Long-term Outcomes in Hypertrophic Cardiomyopathy Caused by Mutations in the Cardiac Troponin T Gene

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Introduction
Hypertrophic cardiomyopathy (HCM) is an autosomal dominant disease caused by mutations in genes that encode proteins of the cardiac sarcomere. One of the first genotype-phenotype associations to be reported was a high prevalence of sudden cardiac death (SCD) in young carriers of mutation in cardiac troponin T gene (TNNT2), paradoxically often in the presence of only mild left ventricular (LV) hypertrophy. Confirmation of this association has been hampered by the small size of patient cohorts and a lack of data on disease expression in relatives. The aim of this study was to examine phenotypic appearance and clinical outcomes in a large cohort of patients and relatives with mutations in TNNT2 followed for more than two decades at a single referral centre.

Methods
552 unrelated HCM probands were screened for TNNT2 mutations using F-SSCP and direct sequencing of abnormal conformers. All relatives at risk of inheriting disease mutations were invited for genetic testing. All patients and relatives with TNNT2 mutations underwent supine 12 lead ECG, echocardiography, Holter ECG and upright exercise testing.

Results
92 Individuals (20 probands and 72 relatives) carried a TNNT2 mutation; 21 were children at first evaluation (2 days to 16 years). Eighteen children (90%) and 16 (24%) adults had a normal Echo; all patients evaluated in 1st decade had normal Echoes compared to 8% in the 5th decade (figure 1); normal ECGs were present in 13 (68%) children and 13 (68%) adults (figure 2). Follow up Echoes were available in 45 adults and 14 children (mean interval 9.3 ± 5 years and 6.9 ± 2.9 years respectively). Three patients developed LV dilatation and impaired systolic function; 2 children and 2 adults with normal baseline Echoes developed hypertrophy. Mean follow up was 9.9 ± 5.2 years. The rate of cardiovascular death was 2% per year and sudden death 1% per year (figure 3). In addition to 92 patients with a genetically confirmed TNNT2 mutation, 29 cases of SCD were identified from the pedigree analysis. Of these, 5 had a post-mortem report consistent with HCM, 5 were obligate carriers of a mutation and 2 were known to be affected with HCM before death; 17 patients (mean age SCD: 24 years) died suddenly in circumstances suggesting cardiac origin, but the diagnosis could not be confirmed. However just considering the cases of sudden death with HCM diagnosis confirmed, a family history of SCD was present in 10 families (50%) and 8 (40%) had multiple cases of SCD.

Conclusion
Non penetrant disease in patients with TNNT2 mutations is rare beyond 2nd decade, but Echo alone failed to detect disease in 23% of carriers. A family history of SCD is very frequent in families with TNNT2 mutations, nevertheless the rate of cardiovascular death and SCD is comparable to the general HCM population, at least in the prospectively followed up cohort. We do not know if genetic, epigenetic, environmental and pharmacological factors can explain these differences between generations, however this study suggests that TNNT2 mutations are not associated with a specific phenotype.

References