THAOS®
Transthyretin Amyloidosis Outcomes Survey

PHYSICIAN FACTSHEET

Disease background – transthyretin amyloidosis

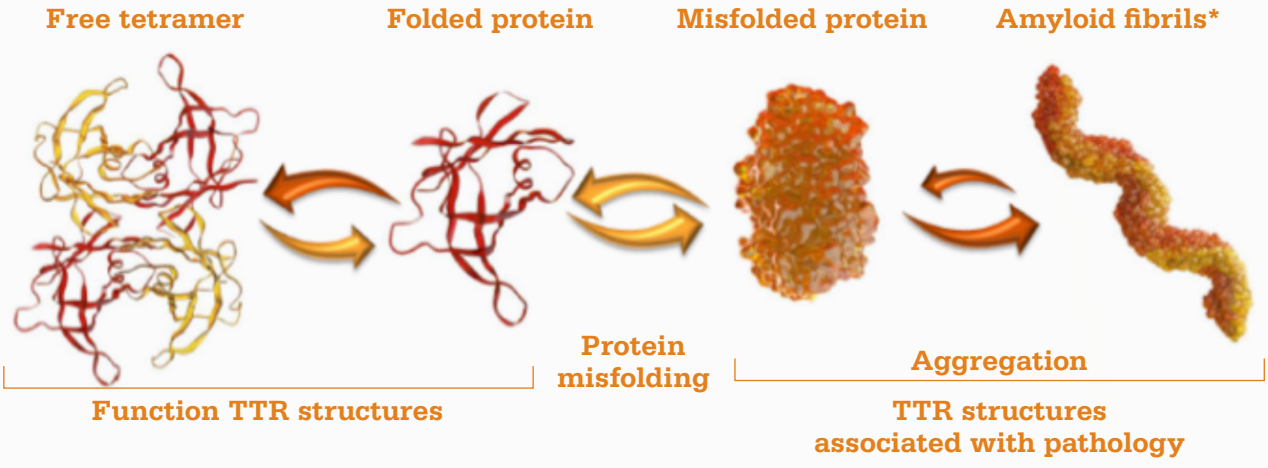
Transthyretin (TTR) amyloidoses are a family of rare diseases induced by misaggregated or misfolded proteins.[1] The clinical spectrum varies widely; subject presentation may feature almost exclusive neurological involvement (TTR-familial amyloid polyneuropathy, TTR-FAP) or a cardiological profile (TTR-familial amyloid cardiomyopathy, TTR-FAC).[2] TTR-FAP, the most common type of hereditary amyloidosis, is an autosomal dominant disease[3] caused by a pathogenic variant of TTR aggregating to form toxic amyloidogenic intermediates and amyloid fibrils,[4] and is typically fatal within 10 years of symptom onset.[3,5]

The varied pattern of onset and organ involvement in TTR-amyloidoses, along with the absence of a unique symptomology, means that subjects may pass through long referral chains; receive multiple misdiagnoses,[2,6] and experience a mean delay to diagnosis of 4 years,[7] which can be detrimental to outcomes.[8]

Transthyretin

Transthyretin, formerly known as pre-albumin[4] is one of three proteins responsible for transporting the thyroid hormone thyroxine (T_4), and is composed of four identical subunits called monomers, which associate non-covalently to form the tetrameric transport protein. The bulk of T_4 within human blood is carried by thyroxine-binding globulin (TBG) and albumin, with transthyretin carrying less than 1% of T4.[3,9] Transthyretin is also involved in the transport of retinol through interaction with the retinol-binding protein (RBP)/vitamin A complex; however, most circulating transthyretin is not bound to RBP/vitamin A and therefore, the majority of transthyretin in circulation remains unbound.[4] Approximately 95% of transthyretin in circulation is produced in the liver.[9]

Genetic mutations in the *TTR* gene can lead to pathogenic variants of the transthyretin protein that cause TTR-FAP.[3] In the case of pathogenic transthyretin tetramers, unstable transthyretin tetramers dissociate into individual monomers, which can then misfold and aggregate into a variety of toxic amyloidogenic intermediates, including small oligomers and amorphous aggregates, which can further aggregate into amyloid fibrils.[9] The process of amyloid formation, and not just amyloid deposition, may be involved in the degeneration of nerve tissue in TTR-FAP, particularly during the early stages of TTR-FAP.[10] Amyloid fibrils can deposit in the peripheral and autonomic nerves and in organs such as the gastrointestinal tract, kidneys, and heart, which can also result in organ dysfunction over time.[3,11]



*Amyloid fibrils can be caused by a variety of toxic intermediates including small oligomers and amorphous aggregates.
Image courtesy of J. Kelly, TSRI.

TTR familial amyloid polyneuropathy

In TTR-FAP, transthyretin amyloid deposition occurs primarily in the peripheral and autonomic nerves. The key characteristic of TTR-FAP is length-dependent axonal degeneration resulting in the loss of neurologic function.

In subjects with TTR-FAP, neurodegeneration progresses in a distal-to-proximal manner.[2] Axonal degeneration of small myelinated (protective sheath around the nerves) and unmyelinated nerve fibers is associated with sensory loss or pain in the lower limbs.[3] Subjects may also experience alterations in temperature sensation and tingling in the lower extremities. Degeneration progresses to larger nerve fibers resulting in muscle atrophy, weakness and difficulty walking. By the time symptoms reach the knee, the nerves in the hands may begin to be affected and undergo similar neurodegenerative progression.[2,12] In addition, subjects with TTR-FAP have autonomic neuropathy that accompanies distal-to-proximal neurodegeneration. Autonomic neuropathy may be the initial presenting symptom or may develop within 1–2 years of disease onset.[2] Symptoms of autonomic neuropathy may include alternating constipation and diarrhea, sweating abnormalities, diarrhea, erectile dysfunction and orthostatic/postural hypotension.[2]

TTR amyloid cardiomyopathy

TTR amyloid cardiomyopathy (TTR-CM) is greatly underdiagnosed, with the clinical picture varying from primarily neurologic involvement, to primarily cardiological.[2] The infiltration of TTR amyloid fibrils into the myocardium leads to diastolic dysfunction, which progresses to restrictive cardiomyopathy and heart failure.[2] There is a wide spectrum of cardiac involvement in TTR-CM, ranging from asymptomatic atrioventricular and branch block, to rapidly progressing heart failure, which can vary depending on the TTR mutation and geographic area.[2]

Several single point mutations in the *TTR* gene have been primarily associated with this condition and include the common substitution of isoleucine for valine at position 122 (V122I), which occurs with a prevalence of approximately 3–4% in African-Americans as well as the less common V20I, P24S, A45T, G47V, E51G, I68L, Q92L, L111M and V122I mutations.[3]

TTR-CM may be associated with genetic variants of transthyretin although TTR CM also occurs in the absence of any genetic mutation. The non-genetic (non-inherited) disease is also known as wild-type (WT) and is caused by WT transthyretin amyloid aggregation.

In the early stages of disease, TTR-CM may not be clinically expressed, often escaping diagnosis until further progression when marked ventricular wall thickening, profound diastolic dysfunction and conduction abnormalities are apparent. Symptoms of TTR-CM are often similar to those seen in other types of heart failure although there are some cardinal features, both cardiac and non-cardiac, that should raise the suspicion of TTR-CM and prompt investigation or referral to an expert center for a confirmed diagnosis.

Such symptoms include evidence of preserved or reduced ejection fraction during echocardiography, with concentric thickening of the interventricular septum and the left ventricular (LV) wall. An ECG recording of low or near-normal QRS voltages despite LV wall hypertrophy (discordant voltage:mass ratio) also supports the diagnosis of TTR-CM. In addition to cardiac signs and symptoms, presence of one or more of the following should further increase suspicion of amyloid disease: history of bilateral carpal tunnel syndrome; neuropathy with paresthesia/sensory impairment; positive troponin in the absence of acute coronary syndrome; and family history of heart failure.[2]

The impact of genetics

TTR-FAP is caused by mutations in the *TTR* gene that are transmitted in an autosomal dominant fashion.

Over 100 mutations in the gene encoding transthyretin have been discovered, most of which are associated with amyloid disease.[3] Genetic mutations in the *TTR* gene can lead to pathogenic variants of the transthyretin protein that cause TTR-FAP.[3] Such mutations have varying geographic distributions, organ predisposition and amyloidosis severity.[11]

Of these variants, V30M, the first variant to be described in Portugal in the 1950s, is the most widely studied. Transthyretin was found in fibrils in several members of the same family with autosomal dominant amyloidosis affecting peripheral nerves, the heart and other organs. TTR V30M has since been identified in Japan and Sweden.[11]

Subjects with the V30M mutation typically experience disease manifestation in their 30s.[4] Irrespective of the age of onset, most subjects with the V30M gene mutation experience sensory neuropathy; however, the typical disease manifestations observed in subjects with early onset or late onset TTR-FAP may differ.[13] In early-onset disease, autonomic neuropathy and gastrointestinal manifestations are commonly observed.[14] In late-onset disease, which is typically experienced in the fifth decade of life, paresthesias in the legs along with mild symptoms of autonomic dysfunction and frequent cardiac involvement have been reported.[5] Other variants, such as T60A, L58H, G6S and V122I, are found in various geographical locations worldwide and vary in terms of symptoms and affected organs.[11] The mutations with predominantly cardiac manifestations include the TTR Ile111M and TTR V122I mutations, found primarily in Danish and African-American subjects.[2]

TTR-FAP demonstrates variable penetrance;[15] not all individuals who inherit the *TTR* gene mutation will have amyloid deposition or develop the symptoms associated with the disease.[3] Family members of individuals with TTR-FAP may also have the mutation, even though they do not display the signs or symptoms. Penetrance has been shown to vary both by country of origin and by the type of *TTR* gene mutation present.[3,5]

Prognosis of TTR amyloidoses

In early-onset TTR-FAP, age of symptom onset is typically in the 30s, while in late-onset TTR-FAP symptom onset usually occurs in the 50s, resulting in a heavy burden for the subject and their family and carers.[1–2] Disease progression is relentless, with severe debilitation and death typically occurring an average of 10 years after symptom onset as a result of autonomic dysfunction, renal failure, cardiac disease or infection.[3–4]

The typical and ongoing loss of physical ambulation experienced by subjects with TTR-FAP has a significant impact on their independence and activities of daily living. Subjects with TTR-FAP typically require assistance, and may eventually be bedridden and/or require wheelchair assistance.[5]

During the early years of TTR amyloidosis, sensory, motor, autonomic and cardiac symptoms are typically mild in severity, with limited impact on activities of daily living (ADL) and no impact on ambulation.[5] TTR-FAP is later characterized by motor dysfunction in the lower limbs and loss of touch sensation. The hands begin to weaken and pain and temperature sensation is impaired. The early pattern of involvement of the feet and hands is called the stocking and glove pattern. At this point, the subject is still mobile but requires assistance to walk with crutches or a stick. Further progression of the disease typically results in the subject becoming bedridden or confined to a wheelchair with generalized weakness. A lack of pain and temperature sensation is evident all over the body, with the exception of the head and neck. Subjects are often unable to care for themselves, are malnourished and, in the late-stages of the disease, have cachexia and urinary and fecal incontinence.[5]

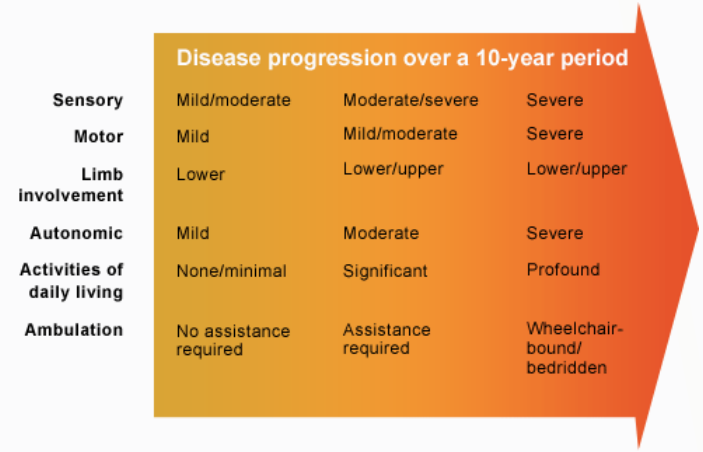


Figure from: http://www.recognizingttr-fap.com/impact

TTR-CM typically results in restrictive cardiomyopathy that manifests late in its course with symptoms of heart failure and conduction abnormalities, ultimately leading to death. The wild-type TTR disease typically shows a slowly progressive course, and treatment is normally restricted to symptom relief with conventional therapy for heart failure. Subjects with either wild-type or inherited disease may develop symptoms that are significant enough to require a heart transplant. In inherited cardiac TTR-cardiomyopathy, the typical clinical picture of cardiovascular involvement ranges from asymptomatic atrioventricular and bundle branch block to severe and rapidly progressive heart failure owing to the significant restrictive cardiomyopathy.[2]

Further information on TTR amyloidosis can be found at www.recognizingttr-fap.com

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