Family Screening After Sudden Death in a Population-Based Study of Children

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abstract

BACKGROUND AND OBJECTIVES: Clinical evaluation of first-degree relatives of sudden death in the young (SDY) victims is recommended but reports of familial evaluation after SDY in population-based studies are limited. The SDY Case Registry is a prospective registry of sudden deaths in infants and children from multiple United States jurisdictions. Our objective was to describe familial evaluation after sudden death in this cohort.

METHODS: Family members of the SDY Case Registry were invited to participate in the family substudy. Consented participants entered information about the decedent and personal medical history into an electronic database. First-degree relatives of noninfant SDY cases were informed of published recommendations for clinical evaluation and were provided with contact information for local inherited heart disease clinics. Saliva kits were mailed to participants for DNA sample collection.

RESULTS: In total, 82 relatives of 44 SDY Registry cases (26 infants, 17 children, 1 unknown age) enrolled in the study. A copy of the medical examiner's report was obtained from 20 (45%) cases. At the time of contact, only 26% were planning to see a physician because of the sudden death of the relative. A total of 62 (76%) participants provided DNA samples, but clinical records were uploaded by only 6 (14%) families. No new diagnoses of inherited diseases were identified with family screening.

CONCLUSIONS: In a population-based registry of SDY, we found rare uptake of family evaluation, despite published recommendations. Educating families, primary care providers, and medical examiners is needed, including training of personnel who can help families navigate this process.

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Dr Kannankeril conceptualized and designed the study, coordinated and supervised data collection, carried out the initial analyses, drafted the initial manuscript, and reviewed and revised the manuscript; Dr Shoemaker and Ms Fountain conceptualized and designed the study, designed the data collection instruments, collected data, and reviewed and revised the manuscript; Drs Roden, Yandell, Tristani-Firouzi, Etheridge, Webster, George, McNally, Burns, and Ms MacLeod critically reviewed the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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WHAT'S KNOWN ON THIS SUBJECT: Sudden death in the young (SDY) is rare but devastating. Clinical evaluation of first-degree relatives of SDY victims is recommended to identify at-risk relatives. Reports of familial evaluation after SDY in US population-based studies are limited.

WHAT THIS STUDY ADDS: In this cohort, few families sought medical care after SDY in their relative despite published recommendations. Public health efforts should focus on provider and family education to recommend screening to families and consider use of navigators to facilitate this process.

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Sudden death in the young (SDY) is a tragedy that has a devastating effect on families and communities and has been identified as a critical public health issue by the National Institutes of Health (NIH) and international medical societies.[1–3] In young people aged 1 to 35 years, many sudden cardiac deaths are caused by potentially inherited heart diseases, including primary arrhythmia syndromes and cardiomyopathies.[2] Clinical evaluation of first degree relatives of (noninfant) SDY victims is recommended,[2,4] as familial disease has been identified in one-third to one-half of families of unexplained sudden death (SD) victims evaluated at expert inherited arrhythmia clinics.[5,6] Reports of familial evaluation after SDY in US population-based studies are limited and may present a different set of challenges.

In 2015, the NIH and the Centers for Disease Control and Prevention created the SDY Case Registry to determine the incidence of SDY in the United States using population-based surveillance, collect data from SDY cases and DNA samples for research, and support families by providing resources for medical evaluation of surviving family members.[7] Data from the first 2 years of the registry reveal an SDY rate for infants (<365 days) of 120 of 100 000 live births and an SDY rate for children (1–17 years) of 1.9 of 100 000 children.[8] In April 2016, the NIH funded 3 academic medical centers to perform cooperative research using data and DNA samples from the SDY Case Registry. In addition to analysis of DNA samples (reported separately), these centers collaborated to facilitate familial evaluation for relatives of decedents from the SDY Case Registry through the SDY Family Substudy. The results illustrate contemporary challenges to familial evaluation after SDY in children in population-based studies.

METHODS

The SDY Case Registry attempts to identify all SDY cases from birth to 20 years among residents of multiple US states and jurisdictions.[7] During the time of the Family Substudy, the participating states were Delaware, Georgia, Minnesota, New Hampshire, New Jersey, Tennessee, and Nevada (2016 only); the jurisdictions were Virginia (cities including Hampton, Newport News, Norfolk, and Virginia Beach); Wisconsin (Fond du Lac, Forest, Kenosha, Milwaukee, Oneida, Racine, Vilas Waukesha, and Winnebago counties); and California (San Francisco county). Cases were identified through medical examiner and coroner systems in each state and jurisdiction. Detailed phenotyping was performed for cases of cardiac SDY, unexplained infant and child death, and sudden unexpected death in epilepsy (SUDEP), with more limited data gathered on other explained SDY cases. Surveillance activities in the SDY Case Registry were classified as public health practice and did not require institutional review board approval. Registry activities involving biospecimen collection and consent of surviving family members for research were approved by the institutional review boards at the Data Coordinating Center (Michigan Public Health Institute, MPHI) and participating states and jurisdictions. DNA was extracted from blood or frozen tissue samples and stored at the SDY Case Registry Biorepository at the University of Michigan. In cases where consent was obtained, an MPHI DNA sample number was assigned and made available for research, and results of sequencing these cases will be reported separately. Data collection for the registry began in 2015. In April 2016, the NIH funded 3 academic medical centers (Northwestern University, University of Utah, and Vanderbilt University) to perform cooperative research using data and DNA samples from the SDY Case Registry. These centers collaborated to perform the SDY Family Substudy.

The SDY Family Substudy was created to serve as a biorepository to collect clinical information and DNA to advance the knowledge of the clinical care and evaluation of surviving family members of the SDY Case Registry decedents. The protocol was approved using a single institutional review board for multisite studies by the Vanderbilt University Medical Center Institutional Review Board in October 2016. The contact information for one individual per family who agreed to be contacted by researchers as part of the SDY Case Registry consent process was provided to the family substudy team by the SDY Case Registry Data Coordinating Center. That individual was contacted by phone or sent an institutional review board-approved script by e-mail inviting participation in the family substudy. Contact was attempted every 2 weeks, up to 3 times, unless the individual consented to the study or replied that they did not wish to participate. In 2020, re-contact by e-mail was attempted for individuals who had not previously responded between 2016 and 2019, to allow them to reconsider participation after time had passed since the death in the family. Informed consent was obtained electronically from adults, and consent or assent was obtained from parents and children as appropriate. Individuals who consented to the substudy had the option of allowing the MPHI DNA sample number from the SDY Case Registry to be provided to the investigators, thereby enabling

linking of the decedent's sample to samples obtained from surviving family members. The detailed phenotyping collected as public health practice for the SDY Case Registry was not made available for the SDY Family Substudy due to privacy regulations in place across various states and jurisdictions; however, phenotype information on the case and the family members could be collected directly from the family with permission.

Once individuals consented to participate in the family substudy, they entered information about the decedent and personal medical history into an electronic database (REDCap).[9] They were also asked to provide contact information for additional family members, who would then be contacted and approached for consent or assent as described above. First-degree relatives of noninfant SDY cases were informed verbally and in writing of the published recommendations for clinical evaluation and provided with contact information for local genetic counselors and inherited heart disease clinics. A guidance document with published recommendations regarding appropriate clinical evaluation that could be shared with their local health care teams was provided as well (Supplemental Information, Supplemental Fig 1). Participants in the family substudy were provided the opportunity to upload medical records via REDCap for expert review by SDY investigators and offered teleconference with inherited heart disease experts. Saliva collection kits were mailed to consented family members for DNA sample collection and returned to the biorepository at Vanderbilt University for long-term storage and potential commercial or research genetic testing according to the participant's wishes. Overall, results and case studies that illustrate outcomes in post mortem evaluations are presented here.

RESULTS

Demographics and Participation

Between 2016 and 2020, the contact information for a family member from 94 unique SDY Registry cases was provided to the study team. Of those, 44 (47%) consented to the family sub study. In 2020, 41 individuals who did not respond to the initial series of 3 attempts were recontacted by e-mail; only 3 consented to the study. While those 3 individuals completed the consent form, they provided no additional information, and are not included in these results. In total, 82 unique relatives of 44 SDY cases consented to the study. Of the 44 cases, 26 were infants (<1 year of age) and 17 were children; age of the decedent was not provided by 1 family. Death occurred during sleep in 22 (85%) infants and 7 (41%) children. Only 1 infant and 2 children had a history of seizures. A copy of the medical examiner's report was obtained from 20 (45%) cases, 11 (42%) infants and 9 (53%) children. In 2 children, the family had been told the deaths were possibly explained due to viral myocarditis (1) and a ruptured cerebral arteriovenous malformation (1); in neither case was the medical examiner's report available.

The 82 participants enrolled in the family substudy were predominantly female (68%) with a median age of 30 years (range 1–61, interquartile range 24–39). Race and ethnicity were requested per NIH guidelines and self-reported as ethnicity: 6 Hispanic, 70 nonHispanic, 6 chose not to answer; Race: 64 White, 6 Black/African American, 2 American Indian/Alaskan, 1 Asian; 9 chose not to answer. Of the 70 participants who answered the question: "Do you have a doctor that will be seeing you in clinic to evaluate you because of the sudden death of your relative?" 18 (26%, 9 relatives of child SD and 9 relatives of infant SD) responded "yes." A total of 62 (76%) participants provided DNA samples.

Case Examples

We provide details for 6 families, which illustrate the wide variety of outcomes in post mortem evaluations. These include the relatives of 4 child and 2 infant SDYs. We provide examples of an entirely nondiagnostic phenotype and genotype workup (family 14 and 43), but also an example of sudden death with a positive family history but negative post mortem genotyping (family 2), an example of a family history with findings of uncertain significance, not likely to be related to the child's death (family 38), and 2 examples where environmental factors may have contributed to the death, but a definitive cause of death could not be assigned.

Family 2 was related to a female 12-year-old SDY Registry case who was found dead in bed. The decedent had a single seizure 5 months before death. A baseline ECG obtained as part of her seizure evaluation was normal. A complete autopsy with microscopic evaluation of the heart was performed with no cause of death identified. A post mortem sample was sent for commercial genetic testing (Invitae Arrhythmia panel, 37 genes) with no pathogenic variants identified. Both parents enrolled in the family substudy and provided DNA samples. Her mother provided an ECG that was normal. Her father had been previously diagnosed with dilated cardiomyopathy and had a primary prevention implantable cardioverter-defibrillator before his daughter's death. He has not undergone genetic testing for

cardiomyopathy. A sibling did not enroll in the family sub study but was evaluated at an expert inherited heart disease clinic and had a normal ECG, echocardiogram, and exercise treadmill test, all of which were uploaded into the study database and were reviewed by investigators.

Family 14 was related to an 18-month-old female SDY Registry case with a history of febrile seizures who was found unresponsive in bed. She was initially resuscitated and transported to a local hospital but suffered severe neurologic injury and care was withdrawn the following day. She had a normal echocardiogram and mild QT prolongation on ECG (QTc 460 ms) felt secondary to post arrest changes. Before death, a sample was sent for commercial genetic testing (GeneDx Arrhythmia Panel, 30 genes) and no pathogenic variants were identified. A complete autopsy was performed, with cause of death listed as "anoxic brain injury due to cardiopulmonary arrest of undetermined etiology." Her mother provided a DNA sample, but no other personal medical records. Three siblings were evaluated locally with normal ECGs and echocardiograms; these were uploaded and reviewed by investigators, and DNA samples were obtained in all siblings.

Family 38 was related to a 16-year-old female who collapsed while going to the bathroom. Resuscitative efforts were unsuccessful. A complete autopsy including microscopic examination of the heart was normal, and the cause of death was "probable cardiac dysrhythmia." Both parents consented to the family substudy and were already under the care of cardiologists. Her father uploaded an echocardiogram showing mild left ventricular hypertrophy (most likely secondary to systemic hypertension) and provided a DNA sample. Her mother uploaded a normal echocardiogram, nuclear study, and ambulatory monitoring.

Family 43 was related to a 19-year-old male who was found dead in bed. A complete autopsy including microscopic examination of the heart was normal, and the cause of death was undetermined. His mother uploaded a normal ECG and provided a DNA sample. Medical records (but no DNA sample) were provided for his brother (2 normal ECGs) and his sister (normal ECG, exercise treadmill test report, and echocardiogram).

Family 8 was related to a 5-month-old girl with distal arthrogryposis (multiple joint contractures) who died in her sleep. A medical examiner's report was available and ruled the death as sudden unexpected death in infancy with unsafe sleep position. She had been previously seen by a pediatric cardiologist and had a normal ECG and echocardiogram. A post mortem sample was sent for commercial genetic testing (Invitae Arrhythmia panel, 37 genes) with no pathogenic or likely pathogenic variants identified. Her mother provided a DNA sample.

Family 10 was related to a 4-month-old boy who died in his sleep. A medical examiner's report was available and labeled the death as "probable asphyxia due to suffocation." His father had a normal ECG and echocardiogram (obtained during a previous hospitalization for trauma). Both parents sent DNA samples.

DISCUSSION

Clinical evaluation of first degree relatives after unexplained SD in children is recommended due to the potential for identification of familial disease, and therefore, initiation of risk-reducing therapy in affected relatives.[2–4] Previous studies of these individuals evaluated in expert inherited heart disease clinics have yielded diagnoses of heritable condition in 10% to 53%.[5,6,10] Systematic protocols for testing family members have resulted in an increasing yield of diagnoses, from 22% using ECG and echocardiography, with discretionary use of exercise tests and Holter monitoring,[11] up to 42% when provocative testing is added systematically.[12] In contrast to these referred patient populations, familial evaluation after SDY in population-based studies is much more challenging. Families that seek medical attention at inherited arrhythmia clinics are to some degree self-selected, more engaged with the medical team, and more amenable to cardiac evaluation and recruitment of additional family members. We found that fewer than one-half of the families contacted from the SDY Registry consented to the family substudy; only 26% were planning to see a physician due to the family history of SDY, and just over 10% provided clinical data. Given this low uptake, it was not surprising that no new heritable conditions were diagnosed. Family studies after SDY can reveal uncertain and even discordant findings in relatives.[10] Furthermore, the complexity of family members having to seek care and coordinate results across both pediatric (for siblings) and adult (for parents) providers can be dismaying, particularly for families who have suffered the unexpected loss of a child.

The low utilization of family screening in this study was likely further hampered by the high inclusion of SDY in infants. In the SDY Registry cases, 78% are infants,[8] and familial evaluation is not routinely recommended after

infant SD. A previous study that attempted family evaluations after infant SD also reported low participation and numerous families who "did not wish to engage or did not reply to messages or attend appointments."[13] However, even among the noninfant SD cases, only 9 of 32 (28%) relatives were planning to see a physician due to the SDY in the family. Studies of SDY under 35 years of age report that family evaluation is actually recommended only 25% of the time after SDY.[14] In one previous population-based study of noninfant SDY in New Zealand, where 70% of families were clinically evaluated, it was noted "that investigation of family members often was difficult and time consuming."[15] Due to the grief families experience,[16,17] it is possible that more families would participate if they were approached by a health care provider with whom they had an existing relationship. Alternatively, a provider who is skilled in counseling and guiding family members could help facilitate family engagement and screening. Participation may also increase among families in whom a genetic variant is identified and suspected to contribute to SDY. A limitation of our study is that we did not collect specific data on why families opted for or against screening.

Families were reapproached by e-mail 1 to 4 years after initial contact in hopes that participation might increase for some families after a period of grieving. Only 3 of these 41 families consented, but none of them provided more information, despite repeated opportunities. Thus, it appears that there is little benefit in delaying attempts at research participation from individuals after SDY. If a health professional were to help families navigate the post SDY screening process, we would advocate not waiting to initiate this process, since uptake did not improve with time.

CONCLUSIONS

In conclusion, familial evaluation after SDY is challenging, with low participation rates from families despite published recommendations and access to specialized inherited arrhythmia centers. The strategy used in this population-based study was not effective at identifying inherited heart disease. We speculate that unawareness of evidence-based recommendations for family screening, deep sorrow after the death of a young child, and the somewhat detached nature of an unfamiliar research team may all contribute to low participation, among other factors. Future research on strategies to enhance participation in such efforts are required to identify, treat, and ultimately prevent SD due to undiagnosed inherited heart disease in the general population. The low uptake of family screening might improve if a knowledgeable health care provider, such as the primary care pediatrician,[3] could guide families across the pediatric and adult clinical spectrum and complexities of cardiovascular and genetic results that come from this evaluation.

ABBREVIATIONSS

MPHI: Michigan Public Health Institute
NIH: National Institutes of Health
SDY: sudden death in the young
SUDEP: sudden unexpected death in epilepsy

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