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Review article

Diagnosis and Treatment of Transthyretin Cardiac Amyloidosis. Progress and Hope

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ABSTRACT

Cardiac amyloidosis is an infiltrative disorder caused by extracellular protein deposition. Transthyretin is a proamyloidotic protein that produces one of the most frequent forms of cardiac amyloidosis, either through mutations or a wild-type form (previously known as senile amyloidosis). Until very recently, diagnosis of transthyretin amyloidosis (ATTR) was very uncommon and histological confirmation was mandatory, making diagnosis of ATTR a real challenge in daily clinical practice. Moreover, the specific therapeutic options to alter the clinical course of the disease were very limited. However, advances in cardiac imaging and diagnostic strategies have improved recognition of ATTR. In addition, several compounds able to modify the natural history of the disease are in the final phases of research, with promising results. Given that effective therapies are on the horizon, cardiologists should be well-versed in this disease and be familiar with its diagnosis and treatment. This review describes the broad clinical spectrum of ATTR in detail, as well as recent advances in the diagnosis and treatment of this condition.

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Palabras clave:
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Transtiretina
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Hereditaria

RESUMEN

La amiloidosis cardiaca es una enfermedad infiltrativa por depósito extracelular de proteínas. De las proteínas proamiloidóticas a nivel cardiaco, la transtiretina produce una de las formas más frecuentes de amiloidosis cardiaca, bien por mutaciones o bien en su forma natural (*wild-type*) conocida previamente como amiloidosis senil. Hasta muy recientemente, el diagnóstico de amiloidosis por transtiretina (ATTR) se producía en reducidas ocasiones y requería confirmación histológica, por lo que establecer el diagnóstico constituía un verdadero reto en la práctica clínica habitual. Además, las opciones terapéuticas específicas para alterar el curso clínico de la enfermedad eran muy limitadas. Sin embargo, avances en el campo de la imagen cardiaca y en la estrategia diagnóstica de la enfermedad están facilitando un reconocimiento creciente de la ATTR. De forma adicional, diversos compuestos capaces de modificar la historia de la enfermedad se encuentran en fases finales de investigación, con resultados prometedores. Dado que una terapia efectiva parece estar cada vez más próxima, se hace imprescindible que los cardiólogos conozcan esta patología en profundidad y estén familiarizados con su diagnóstico y tratamiento. En esta revisión se repasará detalladamente el amplio espectro clínico de la ATTR, así como los recientes avances en el diagnóstico y tratamiento de esta entidad.

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Abbreviations

ATTRm: mutant transthyretin amyloidosis
ATTRwt: wild-type transthyretin amyloidosis
CTS: carpal tunnel syndrome
HCM: hypertrophic cardiomyopathy
HFpEF: heart failure with preserved ejection fraction
LVH: left ventricular hypertrophy
TUDCA: tauroursodeoxicholic acid

INTRODUCTION

Amyloidosis is a deposition disease caused by extracellular accumulation of fibrils whose source consists of proteins with an unstable structure that fold, aggregate, and undergo deposition.[1] Such deposition can alter tissue structure and impair the function of various organs and systems.[2]

Amyloid fibrils are insoluble and proteolysis resistant and are typically stained by Congo red, showing intense yellow-green birefringence under polarized light.[3] More than 30 proteins can cause amyloid deposition, but only 5 cause significant deposition in cardiac tissue[1]:

- Light chains, which cause primary amyloidosis (AL).
- Transthyretin (TTR), which causes TTR amyloidosis (ATTR).
- Apolipoprotein A.
- Fibrinogen.
- Serum amyloid-protein A, which produces secondary amyloidosis.

Primary amyloidosis and ATTR are the most common forms of cardiac amyloidosis, the AL form being historically considered more common in developed countries.[3]

Most of the information on cardiac amyloidosis has been based on AL. However, although the number of patients with AL has remained stable, the number ATTR diagnoses has recently increased and it is now thought that ATTR may be much more prevalent than AL.[2]

Transthyretin amyloidosis has very often been the subject of misdiagnosis or significant delays until its correct diagnosis. Reasons include heterogeneity in its forms, need for histological confirmation, shortages of specialized equipment, and erroneous beliefs among some cardiologists that it is a rare disease without treatment options.[2,3]

However, these aspects are changing. Diagnosis has implications for patient management. Specific therapies have been developed that may delay or stabilize deposition and that are more effective in the early stages. Early diagnosis is therefore crucial. This review describes significant recent advances in the diagnosis and treatment of ATTR, offering hope for patients with this condition.

TRANSTHYRETIN CARDIAC AMYLOIDOSIS

Transthyretin is a tetrameric plasma protein responsible for transporting thyroxine and retinol-bound protein. It is primarily synthesized in the liver and secondarily in the choroid plexus and retinal pigment epithelium.[4]

Transthyretin tends to dissociate to dimers and monomers, which misassemble into fibrils and undergo deposition. Point mutations or the effect of age can increase this tendency, giving rise to the 2 clinical forms of ATTR: mutant (ATTRm) and wild-type (ATTRwt).

MUTANT TRANSTHYRETIN AMYLOIDOSIS

More than 120 mutations are currently known to cause ATTRm. These mutations exhibit an autosomal dominant inheritance pattern, with variable penetrance.[4] Because of its wide geographic diversity, it is difficult to establish the prevalence of ATTR, but it is considered to be a rare disease with a prevalence of less than 1/100 000 inhabitants[2] (Table 1).

The first TTR mutations were reported as familial amyloid polyneuropathy (or Andrade disease), and consequently ATTRm has until recently been considered a neurologic disease. However, recent findings show cardiac involvement in more than half of the cases.[3]

There is a strong genotype-phenotype correlation, with mutations being associated with purely neurologic disease or purely cardiac disease.[3] However, the division of ATTRm into cardiac or neurologic disease may be an oversimplification, as there is considerable overlap between the 2 clinical forms on the disease spectrum.

The Val30Met mutation (now known as Val50Met after 20 positions were added to the traditional mutation name in ATTRm) is the most frequent mutation worldwide and is endemic in Portugal, Japan, and Sweden. Its estimated incidence in Portugal is 1 per 538 inhabitants.[2] Mallorca (Spain) and Valverde del Camino (Huelva, Spain) are also considered to be areas in which ATTRm is endemic. The estimated prevalence in Mallorca in symptomatic patients is 3/100 000 inhabitants.[5]

The Val30Met mutation causes a predominantly neurologic condition with symmetric sensory-motor polyneuropathy, which begins in the lower limbs and follows an ascending pattern. It can be associated with dysautonomia with orthostatic hypotension, erectile dysfunction, urinary incontinence, and gastrointestinal symptoms. It typically begins at the end of the second or third decade of life, and up to 43% of the patients have cardiac involvement that is a frequent cause of death[4] (Table 1).

Of particular relevance is the Val122Ile mutation (p. Val142Ile), which is present in 3% to 4% of the North American black population.[3] Although its penetrance is incomplete,[3] this mutation has been associated with a 47% increased risk of developing heart failure (HF).[6] A recent study showed that Val122Ile amyloidosis was the fourth most common cause of HF in the British Afro-Caribbean population.[7] Although up to 30% of patients with this mutation may have features of mild neuropathy,[6] the clinical phenotype is usually similar to that of ATTRwt.[4] Val122Ile should not be considered a mutation exclusive to the black population, because it can also be present in the white population. For example, we have identified this mutation in 4 white Spanish families without black ancestry.

WILD-TYPE TRANSTHYRETIN AMYLOIDOSIS

Wild-type transthyretin amyloidosis was first described in 1876. It was formerly called senile amyloidosis, but its diagnosis in patients aged 40 to 60 years has rendered this term obsolete. Of interest, the earliest known case of this mutation was found in a 47-year-old American patient.[8]

The exact prevalence of ATTRwt remains unknown. However, studies suggest that it is underdiagnosed and that it may be the most frequent form of cardiac amyloidosis.[2,3] The following results support this hypothesis:

- In patients aged more than 80 years, the prevalence of TTR deposition is 25% at autopsy.[3]
- In patients with HF with preserved ejection fraction (HFpEF), moderate-severe TTR deposition is 5% at autopsy.[9]
- In patients aged more than 60 years admitted for HFpEF and left ventricular hypertrophy (LVH) $\geq$ 12 mm, our group recently found a prevalence of 13%.[10]

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