

Genetic aspects and investigation of sudden death in young people

Pier D Lambiase PhD MRCP, Senior Lecturer in Electrophysiology

Perry M Elliott MD FRCP, Reader in Cardiology

The Heart Hospital, University College London

Clin Med 2008;8:607–10

In most adults, sudden cardiac death (SCD) is caused by coronary artery disease (CAD), but below 35 years of age it is frequently caused by inherited disorders of cardiac muscle or heart rhythm. The familial nature of these diseases means that the relatives of young SCD victims can also be at risk. The 8th National Service Framework (NSF) for Coronary Disease emphasises the importance of family screening when an SCD occurs in a young person. The recommendation is to offer them assessment in a dedicated clinic staffed by individuals trained in the diagnosis and management of inherited cardiovascular disease and family support, with access to genetic counselling and mutation analysis.

Epidemiology

There are approximately 100,000 SCDs in the UK annually, most in the elderly and caused by CAD. They are much less common in young people, in whom they are predominantly caused by congenital cardiac anomalies, cardiomyopathies and inherited arrhythmia syndromes. The term 'sudden unexpected or arrhythmic death syndrome' (SADS) refers to the situation in which no cause of death can be identified at post-mortem. In the past, studies in the USA and Europe have suggested that fewer than 5% of young sudden deaths are unexplained. However, more recent data suggest that autopsy-negative SCD is the leading cause of sudden death in individuals younger than 35 years of age, accounting for 18%, 29% and 35% of sudden deaths in Spain, an

urban population in Sydney and US army recruits, respectively. The estimated annual incidence of SADS in the UK in individuals aged 4–64 is 0.16 per 100,000, although recent studies suggest this is a substantial underestimate.¹

Aetiology of sudden death in the young

The causes of SCD in young people are listed in Table 1.

Cardiomyopathies

The cardiomyopathies are a heterogeneous group of heart muscle disorders defined by the presence of a structurally and functionally abnormal myocardium, in the absence of CAD, hypertension, valvular disease and congenital heart disease, sufficient to cause the observed myocardial abnormality.² Cardiomyopathies are classified according to the ventricular morphology and pathophysiology. Four major types are recognised:

- dilated
- hypertrophic
- restrictive
- arrhythmogenic right ventricular cardiomyopathy.

All cardiomyopathies can be inherited, in most cases in an autosomal dominant fashion. The expression of genetic abnormalities (the 'phenotype') in all the cardiomyopathies can vary enormously between unrelated individuals and within the same family.

Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is defined by the presence of unexplained left ventricular hypertrophy and is the most common genetically determined cardiac disorder (affecting one in 500 young adults). In most cases, the disease is caused by inherited mutations in the

genes that encode cardiac sarcomeric proteins, the commonest of which are β -myosin heavy chain, myosin binding protein C and the components of the troponin complex. Sudden death is a rare complication, with an annual incidence of approximately 1%, but the risk of SCD varies between and within individuals over time.³

Dilated cardiomyopathy

Patients with dilated cardiomyopathy (DCM) have enlargement of the left (and sometimes the right) ventricle and a reduction in contractile performance.⁴ DCM is the most common reason for heart transplant in the UK and accounts for up to 30% of heart failure cases in the general population.

Some patients with DCM may have evidence of prior viral infection or autoimmunity, but 25–50% have evidence for familial disease. In some cases, mutations in genes that encode cytoskeletal proteins such as dystrophin or nuclear envelope proteins such as lamin A/C are responsible. Mutations in the same sarcomeric protein genes that cause HCM can also cause DCM. Specific patterns of disease expression occur in association with some mutations. For example, in lamin A/C disease, the development of heart block requiring pacemaker implantation is common and often precedes the development of heart failure. Dystrophin cardiomyopathies are linked to skeletal myopathy (Becker's and Duchenne muscular dystrophy) and sub-clinical disease expression with elevated creatine kinase levels.

Arrhythmogenic right ventricular cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy (ARVC) is a disorder characterised clinically by ventricular arrhythmia, heart failure and sudden death, and histologically by cardiomyocyte loss and replacement with fibrous or fibro-fatty tissue.⁵ The estimated prevalence of ARVC is one in 5,000 of the population.

In many individuals the disease is caused by mutations in genes that encode

different components of the desmosome responsible for the mechanical coupling of cardiomyocytes. ARVC can be difficult to identify at post-mortem unless serial sections of the whole heart are examined. Clinically, the diagnosis usually requires integration of data from family members, ECG and a range of imaging techniques. The most common ECG anomalies include:

- T wave inversion in the right praecordial leads
- late potentials
- a high ventricular ectopic burden (>1,000 beats/24 h).

Management of ARVC focuses on treatment of symptomatic arrhythmia, prevention of SCD and, in the later stages of the disease, heart failure management.

The ion channelopathies

The ion channelopathies probably account for 30–40% of SADS events.^{6,7} Abnormalities in ion channel function alter the sequence of depolarisation and repolarisation in the myocardium, leading to focal triggered or re-entrant ventricular arrhythmia that can degenerate into ventricular fibrillation (VF). The commonest disorders are:

- long QT syndrome (LQTS)
- Brugada syndrome
- catecholaminergic polymorphic ventricular tachycardia (CPVT).

Long QT syndrome

The estimated population prevalence of LQTS is one in 5,000–6,000.^{8,9} Most cases are autosomal dominant, although the recessive form (Jervell-Lange-Nielson syndrome) associated with congenital deafness is described. Of familial cases, 40–50% are caused by mutations in one of six genes encoding components of the potassium and sodium ion channels responsible for the upstroke and repolarisation phases of the cardiac action potential. The most common LQT subtypes are LQT1, 2 and 3, caused by mutations in genes encoding KVLQT1 (IKs current), HERG (IKr current) and SCN5A (Na⁺ current), respectively. Specific ECG phenotypes are, at best, only a rough guide to the genotype but there are some common patterns, for example:

- a bifid T wave is more common in LQT2
- broad tented T waves are more common in LQT1
- a late onset peaked or biphasic T wave is typical in LQT3.

The triggers for cardiac arrest or syncope also seem to track with specific LQT subtypes.¹⁰ In LQT1, 68% of events occur during exercise versus 15% of events in LQT2. Emotional stimuli are a trigger for 51% of events in LQT2 versus 28% in LQT1. Death during sleep and rest without arousal occurs in 55% of LQT3 cases.¹¹

Brugada syndrome

Brugada syndrome has an estimated prevalence of one in 10,000 of the population.¹² It is defined by coved ST segment elevation in leads V1–V3 with a partial RBBB pattern. Inheritance is autosomal dominant, arising in 20–30% of cases from mutations in the sodium channel gene (SCN5A). The characteristic ECG pattern can be induced by the administration of sodium channel antagonists such as flecainide or ajmaline. Death usually occurs during sleep due to VF. The highest risk patients include those with a history of syncope and spontaneous coved ST elevation in V1–V3. The clinical significance of ventricular arrhythmias induced during an electrophysiological study is contentious.

Catecholaminergic polymorphic ventricular tachycardia

CPVT is a syndrome of exercise- or emotion-induced polymorphic (often bidirectional) VT or VF in children or young adults, occurring in a structurally normal heart. In about 30% of cases, there is a family history of one or multiple premature sudden deaths usually during childhood.^{13,14} CPVT is associated with a completely normal resting ECG but should be suspected when either exercise or catecholamine stress testing demonstrates significant ventricular ectopy or polymorphic VT with a bidirectional pattern. In 50% of familial cases, the disorder is caused by autosomal dominant mutations in the cardiac ryanodine-2 receptor.

Familial bradycardia and heart block

A number of familial disorders can result in bradyarrhythmia and atrioventricular (AV) block,¹⁵ in many cases in association with a clinical cardiomyopathy, for example:

- lamin A/C disease
- dystrophinopathies, and
- mutations of the gamma subunit of the adenosine monophosphate activated protein kinase (PRKAG2). Conduction disease also occurs in

Table 1. Causes of sudden cardiac death in the young.

Structural and vascular causes	Congenital coronary anomalies Premature coronary disease Ruptured aorta Tunnelled LAD Aortic stenosis Mitral valve prolapse
Cardiomyopathies	Hypertrophic cardiomyopathy Arrhythmogenic right ventricular cardiomyopathy Dilated cardiomyopathy (Myocarditis)
Ion channel disorders	Long QT syndrome Brugada syndrome Catecholaminergic polymorphic ventricular tachycardia Lev-Lenegre disease

LAD = left anterior descending artery.

patients with Holt-Oram syndrome (TBX5) and in association with mutations in the gene NKX2.5 that also result in atrial septal defects. Rare cases of isolated familial bradycardia are described in association with mutations in the hyperpolarisation-activated cyclic nucleotide-gated channels. Compound heterozygotes for SCN5A alleles may cause a rare congenital form of sick sinus syndrome, with sinus bradycardia or sinus arrest. Heterozygous SCN5A mutations have also been implicated in occasional families with sinoatrial disease, atrial fibrillation (AF), AV block and dilated cardiomyopathy. Patients with myotonic dystrophy can develop variable degrees of AV block which, in some, may cause sudden cardiac death.

Investigation of sudden unexpected or arrhythmic death syndrome families

Following the sudden unexplained death of a young person, it is extremely important to counsel their family on both the possible cause and the implications of screening tests for their employment, insurance, psychological health and children.¹⁶ Close collaboration with a paediatric cardiologist and genetic teams with specific expertise in this field is invaluable.

Initial investigations frequently result in inconclusive non-diagnostic findings requiring further testing such as magnetic resonance (MR) scanning or pharmacological testing. Some conditions have age-

related penetrance, so regular follow-up on an annual basis with a 24-hour ambulatory ECG or exercise test may be necessary. When a diagnosis is made, relatives may be advised to take medical therapy (eg beta-blockers for long QT) or be asked to consider having an implantable cardioverter defibrillator (ICD).

Structure of a sudden unexpected or arrhythmic death syndrome clinic

A considerable amount of preliminary information must be gathered before the affected family are actually seen in the clinic. Specifically, a detailed post-mortem report should be obtained together with any clinical information (such as ECG) about the index case in life. Whenever possible, tissue sections or, ideally, the whole heart should be reviewed by an expert cardiac pathologist to identify myocyte disarray in the case of HCM or fibrosis and fatty infiltration suggestive of ARVC. Myocardial tissue can be sampled for DNA extraction and subsequent candidate mutation screening, although lymphocytes from the spleen are a more reliable source of good quality DNA.

Family screening for SADS begins with a detailed evaluation of the index case. The mode of death may provide useful clues to the aetiology. Detailed questioning of first-degree relatives can be of great value in ascertaining the details of prior presyncopal or syncopal events and in identifying other family members who are symptomatic. Such individuals may be gene carriers but essentially have sub-clinical manifestations of the disease. There is no common model for the panel of tests to perform routinely in a SADS clinic. In our institution, each at-risk family member undergoes the following tests:

- resting ECG
- exercise ECG
- signal averaged ECG
- transthoracic echocardiogram.

Ajmaline or flecainide challenge to unmask Brugada syndrome is performed in suspected cases after initial review.¹⁷ Where a cardiomyopathy is suspected, contrast echo and cardiac MRI may be considered.¹⁸

The diagnostic yield of clinical testing depends on the degree of utilisation of clinical screening investigations and additional genetic testing. For example, the diagnostic yield is 22% with a screening ECG and echocardiogram; this is raised to 30–35% with additional exercise testing and ajmaline challenge, and to over 40% with additional targeted genetic testing – as many ion channel disorders and cardiomyopathies are not overtly clinically expressed.

Genetic counselling

The counselling of relatives for genetic screening must be undertaken by individuals experienced in the interpretation of genetic results as well as in the psychosocial impact of a genetic diagnosis. Patients will request information on the implications for family planning, prenatal diagnosis, life insurance, ability to obtain a mortgage and occupational health.

In the UK, the NSF for Coronary Disease has acknowledged that effective evaluation of relatives, guided by genetic testing, can prevent further deaths in the family¹ and has made the quality requirement that:

when sudden cardiac death occurs, NHS services have systems in place to identify family members at risk and provide personally tailored, sensitive and expert support, diagnosis, treatment, information and advice to close relatives.

Although genetic testing forms a part of this process, its role varies in different conditions. Importantly, genetic results must be carefully interpreted in the context of the clinical phenotype.

The indications for genetic testing in SADS, recently reviewed by the Heart Rhythm UK Development Group, are summarised in Table 2.¹⁸

References

- 1 Behr ER, Casey A, Sheppard M *et al*. Sudden arrhythmic death syndrome: a national survey of sudden unexplained cardiac death. *Heart* 2007;93:601–5.
- 2 Elliott P, Andersson B, Arbustini E *et al*. Classification of the cardiomyopathies: a position statement from the European

Key Points

Sudden unexpected or arrhythmic death syndrome (SADS) is frequently caused by inherited cardiac disease

The families of SADS victims should be offered screening in dedicated clinics with expertise in inherited cardiovascular disease

Systematic screening of family members identifies a probable cause in 20–40% of families

KEY WORDS: cardiomyopathy, ion channel, sudden arrhythmic death syndrome

Table 2. Summary of clinical indications for genetic testing.

Genetic testing	Genotyped (%)	Genes	Clinical score				
			I	II	III	IV	V
Of clinical value							
Timothy syndrome (LQT8)	100	CACNA1c	+	+		+	
Long QT syndrome (Romano Ward)	>50	KCNQ1, KCNH2, SCN5A, KCNE1, KCNE2	+	+	+	+	+
JLN	>50	KCNQ1, KCNE1	+	+			+
Anderson syndrome	50	KCNJ2	+	+			+
DCM-CB	30–50	LMNA/C	+	+			+
HCM		MYH7, MYL3, MYL2, ACTC, TNNT2, TPM1, TNNI3, MYBPC3, TTNC	+	+			+
CPVT	>50	RyR2, CASQ2	+	+		+	+
Could be considered							
ARVC	30–50	PKP2, DSP, JUP	+	+			+
Brugada syndrome	<30	SCN5A	+	+			
Research only							
Short QT syndrome	0	KCNQ1, KCNH2, KCNJ2	+				+
Progressive cardiac conduction defect	0	SCN5A	+				+
Left ventricular non-compaction	0	Cypher/ZASP	+				
Clinical score:							
I	Presymptomatic diagnosis is clinically relevant						
II	Identification of silent carriers is clinically relevant						
III	Results influence risk stratification						
IV	Results influence therapy/lifestyle						
V	Reproductive counselling is clinically justified						

ARVC = arrhythmogenic right ventricular cardiomyopathy; CPVT = catecholaminergic polymorphic ventricular tachycardia; DCM-CB = dilated cardiomyopathy and conduction block; HCM = hypertrophic cardiomyopathy; JLN = Jervell-Lange-Nielsen.

Society of Cardiology Working Group on Myocardial and Pericardial Diseases. *Eur Heart J* 2008;29:270–6.

3 Elliott P, McKenna WJ. Hypertrophic cardiomyopathy. *Lancet* 2004;363:1881–91.

4 Burkett EL, Hershberger RE. Clinical and genetic issues in familial dilated cardiomyopathy. *J Am Coll Cardiol* 2005;45:969–81.

5 Sen-Chowdhry S, Syrris P, McKenna WJ. Role of genetic analysis in the management of patients with arrhythmogenic right ventricular dysplasia/cardiomyopathy. Review. *J Am Coll Cardiol* 2007;50:1813–21.

6 Tan HL, Hofman N, van Langen IM, van der Wal AC, Wilde AA. Sudden unexplained death: heritability and diagnostic yield of cardiological and genetic examination in surviving relatives. *Circulation* 2005;112:207–13.

7 Tester DJ, Ackerman MJ. The role of molecular autopsy in unexplained sudden cardiac death. Review. *Curr Opin Cardiol* 2006;21:166–72.

8 Modell SM, Lehmann MH. The long QT syndrome family of cardiac ion channelopathies: a HuGE review. *Genet Med* 2006;8:143–55.

9 Keller DI, Carrier L, Schwartz K. Genetics of familial cardiomyopathies and arrhythmias. Review. *Swiss Med Wkly* 2002;132:401–7.

10 Zhang L, Timothy KW, Vincent GM *et al*. Spectrum of ST-T-wave patterns and repolarization parameters in congenital long-QT syndrome: ECG findings identify genotypes. *Circulation* 2000;102:2849–55.

11 Schwartz PJ, Priori SG, Spazzolini C *et al*. Genotype-phenotype correlation in the long-QT syndrome: gene-specific triggers for life-threatening arrhythmias. *Circulation* 2001;103:89–95.

12 Shimizu W. The Brugada syndrome: an update. *Intern Med* 2005;44:1224–31.

13 Laitinen PJ, Swan H, Piippo K *et al*. Genes, exercise and sudden death: molecular basis of familial catecholaminergic polymorphic ventricular tachycardia. Review. *Ann Med* 2004;36(Suppl 1):81–6.

14 Francis J, Sankar V, Nair VK, Priori SG. Catecholaminergic polymorphic ventricular tachycardia. Review. *Heart Rhythm* 2005;2:550–4.

15 Smits JP, Veldkamp MW, Wilde AA. Mechanisms of inherited cardiac conduction disease. *Europace* 2005;7:122–37.

16 Sen-Chowdhry S, McKenna WJ. Sudden cardiac death in the young: a strategy for prevention by targeted evaluation. Review. *Cardiology* 2006;105:196–206.

17 Rolf S, Bruns HJ, Wichter T *et al*. The ajmaline challenge in Brugada syndrome: diagnostic impact, safety, and recommended protocol. *Eur Heart J* 2003;24:1104–12.

18 Garratt CJ, Elliott PM, Behr E *et al*. Clinical indications for genetic testing in familial sudden cardiac death syndromes: an HRUK position statement. *Heart* 2008;94:502–7.