Clinical Course and Significance of Hypertrophic Cardiomyopathy Without Left Ventricular Hypertrophy

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Running title: Outcome of HCM without LVH

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Word count: ~~800~~835

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Increased availability of genetic testing for hypertrophic cardiomyopathy (HCM) has led to emergence of a novel patient subset within the heterogeneous disease spectrum, consisting of asymptomatic genetically affected family members with normal cardiac function without left ventricular hypertrophy (LVH) (1). These genotype-positive (+) - LVH-negative (-) (G+LVH-) individuals raise unresolved clinical issues concerning conversion to HCM phenotypes and risk for cardiovascular complications (2,3). Given the presumed thousands of gene carriers among HCM families, we have assessed here the clinical profiles and outcome of G+LVH- individuals in a large international multicenter cohort.

A total of 203 G+LVH− individuals were identified in 128 HCM families (Table 1) at 4 referral centers (~~in~~ US, Italy, Netherlands, ~~and~~ Australia~~),~~ and followed prospectively. Participants were ≥12 years at initial evaluation (study entry) with: 1) HCM family history; 2) pathogenic/likely pathogenic sarcomere variant~~, per 2015 American College of Medical Genetics Guidelines~~ (4); 3) maximal LV wall thickness ≤12 mm.

Genetic testing was performed with commercial panels that included the most common HCM-associated myofilament-encoding genes. Mutations in 10 sarcomere genes were identified most commonly *MYBPC3* (n= 141; 69%) and *MYH7* (n= 40; 20%).

Patients were followed at 1-5 year intervals with clinical examination, ECG, and echocardiography. Group comparisons were performed with unpaired Student's t-test~~/ or~~ chi-square test. Predictors of conversion to LVH at baseline were assessed with a multivariable analysis.

At initial evaluation, the 203 relatives were 32 ± 11 years (range, 12 to 61), 38% > 40 years; 61% female (Table 1). LV thickness was ≤ 12mm by echocardiography, mean 9±2 mm, range 6 to 11 mm. LV end-diastolic cavity dimension, left atrial size, and ejection fraction were normal (Table 1).

Of the 128 families, 62 (52%) included ≥ 1 relative with sudden death or end-stage HCM. However, no adverse cardiovascular events occurred in any study patient including death, HCM-related complications/events or cardiac symptoms, over follow-up of 6 ± 2 years (739 person-years).

Non-converters. Over follow-up of 5 ± 3 years, 90% of patients (n=182), did not convert to LVH. At most-recent evaluation, patients were 37 ± 16 years old; 37 (18%) were > 50 years, including 10 patients > 60 years old (range to 69). For the group, LV wall thickness increased 1 ± 2 mm but remained ≤ 12mm, 22/182 (12%) patients developed ECG abnormalities.'

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Converters. Over 6 ± 2 years 21 individuals (10%) converted to the HCM phenotype, defined as maximal LV wall thickness ≥ 13mm, usually in anterior ventricular septum (mean 15 ± 2; range to 17), but without hypertension; conversion rate was 0.3%/ year. At most recent evaluation, patients were 39±10 years old; 43 (21%) were > 50 years including 16 (8%) > 60 years.

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LVH converters and non-converters did not differ in LV thickness at entry (10 ± 2 vs. 9 ± 2 mm, p=0.28). Based on serial echocardiograms, LVH conversions occurred with similar frequency by decade (ranging 7% - 13%; average 10) although delayed to ≥ 50 years in 4 patients and to 40-49 in 4 others (p=0.76).

ECGs were abnormal in 24 (21%), most commonly pathologic Q waves (n=17) and ST-T abnormalities (n=11) ~~(6-8)~~. LVH converters had abnormal ECGs more commonly than non-converters (48% vs. 8%; p<0.01) with ECG abnormalities preceding LVH on imaging by 4 ± 2 years in 9 patients. Multivariable analysis showed 2-fold increase in LVH conversion for patients with pathologic Q waves at initial evaluation (HR 2.1; 95% CI: 1.3-5.1; p=0.01).

There is little long-term follow-up data addressing the clinical consequences of G+LVH- status (3). In our prospectively followed multicenter cohort of >200 patients we found no evidence of adverse disease consequences in any patient. This important observation should represent a source of reassurance to G+LVH- individuals and clinicians.

However, we cannot exclude the possibility that with extended surveillance disease-related complications and/or conversion to LVH could occur in ~~some~~ additional patients (2,5). Nevertheless, average age of the study population is 39 years, and about 20% are already > 50 years old (~~,~~ including 5% who are > 60 years old), suggesting that ~~. These observations suggest that~~ many G+LVH- patients will achieve normal longevity without HCM-related complications or development of LVH.

Ten percent of the study group has converted to a HCM phenotype, with a similar frequency in younger and older patients. ECG abnormalities, particularly Q waves, often

preceded LVH serving as a predictor of phenotypic conversion in some patients (2,3,5). These finding needs to be confirmed by larger cohort studies, given the relative small number of converters in the cohort. Present under-recognition of LVH in our younger patients could be related either to the large number of study patients < 18 years who could yet convert to HCM (2,3), exclusion of relatives with LVH at initial evaluation, or because CMR was not a routine part of the study design (2).

In conclusion, in the present multicenter cohort, G+LVH- individuals demonstrated a benign clinical course with virtually no demonstrable risk for disease-related morbidity or mortality including almost 20% who have already achieved relatively advanced age > 50 years. This observation and uncommon conversion to the HCM phenotype suggests that many gene carriers can anticipate normal longevity.

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