



The Cardiac Society of Australia and New Zealand

Cardiac Genetic Investigation of Young Sudden Unexplained Death and Resuscitated Out of Hospital Cardiac Arrest

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Introduction

This document outlines general recommendations for the investigations of families of young sudden unexplained death (SUD) victims and survivors of out-of-hospital cardiac arrest (OHCA) with negative autopsies or normal hearts respectively.

SUD occurs in a significant number of young sudden deaths. Two independent studies of coroner's autopsies in New South Wales found that in approximately 30% of all young SUD cases, the autopsies were negative and the cause of death was unascertained.^{1,2} These deaths were most likely due to genetic cardiac arrhythmias. In the last 20 years a number of cardiac channelopathy disorders have been described, the most common being the familial long QT syndrome. Most of these are monogenic disorders and have an autosomal dominant mode of transmission resulting in familial cardiac arrhythmias. It is therefore important to screen the families of SUD victims with the aim of detecting these conditions at an early stage which may allow initiation of early preventative measures.

The other important group consists of survivors of OHCA where there is no obvious structural abnormality and normal coronary arteries. This group comprises about 5% of patients who have ICD implants following resuscitated cardiac arrest.

Possible Causes of SUD

SUD can be caused by a number of primary arrhythmogenic disorders. Table 1 lists possible disorders likely to cause SUD with normal hearts at autopsy. Apart from WPW syndrome, the commonest causes relate to abnormalities in ion channels, leading to the collective term "ion channelopathies." It is important to note however, that a negative autopsy does not exclude some cardiomyopathies, particularly ARVC (arrhythmogenic right ventricular cardiomyopathy) and HCM (hypertrophic cardiomyopathy), where anatomic and histological features can be subtle. These conditions may be both under- and over-diagnosed in young SUDs.

Over 20 ion channelopathy disorders have been described to date, as a result of loss or gain in function in ion channels affecting transport of Na, K⁺, or Ca⁺⁺ across the cell membrane causing disturbances in the orderly process of cardiac depolarization and repolarisation. Hundreds of disease-causing or contributing mutations have been described and there is considerable genetic and clinical heterogeneity common to all these disorders.³

Cardiac Genetic Services

World-wide experience suggests these patients and their families are best investigated in a multidisciplinary clinic as reported by Ingles and Semsarian (Figure 1).^{4,6} Such multidisciplinary clinics exist in major centres in Australia and New Zealand. A key part of the multidisciplinary team is the forensic pathologist involved in conducting the autopsy. Obtaining a blood sample at autopsy for future genetic analysis is essential. Recommendations regarding preservation of DNA and tissues for pathological examination were drawn up by TRAGADY (now known as Heart@Heart) and have been endorsed by the Royal Australasian College of Pathologists.^{7,8}

The clinical approach to families with SUD starts with a detailed review of the autopsy report. A collaborative and communicative approach between the cardiac genetic service and pathologist is essential. All available information regarding the mode and circumstances of death, and pre-morbid symptoms, if any, should be obtained. Collection of possible information regarding any medical evaluations, and cardiac investigations such as ECGs, should be obtained and scrutinized (Figure 2).

Previously published reports of family screening of SUD are summarised in Table 2. The first two reports describe screening of SUD victim families and the third report by Krahn et al focuses specifically on OHCA survivors. The report by van der Werf et al addresses both SUD families and OHCA survivors. Importantly, in the study by Tan et al, an inherited and underlying cause of death was identified in 17/43 (40%) of families. Resting ECG, exercise ECG and flecainide challenge revealed diagnosis in 12 out of 17 families.⁹ In the study reported by Behr et al over half of SUDs families had inherited cardiac disease and approximately 25% of the first-degree families had suffered syncope and 25% had history of premature sudden deaths. 61% were young males and the majority (63%) died at rest or during sleep and 30% during exertion. 58% had antecedent symptoms, 23% had palpitations and 19% had syncope.¹⁰ Thus the overall diagnostic yield in families of SUD is about 40%. The yield is higher if there is more than one SUD in the family and if a large number of family members (more than 6) are available for cardiac screening. Where a cause is found, LQTS is the commonest followed by CPVT, particularly in the paediatric age group. Exercise testing and pharmacological testing with flecainide (or ajmaline) were the most rewarding tests. In OHCA survivors the diagnostic yield is between 55-60%.

Family Screening of SUD

Where possible, families should be encouraged to attend a combined cardiac genetic service where they can be counselled about the process of investigation, and cardiac and genetic testing (Figure 1).^{4,6} Investigation of first-degree relatives of victims of SUD should be supervised by this clinic. Most families will be at the height of their grief, and there may be anger, fear and despair. A calm, supportive, understanding and patient approach is required. A detailed family pedigree spanning a minimum of three generations is drawn up at the initial meeting with family members. An enquiry regarding any family history of young sudden death, syncope, seizures, miscarriages, etc. should be made. While a family history of premature SUD in the family is strongly suggestive of a familial disorder its absence does not exclude it.

First and second-degree relatives should have baseline cardiac investigations which include a 12-lead ECG, exercise test and transthoracic echocardiography. Further investigations are arranged at the discretion of the cardiologist and include recording of an ECG in RV Leads V₁ to V₃ in the third intercostal space, 24-hour ambulatory monitoring, signal averaged ECG, flecainide or epinephrine challenge and serum lipid analysis. Baseline investigations are frequently helpful in diagnosing many of the conditions responsible for SUD. *12-lead ECG* is useful in the diagnosis of LQTS, Brugada syndrome, SQTS, Early Repolarization syndrome, and ARVC. *24-hour ambulatory monitoring* is helpful in diagnosis of conduction and rhythm abnormalities and quantitates ventricular ectopic load. A load of ≥ 500 beats in 24 hours is one of the diagnostic features of ARVC.¹¹ SQTS and changes of Brugada syndrome can be missed in the presence of a fast heart rate and may become manifest during nocturnal bradycardia during 24-hour ambulatory monitoring. It may also help in the diagnosis of LQTS and short coupled Torsades. *Signal averaged ECG (SAECG)* may be helpful in the diagnosis of ARVC.

Exercise Testing: An accelerated Bruce Protocol reaching maximum heart rate within 4-5 minutes is generally recommended as it probably provides greater adrenergic stimulus. Subjects with LQTS may have a normal QT at rest but show prolonged QT on assuming upright posture and during or after exercise. Exercise testing is particularly helpful in LQT1. In LQT2 exercise testing frequently shows augmentation of T₂ (the second component of bifid T-wave) and may show late prolongation of QTc. There is not much information about exercise testing in LQT3 but theoretically exercise should shorten the QT interval. Exercise testing is also very helpful in the diagnosis of CPVT. Frequent ventricular extrasystoles in a young person should not be considered to be benign.¹²

MRI: MRI with gadolinium enhancement is particularly helpful in supporting the diagnosis of ARVC, which can be difficult and expertise in the area essential. MRI may also be helpful in the diagnosis of subtle forms of HCM, myocardial noncompaction and cardiomyopathy where echocardiography may be negative or nondiagnostic. MRI is expensive and in family screening of SUD, it is considered when other tests have failed to provide an answer.

Genetic Testing in SUDs and OHCA

Genetic testing is rapidly becoming more available and cheaper. Tester and Ackerman (2007) reported 20% LQTS and 14% CPVT1 gene mutations in 17 out of 49 (35%) autopsy negative young SUD victims.¹³ With increasing knowledge and advancement in technology this yield is likely to increase. Genetic testing for LQTS and CPVT should be considered in all families where SUD has occurred, in conjunction with clinical evaluation and the specific circumstances of each family. The most recent study from New Zealand by Skinner et al is the first population based investigation of SUD victims. They combined autopsy molecular genetics for long QT syndrome (currently funded by the coronial service) with family cardiac evaluation. Thirty percent had inherited heart disease, half diagnosed from the DNA and half from family screening.¹⁴ While DNA is being preserved in SUD at autopsy, this diagnostic approach is not currently funded in Australia. The current practice thus is to start with clinical family screening in conjunction with the option of guided genetic testing.

Why no diagnosis in over 50% SUD: Unless examination of first-degree relatives or genetic analysis provides a clue, diagnosis remains elusive in over 50% of SUD victims. It is possible that structural myocardial conditions such as ARVC or HCM may cause SUD even when these conditions cause only subtle changes which are not detectable at autopsy. Also, abnormalities such as myocarditis may be missed or insufficient tissue may be available for proper examination. The quality of post mortem DNA may also be suboptimal. Genetic analysis DNA extracted from archived blood on the neonatal screening card (Guthrie card) DNA has been shown to be helpful in this situation.¹⁵ It is anticipated that newer genetic approaches, which screen many cardiac genes or indeed entire genomes, will increase the diagnostic yield in SUD families.¹⁶

When all possibilities are excluded, some or most of these deaths are presumably due to “idiopathic ventricular fibrillation (IVF)”. A family history is present in 20% of probands of IVF suggesting a genetic basis in at least a subset. Alders et al have identified an abnormality in chromosome 7q36 in some of these families.¹⁷ Many patients with so called IVF have ECG changes of Early Repolarisation (ER) syndrome.¹⁸ Frequently the deaths are nocturnal and ventricular ectopics which initiate VF have short coupling interval, both features common to Brugada Syndrome. Antezelvitich and Yan have used a collective term, “J wave syndromes”.¹⁹

Follow up visits: Where a diagnosis is made the frequency of follow up visits, treatment of the underlying condition, etc. is at the discretion of the treating cardiologist. If no diagnosis is arrived at initially, a reasonable approach is to offer contact with the family 2-5years later as HCM and ARVC have age-dependent expression, and molecular testing is continuing to develop. Importantly, consent is obtained to store the autopsy DNA for possible future reference and for research initiatives in this area, if the initial genetic analysis is negative.

Investigations of OHCA Survivors

The approach to survivors of OHCA with normal heart and normal coronary arteries is somewhat different as the proband is available for clinical investigation. Amongst 69 OHCA subjects reported by van der Werf et al (which was not confined to those with normal hearts and coronary arteries) the cause of event was determined in 61% and 74% of these were due to inherited conditions.²⁰ Krahn et al confined their study to those with normal hearts and coronary arteries the diagnostic yield was 56% and 26/35 (74%) diagnosed patients had genetic conditions.²¹

In survivors of OHCA also, family screening along the lines of SUD victims, needs to be carried out if a genetic cause is diagnosed or suspected. It is important to note that left ventricular stunning is quite common after cardiac arrest and LV dysfunction may take two to three weeks to resolve completely. An erroneous diagnosis of cardiomyopathy is not uncommon in this situation. QT prolongation immediately after cardiac arrest and after therapeutic hypothermia or Brugada ECG pattern immediately following cardioversion for VF, can also be misleading. Noncritical coronary artery disease may cause ventricular fibrillation due to coronary artery spasm leading to OHCA as shown in CASPER study.²¹

Figure 3 shows suggested investigations for OHCA survivors. Targeted genetic analysis is performed if an inherited cardiac condition is diagnosed in the proband. Our current practice is to try to get an MRI before ICD implantation in all cases where possible, particularly where baseline investigations have not made the diagnosis.

Conclusions

Comprehensive cardiac and genetic testing of families of SUD is helpful in the detection of inherited cardiac genetic conditions. It frequently provides a clue to the cause of death in SUD victims and allows early diagnosis and opportunities to prevent SUD in other family members. OHCA victims and their families also require similar assessment, although the role of genetic testing in this group should be reserved to patients where a clinical diagnosis is established. A team approach with multidisciplinary specialised clinics and increased access to genetic analysis is very helpful in achieving these goals.

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TABLE 1: Causes of SUD with normal hearts at autopsy

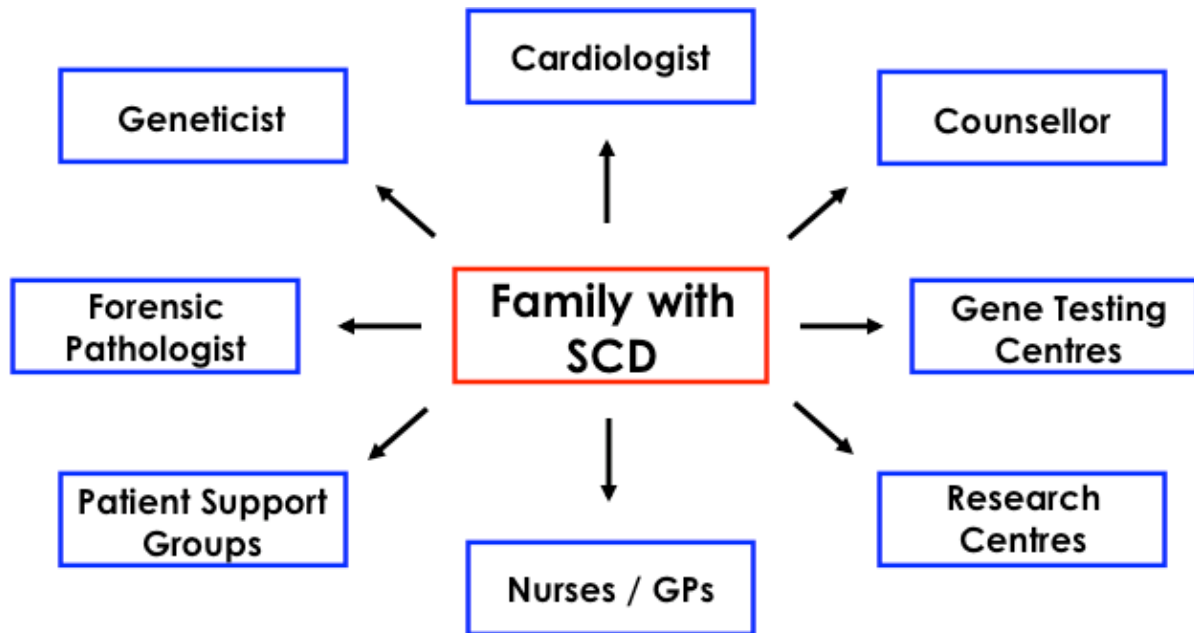
- Long QT Syndrome
- Catecholaminergic Polymorphic VT (CPVT)
- Brugada Syndrome
- Short QT Syndrome
- Early Repolarisation Syndrome
- Idiopathic VF
- WPW Syndrome
- SUD in Epilepsy

NB: Subtle forms of cardiomyopathy, e.g. HCM, ARVC, LVNC, may not cause anatomical changes and the heart may appear normal at autopsy.

TABLE 2: Published reports of family screening of SUD and OHCA

- Tan et al, 2005: 43 families, comprehensive pick up rate to 40%.
- Behr et al, 2008: 57 families with at least one SUD. Pick up rate 54%.
- Krahn et al, 2009: 63 cardiac arrest survivors, systematic clinical testing, including drug provocation and advanced imaging. Diagnostic yield 56%.
- Van der Werf et al, 2010: 140 SUD families and 69 ACA patients. Diagnostic yield: 33% SUD families and 61% of ACA victims.

FIGURE 1: Multidisciplinary approach to care of families



Modified from Ingles & Semsarian. Int Med J, 2007

FIGURE 2: Algorithm for investigation of SUD families

Detailed study of the autopsy report including circumstances of death, any premonitory symptoms or medical attendances. Ensure availability of victim’s DNA.

