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Cardiac Amyloidosis – Recognition, Diagnosis, and Referral for Treatment

As you undoubtedly know, end-stage heart failure affects approximately 6,000,000 Americans with over 500,000 new cases being diagnosed each year. Although the illness is not confined to the elderly population, most new cases are seen in those over 55 years of age and disproportionately in the African American population.

Recent work has demonstrated that 4% of African Americans (and in other populations as well) carry a mutation in a gene coding for a tetrameric thyroid hormone transporter protein known as transthyretin (TTR). This mutation, in which valine is changed to isoleucine in the gene's 122 position (V122I), results in an unstable transthyretin tetramer. This allows the tetramer to fold incorrectly and subsequently deposit in the myocardial interstitium. These deposits are responsible for the infiltrative cardiomyopathy we refer to as amyloid heart disease. Because this is a genetic mutation, the offspring of the affected individuals are also at risk for the illness; hence the name "familial amyloid cardiomyopathy."

In those patients who develop amyloidosis due to a genetic mutation, the illness is known as *mutant* TTR (aTTRm).

Cardiac amyloidosis can also be seen in the absence of genetic mutations. This disease is referred to as *wild-type* (formerly senile) TTR (aTTRwt). Why transthyretin deposits in the myocardium in patients with non-mutated TTR is unclear. Clinically, the presentation of these patients is indistinguishable from the familial version of the disease, although they tend to occur a bit later in life. Senile or wild-type disease is seen predominantly, but not only, in males.

The actual number of cases of TTR-related (aTTR) amyloid heart disease in New Jersey (as distinguished from primary (aL) amyloid heart disease due to hematologic malignancies) is probably far in excess of the number of cases actually diagnosed each year. This is due in part to the "out of sight, out of mind" problem and because the definitive diagnosis of cardiac amyloid used to require an endomyocardial biopsy and immunohistochemical staining.

Today, however, the diagnosis can be suggested by echo and semi-confirmed by contrast MRI. MRI, however, does not distinguish between light chain amyloid (aL) and TTR amyloid. Fortunately, only aTTRm and aTTRwt light up on Tc99 PYP scans while aL amyloid generally does not.

The presence of atrial fibrillation and low voltage on an ECG or biventricular hypertrophy and/or biatrial enlargement on echocardiography can sometimes suggest the diagnosis, especially in the presence of carpal tunnel syndrome or spinal stenosis.

Until now, making the diagnosis of aTTR amyloid heart disease was intellectually satisfying but somewhat irrelevant as no real treatment option (other than diuretics) existed. Over the past few years, however, a number of novel agents have been studied.

Tafamidis a stabilizer of TTR is now available and is has proven to be very effective. While the medication may not reverse the illness it is now clear that the medication will slow progression of the disease by decreasing the deposition rate of the TTR.

Some investigational medications don't *stabilize* the TTR tetramer but rather *silence* the gene thereby eliminating its production. At present, two "silencers" are available for use in patients, but even though aTTR(m) and aTTR(wt) present the same and are effectively the same illness, silencers are approved only for *mutant or hereditary* disease and not *wild-type* disease.

New investigational studies to treat *wild-type* amyloid are presently ongoing.

The primary reason for this correspondence is to remind each of you that now that treatment is available for at least some patients it is important to entertain the diagnosis in all susceptible patients in order to initiate therapy early and to screen offspring.

As you probably know, I would be happy to speak to you at any time regarding this illness (including the matter of genetic testing) or any matters that may pertain to end-stage heart failure, cardiac transplantation, or LVADs.

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