Research Correspondence

Transthyretin V122I in African Americans With Congestive Heart Failure

To the Editor: Hereditary cardiomyopathies are not usually considered in the diagnosis of elderly individuals with congestive heart failure (CHF). It is even more problematic in African Americans, because hypertensive cardiovascular disease is so pervasive; however, a large autopsy study showed that above the age of 60 years, transthyretin (TTR) cardiac amyloidosis is more common in African Americans than in two other ethnic groups (1). Furthermore, in that analysis more than one-fourth of the African Americans with TTR cardiac amyloidosis were heterozygous for an allele encoding isoleucine rather than wild type valine at position 122 (V122I) in TTR, the serum carrier of retinol binding protein charged with retinol and a portion of thyroxine. Eighty-two TTR mutations have been associated with tissue (including cardiac) amyloid deposition with autosomal dominant inheritance; V122I is common in African Americans and rare in other populations (Table 1)(1–3). Very few other variants have been reported in individuals of African descent.

Because the clinical role of V122I was not established in the autopsy study and its association with heart disease had been examined in only a small number of patients with overt cardiac amyloidosis, we determined its frequency in a cardiologically well-characterized African–American population with New York Heart Association (NYHA) functional class III and class IV CHF participating in the Beta-Blocker Evaluation in Survival Trial (BEST) (4).

Polymerase chain reaction amplification and restriction digestion of the fourth exon of the TTR gene detected the mutant codon in 13 (6.28 ± 1.7%) of the 207 African-American BEST participants, a proportion statistically significantly different from a sample of African-American newborns in Indiana (p = 0.036), newborns from New York State (p = 0.0452), and the African-American cohort of the Cardiovascular Health Study (CHS) (5) (p = 0.004) (Table 1). There were no significant differences in the distribution of presumed etiologies between the V122I carriers and homozygous wild type individuals.

Four of the 116 individuals in the under age 60 years cohort (3.5 ± 1.7%) were positive, whereas 9 of the 91 over age 60 years (10 ± 3.1%) carried the amyloidogenic allele. The difference in prevalence between the under-60 and over-60 age groups was suggestive but not quite statistically significant (p = 0.08); however, in the over-60 cohort the prevalence was almost five times that in African Americans of similar age participating in the community-based CHS; an ascertainment-bias minimized control population for the over-60 group (10 ± 3.1% vs. 2.12 ± 0.5%; p = 0.0006). The significant difference indicates the allele is far more prevalent in African Americans with CHF than in a community cohort of comparable age.

Several features of the BEST study minimize the frequency of cardiac amyloidosis among the African-American deoxribonucleic acid donors. A diagnosis of cardiac amyloidosis was exclusionary. Moreover, the age distribution in the randomly chosen deoxribonucleic acid donors differed from that in the entire BEST population (116 subjects were 59 years or younger, and 91 [44%] were older among the African-American deoxribonucleic acid donors; whereas 261 individuals were under 60 years of age, and 366 [58%] were over 60 years of age in the entire African American cohort). Because TTR cardiac amyloidosis occurs after age 60 years, the age distribution of the deoxribonucleic acid donors would tend to reduce the apparent frequency of heart failure caused by late-onset disease relative to that in the entire study population (1,6).

The diagnostic echocardiographic studies most likely to distinguish cardiac amyloidosis from other causes of CHF were not performed in all the deoxribonucleic acid donors. Thus we could not determine whether amyloidosis played a role in the etiology of the heart failure. Given the relatively small number of gene carriers, no survival differences were seen. Furthermore, the presence of cardiac amyloidosis does not protect the individual from other forms of heart disease (1).

Multiple studies have shown that cardiac amyloidosis causes CHF and arrhythmias in older adults; however, these features are non-specific, and the clinical diagnosis might not be obvious without careful echocardiographic analysis and endomyocardial biopsy (6,7). Because we could not perform endomyocardial biopsies to demonstrate cardiac amyloid deposition pathologically in any of the V122I carriers, it is formally possible that the allele imparts risk via some other mechanism. In the earlier autopsy study there was sufficient clinical information available to ascertain the presence or absence of CHF in 27 of the 126 subjects with pathologically established TTR amyloidosis related to either wild type (both African Americans and Caucasian Americans) or TTR V122I (African Americans only). In almost one-half of those (13

Table 1. Prevalence of the Amyloidogenic Transthyretin V122I Allele in Individuals Without Clinically Apparent Amyloidosis

<table>
<thead>
<tr>
<th>Sample</th>
<th>Number</th>
<th>Age (yrs)</th>
<th>Prevalence (%)</th>
<th>Allele Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caucasian (convenience) (2)</td>
<td>86</td>
<td>Not noted</td>
<td>&lt;1.2 (0/86)</td>
<td>&lt;0.006</td>
</tr>
<tr>
<td>Caucasian (3)</td>
<td>453</td>
<td>Newborn</td>
<td>0.4 (2/453)</td>
<td>0.002</td>
</tr>
<tr>
<td>African American*</td>
<td>1,219</td>
<td>Newborn</td>
<td>3.3 (40/1219)</td>
<td>0.016</td>
</tr>
<tr>
<td>African American (3)</td>
<td>1,000</td>
<td>Newborn</td>
<td>3.0 (30/1000)</td>
<td>0.015</td>
</tr>
<tr>
<td>African American (CHS)*</td>
<td>802</td>
<td>Community</td>
<td>2.12 (17/802)</td>
<td>0.011</td>
</tr>
<tr>
<td>BEST: NYHA class III and IV heart failure*</td>
<td>207</td>
<td>19–93</td>
<td>6.3 (13/207)</td>
<td>0.032</td>
</tr>
<tr>
<td>Under age 60 yrs</td>
<td>116</td>
<td>&lt;60</td>
<td>3.5 (4/116)</td>
<td>0.018</td>
</tr>
<tr>
<td>Age 60 yrs or over</td>
<td>91</td>
<td>&gt;60</td>
<td>10 (9/91)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

*Present study.

BEST = Beta-Blocker Evaluation in Survival Trial; CHS = Cardiovascular Health Study; NYHA = New York Heart Association.
of 27), there was no anatomic evidence of any cardiac disease other than amyloidosis (1). That study also suggested that the V122I allele was always associated with some degree of anatomic ventricular amyloid in African Americans 60 years or older and is consistent with the notion that age-dependent, autosomal dominant cardiac amyloidosis could contribute to congestive failure. Thus, if the BEST participants were representative of all African Americans age 60 years or over with NYHA functional class III and class IV CHF, late onset, autosomal dominant cardiac amyloidosis due to the TTR V122I allele could be responsible for 10% of severe heart failure in this population, a possibility that should be investigated by a more formal study, rather than as an add-on to a therapeutic trial.

Once considered, the diagnosis is possible by echocardiography in the majority of cases and by endomyocardial biopsy in all (subcutaneous fat aspiration might have a low diagnostic yield in late onset cardiac deposition) (7,8). Although specific therapy is not available at this time and liver transplantation is denied to these individuals because of their age, the diagnosis suggests that digoxin and calcium channel blockers might be avoided (9,10).

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Influence of Proteinuria on Cardiovascular Risk and Response to Angiotensin-Converting Enzyme Inhibition After Myocardial Infarction

To the Editor: Proteinuria is a known predictor of cardiovascular (CV) morbidity and mortality in diabetics, hypertensive patients, and the general population (1–3), but the impact of proteinuria as a risk factor after acute myocardial infarction (MI) is less well-defined. We analyzed a subset of patients enrolled in the Survival And Ventricular Enlargement (SAVE) trial in whom dipstick urinalyses were recorded to determine the prognostic importance of baseline proteinuria on outcomes, and to evaluate whether the response to angiotensin-converting enzyme (ACE) inhibition is affected by the presence of proteinuria.

The SAVE trial was a randomized, double-blind, placebo-controlled trial examining the use of ACE inhibition in 2,231 patients with acute MI and left ventricular dysfunction (left ventricular ejection fraction [LVEF] ≤40%) (4). Patients with serum creatinine <2.5 mg/dl were randomized to captopril (50 mg three times a day) or placebo on average 10 days post-MI. A total of 658 patients from the Canadian cohort underwent dipstick urinalyses because of safety concerns, and baseline dipstick measures were available in 583 patients. Dipstick classification included none, trace, 1+, 2+, 3+, 4+, corresponding to protein concentrations of <10 mg/dl, 10 to 30, 30 to 100, 100 to 300, and >1,000 mg/dl, respectively (5). The four-variable Modification of Diet in Renal Disease equation was used to estimate glomerular filtration rate (eGFR) (6). Univariate and multivariate estimates of risk for outcomes were derived using Cox proportional hazards models, and the interaction between proteinuria and treatment effect was assessed. All-cause mortality, CV mortality, and a composite outcome of death, stroke, recurrent MI, and hospitalization for congestive heart failure over 42 months of follow-up were primary end points.

Of 583 subjects, 122 (20.9%) had trace or greater proteinuria (trace, 14.9%; greater-than-trace, 6.0%). Proteinuric subjects were older, more often hypertensive (p = 0.03), with higher baseline serum creatinine (p < 0.001) Killip class (p < 0.001), and lower LVEF (p < 0.001). Diabetes prevalence (p = 0.18), use of lipid-lowering agents (p = 0.21), or use of aspirin (p = 0.90) did not significantly differ between patients groups. Proteinuria in-