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

Running title: Wong et al.; Cardiac evaluation of pediatric relatives in SADS

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Abstract

Background - Sudden Arrhythmic Death Syndrome (SADS) 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 SADS probands.

Methods and Results - Retrospective review was undertaken of pediatric patients with a family history of SADS assessed from 2010 to 2013 in 2 centers. Clinical history, cardiac and genetic investigations were assessed, including diagnoses made following evaluation of adult relatives. A total of 112 pediatric relatives from 61 families were evaluated (median age at presentation of 8 years (range 0.5 to 16 years)). A probable diagnosis was made in 18 (29.5%) families: Brugada syndrome (BrS) 13/18 (72%); long QT syndrome (LQTS) 3/18 (17%); and catecholaminergic polymorphic ventricular tachycardia (CPVT) 2/18 (11%). Genetic testing identified mutations in 20% of BrS (2/10), and 50% of LQTS (1/2) and CPVT 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 upon first degree relatives and on conditions usually expressed in childhood. We propose a management pathway for these children.

Key words: sudden cardiac death, arrhythmia, genetic heart disease, pediatric, screening, sudden arrhythmic death syndrome, inherited cardiac condition, pediatric cardiac evaluation
Introduction

Sudden Arrhythmic Death Syndrome (SADS) defines a sudden unexpected cardiac death that remains unexplained after comprehensive post mortem examination, histology and toxicology studies.\(^1\) It accounts for around 500 deaths in the UK every year, corresponding to an annual incidence of 1.38/100000 population.\(^2\) International estimates vary partly due to different populations and inclusion criteria. The incidence of SADS in other Caucasian populations ranges from 0.81/100000 (Danish) to 1.2/100000 (USA).\(^3\)

A significant proportion of SADS cases are due to inherited cardiac conditions (ICC). These have been identified through cardiological evaluation of families and post mortem genetic testing (‘molecular autopsy’) and have laid the groundwork for much of our current clinical practice.\(^4\)\(^,\)\(^1\)\(^1\) In particular around a half of families may be identified with an ICC.\(^5\)

Diagnosing an underlying ICC not only allows the identification of at risk family members and timely institution of appropriate treatment, in our experience it also provides psychological benefit to the bereaved family. However, the aforementioned studies have largely focused on adult relatives and there is a lack of pediatric data in the literature. As a result, the assessment of pediatric relatives is highly variable and often based on data extrapolated from adult data. The aim of our study is to determine the clinical utility of screening pediatric relatives following a SADS death and to provide a framework for the structured management of this population.

Methods

Inclusion criteria

Pediatric relatives (age 16 or below) with a family history of SADS were included in the study if they were assessed between March 2010 and November 2013 in the ICC Clinic at 2 specialist
centers: St George’s Hospital London and Royal Brompton Hospital. These were either new referrals to the ICC service or attending follow-up appointments. This study was approved by the local ethics committee.

**Data collection**

Retrospective review of case notes, cardiac and genetic investigations was carried out. Data were obtained regarding the patients’ 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 elsewhere.\(^1,5,12,13,14\)

**Pediatric cardiac evaluation**

Initial cardiac investigations included a 12-lead ECG, transthoracic 2D 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 as 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 following comprehensive testing of adult relatives. This was discussed carefully with parents and a consensual decision arrived at, particularly as 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. No post-mortem 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 carried out 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’s exact test. Probability values were based on two-sided tests considered significant at $P<0.05$. Analysis was conducted with SPSS version 18.0 software (SPSS Chicago III).

**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 to 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 1st degree relatives while 27 (24%) were 2nd or 3rd degree relatives and 54/112 (48%) were male. The median age at presentation was 8.0 years (range 0.5 to 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 to 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 secondary to 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 attendance, 110/112 (98%) relatives underwent 12-lead ECGs; 106 (95%) had transthoracic 2D echocardiograms and 95 (85%) had 24-hour Holter monitoring. Thirty (27%) also underwent signal-averaged ECG while 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%) following a diagnosis of BrS in an adult relative.

Three out of 110 relatives (2.7%) had a prolonged QT interval on 12-lead ECGs, 1 out of 47 relatives (2.1%) had an abnormal exercise test while 2 out of 13 (15.4%) had positive ajmaline tests. Five out 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 following the screening of an adult relative in 15/18 (83%) families while evaluating pediatric relatives resulted in 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 out of 112 (5.4%) pediatric relatives were affected (Table 2). Of the 6 affected pediatric relatives, 2 were diagnosed with BrS following an ajmaline provocation test; 4 had long QT syndrome (1 following clinical/genetic screening, 3 after clinical screening).

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

There was at least one first degree pediatric relative screened in 36 out 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 out of 18 (78%) families with an ICC diagnosis. Two out 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).
Intervention

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

Follow-up

The median duration of follow-up for the pediatric relatives was 2.1 years (range 0.2 to 8.2 years), attending a total of 215 outpatient appointments. The median duration between outpatient visits was 12 months (range 3 to 36 months). Seventy-five out of 215 (35%) were less than 12 months; 133 (62%) between 12-24 months and 7 (3%) longer than 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 following 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 out of the 61 included families (29.5%) were identified with an ICC. This is comparable to the 18-33% yields in more recently published studies with larger cohorts, including a report on the 15-year experience of familial screening in a Dutch cohort. 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%) vs 3/18 (17%)). Most of the family diagnoses made by screening an adult relative were BrS (12/15) while the most common family diagnosis made following 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 to male adults. Conversely, LQTS is more likely to present in childhood and adolescence. 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 carried out routinely in pediatric relatives.

**Screening of non-first degree relatives**

The utility of screening first degree relatives following a SADS death is well established. 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 following 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. 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 unheralded 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.\textsuperscript{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 2D 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 above 5 years old who are able to use the treadmill while 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,\textsuperscript{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.\textsuperscript{1,14} However in our study, this is limited by the lack of appropriate post mortem 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 UK, 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. 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 following 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 and summarized in Figure 2 & Figure 3. The emphasis is placed upon basic cardiac evaluation of all first degree or symptomatic pediatric relatives. However, thorough investigation of all immediate adult relatives should be carried out...
prior to more invasive provocation testing in children that may not alter immediate management or may otherwise prove unnecessary. While the results from this study and others are consistent in finding an ‘inactive or asleep’ mode of death amongst most SADS cases, it is important not to limit investigations in adults to more ‘likely’ conditions as 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 prior to 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 as initial testing is usually limited by age or choice. This may be more frequent in patients with prior symptoms or borderline features according to the physician’s discretion. It may also be re-initiated if there are new symptoms or a change in family circumstance such as a diagnosis or SCD in another relative including infants. While 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 as they are the most likely relatives to be at risk of genetic disease and its complications in the future.\textsuperscript{1,14}

Limitations

The cohort assessed, whilst 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\textsuperscript{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 due to the use of ajmaline rather than flecainide or procainamide and the utilization of high right ventricular lead placements with V1 & V2 in the 2nd and 3rd intercostal spaces. Our results may also reflect that our group sees families of autopsy confirmed SADS cases across most age groups and only three of the diagnosed family cases were children. This may also be why CPVT was not diagnosed in any pediatric relative as CPVT as a cause of death has been identified mainly in young children and may reflect sporadic rather than inherited disease. The inability to undertake all investigations in all children is an unavoidable limitation but does reflect the real world.

Conclusions
The yield of screening pediatric relatives is significant and higher when focused upon first degree relatives and on inherited cardiac conditions usually expressed in childhood such as LQTS. A higher proportion of diagnoses were provided by evaluation of adults as the primary source of a family diagnosis when compared to children in these same families. This may have been affected by the high prevalence of BrS in our cohort, a disease with greater expression in adults, and our reluctance to perform ajmaline testing in children without careful consideration. We propose a pathway that will provide a framework for the considered and considerate management of these children.

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Conflict of Interest Disclosures: None.

References:


Table 1: Proband characteristics in families with a positive diagnosis

<table>
<thead>
<tr>
<th>Family</th>
<th>Gender</th>
<th>Age (y)</th>
<th>Circumstances of death</th>
<th>1st diagnosis source</th>
<th>Family diagnosis</th>
<th>Gene Mutation</th>
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<td>LQTS</td>
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<td>2</td>
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<td></td>
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<tr>
<td>18</td>
<td>Female</td>
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<td>Adult</td>
<td>LQTS</td>
<td>KCNH2 c.1744C&gt;T p.Arg582Cys</td>
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1st primary, CPVT catecholaminergic polymorphic ventricular tachycardia, LQTS long QT syndrome, BrS Brugada syndrome
Table 2: Characteristics of affected pediatric relatives

<table>
<thead>
<tr>
<th>Relative</th>
<th>Gender</th>
<th>Age of Diagnosis (y)</th>
<th>Diagnostic Investigation</th>
<th>1º diagnosis source</th>
<th>Diagnosis</th>
<th>Management</th>
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<td>Pediatric</td>
<td>BrS</td>
<td>Lifestyle advice</td>
</tr>
<tr>
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<td>11</td>
<td>Ajmaline test</td>
<td>Adult</td>
<td>BrS</td>
<td>Lifestyle advice</td>
</tr>
<tr>
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<td>Male</td>
<td>14</td>
<td>Exercise test</td>
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<td>LQTS</td>
<td>Beta blocker</td>
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<tr>
<td>4</td>
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1º primary, LQTS long QT syndrome, BrS Brugada syndrome

Figure Legends:

Figure 1: Flow diagram of positive diagnoses in 61 SADS families.

SADS sudden arrhythmic death syndrome, LQTS long QT syndrome, CPVT catecholaminergic polymorphic ventricular tachycardia, BrS Brugada syndrome

Figure 2: Proposed pathway for initial evaluation of pediatric family members after a SADS death (partly adapted from1,14).

+ Diagnostic, – Non-diagnostic
* Children to complete as much as age and maturity permits.

† Exercise test > 5 years of age.

‡ Consider further testing of pediatric relatives if no diagnosis made from adult screening.

§ Class I antiarrhythmic challenge following careful discussion with parents and/or prior to discharge from Pediatric ICC 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 following initial evaluation after a SADS death (partly adapted from[1,14]).

Ix Investigation, F/U Follow-up, CMRI Cardiac MRI, BrS Brugada syndrome

* Children to complete as much as age and maturity permits. Investigations to be performed as indicated by symptoms.

† Echocardiogram 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 following careful discussion with parents and/or prior to discharge from Pediatric ICC 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.
SADS Death

Referral to dedicated Inherited Cardiac Conditions (ICC) Clinic
  - First degree relatives
  - Symptomatic relatives

Cardiological Investigation
  - ECG
  - Echocardiogram
  - Exercise test

Molecular autopsy: Arrhythmia gene panel

If no diagnosis from comprehensive screening of adult relatives

Consider further testing
  - Class I antiarrhythmic challenge
  - Cardiac MRI
  - 24h Holter
  - Signal averaged ECG

Genetic diagnosis in proband

Proposed follow-up pathway (Fig 3)

Clinical diagnosis

Genetic testing, management & follow-up in affected relatives, family and/or mutation carriers according to diagnosis
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