JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY
VOL. 66, NO. 21, 2015
ISSN 0735-1097
http://dx.doi.org/10.1016/j.jacc.2015.09.075

THE PRESENT AND FUTURE

REVIEW TOPIC OF THE WEEK

Diagnosis, Prognosis, and Therapy of Transthyretin Amyloidosis

Morie A. Gertz, MD,* Merrill D. Benson, MD,† Peter J. Dyck, MD,‡ Martha Grogan, MD,§ Terresa Coelho, MD,‖ Marcia Cruz, MD,¶ John L. Berk, MD,# Violaine Plante-Bordeneuve, MD,** Hartmut H.J. Schmidt, MD,†† Giampaolo Merlini, MD‡‡

ABSTRACT

Transthyretin amyloidosis is a fatal disorder that is characterized primarily by progressive neuropathy and cardiomyopathy. It occurs in both a mutant form (with autosomal dominant inheritance) and a wild-type form (with predominant cardiac involvement). This article guides clinicians as to when the disease should be suspected, describes the appropriate diagnostic evaluation for those with known or suspected amyloidosis, and reviews the interventions currently available for affected patients. (J Am Coll Cardiol 2015;66:2451–66) © 2015 by the American College of Cardiology Foundation. Published by Elsevier. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

In 1858, Rudolf Virchow described the reaction of tissue deposits with iodine and sulfuric acid. This reaction was known as a marker for starch in plants; thus, Virchow referred to the deposits as starch-like or "amyl*oid*." Recognition that these deposits stained with Congo red occurred in 1922, and the apple-green birefringence was discovered in 1927 in the brain of a patient with Alzheimer's disease (1). Deposits of transthyretin (TTR), a tetrameric protein rich in β strands that is highly conserved and present in all human serum, can cause amyloidosis. TTR's physiological function includes transportation of thyroxine and retinol-binding protein; the name *transthyretin* was coined from *trans*ports *thy*roxine and *retin*ol.

TTR is synthesized primarily by the liver, with <5% synthesized in the choroid plexus of the brain and the retinal pigment epithelium. TTR has important roles in behavior, cognition, nerve regeneration, and axonal growth (2). TTR has an innate ability to aggregate into insoluble amyloid fibers. Transient accumulation of TTR oligomers, composed of 6 to 10 monomers, may cause cell toxicity or tissue damage. Single point mutations can increase the likelihood of TTR misfolding into an insoluble β-pleated sheet, which deposits in the heart, nerves, and other tissues, causing familial amyloid cardiomyopathy, familial amyloid polyneuropathy (FAP), and leptomeningeal amyloidosis (3,4). **Table 1** provides the most common mutations recently reported from a single U.S. center. More than 80 TTR mutations have been described, including the nonpathogenic G6S mutation found in 6% of the white population. V30M is the second most

From the *Division of Hematology, Mayo Clinic, Rochester, Minnesota; †Indiana University School of Medicine, Indianapolis, Indiana; ‡Division of Peripheral Nerve, Mayo Clinic, Rochester, Minnesota; §Division of Cardiovascular Diseases, Mayo Clinic, Rochester, Minnesota; ‖Hospital de Santo Antonio, Porto, Portugal; ¶Federal University of Rio de Janeiro of Brazil, University Hospital, Rio de Janeiro, Brazil; #Amyloidosis Center, Boston University School of Medicine, Boston, Massachusetts; **University Hospital, Henri Mondor, Créteil, France; ††Universitätsklinikum Münster, Münster, Germany; and the ‡‡Department of Molecular Medicine, University of Pavia, Pavia, Lombardy, Italy. Dr. Gertz is an advisory board member of and has received honoraria from Isis Pharmaceuticals. Dr. Coelho has received financial support to attend scientific meetings from Isis Pharmaceuticals, Alnylam, and Pfizer; and has received honoraria from Pfizer for educational activities. Dr. Cruz has served as an advisor for Pfizer, Isis Pharmaceuticals, Alnylam Pharmaceuticals, and FoldRx Pharmaceuticals; has received support as a clinical investigator from FoldRx Pharmaceuticals, Isis Pharmaceuticals, and Alnylam Pharmaceuticals; and currently serves on the THAOS (a disease registry capturing natural history and effect of the therapies on TTR amyloidosis) scientific advisory board. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received June 23, 2015; revised manuscript received September 24, 2015, accepted September 25, 2015.

Listen to this manuscript's audio summary by *JACC* Editor-in-Chief Dr. Valentin Fuster.

ABBREVIATIONS AND ACRONYMS

AL = immunoglobulin light chain

ATTR = transthyretin amyloidosis

CMR = cardiac magnetic resonance

DPD = diphosphono-propanodicarboxylic acid

FAP = familial amyloid polyneuropathy

NT-proBNP = N-terminal pro-B-type natriuretic peptide

siRNA = small interfering ribonucleic acid

TTR = transthyretin

wt = wild type

common mutation in the United States, but, to date, it is the most frequent reported globally. Three major clusters in Portugal, Sweden, and Japan have been described. The Portuguese and Japanese appear to have a single founder in the 15th century (brought from Portugal to Japan by explorers) (5,6). The V30M mutation seems to have appeared later in Sweden than in Portugal and Japan (7). The largest populations of mutant TTR, V30M (p.V50M), are in endemic areas of Japan, Sweden, and Portugal, with large cohorts in Brazil (8). The T60A mutation originated in northwest Ireland and came to the United States, where it was termed *Appalachian amyloidosis*. The V122I founder likely originated in West Africa, as indicated by V122I TTR expression in the Caribbean islands.

Wild-type (wt) TTR can also misfold into the amyloid configuration. Previously termed *senile cardiac amyloidosis* and subsequently as *senile systemic amyloidosis*, wt TTR amyloidosis will be called wt transthyretin amyloidosis (ATTR) in this paper. Wt ATTR is sporadic, with no known biomarkers for its diagnosis. Deposition of the wt protein occurs almost exclusively (90%) in men >60 years of age.

CLINICAL CHARACTERISTICS OF CARDIAC AMYLOIDOSIS

Amyloid infiltration results in poor diastolic relaxation (poor filling, with low end-diastolic volume). Doppler measures of inflow velocity can detect left ventricular diastolic filling abnormalities, and Doppler diastolic filling variables are prognostic in cardiac amyloidosis. Shortened deceleration time and an increased early diastolic filling velocity to atrial filling velocity ratio are stronger predictors of cardiac death (9). Amyloid cardiomyopathy should be suspected in any patient who presents with heart failure and preserved ejection fraction. Findings of right-sided heart failure predominate, including lower-extremity edema, hepatomegaly, ascites, and elevated jugular pressure. Right ventricular dilation is linked to more severe cardiac involvement and short survival (median 4 months) (10). A study of 74 patients with biopsy-proven immunoglobulin light chain (AL) amyloidosis showed an association of right ventricular dysfunction with more severe involvement of the left ventricle, higher plasma levels of N-terminal pro-B-type natriuretic peptide (NT-proBNP), and poor prognosis (11).

Using strain echocardiography, left atrial dysfunction was identified in 32% (lateral left atrial criteria) and 60% (septal left atrial criteria) of patients with amyloidosis (12). Severe atrial and ventricular infiltration by amyloid may result in mechanical atrial standstill, with resultant thrombus formation (13). These findings have been identified by cardiac magnetic resonance (CMR) imaging (14). CMR has also been used to estimate cardiac amyloid burden by quantification of myocardial extracellular volume fraction (15). In addition to heart failure, patients may present with atrial arrhythmias or conduction system disease. In patients who have ventricular thickening without a history of hypertension or valvular disease, an infiltrative cardiomyopathy should be considered (16). Deposition of amyloid into the myocardial wall causes diastolic dysfunction, restrictive physiology with late loss of systolic function, arrhythmias, and heart failure (17). The finding of increased wall thickness, small ventricular volume, and occasional dynamic left ventricular outflow tract obstruction can be confused with true hypertrophic conditions such as hypertrophic cardiomyopathy and hypertensive heart disease. Although the electrocardiogram classically shows low voltage in the QRS complex in amyloidosis and increased voltage in myocyte hypertrophy disorders, the overlap is great; voltage can be useful but is not reliable (18,19).

Clues to the presence of amyloid cardiomyopathy are seen in the widespread deposition of amyloid. In patients with wt ATTR, one-half have associated carpal tunnel syndrome caused by deposition of TTR amyloid into the carpal tenosynovial tissue, with hand symptoms typically preceding cardiac manifestations by 8 to 10 years. Of patients with idiopathic carpal tunnel syndrome, 34% will have amyloid deposition in tenosynovial tissue, possibly representing an early symptom of wt ATTR cardiomyopathy (20).

Clinical presentation of mutant ATTR is variable and driven by the specific mutation, of which ~110 have been described. Patients with mutant ATTR present on a spectrum from exclusive neuropathy to

TABLE 1 Most Common TTR Mutations Identified in Patients With Symptomatic Amyloidosis

TTR Mutation	Mayo Clinic	TTR Amyloidosis Outcomes Survey
T60A	26.0	1.7
V30M	16.0	73.3
V122I	11.0	4.4
S77T	6.0	1.6
L111M	0.0	1.9
E89Q	0.0	2.1
All others	41.0	16.7

Values are %. Data from Coelho et al. (21) and Swiecicki et al. (22).
TTR = transthyretin.