A Clinical Approach to a Family History of Sudden Death

Boon Yew Tan, MD; Daniel P. Judge, MD

Sir William Osler reportedly once said, “Varicose veins are the result of an improper selection of grandparents.” Indeed, our family history strongly influences many aspects of our cardiovascular system, with the magnitude of effect ranging from very strong for autosomal dominant genetic disorders to more subtle in the setting of complex multigenic diseases like coronary atherosclerosis and hypertension. Accordingly, the standard evaluation of any new patient who presents to a physician includes assessment of their family history. Unfortunately, the family history may sometimes be discounted as noncontributory without detailed review. This can be exacerbated by busy office schedules with declining amounts of time available for comprehensive evaluations. A few minutes saved might seem to justify the lack of focus on an aspect of history that is sometimes deemed not to be particularly useful. However, a thorough assessment of family history also may provide the key diagnostic information to determine the cause of an illness, to determine who else is at risk of disease within the family, to add useful prognostic information, and to help for family planning and reproductive decisions.

A family history of sudden death should prompt consideration of a wide range of heritable cardiovascular conditions, including many monogenic disorders (Table). However, the terms used by the lay public to describe sudden death may not adequately explain the cause of death on initial consideration. For instance, the phrase “heart attack” may be used to describe sudden death due to a monogenic disorder in a large family. When possible, one should obtain at least 3 generations of antecedent family history. Several factors may complicate its assessment. An autosomal dominant pattern of inheritance of sudden death in the absence of coronary atherosclerosis risk factor (Figure 1B). The proband’s maternal grandmother has unexplained dilated cardiomyopathy (DCM), and 3 of her 4 siblings also had unexplained DCM, 2 of whom died suddenly at younger ages. This additional historical information helps target the proband’s assessment now and serially for his risk of inheriting the genetic predisposition for DCM that runs in his family, and importantly it also helps to identify other family members who are at risk of sudden cardiac death (SCD) or DCM. In such a family, all offspring of an affected individual carry a 50% chance of inheriting a genetic predisposition to DCM.

Typical Case
A 40-year-old man presents to a physician for evaluation of palpitations. These occur briefly about once per month without dizziness or lightheadedness, and he is otherwise without symptoms. He exercises twice weekly, running approximately 2 miles, and he is not limited by unexpected dyspnea or chest discomfort. His past medical history is negative. On discussion of his family history, he notes that his father died suddenly at age 41 years without antecedent medical history (Figure 1A). His mother is well at age 63 years of age. He has a younger brother and sister who are well, and 2 children 5 and 7 years of age who are well. He consumes approximately 4 alcoholic beverages weekly and does not use tobacco.

This scenario is seen commonly in medical practice. This 40-year-old man undoubtedly is considering strongly his father’s sudden death at a similar age, but healthcare providers do not always recognize the significance, the range of potential contributing factors, and the latest technologies that are impacting the approach to improve the diagnosis. His palpitations are nonspecific, and his paucity of other symptoms does not exclude coronary disease, cardiomyopathy, inherited arrhythmic disease, or aortic aneurysm. Although genetic analysis in a clearly affected proband would be ideal, DNA is usually not available from people who died in the remote past. As such, clues to target the phenotypic assessment of subsequent generations may be obtained from a carefully obtained family history.

From an extended discussion of his father’s sudden death, it would be clear that he had heart failure prior to his sudden death in the absence of coronary atherosclerosis risk factor (Figure 1B). The proband’s paternal grandmother has unexplained dilated cardiomyopathy (DCM), and 3 of her 4 siblings also had unexplained DCM, 2 of whom died suddenly at younger ages. This additional historical information helps target the proband’s assessment now and serially for his risk of inheriting the genetic predisposition for DCM that runs in his family, and importantly it also helps to identify other family members who are at risk of sudden cardiac death (SCD) or DCM. In such a family, all offspring of an affected individual carry a 50% chance of inheriting a genetic predisposition to DCM.

Adequate Family History
When possible, one should obtain at least 3 generations of antecedent family history. Several factors may complicate its assessment. An autosomal dominant pattern of inheritance of sudden death due to a monogenic disorder in a large family cannot be recognized with only limited questioning. Age-dependent phenotypes, small families, and the inability to track down accurate antecedent family history can limit the...
**Table. Monogenic Disorders Associated With Sudden Death**

<table>
<thead>
<tr>
<th>Disorder</th>
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<tbody>
<tr>
<td>Long QT syndrome</td>
<td>Noonan syndrome</td>
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<tr>
<td>Brugada syndrome</td>
<td>Fabry disease</td>
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<tr>
<td>Short QT syndrome</td>
<td>Danon disease</td>
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<td>Timothy syndrome</td>
<td>Marfan syndrome</td>
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<tr>
<td>Andersen-Tawil syndrome</td>
<td>Loeys-Dietz syndrome</td>
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<tr>
<td>Catecholaminergic polymorphic VT</td>
<td>Ehlers Danlos syndrome (notably type IV)</td>
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<tr>
<td>Dilated cardiomyopathy</td>
<td>Nonsyndromic familial thoracic aortic aneurysm</td>
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<tr>
<td>Hypertrophic cardiomyopathy</td>
<td>Limb-girdle muscular dystrophies</td>
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<tr>
<td>Restrictive cardiomyopathy</td>
<td>Dystrophin-related muscular dystrophies</td>
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<tr>
<td>Noncompaction cardiomyopathy</td>
<td>Friedreich ataxia</td>
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<tr>
<td>Arrhythmogenic right ventricular cardiomyopathy</td>
<td>Mitochondrial myopathies</td>
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<tr>
<td>Naxos syndrome</td>
<td>Myotubular myopathies</td>
</tr>
<tr>
<td>Carvajal syndrome</td>
<td>Cavernous cranial malformations</td>
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VT indicates ventricular tachycardia.

Sudden Cardiac Death Associated With Coronary Atherosclerosis

In attempting to categorize the cause of antecedent sudden death, it is important to consider the possibility of coronary atherosclerosis and ischemic cardiomyopathy. A history of chest pain, a confluence of coronary disease risk factors, or a prior history of coronary disease and myocardial infarction readily help to assign sudden cardiac death to ischemic arrhythmia in this setting. The age of the deceased should be considered in this context. Although the majority of SCD cases do not occur in individuals with a prior history of coronary disease or ischemic cardiomyopathy, the prevalence of SCD among individuals with these conditions makes SCD more likely for them.

Several trials have investigated the genetic contribution to SCD among individuals with coronary artery disease. In a study cohort of people after ST-elevation myocardial infarction (MI), Dekker et al demonstrated that a family history of SCD occurred more frequently among primary ventricular fibrillation (VF) survivors after their first MI as compared with controls without VF who were matched for age, gender, and infarct size (OR, 2.72, 95% CI, 1.84–4.03).

Figure 1. A pedigree representing this individual’s family members. Circles indicate females and squares indicate males. The arrow identifies the proband in the text. A diagonal line indicates family members who are deceased. Circles or squares with white filling are without known cardiac disease. Those with the left half in black have experienced sudden death, and those with the right half in black have known dilated cardiomyopathy. B A more extended pedigree. Circles indicate females and squares indicate males. The arrow identifies the proband in the text. A diagonal line indicates family members who are deceased. Circles or squares with white filling are without known cardiac disease. Those with the left half in black have experienced sudden death, and those with the right half in black have known dilated cardiomyopathy.
Similarly, Kaikkonen et al. reported a higher incidence of SCD among first degree relatives of SCD acute MI victims compared with acute MI survivors (OR, 1.6, CI 95%, 1.2–2.2, \(P<0.01\)).

These studies have led to further investigation for specific genetic variants that confer SCD risk. A chromosomal locus in close proximity to \(\text{NOSIAP}\) that is associated highly with QT duration has been linked to SCD.\(^7\) More recently, genome-wide analysis of 515 Dutch individuals with MI and VF compared with 457 controls with MI but without VF identified a highly associated chromosomal locus in close proximity to \(\text{CXADR}\), encoding the human coxsackie virus and adenovirus receptor.\(^8\) Although SCD is often difficult to definitively characterize, this investigation benefited greatly by use of a highly refined clinical phenotype. Recognition of the genetic basis for the heritability of sudden death is the first step in the complex but critical process of improving our understanding of disease pathogenesis so that novel targeted therapies can be designed and tested.

The utility of clinical genetic testing for these conditions seems low at this point. Atherosclerosis is a complex genetic disorder that is influenced strongly by environmental factors and other heritable traits, such as hyperlipidemia, hypertension, and diabetes mellitus. The chromosomal locus 9p21 has been very highly associated with coronary atherosclerosis and acute myocardial infarction, but it is associated only with a 1.5 to 2.0 fold increase in relative risk of coronary disease.\(^9,10\) While a high-risk genotype for these 9p21 markers may help with either preventative therapy or closer phenotypic evaluation, a low risk genotype does not exclude other genetic or environmental contributors to atherosclerosis. The use of \(\text{NOSIAP}\) or \(\text{CXADR}\) single nucleotide polymorphism analysis is only theoretical, as variations in the coding sequence or expression of these genes have not yet been reported to associate with the noncoding single nucleotide polymorphisms in their proximity that are linked to SCD risk.

**Sudden Death From Cardiomyopathy**

**Dilated Cardiomyopathy**

Dilation of the left ventricle with normal wall thickness along with systolic dysfunction, with or without right ventricular involvement, is the hallmark of DCM. The prevalence in adults has been reported to be 1 in 2500 individuals, with an incidence of 7 per 100,000 per year.\(^11\) Familial dilated cardiomyopathy accounts for 20% to 48% of cases in studies that used echocardiography to assess first degree relatives of an individual with unexplained DCM.\(^12–14\)

A family history of unexplained sudden death prior to the age of 35 years is considered a criterion for familial DCM.\(^15\) Indeed, if an individual presents with unexplained DCM, assessment of family members for the same condition is a class I recommendation by American Heart Association (AHA)/American College of Cardiology (ACC)/American Society of Echocardiography guidelines.\(^16\) Within families who have a familial form of cardiomyopathy, the risk of arrhythmia is influenced strongly by family history of SCD.\(^17,18\) Current ACC/AHA/Heart Rhythm Society (HRS) guidelines recommend implantable cardioverter-defibrillator (ICD) therapy in nonischemic cardiomyopathy patients with an ejection fraction (EF) \(\leq 35\%\) (New York Heart Association class II or III) as a class I indication, provided a reversible cause of left ventricular (LV) dysfunction has been excluded.\(^19\) However, some of the studies that were used to establish these criteria excluded individuals with familial DCM associated with a family history of SCD, with the expectation that ICD already was justified on that basis.\(^20\) In such families, one need not wait for the EF to be [itex]\geq35\%\) before recommending an ICD.

Several syndromic disorders are associated with familial DCM, and such details should be considered when assessing a family history that may involve 1 of these conditions. The most common association with familial DCM is skeletal myopathy or muscular dystrophy. A severe form of skeletal myopathy, such as Duchenne muscular dystrophy where use of a wheelchair in early teenage years is common, is typically much more obvious than many of the limb girdle muscular dystrophies. For X-linked disorders (such as Duchenne and Becker), female carriers may only manifest with DCM, sometimes obscuring the connection to the condition of their affected male relatives.

Mitochondrial gene mutations can cause DCM.\(^21,22\) Mutations in mtDNA genes can present with isolated nonsyndromic cardiomyopathy, or may be associated with systemic features, such as early hearing loss, visual problems, diabetes, skeletal myopathy, lactic acidosis or elevated lactate-to-pyruvate ratio, or cognitive impairment.\(^21,22\) An mtDNA mutation can be excluded as the sole cause of disease in a family if any offspring of an affected male also are affected, because we inherit our mtDNA from our mothers. Variability in severity or phenotypic expression may depend on the percentage (heteroplasmy) of the mtDNA that carry a specific mutation.

**Hypertrophic Cardiomyopathy**

Hypertrophic cardiomyopathy (HCM) is characterized by unexplained left ventricular hypertrophy (LVH), a disorder that occurs in 1 in 500 individuals on population screening.\(^23\) It is one of the most common causes of sudden death among athletes.\(^24\) Histologically, there is myocyte disarray and myocardial replacement with scar. HCM typically is caused by a mutation in 1 of the genes encoding an element of the cardiac sarcomere, although nonsarcomere gene mutations also may result in left ventricular hypertrophy.\(^25\) Prospective randomized trials designed to determine who should receive an ICD for primary prevention of SCD have not been reported. The standard criteria used to determine risk of arrhythmia include substantial septal wall thickness, history of unexplained syncope, nonsustained ventricular tachycardia (VT), decline in blood pressure with exercise, and family history of SCD.\(^26\) Additional criteria include delayed contrast enhancement on cardiac magnetic resonance imaging, LV aneurysm, LV outflow tract gradient, and occasionally a specific gene mutation from which arrhythmia risk can be inferred.\(^27–30\) For instance, mutations in \(\text{TNNT2}\) encoding cardiac troponin T are known to carry increased risk of arrhythmia despite a relative paucity of left ventricular hypertrophy.\(^31\)

A few syndromic disorders can present with HCM, and family history may help to recognize some of them.\(^32\) Fabry...
Cardiac amyloidosis can mimic HCM. Although the most common cause in the United States is related to monoclonal light chain immunoglobulin overproduction, genetic forms of cardiac amyloidosis also occur. In particular, TTR mutations can cause syndromic features along with cardiac amyloidosis, including carpal tunnel syndrome, peripheral neuropathy, autonomic insufficiency, and gastrointestinal vistas. TTR amyloidosis has strong ethnic associations. For instance, 3% to 4% of African-Americans carry a specific mutation, p.Val122Ile, that is known to cause late-onset cardiac amyloidosis, and the p.Val30Met mutation often is seen in Portugal and Japan.

**Arrhythmogenic Right Ventricular Dysplasia/Cardiomyopathy**

Arrhythmogenic right ventricular dysplasia/cardiomyopathy (ARVD/C) is an inherited form of cardiomyopathy with an estimated prevalence of 1 in 5000 individuals. The typical age of diagnosis is within the second and third decade of life, though very early and very late diagnoses do occur. Tragically, the first manifestation is often SCD, with the diagnosis made on autopsy. In many affected patients, a preceding history of symptoms, including syncope, often occurs. It is usually possible to discern a period when right ventricular (RV) dilation and dysfunction is present prior to the onset of symptoms. This has been described as the "concealed phase." For reasons that are not clear, many people with this condition are highly trained athletes, particularly those who engage in long-distance aerobic activities. Indeed, murine models of ARVD/C can be induced to develop RV cardiomyopathy with exercise.

Arrhythmogenic right ventricular dysplasia/cardiomyopathy is a disease that often is caused by a mutation in genes encoding the desmosome proteins in the heart, resulting in electric and mechanical uncoupling of cardiomyocytes. This leads to cell death with fibro-fatty replacement, primarily affecting the right ventricle but sometimes extending to the left ventricle. A similar condition, termed arrhythmogenic left ventricular cardiomyopathy (or simply arrhythmogenic cardiomyopathy), also has been reported. Focal ventricular scar becomes a substrate for VT. In 1 study, up to one half of patients with ARVD/C presented with malignant or potentially malignant ventricular arrhythmia.

A family history of sudden death occurring during athletic activity suggests either ARVD/C or HCM, particularly if the death occurs in the 2nd or 3rd decade of life. Although rare, some people with ARVD/C also have skin or hair abnormalities. Naxos syndrome first was reported in 1986 as a curious disorder on the Greek island of Naxos, in which affected individuals had cardiomyopathy, palmar plantar keratoderma, wooly hair, VT, and sudden death. Carvajal syndrome subsequently was reported with similar syndromic features involving both hair and skin, along with RV cardiomyopathy in the setting of fibro-fatty scar in the heart.

**Other Forms of Familial Cardiomyopathy**

Forms of cardiomyopathy typically are classified based on the appearance of the heart, yet overlap certainly exists. For instance, HCM can "burn out" with loss of systolic LV function and LV dilation. Noncompaction cardiomyopathy (also known as LV hypertrabeculation) can mimic either HCM or DCM. At least 1 form of ARVD/C is predominantly a left ventricular cardiomyopathy. These patients with overlapping phenotypes, in particular, may not fit into the standard guidelines for receiving an ICD. This group of individuals would benefit from assessment in a center with expertise in the management of inherited heart diseases.

**Genetic Testing for Familial Cardiomyopathies**

The use of genetic analysis for individuals with monogenic forms of familial cardiomyopathy is far greater than with complex genetic disorders, such as coronary disease. It should be considered to help determine the cause of a condition, to assess for syndromic manifestations, to facilitate cascade screening within the family (particularly in the context of sudden death), and to assist with family planning. Such testing should be restricted initially to a family member who is unequivocally affected. If more than 1 is available, those with the youngest age of onset typically are assessed with the most comprehensive panel of genetic testing, as compound heterozygosity and digenic inheritance occur in about 5% of cases, and cascade screening in the family may need to assess for more than 1 mutation or rare genetic variant. If a definite mutation is recognized, analysis in additional family members who are at risk but without phenotypic features can be performed. One cost-effectiveness analysis compared the use of serial echocardiographic assessment for family members who were at risk of HCM with family screening that was guided by genetic analysis. The use of genetic testing to guide investigation of phenotypic manifestations within families was lower in cost than serial screening alone without genetic testing in this model. A recent report shows the high use of cascade family member evaluations in the setting of sudden death associated with ARVD/C. This same report also demonstrates certain cases when the genetic test results can be ambiguous or uncertain. Published guidelines for the use of genetic testing in cardiomyopathy by 2 different expert committees are available, and both emphasize the importance of referral to specialized centers with genetic counseling.
Sudden Death From Aortic Dissection
Both syndromic and nonsyndromic forms of familial aortic aneurysm should be considered in the differential diagnosis for unexplained sudden death. The criteria used to assign a diagnosis of Marfan syndrome are based on cardiovascular, skeletal, ophthalmologic, pulmonary, and integumentary systems, along with family history or genetic data. When considering an individual who had unexpected sudden death, historical questions should interrogate features of disproportionate long bone overgrowth (arm span:height ratio >1.05, arachnodactyly, dolichostenomelia, wrist, and thumb signs) and pectus deformities of the chest. Pictures may help to assess for facial characteristics of Marfan syndrome, such as dolichocephaly, malar hypoplasia, downsloping palpebral fissures, and retrognathia. With regard to ophthalmologic manifestations of Marfan syndrome, myopia is widely prevalent and nonspecific, but its presence along with ocular lens dislocation in the setting of aortic aneurysm or sudden death strongly suggests Marfan syndrome. Other notable aspects of Marfan syndrome include spontaneous pneumothorax, scoliosis, unexplained dermal striae, pes planus (flat feet), and myxomatous mitral valve prolapse.

A related disorder, known as Loeys-Dietz syndrome, more recently was reported to have features similar to Marfan syndrome. It is associated with higher rates of death from aortic dissection, often occurring at smaller aortic dimension. Its hallmark features include arterial tortuosity and midline facial abnormalities, such as hypertelorism (widely spaced eyes), cleft palate, or bifid uvula. Marked arterial tortuosity can be present among any medium or large arteries, sometimes involving the cranial vessels. Additional characteristics of Loeys-Dietz syndrome that may be present include easy bruising, thin skin, blue sclerae, and joint hypermobility. Mutations in the genes encoding components of the TGFβ-receptor complex (TGFBR1 and TGFBR2) are responsible.

Nonsyndromic aortic aneurysm is a more difficult disorder to recognize by historical questioning. By its very nature, it typically is not associated with systemic manifestations, though a subtle abnormality of the skin, lvedo reticularis, has been reported. Known genetic causes include mutations in ACTA2 and MYH11 encoding smooth muscle actin and myosin, components of the smooth muscle sarcomere.

The diagnosis of syndromic aortic diseases, such as Marfan syndrome, typically is established by phenotypic criteria. A proposed modification of the diagnostic criteria recently was published to include FBN1 mutation analysis. Such testing within a family initially should be restricted to an individual who is unequivocally affected. Cascade screening of at-risk family members then can be performed if a definite mutation is identified. Because many families with Marfan syndrome have their own unique mutation, a rare nonpathogenic DNA variant may be difficult to distinguish from a pathogenic mutation. When a DNA variant of unknown significance (VUS) is identified, other definitively affected family members should be tested for this variant, and its absence in an unequivocally affected family member would exclude it as the sole cause of the condition in the family.

Sudden Death From Ion Channel Disorders
There are several related disorders that fit into this category, and this review will focus on 3 distinct phenotypes: long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic VT. The general concepts that are outlined for these conditions also apply to related phenotypes such as short QT syndrome, J-wave syndrome, idiopathic VT, and early repolarization syndrome, all of which share similar pathogenesis involving abnormalities in ion channel genes with a paucity of structural heart disease. Similarities and differences among these specific disorders are well described elsewhere.

Long QT Syndrome
Long QT syndrome is a genetically heterogeneous disorder with a reported prevalence of 1 in 2500 people. While a diagnosis of LQTS is apparent in an individual with persistent severe prolongation of the corrected QT (QTc) interval (> 500 ms), its diagnosis can be challenging in borderline cases. This in part is due to, (1) the overlap in the QTc duration between LQTS patients and unaffected individuals, (2) individual variability in QTc length for people with this condition, and (3) miscalculation of QTc. The Bazett formula, for example, consistently underestimates the QTc in low heart rates, and overestimates it in high heart rates. The QT interval also may be measured erroneously in the presence of U waves or complex T waves.

Unexplained drowning or sudden death while swimming should suggest either LQTS or catecholaminergic polymorphic ventricular tachycardia (CPVT). A history of seizures or recurrent syncope in the absence of structural heart disease should suggest the possibility of LQTS. One study reported a presumed diagnosis of seizures among approximately one third of patients with LQTS. While arrhythmic syncope sometimes is attributed erroneously to seizures, attempts to link the 2 phenotypes of LQTS and seizures has led to a recent report of brain expression of KCNQ1 and KCNE1, 2 genes in which mutations are known to cause LQTS.

In addition, mice carrying knock-in missense mutations in Kcnq1 developed QTc prolongation and both partial and generalized seizures.

Rare syndromic conditions may occur with LQTS. Jervell and Lange-Nielsen syndrome is a recessive disorder characterized by congenital deafness, QT prolongation, and recurrent syncope with SCD caused by mutations in KCNQ1. Andersen-Tawil syndrome is a multisystemic autosomal dominant disorder with variable penetrance. Features that suggest Andersen-Tawil include QT prolongation with potassium-sensitive periodic paralysis, short stature, clinodactyly, and characteristic facial features, including a broad forehead, malar hypoplasia, low set ears, and hypertelorism. Timothy syndrome is a multisystemic disorder caused by dominant de novo mutations in CACNA1C. Affected individuals have congenital prolongation of the QT interval along with webbing of fingers and toes, autism, developmental delay, intermittent hypoglycemia, abnormal teeth, and immune deficiency. Some affected individuals also have congenital cardiac malformations, such as patent ductus arteriosus, patent foramen ovale, and ventricular septal defects.
Brugada Syndrome
Brugada syndrome (BrS) is a genetically heterogeneous disorder with a reported prevalence of 0.5% to 0.7% and male preponderance. It is thought to account for up to 4% of all SCD and up to 20% of SCD in structurally normal hearts. The ECG manifestations of ST elevation in BrS can occur spontaneously, or in the presence of a sodium-channel blocker. More detailed electrophysiological manifestations and patterns of ST elevation in BrS have been reviewed elsewhere. The ACC/AHA/HRS 2008 guidelines have designated ICD implantation as a class IIa indication (level of evidence C) for BrS patients who present with syncope, or have documented VT that has not resulted in cardiac arrest.

The differential diagnosis for a BrS-like pattern of ST elevation on ECG includes acute myocardial infarction, electrolyte abnormalities, myopericarditis, and ARVD/C. In the absence of diagnostic ECG findings, suspicion for BrS should arise in the setting of unexplained SCD without structural heart disease. It is not associated with syndromic or systemic manifestations. Asian ethnicity may indicate a higher likelihood of BrS, as several reports have indicated higher prevalence of this condition or “sudden unexplained nocturnal death syndrome” among different Asian groups. One important factor contributing to BrS among Asians was reported by Bezzina and colleagues. They identified a haplotype within the SCN5A promoter that results in lower gene expression. It was present with an allele frequency of 22% among Japanese individuals in 2 cohorts and was absent among individuals of Caucasian or black African ancestry. This corresponds to 5% of this population with homozygosity for this haplotype and approximately 35% having 1 copy, assuming normal Hardy-Weinberg equilibrium. The presence of this SCN5A promoter haplotype also influenced the response to sodium channel blocking drugs, but its presence alone was not sufficient to result in BrS.

Catecholaminergic Polymorphic Ventricular Tachycardia
Catecholaminergic polymorphic ventricular tachycardia is a rare disorder of stress-related bidirectional VT in the absence of structural heart disease or rearing ECG abnormalities. Autosomal dominant CPVT is caused by heterozygous mutation of the cardiac ryanodine receptor gene, and an autosomal recessive form is caused by mutations in CASQ2, encoding the calsequestrin-2 gene. The typical age of onset for both forms is childhood or adolescence. Syncopae in the setting of exercise or emotional stress is common among affected individuals. One study reported a family history of unexplained SCD ≤40 years of age among 33% of affected individuals. Noncardiac or systemic manifestations are not known to occur with CPVT.

Sudden Infant Death Syndrome
Sudden infant death syndrome (SIDS) is the sudden death of an infant <1 year of age that remains unexplained after thorough investigation. Its cause remains unknown, and there are probably many different disorders that present with this same end result. Its incidence is declining, and it now occurs in about 0.5 per 1000 live births in the United States. Although rare, it is the leading cause of death among infants age 1 to 12 months, and it is the third-leading cause overall of infant mortality in the United States (http://www.cdc.gov/sids). Research into the genetic basis of SIDS has focused on genes in which mutations cause LQTS or CPVT. Currently, it is estimated that ~10% of cases of SIDS are caused by mutations in these genes, whereas sudden unexplained death in those >1 year of age is estimated to be caused by a LQTS or CPVT gene mutation in 25% to 30% of cases.

Postmortem Genetic Investigation
At the time of the decedent’s death, an autopsy may represent the best and last opportunity to make a proper diagnosis. To facilitate genetic investigation within families, the use of molecular techniques has been recommended in recent guidelines for autopsy investigation of sudden death by the Association for European Cardiovascular Pathology. Unclotted blood may be obtained from the heart, or frozen tissue may be used. The isolation of DNA from formalin-fixed, paraffin-embedded tissue is generally poor because DNA becomes fragmented in this process, though one report shows promise along these lines. Although a broad range of testing using large gene panels may not be possible from fixed tissue, small amounts of fragmented DNA may be perfectly acceptable for testing for a known mutation that is recognized in another family member, or perhaps more importantly, for investigating cosegregation of a novel DNA sequence VUS. Another practical consideration for postmortem genetic testing is that medical insurance is unlikely to pay for the decedent’s subsequent genetic characterization. Guidelines for the use of genetic testing for monogenic arrhythmias and postmortem testing for sudden cardiac death recently have been published.

DNA Banking
Despite extensive efforts, the cause of death sometimes may not be discernible. Genetic testing may or may not be feasible at that point. Long-term storage of DNA, either premortem or postmortem, is a low-cost method of facilitating the availability of DNA for future generations to access and use. This can be particularly helpful if a VUS is recognized in another family member with a familial form of cardiovascular disease. Targeted testing for this VUS in a deceased family member whose phenotypic characterization found the same features can allow determination of cosegregation of the VUS and disease in the family. In instances where sudden death of unknown cause occurs and genetic testing for ion channel disorders is negative, remaining DNA can be transferred from a Clinical Laboratory Improvement Amendments (CLIA)-certified testing laboratory to a long-term DNA storage facility for future use. As the molecular genetic characterization of the numerous monogenic cardiovascular diseases improves, access to DNA from deceased affected family members may be very helpful.

Next-Generation DNA Sequencing
Improvements in technology have led to lower cost and higher throughput for DNA sequence analysis. The determination of DNA sequence on radiolabeled polyacrylamide gels was
sudden deaths within a family. A family history of sudden death is a well-recognized risk factor for sudden death in many different cardiovascular conditions. A thorough family history should be obtained, with emphasis on features that could suggest an underlying disorder causing the sudden death, including coronary artery disease, cardiomyopathy, an inherited arrhythmia syndrome, or aortic disease. The pattern of inheritance within a family helps to determine others who are at risk for the condition. Improvements in DNA sequence analysis are leading to lower costs for genetic testing, and efforts to obtain or bank DNA for future use should help to determine genetic contributions to sudden death, with an ultimate goal of preventing subsequent sudden deaths within a family.

Disclosures

None.

References


KEY WORDS: aorta ▪ arrhythmia ▪ cardiomyopathy ▪ death ▪ sudden ▪ genetics
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