EDITORIAL COMMENT

Detection of Subclinical Fabry Disease in Patients Presenting With Hypertrophic Cardiomyopathy*

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In the post-genomic era of science and medicine, genetic testing to determine subclinical disease, which escapes conventional clinical diagnosis, is being increasingly used. In addition, clinical genetic testing plays an important role in the diagnosis of pleomorphic disorders that might not only present subclinically but also with variable symptomology.

Anderson-Fabry disease (AFD), an inborn error of metabolism, affects an estimated 1 in 50,000 men and is due to loss-of-function mutations in *GLA*-encoded lysosomal alpha-galactosidase A (α-gal), an enzyme responsible for breaking down fatty substances in the body called globo-triaosylceramides (GL-3) [1,2]. The resulting accumulation of GL-3 in the vascular endothelial lysosomes causes a highly variable clinical presentation that might manifest as acroparesthesias, angiokeratoma, corneal and lenticular opacities, and anhidrosis [3]. In addition, the gradual accumulation of GL-3 in the walls of the blood vessels and tissues such as the heart, kidneys, and brain causes progressive tissue damage and potentially life-threatening problems. Unabated, this disease results in severe microvascular dysfunction and early death. Importantly, although AFD is often a systemic disorder, cardiac involvement can occur exclusively in the presence of specific *GLA* mutations [4,5]. Furthermore, in this AFD variant, the resulting myocardial hypertrophy and mitral valve thickening can mimic hypertrophic cardiomyopathy (HCM) [6].

Localizing to the long arm of chromosome X (Xq22), *GLA*-opathies are far more expressive in men than women. Men with <1% residual α-gal activity generally manifest AFD, whereas men with 5% to 15% residual levels of α-gal activity are more likely to display a cardiac-only phenotype that, to the eyes of an echocardiographer, looks for all the world to be indistinguishable from classical HCM. Depending on the nature of the X chromosome inactivation in women (lyonization), women might variably express the spectrum of AFD as well [7,8]. Furthermore, as many as 3% of men with unexplained left ventricular hypertrophy (LVH) in 1 study [6] and 6.3% of men with late-onset HCM in another [7], had low α-gal enzyme activity. Conversely, among a cohort of women hosting heterozygous mutations in *GLA*, 55.6% of women <38 years of age demonstrated LVH, whereas all women over 45 years had significant LVH [9].

Unlike sarcomeric/myofilament HCM that lacks gene-specific therapy, AFD and *GLA*-mediated HCM are potentially very treatable, given the availability of recombinant α-gal enzyme replacement therapy since 2001 [10]. Early detection of at-risk individuals is vital to ensure proper surveillance of disease expression and gene-specific pharmacotherapy (i.e., enzyme replacement therapy) [10,11].

Fabry Disease Within an HCM Cohort

In this issue of the *Journal*, Monserrat et al. [12] provide an elegant study demonstrating that, within a Spanish cohort of 508 unrelated patients with clinically diagnosed HCM, approximately 3% (6 of 328 men, 9 of 180 women) had reduced α-gal enzymatic activity ranging from 0% to 30% in men and 0% to 50% in women. Genetic analysis of this subset of 15 patients with reduced α-gal enzymatic activity revealed 5 (33%) having *GLA* mutations associated with AFD. This proportion of mutation-positive cases within AFD is similar to the 12 (29.2%) mutation-positive cases in 41 neonates with reduced α-gal activity observed previously [13]. When the residual levels of α-gal enzymatic activity were ≤20%, the probability of detecting a *GLA* mutation approached 100%. Furthermore, the highest residual level of α-gal for which a positive mutation was nonetheless detected was 25%.

None of the mutations previously seen in patients with cardiac-only AFD or isolated GLA-HCM were detected here [6]. Instead, 3 of the 4 *GLA* mutations (L89P, A143T, and E358del) discovered by Montserrat et al. [12] have been associated previously with classical or delayed-onset AFD. Importantly, although neither the L89P- nor A143T-positive index case had a personal history to suggest AFD, retrospective sleuthing revealed clues in the family that could have prompted suspicion as to the presence of a heritable multiorgan syndrome. For example, the index case with L89P-GLA had a nephew who developed renal failure at 35 years of age, without a specific diagnosis, after suffering from acroparesthesias as a child. He went on to

develop concentric LVH and suffered from multiple cerebral infarctions. Furthermore, the index case's sister died after dialysis of renal failure at 24 years.

In addition, the E358del-GLA–positive subject did have symptoms compatible with AFD, including a history of hypohidrosis and mild renal failure. Only the novel missense mutation, S238N, was detected in 2 patients with seemingly isolated GLA-HCM or cardiac only, atypical AFD. Exclusion of these 3 patients that had a compelling personal/family history consistent with AFD, albeit in retrospect, would suggest that the frequency of GLA-HCM might be approximately 0.4% (2 of 505) with clinically/echocardiographically diagnosed HCM.

Screening for Fabry Disease in Patients Presenting With LVH

Given this low frequency, it seems debatable as to whether biochemical testing to determine α-gal activity should be a standard part of the clinical evaluation of HCM. To be sure, the identification of a GLA-positive subject will permit: 1) establishing the correct diagnosis— cardiac AFD or GLA-mediated HCM rather than sarcomeric HCM; 2) proper surveillance for disease/organ expression; 3) proper classification of at-risk relatives; 4) proper counseling of transmission risk, including affected men (having 0% transmission risk to men, 100% transmission risk to female offspring, whereas affected women have 50% transmission risk to their children, with men being affected and women being "carriers"); and 5) treatment with genotype-specific enzyme replacement therapy. Indeed, failure to distinguish cardiac hypertrophy secondary to AFD from "classical" HCM (i.e., sarcomeric/myofilament-HCM) can cause the patient to be deprived of potentially life-saving enzyme replacement therapy.

At first blush, this tandem biochemical screen and subsequent deoxyribonucleic acid sequencing of GLA seems a most prudent recommendation. In the study by Monserrat et al. (12), precisely because of the detection of reduced α-gal activity and subsequent genetic confirmation of a GLA defect in the 5 index cases, 14 GLA mutation-positive relatives—6 of whom demonstrated no clinical manifestations of AFD—were exposed. Thus, at-risk individuals were discovered pre-clinically, which enabled initiation of careful surveillance for the early detection of organ(s) involvement and treatment with enzyme-replacement therapy.

Despite this obvious clinical benefit, formal cost-effective analyses have not been performed for routine biochemical screening of α-gal activity in the evaluation of HCM. Biochemical assays to determine α-galactosidase enzymatic activity cost approximately $250. If done as clinical practice in the U.S., the cost to screen the 508 patients in this study would exceed $125,000. For the 3% that exceeded the pre-specified cut-off value prompting GLA genetic testing,

another $10,000 would be required for the GLA genetic test ($700/test in the U.S.). Given the thresholds used here, only one-third of the patients directed to the second tier of AFD testing will have a positive genetic test. Thus, the cost to establish either clinically unrecognized AFD or GLA-HCM status for the 5 index cases was $135,000. The potential cost of screening increases when one considers that the time-honored and relatively inexpensive past medical history and family history perhaps should have prompted a targeted suspicion of AFD for 3 of the 5 positive cases. If these back-of-the-napkin calculations are validated by formal cost-effective analyses, then a recommendation for universal α-gal screening in the evaluation of hypertrophic cardiomyopathy might fall on deaf ears.

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