Prevalence of Anderson-Fabry Disease in Male Patients With Late Onset Hypertrophic Cardiomyopathy

To the Editor:

Sachdev et al describe the utility of plasma α-galactosidase for diagnosing Anderson-Fabry disease. As the authors emphasize, this disease is not particularly common, but it may be potentially treatable or stabilized with recent advances in treatment. A recent study documented stabilization of cardiac disease using galactose infusions in a patient with Fabry’s disease who had been a transplant candidate.

Fabry’s disease may also be diagnosed using endomyocardial biopsy. Fabry’s disease may be encountered in individuals being examined because of unexplained left ventricular hypertrophy, hypertrophic cardiomyopathy, restrictive cardiomyopathy, and dilated cardiomyopathy. In the investigation of patients with unexplained cardiomyopathy or ventricular hypertrophy, the pathologist responsible for assessing the biopsy specimens and the clinician must consider the possibility of Fabry’s disease.

Fabry’s disease has a characteristic electron microscopic appearance, with lysosomal lamellar bodies, and thus requires special processing and fixation for this evaluation. The biopsy specimens may also be easily evaluated for the presence of myocyte iron and interstitial amyloid. Hemochromatosis and amyloidosis enter into the differential diagnosis of disorders causing systolic and diastolic dysfunction.

Variants of Fabry’s confined to the heart have been described. Cardiomyopathy in heterozygote individuals has been detected using endomyocardial biopsy. As Sachdev et al note, biopsy evaluation may be important because the female heterozygotes may be difficult to diagnose biochemically because of intermediate levels of enzyme activity overlapping with that of normal individuals.

Use of endomyocardial biopsy is declining, except in the evaluation of post-transplant rejection, and it may be forgotten as an important tool for diagnosis. In addition to the assessment of transplant rejection, these biopsies may be evaluated for myocarditis, cardiomyopathy, drug toxicity, cardiac neoplastic involvement, and secondary myocardial involvement by systemic diseases, including hemochromatosis, amyloidosis, and storage diseases. Some of these disorders might be diagnosed, treated, and cured or controlled.

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Response

We thank Dr Veinot for his comments on the potential value of endomyocardial biopsy (EMB) in patients with Anderson-Fabry disease (AFD) and other myocardial disorders. Most cases of hypertrophic cardiomyopathy (HCM) are thought to be caused by autosomal dominantly inherited mutations in a number of genes that encode different cardiac sarcomeric proteins. Although the disease is characterized histologically by myocyte disarray and myocardial fibrosis, EMB is not routinely performed in patients with unexplained left ventricular hypertrophy in most centers because of the high false-negative rate caused by sampling error. Nevertheless, our recent article describing Anderson-Fabry disease in 4% of a consecutively referred series of male patients with a clinical diagnosis of HCM suggests that the role of cardiac biopsy in patients with unexplained left ventricular hypertrophy may have to be reconsidered. In particular, it may assist in the diagnosis of AFD in female “carriers” who can develop significant cardiac abnormalities despite normal or near normal plasma α-galactosidase A levels. EMB may also be of value in detecting other disorders of myocardial metabolism, such as mitochondrial disease or the recently reported cardiomyopathy associated with mutations in the gene encoding the gamma sub-unit of AMP-kinase.

Even in the best hands, EMB exposes patients to a small risk, and so before advocating its more widespread use in patients with unexplained myocardial hypertrophy, further studies are required to determine those patient cohorts in whom EMB is likely to be of value in making a diagnosis and in guiding therapy. Comparisons with noninvasive diagnostic strategies or information obtained from more easily obtained tissues such as skeletal muscle and skin are also required.

In summary, left ventricular hypertrophy can be caused by a large number of diseases, some of which can be diagnosed by direct examination of myocardial tissue. It is likely, that as the true spectrum of disease is clarified by ongoing genetic studies, EMB will be used more frequently in selected patients with “unexplained” hypertrophy.

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