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Review

Renal impairment in transthyretin amyloidosis

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Abstract. Amyloidosis are a group of diseases that occur when an abnormal protein builds up in the organs and leads to organ dysfunction. Amyloidosis is classified according to the proteins involved. The most common hereditary amyloidosis is transthyretin amyloidosis. This is an autosomal dominant disease and is associated with more than 100 mutations. Renal impairment is found especially in patients with neuropathy and cardiac arrhythmias. This kidney damage can lead to chronic kidney disease in the final stage. Patients who needed renal replacement had a poor prognosis. Simultaneous kidney-liver transplant is an optimal treatment option, given that mutant transthyretin is secreted by the liver. New drugs for transthyretin amyloidosis are being developed and require further studies in patients with kidney failure. An early diagnosis is the key to a better outcome.The last 20 years, the treatment for transthyretin amyloidosis has been liver transplantation, given the transthyretin is produced by the liver. The last 10 years, new treatments have been available, like Tafamidis which stabilizes the transthyretine tetramer. New treatment like gene therapy, witch blocks the production of transthyretin are now available, promising to transform the outcomes in systemic amyloidosis.

Key Words: amyloidosis, transthyretin, kidney damage, hemodialysis, transplant

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Introduction

Amyloidosis comprises a number of rare diseases that occur due to extracellular deposits of amyloid, derived from a precursor, a protein. This amyloid deposit occurs in the presence of an abnormal protein (hereditary amyloidosis, AL amyloidosis), in association with an excess of normal protein (amyloidosis AA, amyloidosis with beta 2 microglobulin), or due to the aging process (amyloidosis with wild transthyretin-TTR).

Classification of amyloidosis is done according to the precursor. Among the types of amyloidosis we mention:

1. AL amyloidosis: the precursor is the light lambda or kappa chain of an immunoglobulin
2. Amyloidosis AA: the precursor is the systemic amyloid A, an acute phase reactant
3. TTR amyloidosis: the precursor is transthyretin
4. Beta 2 microglobulin amyloidosis occurs in patients with chronic kidney disease who have elevated levels of beta 2 microglobulin, which is predominantly deposited in the osteoarticular system

Other types of systemic amyloidosis are rare. In the case of patients with a family history of amyloidosis, hereditary amyloidosis should be sought. In patients with predominantly renal impairment, fibrinogen amyloidosis, apolipoprotein A I, A II, A IV should be considered.

Amyloid deposits can be deposited in any organ, so the clinical manifestations are multiple and diverse, not being specific to a type of amyloidosis. Heart damage is the leading cause of mortality and morbidity in amyloidosis. It is found in about 50% of patients with AL amyloidosis, in most of the patients with TTR amyloidosis, but is rarely found in patients with AA amyloidosis. It manifests as a restrictive cardiomyopathy, with signs of right ventricular failure (edema, congestive hepatomegaly, venous stasis), low cardiac output and hypotension in severe forms. Rhythm and conduction disorders may occur, more commonly in amyloidosis with TTR.

Renal impairment is common in amyloidosis AL, AA, AFib, AApoA1. Albuminuria typically progresses to nephrotic syndrome, usually renal dysfunction is asymptomatic up to the advanced stages.

Neuropathy is found in AL amyloidosis, TTR amyloidosis and ApoA1 amyloidosis (Wechalekar et al 2016; Hazenberg et al 2013).

Osteoarticular manifestations are found predominantly in amyloidosis with beta 2 microglobulin and are manifested by shoulder pain, periarticular cysts, pathological fractures and spondyloarthropathy.

For the diagnosis of amyloidosis, the first step is to obtain a histological examination to confirm the existence of amyloid (this is done by histopathological examination, with Congo Red staining), then systemic amyloid deposits will be sought. The next step is to determine the type of amyloid (immunohistochemistry of the biopsied tissue, using specific antibodies). This technique is sensitive enough to detect AA amyloidosis, where monoclonal antibodies are used. The clinical evaluation must assess the severity of the organic damage, the associated risks, the prognosis and the therapeutic alternatives (Hazenberg et al 2013).

Renal impairment in amyloidosis

It is most common in AA, AL and some of the hereditary amyloidosis. The formation of amyloid fibrils begins with the

"misfolding" of the protein precursor. This will form protofilaments that interact to form the fibers.
Regarding the kidney, amyloid can be found at any level, but glomerular deposits predominate. Deposits at the tubulo-interstitial level produce tubular atrophy and interstitial fibrosis (Dember et al 2006).
Kidney damage is almost identical in any amyloidosis.
The evolution of the disease includes several stages:
- The preclinical stage is characterized by the absence of clinical manifestations, although there are already amyloid deposits in the renal parenchyma. This stage can take years.
Subsequently, a proteinuria progressively occurs, usually non-selective, initially intermittent and then permanent, in variable amounts. Microscopic hematuria occurs in 5-10% of cases. Renal function is generally maintained at this stage.
- Later on there is an increase in proteinuria with the onset of a nephrotic syndrome, accompanied by specific complications: thrombotic complications (especially in the renal vein) and malnutrition. The course of kidney failure depends on the type of amyloid.
On an ultrasound examination, the kidneys are enlarged in about 20% of cases. Hypertension is present in 20-60% of cases.
Nephropathy in amyloidosis can be complicated by acute renal failure if there is a triggering factor such as: dehydration, surgery, use of nephrotoxics (Ando et al 2013).

Anatomopathological diagnosis

1. Optical microscopy: amorphous deposits, poorly chromatophilic at the level of basal membranes, interstitial or intercellular connective tissue and vascular walls. The diagnosis of amyloidosis is evoked by the usual staining and is confirmed by the Congo Red stain.
Simple Congo red staining is not sufficient because the elastic and collagen fibers also appear red with this staining, which is why the sample must be analyzed in polarized light, where amyloid deposits appear phosphorescent green.
2. Electron microscopy: amyloid fibrils look like "cotton". They are generally 7.5-10 nm in diameter, with variable length, they are straight and rigid, resembling pine needles.
Determining the amyloid precursor protein is essential to establish an accurate diagnosis and prognosis. Immunohistochemistry is the current reference technique. Mono or polyclonal antibodies directed against most amyloid-forming proteins are used.
In the kidney, amyloid deposits can exist at any level, but glomerular and vascular damage is more common. This distribution can guide us to the nature of the amyloid, as follows:
- The predominantly extramembrane and endomembrane distribution is specific for AL amyloidosis
- Mesangial distribution is more common in AA amyloidosis
- Vascular damage is very common (80-100% of cases) and mainly affects the arterioles, then the arteries, peritubular capillaries and veins. Amyloid deposits generally occur in the middle.
- Tubulointerstitial impairment occurs in 50-100% of cases. In the cortex, it occurs along the membranes of the peritubular capillaries and along the tubular basement membrane. In the medulla, amyloid is found predominantly in the vasa recta, the Henle loop and the collecting tubes. In some hereditary forms of amyloidosis (AApoAI and amyloidosis with TTR) interstitial deposits predominate in the medulla (CHOUKROUN et al 2000) (Shiiki et al 1988)(Noel et al 2008).

Characteristics of transthyretin amyloidosis

Transtiretin is a 55KDa plasma protein, synthesized by the liver, made up of 127 amino acids and encoded by a gene found on chromosome 18 (18 q 23). Its main role is to transport thyroxine and the Retinol Binding Protein complex.
Transstyretin amyloidosis is a systemic disease characterized by the storage, in the extracellular space, of amyloid fibrils. The precursor of this amyloid is prealbumin (transthyretin), produced by the liver in the form of a tetramer.
There are 2 types of amyloidosis with TTR:
- Hereditary: there is a genetic mutation that destabilizes transthyretin. TTR amyloidosis is the most common hereditary amyloidosis.
- Senile: there is no mutation, it is generally found in people over 50 years, it occurs due to wild transthyretin deposits.
For the hereditary form, more than 100 mutations have been described. These mutations lead to altered molecular structure and accumulation of products in the form of amyloid fibrils, that cannot be degraded (Magy-Bertrand et al 2007).

Clinical picture

Because transstyretin amyloidosis (TTR) is a systemic disease, various organs will be affected:
- Heart: infiltrative cardiomyopathy, congestive heart failure with preserved ejection fraction, conduction disorders and arrhythmias
- Nervous system: familial polyneuropathy - axonal, sensory and motor neuropathy
- Kidneys
- Eyes (Magy-Bertrand et al 2007)
The predominant symptoms are associated with gene mutation, as follows:
- Val30Met- polyneuropathy
- Wave 122 Ile and Leu111Met - cardiomyopathy
- Glu89Gin- mixed damage (Coelho et al 2013)
Impairment of organs and systems can be simultaneous. Organic damage depends on the genetic mutation, for example the Leu55Pro mutation is responsible for dysautonomic neuropathy, cardiomyopathy and vitreous deposits, while the His56Arg mutation is responsible for an isolated cardiomyopathy.
Renal impairment is present in 10-20% of cases; only some mutations are associated with renal impairment (eg Ser52Pro, Ser77Tyr); the most common condition is tubointerstitial, and sometimes glomerular (Magy-Bertrand et al 2007).
At the renal level, the distribution of amyloid deposits correlates with the degree of proteinuria, glomerular and vascular deposits predominating in patients with proteinuria (Rocha et al 2017).
Pathology: renal damage predominates in the renal medulla, especially around the distal tubules and the loop of Henle. However, amyloid deposits can often be seen in the glomeruli (mesangial, segmental and focal deposits). Vascular damage predominates in the cortex, especially affecting the arterioles (Noel et al 2008).
Patients with amyloidosis have ventricular and supraventricular arrhythmias, nephrotic syndrome, all of which are associated with arterial thromboembolic events, such as renal infarction.

Renal infarction can occur due to amyloid deposits in the renal vessels, severe nephrotic syndrome or emboli of cardiac origin (Dang et al 2019).

Diagnostic

The diagnosis is made clinically, using pathological examination (identification of amyloid deposits, then amyloid typing by immunohistochemistry) and using molecular biology (identification of gene mutation).

Ideally, the target tissue (heart, kidneys, nerves) should be biopsied. Due to the hemorrhagic character of the biopsy, the sometimes difficult technique (ex endomyocardial biopsy), but also to the systemic character of the disease, biopsies of rectal mucosa, subcutaneous fat or accessory salivary glands are preferred.

The immunohistochemical diagnosis allows the identification of the transthyretin precursor. Anti-TTR antibodies are used, in order to exclude AA and AL amyloidosis. This technique does not allow the differentiation between TTR amyloidosis due to certain mutations and senile TTR amyloidosis. Molecular biology is needed to detect the mutation.

Treatment

•Liver transplantation: mutant TTR synthesis is stopped

Pre-existing heart damage is a negative prognostic factor, as it progresses after transplantation.

The liver of the patient affected by amyloidosis is often transplanted to a patient with end-stage liver disease (domino transplantation), the liver will continue to produce modified amyloid, but amyloidosis will only set in after a several years (approximately 20 years)(Magy-Bertrand et al 2007).

•TTR stabilizers: Tafamidis (Vyndaquel), diflunisal, NSAIDs

Tafamidis attaches to the thyroxine binding site on the tetramer and prevents dissociation into monomers.

•Inhibitors of amyloid deposits: doxycycline, tauroursodeoxycholic acid (TUDCA)

•Gene therapy: TTR oligonucleotides - reduce the production of mutant and wild TTR

•Symptomatic treatment (Rocha et al 2017)

Non-specific treatment includes

1. Treatment of nephrotic syndrome

- In the proteinuric phase, without renal failure, an increased protein intake is required

- In case of massive edema, loop diuretics will be used, in combination with spironolactone; for thrombosis prophylaxis anticoagulant treatment will be introduced if serum albumin is less than 2 g / dl

2. The appearance of renal failure implies strict measures regarding the hygienic-dietary regime, the correction of the anemia, of the phospho-calcium metabolism disorders and of the hypertension.

The progression of renal failure requires, at some point, extrarenal clearance or kidney transplantation. Heart damage is a predictor of mortality in hemodialysis patients with amyloidosis. Kidney transplantation is limited by heart damage and recurrence of amyloidosis at the graft (Thervet et al 2017; Feehally et al 2019; Ursea et al 2006).

There is no specific treatment for kidney damage. Clinical trials of anti-amyloid drugs have never been applied to patients with severe renal impairment.

A non-randomized, prospective study evaluated 12 patients with stage I neuropathy and GFR> = 60 ml / min. Tafamidis 20 mg / day was administered (Rocha et al 2017).

Tafamidis is a benzoxazole carboxylic acid without non-steroidal anti-inflammatory activity (unlike other TTR stabilizers, such as Diflunisal) which binds to the binding site of T4 (Lorenzini et al 2019).

Renal function was assessed by measuring creatinine, cystatin C and proteinuria. Patients were evaluated at the beginning of the study and thereafter every 6 months. Patients were divided into 2 groups at the end of the study according to proteinuria: 5 patients with proteinuria <30 mg and 4 patients with proteinuria> 30 mg. Of the 12 patients, 9 underwent 36 months of treatment, 2 patients underwent 30 months of treatment, and one patient underwent 18 months of treatment. Two patients had renal biopsies. During the study, renal function remained stable, and a significant decrease in proteinuria was observed. At the end of the 36 months of treatment with Tafamidis, no change in renal function was observed, but a reduction in proteinuria was observed. It was concluded that Tafamidis could slow the kidney damage. It should be used in patients with TTR amyloidosis before the kidney damage is severe (Rocha et al 2017).

Conclusions

Transthyretin amyloidosis is a multisystemic disease with a bad prognostic. The most important clinical manifestation are the cardiomyopathy and the polyneuropathy , but the disease can also affect the kidneys, the digestive system and the eyes. The most important issue for the diagnostic is think about the transthyretin amyloidosis because you will never make a diagnosis that doesn't enter into your differential.

All forms of transthyretin amyloidosis are progressive and death is due to malnutrition renal failure cardiac disease or sudden death. A lot has been achieved for the treatment of transthyretin amyloidosis lately and early diagnosis is critical for a good prognostic.

References

Ando Y, Coelho T, Berk JL, et al. Guideline of transthyretin-related hereditary amyloidosis for clinicians. Orphanet J Rare Dis 2013;8:31.

Choukroun G, Goupy Ch, Noël LH, Droz D, Grunfeld JP. Amylose du rein et de l'appareil urinaire. In: Grateau G, Merill D, Benson D, Delpech M, editors. Les amyloses. Paris: Flammarion Médecine; 2000. pp. 163–178 Eric T. Traite de Nephrologie. Lavoisier Medecine 2017. p.141-143. ISBN : 978-2-257-20671-8.

Coelho T, Maurer MS, Suhr OB. THAOS - The Transthyretin Amyloidosis Outcomes Survey: initial report on clinical manifestations in patients with hereditary and wild-type transthyretin amyloidosis. Curr Med Res Opin 2013;29(1):63-76.

Dang J, Abulizi M, Moktefi A, et al. Renal Infarction and Its Consequences for Renal Function in Patients With Cardiac Amyloidosis. Mayo Clin Proc 2019;94(6):961-975.

Dember LM. Amyloidosis-associated kidney disease. J Am Soc Nephrol 2006;17(12):3458-71.

Hazenberg BP. Amyloidosis: a clinical overview. Rheum Dis Clin North Am 2013;39(2):323-45.

Johnson RJ, Feehally J, Floege J, Tonelli M. Comprehensive Clinical Nephrology. Sixth edition, p.320-331, Elsevier, 2019.

Lorenzini M, Elliott PM. Tafamidis for the treatment of transthyretin amyloidosis. Future Cardiol 2019;15(2):53-61.

Magy-Bertrand N. Les amyloses à transthyrétine [Transthyretin amyloidoses]. Rev Med Interne. 2007;28(5):306-13.

Noel LN. Atlas de Pathologie renale. p 345-265.Medecine-Sciences Flammarion 2008.

Rocha A, Silva A, Cardoso M, et al. Transthyretin (ATTR) amyloidosis nephropathy: lessons from a TTR stabilizer molecule. Amyloid 2017;24(sup1):81-82.

Shiiki H, Shimokama T, Yoshikawa Y, Toyoshima H, Kitamoto T, Watanabe T. Renal amyloidosis. Correlations between morphology, chemical types of amyloid protein and clinical features. Virchows Arch A Pathol Anat Histopathol. 1988;412(3):197-204.

Ursea N. Tratat de Nefrologie. vol 2. Fundatia Romana a Rinichiului, 2006. pag 2583-2586.

Wechalekar AD, Gillmore JD, Hawkins PN. Systemic amyloidosis. Lancet 2016;387(10038):2641-2654.

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