

Time is life

Why recognizing amyloidosis in time changes a person's destiny

Systemic amyloidosis progresses silently. The amyloid protein slowly and progressively damages vital organs — the heart, kidneys, liver, nervous system, and digestive system — for months or years without producing any warning symptoms. People affected by it go on living their lives, perhaps noticing a bit more fatigue, some tingling in the hands, or the occasional digestive discomfort: symptoms so common and so nonspecific that they are easily attributed to stress, advancing age, or countless other trivial causes.

It is precisely this apparent triviality that so often delays the diagnosis of amyloidosis. The patient moves from one specialist to another — a cardiologist for shortness of breath, a neurologist for the tingling, a gastroenterologist for digestive trouble — and each of them, looking at their own piece of the puzzle, does not always manage to see the complete picture. Meanwhile, the disease continues its silent work, and every month that passes without a diagnosis is a month in which the amyloid keeps damaging the organs. This is particularly true for amyloidosis caused by light chains (AL amyloidosis), which, unlike transthyretin amyloidosis (ATTR amyloidosis), usually progresses rapidly, and a diagnostic delay of just a few weeks can have consequences for survival.

This point deserves to be stated clearly: the damage amyloidosis causes, particularly to the heart, can become difficult to reverse — irreversible — despite therapies that are effective at reducing or eliminating the amyloid protein. The therapies available today, increasingly effective and increasingly targeted, can halt the progression of the disease, but they work best when the affected organ still has functional reserve to protect and the capacity to repair the damage already sustained. Diagnosing early means being able to intervene while there is still something to save.

In recent years, the therapeutic landscape of amyloidosis has changed radically. Drugs that did not exist until recently now make it possible to strike at the root of the disease: by blocking the production of the responsible protein, stabilizing it before it turns into amyloid, or by helping the body clear deposits that have already formed. These are extraordinary advances, the fruit of

decades of scientific research. But all of this therapeutic potential risks going unused if the diagnosis comes too late, when organ damage has already passed the point beyond which no therapy can truly reverse the course.

This is why the real challenge today is no longer just treating amyloidosis: it is recognizing it in time. It means training general practitioners and specialists not to dismiss as irrelevant a combination of several seemingly unrelated signs — bilateral carpal tunnel syndrome together with unexplained heart failure, for example, is exactly the kind of combination that should always raise a red flag. It means investing in simple, inexpensive tests, such as the blood markers that now make it possible to monitor patients at greatest risk. Above all, it means not giving up in the face of vague symptoms and not letting months or years go by before reaching a specialized center.

Behind every timely diagnosis is a person who today lives actively with their disease, who responds well to therapy, and who can go on living alongside their family with a preserved quality of life. And this is precisely the goal that must guide every one of our efforts, clinical and in research: to make sure that time, in this silent disease, once again becomes the patient's ally rather than its most insidious adversary.

Amyloidosis: symptoms to know

A simple guide to the signs that may indicate systemic amyloidosis, organized by the organ or system involved.

Legend: AL = light chain amyloidosis • ATTRwt = non-hereditary transthyretin amyloidosis • ATTRv = hereditary transthyretin amyloidosis

The symbol "✓" indicates that the symptom is common in that form of amyloidosis; the symbol "-" indicates that it is not typical.

Symptom or warning sign	AL	ATTRwt	ATTRv
 Heart			
Shortness of breath, leg swelling, fluid retention (heart failure)	✓	✓	✓
Irregular heartbeat (arrhythmia)	✓	✓	✓
Fatigue and breathlessness on exertion	✓	✓	✓
Dizziness or fainting on standing up	✓	✓	✓
Low blood pressure that worsens over time, or need to reduce blood pressure medication	✓	✓	✓
Poor response to standard heart medications	✓	✓	✓
Sudden-onset very high cholesterol associated with protein loss in the urine	✓	-	-
 Nervous system			
Tingling, burning, or pain in the hands and feet, altered perception of heat	✓	-	✓
Autonomic nervous system disorders (low blood pressure especially on standing, irregular bowel habits, erectile dysfunction)	✓	-	✓
 Digestive system			

Symptom or warning sign	AL	ATTRwt	ATTRv
Weight loss	✓	–	✓
Change or loss of taste	✓	–	–
Early satiety (feeling full after a small amount of food)	✓	–	–
Nausea, digestive difficulties	✓	–	✓
Persistent diarrhea	✓	–	✓
Enlarged liver	✓	–	–
 Muscles and joints			
Carpal tunnel syndrome in both hands	✓	✓	✓
Narrowing of the spinal canal, difficulty walking for long periods	–	✓	✓
Rupture of the biceps tendon	–	✓	–
 Kidneys			
Protein in the urine (sometimes in large amounts)	✓	–	✓
Widespread swelling (legs, abdomen)	✓	–	–
Progressive worsening of kidney function	✓	–	✓
 Skin and soft tissue			
Bruising or purplish patches on the face or neck, periorcular subcutaneous bleeding (“raccoon eyes”)	✓	–	–
Enlarged tongue	✓	–	–
“Shoulder pad sign” from amyloid buildup	✓	–	–
 Blood			
Anemia	✓	–	–
Venous thrombosis	✓	–	–

Symptom or warning sign	AL	ATTRwt	ATTRv
Tendency to bleed or bruise easily	✓	–	–
 Genitourinary sphere			
Erectile dysfunction, vaginal dryness	✓	–	✓

An important note. With the exception of macroglossia and periorbital purpura (especially when they occur together), which are characteristic, none of these symptoms is, on its own, specific to amyloidosis: they are also common to other diseases. It is the combination of several symptoms — especially together with unexplained heart problems — that should raise suspicion of this diagnosis and make specialist evaluation worthwhile.

Source: adapted from Bianchi G, Santhorawala V, Wechalekar A, Grogan M, Cuddy SAM, Merlini G. "Systemic light chain and transthyretin amyloidosis—treatment advancements and future directions." The Lancet, published online July 8, 2026.

The diagnostic pathway for cardiac amyloidosis

How a definitive diagnosis is reached, and why every day gained counts

The stages of the diagnostic pathway

Whenever amyloidosis is suspected, the treating physician should immediately refer the person to a specialized center able to rapidly carry out every stage of the diagnostic pathway, including typing of the amyloid deposits by mass spectrometry and any necessary genetic testing.

The diagnostic pathway is structured in successive stages, designed to reach an accurate diagnosis as quickly as possible.

1	Clinical suspicion The pathway begins when one or more warning signs appear (see the symptom table): unexplained cardiac problems, bilateral carpal tunnel syndrome, neuropathy, or other characteristic signs. The more signs that are present together, the greater the suspicion.
---	---



2

First-level blood and urine tests

Tests are performed to detect any proliferation of plasma cells (bone marrow cells), which underlies AL-type amyloidosis: serum and urine protein electrophoresis, serum and urine immunofixation, and measurement of serum free light chains. These are tests that can be carried out easily and quickly in any hospital laboratory. This step is crucial: it must be performed first and without delay, because it determines the subsequent pathway.



3

Crossroads: is plasma cell proliferation present?

If the tests show findings consistent with a plasma cell disorder, the pathway proceeds directly to tissue biopsy (step 4A). If, instead, these tests are negative, it is possible to proceed with non-invasive imaging, avoiding biopsy in selected cases (step 4B).



4A

Pathway with suspected plasma cell proliferation → Tissue biopsy

A small tissue sample is taken (often abdominal fat, bone marrow, or the affected organ) to check for the presence of amyloid using a specific stain (Congo red). If positive, amyloid typing is carried out to establish whether it is AL, ATTR, or another, rarer form.



4B

Pathway without signs of plasma cell proliferation → Non-invasive imaging

A cardiac scintigraphy with bone-seeking tracers (SPECT) is performed, which demonstrates marked cardiac uptake. This test makes it possible, in many cases, to diagnose ATTR amyloidosis without the need for a biopsy, provided the first-level test results allow it and the scintigraphy result is clearly positive (see Figure).



5

Amyloid typing

This is a fundamental step: knowing whether the amyloid is of AL or ATTR type completely changes the treatment. The most accurate test is mass spectrometry, which precisely identifies the protein responsible for the deposits.



6

Genetic analysis of transthyretin (if the amyloid is ATTR type)

If the SPECT indicates a diagnosis of ATTR amyloidosis, a genetic test is performed to distinguish the hereditary form (ATTRv, linked to a transmissible mutation) from the non-hereditary, age-related form (ATTRwt). This also has implications for the patient's family members.



Definitive diagnosis and start of therapy

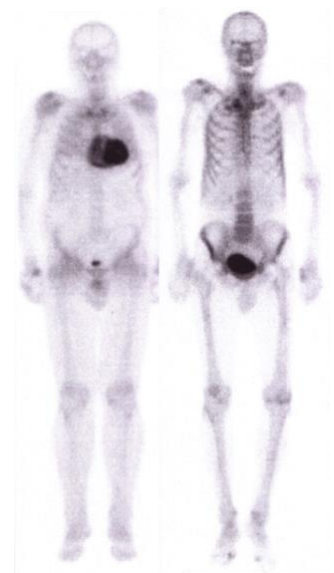
7

Once the type of amyloidosis and the organs involved have been established, the multidisciplinary team sets the most appropriate therapy. Starting treatment as soon as possible, before organ damage becomes irreversible, is the factor that most influences long-term outcome.

The key message

A single isolated symptom is rarely enough to raise suspicion of amyloidosis. It is the combination of several signs, especially when associated with an unexplained cardiac problem, that should prompt rapid investigation. Every stage of diagnostic delay is a lost opportunity to protect the heart and other organs from damage that, once established, can be difficult to reverse. For this reason, raising awareness among family doctors, specialists, and patients about warning signs remains one of the most powerful tools we have.

Figure. Scintigraphy with the bone tracer DPD. In the scan on the left, strong cardiac uptake is evident in an 81-year-old patient with cardiac amyloidosis caused by normal (wild-type) transthyretin. Until a few years ago, this type of amyloidosis was called senile amyloidosis, because it affects older individuals, usually men. This form of amyloidosis is now the most common cause of cardiac amyloidosis. In patients with cardiac amyloidosis caused by light chains, there is usually no DPD uptake, as shown in the scan on the right. Therefore, a positive DPD scan, or a scan with another bone tracer, allows a diagnosis of transthyretin cardiac amyloidosis to be made without the need for a biopsy.



In patients with a monoclonal protein three simple tests can anticipate the diagnosis of amyloidosis

The role of biomarkers in monitoring patients with MGUS

Anyone living with monoclonal gammopathy of undetermined significance (MGUS) knows that, in most cases, it is a condition to be monitored over time, without the need for immediate treatment. But in a small percentage of patients, the plasma cells underlying the MGUS can produce light chains capable of depositing in the organs in the form of amyloid, giving rise to AL amyloidosis — often years before evident symptoms appear.

The good news is that this process leaves measurable traces that can be detected with simple, inexpensive tests already available in routine clinical practice. Three biomarkers, in particular, make it possible to “listen” early to the three organs most frequently affected:

NT-proBNP → Heart

A hormone released by the heart under stress: it signals possible cardiac involvement even before shortness of breath or fatigue appear.

Proteinuria → Kidneys

The presence of protein in the urine indicates early, often silent, kidney damage.

Alkaline phosphatase → Liver

An increase in this marker can reveal liver involvement before obvious clinical signs emerge.

Why the timing of diagnosis is crucial

Regularly monitoring these three parameters in patients with MGUS — especially when free light chains in the blood are elevated — makes it possible to detect AL amyloidosis while it is still at an early stage, when organ damage is minimal or absent. It is precisely within this time window that early diagnosis makes the greatest difference: starting therapy before the heart, kidneys, or liver have suffered irreversible damage means giving the patient the best chance of responding to treatment and of a long, healthy life.

For this reason, guidelines recommend periodic monitoring, at least annually, of these three simple tests in all patients with MGUS or smoldering myeloma and abnormal free light chains: a small surveillance measure that can translate into a timely diagnosis.