Sudden cardiac death: clinical evaluation of paediatric family members

Maren Tomaske1*, Dagmar I. Keller2,3, and Urs Bauersfeld1

1Division of Paediatric Cardiology, University Children’s Hospital, Steinwiesstrasse 75, 8032, Zurich, Switzerland; 2Department of Internal Medicine, University Hospital, Zurich, Switzerland; and 3Department of Biomedicine, University Hospital Basel, Basel, Switzerland

Received 25 June 2010; accepted after revision 30 September 2010; online publish-ahead-of-print 2 November 2010

Aims
To evaluate paediatric relatives of first- and non-first-degree family victims with a history of premature sudden cardiac death (SCD) or aborted cardiac arrest (ACA).

Methods and results
Thirty-six consecutive referred families after SCD (n = 29) or ACA (n = 7) of a family member were analysed. Referral was either due to an inherited heart disease identified after autopsy, post-event, or family evaluation (n = 20 families) or due to sudden unexplained death (SUD, n = 16 families). In 3 of 16 (19%) SUD families, an inherited heart disease was diagnosed by evaluation of the paediatric relatives. In 5 of 25 (20%) referred paediatric relatives of SUD families, an inherited heart disease was identified, mainly sinus node dysfunction (n = 3). A total of 13 of 33 (39%) referred paediatric relatives of families with known inherited heart disease were affected, mainly with cardiomyopathy (n = 5) and primary electrical disease (n = 7). Prevention of SCD was initiated in 16 of the affected children by implantation of an antibradycardia device (n = 3), an implantable cardioverter defibrillator (ICD, n = 6), and/or antiarrhythmic medication (n = 8). Appropriate and successful ICD discharges occurred in four.

Conclusion
A stepwise, comprehensive clinical investigation of SCD or ACA families identifies a substantial number of paediatric relatives at risk of SCD. This allows for targeted prevention by effective treatments and evaluation of further relatives.

Keywords
Sudden cardiac death • Inherited heart disease • Paediatric

Introduction
The annual incidence of premature sudden cardiac death (SCD) is estimated as 1–1.8 in 100 000 in subjects under the age of 35 with sudden infant death syndrome excluded.1,2 A potential number of SCDs are caused by an inherited heart disease in this age group, such as predominantly autosomal dominant inherited cardiomyopathies, primary electrical diseases, and conduction system disorders.3

Even though new guidelines to improve survival rates from out-of-hospital cardiac arrests are steadily designed,4 outcome is still poor. Thus, primary or secondary prevention is key to reducing the burden of SCD. The use of antiarrhythmic medication, lifestyle advice, and implantable cardioverter defibrillators (ICDs) in patients with cardiomyopathies or primary electrical diseases at risk for ventricular arrhythmias has become a widely accepted therapy even in the young.5–7 However, a timely diagnosis of an inherited heart disease remains even in the absence of clinical symptoms.

The purpose of this study was to evaluate paediatric relatives of first- and non-first-degree family victims with a history of SCD or near fatal event and to identify those infants at risk of SCD.

Methods
Index patients
Between January 2003 and December 2008, referred families were retrospectively enrolled into the study. Inclusion criteria were premature SCD or aborted cardiac arrest (ACA) after successful resuscitation of a family member younger than 50 years. Reports from autopsy, post-event, or family evaluation were assessed for causes of the (near) fatal event.

Paediatric relatives
Paediatric family members were referred to our tertiary care centre. Paediatric relatives were analysed after (i) the inherited heart disease...
that caused the (near) fatal event in the family was identified or (ii) the cause of the (near) fatal event remained unexplained at referral [sudden unexplained death (SUD)]. The degree of relationship to the index patient was first degree, sibling, or non-first degree. Non-first-degree relatives were evaluated due to familial anxiety or as part of clinical evaluation after diagnosis of an inherited heart disease in a first-degree family member.

The study complies with the declaration of Helsinki. The institutional Ethics Committee approved the study design and parental written informed consent was obtained.

Evaluation
Stepwise evaluation included prior history, 12-lead and 24 h electrocardiogram (ECG), as well as two-dimensional echocardiography in all patients. Standard criteria were used to assess the probability of long QT syndrome (LQTS), short QT syndrome (SQTS), and Brugada’s syndrome (BrS).8–10 Additional investigations were signal average ECG, cardiac magnetic resonance imaging (cMRI), or event recorder when indicated. Genetic testing was performed in patients with a primary electrical disease phenotype. To date, genetic testing for inherited cardiomyopathies is not available in our institution.

After evaluations were completed, we distinguished between a definite or possible presence of an inherited heart disease. Proven structural heart disease was defined as the presence of a Z-score >2 for wall thickening in hypertrophic cardiomyopathy (HCM); a Z-score >2 for ventricular dilatation in dilated cardiomyopathy (DCM); fulfilled criteria for arrhythmogenic right ventricular cardiomyopathy (ARVC) according to the Task Force criteria.11 Proven sinus node dysfunction was defined as findings of severe sinus bradycardia, sinus arrest, or exit block in the 24 h ECG. Proven primary electrical disease was defined as the presence of a QTc >470 ms for LQTS, a QT interval, 4a), LQTS with KCNQ1 mutation (n = 2), SQTS with KCNH2 mutation (n = 1), and BrS with SCN5A mutation (n = 1). In two of these relatives, evolving left ventricular hypertrophy was seen and HCM was diagnosed during the course after 2 and 3 years, respectively. In the remaining, the inherited heart disease was likely due to borderline findings for patients with sinus node dysfunction (n = 1) and borderline findings with a QTc of 440–460 ms for patients with LQTS (n = 4).

Unaffected paediatric relatives were significantly younger than the affected ones in both family groups (P = 0.007).

Evaluation of paediatric relatives of sudden unexplained death families
In 3 of the 16 SUD families, an inherited disease could be diagnosed by evaluation of the paediatric relatives: (i) diagnosis of ARVC in a paediatric relative was based on four minor criteria11 after echocardiography, cMRI, and signal average ECG were performed. (ii) Diagnosis of an SQTS with a QTc of 270 ms in a paediatric relative was detected on the 12-lead ECG and confirmed by identification of a KCNQ1 mutation. (iii) Severe sinus node dysfunction was seen in a paediatric relative during stepwise evaluation in the 24 h ECG. Identification of an inherited heart disease was established in 5 of 25 (20%) referred paediatric relatives, with proven inherited heart disease in 4 relatives: ARVC (n = 1), SQTS with KCNQ1 mutation (n = 1), and sinus node dysfunction.
In one patient, sinus node dysfunction was likely due to borderline findings. Unaffected paediatric relatives were significantly younger than the affected ones in both family groups (P = 0.04).

**Clinical outcomes**

Prevention of SCD or of a cardiac event was initiated in 16 of the total of 18 affected children by implantation of an antibradycardia device (n = 3), an ICD (n = 6), and/or antiarrhythmic medication (n = 8) (Table 2). Subsequently, no fatal cardiac event was noted in any patient during a follow-up period of 3.6 (0.8–6.7) years. Appropriate and successful ICD discharges occurred in four of the affected patients with HCM (n = 3) and SQTS (n = 1).

In the present study, more than half of the evaluated families were referred due to known inherited heart disease. As expected in the dominant Mendelian inheritance pattern, half of the first-degree relatives or siblings were found to be affected or carriers. Conditions detected and potentially accountable for the SCD in these families mainly were cardiomyopathies and primary electrical disease.

Death was unexplained after autopsy in 21 families in our study population. Family evaluation and evaluation of paediatric relatives revealed an inherited heart disease as the probable cause of death in 38% of the families, predominantly primary electrical diseases in 29%. Our data approach former results. Tan et al. identified an inherited heart disease in 40% of the families with an unexplained death in victims ≤40 years of age, likewise predominantly primary electrical disease in 28%. Compared with the mentioned study, BrS and catecholaminergic polymorphic ventricular tachycardia (CPVT) were underrepresented in our study population.

However, the identification and distribution of the underlying inherited heart disease after SCD does not go in line with the reported data in a previous study investigated in victims died between 4 and 64 years of age. Behr et al. identified an inherited heart disease in more than half of the families, with a higher proportion of underlying primary electrical disease and cardiomyopathy. A potential reason for the higher rate of identification of an inherited heart disease in their study cohort is the systematic genetic study performed in SUD victims and their families. In one-third of the SUD victims with molecular autopsy, a probable
cause of death was detected, mainly primary electrical diseases. Moreover, affected first-degree relatives were adults and considerably older than our study population, making a diagnosis for a structural heart disease more likely.

Especially, the morphological expression of HCM and other inherited cardiomyopathies may not be present until adolescent when body growth and maturation are most accelerated. In two of our study patients, HCM was found during the course. Thus, a single evaluation during childhood may not be sufficient to definitely exclude an inherited heart disease; repetitive assessment has to be encouraged. The occurrence of SCD in a family should dictate regular follow-up at 2- to 3-year intervals until full growth and maturation is achieved. A further 2- to 3-year interval beyond the age of 18 years is recommended for further risk stratification even without manifest inherited heart disease. For manifest HCM, recommendations for follow-up are within a 5-year interval, which in practise is shortened to a 2- to 3-year follow-up in our centre.\(^\text{17}\) The occurrence of cardiomyopathies during adolescence might explain the age difference in our study group with those unaffected being significantly younger.

Genetic testing in our study cohort was done based on ECG phenotypes from family members. However, the use of genetic testing in affected families as a post-mortem screening and screening of other family members without clear phenotype might be a further perspective to identify concealed carriers of an inherited heart disease and contribute to an effective SD prevention.\(^\text{18}\)

### Table 1 Families with confirmed diagnosis (n = 23)

<table>
<thead>
<tr>
<th>Family</th>
<th>Diagnosis</th>
<th>Diagnosis made by</th>
<th>Event</th>
<th>Index patient: age at event (years)</th>
<th>Previous SCD in family (n)</th>
<th>Examined paediatric relatives (n)</th>
<th>Degree of relation to index patient</th>
<th>Affected paediatric relatives (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>ARVC</td>
<td>Autopsy</td>
<td>SCD</td>
<td>47</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>ARVC</td>
<td>Autopsy</td>
<td>SCD</td>
<td>17</td>
<td>0</td>
<td>2</td>
<td>1(^\text{1}) sibling</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>ARVC</td>
<td>Autopsy</td>
<td>SCD</td>
<td>45</td>
<td>0</td>
<td>2</td>
<td>1(^\text{1})</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>ARVC</td>
<td>Evaluation of a paediatric relative</td>
<td>SCD</td>
<td>23</td>
<td>1</td>
<td>2</td>
<td>Siblings</td>
<td>1</td>
</tr>
<tr>
<td>5</td>
<td>HCM</td>
<td>Autopsy</td>
<td>SCD</td>
<td>25</td>
<td>1</td>
<td>3</td>
<td>3(^\text{1})</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>HCM</td>
<td>Autopsy</td>
<td>SCD</td>
<td>35</td>
<td>0</td>
<td>2</td>
<td>3(^\text{1})</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>HCM</td>
<td>Autopsy</td>
<td>SCD</td>
<td>13</td>
<td>0</td>
<td>1</td>
<td>4(^\text{1})</td>
<td>1</td>
</tr>
<tr>
<td>8</td>
<td>HCM</td>
<td>Autopsy</td>
<td>SCD</td>
<td>45</td>
<td>0</td>
<td>2</td>
<td>1(^\text{1})</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>HCM</td>
<td>Post-event evaluation</td>
<td>ACA</td>
<td>18</td>
<td>0</td>
<td>1</td>
<td>Sibling</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>HCM</td>
<td>Post-event evaluation</td>
<td>ACA</td>
<td>38</td>
<td>0</td>
<td>1</td>
<td>1(^\text{1})</td>
<td>1</td>
</tr>
<tr>
<td>11</td>
<td>DCM</td>
<td>Autopsy</td>
<td>SCD</td>
<td>36</td>
<td>0</td>
<td>1</td>
<td>1(^\text{1})</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>DCM</td>
<td>Post-event evaluation</td>
<td>ACA</td>
<td>40</td>
<td>1</td>
<td>1</td>
<td>1(^\text{1})</td>
<td>1</td>
</tr>
<tr>
<td>13</td>
<td>LQTS</td>
<td>Post-event evaluation</td>
<td>ACA</td>
<td>17</td>
<td>0</td>
<td>2</td>
<td>Siblings</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>LQTS</td>
<td>Post-event evaluation</td>
<td>ACA</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>Sibling</td>
<td>0</td>
</tr>
<tr>
<td>15</td>
<td>LQTS</td>
<td>Post-event evaluation</td>
<td>ACA</td>
<td>49</td>
<td>0</td>
<td>3</td>
<td>1(^\text{1})</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>LQTS</td>
<td>Family evaluation</td>
<td>SCD</td>
<td>36</td>
<td>1</td>
<td>3</td>
<td>3(^\text{1})</td>
<td>0</td>
</tr>
<tr>
<td>17</td>
<td>LQTS</td>
<td>Family evaluation</td>
<td>SCD</td>
<td>34</td>
<td>3</td>
<td>1</td>
<td>3(^\text{1})</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>LQTS</td>
<td>Family evaluation</td>
<td>SCD</td>
<td>32</td>
<td>3</td>
<td>1</td>
<td>1(^\text{1})</td>
<td>1</td>
</tr>
<tr>
<td>19</td>
<td>LQTS</td>
<td>Family evaluation</td>
<td>SCD</td>
<td>26</td>
<td>3</td>
<td>3</td>
<td>3(^\text{1})</td>
<td>2</td>
</tr>
<tr>
<td>20</td>
<td>SQTS</td>
<td>Evaluation of a paediatric relative</td>
<td>SCD</td>
<td>28</td>
<td>2</td>
<td>1</td>
<td>1(^\text{1})</td>
<td>1</td>
</tr>
<tr>
<td>21</td>
<td>BrS</td>
<td>Family evaluation</td>
<td>SCD</td>
<td>45</td>
<td>0</td>
<td>1</td>
<td>1(^\text{1})</td>
<td>1</td>
</tr>
<tr>
<td>22</td>
<td>SND</td>
<td>Post-event evaluation</td>
<td>ACA</td>
<td>42</td>
<td>0</td>
<td>1</td>
<td>1(^\text{1})</td>
<td>1</td>
</tr>
<tr>
<td>23</td>
<td>SND</td>
<td>Evaluation of a paediatric relative</td>
<td>SCD</td>
<td>35</td>
<td>0</td>
<td>3</td>
<td>3(^\text{1})</td>
<td>3</td>
</tr>
</tbody>
</table>

ARVC, arrhythmogenic right ventricular cardiomyopathy; DCM, dilated cardiomyopathy; HCM, hypertrophic cardiomyopathy; LQTS, long QT syndrome; BrS, Brugada’s syndrome; SQTS, short QT syndrome; SND, sinus node dysfunction; ACA, aborted cardiac arrest; SCD, sudden cardiac death.
The major drawbacks of molecular diagnostics first are the time-consuming and expensive analysis, which limits their routine use. Secondly, post-mortem blood and tissue samples can be difficult to be analysed. In addition, if a clear phenotype is missing in autopsy, genotyping cannot be performed on a candidate gene approach which makes genotyping more challenging and more time- and cost-intensive. Moreover, the constantly increasing number of genetic disorders and involved genes especially responsible for ion channel diseases indicates that a negative genetic test cannot definitely rule out an underlying inherited heart disease. If a responsible gene mutation can be identified in an index patient, mutation screening should be performed in at least the first-degree family members. Genotype- and phenotype-positive family members during evaluation should receive treatment according to the accepted guidelines. Genotype-positive–phenotype-negative family members should be followed up regularly.

Similar to former findings, one-quarter of all admitted families had a history of additionally unexplained premature SCDs in relatives younger than 50 years not leading to former evaluation of the family members. The high rate to establish a diagnosis or identify a disease carrier in half of the paediatric relatives with known inherited heart disease reflects the inheritance pattern. However, it also highlights the importance of a thorough evaluation of surviving relatives and indicates that active examinations should strongly be advised. Given the lack of awareness of an inherited heart disease as the cause of a (near) fatal event among primary care physicians and paediatricians, further families with SCD or successful resuscitation in this 6-year study period might not have been recruited. This is of concern, especially as effective treatments to prevent SCD are available. In one half of the affected paediatric family members of families with explained or unexplained SCD in our study cohort, therapeutic intervention with device implantation following the guidelines was initiated in an asymptomatic, pre-clinical state.

### Study limitations

In 20 families of our study population, the inherited heart disease that caused the (near) fatal event was known when the paediatric relatives were referred and analysed, including adult family evaluation of first-degree relatives. Thus, the comparatively high number of detected carriership of the known inherited cardiac disease within our study group relates to the heredity. Moreover, there was a possibility of referral bias to our tertiary care centre for children.

In 13 families, the fatal event remained unexplained. Exercise testing, epinephrine stress testing, Ajmaline testing, or other...
pharmacological testing may have helped to unmask those patients with concealed LQTS, BrS, or CPVT. However, a uniform diagnostic strategy for the evaluation of the paediatric population does not exist and the above-mentioned tests are not routinely performed in our centre. Given these special circumstances in the approach to our paediatric family members, the above-mentioned primary electrical diseases as the probable cause of SCD might be underrepresented in our study group.

**Conclusion**

A stepwise, comprehensive clinical investigation of SCD or life-threatening event families identifies a substantial number of paediatric relatives at risk of SCD. Referral to a department of paediatric cardiology allows for targeted prevention of SCD by effective treatment of paediatric family members, even in asymptomatic family members showing a distinct phenotype of inherited cardiac disorder. After baseline assessment, families should be discussed interdisciplinarily involving paediatric and adult cardiologists, clinical geneticists specialized in inherited cardiac disorders, and psychologists if needed. Regular clinical and apporative follow-up in those with normal findings at first evaluation during childhood to adolescence is mandatory.

**Conflict of interest:** none declared.

**References**
