Genetic Counselors: An Important Resource for Families Following a Young Sudden Cardiac Death

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ABSTRACT: Sudden cardiac death is a tragic result of a number of cardiovascular diseases. While the majority of sudden cardiac death cases are in older individuals with coronary artery disease, victims also include younger people (those less than 40 years old). At least 40% of cases of young sudden death are attributable to genetic causes, including diagnoses such as long QT syndrome and hypertrophic cardiomyopathy. In 50% of young sudden death cases, there are no warning signs or family history of sudden death. These young sudden deaths are a tragedy for families and in many cases are devastating for communities as well. Awareness is spreading among medical examiners and cardiologists on how to assess and treat these families but few healthcare providers see cases routinely. The combination of an unexpected death and the burden of potentially having a genetic disease themselves leaves family members in a vulnerable and often overwhelming position. Genetic counselors, particularly those who specialize in cardiovascular disease, are uniquely qualified to help surviving family members navigate the medical and psychosocial issues present in these cases.

KEYWORDS: Forensic pathology, Sudden cardiac death, Postmortem genetic testing, Genetic counseling

INTRODUCTION

Genetic counselors are healthcare professionals with specialized graduate degrees. They have expertise in medical genetics and psychosocial counseling. They are skilled in obtaining and assessing medical and family history, facilitating genetic testing, and providing emotional support and/or resources. Cardiac genetic counselors have specific expertise in inherited heart disease (1). Resources to find a genetic counselor are listed in **Table 1**.

Genetic counseling for sudden death can be a complex and time-consuming process that often requires multiple visits. The essential components of the genetic counseling process include psychosocial assessment and support, review of natural history of disease, review of personal and family medical history, collection of medical records and autopsy reports, and family screening. Additional responsibilities include coordinating DNA banking, reviewing genetic testing options, acquiring informed consent, and interpreting genetic test results. Although non-cardiac genetic causes of sudden death exist, this paper details the cardiac genetic counselor's role in assisting both the family of a young individual who dies of sudden cardiac death and the medical examiner's and coroners who investigate such deaths.

DISCUSSION

Psychosocial Assessment and Support

Genetic counselors are specially trained to address the psychosocial issues that arise when dealing with a genetic condition or potentially genetic condition (2). These issues may be magnified in families who have lost a young person to sudden cardiac death. Cases should be approached in a psychosocially sensitive manner with anticipation of the many stages of grief including shock, fear, anxiety, anger and depression (3). Genetic counselors can perform a psychosocial assessment and are knowledgeable about referral resources including support groups and psychologists and psychiatrists, if needed (**Table 1**).

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Table 1: Genetic Counseling, Referral and Support Resources

Resource	Website	Information Provided
National Society of Genetic Counselors (NSGC)	www.nsgc.org	Genetic counselors available in a specific geographical area. Can search specifically for cardiac genetic counselors
Canadian Association of Genetic Counsellors (CAGC)	https://cagc-accg.ca/	Genetic counselors available in Canada
Postmortem Genetic Testing	http://www.nsgc.org/ForHealthcareProviders/PostMortemTesting/tabid/509/Default.aspx	Resource through NSGC specific to postmortem genetic testing
Gene Tests	www.ncbi.nlm.nih.gov/sites/GeneTests	Up to date list of laboratories offering cardiac genetic testing
DNA Banking	http://www.ncbi.nlm.nih.gov/sites/GeneTests/lab/clinical_lab_service_id/2561?db=genetests	Up to date list of genetic laboratories offering DNA banking
Heart Failure Society (HFSA)	www.hfsa.org	Cardiologists specialized in heart failure
Heart Rhythm Society (HRS)	www.hrsonline.org	Cardiologists specialized in heart rhythm abnormalities (electrophysiologists)
Pediatric And Congenital Electrophysiology Society (PACES)	www.pediatricepsociety.org	Pediatric cardiologists specialized in heart rhythm abnormalities (pediatric electrophysiologists)
Childrens Cardiomyopathy Foundation	www.childrenscardiomyopathy.org	Patient support group for pediatric cardiomyopathy
Hypertrophic Cardiomyopathy Association (HCMA)	www.HCMA.org	Patient support group for hypertrophic cardiomyopathy
Parent Heart Watch	www.parentheartwatch.org	Patient support group for sudden death in the young
Sudden Arrhythmia Death Syndromes Foundation (SADS)	www.sads.org	Patient support group for genetic heart rhythm abnormalities

Review Natural History of Disease

Frequently a specific diagnosis as the cause of the decedent's death is not known at the initial visit with surviving family members, but a general discussion of diseases that can cause sudden cardiac death including inherited aneurysm, arrhythmias, cardiomyopathies and congenital heart disease provides context to the meeting. Symptoms of these diseases should be reviewed and this provides a useful focus for questions used in the family history assessment.

Personal and Family Medical History

Construction of (at least) a three-generation pedigree (family tree) focusing on any history of young or sudden death, heart disease, syncope, seizures or other findings as listed in **Table 2** is considered standard of care. Circumstances surrounding the sudden death of the decedent (e.g., during exertion versus at rest) and information obtained from the autopsy and past medical history with a focus on cardiac symptoms should be recorded on the pedigree. Review of the family history with the family should include a discussion of inheritance of the suspected disease. This may also require accessing autopsy reports for other family members that died unexpectedly or medical records for family members to clarify diagnoses, when permitted following proper consent protocols. Most of the single gene disorders that cause sudden cardiac death in the young are inherited as autosomal dominant disease but there are exceptions. Assuming autosomal dominant inheritance will allow for the identification of the maximum number of at risk family members and will direct family cardiac screening.

Collection of Medical Records and Autopsy Reports

The family history should be verified with medical records and autopsy reports. Any cardiac records should be collected on the decedent to look for information suggestive of a cardiac condition. In at least 50% of cases there are no warning signs prior to the sudden death (4); therefore, in many cases, no formal cardiac workup was performed on the decedent. Medical testing that was performed for other reasons prior to death such as an electrocardiogram prior to prescribing attention deficit hyperactivity disorder medications or a chest radiograph for pneumonia, may provide information on a cardiac history.

Table 2: Family History Red Flags to Record on Pedigree
Blood relative who have died young (Record circumstances)
Blood relative who have died suddenly (Record circumstances)
Blood relatives with heart disease or heart related conditions
Blood relatives with syncope (fainting) and/or seizures
Sudden death
"Heart attack"
Syncope or pre-syncope
Exercise intolerance
Seizures
Drowning
Unexplained single motor vehicle accidents
Sudden infant death syndrome (SIDS)
Enlarged heart or cardiomyopathy
Cardiac Device: implanted cardioverter defibrillator (ICD), pacemaker
Deafness
Syndactyly

Family Screening

All first-degree relatives of the decedent should undergo cardiac screening. This typically involves electrocardiogram and echocardiogram screening, but other tests may be appropriate based on the suspected diagnosis (e.g., exercise testing for long QT syndrome). Other family members identified as at risk based on symptoms or suspected mode of inheritance should also be screened by electrocardiogram and echocardiogram. Screening guidelines and recommendations have been published in the medical literature for cardiac evaluation when there is a known family history of an inherited cardiac condition (5-7). At risk family members should be referred to a knowledgeable center (8) and if possible, provided documentation detailing the sudden death event in their family, including any pertinent family history and recommended tests based on suspected cause of death. If a specialized cardiac genetics center is not available, family members should be referred to an electrophysiologist or a cardiologist with expertise in cardiomyopathies (**Table 1**). Family member screening information should be added to the pedigree when available. It should be noted that family history is not static and should be updated as time goes on to assess for development of disease in other relatives and to serve as a reminder to continue screening for those family members who are at risk (either mutation positive or genetic status unknown).

The timing of screening for family members is debated. Genetic testing is a possibility in these cases but takes time and does not always provide a useful tool for family risk assessment. In the meantime, since relatives could be at risk of sudden death, there is debate about whether to wait on genetic results or offer all relatives cardiac screening as soon as possible. The issue is whether the duty to warn should wait until specific details are available, or if the warning should be more general, (i.e., that the family members may be at risk, until testing proves otherwise) (9). Due to the potential risk of sudden cardiac death in other relatives and the possibility of identifying an additional affected relative for clinical genetic testing, family cardiac screening prior to attempting genetic testing is the most cautious approach.

DNA Banking

DNA banking of samples should be offered to families regardless of their decision to pursue genetic testing. DNA banking is the process of extracting DNA from an appropriate blood sample (EDTA tube) and storing that DNA for future

use at a DNA bank. DNA banks are specialized labs set up to store DNA, and recommendations exist about quality assurance and laboratory procedures for DNA banking facilities (10). A "banked" DNA sample is split in two samples and stored in ideal conditions for preservation in at least two locations. DNA banking will save a sample if a family is not ready to pursue genetic testing due to financial or other reasons, or if current clinical testing was negative. DNA banking is significantly less expensive than clinical genetic testing and prevents loss of the sample at the end of a medical examiner's or coroner's office retention period. DNA banking facilities can be found by searching "Genetests" (**Table 1**) under "Miscellaneous Testing and Banking" and selecting "DNA Banking." Funding for DNA banking will vary by region and may be an out of pocket cost that is covered by the deceased's family.

Informed consent is the standard in DNA banking for living individuals when DNA will be used for clinical or research purposes. The informed consent process does not specifically apply to deceased individuals, but rather, shifts to the next of kin or proper legal authority. This is an important consideration; given that DNA banking is for the purpose of obtaining genetic data for relatives to utilize, they should be consulted about DNA banking. In order to utilize the DNA sample, relatives must be informed where the sample is banked.

Genetic Testing

At least 40% of cases of young sudden death are attributable to genetic causes (11), making genetic testing an important tool in these cases. The decision to pursue genetic testing should be made after a multidisciplinary review of the case. The individuals forming this multidisciplinary team include the surviving family members, medical examiner or coroner, genetic counselor, cardiologist, genetic testing lab and/or DNA bank, and patient support groups (12) (**Table 3**). Identification of appropriate testing should be based on the suspected diagnosis, and if a specific diagnosis is not suspected (autopsy negative), genetic testing panels for the most common genetic causes of sudden death should be considered (13, 14). If another affected family member has been identified by family cardiac screening, the living family member should be the first candidate for clinical genetic testing as opposed to the postmortem sample from the deceased. As the sample saved on the deceased is finite, testing a living relative allows for testing numerous genes and saving the decedent sample for confirmation testing of a known disease-causing mutation (family specific testing), once identified.

There are logistical issues in obtaining genetic testing in postmortem cases, including: cost, lack of medical insurance coverage for genetic testing, and very often, a lack of an appropriate sample (15, 16). Clinical cardiovascular genetic testing for many of the inherited diseases (**Table 4**) is rapidly evolving and the yield of such testing varies based on the diagnosis. Some of these diagnoses will have morphological findings on autopsy, which can guide testing. In other cases, there will be no cardiac findings on autopsy (autopsy negative), but a genetic arrhythmia condition remains a possible diagnosis. Genetic testing companies have developed panels specifically for postmortem genetic testing, including the major genes responsible for a range of cardiac conditions. This clinical genetic testing involves multi-gene panels that require a minimum of 5-10 μg of DNA, which is the average yield of DNA extracted from a 7 mL K_2EDTA tube of blood from a living person. The choice of a clinical genetic testing lab should take into consideration the genetic methodology, scientific evidence for testing of specific genes, Clinical Laboratory Improvement Amendments (CLIA) certification status and comprehensiveness of the result reports.

Genetic counseling and genetic testing for sudden cardiac death should involve a discussion of the benefits and limitations of genetic testing (**Table 5**).

Informed Consent

When performing any type of genetic testing, it is essential that a patient understand the benefits and limitations of such testing. This differs, however, in cases of sudden cardiac death, where genetic testing is being performed on a deceased individual. Ideally, in cases involving postmortem genetic testing and/or DNA banking, next of kin and/or family members should be informed about genetic testing and provide consent for the testing to be performed. The legal aspects of consent, including who is responsible for obtaining consent, will vary by jurisdiction and should be dealt with on a case-by-case basis. In some cases, consent can be complex. For instance, if the deceased's spouse provides consent, but is estranged from the biological family of the deceased, care should be taken to assist all biological relatives in being informed of testing and/or banking. There are key elements to informed consent that need to be addressed with family members.

When not ordered by a medical examiner or coroner under statutory authority, the family must be informed that the testing is voluntary and that the results may reveal that they themselves may

Table 3: The Roles of the Individuals Forming the Multidisciplinary Team for Genetic Assessment in Young Sudden Death Cases

Roles
Medical Examiner/Coroner
Autopsy
Save appropriate biological sample
Refer family to their primary care physician or a cardiac genetics specialist, such as a cardiologist or genetic counselor
Psychosocial support/referral to support groups
Cardiologist
Review autopsy and past medical records on deceased
Evaluation of first degree relatives of deceased
Psychosocial support/referral to support groups
Genetic Counselor
Family history (verification by medical records)
Identification of appropriate genetic testing/facilitating testing
Psychosocial support/referral to support groups
"Dear Family member" letter (Duty to warn)
Needed Information
Autopsy report
Past medical history/medical records on deceased
Medical evaluations of first degree relatives
Family history
Information needed from
Decedent
Past medical history/medical records on deceased
Circumstances of the event
Sample type saved
Family
Family history (and verification of history by medical records)
Cardiac evaluation of first degree family members tailored to diagnosis of concern
Psychosocial support/referral to support groups

Table 4: Cardiovascular Genetic Testing in 2013

Disease	Prevalence	Number of Genes	Percentage of Cases with an Identifiable Mutation by Current Testing
Arrhythmogenic right ventricular cardiomyopathy (ARVC)	1:1000-1:2500 (17, 18)	At least 7	40-55% (19, 20)
Brugada syndrome (BRS)	1:2000 (21)	At least 9	25-40% (19, 20, 22)
Catecholaminergic polymorphic ventricular tachycardia (CPVT)	1:10000 (23)	At least 4	50-75% (19, 20)
Dilated cardiomyopathy (DCM)	1:2700 (24)	At least 38	Up to 40% (19, 20, 22)
Hypertrophic cardiomyopathy (HCM)	1:500 (25)	At least 31	Up to 80% (19, 20, 22)
Long QT syndrome (LQTS)	1: 2,500 (26)	At least 13	75-80% (19, 20, 22)
Familial thoracic aneurysm	Unknown	At least 12	~20% (27)
Short QT syndrome (SQTS)	Unknown/rare	At least 3	Unknown

Table 5: The Potential Benefits and Limitations of Genetic Testing

Potential Benefits
Determining the genetic etiology for an individual's sudden cardiac death, which can also provide psychological relief for surviving family members.
Allowing for genetic screening of family members to determine who is at risk for sudden cardiac death or cardiac disease.
Refining the differential diagnosis for an individuals' sudden cardiac death (e.g., in the case of a negative genetic test) reducing the likelihood of a particular diagnosis by testing negative for currently known genes.
Potential Limitations
Genetic mutations screened on the testing panel were not present, but there is another genetic etiology for the individual's sudden cardiac death. This can lead to false reassurance for a family.
Imperfect sensitivity (e.g., current genetic testing for hypertrophic cardiomyopathy will identify a mutation in up to 70% of genetic cases). Thirty percent of familial cases of HCM will not have a mutation identified by current testing because not all of the genes have been identified at this time (28). Therefore, a negative genetic test result does not allow for genetic testing of family members to determine their risk. Rather, all family members will be treated as at risk for an inherited cardiac condition and potential sudden cardiac death.

be identified as being at risk for a genetic condition. If this is the case, then there are insurance and medical issues that need to be understood by the family before receiving such results. These potential issues (in a mutation positive individual) may include but are not limited to: higher premiums from life insurance companies, recommendations for cardiac screening, and medical management tailored to the diagnosis. Family members need to understand that testing may improve in years to come, offering more sensitive tests and that DNA banking is an option for families.

Interpretation of Genetic Results

Cardiac genetics expertise is necessary to put genetic test results into context for both patients and other healthcare providers. Genetic counselors and cardiologists with expertise in cardiac genetic conditions must be involved with correlating the laboratory genetic results with the clinical

cardiac findings. The growing number and size of cardiac genetic testing panels makes accurate assessment and communication of results an important piece of the genetic evaluation process. Because of the genetic and clinical complexity of these conditions, the interpretation of the genetic results is often complicated and requires further analysis than is provided by a laboratory report, such as consulting the medical literature or databases for previous correlations of genetic findings to clinical findings. Since there is not a standard nomenclature for classifying or reporting results, interpretation of genetic results is difficult for healthcare providers without molecular genetics training (29).

Review of Management Recommendations

Guidelines and recommendations have been published in the medical literature for cardiac evaluation when there is a known family history of an inherited cardiac condition, with or without the availability of genetic results (5-7). These publications also refer to the benefit of reaching a genetic diagnosis through genetic testing. The primary benefits of a DNA diagnosis are identifying the at risk relatives who require medical management and if possible, identifying the relatives who are at low risk because they do not appear to carry the disease-causing genetic marker, and thus either do not need continued surveillance or need very limited surveillance.

Documentation/Family Member Letter

The surviving first degree family members and their providers should be sent a summary report documenting the findings and suspected or confirmed diagnosis in the family, the pedigree, and copies of any genetic testing performed. In addition to providing this to the immediate family members of the decedent, it is helpful to provide a shorter letter the family may distribute to other at risk family members explaining what type of cardiac screening or genetic testing is available to them. There is an ethical duty to warn these relatives, though there might not be a legal duty. The ethical duty to warn exists because there is a risk to the relative, and they might want to know of this risk. Since the information pertains to the decedent, there is no breach of confidentiality, unlike a case of a living patient who refused to let relatives be informed. While genetic testing on a deceased individual could legally be performed as part of the investigation of sudden death, it is ethically preferable to provide genetic counseling before any genetic testing is done. From a public health perspective, data are emerging that supports the cost-effectiveness of testing at risk family members in some scenarios (30).

CONCLUSION

Genetic counseling in postmortem cases requires expertise and is usually a long process involving collection of documents and materials, input from different healthcare providers, and communication with multiple family members. Numerous resources are available to assist medical examiners and coroners in assisting decedent's families with genetic counseling consultation (**Table 1**). Genetic counselors are an integral part of the healthcare team in the evaluation of a young sudden cardiac death case. Included in the team would also be medical examiners/coroners, family doctors, cardiologists, pathologists, genetic testing laboratories, and geneticists. Genetic counselors have training and experience working with different disciplines and with families in a time of grief making them a uniquely qualified resource to coordinate the many pieces involved in the work-up of young sudden death cases.

DISCLOSURES

The authors, reviewers, editors, and publication staff do not report any relevant conflicts of interest.

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