy of undetermined significance (MGUS)
- Monoclonal gammopathy of renal significance
- Multiple myeloma
- Waldenstrom's Macroglobulinaemia



REFERRAL AND DIAGNOSIS

If you suspect a patient has amyloidosis, based on their symptoms and test results, you should contact or refer them to a specialist amyloidosis clinic, haematologist or other relevant specialist (e.g., cardiologist or nephrologist) for further tests and investigations.

FURTHER TESTS AND INVESTIGATIONS

- Bone marrow biopsy and aspirate, if M-protein is present.
- Tissue diagnosis and typing: biopsy of affected organ or abdominal fat pad, Congo red staining to identify amyloid fibrils, mass spectrometry (or other accepted method for amyloid deposits typing according to guidelines).
- Electrocardiogram.
- Echocardiogram.
- 99m-Tc-PYP/DPD/HMDP scan (particularly if a patient has cardiac symptoms).
- Cardiac Magnetic Resonance (CMR) or Magnetic Resonance Imaging (MRI) scans.
- Chest X-ray.
- Genetic testing (particularly where ATTR is indicated or other rarer forms suspected).

SPECIALIST AMYLOIDOSIS CENTRES

In some European countries, there are Amyloidosis Centres of Expertise which specialize in the diagnosis and treatment of AL amyloidosis and other types of amyloidosis. These are listed below:

- National Amyloidosis Centre, University College London, UK
- Amyloidosis Research and Treatment Centre, University of Pavia, Italy
- Amyloidosis Centre of Expertise, University Medical Centre, Groningen and Utrecht, The Netherlands
- National and Kapodistrian University of Athens, Greece
- National Reference Centre for Amyloidosis, CHU Limoges
- Amyloidosis Centre, Heidelberg University Hospital, Germany
- University of Uppsala, Sweden
- University Hospital of Salamanca-IBSAL, Salamanca, Spain
- Hospital Clínic de Barcelona, IDIBAPS, Barcelona, Spain
- University Hospital Puerta de Hierro Majadahonda, Madrid, Spain

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ADDITIONAL RESOURCES

1. **Palladini, G. Milani, P. Merlini, G. Management of AL amyloidosis in 2020.** *Blood* 2020; 136 (23): 2620–2627. 84.
2. **Oerlemans, M.I.F.J., Rutten, K.H.G., Minnema, M.C. et al. Cardiac amyloidosis: the need for early diagnosis.** *Neth Heart J* 27, 525–536 (2019).
3. **Pablo Garcia-Pavia and others, Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases, European Heart Journal, Volume 42, Issue 16, 21 April 2021,** Pages 1554–1568.
4. **Palladini G, et al. The management of light chain (AL) amyloidosis in Europe: clinical characteristics, treatment patterns, and efficacy outcomes between 2004 and 2018.** *Blood Cancer J.* 2023 Jan 25;13(1):19.
5. **Buxbaum JN, et al. Amyloid nomenclature 2022: update, novel proteins, and recommendations by the International Society of Amyloidosis (ISA) Nomenclature Committee.** *Amyloid.* 2022 Dec;29(4):213-219.
6. **Benson MD, et al. Tissue biopsy for the diagnosis of amyloidosis: experience from some centres.** *Amyloid.* 2022 Mar;29(1):8-13.
7. **Gillmore JD, et al. Non-biopsy Diagnosis of Cardiac Transthyretin Amyloidosis.** *Circulation.* 2016 Jun 14;133(24):2404-12.

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