

CLINICAL PERSPECTIVES

Sudden cardiac death in the young: a clinical genetic approach

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Key words

sudden cardiac death, screening, gene, family, multidisciplinary.

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doi:10.1111/j.1445-5994.2006.01241.x

Abstract

The sudden death of a young person is a devastating event for both the family and community. Over the last decade, significant advances have been made in understanding both the clinical and genetic basis of sudden cardiac death in the young. Many of the causes of sudden death in the young are due to genetic heart disorders, which can lead to both structural (e.g. hypertrophic cardiomyopathy) and arrhythmogenic (e.g. familial long QT syndrome) abnormalities. Most commonly, sudden cardiac death in the young can be the first presentation of an underlying heart problem, leaving the family at a loss as to why an otherwise healthy young person has died. Not only is this a tragic event for those involved, but it also presents a medical challenge to the clinician involved in the management of the surviving family members. Evaluation of families requires a multidisciplinary approach, which should include cardiologists, a clinical geneticist, a genetic counsellor and the forensic pathologist directly involved in the sudden death case. This multifaceted cardiac genetic service is crucial in the evaluation and management of the clinical, genetic, psychological and social complexities observed in families in which there has been a young sudden cardiac death.

Causes of sudden cardiac death in the young

Sudden death is a tragic complication of a variety of medical disorders. The most common causes of sudden death correlate to the underlying cardiovascular disease. Recent studies indicate that in the USA alone, sudden cardiac death occurs in over 450 000 people each year.¹ In Australia and New Zealand, up to 50 000 people die suddenly each year from various causes.² Although coronary artery disease accounts for a majority of these deaths overall, many other aetiologies have been shown to contribute to this problem when it occurs specifically in the young (those aged ≤ 35 years). Genetic heart disorders are an important cause of sudden cardiac death in the young, as a consequence of both structural abnormalities and primary arrhythmogenic predisposition.³

Until recently, studies investigating the causes of sudden cardiac death in the young emanated predominantly from North America and Europe. In 2004, we described for the first time the causes of sudden cardiac death in a young Australian population.⁴ The study by Doolan *et al.*, reported the causes of sudden cardiac death from post-mortems carried out in over 10 000 subjects from 1994 to 2002. In those aged ≤ 35 years, the most common cause of sudden cardiac death in the young was a primary arrhythmogenic event (31%; Fig. 1). These young deaths were found to have a negative post-mortem, that is, no identifiable cause of death found at post-mortem, with the heart appearing structurally and histologically normal. Such deaths are most likely to be caused by primary arrhythmogenic disorders, such as familial long QT syndrome (LQTS). Other important causes of sudden cardiac death that were identified in this young Australian cohort included hypertrophic cardiomyopathy (HCM)/unexplained left ventricular hypertrophy (15%), myocarditis (12%), congenital heart disease (7%) and other less common causes (11%; including aortic dissection, valvular heart disease and arrhythmogenic right ventricular dysplasia (ARVD); Fig. 1).⁴

Funding: C. S. is the recipient of a co-funded National Health and Medical Research Council and National Heart Foundation of Australia Practitioner Fellowship.

Potential conflicts of interest: None

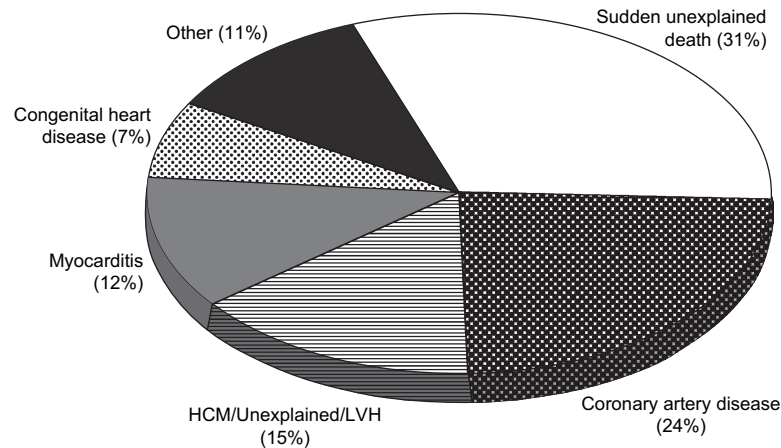


Figure 1 Causes of sudden cardiac death in young Australians (Modified from Doolan *et al.*⁴). HCM, hypertrophic cardiomyopathy; LVH, left ventricular hypertrophy.

The majority of these cardiac disorders leading to sudden death are caused by genetic abnormalities. Currently, over 40 genetic heart diseases have been described,⁵ with many of these disorders associated with an increased risk of sudden cardiac death.¹ Genetic heart diseases can be broadly categorized into those in which structural abnormalities are prominent, such as HCM and ARVD, or diseases in which there is a primary arrhythmogenic abnormality, which include LQTS, Brugada syndrome and catecholaminergic polymorphic ventricular tachycardia. The genetic basis of these is summarized in Table 1. Identification of the genetic basis of sudden cardiac death is the cornerstone of management for families in which sudden death has occurred.

A clinical approach to families with sudden cardiac death

One of the most difficult and challenging problems for a clinician is sitting down face-to-face with a parent who has just experienced the death of his or her son or daughter. Sudden cardiac death in the young is always unexpected, is frequently unexplained and is a tragedy that is never fully overcome in a family. It is therefore not surprising that managing a family in which a sudden cardiac death has occurred involves many aspects of clinical medicine. In general terms, the two areas of clinical management involve trying to establish the exact cause of death in the young deceased and ongoing management of the surviving family members.

The victim

In beginning to clinically evaluate the surviving relatives of a young sudden death victim, it is important to pursue all available avenues to determine the exact cause of death.

Such an investigation should include obtaining any premonitory medical information such as prior symptoms, for example, syncopal episodes, previous electrocardiograms (ECG) or other relevant studies. In addition, it is important to identify the circumstances of sudden death, for example, during activity, at rest, presence of chest pain, by talking to any witnesses as well as obtaining information from ambulance and police reports. Finally, investigation of the information from the forensic (post-mortem) examination is crucial and should include evaluation of the post-mortem report, with a particular focus on the macroscopic and histological evaluation of the heart, as well as in some cases, a direct discussion with the attending forensic pathologist. The availability of post-mortem tissue for subsequent DNA analysis should also be considered, as genetic testing strategies in autopsy negative cases are likely to form an important aspect of identifying the cause of sudden death. The concept of a 'molecular autopsy' is currently a major focus of research studies in this area.⁶

Tragically, when a young person dies suddenly from a cardiac cause, frequently the event is either the first presentation of the disease or the person had symptoms but never presented to a medical practitioner. Therefore in many cases, no premonitory clinical information is available. Furthermore, the deaths are frequently unwitnessed and the ambulance and police reports shed minimal light on identifying a cause of death. Finally, as reported by Doolan *et al.*, in approximately one-third of young sudden deaths, the post-mortem is negative.⁴ Taken together, this indicates that establishing the cause of death in a young person may often require extensive investigation and in many cases, no cause will be identified. However, as this will have major implications for clinical screening and management of the surviving relatives, every effort should be made to investigate the cause of death.

Table 1 Genetic causes of sudden cardiac death

Disease	Gene name	Encoded protein	Disease (%)
LQT1	<i>KCNQ1</i>	I _{Ks} potassium channel α -subunit	35–40
LQT2	<i>HERG</i>	I _{Kr} potassium channel α -subunit	30–35
LQT3	<i>SCN5A</i>	I _{Na} sodium channel α -subunit	5–10
LQT4	<i>ANKB</i>	Ankyrin B	<1
LQT5	<i>KCNE1/minK</i>	I _{Ks} potassium channel β -subunit	<1
LQT6	<i>KCNE2/MiRP1</i>	I _{Kr} potassium channel β -subunit	<1
LQT7 (Andersen–Tawil syndrome)	<i>KCNJ2</i>	Inwardly rectifying potassium channel	50
LQT8 (Timothy syndrome)	<i>CACNA1C</i>	Voltage-dependent L-type calcium channel	Unknown
Short QT syndrome-1	<i>HERG</i>	I _{Kr} potassium channel α -subunit	Unknown
Short QT syndrome-2	<i>KCNQ1</i>	I _{Ks} potassium channel α -subunit	Unknown
Brugada syndrome	<i>SCN5A</i>	I _{Na} sodium channel α -subunit	15–30
CPVT1	<i>RyR2</i>	Cardiac ryanodine receptor	65
CPVT2	<i>CASQ2</i>	Calsequestrin	5
HCM	<i>βMHC</i>	β -myosin heavy chain	30–35
	<i>MyBP-C</i>	Myosin binding protein C	20–30
	<i>cTnT</i>	Cardiac troponin T	10–15
	<i>TPM</i>	Tropomyosin	5–15
	<i>cTnI</i>	Cardiac troponin I	<5
	<i>CSRP3</i>	Cardiac muscle LIM protein	<5
	<i>TCAP</i>	Telethonin	<2
	<i>MYL2</i>	Regulatory light chain	<1
	<i>MYL3</i>	Essential light chain	<1
	<i>ACTC</i>	Actin	<0.5
	<i>TTN</i>	Titin	<0.5
	<i>MYH6</i>	α -myosin heavy chain	<0.5
	<i>TNNC1</i>	Cardiac troponin C	<0.5
ARVD	<i>PKP2</i>	Plakophilin-2	14–43
	<i>DSP</i>	Desmoplakin	15
	<i>DSG2</i>	Desmoglein-2	10
	<i>TGFβ-3</i>	Transforming growth factor- β 3	2.5
	<i>RyR2</i>	Cardiac ryanodine receptor	Unknown
Naxos disease	<i>JUP</i>	Junction plakoglobin	Unknown

ARVD, arrhythmogenic right ventricular dysplasia; CPVT, catecholaminergic polymorphic ventricular tachycardia; HCM, hypertrophic cardiomyopathy; LQT, long QT.

The surviving family

As many causes of sudden cardiac death are familial, investigation of the surviving relatives is crucial in identifying further affected individuals, who may themselves be at increased risk of sudden death. The majority of genetic heart diseases show autosomal dominant inheritance and marked clinical heterogeneity. This means the probability of other family members being affected is high, but the variability in presenting phenotypes can often make a diagnosis very difficult. Clinical screening of family members should be tailored based on the suspected underlying disease.⁷ The cardiac investigation of surviving family members should include a thorough clinical history, physical examination, 12-lead resting ECG, M-mode and 2-D echocardiography, and in most instances, an exercise ECG stress test. Additional tests may be required for specific cardiac genetic diseases. For example, if Brugada syndrome is suspected, flecainide challenge should be

carried out, whereas if ARVD is suspected then cardiac magnetic resonance imaging is most informative.⁷ Electro-physiological testing may also be indicated in some instances. In the first instance, clinical screening of first-degree relatives should be carried out. Family members who are clinically screened and found to have no evidence of disease should be followed up at regular intervals. The frequency of follow up is largely dependent on the disease in question and the age of the individual. In general terms, unaffected family members aged 10 to 20 years should be clinically screened on a yearly basis, those aged 20 to 30 years on a 2- to 3-yearly basis and those aged 30 years and over on a 3- to 5-yearly basis. It should be strongly communicated that if an individual becomes symptomatic at any time, they should re-present for medical assessment and investigation. Such screening time intervals are based on both the knowledge that many genetic heart diseases most commonly manifest clinical disease in the second decade of life and recommendations on genetic screening

by expert panels, as seen in HCM.⁸ Although there is currently a lack of scientific data in large cohorts to support the notion that rates of sudden death can be reduced by such clinical screening programmes, there is good evidence that treatment of individuals with genetic heart disease (e.g. with implantable defibrillators, beta-blockers) who are identified as 'high-risk' reduces sudden death events in these individual patients.

Clinical screening of surviving family members after a sudden death is not only useful in identifying affected individuals, but particularly in the case of a sudden unexplained death, can provide useful insight into the cardiac disease affecting the family and therefore the cause of death in the young deceased individual. Clinical assessment of surviving family members after a sudden unexplained death has recently been reported to lead to the diagnosis of the underlying cardiac disease, and likely cause of death, in 40% of cases.⁷

Apart from trying to establish the cause of the young sudden death and carrying out clinical screening of surviving relatives, there are clearly many other medical issues that need to be addressed in this complex medical presentation. The family experiences a range of emotions from grief following the death of a loved one, to fear that it will happen again in the family, to a feeling of hopelessness not knowing why their loved one died and to anger over why it happened to them. These normal psychological responses need to be managed sensitively and appropriately. Furthermore, with the major advances in our knowledge of the genetic basis of many cardiovascular diseases which can lead to sudden cardiac death, informed discussions relating to genetic counselling and testing, as well as issues relating to medicolegal and insurance implications of clinical and genetic screening, need to be part of the overall management strategy of the family. Therefore, the investigation and appropriate management of a family with a young sudden cardiac death cannot be carried out solely by the attending cardiologist, but requires a dedicated multidisciplinary team, in the form of a cardiac genetic service (Fig. 2).

The role of a cardiac genetic service

The role of a cardiac genetic service in the setting of a sudden cardiac death is not only to provide appropriate clinical screening to surviving family members, but also to offer information and discussion regarding the genetic aspects of inherited heart diseases. Genetic counselling after a sudden death is a key component in the overall management of families. This includes the collection of a detailed family history, discussion of genetic issues such as inheritance and recurrence risk to children, and most

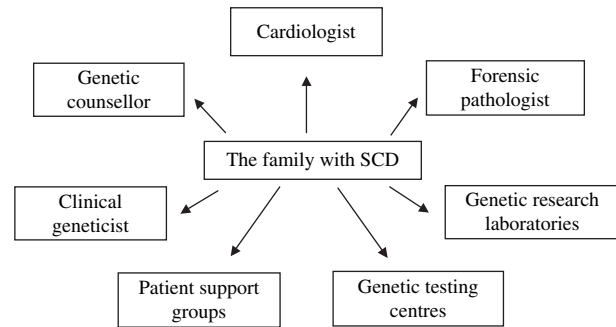


Figure 2 Features of a cardiac genetics service. SCD, sudden cardiac death.

importantly, ongoing support to the family. Genetic testing may be an option and this should be discussed on a case-by-case basis. Therefore, a multidisciplinary approach to the family, as offered through a cardiac genetic service and including cardiologists, clinical geneticists, genetic counsellors and forensic pathologists, is crucial in the overall management of families who have lost a relative suddenly (Fig. 2).

Taking a complete family history

A thorough family history includes detailed information spanning a minimum of three generations, including the young deceased individual. Particular attention should be focused on family members who have suffered suspicious symptoms, such as syncope and seizures, as well as any additional members who may have passed away at a young age. It is very useful to pursue medical records, post-mortem reports and death certificates to confirm any suspected diagnoses in relatives. In addition to identifying individuals who may be affected by a genetic heart disease, a family history is very useful in becoming familiar with the family dynamics, as this helps in relaying important messages through key members, promoting effective communication and may mean individuals are more likely to undergo clinical and genetic screening. Finally, particularly in sudden unexplained deaths, further information about the family history can often provide useful insight as to the genetic heart disease affecting the family.⁷

Genetic counselling in the family

A common misconception is that genetic counselling is only required if a genetic test is to be carried out. All families in which a familial cause of sudden cardiac death is either identified, or a possibility, require genetic counselling. Discussion of genetic issues includes explanation of the inheritance of a gene mutation in a family, as well as the recurrence risk this poses to a variety of family

Table 2 Key points for clinicians

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- Genetic heart diseases can lead to sudden cardiac death in the young
 - Take a thorough family history
 - Investigate all information pertaining to the possible cause of sudden cardiac death in the young victim
 - Structural genetic heart problems (e.g. hypertrophic cardiomyopathy) can be identified at post-mortem
 - Arrhythmogenic heart diseases (e.g. long QT syndrome) in many cases lead to a negative post-mortem, often termed a 'sudden unexplained death'
 - Clinical screening of first-degree relatives is essential
 - Consider the role of genetic counselling and testing in all cases
 - Management of families with sudden cardiac death requires a multidisciplinary approach
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members. The majority of genetic heart diseases predisposing to sudden death are autosomal dominant, meaning there is a 1 in 2 (50%) chance of passing the gene mutation on to offspring. Importantly, almost all of these diseases show extreme clinical variability, whereby one individual may develop a severe phenotype such as sudden death, whereas within the same family another person may have only very mild clinical disease with no symptoms. It is thought that factors other than the causative gene mutation, such as the environment and modifying genes, may contribute to some of this variability and stresses the importance of further research aimed at understanding genetic heart diseases.⁹

Genetic testing issues in sudden cardiac death families

Genetic testing for inherited heart diseases provides extremely useful information to the family and clinicians. Specifically, any family member can have a gene test to determine if they too carry the genetic abnormality. This can prove extremely useful in family members who have a borderline phenotype, for example, a young person with an 'athlete's heart'. Currently, there are limitations to this technology, therefore discussion with staff at a cardiac genetics clinic is particularly important. The process of genetic testing is time-consuming and costly and because of the large number of genes implicated in inherited cardiac disease, it is not feasible to screen every gene. Furthermore, implications of clinical and genetic screening in terms of personal issues, such as insurance and employment, need to be considered. It is well established that a targeted approach is more cost-effective and informative when a clinical diagnosis is first made,^{7,10} allowing the list of potential causative genes to be narrowed down. It should be noted that in every inherited cardiac disease listed in Table 1, there exists a proportion of patients who have no gene mutation identified in the known causative genes. In addition, where a clinical diagnosis of LQTS or HCM is made, genetic testing can uncover a more complex genotype, involving the identification of more than one disease causing mutation, leading to compound and double heterozygotes.^{11,12} This has

important implications for recurrence risk and further emphasizes the need for discussion at a cardiac genetics clinic. Finally, the availability of genetic testing is always changing, with tests for many diseases still being in the research phase. In some instances, commercial genetic testing is available through private testing centres, providing a rapid result, but in most cases must be paid for by the family. All of these genetic testing issues need to be discussed with families on a case-by-case basis.

Ongoing support for sudden cardiac death families

A major role of the cardiac genetics service is to provide ongoing support to families following a sudden death. This is emphasized most by the constant availability of accurate and up-to-date information provided by the staff. It is well described that family members confronted with a sudden unexpected death show a great need for understanding the cause of death.^{13,14} In the case of a sudden unexplained death, no conclusive information can be given to the family, therefore the process of actively searching for answers, by clinically screening relatives, gathering family history information and genetic testing, would be expected to be very helpful in the grieving process. Family members may also benefit from joining patient support groups, such as the Cardiomyopathy Association of Australia and the Sudden Arrhythmia Death Syndrome group, which provide an ongoing educational and emotionally supportive environment.

Conclusion

Sudden death is a devastating complication of a number of cardiovascular diseases. In the young, sudden death is frequently caused by an underlying genetic heart disorder. In families where a young sudden cardiac death has occurred, management needs to involve a multidisciplinary team approach in the setting of a cardiac genetic service (Table 2). The key aspects of management in these families not only includes clinical cardiological evaluation, but also genetic counselling and testing, education and support for

individual family members, and longer-term ongoing medical and emotional support. Research into understanding the genetic basis of sudden cardiac death, investigating the molecular mechanisms that lead from the gene defect to the clinical phenotype and elucidating the specific molecular and environmental triggers for sudden cardiac death will most likely lead to improvements in the management and prevention of sudden cardiac death in the young.

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