

Prognosis and differences in mortality pattern between familial, sporadic and Noonan-syndrome associated hypertrophic cardiomyopathy presenting in childhood.

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INTRODUCTION: Hypertrophic cardiomyopathy (HCM) presenting in childhood may be either familial, sporadic new mutations, or associated with the Noonan-group of syndromes. It has been reported that Noonan-associated HCM is a risk-factor for heart failure-related death but the size of risk has not been quantified compared with the other two types of childhood-HCM. Annual mortality is an in-correct measure to compare mortality in childhood HCM since mortality rate varies significantly in different age-ranges.

METHODS: A Swedish national cohort of 144 patients diagnosed with HCM <19 yrs of age were categorized in familial non-syndrome associated HCM (Fam-HCM, n=67), HCM associated with Noonan-group of syndromes (NS-HCM, n=36), and sporadic new cases without syndrome-association with storage-disorders excluded (Spor-HCM, n=29). The remaining 12 could not be categorized with certainty and were not included in the analysis. Survival was compared with Kaplan-Meier survival analysis, and hazard of different types of cardiac mortality compared. There were 36 deaths: 24 sudden cardiac deaths (SCD), 9 heart-failure related, and 3 other cardiac deaths in the categorized groups.

RESULTS: Overall long-term survival was not significantly different between Fam-HCM and NS-HCM ($p=0.14$), whereas Spor-HCM had significantly worse survival than Fam-HCM ($p=0.026$). The respective 10- and 20-yr survival were 88% and 84% for Fam-HCM, 80% and 70% for NS-HCM, and 70% and 56% for Spor-HCM. Mortality patterns were however very different with no heart-failure deaths in Fam-HCM, and 8/9 heart-failure deaths in NS-HCM. Hazard ratio for SCD was non-significantly higher in Spor-HCM than Fam-HCM (2.1 [95%CI 0.8-5.5], $p=0.075$). The hazard ratio of heart-failure death was 13.9 [3.1-61; $p=0.0005$] comparing NS-HCM with Fam-HCM, and 4.0 [1.1-15; $p=0.04$] comparing NS-HCM with Spor-HCM. Genetic investigations in Spor-HCM revealed mutations in sarcomere genes in the majority. Right ventricular outflow-obstruction at rest occurred in 50% in NS-HCM, 10% Spor-HCM and 1.5% in Fam-HCM, whereas left ventricular outflow-obstruction at rest was present in 75%, 100% and 23 % respectively.

CONCLUSIONS: NS-HCM is the dominant cause of heart-failure deaths in childhood HCM, whereas SCD occur in all three HCM-groups. Although Spor-HCM like Fam-HCM is commonly associated with sarcomere-protein mutations, the prognosis of de-novo mutations is worse than in patients with inherited mutations.