FEATURE

Sudden cardiac death in the young

BELINDA GRAY BSc(Med), MB BS, FRACP
JIPIN DAS K MB BS
CHRISTOPHER SEMSARIAN MB BS, PhD, FRACP, FCSANZ, FAHA, FHRS

Sudden cardiac death is a tragic and devastating complication of several cardiovascular diseases. In up to one-third of sudden deaths in the young, no cause is identified at postmortem. DNA analysis of appropriate blood and tissues plays a key role in the identification of any underlying genetic cause of death.

Sudden cardiac death (SCD) is defined as a death occurring usually within an hour of the onset of symptoms, due to an underlying cardiac disease. SCD is a tragic and devastating complication of a number of cardiovascular diseases. The death is most often unexpected leading to a complex situation for the family and the community.

SCD can occur at any age. Although SCD in older populations is most frequently due to underlying coronary artery disease and heart failure, in individuals aged younger than 40 years, the causes of SCD span several diverse diseases often with an underlying genetic cause, such as the inherited cardiomyopathies and primary arrhythmogenic diseases. Identification of the cause of SCD in the young is a critical step in determining whether there is an underlying genetic aetiology and, if there is, how this impacts on the clinical and genetic evaluation of surviving family members who are at risk of inheriting the same disease. This is particularly important in the evaluation of SCD cases where no cause of death is identified at postmortem, so called sudden unexplained death (SUD), which occurs in about 30% of cases of SCD in the young (Figure 1).

CARDIOLOGY TODAY 2014; 4(1): 10-14

Dr Gray is an Honorary Cardiologist at the Royal Prince Alfred Hospital; a Heart Foundation PhD Scholar at the Centenary Institute; and a Clinical Associate Lecturer at The University of Sydney, Sydney. Dr Das K is a Junior Medical Officer and PhD Scholar at the University of Sydney, Sydney. Professor Semsarian is a Professor of Medicine at The University of Sydney; a Cardiologist at the Royal Prince Alfred Hospital; a NHMRC Practitioner Fellow; and Head of the Molecular Cardiology Program at the Centenary Institute, Sydney, NSW.

Causes of SCD in the young

SCD in the young, defined as those aged younger than 40 years, is caused by a variety of disorders that can broadly be categorised into structural and arrhythmogenic causes (see Box 1).

Structural causes of SCD include the inherited cardiomyopathies, such as hypertrophic cardiomyopathy, dilated and restrictive cardiomyopathies, arrhythmogenic right ventricular cardiomyopathy and left ventricular noncompaction. Other structural causes of SCD in the young include myocarditis, congenital heart diseases and coronary artery disease. Hypertrophic cardiomyopathy remains the most common structural cause of SCD in the young, including competitive athletes. Importantly, in all structural causes of SCD in the young, the postmortem examination has a high probability of identifying the cause of death.

Primary arrhythmogenic disorders include familial long QT syndrome (LQTS), catecholaminergic polymorphic ventricular tachycardia (CPVT), Brugada syndrome (BrS) and short QT

Key points

- **Sudden cardiac death is a major and tragic complication of cardiovascular disease.**
- **In patients aged younger than 40 years, most causes of sudden cardiac death are either primary structural or primary arrhythmogenic abnormalities.**
- **Many of these diseases are familial, usually with autosomal dominant inheritance.**
- **The first presentation of an inherited heart disease may be sudden cardiac death.**
- **Management of patients and their families following a sudden cardiac death requires a comprehensive multidisciplinary care model in a specialised cardiac genetic clinic.**

syndrome (SQTS). These primary arrhythmogenic disorders rarely cause any cardiac structural abnormalities, so they are more difficult to diagnose during a postmortem examination (so called 'negative' postmortem). Such cases in which no abnormalities are found at postmortem have been classified as being of unknown aetiology or 'unascertained', resulting in an underestimation of the incidence of arrhythmogenic causes of SCD.

Collectively, these primary arrhythmogenic disorders have been defined as 'ion channelopathies', predominantly involving potassium, sodium and calcium channels expressed in the heart. Genetic studies over the past 20 years have been crucial in identifying the specific gene abnormalities that underpin these diseases. The main genes involved in the pathogenesis of familial LQTS1-3, CPVT1 and BrS are listed in the Table.

About 75% of all family members with LQTS1-3 studied to date have been found to have mutations in the *KCNQ1*, *HERG* and *SCN5A* genes, whereas about 70% of CPVT1 cases have a mutation in the ryanodine receptor gene (*RyR2*), and about 25% of cases of BrS have a mutation in the *SCN5A* gene (Table). Importantly, about 95% of mutations in these primary arrhythmogenic diseases are inherited as an autosomal-dominant trait, meaning 50% of the offspring of an affected individual will also carry the disease-causing gene mutation (Figure 2). This has important implications on the evaluation of families in which a sudden death has occurred, including families in which SUD has occurred in a 0- to 1-year-old, that is, sudden infant death syndrome (SIDS) deaths, with gene mutations known to cause familial LQTS identified in up to 10% of cases.

Primary arrhythmogenic disorders can also be potentially overlooked when they serve as a trigger for death seemingly due to another cause. For example, deaths attributed to events such as drowning and motor vehicle accidents may have been directly precipitated by a ventricular arrhythmia, as illustrated by an association between swimming and the development of ventricular arrhythmias in patients with familial LQTS. Therefore, the exact percentage of SUD may be underestimated.

Key role of 'molecular autopsy'

In all cases of SCD, postmortem examination is crucial in potentially identifying the cause of death. A complete postmortem investigation should be performed including family history, clinical history surrounding the death, macroscopic and microscopic examination of the organs, and toxicology. In all cases of SCD in the young, a 5 to 10 mL blood sample should be collected from the decedent for subsequent DNA extraction and analysis. In addition, frozen sections of liver or spleen (which are rich in DNA) should be collected and stored (see Box 2). In cases of SUD where no cause of death is identified after a complete and thorough postmortem examination, genetic testing of the decedent's blood sample may identify an underlying cause.

Implications of identifying a genetic cause of SUD

Identification of an underlying cause of death through genetic testing in cases of SUD has major implications for relatives, as well as giving

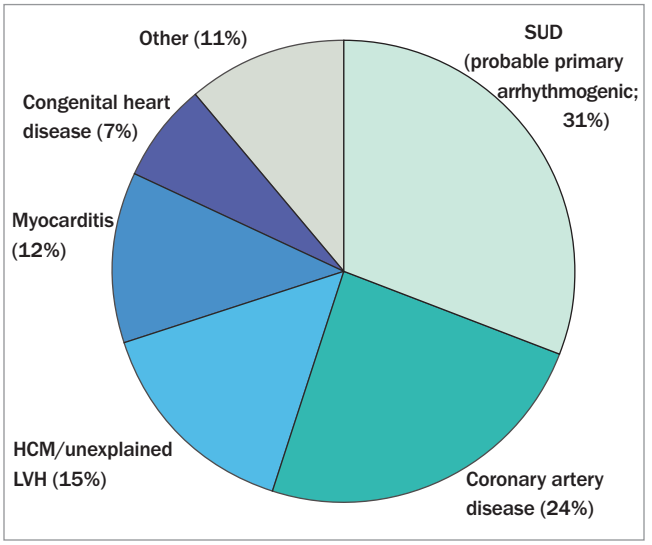

Figure 1. Causes of sudden cardiac death in young Australians aged less than 35 years.

Adapted from: Doolan A, et al. Med J Aust 2004; 180: 110-112.[1]

Abbreviations: HCM = hypertrophic cardiomyopathy; LVH = left ventricular hypertrophy; SUD = sudden unexplained death.

1. Causes of sudden cardiac death in the young

Structural causes (abnormal postmortem)

- Hypertrophic cardiomyopathy (HCM)
- Coronary artery disease
- Myocarditis
- Coronary anomalies
- Arrhythmogenic right ventricular cardiomyopathy (ARVC)
- Left ventricular noncompaction (LVNC)
- Aortic dissection
- Congenital heart disease

Arrhythmogenic causes ('normal' postmortem)

- Long QT syndrome (LQTS)
- Brugada syndrome (BrS)
- Catecholaminergic polymorphic ventricular tachycardia (CPVT)
- Idiopathic ventricular fibrillation
- Short QT syndrome (SQTS)

the family some closure as to why their relative has died suddenly at a young age. The Heart Rhythm Society recommends: 'Mutation-specific genetic testing for family members and other appropriate relatives following the identification of a SUDS-causative mutation in the decedent.'[1]

In all situations in which an inherited heart disease is suspected in the setting of a sudden death, appropriate clinical screening is indicated. The cardiac investigation of surviving family members should include taking a thorough clinical history and performing a physical examination, a 12-lead resting ECG, an echocardiography and, in most instances, an exercise ECG stress test. Additional tests may be required for specific cardiac genetic diseases (e.g. flecainide challenge in patients with possible BrS and cardiac magnetic resonance imaging in patients with possible arrhythmogenic right ventricular cardiomyopathy. This approach of using clinical screening alone (without genetic testing) of at-risk relatives may identify the underlying cardiac disease in the family in up to 40% of cases.

Establishing a clinical diagnosis in the surviving family is important on many levels, including in assisting the subsequent selection and interpretation of genetic findings in the decedent. The clear goal of both clinical and genetic screening of family members is to identify those who may have the same disease or who may be phenotypically normal but carry the same pathogenic mutation as the decedent (genotype positive, phenotype negative). Early identification of these at-risk individuals provides opportunities to initiate therapies aimed at preventing the complications of the particular disease. For example, gene carriers for LQTS may require modification of lifestyle activities, avoidance of QT-prolonging medications, initiation of beta-blocker therapy and, in some people, consideration of implantable cardioverter defibrillator therapy. These strategies all aim to reduce the incidence of sudden death.

Management of families following a SCD

The management of families following a SCD is complex. Clinical evaluation, co-ordination of services including forensics and genetic

Table. Major genetic causes of sudden unexplained death in the young

Disease	Gene	Encoded protein	% of disease caused by gene	% of SUD caused by gene
LQTS1	*KCNQ1*	I_{Ks} potassium channel α-subunit	35 to 40	10 to 15
LQTS2	*HERG*	I_{Kr} potassium channel α-subunit	30 to 35	<5
LQTS3	*SCN5A*	I_{Na} sodium channel α-subunit	5 to 10	<1
BrS	*SCN5A*	I_{Na} sodium channel α-subunit	15 to 30	<1
CPVT1	*RyR2*	Cardiac ryanodine receptor	65	10 to 20

Abbreviations: BrS = Brugada syndrome; CPVT1 = catecholaminergic polymorphic ventricular tachycardia 1; LQTS = long QT syndrome; SUD = sudden unexplained death.

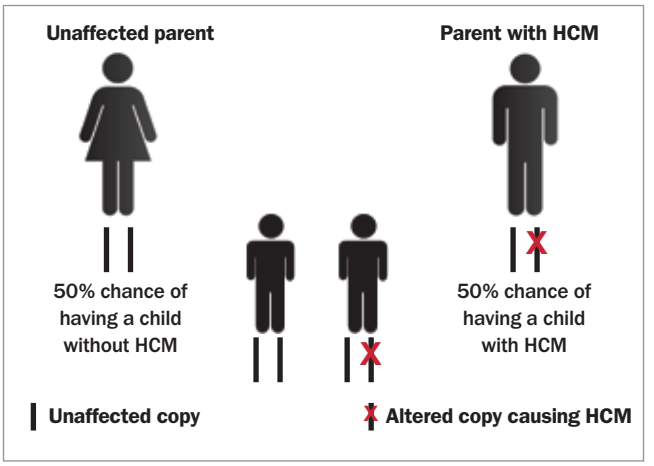

Figure 2. Autosomal-dominant inheritance pattern in patients with hypertrophic cardiomyopathy (HCM). Most genetic heart diseases (structural or arrhythmogenic) are through this pattern of inheritance. For each pregnancy there is a one in two chance the child will inherit the mutation. The child is guaranteed to get an unaffected copy of the gene from the parent who does not have HCM. However, they will get either the unaffected copy or the HCM copy from the affected parent.

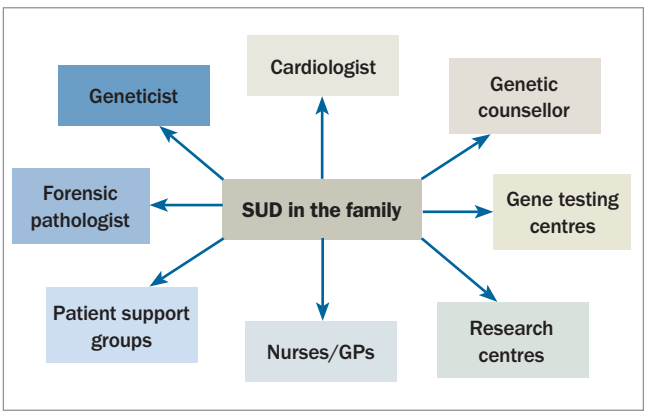

Figure 3. Multidisciplinary approach to care of families with sudden unexplained death (SUD) in the young.
Adapted from Ingles J, Semsarian C. Intern Med J 2007; 37: 32-37.[2]

testing, grief and genetic counselling, patient education and support, and awareness of psychological and social issues are all important components of care. 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 of not knowing why their loved one died, to anger over why it happened to them. These normal psychological responses need to be managed sensitively and appropriately.

Even in families in whom genetic testing in the decedent does not identify a specific genetic cause, the family's interaction with the cardiologist-led clinic has many benefits in terms of education and counselling, aspects that would not be seen in a purely laboratory-based approach. Therefore, the ideal model that encompasses all these facets of care is the specialised multidisciplinary cardiac genetic clinic, in which expertise in all these areas can be provided to families in whom sudden death in the young has occurred (Figure 3).

2. Key features of a postmortem evaluation in cases of sudden cardiac death

- Performed in all cases of sudden unexplained death in the young (0 to 40 years of age)
- Detailed premorbid clinical history and family history obtained
- Skilled macroscopic and microscopic examination of all organs, particularly of the heart and brain
- Adequate histological material for review or referral obtained
- Collection of 5 to 10 mL of whole blood and frozen sections of highly cellular tissues (e.g. liver or spleen) for future DNA extraction and analysis
- Liaison with a multidisciplinary specialised cardiac genetics service

Conclusion

SCD is a tragic and devastating complication of a number of cardiovascular diseases. In up to one-third of sudden deaths in the young, no cause is identified at postmortem. In these cases of SUD, postmortem evaluation and specifically the collection of appropriate blood and tissues for subsequent DNA analysis, plays a key role in the identification of any underlying genetic cause of death. Identification of the precise gene mutation causing disease leading to sudden death subsequently can be used, in conjunction with comprehensive clinical screening, in the identification of at-risk family members, with the ultimate aim of diagnosing disease early and therefore providing a platform for the initiation of therapeutic and prevention strategies.

Genetic testing both in living affected individuals and in the setting of a 'molecular autopsy' is emerging as a key factor in the early diagnosis of any underlying cardiovascular genetic disorder and most likely will lead to a reduction in the incidence of sudden death among the young in our communities. **CT**

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Further reading

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COMPETING INTERESTS: None.