UNEXPECTED IDENTIFICATION OF FABRY DISEASE AMONG PATIENTS WITH THE CLINICAL DIAGNOSIS OF HYPERTROPHIC CARDIOMYOPATHY IN ICELAND

Poster Contributions
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The aim of this study was to investigate the prevalence of Fabry disease (FD) among all hypertrophic cardiomyopathy (HCM) patients in Iceland.

Methods: 137 patients with clinically diagnosed HCM were studied; 76 carried the MYBPC3 c.927-2A>G founder mutation; the remaining 61 underwent targeted sequencing of 8 HCM genes and the α-galactosidase A gene (GLA). If a GLA sequence variant was found, then the enzyme activity of plasma and leukocyte alpha-galactosidase A (α-Gal A) and the urine concentration of globotriaosylceramide (Gb3) were measured. In vitro protein expression was performed in cases of new mutations. Patients were evaluated clinically and kidney function tests made. Brain and cardiac MRI was performed on patients with GLA sequence variants.

Results: Eight of the 137 patients (5.8%) had pathogenic GLA mutations, 5 males and 3 females, all without sarcomeric gene mutations. Of patients with sarcomere mutation-negative left ventricular hypertrophy (LVH) 15% had pathogenic GLA mutations. Age at diagnosis was 46 ± 10 years (34-59), left ventricular wall thickness was 21 ± 4 mm (15-27). Two novel mutations were identified. The I232T mutation was found in 3 patients from two families. In vitro protein expression showed 32% α-Gal A activity compared to wild type (WT). I232T was related to late onset disease with cardiac and cerebral manifestations. The D322E mutation was found in 5 patients from two families. In vitro protein expression showed 3% α-Gal A activity compared to WT. D322E seems to cause classical FD. The D313Y variant previously associated with enzyme pseudo-deficiency was found in two unrelated females. Familial studies allowed the diagnosis of FD in 12 additional patients: 2 males with classical FD, 3 males with cardiomyopathy as the only manifestation of FD, 7 young females without Fabry manifestations.

Conclusions: In Iceland, the prevalence of FD is high (about 6%) among patients with a clinical HCM diagnosis. Our results underscore the importance of considering FD in the differential diagnosis of unexplained LVH and presumed HCM.