Explaining Sudden Unexplained Death
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Sudden unexplained death (SUD) of the young is the term used for sudden deaths occurring before the age of 40 years, which remain unexplained despite analysis of all available antemortem information (usually because the victims had no family history of heart disease or warning symptoms) and a postmortem examination that was unrevealing or was not performed. For the surviving family members, the fact that the tragic death of a previously healthy relative remains unexplained only adds frustration and confusion to grief. Furthermore, because arrhythmic death in the young is often caused by familial diseases, reaching the correct diagnosis is important for those left behind, who may then receive appropriate prophylactic measures. Therefore, it is good clinical practice to systematically evaluate families of SUD victims in attempts to minimize the unexplained. Having said that, it is also important that family members considering screening be aware of the potential negative consequences associated with the diagnosis of an asymptomatic inheritable disease. Unjustified remorse or recrimination may torment parents of a deceased child, whereas unforeseen anxiety or disqualification from sports or life insurance policies may become problematic for asymptomatic, yet affected, siblings. A 1%/year risk of sudden death, as currently estimated for asymptomatic individuals with Brugada syndrome discovered through screening, may be perceived as reassuring by some but may be terrifying to others.

Evaluation of SUD families should begin with a meticulous review of available data concerning the index SUD victim. The circumstances of death are important: sleep-related death favors long-QT syndrome (LQTS) of the LQT3 type, short-QT syndrome, or Brugada syndrome (if male); sudden death during stress favors coronary disease (congenital coronary anomalies or premature atherosclerosis), cardiomyopathies, catecholaminergic polymorphic ventricular tachycardia (CPVT), or LQTS, whereas unexplained drowning favors LQT1 and CPVT. Favoring a diagnosis by no means establishes the same; sleep-related death by no means excludes CPVT. Every effort should be made to retrieve all the medical tests performed by the SUD victim. A report of normal ECG should not be taken at face value because too many physicians will not recognize a long-QT interval and because, until recently, traces with short-QT interval were defined as normal simply because the QT was not prolonged. On the other hand, not all forms of ECG abnormalities retrospectively identified in an SUD victim should be automatically assumed to be the cause of death. Early repolarization, for example, is an ECG finding that is strongly associated with idiopathic ventricular fibrillation but is also prevalent among healthy individuals. Except for cases where the arrhythmias pathognomonic of idiopathic ventricular fibrillation are recorded, caution should be exercised before an SUD case is diagnosed as an early repolarization syndrome, solely on the basis of retrospective ECG interpretation. This point is especially important because early repolarization is a familial trait, regardless of the presence or absence of arrhythmic disease. Consequently, if early repolarization is present on the ECG of an SUD victim, his/her siblings are twice as likely to display the same ECG variant even if this finding has nothing to do with the victim’s death.

In countries where forensic examination of sudden death cases is not mandatory, relatives may refuse authorization of the examination for a variety of reasons, including religious principles. They are likely to regret this decision years down the road, when symptoms or ECG findings in other family members raise concerns about possible familial syndromes. A well-performed forensic examination, including a toxicology screen, may establish the diagnosis in cases of traumatic, toxic, noncardiac, or some forms of cardiac death (eg, cardiomyopathies, coronary anomalies), whereas a negative pathological examination, as happens in 30% of young SUD cases, will favor a primary electric disease or channelopathy. Postmortem radiology, with computed tomography coronary angiography, should be proposed when forensic examination is refused. Importantly, blood should be collected in EDTA (the purple-top tube) to enable DNA extraction, which should be stored for a molecular autopsy (ie, screening the DNA of the SUD victim for known genetic diseases). It should be emphasized, however, that the list of genetic diseases potentially leading to SUD is long and that for each disease several genotypes exist. Therefore, wide-spectrum screening of all possible arrhythmogenic genetic disorders is too expensive to be practical at the present time. Instead, screening should be selectively directed at candidate genes based on a comprehensive evaluation of the SUD victim and the surviving siblings. Genetic results, however, should not be accepted as gospel truth because distinguishing disease-causing mutations from innocent genetic variants requires expertise.

Several series report on the yield of systematically evaluating family members of SUD victims. In these studies, 100 to 260 surviving relatives (of 32–57 index SUD victims) were evaluated with an ECG, echocardiogram, exercise testing, and Holter monitoring; additional tests, such as cardiac magnetic resonance imaging or challenges with sodium channel blockers...
systematically evaluating survivors of apparently unexplained upper limit of the 95% CI for the frequency of false-positive epinephrine premature given the limited number of healthy controls (the Although none of these healthy individuals had a positive epinephrine to 53% of the families,2,3,18 with LQTS2,18 and CPVT3 being the most common diagnoses. Importantly, successful identification of the familial disease was more likely as more family members agreed to be screened.9 More recently, the yield of systematically evaluating survivors of apparently unexplained cardiac arrest was studied in the Cardiac Arrest Survivors With Preserved Ejection Fraction Registry (CASPERS).19 Cardiac arrest survivors with normal coronary arteries and preserved left ventricular function underwent ECG and echocardiographic evaluation, and those with obvious anatomic (ie, hypertrophic cardiomyopathy) or electric diseases (frank QT prolongation or Brugada pattern) identified on initial screening were excluded. The remaining 63 survivors of unexplained cardiac arrest (aged 43±13 years) were evaluated with provocative tests (exercise tests and epinephrine and procainamide infusions), yielding a specific diagnosis in 35 (56%) patients, most commonly LQTS, CPVT, and arrhythmogenic right ventricular dysplasia (in 23%, 23%, and 17% of diagnosed patients, respectively).19

In this issue of Circulation: Arrhythmia and Electrophysiology, Krnah et al20 report on the expanded CASPER data, emphasizing the value of the epinephrine test for diagnosing an occult LQTS among victims of unexplained cardiac arrest and their siblings. A total of 170 patients, mainly cardiac arrest survivors (58%) and siblings of cardiac arrest victims (38%), were studied. A positive epinephrine response, defined as a ≥230 ms QT-interval increment in response to low-dose epinephrine (based on the Ackerman protocol)21 was observed in 31 (18%) patients. Integration of all clinical testing and genetic data led to a working diagnosis of LQTS in 71% of the latter. This finding has important clinical implications because highly effective therapy exists for the LQTS, which is often lethal when left untreated. However, before the epinephrine test is universally adopted as part of the evaluation of SUD, limitations of the present study must be emphasized. First, the fact that most SUD victims/relatives with a positive epinephrine test were ultimately given a working diagnosis of LQTS must be viewed with caution. This is because the results of the epinephrine test were probably taken into consideration when diagnosing LQTS, and this diagnosis was then used as one of the criteria for evaluating the performance of the test. This circular reasoning inevitably made the test look better than what it actually is. Second, this was an uncontrolled study. So far, only 51 healthy controls have received similar doses of epinephrine in the context of control studies (27 by Ackerman et al21 and 24 by Magnano et al22). Although none of these healthy individuals had a positive epinephrine response as defined here, claiming a 100% specificity is premature given the limited number of healthy controls (the upper limit of the 95% CI for the frequency of false-positive epinephrine test approaches 6%,23 which is not very different from the 18% rate of positive tests in the present study). Furthermore, the epinephrine dose defined as low dose in the original Ackerman study was 0.05 µg/kg per minute but was ≤0.1 µg/kg per minute in the present study. This difference is important because ≥25% of healthy individuals may develop ≥30 ms QT increment in response to higher doses of epinephrine.21,22

Evaluation of SUD is an art, best performed at referral centers; it involves detective-like investigation of the victim’s data and systematic evaluation of the surviving relatives. The evidence supporting the diagnosis should be carefully weighted when selecting therapy. For example, the long-term risk for asymptomatic family members with Brugada syndrome is lowest when the characteristic ECG is only revealed by a drug challenge with a sodium channel blocker.24 In a similar fashion, asymptomatic SUD relatives with mild QT prolongation and abnormal epinephrine test are probably at low risk because the duration of the QT interval is the strongest prognostic factor in asymptomatic, genetically confirmed, LQTS.25 Avoidance of potentially proarrhythmic medications (http://www.brugadadrugs.org/ and www.qtdrugs.org) may be the only therapeutic intervention needed for such patients.

Disclosures

None.

References


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