Background—Sudden arrhythmic death syndrome defines a sudden unexpected and unexplained death despite comprehensive pathological and toxicological investigation. Previous studies have focused on evaluation of adult relatives. There is, however, a lack of data in children, leading to highly variable management. We sought to determine the clinical utility of cardiac evaluation in pediatric relatives of sudden arrhythmic death syndrome probands.

Methods and Results—Retrospective review was undertaken of pediatric patients with a family history of sudden arrhythmic death syndrome assessed from 2010 to 2013 in 2 centers. Clinical history, cardiac, and genetic investigations were assessed, including diagnoses made after evaluation of adult relatives. A total of 112 pediatric relatives from 61 families were evaluated (median age at presentation, 8 years; range, 0.5–16 years). A probable diagnosis was made in 18 (29.5%) families: Brugada syndrome, 13/18 (72%); long QT syndrome, 3/18 (17%); and catecholaminergic polymorphic ventricular tachycardia, 2/18 (11%). Genetic testing identified mutations in 20% of Brugada syndrome (2/10) and 50% of long QT syndrome (1/2) and catecholaminergic polymorphic ventricular tachycardia families (1/2) who were tested. Pediatric evaluation diagnosed 6/112 relatives (5.4%), increasing to 7% (6/85) if only first-degree relatives were assessed. The only useful diagnostic tests were the 12-lead and exercise electrocardiograms and ajmaline provocation test. The median duration of follow-up was 2.1 years (range, 0.2–8.2 years) with no cardiac events.

Conclusions—The yield of evaluating pediatric relatives is significant and higher when focused on first-degree relatives and on conditions usually expressed in childhood. We propose a management pathway for these children. (Circ Arrhythm Electrophysiol. 2014;7:800-806.)

Key Words: arrhythmias, cardiac death, sudden, cardiac diagnosis
demographics, symptoms (including syncope, presyncope, and palpitation) and clinical history, the index SADS case (proband) autopsy report, and results of the cardiac investigations performed. Family history was also assessed, especially for a diagnosis of an ICC in adult relatives. Adult relatives were evaluated according to protocols described previously.1,5,12–14

**Pediatric Cardiac Evaluation**

Initial cardiac investigations included a 12-lead ECG, transthoracic 2-dimensional echocardiogram, exercise ECG when possible, and 24-hour Holter monitoring. Additional investigations included signal-averaged ECG, cardiac MRI, and ajmaline provocation tests where indicated. Standard criteria were used to determine a positive diagnosis of long QT syndrome (LQTS), Brugada syndrome (BrS), or catecholaminergic polymorphic ventricular tachycardia (CPVT).1

In our practice, first-degree adult relatives were offered an ajmaline provocation test preferentially because they were able to understand the risks and benefits of the test. Ajmaline provocation testing of pediatric first-degree relatives was offered to parents only when it was not possible to test an immediate adult relative first, or if no diagnosis had been made after comprehensive testing of adult relatives. This was discussed carefully with parents and a consensual decision arrived at, particularly because asymptomatic BrS diagnosed by ajmaline provocation carries low risk in childhood.1,15 Particular attention was paid to whether the primary diagnosis in a family resulted initially from evaluating an adult or pediatric relative. If a diagnosis was made in a family, it was presumed to be the cause of death in the index SADS case. Genetic testing was undertaken in accordance with accepted clinical guidelines.14 No postmortem samples were available for molecular autopsy.

**Follow-Up**

Details of further outpatient appointments were recorded, including time between appointments and total length of follow-up. Data were acquired in relation to new symptoms and results of repeat investigations. Twelve-lead ECGs were performed routinely. Echocardiography was repeated if there were prior equivocal findings or if there were new ECG findings suggestive of a cardiomyopathy. Other investigations were performed only if indicated by clinical history or abnormal investigations.

**Statistics**

Continuous variables were expressed as mean±SD or median (range) depending on their normality distribution, which was assessed using Kolmogorov–Smirnov and Shapiro–Wilk tests. Categorical variables were expressed with number of patients and percentage and compared with Fisher exact test. Probability values were based on 2-sided tests considered significant at \( P<0.05 \). Analysis was conducted with SPSS version 18.0 software (SPSS, Chicago, IL).

**Results**

**Demographics**

A total of 112 pediatric relatives from 61 families attended for an outpatient appointment. The median number of pediatric relatives seen per family was 2 (range, 1–6). In 30/61 (49%) families, only 1 pediatric relative was seen from each family. In the other 31 families, 2 pediatric relatives each were seen from 16 (26%) families, 3 each from 12 (20%) families, 4 each from 2 (3%) families, and 6 from 1 (2%) family. Eighty-five out of 112 (76%) were first-degree relatives, whereas 27 (24%) were second- or third-degree relatives and 54/112 (48%) were of male sex. The median age at presentation was 8.0 years (range, 0.5–16 years). In these 61 families, a total of 129 adult relatives were screened, with a median of 2 relatives seen per family (range, 0–8).

**Symptoms**

Nineteen out of 112 (17%) relatives reported either syncope (12/19) or presyncope (7/19). Fifteen out of 19 of these episodes were typical of a vasovagal origin; 2/19 were second- or a generalized seizure disorder, and 2/19 was exertional. Three out of 112 (2.7%) reported an episode of palpitation.

**Investigations**

Initial investigations were variable depending on the relative’s age and ability to cooperate. At the first outpatient appointment, 110/112 (98%) relatives underwent 12-lead ECGs; 106 (95%) had transthoracic 2-dimensional echocardiograms, and 95 (85%) had 24-hour Holter monitoring. Thirty (27%) also underwent signal-averaged ECG, whereas subsequent to the consultation, 47 (42%) had exercise testing and 7 (6.3%) underwent a cardiac MRI scan. Thirteen relatives underwent ajmaline testing, 9 (8.0%) without evidence of BrS in an adult relative and 4 (3.6%) after a diagnosis of BrS in an adult relative.

Three of 110 relatives (2.7%) had a prolonged QT interval on 12-lead ECGs, 1 of 47 relatives (2.1%) had an abnormal exercise test, whereas 2 of 13 (15.4%) had positive ajmaline tests. Five of 95 (5.3%) relatives had equivocal findings on echocardiography, although these were not diagnostic for an ICC and were deemed unrelated to the SADS death. All other investigations were unremarkable.

**Diagnoses**

A probable diagnosis of an inherited cardiac condition was made in 18/61 families (29.5%). The primary diagnosis was made after the screening of an adult relative in 15/18 (83%) families, whereas evaluating pediatric relatives resulted in

![Figure 1. Flow diagram of positive diagnoses in 61 sudden arrhythmic death syndrome (SADS) families. BrS indicates Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; and LQTS, long QT syndrome.](image-url)
3/18 (17%) families receiving a diagnosis. BrS was the most common diagnosis, affecting 13 families (72%) with LQTS in 3 families (17%) and CPVT in 2 (11%). These 18 family diagnoses, including the proband’s characteristics, are further illustrated in Figure 1 and Table 1. Six of 112 (5.4%) pediatric relatives were affected (Table 2). Of the 6 affected pediatric relatives, 2 were diagnosed with BrS after an ajmaline provocation test; 4 had LQTS (1 after clinical/genetic screening, 3 after clinical screening).

In the 15 families diagnosed after an adult screening, 2 pediatric relatives from 2 families were subsequently diagnosed with the condition already identified in the family: 1 with BrS after ajmaline testing of 4/24 (17%) first-degree pediatric relatives in 12 families, and 1 with LQTS. In the 3 families diagnosed primarily through pediatric screening, no further diagnoses were made in other adult relatives.

There was at least 1 first-degree pediatric relative screened in 36 of the 43 families without a diagnosis. Only 8/62 (13%) pediatric relatives from these 36 families underwent ajmaline testing, all of which were negative.

Targeted genetic testing was undertaken in 14 of 18 (78%) families with an ICC diagnosis. Two of 10 families (20%) with BrS were identified with a SCN5A mutation. The yield of genetic testing for both LQTS (1/2) and CPVT (1/2) was 50%. A KCNH2 mutation was identified in the LQTS family and a RyR2 mutation in the CPVT family (see Table 1).

### Table 1. Proband Characteristics in Families With a Positive Diagnosis

<table>
<thead>
<tr>
<th>Family</th>
<th>Sex</th>
<th>Age, y</th>
<th>Circumstances of Death</th>
<th>Primary Diagnosis source</th>
<th>Family Diagnosis</th>
<th>Gene Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male</td>
<td>46</td>
<td>Inactive (sleep)</td>
<td>Pediatric</td>
<td>LQTS</td>
<td>Results awaited</td>
</tr>
<tr>
<td>2</td>
<td>Male</td>
<td>56</td>
<td>Inactive (awake)</td>
<td>Pediatric</td>
<td>LQTS</td>
<td>Negative</td>
</tr>
<tr>
<td>3</td>
<td>Male</td>
<td>37</td>
<td>Active (swimming)</td>
<td>Pediatric</td>
<td>BrS</td>
<td>Negative</td>
</tr>
<tr>
<td>4</td>
<td>Female</td>
<td>30</td>
<td>Inactive (awake)</td>
<td>Adult</td>
<td>BrS</td>
<td>Negative</td>
</tr>
<tr>
<td>5</td>
<td>Male</td>
<td>30</td>
<td>Inactive (sleep)</td>
<td>Adult</td>
<td>BrS</td>
<td>SCN5A; c.1127G&gt;A; p.Arg376His</td>
</tr>
<tr>
<td>6</td>
<td>Male</td>
<td>43</td>
<td>Inactive (awake)</td>
<td>Adult</td>
<td>BrS</td>
<td>Negative</td>
</tr>
<tr>
<td>7</td>
<td>Male</td>
<td>28</td>
<td>Inactive (sleep)</td>
<td>Adult</td>
<td>BrS</td>
<td>SCN5A; c.3207_3211dupGGAGG; p.Glu1071fs</td>
</tr>
<tr>
<td>8</td>
<td>Male</td>
<td>25</td>
<td>Inactive (sleep)</td>
<td>Adult</td>
<td>BrS</td>
<td>Negative</td>
</tr>
<tr>
<td>9</td>
<td>Female</td>
<td>37</td>
<td>Inactive (sleep)</td>
<td>Adult</td>
<td>BrS</td>
<td>Results awaited</td>
</tr>
<tr>
<td>10</td>
<td>Male</td>
<td>30</td>
<td>Unknown</td>
<td>Adult</td>
<td>BrS</td>
<td>Negative</td>
</tr>
<tr>
<td>11</td>
<td>Male</td>
<td>16</td>
<td>Inactive (awake)</td>
<td>Adult</td>
<td>BrS</td>
<td>Negative</td>
</tr>
<tr>
<td>12</td>
<td>Male</td>
<td>29</td>
<td>Inactive (awake)</td>
<td>Adult</td>
<td>BrS</td>
<td>Results awaited</td>
</tr>
<tr>
<td>13</td>
<td>Male</td>
<td>7</td>
<td>Active (football)</td>
<td>Adult</td>
<td>BrS</td>
<td>Not tested</td>
</tr>
<tr>
<td>14</td>
<td>Female</td>
<td>35</td>
<td>Unknown</td>
<td>Adult</td>
<td>BrS</td>
<td>Negative</td>
</tr>
<tr>
<td>15</td>
<td>Male</td>
<td>39</td>
<td>Active (climbing)</td>
<td>Adult</td>
<td>BrS</td>
<td>Negative</td>
</tr>
<tr>
<td>16</td>
<td>Female</td>
<td>30</td>
<td>Inactive (emotional)</td>
<td>Adult</td>
<td>CPVT</td>
<td>Negative</td>
</tr>
<tr>
<td>17</td>
<td>Male</td>
<td>40</td>
<td>Inactive (awake)</td>
<td>Adult</td>
<td>CPVT</td>
<td>RyR2</td>
</tr>
<tr>
<td>18</td>
<td>Female</td>
<td>22</td>
<td>Inactive (awake)</td>
<td>Adult</td>
<td>LQTS</td>
<td>KCNH2; c.1744C&gt;T; p.Arg582Gys</td>
</tr>
</tbody>
</table>

BrS indicates Brugada syndrome; CPVT, catecholaminergic polymorphic ventricular tachycardia; and LQTS, long QT syndrome.

### Intervention
Lifestyle advice only was given to the 2 affected pediatric relatives with BrS. All 4 affected with LQTS were commenced on β-blocker therapy.

### Follow-Up
The median duration of follow-up for the pediatric relatives was 2.1 years (range, 0.2–8.2 years), attending a total of 215 outpatient appointments. The median duration between outpatient visits was 12 months (range, 3–36 months). Seventy-five of 215 (35%) were <12 months, 133 (62%) between 12 and 24 months, and 7 (3%) >24 months. There were no significant cardiac events during follow-up, and no new diagnoses were made.

### Discussion
Previous studies of the cardiological evaluation of SADS families have focused mainly on adult family members, and recent guidelines regarding management of SADS families are based mainly on these results. SADS often affects young adults and, consequently, pediatric relatives such as siblings and children of the proband may make up a significant proportion of immediate family members who may be at risk. The utility of screening pediatric relatives of SADS victims has, however, yet to be fully studied. To our knowledge, we report
the largest cohort of pediatric relatives undergoing cardiac evaluation after a SADS death.

Diagnostic Yield of Pediatric Screening

The study describes a significant diagnostic yield of 6/112 pediatric relatives (5.4%) with an ICC. This increases to 7% (6/85) if only first-degree relatives are included. Eighteen of the 61 included families (29.5%) were identified with an ICC. This is comparable with the 18% to 33% yield in more recently published studies with larger cohorts, including a report on the 15-year experience of familial screening in a Dutch cohort.1,16,17 Five of these families (27%) contained an affected pediatric relative. The percentage of diagnoses established by screening adult relatives was higher than by screening pediatric relatives (15/18 [83%] versus 3/18 [17%]). Most of the family diagnoses made by screening an adult relative were BrS (12/15), whereas the most common family diagnosis made after a pediatric screening was LQTS (2/3; Figure 1).

This finding is consistent with the natural history of these conditions. The spontaneous type 1 Brugada pattern is less common in children compared with male adults.15,18,19 Conversely, LQTS is more likely to present in childhood and adolescence.19 In addition, we were reluctant to perform ajmaline testing in pediatric relatives without careful discussion. The pediatric yield may, therefore, have been higher if ajmaline testing was performed routinely in pediatric relatives.

Screening of Non–First-Degree Relatives

The utility of screening first-degree relatives after a SADS death is well established.2–7 All 6 affected pediatric relatives were children of the proband. Despite the diagnostic yield of screening more distant relatives falling significantly, it is often unavoidable. Parental concern after a SADS death is frequently overwhelming, leading to premature referral of non–first-degree pediatric family members for assessment. In our study, 24% of the pediatric relatives assessed were not first-degree.

Symptoms Are Common in Pediatric Relatives

Symptoms were relatively common in pediatric relatives with the majority being syncope or presyncope. However, the episodes were predominantly vasovagal in nature and are common in the pediatric population.20 It is thus essential that a detailed and comprehensive history is taken to avoid the need for more invasive and unnecessary investigations or follow-up. The presence of red-flag symptoms such as exertional or un heralded syncope or symptoms that are atypical for age or circumstances should be taken seriously, especially with a family history of SADS death, regardless of the degree of relatedness.1 Nonetheless, in our study, the 2 pediatric relatives with exertional syncope were phenotypically normal despite thorough investigation.

Diagnostic Utility of Different Cardiac Investigations

The majority of the pediatric relatives underwent a 12-lead ECG, transthoracic 2-dimensional echocardiogram, and Holter monitoring at their initial assessment. Although echocardiography was unlikely to result in a diagnosis in view of a negative autopsy in the proband ruling out a cardiomyopathy, we felt it important to confirm a structurally normal heart as part of cardiovascular assessment. Exercise testing was performed only in children aged ≥5 years who are able to use the treadmill, whereas signal-averaged ECG was reserved again for older children who can stay still for the test. The only useful diagnostic tests were a 12-lead ECG, exercise testing, and ajmaline testing. Holter monitoring and signal-averaged ECGs did not prove to be of utility.

Genetic Testing and Molecular Autopsy

In line with recommendations from the expert consensus statements on genetic testing and diagnosis and management of arrhythmia syndromes,1,14 genetic testing was useful in the management of our families with a positive ICC diagnosis. The yield of targeted genetic testing was significant, ranging from 20% in BrS to 50% in LQTS and CPVT. These guidelines also recommend the retention of tissue or blood samples for molecular autopsy, with a channelopathy-focused genetic test to be considered in SADS.21,22 However, in our study, this is limited by the lack of appropriate postmortem material for genetic testing. Fresh frozen blood or tissue, the gold standard source of DNA for genetic testing, is not routinely retained at autopsy and, in the United Kingdom, could partly be as a result of consent issues raised by the Human Tissue Act and the lack of awareness regarding the utility of molecular autopsy in SADS.21 Molecular autopsy should be viewed as complementary to familial cardiological evaluation, and a combined approach will provide the best chance of identifying an ICC in the family.
Follow-Up of Pediatric Relatives

The main goal of screening pediatric relatives after a SADS death is to evaluate a child for signs of an ICC and provide reassurance about normality. However, the nature of ICCs and limitations of pediatric testing is such that we cannot fully reassure parents, necessitating a period of follow-up throughout childhood and adolescence. During follow-up, none of our pediatric relatives, including affected children, had a significant cardiovascular event. The follow-up duration between outpatient assessments ranged from 3 to 36 months. In our experience, a short initial follow-up was useful to reassure the family. Extending the follow-up duration between assessments did not result in any harm but reduced disruption to the family. It is, however, essential that families feel supported in the period between assessments and are able to easily access the multidisciplinary team comprising the pediatrician, cardiologist, geneticist, and psychologist to address any concerns in the interim. The assessment and follow-up of a pediatric relative require a fine balance between the need to be thorough and to minimize intrusion in a family that has already undergone the psychological trauma of a premature sudden death.

A Proposal for Pediatric Management Pathways in SADS Families

Based on our findings and experience, we propose a pathway for the management of pediatric relatives adapted from existing guidelines\textsuperscript{1,14} and summarized in Figures 2 and 3. The emphasis is placed on basic cardiac evaluation of all first-degree or symptomatic pediatric relatives. However, thorough investigation of all immediate adult relatives should be performed before more invasive provocation testing in children that may not alter immediate management or may otherwise prove unnecessary. Although the results from this study and others are consistent in finding an inactive or asleep mode of death among most SADS cases, it is important not to limit investigations in adults to more likely conditions because there will always be a range of circumstances of death regardless of the ultimate familial diagnosis.\textsuperscript{7,13,17} Ajmaline testing may be considered in children without a diagnosis from undiagnosed families and after careful discussion with parents but if delayed may best be undertaken before discharge from the pediatric ICC clinic and before transition to adult services. In the interim, advice may be given about lifestyle such as careful monitoring when exposed to drugs that exacerbate BrS and prompt treatment of fever.\textsuperscript{22} A period of follow-up throughout childhood is required in undiagnosed children because initial testing is usually limited by age or choice. This may be more

Figure 2. Proposed pathway for initial evaluation of pediatric family members after a sudden arrhythmic death syndrome (SADS) death (partly adapted from Priori et al\textsuperscript{1} and Ackerman et al\textsuperscript{14}). + indicates diagnostic; and –, nondiagnostic. *Children to complete as much as age and maturity permits. †Exercise test >5 y of age. ‡Consider further testing of pediatric relatives if no diagnosis made from adult screening. §Class I antiarrhythmic challenge after careful discussion with parents and before discharge from pediatric inherited cardiac condition clinic. The use of ajmaline is recommended with procainamide, flecainide, or pilsicainide as alternative medications. ||Cardiac MRI if abnormal ECG or echocardiogram suggestive of cardiomyopathy.

Figure 3. Proposed pathway for follow-up of unaffected pediatric family members after initial evaluation after a sudden arrhythmic death syndrome (SADS) death (partly adapted from Priori et al\textsuperscript{1} and Ackerman et al\textsuperscript{14}). BrS indicates Brugada syndrome; CMRI, cardiac MRI; F/U, follow-up; and Ix, investigation. *Children to complete as much as age and maturity permits. †Exercise test to be performed on follow-up appointments only if equivocal abnormal on previous echo and/or abnormal ECG suggestive of cardiomyopathy. §Class I antiarrhythmic challenge after careful discussion with parents and before discharge from pediatric inherited cardiac condition clinic. The use of ajmaline is recommended with procainamide, flecainide, or pilsicainide as alternative medications. ‡Development of significant cardiovascular symptoms such as syncope or palpitations or subsequent occurrences within the family of relevant cardiovascular events such as sudden unexplained death (including in infancy) or sudden cardiac arrest since the last clinical review. §Three yearly follow-up with option of earlier review at discretion of the physician.
frequent in patients with prior symptoms or borderline features according to the physician’s discretion. It may also be reinitiated if there are new symptoms or a change in family circumstance such as a diagnosis or SCD in another relative, including infants. Although there were no molecular autopsies undertaken in our group, it is possible that an arrhythmia gene–focused molecular autopsy may be especially useful for the management of children of SADS cases because they are the most likely relatives to be at risk of genetic disease and its complications in the future.1,14

Limitations

The cohort assessed, although of a significant size, may be subject to bias, particularly given the prevalence of BrS as the cause of death in our SADS families. This is, however, consistent with our population and previous experience,12,13 although there is no overlap between previously reported groups and this current study. The higher prevalence of BrS may partly be explained by provocation testing with a class I antiarrhythmic being a routine part of the cardiological evaluation performed on adult relatives during familial screening for SADS in our center. Our provocation testing protocol is also likely to be more sensitive because of the use of ajmaline rather than flecainide or procainamide and the utilization of high right ventricular lead placements with V1 and V2 in the second and third intercostal spaces.22,23 Our results may also reflect that our reluctance to perform ajmaline testing in children without the majority of families. urge Heart J. 2008;29:1670–1680.


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Disclosures

None.

References


CLINICAL PERSPECTIVE

Sudden arrhythmic death syndrome defines a sudden death that remains unexplained despite a comprehensive autopsy and toxicology. Previous studies on molecular autopsy and evaluation of adult relatives have attributed a significant proportion of these deaths to inherited cardiac conditions. The identification of at-risk relatives is paramount and allows for the timely institution of appropriate treatment. There is, however, a lack of literature on clinical evaluation of pediatric relatives in sudden arrhythmic death syndrome, leading to highly variable management. We describe our experience of evaluating 112 pediatric relatives after a sudden arrhythmic death syndrome death, the largest cohort reported so far. The yield of screening pediatric relatives is significant and increases when targeting first-degree relatives and inherited cardiac conditions usually expressed in childhood. The nature of inherited cardiac conditions and limitations of pediatric testing is such that a period of follow-up throughout childhood and adolescence is necessary, with continued support provided to families by a multidisciplinary team comprising a paediatrician, cardiologist, geneticist, specialist nurse, and psychologist. The assessment and follow-up of a pediatric relative require balancing the need to be thorough while minimizing intrusion in a family that has already undergone the psychological trauma of a premature sudden death. Based on our findings and existing international consensus guidelines, we have proposed a pathway focussed particularly on the management of pediatric relatives that will provide a framework for health professionals involved in the care of these children. We emphasize in particular the need to avoid unnecessary provocation testing in asymptomatic low-risk children.

Cardiac Evaluation of Pediatric Relatives in Sudden Arrhythmic Death Syndrome: A 2-Center Experience
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