Age- and gender-specific mortality rates in childhood hypertrophic cardiomyopathy

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Aims
Hypertrophic cardiomyopathy (HCM) is the commonest inherited cause of sudden cardiac death in children; current guidelines suggest HCM screening after 12–15 years of age. The study aims to establish the age range at highest risk.

Methods and results
Cohort study from six regional centres of paediatric cardiology, including children presenting with sudden death; n = 150 (59% male; 39% familial HCM). Age- and gender-specific mortality was calculated, and compared with rates calculated from the Swedish National Cause of Death Registry. There were 56 deaths within the cohort, 39 were sudden arrhythmia deaths, with 31 at <19 years of age. Between 9–13.9 years of age annual sudden death mortality averages 7.2%, vs. 1.7% after 16 years of age; P = 0.025, odds ratio for proportions 3.75 [95% confidence intervals (CI) 1.18–11.91], similar in both familial and idiopathic HCM. The risk for sudden death peaks earlier in girls (10–11 years), with male preponderance after the age of 15. National cause of death statistics confirm that the mortality rate from HCM is significantly higher in the 8–16 year olds (0.112 per 100 000 age-specific population) than in the 17–30 year olds (0.055 per 100 000; 95% CI 0.011–0.099).

Conclusion
In families with HCM, children should be screened at an early age.

Keywords
Hypertrophic cardiomyopathy • Sudden death • Mortality • Screening • Familial hypertrophic cardiomyopathy • Gender

Introduction
Hypertrophic cardiomyopathy (HCM) has a prevalence in the general adult population of 1:500,1,2 and the disease is the commonest cause of sudden unexpected death in older children,3 and in competitive athletes.4 In childhood the prevalence of clinically overt cases is lower,5 but the annual mortality in diagnosed cases is higher in HCM with childhood onset than in adults,6,7 with an annual mortality rate in a geographical cohort of 6.6% in untreated patients, out of which over half were sudden deaths in asymptomatic subjects.8 Familial HCM often shows marked progression of hypertrophy during puberty,9 which is sometimes used as a justification for delaying family screening until after puberty. Official guidelines from American Task Force recommendations on pre-participation screening of athletes suggest that this should be commenced at around 15 years of age.10 A large population-based study on sudden death found a median age of 23 years for deaths associated with HCM, but only included sudden deaths between age 12–35 years and can give no indication of relative risk at younger ages.11 However, in the so far largest cohort study of HCM cases presenting in childhood the youngest age at sudden death was 8 years, and median age 13.3 years.12 Among 134 athletes dying suddenly from cardiovascular causes, the median age was 17 years, and the youngest was 12 years.4 Clearly, if the risk of sudden death caused by HCM is substantial below 15 years of age, then screening of all children with a parent with HCM should be carried out at an early age. This study therefore sets out to determine the risk of sudden death in familial and non-familial childhood HCM, including children where sudden death was the presenting feature, and relates risk both to the population of children known to have overt disease, and to age-specific population size. The Italian population study

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and others have also remarked on a clear male preponderance, from 2.8:1 upwards, in sudden deaths caused by HCM, and we have therefore also studied age-related variations in gender proportions among sudden death victims.

Methods

Study patients
All patients with a diagnosis of HCM before 19 years of age and attending the Divisions of Paediatric Cardiology at John Radcliffe Hospital, Oxford, Southampton General Hospital in Great Britain, University Hospital, Lund, Academic Hospital, Uppsala, Queen Silvia Hospital for Children, Gothenburg, and Astrid Lindgren Hospital, Stockholm, in Sweden were included, largely retrospectively, but from 1998 cases fulfilling identical definitions were also prospectively entered. Data collection started for patients under follow-up from the date that the hospital had a complete diagnostic index, and availability of echocardiographic diagnostic facilities, between 1972 and 1976 for all units except Southampton, where data collection commenced 1988. Data collection for new cases into the cohort ended at the end of 2004, as 12 months follow-up was required for inclusion of surviving patients. As the recruiting centres are the only paediatric cardiology centres in their regions, the patients represent complete geographical cohorts. HCM was defined as primary, inappropriate hypertrophy in a non-dilated heart with normal or exaggerated systolic function in the absence of valvular outflow obstruction or underlying systemic disease, with absolute wall thickness above ±2 SD for age (see Table 1), and wall-to-cavity ratios exceeding the 99th centile. Original patient records of all 164 patient records coded HCM were reviewed at site visits by study cardiologists. Of these 32 patients had secondary HCM (10 cases of infants of diabetic mothers, and 22 cases secondary to myopathy, storage disorder, Friedreich’s ataxia, or mitochondrial disorder), leaving 132 patients with primary HCM. Patients with co-existing Noonan and Leopard syndrome were included, and constitute virtually an identical proportion to that found in Australia. All but one of the patients that died had post-mortem performed, with histology typical of HCM and excluding storage disorders; the exception had Noonan’s syndrome and recent ECG and echocardiographic data were available. In addition, all cases below 19 years of age that presented with sudden death caused by HCM without previous clinical diagnosis were retrieved from the registers of paediatric pathology departments, and within Sweden identified from the Forensic Medicine Nationwide database, Rattsbase, and those cases with a heart weight above normal for age and weight showing typical histology and absence of storage disorders were included. A further 18 cases of HCM were thus identified, giving a total HCM cohort of 150 cases. Four cases that survived a resuscitated cardiac arrest requiring defibrillation, and either died later (from heart failure), or are still alive with an internal cardioverter device (ICD) (n = 3), are for statistical purposes included as sudden deaths at the age of aborted cardiac death.

Registry studies
Within Sweden all deaths are registered in a National Cause of Death registry coded with ICD-9 since 1997. The Department of Health also has a central registry of age-specific population size that is updated annually. Data from these registries were therefore used to calculate age-specific mortality rates in the whole of Sweden between 1997 and up to end of 2002, the last year where the coding input was completed. Cross-referencing with Rattsbase, a total of 15 deaths in the age range 0–30 years were recorded as being due to HCM. For comparison, the mortality rates for some other diagnoses that cause sudden death in childhood, namely, dilated cardiomyopathy (DCM), aortic stenosis, coronary malformation, and acute myocarditis, were also calculated.

Statistics
Statistical analysis was carried out using commercial software (Stat-graphics Plus v5.2 and GraphPad Prism 4). In order to quantify the risk the number of observed sudden deaths was related to the number of known patients with a clinical diagnosis of HCM within the same age band, where patients presenting with sudden death were considered ‘diagnosed’ in the year-band of the death. For example, a patient diagnosed at the age of four, dying at the age of eight was counted within all the age bands of four, five, six, seven, and eight. Comparisons of mortality proportions within age bands of the HCM cohort were carried out by two-tailed Fisher’s exact test, and odds ratios (OR) and their 95% confidence intervals (95% CI) were calculated. CIs for mortality rates for the population-based mortality statistics were calculated as the CI of proportions as described by Motulsky.

Results

Geographical cohort data
Altogether 150 patients presented within the geographical regions included at between one day and 18 years of age, with 63 females, giving a 58% male preponderance. The male preponderance is a constant feature both in infants, older children, and cases diagnosed as teenagers. Demographic and clinical data are summarized in Table 1. In 57 of the patients (38%) there was clear autosomal dominant inheritance (60% males); 39 were diagnosed following family screening and 18 were presenting case within the family. Forty-six of 146 patients with clinical details had Noonan’s (29%) or Leopard syndrome (3%). Details of family background are scanty or non-existent in eight of 18 patients that presented with sudden death.

There were 56 deaths within the cohort, 47 occurring before 18.9 years of age. However, as illustrated in Figure 1 the deaths are clustered at certain ages, with no deaths in the 3–7 years age range, making averaging to an overall annual mortality rate misleading.

Heart failure-related deaths
About 20 deaths were related to congestive heart failure (CCF), with co-existing Noonan’s or Leopard syndrome occurring more frequently with CCF deaths than in survivors (P = 0.0018; Table 1). Twelve deaths were in the first 3 years of life, all with congestive symptoms caused by diastolic dysfunction in the setting of non-dilated hearts, vigorous systolic function, and dynamic left-ventricular outflow obstruction (LVOTO). The remaining eight died of CCF complications relating to a dilated end-stage of the disease, between 15.3 and 50 years of age (see Figure 1). LVOTO was significantly more common in HCM patients with CCF deaths than in survivors (P = 0.0006; Table 1).

Sudden deaths
Altogether 39 sudden arrhythmia deaths occurred; 31 below 19 years of age. The age-distribution of sudden deaths is illustrated...
Table 1 Demographic and clinical data in the total HCM cohort, and values of known risk factors for disease-related death

<table>
<thead>
<tr>
<th>Group</th>
<th>Total cohort = 150 median (range)</th>
<th>Survivors n = 95 median (range)</th>
<th>Sudden deaths = 39 median (range)</th>
<th>CCF deaths = 20 median (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at diagnosis (years)</td>
<td>4.6 (0.003–18)</td>
<td>3.3 (0.003–18)</td>
<td>9.0 (0.1–17.9)</td>
<td>0.5 (0.003–13.0)</td>
</tr>
<tr>
<td>Age at death (years)</td>
<td>11.8 (0.08–50)</td>
<td>13.0 (0.1–42.3)</td>
<td>2.1 (0.2–50)</td>
<td></td>
</tr>
<tr>
<td>Duration of FU (years)</td>
<td>7.0 (0.2–37.2)</td>
<td>7.4 (1.0–35.0)</td>
<td>9.8 (1.0–29.7)*</td>
<td>3.0 (0.2–37.2)</td>
</tr>
<tr>
<td>M:F ratio</td>
<td>1.4:1</td>
<td>1.5:1</td>
<td>1.4:1</td>
<td>1.5:1</td>
</tr>
<tr>
<td>First SEPPER (%)</td>
<td>175 (106–341)</td>
<td>169 (106–341)</td>
<td>203 (112–322)</td>
<td>185 (113–279)</td>
</tr>
<tr>
<td>First LVPER (%)</td>
<td>111 (64–246)</td>
<td>108 (64–212)</td>
<td>122 (72–215)</td>
<td>127 (85–246)</td>
</tr>
<tr>
<td>SEPCAVR</td>
<td>0.55 (0.26–1.54)</td>
<td>0.47 (0.26–1.54)</td>
<td>0.56 (0.26–0.96)</td>
<td>0.60 (0.44–1.36)</td>
</tr>
<tr>
<td>LVCAVR</td>
<td>0.30 (0.15–1.20)</td>
<td>0.29 (0.15–1.20)</td>
<td>0.29 (0.16–0.62)</td>
<td>0.55 (0.16–1.0)*</td>
</tr>
<tr>
<td>First RS-SUM (mV)</td>
<td>9.0 (2.3–39.4)</td>
<td>8.2 (2.3–28.8)</td>
<td>13.7 (5.2–39.4)*</td>
<td>10.6 (5.5–19.6)</td>
</tr>
<tr>
<td>% with LVOTO</td>
<td>55</td>
<td>46</td>
<td>79*</td>
<td>89*</td>
</tr>
<tr>
<td>% w. Noonan (Leop)</td>
<td>29 (3)</td>
<td>28 (4)</td>
<td>13 (0)*</td>
<td>60 (5)*</td>
</tr>
<tr>
<td>% w. familial HCM</td>
<td>38</td>
<td>46</td>
<td>46*</td>
<td>10</td>
</tr>
<tr>
<td>% w. sporadic HCM</td>
<td>30</td>
<td>22</td>
<td>41*</td>
<td>25</td>
</tr>
<tr>
<td>Latest therapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NST = 11</td>
<td></td>
<td>NST = 20</td>
<td>NST = 5</td>
<td></td>
</tr>
<tr>
<td>LDBB = 30</td>
<td></td>
<td>LDBB = 8</td>
<td>LDBB = 7</td>
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<tr>
<td>HDDB = 47</td>
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<td>HDDB = 2</td>
<td>HDDB = 2</td>
<td></td>
</tr>
<tr>
<td>Diso = 20</td>
<td></td>
<td>Diso = 1</td>
<td>Diso = 1</td>
<td></td>
</tr>
<tr>
<td>Amio = 2</td>
<td></td>
<td>Amio = 2</td>
<td>Amio = 1</td>
<td></td>
</tr>
<tr>
<td>CaBl = 4</td>
<td></td>
<td>CaBl = 3</td>
<td>CaBl = 5</td>
<td></td>
</tr>
<tr>
<td>Sotalol = 0</td>
<td></td>
<td>Sotalol = 1</td>
<td>Sotalol = 0</td>
<td></td>
</tr>
<tr>
<td>ICD = 1</td>
<td></td>
<td>ICD = 0</td>
<td>ICD = 0</td>
<td></td>
</tr>
<tr>
<td>Previous myectomy</td>
<td>n = 8</td>
<td>n = 3</td>
<td>n = 4</td>
<td></td>
</tr>
</tbody>
</table>

*values calculated excluding cases presenting with sudden death; FU, follow-up; *significantly different from survivors, P = 0.005–0.0008; M:F, male:female; SEPPER, septal thickness in % of 95th centile value for age; LVPER, left ventricular wall thickness in % of 95th centile value for age; SEPCAVR, septum-to-left ventricular end-diastolic diameter ratio; LVCAVR, left ventricular wall-to-left ventricular end-diastolic diameter ratio; RS-SUM, QRS-amplitude sum in the six limb leads; LVOTO, left ventricular outflow tract obstruction; w., with; Leop, Leopard syndrome; NST, no specific therapy; LDBB, low-dose betablocker (<4.5 mg/kg propranolol); HDDB, high-dose betablocker (>4.5 mg/kg propranolol); Diso, disopyramide (all also received LDBB or HDDB); amio, amiodarone; CaBl, calcium-channel blocker; ICD, internal cardioverter device.

Figure 1 Frequency distribution plot showing number of deaths within each age-band, illustrating those that were related to congestive heart failure below the line (columns with background colour in pale grey), and deaths related to sudden arrhythmia above the line (white background colour). Deaths occurring in cases of sporadic disease are shown as open columns, cases associated with Noonan’s syndrome as vertical stripes, and cases associated with familial HCM as diagonal stripes within the columns. CCF deaths, deaths associated with congestive heart failure; SCD deaths, sudden cardiac deaths, including four individuals that were resuscitated from ventricular fibrillation.
in Figure 1, and it is not even. Apart from a single case in infancy the sudden deaths appear after 8 years of age, reaching a peak rate among 10 year olds and remaining high until 15 years of age, after which the rate drops. Four sudden deaths occurred in patients with dilated end-stage and some features of heart failure, and are shown in both categories in Figure 1. The annual mortality rates within different age bands are illustrated in Figure 2, and again it is observed that the risk peaks in 10–10.9 year olds where it reaches 9.7%, and is averaging 7.2% between 9 and 13.9 years of age. After 16 years of age it drops to an average annual mortality of 1.7% (see Figure 2). Related to number of patients diagnosed with HCM within the age bands, the proportion of sudden deaths is significantly higher in the 9–13.9 year age band, both compared with the 16–18.9 year age band (P = 0.025) with an OR of 3.75 (95% CI 1.18–11.91), and compared with 1–7 year olds (P < 0.0001), OR 45.7 (2.7–761).

Sudden death occurred both in familial, Noonan’s syndrome-associated and sporadic HCM, with a possible trend for earlier appearance in sporadic cases (see Figure 1). However even in familial cases, the risk of sudden death is higher in the 10–13.9 year age range than in the 16–18.9 year age range (P = 0.025), OR of 9.45 (1.08–83.11), see Figure 3. It has been reported that high-dose beta-blocker therapy reduces the risk of sudden death,8,12 but use of such therapy does not account for the age pattern in mortality, as the proportion of patients receiving high-dose beta-blocker therapy was the same in both age groups, 40 and 39%, respectively. A higher mortality in the 8–15.9 year olds than in the 16–19 year olds is seen also among patients not on high-dose beta-blocker therapy (see Figure 4), averaging 9.7% in the 9–12 year age range, and falling to 2.4% in the 16–19 year olds with an OR of 4.3 (95% CI 1.2–13.6) comparing the latter age bands (P = 0.019). The medical therapy used is summarized in Table 1, but for discussions on the effect of therapy we refer to our earlier publications.8,12

Gender aspects
When deaths are separated according to gender a striking pattern appears (see Figure 5). Between 8–10 years of age the annual mortality in sudden death tends to be higher in girls than boys, whereas after 11 years of age the sudden death mortality tends to be higher in boys. Overall, the risk for sudden death in girls peaks at 10–11 years of age, and in boys at 15–16 years of age. Thus, it is only after 15 years of age the male preponderance for sudden death starts to reach the values reported in adults, with a 7:2 male:female ratio in the 15–19 year age range. As regards heart-failure deaths in the first 3 years of life there were seven boys and five girls, a proportion which mirrors the overall 59% male preponderance in diagnosed cases. Among individuals dying from dilated end-stage there was a trend towards a female preponderance with a 3:5 male:female ratio (63% females), which should be interpreted also in the context of the overall male preponderance. Thus later heart failure deaths are encountered in 7.7% of male cases alive at 15 years of age, vs. 18.5% of female cases alive at 15 years of age.

Cause of death registry data
The mortality rates from the cause of death registry (Table 2) do not distinguish mode of death, but in the case of HCM we can see from the cohort study that 96% of deaths in the 8–16 year age range are sudden cardiac deaths. For comparison, deaths were therefore analyzed in three age bands, 0–7, 8–16, and 17–30 years of age, the latter which is conventionally considered the ages at highest risk of sudden cardiac deaths in adult HCM patients. As the denominator of age-specific population is largest in 17–30 year olds the 95% CI for age-specific mortality rates
were calculated for this group. From Table 2 it is clear that the mortality rate from HCM is significantly higher in the 8–16 year olds (0.112 per 100 000 age-specific population) than in the 17–30 year olds (0.055 per 100 000 age-specific population; 95% CI 0.011–0.099). The mortality rate for aortic stenosis and myocarditis was highest in the 0–7 year age range, and that of dilated cardiomyopathy in the 17–30 age range, so HCM was the only cardiac diagnosis studied with the highest mortality in the 8–16 year age range. The Registry data thus confirm the findings from the cohort data. As regards the gender proportions in HCM deaths there was a 3:4 male:female ratio in the 8–16 year age range, and a 4:3 male:female ratio in the 17–30 year age range. The latter figure certainly shows that there is not a dramatically higher overall mortality in young male adults with HCM, and would lend some support to the suggestions from the cohort data that in young adults with HCM the male propensity for sudden death is at least partially offset by an increased mortality from heart failure in females.

### Discussion

It has often been assumed that the higher mortality seen in HCM with childhood presentation compared with annual mortalities reported from adult HCM populations is a reflection of a low proportion of familial autosomal dominant disease due to sarcomeric mutations, and a high proportion of inherently malignant sporadic cases. However, even in adult patients there is a high proportion of sporadic disease. What our observations establish are three new findings, first that overall within a population, the annual mortality due to HCM is higher in the 8–16-year-old age range than in the 17–30-year-old age range peaking among 9–12 year olds. Secondly, that this pattern of early peaking mortality is seen even with familial sarcomeric HCM, and thirdly that male preponderance for sudden arrhythmic deaths only is apparent after 15 years of age.

Estimates of sudden death risk in HCM based on regional cohorts and age-specific populations are rare. Wren et al. found an annual sudden death mortality of 0.074 per 100 000 in the age range 1–20 years. Considering that they include in their estimates the 0–8 year age range where virtually no sudden deaths occur, and that sudden deaths are fewer after age 16 (Figure 2), there is actually good agreement between their figures and our estimate of a risk of 0.112 per 100 000 in the 8–16 year age range. Cohort outcome data from Australian and

### Table 2 Population based annual mortality per 100 000 age-specific population in Sweden according to coding on death certificates

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>0–7 years</th>
<th>8–16 years</th>
<th>17–30 years</th>
<th>95% CI 17–30 year age range</th>
</tr>
</thead>
<tbody>
<tr>
<td>HCM</td>
<td>0.052</td>
<td>0.112</td>
<td>0.055</td>
<td>0.011–0.099</td>
</tr>
<tr>
<td>DCM</td>
<td>0.052</td>
<td>0.112</td>
<td>0.151</td>
<td>0.072–0.230</td>
</tr>
<tr>
<td>Aortic stenosis</td>
<td>0.209</td>
<td>0.042</td>
<td>0.009</td>
<td>0.000–0.027</td>
</tr>
<tr>
<td>Cor. malformation</td>
<td>0.017</td>
<td>0.014</td>
<td>0.046</td>
<td>0.006–0.086</td>
</tr>
<tr>
<td>Myocarditis</td>
<td>0.052</td>
<td>0.028</td>
<td>0.018</td>
<td>0.000–0.043</td>
</tr>
</tbody>
</table>

CI, confidence interval; HCM, hypertrophic cardiomyopathy; DCM, dilated cardiomyopathy; Cor, coronary.
American Pediatric Cardiomyopathy Registries have recently been published claiming lower mortality than earlier studies; these studies do not separate modes of death. The Australian Registry uses the same inclusion criteria as ours, except only including the 1–10 year age range, whereas The American Registry have excluded patients with familial HCM and a known genetic mutation from their analysis, and do not contain patients presenting with sudden death, so the latter patient group is not directly comparable with our cohort either. The Australian Registry reports an average annual mortality of 3.39%, with 1.52% annual mortality for those diagnosed after 1 year of age, but with a median age of presentation of 0.5 years, and a median follow-up of 5.25 years very few of their patients have reached the age range at highest risk for sudden death. The American prospective data have a median follow-up of only 2.1 years (maximum 7 years) and 35.8% of the patients were diagnosed at <1 years of age, and 12.3% 1–5 years, so about half of the cohort have not yet reached the age range of higher risk for sudden death. However, it is illustrated in their Figure 3B that they too observe a clear clustering of deaths in the 12–16 year age range in their cases of idiopathic HCM, and no deaths in the 4–8 year age range, although the authors do not comment on this. Thus, calculating a flat mortality trend of deaths in the 12–16 year age range in their cases of idiopathic HCM, and no deaths in the 4–8 year age range, although the authors do not comment on this. In contrast, males show a greater inhomogeneity of repolarization as reflected by a greater QTc dispersion. Increased QTc dispersion is a known risk factor for sudden death in HCM. We have observed progressive broadening of the QRS duration as the disease progresses, and one might therefore hypothesize that the QTc prolongation occurring in early puberty in females may contribute to the early high risk in females, whereas disease progression associated with higher androgen levels might result in increasing QTc dispersion towards later puberty in males.

In relation to the suggestion in our cohort data that failure-related deaths may be more common in post-puberty females than in males, there are also interesting parallels in gender differences following acute myocardial infarction, where there is a higher rate of pre-hospital sudden death in males and a higher rate of post-infarct heart failure deaths in females, resulting in an overall equal gender proportion in deaths.

Why is the risk for sudden arrhythmia death higher in 8–16 year olds?

When one studies the age- and gender-specific pattern of annual mortality shown in Figure 5 one can see a striking temporal association not with onset of puberty (gonadarche), but with onset of adrenarche, the age at which the adrenal glands start to produce androgens. The first androgen to rise is dehydroepiandrosterone which starts rising at 5 years of age in girls, and 8 years of age in boys. Testosterone levels start to rise at 8 years of age in both girls and boys, and after 12 years of age boys have higher testosterone levels than girls, which is the age after which the annual mortality rate in boys starts to exceed that observed in girls (see Figure 5). On average girls reach onset of puberty about a year earlier than boys, in Sweden at 11.1 years of age compared with 12.1 years. A close temporal association is not a proof of causality, but there are some other pointers suggesting that androgens may increase the risk of sudden death. Victims of sudden unexpected infant death, both boys and girls, had significantly higher testosterone levels than controls. Sudden death associated with androgen abuse has been reported, and at least 35% of those deaths show cardiac hypertrophy. This suggests that higher levels of androgens could be associated with rapid disease progression in HCM.

Gender differences

Male gender is associated with higher risk of sudden cardiac deaths in general, and sudden deaths in athletes, in epilepsy, in young adults with HCM, arrhythmogenic right ventricular cardiomyopathy, and in the Brugada, Jervell and Lange-Nielsen syndromes. Female gender, on the other hand, is associated with a higher risk of drug-induced torsade-de-pointes, and cardiac events in some Long QT syndromes, particularly LQT2. Interestingly, the Kaplan–Meier analysis on freedom of cardiac events in LQT1, LQT2 and LQT3 mutations show an increased slope with a greater event rate, after about 6–8 years of age, i.e. after adrenarche. After puberty females show a longer QTc than males, a difference that can be abolished by orchidectomy of the male or testosterone treatment of the female. In contrast, males show a greater inhomogeneity of repolarization as reflected by a greater QTc dispersion. Increased QTc dispersion is a known risk factor for sudden death in HCM. We have observed progressive broadening of the QRS duration as the disease progresses, and one might therefore hypothesize that the QTc prolongation occurring in early puberty in females may contribute to the early high risk in females, whereas disease progression associated with higher androgen levels might result in increasing QTc dispersion towards later puberty in males.

How great is the risk of sudden death caused by hypertrophic cardiomyopathy in childhood and adolescence?

The high annual mortality seen in the childhood cohort, peaking at over 9%, needs to be interpreted in the context that 74% of our cases had a clinical presentation of the disease in childhood and therefore likely belonged to the most malignant spectrum of HCM mutations, and only 26% were children diagnosed by routine screening. Overt clinical presentation of HCM in childhood is seen in only 2.9 per 100 000 age-specific population as distinct from the prevalence detected in echocardiographic population screening of young adults of 0.2%. I.e. childhood HCM represents at most only 1.5% of the total number of mutation carriers in the population. Thus among the total population of HCM mutation carriers including asymptomatic and undiagnosed cases the annual mortality is probably around 0.056% in the 8–16 year age range, and 0.028% in the 17–30 year age range as calculated from our cause of death registry figures. Thus, there seems to be no case for general population screening for HCM. However, the situation is different in populations with increased risk. Pre-participation screening of athletes is compulsory in Italy, and...
appears largely effective in detecting individuals with HCM\textsuperscript{36} with a concomitant reduction in sudden deaths caused by cardiomyopathy.\textsuperscript{37} The group with the highest risk of HCM is children with one parent with HCM and thereby at 50\% risk of being a mutation carrier. It has been suggested that family screening for HCM should be commenced after 12 years of age,\textsuperscript{38} but as seen in Figure 3 those children with familial disease that show disease expression in childhood have a very high annual mortality in the 10–13 year age range. Those children with HCM that are at high risk for sudden death can be identified by ECG-amplitude sums in limb leads exceeding 10 mV, and by maximal wall thickness exceeding upper limit of normal for age by >90\%, and thereby by simple ECG and echocardiographic measures differentiated from a low-risk group with an annual mortality of only 0.2\%.\textsuperscript{12} As the risk of sudden death increases appreciably from 8 years of age, family screening for HCM should be carried out early for the first time, ideally no later than 6 years of age, since most high-risk patients can be identified already at first examination.\textsuperscript{12} There will be mutation carriers that do not express the disease that early, but they will be at very low risk of sudden death,\textsuperscript{12} and increased septum-to-cavity ratios and/or systolic wall-to-cavity ratios on echocardiography may be one tool for identifying mutation carriers that will later develop overt disease,\textsuperscript{12} and might require more frequent reviews during the pubertal growth spurt.

Conclusions

The risk of sudden arrhythmia death in patients with HCM is significantly higher in the 8–16 year age range than in the 17–30 year age range, which is a strong argument for family screening to be carried out at an early age in families with HCM, and for pre-participation screening for inclusion in sporting activities being carried out much earlier than 15 years of age for all children with a family history of heart muscle disease. The misleading practice of averaging annual mortality rates in HCM over paediatric age groups with significantly different mortality rates should be abandoned.

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References

19. Colan SD, Lipshultz SE, Lowe AM, Sleeper LA, Messere J, Cox GF, Lurie PR, Orav EJ, Towbin JA. Epidemiology and cause-specific


