

Transthyretin Amyloidosis – an Overview

Disease Summary

Familial amyloidosis describes a group of late-onset autosomal dominant diseases with amyloid protein deposition occurring in various tissues throughout the body and in the bloodstream (reviewed in (1)). Transthyretin Amyloidosis (ATTR), the most common familial amyloidosis, is associated with mutations in the *TTR* gene and is generally characterized by progressive neuropathy, cardiomyopathy, nephropathy, rheumatopathy, CNS abnormalities, and/or vitreous opacities (reviewed in (1,2); Table 1). ATTR is generally considered a rare disease, but is endemic in regions of Portugal, Japan, and Sweden, where prevalence can be as high as 1 in 538 (2). These regional differences are due to both prevalence of certain *TTR* mutations in different ethnicities and to penetrance of the same mutation in different ethnicities. For example, Val30Met, the most common pathogenic *TTR* gene mutation, has been reported to be much more penetrant in Portugal (87%) than in Sweden (2%)(2), suggesting that genetic background plays a large role in disease etiology.

Pathogenesis of ATTR arises from mutations in the *TTR* gene resulting in an abnormal trans-thyretin protein structure, which forms sticky amyloid fibrils that can travel through the serum or CNS fluid and adhere to organs (3, 4). A leading cause of death from ATTR is congestive heart failure from progressive cardiomyopathy caused by amyloid infiltration of the myocardium (1). While cardiomyopathy is a common manifestation in ATTR, in some cases, it may also be the primary manifestation of disease (2, 5, 6). This cardiac-specific subset of ATTR is typically characterized by restrictive cardiomyopathy, coronary insufficiency, valvular thickening, conduction system disease, and arrhythmias (5-7). Cardiac-specific ATTR is associated with *TTR* gene mutations that differ from those associated with systemic ATTR, with the most common pathogenic variant (Val122Ile) being present in about 3% to 4% of African-Americans (2).

While patients with systemic ATTR often present with neuropathological symptoms between the ages

of 40 and 60 years (and even earlier in endemic regions (2)), patients with cardiac-specific ATTR typically present with symptoms of congestive heart failure (see Table 1) between the ages of 60 and 70 years (2, 6). It is not uncommon for patients with cardiac-specific ATTR to also present with carpal tunnel syndrome (1). Echocardiography may show several features indicative of cardiac-specific ATTR; however, the features are not clear until late in disease (5). In addition, echocardiography cannot be used in isolation to diagnose cardiac-specific ATTR since the characteristic echocardiological feature of cardiac-specific ATTR is thickening of the left ventricular wall, which can also be seen in hypertensive heart disease, hypertrophic cardiomyopathy, and other infiltrative cardiomyopathies (glycogen storage diseases, sarcoidosis, and hemochromatosis) (5). The majority of therapies that exist for ATTR are for treatment of symptoms (Table 1) with the exception of transplantation of the affected organs (2, 5, 8). Liver transplantation is the most effective treatment since the source of transthyretin production is removed; however, liver transplantation is only effective when performed at early stages of disease (2). In cardiac-specific ATTR, it is recommended that both the heart and liver are transplanted to prevent infiltration of the transplanted heart with amyloid deposits (6).

Definitive diagnosis of ATTR is achieved by genetic testing in combination with biochemical proof of amyloid transthyretin protein deposition (biopsy and staining) in affected tissues (1, 2). As part of the diagnostic process, genetic testing can also help to determine whether disease is systemic or limited to specific organs, since certain *TTR* gene mutations have been associated with either form of disease (2, 4). Once the exact *TTR* gene mutation is found in a patient, genetic testing of family members can alert them to their risk of ATTR even before symptoms appear (1). Importantly, early diagnosis through genetic testing makes it more likely that liver transplantation can be performed at early stages of disease, when it is most effective (5).

Table 1: Disease Facts about ATTR (based on references 2-6)		
Disease Names	Transthyretin Amyloidosis Familial Amyloid Polyneuropathy	Cardiac-specific Transthyretin Amyloidosis Familial Amyloid Cardiomyopathy
MIM* number	105210	
Estimated Prevalence	1 in 100,000; as high as 1 in 538 in endemic areas (Japan, Portugal, and Sweden)	unknown
Average Age at Diagnosis	40 to 60 years (30 to 50 years in endemic areas)	60 to 70 years
*MIM: Mendelian Inheritance in Man, see http://www.ncbi.nlm.nih.gov/omim		

Table 2: Molecular Genetics of ATTR (based on reference 2)

Gene (Protein)	Transmission	Mutation type	Penetrance	Comments
<i>TTR</i> (transthyretin)	Autosomal dominant	Loss-of-function (protein) Gain-of-function (toxic deposits formation)	Varies widely based on genetic variant and geographic location	The most common <i>TTR</i> variant associated with systemic ATTR is Val30Met (a.k.a. Val50Met), which is highly penetrant in Japan (87%) but not in Sweden (2%). ² The most common <i>TTR</i> variant associated with cardiac-specific ATTR is Val122Ile (a.k.a. Val142Ile), which is found in 3.9% of the African American population. ²

References

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