Penetrance of Hypertrophic Cardiomyopathy in Children Who Are Mutation Positive

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Objectives To investigate the presence of hypertrophic cardiomyopathy (HCM) at first cardiac evaluation and during follow-up and cardiac events in predictively tested children who are mutation positive.

Study design The study included 119 predictively tested children who were mutation positive, with a mean age of 12.1 years. A family history and clinical variables from all cardiac evaluations after predictive genetic testing were recorded. Outcome measures were a clinical diagnosis of HCM, death, and cardiac events.

Results No child died during a mean follow-up of 6.9 ± 3.8 years: 95 children were evaluated more than once. Eight (6.7%) children who were mutation positive were diagnosed with HCM at one or more cardiac evaluation(s), some with severe hypertrophy. In one patient who fulfilled the diagnostic criteria for HCM a cardiac event occurred during follow-up. She received an appropriate implantable cardioverter-defibrillator shock 4 years after a prophylactic implantable cardioverter-defibrillator was implanted.

Conclusion The risk for predictively tested children who are mutation positive to develop HCM during childhood and the risk of cardiac events in children who are phenotype negative are low. In children who are phenotype positive, however, severe hypertrophy and cardiac events can develop. Further research is necessary to study whether the interval between cardiac evaluations in children can be increased after a normal first evaluation and whether risk stratification for sudden cardiac death is necessary in children who are phenotype negative. *(J Pediatr 2017;188:91-5).*

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Hypertrophic cardiomyopathy (HCM) is a common genetic heart disease affecting about 1 in 200 persons worldwide (based on genotype).[1,2] It is characterized by (asymmetric) left ventricular hypertrophy (LVH) in the absence of other conditions that may cause cardiac hypertrophy, such as hypertension and aortic valve stenosis.[3] Of note, sudden cardiac death (SCD) often is the first manifestation of the disease in the young.[4] HCM displays autosomal-dominant inheritance, and in about 50%-60% of patients a pathogenic mutation can be detected.[5] Most of these mutations are found in genes encoding sarcomeric proteins.[6,7] After identification of a pathogenic mutation, predictive genetic testing is offered to relatives to identify mutation carriers. Relatives who carry mutations are advised to undergo regular cardiac evaluations, because SCD can be prevented effectively.

According to the European Society of Cardiology (ESC) guidelines, clinical or genetic testing in asymptomatic relatives should be considered from the age of 10 years onwards. Cardiac screening or genetic testing of younger children must be considered when children have symptoms of HCM, when there is a malignant family history (early onset, SCD in childhood), or when children enroll in a competitive sport program with particularly demanding physical activity.[8] Predictive testing in children remains controversial, however, because prospective clinical data on predictively tested children who are mutation positive are limited and guidelines/screening intervals are based on data derived from children with manifest HCM.[9-12] A diagnosis of HCM is made infrequently in childhood, but on the contrary, cases of severe HCM in childhood and with SCD as first manifestation of the disease have been reported.[4,13,14] In addition, possible adverse psychological effects can play a role.[15] Here, we report the results of systematic cardiac follow-up in a cohort of predictively tested children (<18 years of age at the time DNA diagnostics was performed) with a pathogenic mutation.

ESC	European Society of Cardiology
HCM	Hypertrophic cardiomyopathy
ICD	Implantable cardioverter-defibrillator
LVH	Left ventricular hypertrophy
NSVT	Nonsustained ventricular tachycardia
SCD	Sudden cardiac death

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Methods

All predictively tested children (<18 years of age at the time DNA diagnostics was performed) referred to our cardiogenetics outpatient clinic from 2001 until January 1, 2016, with a putative pathogenic mutation were selected. Children with >1 putative pathogenic mutation (tested because of multiple mutations in the family; n = 3) or an additional (hereditary) cardiovascular disease were excluded. Most included children (n = 102) had not been evaluated cardiologically before the DNA test. No probands were included, and all included children were not known to have a clinical diagnosis of HCM at the time of DNA testing. All children and their parents received genetic pretest counseling by a specialized genetic counselor or clinical geneticist and an appointment with a psychosocial worker. This study was approved by the local ethics committee. All children and/or parents provided written informed consent for anonymous scientific use of their data. Included children who were carrying mutations had to have at least one cardiac evaluation. In total 119 children were included in this study.

From all included children, a family history was recorded with information on HCM and SCD in relatives up to the third degree at the time of DNA testing. After the genetic diagnosis, all children were advised to regularly undergo cardiac evaluation, including at least an electrocardiogram and echocardiogram. Often, cardiac evaluation also included a Holter recording and an exercise test. We did not use the results of the exercise test because it is not included in the risk stratification model for children according to the ESC guidelines.[8] Clinical variables from all cardiac evaluations after predictive genetic testing were recorded and z scores (corrected for height and weight) calculated.[16] A clinical diagnosis was made when on echocardiography or cardiac magnetic resonance imaging a maximal left ventricular wall thickness of ≥13 mm or ≥2 SD for body surface area was present.[8] In children who became >18 years during follow-up, a maximal left ventricular wall thickness ≥13 mm was used for HCM diagnosis at subsequent cardiac evaluations.

In 2014, a new model for predicting the risk of SCD in patients with HCM was published.[17] This risk model, however, should not be used in patients <16 years of age.[17] Therefore, as per the ESC guidelines, the following major risk factors for SCD in children were assessed: (1) severe LVH: a maximum left ventricular wall thickness ≥30 mm or a z score ≥6; (2) unexplained syncope: non-neurocardiogenic syncope for which there is no explanation after investigation; (3) nonsustained ventricular tachycardia (NSVT): ≥3 consecutive ventricular beats at ≥120 bpm lasting <30 seconds; (4) family history of SCD: one or more first-degree relatives who died suddenly aged <40 years with or without a diagnosis of HCM, or when SCD has occurred in a first-degree relative at any age with an established diagnosis of HCM.[8] The cumulative number of risk factors is the number of the abovementioned 4 risk factors for SCD that are positive. In children, implantable cardioverter-defibrillators (ICDs) should be considered when they have 2 or more major risk factors and are indicated after a life-threatening ventricular arrhythmia.[8]

Table I. Clinical variables of 119 predictively tested children who were mutation positive at first clinical evaluation

Clinical variables	All mutation carriers	
Age, y	12.1 ± 3.4	119
Male	61	119 (51.3%)
Clinical diagnosis of HCM	5	119 (4.2%)
Mutated gene		
MYBPC3	95	119 (79.8%)
c.2373_2374insG	–52	95 (54.7%)
c.2827C>T	–13	95 (13.7%)
c.2864_2865delCT	–1	95 (1.1%)
MYH7	14	119 (11.8%)
TNNT2	10	119 (8.4%)
Presence of risk factors for SCD		
Extreme LVH	0	119 (0%)
NSVT	1	85 (1.2%)
Unexplained syncope	2	119 (1.7%)
Family history of SCD	11	119 (9.2%)
Cardiac events	0	119 (0%)
Complete evaluation of risk factors	85	119 (71.4%)
Cumulative number of risk factors for SCD		
0	105	119 (88.2%)
1	14	119 (11.8%)
2	0	119 (0%)

Data are mean ± SD or number and proportion (%).

Mean follow-up until January 1, 2016, of all 119 children was 6.9 ± 3.8 years. Outcome measures were a clinical diagnosis of HCM, death, and cardiac events (heart transplantation, sustained ventricular tachycardia, appropriate ICD shock, [aborted] SCD, other cardiac mortality).

Statistical Analyses

Data were analyzed with Statistical Package of Social Sciences, version 22.0 (IBM, Chicago, Illinois). Data are presented as mean (SD) or frequency. Fisher exact test and McNemar test were used for the comparison of categorical variables. A *P* value of <.05 defined statistical significance.

Results

Predictively tested children (61 boys and 58 girls) from 74 different families were included in this study. Mean age was 12.1 ± 3.4 years at study entry. Almost 80% (79.8%) of the children carried a *MYBPC3* mutation, of whom 69.5% (n = 66) had a founder mutation (**Table I**). On January 1, 2016, 95 of 119 children (80%) had been evaluated more than once, with a mean time of 5.1 ± 3.3 years between the DNA test and last cardiac evaluation. Eight (6.7%) of the 119 children who were mutation positive were diagnosed with HCM at first (n = 5) or follow-up (n = 3) cardiac evaluation(s). There were no significant differences ($P < .05$) between children with or without follow-up at first evaluation and in children with follow-up between first and last evaluation (**Table II**).