DISEASE INFORMATION

What is amyloidosis?

Amyloidosis is a collective term for a group of diseases characterized by misfolding and deposition of insoluble extracellular fibrils in tissues. Amyloid fibrils originate from soluble precursor proteins that circulate in the body.

Multiple precursor proteins can undergo the conformational changes that lead to amyloid fibril formation. Amyloid precursor proteins like monoclonal light chains are produced by clonal (malignant) plasma cells that are commonly found in the bone marrow. Non-pathological proteins which perform normal functions and are produced by organs such as the liver, can also form amyloid fibrils when inherited mutations are present that cause them to misfold. Other normal proteins can also undergo conformational changes and form amyloid fibrils under certain circumstances.

Once formed, amyloid fibrils deposit in various organs, disrupting tissue architecture and causing organ dysfunction. Target organs include the heart, kidney, liver, peripheral nerves, intestine and skin.

Amyloid deposition in the kidney causes loss of a large amount of protein in the urine (albuminuria, nephrotic syndrome), which manifests clinically as leg edema (swelling), periorbital (around the eye) edema and in many cases renal failure.

Amyloid deposition in the heart, leads to cardiac wall thickening and “stiffening” and progressive cardiac failure which causes symptoms such as shortness of breath, leg swelling, low blood pressure, dizziness, orthostatic hypotension, arrythmias and more.

Liver amyloidosis is characterized by hepatomegaly (large liver), a sensation of early satiety, abnormal increase in the values of certain liver enzymes and liver failure in advanced disease stages.

When the clinical syndrome of amyloidosis involves the peripheral nervous system, the patients experiences numbness, tingling and a burning sensation in the legs or arms. The involvement of the part of the nervous system that controls functions such as blood pressure, gastrointestinal motility, urination and erectile function can lead to orthostatic hypotension (the sense of dizziness or loss of consciousness upon standing up, particularly if the change in position is abrupt), intestinal (bowel) or stomach dysfunction, erectile dysfunction, increased or decreased sweating, dry mouth and more.

A multitude of other signs and symptoms are typical of amyloidosis, such as macroglossia (tongue enlargement secondary to amyloid deposition), voice changes, periorbital purpura (bruising around the eyes), joint swelling and difficulties in food chewing due to jaw pain.

How is amyloidosis diagnosed?

The diagnosis of amyloidosis requires a high degree of suspicion and is often not easy to make. Histological confirmation is necessary to set the diagnosis, that is a tissue biopsy which proves

the presence of amyloid using specialized techniques. Biopsies can be obtained from subcutaneous fat, the salivary glands, the bone marrow, the rectum but also other involved organs such as the kidney, liver, intestine and even the heart. The decision to biopsy a certain tissue or organ is guided by the patient's symptoms and potential organ involvement, the potential risks involved and the ease of accessing the organ. Quite often more than one biopsy from more than one organ/tissue is required to set the diagnosis and identify the amyloid.

Following histological confirmation of the presence of amyloid, the type of amyloid also needs to be determined. Correct classification of the amyloid type is very important as it will determine the type of treatment the patient will receive. AL amyloidosis, or primary amyloidosis is the most common type of amyloidosis. The amyloid fibrils are formed from immunoglobulin (antibody) light chains that are produced by malignant (clonal) plasma cells that originate in the bone marrow. To set the diagnosis of AL amyloidosis it is necessary to prove the presence of amyloid in tissue by histological confirmation but also of monoclonal paraprotein (immunoglobulin light chain), either in the blood or urine. In some cases specialized techniques can be used to determine the exact type of amyloid following histological confirmation.

Other forms of amyloidosis are referred to as secondary or reactive and occur in the context of chronic inflammatory conditions, such as rheumatoid arthritis (when the disease is not well controlled over a long period of time), chronic osteomyelitis, tuberculosis, and other rarer diseases like familial Mediterranean fever.

Amyloidosis can also occur due to mutations in certain genes.

The mutations cause small changes in the structure of proteins (usually a single amino acid change) that are normally found in the organism and although the proteins remain functional that also acquire a tendency to form amyloid fibrils. Examples of such proteins include transthyretin (TTR), apolipoprotein A-I and A-II, gelsolin, cystatin-C, fibrinogen Aa, lysozyme and others. This type of amyloidosis is rare (except perhaps from transthyretin-related amyloidosis).

One type of amyloidosis, non-mutated ("wild-type") transthyretin amyloidosis, is being increasingly diagnosed in recent years. The heart is always affected and other organs often involved include the peripheral nervous system, the joints and the gastrointestinal system. It is most often seen in men (80-90%) over 70 years of age.

Bone scintigraphy with the use of bone-seeking radiopharmaceuticals is an important tool for the correct and non-invasive diagnosis of ATTR amyloidosis. In patients with ATTR cardiac amyloidosis there is very sensitive and specific radiolabeling of the amyloid deposits in the heart offering a great diagnostic tool. To set the diagnosis of ATTR using bone scintigraphy it is necessary however to also exclude the presence of monoclonal paraprotein as the two can co-exist. The above diagnostic tests should be performed in specialized centers which offer diagnostic expertise and further testing when indicated.

Unfortunately amyloid typing is a complex procedure which cannot be based solely on clinical data and imaging techniques and often requires elaborate genetic testing and other sophisticated techniques

What is the prognosis?

Prognosis varies based on the type of amyloidosis and is usually more adverse for patients with primary AL light chain amyloidosis.

Organ involvement is a major determinant of outcome in patients with primary light chain (AL) amyloidosis and is significantly determined by the presence but also the extent of cardiac involvement as well as the response to treatment that the patient achieves.

Optimal management requires an early diagnosis, correct amyloid typing (to exclude other forms of amyloidosis), effective treatment administration, close monitoring, re-evaluation, frequent assessment of the response to treatment and careful administration of supportive medication.

The treatment options and therapeutic agents available for these patients have expanded significantly in recent years following the testing of different drugs. The serum concentration of two markers of cardiac dysfunction/damage, N-terminal B-natriuretic peptide (NT-proBNP) and cardiac troponins (troponin-T or troponin-I) are of significant prognostic value in patients with primary amyloidosis. The assessment of circulating free light chains in the serum (in the case of AL amyloidosis) offers a simple and fast method for evaluating the patient's haematological response to treatment.

What are the treatments for primary light chain (AL) amyloidosis?

The treatment of primary light chain amyloidosis is based on the administration of chemotherapy that aims to reduce/eradicate the production of free light chains by abnormal plasma cells.

- Chemotherapy regimens may include alkylating agents such as melphalan or cyclophosphamide but also newer agents such as bortezomib and lenalidomide, pomalidomide and daratumumab. Corticosteroid are almost always co-administered. The treatment agent and dosage schedule is determined by the patient's age, general functional status, existing comorbidities, the degree of cardiac and kidney dysfunction and other factors. In the future other agents, which are currently in clinical development may become available.
- Hematopoietic stem cell transplantation: Melphalan in high doses followed by autologous hematopoietic stem cell transplantation is considered an effective treatment for patients with primary light chain amyloidosis, but only for patients who are suitable candidates. Less than 15% of patients with primary AL amyloidosis will meet the criteria to safety undergo this procedure. Very strict criteria to determine suitability for this procedure are used as the risk of serious complications is high, particularly in patients with severe organ dysfunction (e.g. heart, liver, kidney).

Primary light chain amyloidosis is a relatively rare disease and its treatment is painful and complicated. The available treatments have improved the prognosis of the disease, but it remains poor for many patients. Involving patients in clinical trials when they are available may provide an opportunity for new and perhaps more effective treatment. Patients should discuss with their physicians at our center if there is a clinical study they could join.

Primary systemic (AL) light chain amyloidosis is a rare disease and its management is complicated and laborious. Available treatment options have improved disease prognosis which however remains poor for a large proportion of patients. Enrollment in clinical trials, when these are available, can often offer the option of a new and perhaps more effective treatment. Patients should get involved in discussions with their treating physicians, become informed and decide whether there are running clinical trials appropriate for them to enroll.

What are the treatments for amyloidosis from transthyretin (ATTR)?

There are also currently available treatment options for amyloidosis from transthyretin, both mutated and "wild-type".

These therapies fall into two broad categories: therapies that aim to stabilize transthyretin so that it does not form amyloid fibrils, and therapies that reduce transthyretin production from the liver.

Tafamidis belongs to the first drug category and has been used for the treatment of patients with transthyretin-related familial amyloid polyneuropathy (TTR-FAP). At higher doses, it also seems to be an effective treatment option for patients with transthyretin-related cardiomyopathy (i.e., cardiac dysfunction secondary to amyloidosis from transthyretin).

The second category includes drugs such as inotersen and patisiran . These drugs decrease the synthesis of transthyretin by inhibiting the translation (conversion) of messengerRNA tranthyretin to the transthyretin protein in the liver cells. They act mostly in the liver, which is the main site of transthyretin production. They are adminstered either intravenously or subcutaneously, under the supervision of specialized physicians. Both drugs have been shown to be effective for the treatment of patients with transthyretin-related familial amyloid polyneuropathy (TTR-FAP).