Europace (2014) **16**, 1706–1713
doi:10.1093/europace/euu037

REVIEW

Sudden unexplained death in infants and children: the role of undiagnosed inherited cardiac conditions

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Received 4 December 2013; accepted after revision 29 January 2014; online publish-ahead-of-print 28 February 2014

Sudden unexplained death in childhood is a traumatic event for both the immediate family and medical professionals. This is termed sudden unexplained or arrhythmic death syndrome (SUDS/SADS) for children over 1 year of age while sudden unexplained death in infancy or sudden infant death syndrome (SUDI/SIDS) refers to unexplained deaths in the first year of life. There is increasing evidence for the role of undiagnosed inherited cardiac conditions, particularly channelopathies, as the cause of these deaths. This has far-reaching implications for the family regarding the potential risk to other family members and future pregnancies, providing a challenge not only in the counselling but also in the structured assessment and management of immediate relatives. This review will discuss the cardiac risk involved in sudden unexplained deaths of infants and children, the role of molecular autopsy, family cardiological screening, current management strategies, and future directions in this area.

Keywords Sudden infant death syndrome • Sudden arrhythmic death syndrome • Inherited cardiac conditions • Molecular autopsy

Introduction

The sudden death of an infant or a child is a tragic event and has a profound impact on not only the immediate families but also the surrounding community and medical profession. Anecdotal experience suggests that the psychological trauma of losing a child is often worse when the cause of death cannot be ascertained. As defined in the recently published HRS/EHRA/APHRS expert consensus statement, this is termed sudden unexplained death syndrome (SUDS) in children over 1-year old with sudden arrhythmic death syndrome (SADS) referring to the subgroup of cases with negative pathological and toxicological assessment. Unexplained deaths under the age of 1 year fall into the category of sudden unexplained death in infancy (SUDI) of which sudden infant death syndrome (SIDS) is a subset fulfilling stricter circumstantial and forensic criteria.[1] Sudden infant death syndrome and SADS are thus essentially pathological diagnoses of exclusion. Sudden unexplained deaths present a challenge to the medical profession with regards to the counselling and future management of possible risk to other family members. This review will discuss the potential cardiac risk involved in sudden unexplained deaths of infants and children, the role of molecular autopsy, family cardiological screening, current management strategies and future directions in this area.

Epidemiology

One of the first epidemiological studies on sudden death in the young reported a sudden unexpected death rate of 1.3/100 000 person years in children and young adults aged 1–22 years.[2] Subsequent studies have shown a sudden cardiac death (SCD) rate of 1.6–2.8/100 000 person years in the age group 1–40 years.[3–5] Many of these deaths can be explained by cardiovascular abnormalities identified with macro and microscopic examination at autopsy such as cardiomyopathies, congenital heart defects, coronary artery anomalies and myocarditis. However, up to a third of these sudden deaths in the young are unexplained following a detailed autopsy and investigations[6–8], with the figure increasing to around 40–52% in the under −19 age group.[9,10]

In contrast to older children, sudden unexplained deaths in infants under the age of 1 year represent 70–80% of all sudden unexpected

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infant deaths. There were 279 unexplained infant deaths in England & Wales in 2009, representing an incidence of 0.4/1000 live births which is similar to that in USA at 0.5/1000 live births.[11,12] Sudden infant death syndrome is commonly associated with risk factors relating to maternal and infant characteristics and environmental influences. It is more common in low birth weight and preterm infants, male gender, maternal smoking, co-sleeping, or prone sleeping position.[13] Peak incidence occurs in the post-neonatal period before 6 months of age. Ethnic differences have also been observed, with higher rates documented in the African American and Maori populations.[13] Despite the introduction of targeted risk reduction campaigns that have halved the number of unexplained infant deaths over the past two decades, it remains the leading cause of post-neonatal mortality.[13]

Cardiac pathology

Cardiac disease resulting in sudden death in children can be broadly divided into structural diseases and arrhythmia syndromes. Whereas structural heart disease includes cardiomyopathies and congenital abnormalities and can usually be picked up on a detailed post-mortem examination, arrhythmia syndrome associated sudden deaths leave no obvious signs on autopsy.

Expert cardiac pathology plays a vital role in ensuring that these conclusions are reliable and accurate due to the implications of an underlying inherited cardiac condition for the immediate family. Not only could structural heart disease be missed by an incomplete cardiac autopsy but also conversely, minor structural changes of insignificant relevance may be overcalled by non-expert pathologists. This, in turn, leads to incorrect classification of a sudden death resulting in either unnecessary investigation of the immediate family or worse; potentially missing the diagnosis of an inherited cardiac condition and not carrying out the screening of at-risk relatives.[14–16] Three-dimensional imaging or 'virtual autopsy' requires further evaluation as a possible tool to complement post-mortem cardiac investigation. It may have a particular application in the accurate identification of myocardial scar tissue and targeted histological sampling.[17–19]

Several studies involving cardiological and genetic assessment of family members and targeted post-mortem genetic testing, known as 'molecular autopsy', have suggested that a significant number of SADS deaths are associated with inheritable monogenic arrhythmia syndromes.[20–23] In addition, a number of molecular autopsy studies of a range of genes have implicated the same conditions (see *Table 1*).[24–29]

Sudden unexplained death in infancy and SIDS are also diagnoses of exclusion. It is thought to be a more diverse condition involving a complex interplay of factors. The triple risk hypothesis proposed by Filiano and Kinney postulates that a sudden unexplained infant death results from a host with an underlying genetic predisposition, going through a critical development period and experiencing an environmental trigger such as those targeted as part of risk-reduction campaigns.[43] Epidemiological and anecdotal narratives have shown SIDS to be an acute event, pointing to a lethal arrhythmia as a plausible mechanism. This has been substantiated by the identification of channelopathy-associated gene mutations in a significant proportion of SIDS undergoing molecular autopsy (see *Table 1*).[30–42]

Molecular autopsy

Long QT syndrome

Long QT syndrome (LQTS) describes a group of disorders characterized by QT interval prolongation secondary to delayed cardiac repolarization that may be either genetic (otherwise known as 'congenital') or acquired. The substrate of abnormal cardiac repolarization predisposes to development of a characteristic polymorphic ventricular tachycardia, torsades de pointes, and cardiac arrest. Congenital LQTS has a population prevalence of 1 in 2000 and is caused by mutations in genes coding for cardiac ion channels and their

Table 1 Genes with mutations associated with SIDS and SADS

Disease	Gene	Encoded protein	Frequency in SADS (%)	Frequency in SIDS (%)
LQT1	KCNQ1	Kv7.1 potassium channel α-subunit	6.4[29]	1.0[30–32]
LQT2	KCNH2/HERG	Kv11.1 potassium channel α-subunit	3.5[29]	0.5[30]
LQT3/BrS1	SCN5A	Nav1.5 sodium channel α-subunit	3.5[29]	4.8[30–34]
LQT6	KCNE2	MiRP1 potassium channel β-subunit	1.2[29]	0.5[30]
LQT9	CAV3	Caveolin 3		1.5[30,35]
LQT10	SCN4B	Navβ4 sodium channel β-subunit		0.3[36]
LQT12	SNTA1	Alpha-1-syntrophin		1.0[37]
CPVT1	RYR2	Cardiac ryanodine receptor	11.6[29]	1.5[38]
BrS2	GPD1-L	Glycerol-3-phosphate dehydrogenase 1-like sodium channel interacting protein		0.9[39]
BrS7	SCN3B	Navβ3 sodium channel β-subunit		0.7[36]
BrS8	KCNJ8	Kir6.1 potassium channel α-subunit		0.7[40]
	GJA1	Cx43 gap junction protein		0.3[41]
HCM	MYBPC3	Cardiac myosin-binding protein C		0.6[42]
HCM	TNNI3	Cardiac troponin I		0.3[42]

channel-interacting proteins.[44] These were first described in the 1990s and since then, hundreds of mutations have been identified in the 13 genes associated with the condition.[45] Delayed cardiac repolarization results mainly from loss-of-function mutations affecting rectifying potassium currents (I_{Ks}, I_{Kr}, and I_{K1}) or gain-of-function mutations affecting the inward sodium (I_{Na}) and calcium (I_{Ca}) currents. The major LQT subtypes are LQT1 (*KCNQ1*—alpha subunit of $K_v7.1$ associated with I_{Ks}), LQT2 (*KCNH2*—alpha subunit of $K_v11.1$ associated with I_{Kr}) and LQT3 (*SCN5A*—alpha subunit of $Na_v1.5$ associated with I_{Na}).[45] Two patterns of monogenic inheritance have been described: the commoner autosomal dominant form known as Romano–Ward syndrome or the rarer Jervell–Lange–Nielsen syndrome, an autosomal recessive disease associated with sensorineural deafness. There is, however, increasing evidence of oligogenic inheritance.[46]

Chugh *et al.*[24] examined SADS cases for LQT1, −2 and −3 mutations and found 2/12 (15%) to harbor a *KCNH2* mutation. In a larger study in 2007, Tester *et al.*[25] reported on a cohort of 49 young US SADS cases where they found LQT1, −2 or −3 mutations in 20% (10/49 probands). This has been followed by an extended cohort of 173 cases with a lower yield of 14% similar to other studies.[29] For example, Skinner *et al.*[26] studied 33 SADS cases aged 1–40 years from New Zealand with a wider panel of LQTS susceptibility genes and demonstrated a yield of 15% for LQT1, −2, −3, −5, or −6 mutations. More recently, Winkel *et al.*[27] reported a yield of 11% for LQT1-3 mutations in an unselected cohort of Danish SADS cases.

Long QT syndrome was first implicated in SIDS by Schwartz *et al.* in 1998 following a 19-year prospective study assessing 12-lead electrocardiograms (ECGs) of 34 442 newborns. Thirty-four of these infants failed to reach their first birthday, with 24 of the deaths due to SIDS. The average QTc interval of the 24 infants dying secondary to SIDS was 435 ± 45 ms, significantly longer compared with an interval of 400 ± 20 ms for the non-SIDS cohort.[47] The results and subsequent conclusions generated much debate regarding the utility of newborn ECGs in the diagnosis of LQTS but did support a prolonged QT interval as a risk factor for SIDS.

Schwartz *et al.*[48] went on to identify a de novo *SCN5A* mutation in a 7-week old infant who was resuscitated successfully from ventricular fibrillation—a 'near miss SIDS'. This was diagnosed clinically as LQT3 which is associated with an increased risk of cardiac events during sleep, which parallels the clinical manifestation of SIDS. A study focusing on post-mortem molecular autopsy of *SCN5A* subsequently demonstrated potentially pathogenic mutations in 2% of SIDS.[33] *SCN5A* mutations were not demonstrated in the non-white cohort, suggesting not only genetic heterogeneity but also ethnic variability. Eighteen variants were also identified in potassium channel-coding genes associated with LQTS but only two were potentially pathogenic. In the absence of functional and segregation studies, a causal link to SIDS was not definitive.[49]

A large cohort of Norwegian SIDS cases was subsequently investigated for LQTS mutations. Arnestad *et al.* found a 9.5% prevalence of functional LQT gene variants with 19 out of 201 SIDS victims carrying at least one mutation or rare variant. These were found most frequently in *SCN5A* (50% of cases) followed by *KCNQ1* and *KCNH2* (38%).[30]

Ethnic differences were also observed by the same group when LQT9-associated caveolin-3 (*CAV3*) was studied in 134 cases of SIDS. They identified three distinct *CAV3* mutations which were found exclusively in the non-Caucasian cohort.[35] LQT12-associated α1-syntrophin (*SNTA1*) mutations have also been demonstrated in 3% of a cohort of 292 SIDS cases.[37]

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is characterized by syncope or sudden cardiac arrest during exercise or acute emotion in young individuals without underlying structural heart disease. The characteristic arrhythmia is bidirectional or polymorphic ventricular tachycardia which may degenerate into ventricular fibrillation and result in sudden cardiac death. Catecholaminergic polymorphic ventricular tachycardia is often clinically diagnosed by an exercise stress test or an epinephrine challenge. The prevalence of CPVT has been estimated at 1 : 10 000 with symptom onset in childhood. Catecholaminergic polymorphic ventricular tachycardia is caused predominantly by mutations in the ryanodine receptor (*RyR2*) that accounts for around 60% of CPVT and is inherited in an autosomal-dominant manner. Other genes include calsequestrin *(CASQ2)* related autosomal-recessive CPVT, causing only 1–2% of the condition;[50] triadin (*TRDN*), identified in 3 of 97 CPVT patients;[51] and calmodulin (*CALM1*) implicated in 2 families.[52] These are all involved in the sarcoplasmic reticulum pathway regulating intracellular calcium fluxes and cytosolic-free calcium concentration.

Tester *et al.*[28] undertook the first molecular autopsy of *RyR2*, targeted according to the most frequently affected exons, in their original cohort of 49 SADS cases. They identified mutations in 7 probands, representing a yield of 14%. Their larger follow-on study demonstrated a similar prevalence of *RyR2* mutations in 20 of 173 (12%) cases.[29]

Tester *et al.*[38] also performed targeted molecular autopsy on 134 unrelated cases of SIDS, identifying two novel *RyR2* mutations resulting in significant gain of function similar to that seen in CPVT. Although CPVT normally manifests under conditions of exertional or emotional stress, arrhythmic events have been reported during sleep in individuals with *RyR2* mutations.[53] Sympathetic activation during rapid eye movement (REM) sleep was proposed by Schwartz in 1976 to be a mechanism underlying SIDS[54] and as infants spend a greater proportion of their sleep in REM sleep, this may be particularly pertinent in linking CPVT to SUDI.

Brugada syndrome

Brugada syndrome (BrS) is characterized by the presence of a typical Brugada Type 1 ECG with J-point elevation, coved-type ST segment and negative T wave in the right precordial leads, either spontaneously or provoked by a sodium channel blocker.[55] The prevalence has been estimated at 1 in 2000, although it is higher in parts of East and Southeast Asia. Genetic mutations have been identified in around 30% of individuals and cause either a loss of function in the sodium and calcium channels responsible for the inward current or a potassium channel gain of function increasing the outward current. *SCN5A* mutations make up the majority of those associated with the condition.[56] The clinical manifestation is up to 10 times more common in men and typically presents in adulthood.[56] Studies of

SADS families suggest that it is responsible for sudden death mainly in young adults and not commonly in children.[57]

Targeted molecular autopsy has, however, suggested a potential role for BrS in causation of SIDS. Two hundred and ninety-two SIDS cases underwent testing for mutations in sodium channel β-subunits identifying three rare missense mutations that were found to result in a marked loss of function with reduction in I_{Na}.[36] In another study, Van Norstrand *et al.*[39] analysed 228 cases of SIDS, demonstrating three mutations in *GPD1-L* which disrupted the trafficking of the channel and significantly attenuated I_{Na}. In addition to the cohort studies, there have been a number of case reports linking BrS to SIDS. In 2005, Skinner *et al*. reported an *SCN5A* mutation in a 19 day old infant with 'near-miss SIDS'.[58] Another reported the death of both monozygotic twins found to carry a heterozygous nonsense *SCN5A* mutation which had been linked to BrS previously in another study.[59] Hu *et al.*[60] reported a novel rare variant in *SCN1Bb* in a SIDS case which may lead to a BrS phenotype through combined modulation of the $Na_v1.5$ sodium and $K_v4.3$ potassium channel currents.

Five infants presenting with rapid monomorphic ventricular tachycardia or ventricular fibrillation were found to harbour loss-of-function mutations in *SCN5A* or *CACNB2* (an L-type calcium channel β-subunit). Loss-of-function mutations in these genes have also been associated with BrS.[61] Interestingly, their ECGs demonstrated mainly intraventricular conduction delay rather than a Type 1 pattern. There is therefore a possibility that BrS and conduction disease associated mutations may be responsible for a number of infants and children presenting with 'idiopathic' ventricular arrhythmias and may be more significant than previously recognized.

Other channelopathy-associated targets

Apart from the known monogenic arrhythmic conditions, Ackerman *et al*. have also identified several targets, which may contribute to unexplained sudden infant death through a channelopathy-mediated lethal arrhythmia. Two mutations were detected in 292 SIDS cases in the *GJA1* gene encoding connexin43, an important gap junction protein. Impaired gap junction function was thought to underlie the risk of arrhythmias.[41] Two loss-of-function mutations in the *KCNJ8* gene encoding the Kir6.1 potassium channel were also identified in the same cohort and may predispose to sudden infant death through a maladaptive cardiac response to systemic metabolic stress, further supporting the triple risk hypothesis.[40]

A significant number of variants identified in SIDS may not be rare or cause lethal arrhythmias independently but may also have a role in increasing the risk. Their effects could be additive or require a certain trigger to result in an arrhythmia. Nof *et al.*[62] suggest that a common SNP can act synergistically to exacerbate mildly defective I_{Kr} channels and produce a much greater loss of function resulting in the LQT2 phenotype. The excess prevalence of the common gain-of-function variant, *SCN5A*-S110Y3, in SIDS and SADS cases of African-American descent also suggests an ethnic specific genetic risk for sudden death.[34,63]

The observation that SIDS victims often have accompanying risk factors may also be important in the pathophysiology of the condition. Fever is known to alter ion channel dynamics and increase the tendency for ventricular arrhythmias. Overheating, minor illnesses, or recent vaccinations may thus provide the trigger in these cases. The results from a study by Wang *et al*. also support the theory of a latent dysfunctional phenotype in SIDS. Through functional analyses of variants previously reported in SIDS cohorts, they demonstrated that a significant proportion exhibited abnormal function only under conditions of acidosis or with co-expression of a common splice variant.[64]

Cardiomyopathy

Cardiomyopathies such as hypertrophic cardiomyopathy (HCM) or arrhythmogenic right ventricular cardiomyopathy (ARVC) causing sudden death should usually be picked up on post-mortem examination and as such preclude the deaths being described as SIDS or SADS. A recent study analysing 286 SIDS cases for the most common genes implicated in HCM in adults identified rare genetic variants in 10 cases, 3 of which are predicted to be functionally significant using in silico prediction software.[42] This study, however, suffered from a lack of conclusive linkage data to prove causality. In addition, it is doubtful that single sarcomeric mutations alone will result in a sudden infant death with such an early-onset phenotype more likely to be associated with double or compound mutations and structural abnormality at autopsy.[65] Sudden arrhythmic death syndrome families have been found to have evidence of ARVC and occasionally HCM despite a normal autopsy.[21] It has therefore been suggested that the presence of a genetic mutation independent of any clear phenotypic manifestation of a cardiomyopathy could potentially impart an arrhythmogenic risk in an early 'concealed' phase of the disease.

Family screening and molecular autopsy: the role in the clinic

Several studies have demonstrated the clinical utility of cardiological screening in first-degree family members,[66–68] the first being published in 2003 assessing 147 relatives in 32 cases of SADS.[20] Through detailed history and cardiovascular investigations, an inherited cardiac condition was identified in seven families (22%) with six of seven probands under the age of 20 years. A follow-up study in 2008 using more comprehensive investigations including cardiac MRI imaging and ajmaline provocation demonstrated the presence of inherited cardiac disease in 30 of 57 families (53%).[21] The yield is also high in two Dutch studies carrying out comprehensive cardiological testing.[22,23] The same group from Amsterdam has recently reported on a 15-year experience of cardiogenetic screening in families with sudden unexplained death, showing that the yield has apparently decreased over time. It is, however, worth noting that their study population was a mixture of SUDS and SADS families, and that results from different studies are not directly comparable due to differences in definitions, inclusion criteria and family workup. The decrease in yield may also be the result of assessing families where familial disease is less likely.[69] Another study in the Netherlands focusing on sudden cardiac death in childhood also demonstrated a 46% yield (8 of 17 families) of familial screening in SADS.[70] Combined cardiogenetic evaluation of immediate family members has shown that channelopathies underlie 40% of cases of SADS in the 1–18 years age group, while a higher 71% burden is seen in the younger age group of 1–10 years.[23,70] Similarly, and as described above,

Tester *et al.*[29] have demonstrated a yield of 26% for molecular autopsy of LQTS and CPVT genes. In SIDS, however, molecular autopsy data points to a lower 10–15% frequency of underlying disease.

Unfortunately, many of these studies are restricted to anonymized samples with limited follow-up functional data. In addition, the frequency of background rare genetic variation often results in great uncertainty over the role for variants of unknown significance. There are also no data on co-segregation of phenotype with genotype in families or whether disease is likely to be sporadic or not. The applicability of a molecular autopsy study results in clinical practice and the delineation of the potential cardiac risk to immediate family members or in subsequent pregnancies must therefore be viewed with a degree of caution. Nonetheless, early recognition of an inherited cardiac condition is crucial in preventing further sudden cardiac deaths in the family through lifestyle modification, medical therapy, and/or device therapy. The identification of a cause of death of a loved one may also bring psychological closure for families.

The role of molecular autopsy is also highlighted in the HRS/EHRA Expert Consensus Statement on genetic testing, where it is recommended that tissue or blood samples are retained at post-mortem for future genetic testing, and that channelopathy-focused genetic testing should be considered in SUDS and SADS, especially if circumstantial evidence points towards a diagnosis of LQTS or CPVT.[71] These recommendations have been backed up by the HRS/EHRA/APHRS Expert Consensus Statement on diagnosis and management of arrhythmia syndromes.[1] It is therefore likely that a combined approach of molecular autopsy and familial cardiological evaluation will provide the best chance of identifying an inherited cardiac condition in the family of an SUDS or SADS victim. The first study to attempt to address this was limited by the use of formalin-fixed paraffin-embedded blocks for molecular autopsy and incomplete genotyping as a consequence.[21] Retention of appropriate *frozen* tissue at autopsy is therefore vital. The diagnostic value of cardiological investigation of first-degree relatives in SUDI/SIDS remains to be

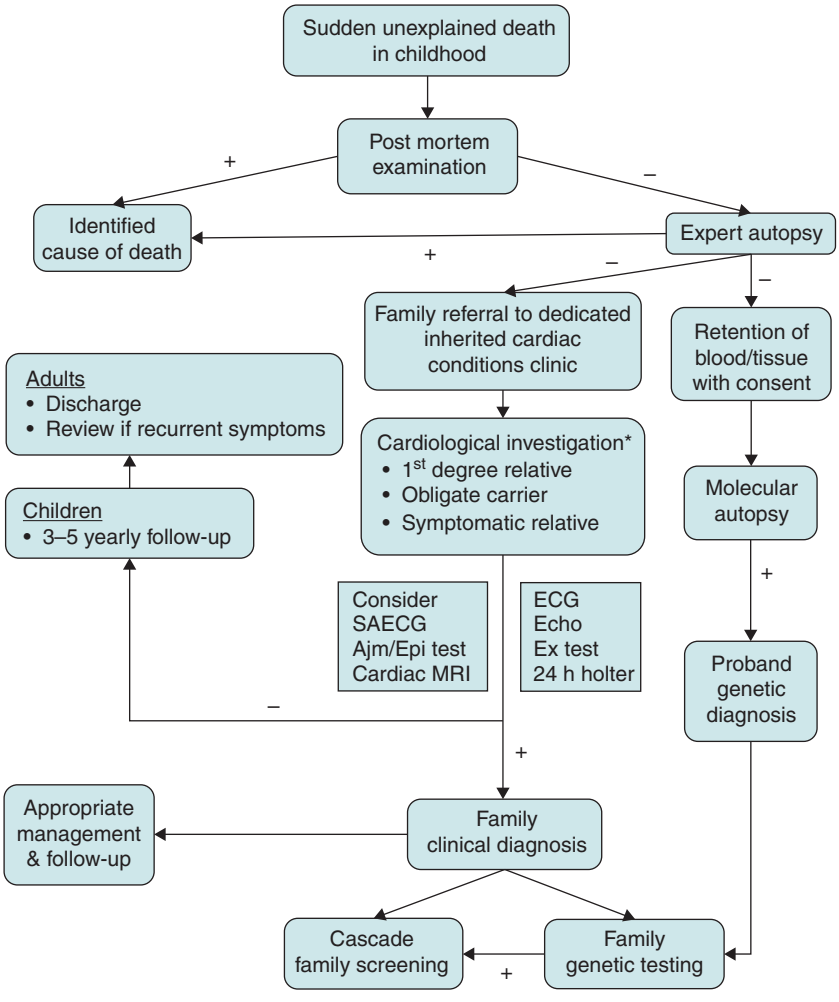

Figure 1 Proposed pathway for familial cardiogenetic evaluation and molecular autopsy after a sudden unexplained death in childhood. +, positive; −, negative; Ajm, ajmaline; Epi epinephrine; SAECG, signal averaged ECG; Ex test, exercise test. *Children to complete as much as age and maturity permits.

proven. Guidelines recommend that molecular autopsy can be useful to uncover potential-inherited cardiac conditions and if positive it is recommended that family members are investigated. The threshold for familial investigation is, however, higher than in SUDS/SADS and only considered useful in family members with other suspicious family history for SIDS, SADS, or cardiac genetic disease in which case clinical testing is limited to resting and exercise ECG.[1]

Current management

Management of a family following a sudden unexplained death requires attention to both their physical and psychological needs. We believe that this should be undertaken in the integrated setting of a dedicated outpatient clinic with multidisciplinary input from specialist adult and paediatric cardiologists, a geneticist, bereavement counselling service, and the availability of appropriate cardiological and genetic investigations. In our practice, cardiological assessment of adults and children following an SUDS or SADS death takes the form of a comprehensive personal and family history, followed by an initial panel of investigations including a 12-lead ECG with high right ventricular leads, echocardiogram, exercise stress test and 24 h Holter monitor. For adults an ajmaline provocation test is performed if an ECG is normal or suggests BrS. In children, this is only undertaken after careful counselling and in the context of other family findings. An epinephrine test is only carried out if the exercise stress test has not been helpful and a diagnosis of LQTS and/or CPVT is being contemplated based on the index case's mode of death and other findings in the family. A signal-averaged ECG and cardiac MRI is indicated for any suspected cardiac structural abnormalities following the initial tests. Genetic counselling is of paramount importance and discusses issues regarding molecular autopsy (if available) and further genetic testing of family members should the molecular autopsy or clinical evaluation provide evidence of an inherited cardiac condition. The diagnosis of an inherited cardiac condition will have implications for lifestyle, occupation and insurance, especially for the pediatric population. The patient should be made aware that genetic testing does not always give an answer and occasionally may provide results of unknown significance. Both cardiological and genetic evaluations should be structured and a management pathway for cases of childhood SUDS or SADS is proposed in *Figure 1*. As stated above, a more limited approach is taken when SUDI/SIDS families are referred given the lack of evidence.

Future directions

Recent advances in cardiovascular genetics have provided clinicians with new challenges and dilemmas. With increasing ability to test for cardiac conditions and the wealth of information that comes with current genetic testing, we need to be able to translate that into benefit for bereaved families. In SADS cases, the data support the role for molecular autopsy and cardiogenetic evaluation of families. However, genetic testing represents added cost to individuals and health care institutions and it is important that it is performed in selected groups to maximize the yield and cost-effectiveness. In an SADS family, this should initially be targeted at individuals with a clinical phenotype; either molecular autopsy of the proband or genetic testing of family members with a conclusive diagnosis of an underlying inherited cardiac condition.[72] Molecular autopsy should be regarded as a cost-saving approach that is complementary to familial cardiological assessment.[73,74]

There is growing evidence for the role of inherited cardiac conditions, particularly channelopathies, in SUDI and SIDS. However, the studies to date have been carried out on small cohorts and targeting specific cardiac conditions. The full extent of cardiac risk in SIDS is yet to be elucidated although this will likely become clearer with advances in genetic techniques permitting the condition to be studied more extensively. The risk posed to immediate family members is also unclear. Prospective family studies will be necessary not only for confirmation of molecular autopsy findings and identifying risk in the family, but will also help to determine the true hereditary nature of SIDS.

Conflict of interest: none declared.

Funding

This work was supported by Cardiac Risk in the Young, The Trustees of St George's Hospital Charity, Biotronik and Wellcome Trust Institutional Strategic Support Fund.

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EP CASE EXPRESS

doi:10.1093/europace/euu067
Online publish-ahead-of-print 2 April 2014

Wolff–Parkinson–White syndrome unmasked by atrial pacing in a patient with cardiac sarcoidosis

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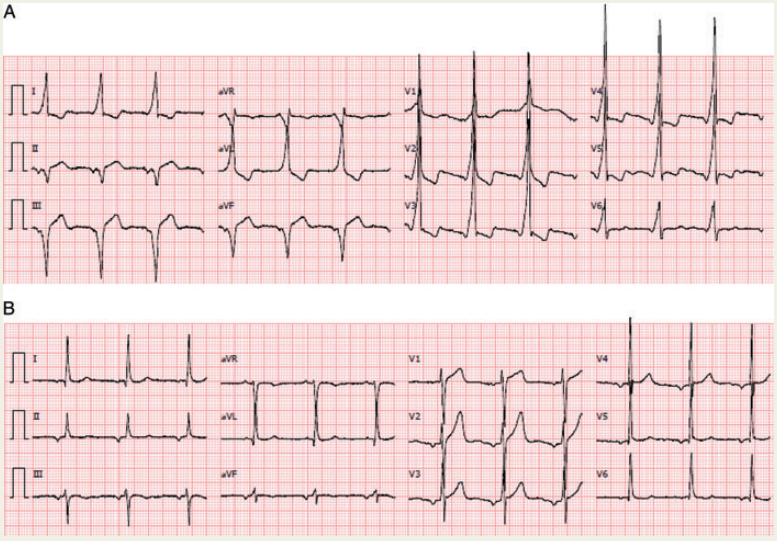
Male patient, 55 years old, diagnosed with cardiac sarcoidosis, underwent dual-chamber pacemaker implantation for sick sinus syndrome.

Following implantation, electrocardiogram showed atrial pacing, short PR interval, and ventricular pre-excitation (*Figure 1A*). During pacemaker follow-up, several episodes of sustained tachyarrhythmia were documented. Considering the potentially high risk of sustained ventricular arrhythmias and sudden death in a context of cardiac sarcoidosis, the patient was referred to electrophysiological study. Ventricular arrhythmias were not inducible; however, a short HV interval was documented, associated with an overt left postero-septal accessory pathway, which was successfully ablated (*Figure B*).



Cardiac sarcoidosis is a rare and potentially fatal condition due to ventricular arrhythmias. Supraventricular arrhythmias are less often reported and association with Wolff–Parkinson–White is rare. Pre-excitation had never been recorded in our patient, yet the close proximity of the atrial led to the accessory pathway and the increased atrial rate by pacing unmasked an otherwise concealed accessory pathway.

The full-length version of this report can be viewed at: http://www.escardio.org/communities/EHRA/publications/ep-case-reports/Documents/Wolff-Parkinson-White-syndrome.pdf.