Genetic testing of child and adolescent relatives in a family screening program for Hypertrophic Cardiomyopathy

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Introduction: Hypertrophic cardiomyopathy (HCM) is most often autosomal dominantly inherited with incomplete penetrance and variable expressivity. The main purpose of family screening is to identify relatives who have the same disease as the proband. The 2014 ESC Guidelines on diagnosis and management of HCM recommend the screening of child relatives beginning at 10 years of age. However, the prognostic value of identifying sarcomere gene mutations in children without phenotypic manifestations of HCM remains unclear.

Aims: We retrospectively studied the outcome of clinical screening and predictive genetic testing of child probands and relatives (<18 years of age) from families with HCM and assessed the age-related penetrance of HCM during the follow-up in these young relatives.

Methods and results: Twenty patients from 10 families were included in a family screening program for HCM (2004–2013). Patients were offered clinical examination, standard resting 12-lead ECG, ambulatory ECG monitoring, transthoracic echocardiogram and genetic testing for the 10 most common sarcomeric protein gene mutations. The diagnosis of HCM was made when left ventricular wall thickness was > 2 standard deviations over the predicted mean for body surface. "At-risk child relatives" were defined as those positive for the mutation, either they had a positive or a negative phenotype at enrollment. Two probands and 18 first-degree relatives were included (80% male; median age = 9.5 years). Fourteen child relatives were mutation carriers (70%; median age = 7.9 years), and 5 were noncarriers (25%; median age = 11.5 years). One child had unknown genetic status.

Twelve (86%) of the 14 mutation carriers were diagnosed with HCM at first evaluation. After 6 ± 3.5 years follow-up, the two mutation carriers without phenotypic expression developed HCM at 10 and 18 years of age (14% penetrance rate). Both had mutations in the MYBPC3 gene.

Conclusions: The penetrance of HCM in phenotype-negative child relatives at risk of developing HCM was 14% after 6 years of follow-up. This underlines the relevance of the long term follow-up of mutation carriers irrespective of the presence of a positive phenotype.