biomnis
SPECIALISED MEDICAL PATHOLOGY
Focus
issue 09

AL Amyloidosis

Definition

Amyloidosis consists of a set of heterogeneous molecules with common histological characteristics, in particular:

- Extracellular deposits of pathological fibrillary proteins that have become insoluble in organs and tissues.
- These amyloid protein deposits are characterised by their β-pleated sheet structure.
- There are several types of amyloid substances characterised by the fibrillary protein contained: more than 15 amyloid proteins are known to date.

Ig free light chains (IgLC):

are responsible for Primary or AL (amyloid light chain) amyloidosis.

Amyloid protein A:

responsible for Secondary or AA amyloidosis, found in cases of chronic inflammatory disease.

Mutated transthyretin:

responsible for Genetic / hereditary amyloidosis, marked by symptoms primarily in the liver.

Beta protein precursor:

responsible for Alzheimer's disease.

Prion protein:

responsible for Spongiform encephalopathy.

Cases of secondary amyloidosis, which are not caused by light chains, are less severe and require treatment of the underlying disease.

Introduction

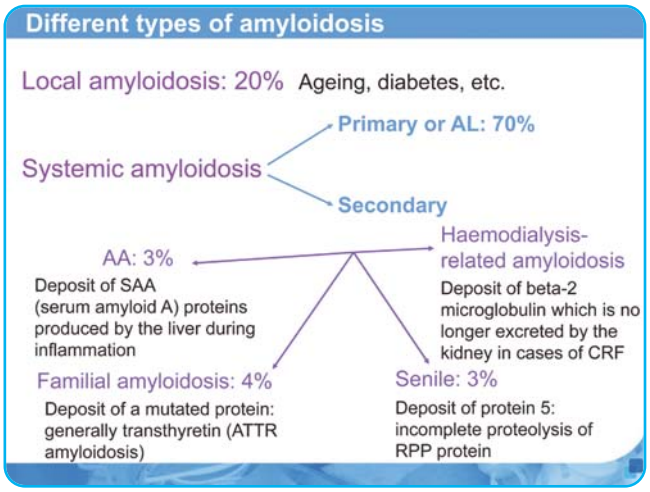
Amyloid substance structure:

This substance consists of:

- 10% common components in all amyloid structures: amyloid P component and glycoaminoglycans (GAG)
- 90% protein component organised in a fibrillary fashion, characteristic of each variety of amyloidosis. The fibrillae have a characteristic appearance in electron microscopy: rectilinear, interlocked with each other.
- The fibrillary nature of the amyloid substance and the β-pleated sheet configuration are responsible for the affinities of this amyloid substance with Congo red staining, the birefringence optical properties in polarised light and protein degradation resistance.

Different types of amyloidosis:

- Local amyloidosis: in 20% of cases, associated with ageing or chronic diseases such as diabetes.
- Systemic amyloidosis: primary (in 70% of cases) or secondary.



AL amyloidosis:

AL Amyloidosis or Immunoglobulin (Ig) light chain amyloidosis is the most frequent form of systemic amyloidosis, caused by the formation of fibrillae by monoclonal free light chains or Ig free chain fragments: the primary constituent of AL deposits is the variable region of free light chains (in 75% of cases, the AL Amyloidosis type is lambda).
These deposits are applicable to all organs, and on rare occasions the brain.
The incidence is 0.9 cases/100,000 people/year with an average age of 60 to 70 years at the time of diagnosis. They are idiopathic, primary or associated with a myeloma in 15% of cases or Waldenström type monoclonal gammopathy.

Clinical profile:

This is polymorphous. The main organs affected are the kidneys (46%), heart (30%), but amyloid deposits are also detected in the liver (9%), digestive tract (7%), soft tissue (3%) and PNS (5%).

▶ Renal amyloidosis:

- Glomerular deposits → Nephrotic syndrome
- Vascular deposits → terminal renal failure (dialysis in 20% of cases).

- Tubular deposits → tubular acidosis or polyuria due to diabetes insipidus.

▶ Cardiac amyloidosis:

- Restrictive cardiomyopathy progressively inducing heart failure.
- Rhythm disorders.
- Atrial thrombus formation with very high thrombogenic risk.

▶ Peripheral nervous system damage:

- Autonomous and sensorial neuropathy.
- Carpal channel syndrome.
- Dysautonomia: orthostatic hypotension, impotence
- Gastrointestinal transit disorder (diarrhoea / constipation).

▶ Cutaneous amyloidosis (rare):

Non-pruritic lesions in papule form.

▶ Rarer, but pathognomonic, signs of AL Amyloidosis:

Orbital ecchymotic purpura: pathognomonic sign of AL Amyloidosis and Macroglossia

▶ Other signs: less frequent

- Hepatomegaly frequently associated with kidney and heart damage.
- Lung damage.
- Endocrine gland damage: hypothyroidism, adrenal deficiency, pituitary gland deficiency, etc.
- Haematopoietic system: haematological modifications (decrease of fibrinogen, decrease of coagulation factor X associated with Ca-dependent fixation of factor X on amyloid fibrillae, increase in fibrinolysis due to decrease in antiplasmin).

Diagnosis: this is essentially based on:

▶ Anatomical pathology testing:

suspected on the basis of the clinical profile, but confirmed on the biopsy of a diseased organ. The biopsy of the symptomatological organ is the first-line test. The dissemination of deposits makes it possible to perform less invasive biopsies.

- Kidney, liver, heart biopsy
- Rectal biopsy... used for a long time
- Saliva gland biopsy
- Subcutaneous fat biopsy

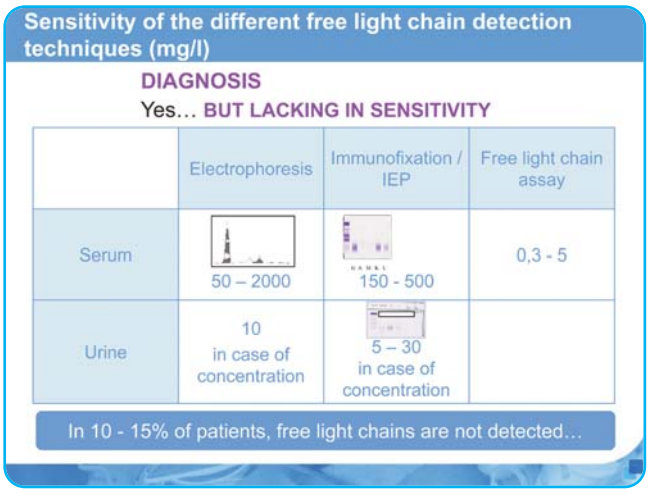
The first-line staining agent is Congo red as it is inserted in the beta sheet organisation of the amyloid substance. Immunohistochemistry is used to determine the isotype of the light chain (lambda isotype in 75% of cases).

▶ Imaging:

125I-SAP (Serum amyloid protein) scintiscan used to view the amyloid deposits.

▶ Immunochemistry:

Electrophoresis and serum immunofixation procedures display a peak with a +/- migrating aspect on β or γ globulins: IFX makes it possible to detect κ or λ light chains with no correspondence with a heavy chain. Urinary EP reveals an abnormal band characterised by IFX as free light chains.
These various techniques are lacking in sensitivity, due to their limit of detection.
Free light chains are not detected in 10 to 15% of amyloid patients. Moreover, these techniques are qualitative and not quantitative (rare serum electrophoresis peak that is difficult to interpret). It is sometimes difficult to collect and store urine.



▶ Free light chain assay:

At the present time, the free light chain assay is the most sensitive test for detecting the disease and monitoring whether the subject is responding to treatment or not.

In cases of AL amyloidosis, the free light chain level is similar to those observed in non-secretory myeloma and significantly lower than those in light chain myeloma.

Prognosis

mediocre with a median survival of 1 to 2 years without therapy.
Once AL amyloidosis has been diagnosed, the overall survival at 10 years, after treatment, is 5%.
Primary causes of morbidity: chronic heart failure, renal failure, hepatocellular failure.
Aggravating factors: myeloma-amyloidosis, heart condition.

Treatment

The aims of treatment are to reduce precursor production, amyloid fibrillae synthesis and deposition and promote the lysis of existing amylosis deposits.
The symptomatic treatment is dialysis in cases of renal failure, diuretics in cases of congestive heart failure at very high doses, fitting of a pacemaker in cases of bradycardia.
At the present time, there is no clearly defined consensus.
The French proposal is to start with an oral Melphalan®+DXM treatment and reserve intensive treatment as a second-line treatment for non-responsive patients. The response to the treatment is evaluated with the positive progression of the clinical profile and also the imaging. The free light chain assay could be a good tool to assess the progression of the disease, particularly since the emergence of the nephelometric free chain assay.

Important points:

- 98% of AL patients have abnormal free light chain levels, which is an indispensable diagnostic aid.
- The initial free light chain level is well correlated with the severity of the disease and appears to have a good prognostic value in terms of survival.
- The free light chain assay appears to be the most discriminatory biological marker in patient monitoring.
- The free light chain level after treatment is well correlated with the clinical response such as amyloid deposit imaging, the haematological response and survival.
- Treatment must be, insofar as it is possible, continued until the free light chain concentration is decreased by 50-70%; otherwise, a modification of the treatment (intensification) should be envisaged.