PEDIATRICS PERSPECTIVES

A New Approach to the Investigation of Sudden Unexpected Death

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Sudden unexplained death in pediatrics (SUDP) is an inclusive term for sudden deaths in children that remain unexplained by standard autopsy and death scene investigation, including sudden infant death syndrome (SIDS), sudden unexpected infant death, sudden unexplained death in childhood, and undetermined deaths. Mortality from SUDP is significant and exceeds that from either cardiac disease or cancer in children <19 years of age.[1] Its diagnostic considerations overlap with sudden unexpected death in epilepsy and unexplained sudden cardiac death in youth, also occurring predominantly during sleep, although salient findings in such cases include a history of epilepsy or notable cardiac results. Among children ultimately diagnosed with SUDP, those dying unexpectedly who are <3 years of age are the least likely to have explanations found with the current standard approach to investigation.[2]

Pediatricians have focused largely on preventive measures in the child's sleep environment and the detection of child abuse in SUDP. Achievements in research and new approaches in medical care have created possibilities for understanding unapparent biological vulnerabilities in a small child that may become lethal. Research continues to find evidence for a biological basis in SUDP,[3] including abnormalities in the hippocampus seen both across the age ranges of SUDP[4] and epilepsy. The epidemiology of SIDS is predicted by general trends in infant mortality that are themselves attributed to biological risk reduction and medical care.[5] Undiagnosed diseases programs, where living patients undergo extensive clinical evaluation to diagnose rare presentations of known diseases and identify new disease mechanisms, inform new clinical approaches to the unknown, with diagnostic rates of 25% to 50%, as do developments in epilepsy, where what was once idiopathic is now classified according to genetic findings.[6] Robert's Program on SUDP endeavors to incorporate these developments into a clinical model that systematically considers the possibility that SUDP is due to undiagnosed, possibly undiscovered, diseases in children <3 years of age. This approach promises new insights and a new role for pediatricians, including the support of affected families. Initial findings are notable for genetic variants (5 of 14), abnormalities of the hippocampus (10 of 14), the predominantly natural manner of death (11 of 14), and sibling observations (Table 1).

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Dr Goldstein conceptualized and designed the study and drafted the initial manuscript; Drs Nields and Kinney conceptualized and designed the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

DOI: https://doi.org/10.1542/peds.2017-0024

Accepted for publication Mar 20, 2017

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PEDIATRICS (ISSN Numbers: Print, 0031-4005; Online, 1098-4275).

FINANCIAL DISCLOSURE: The authors have indicated they have no financial relationships relevant to this article to disclose.

FUNDING: Clinical costs for this program are supported by donors to Robert's Program on Sudden Unexplained Death in Pediatrics, the Barrett Edward Tallman Memorial Fund, the Cooper Trewin Memorial SUDC Research Fund, the Three Butterflies SIDS Foundation, and the Nathan Lounsbury Foundation.

POTENTIAL CONFLICT OF INTEREST: The authors have indicated they have no potential conflicts of interest to disclose.

To cite: Goldstein RD, Nields HM, Kinney HC. A New Approach to the Investigation of Sudden Unexpected Death. *Pediatrics.* 2017;140(2):e20170024

TABLE 1 Summary of First 17 Cases in Robert's Program on SUDP

Age at Death	Circumstances of Death	Findings	Referrals/Follow-up	Cause	Manner
20 d	Sleep-related SUDP; placed supine; found supine	Bacterial meningitis without clinical prodrome	—	Sudden unexpected infant death in the setting of probable sepsis and early stage meningitis	Natural
21 d	Sleep-related SUDP; supine in father's arm on couch	HFM-SUDP; no anoxic changes observed	—	Sudden unexplained infant death with hippocampal malformation	Could not be determined
5 wk	Sleep-related SUDP in a car seat with nearby observers	HFM-SUDP; SCN5A variant (damaging)	Referral of parent to cardiology with positive findings	Undetermined[a]	Could not be determined[a]
6 wk	Sleep-related SUDP while being watched by a nanny; placed supine; found supine	HFM-SUDP; channelopathy variants of uncertain clinical significance on "sudden death panel" not substantiated by program analysis	Referral of parent to cardiology based on ME gene panel finding	Cardiac arrhythmia due to long QT syndrome[a]	Natural
4 mo	Sleep-related SUDP at day care; placed supine, found prone	HFM-SUDP; channelopathy variant of uncertain clinical significance	—	Sudden unexplained infant death with hippocampal malformation	Natural
4.5 mo	Sleep-related SUDP at day care; placed supine, found on side	Meningoencephalitis, without clinical prodrome; no suspicious genetic variants identified	—	Hypoxic-ischemic encephalopathy with associated perivascular inflammatory changes consistent with underlying meningoencephalitis of uncertain etiology	Natural
4.5 mo	Sleep-related SUDP at day care; placed supine, found prone	Brainstem encephalitis without clinical prodrome; enterovirus; ANK2 mutation (affected brain region versus heart)	Referral of parent and subsequent sibling to cardiology	Lymphocytic meningoencephalitis due to probable human parechovirus 1 infection	Natural
5.5 mo	Sleep-related SUDP; placed supine with pacifier, found prone	HPM-SUDP; no suspicious genetic variants identified	Birth plan developed for subsequent child	Sudden unexplained infant death	Could not be determined[a]
18 mo	Sleep-related SUDP during febrile illness. Slept prone; found prone. Family history of febrile seizures	Hamartia of the amygdala (microdysgenetic feature of temporal lobe epilepsy); no suspicious genetic variants identified	Consultation at birth of subsequent child	Sudden unexpected death of a child associated with hamartia of the amygdala and NKX2-5 mutation	Natural
19 mo	Sleep-related SUDP during febrile illness; slept prone; found prone	HFM-SUDP; respiratory tract infection; no suspicious genetic variants identified	—	Sudden unexpected death of a child with respiratory tract infection and hippocampal maldevelopment	Natural
23 mo	Sleep-related SUDP with personal and family history of febrile seizures	HPM-SUDP; no suspicious genetic variants identified	Twin sibling evaluated (case 13)	Sudden and unexpected death in childhood associated with end folium sclerosis in the hippocampus and a personal and family history of febrile seizures	Natural
2 y 6 mo	Sleep-related SUDP with history of paralyzed vocal cords, dilated aortic root, and sacral dimple/ tethered cord; slept on side; found prone	Asymmetry of hippocampus; infection; MYH11 and COL3A1 mutations	—	Sudden unexpected death of a child due to *MYH11* and *COL3A1* gene mutations and recent influenza virus (type A1H3) infection	Natural

TABLE 1 Continued

Age at Death	Circumstances of Death	Findings	Referrals/Follow-up	Cause	Manner
2 y 10 mo	Sleep-related SUDP with personal and family history of febrile seizures	Asymmetry of hippocampus; no suspicious genetic variants identified	—	Sudden unexpected death in a child with history of febrile seizures	Natural
8 y 2 mo	Sleep-related SUDP in child with repaired Chiari I malformation and seizure disorder	Asymmetry of hippocampus, focal cortical dysplasia; cytomegaly in medulla	Cardiology referral for father; cardiology referral for sibling after syncopal episode	Sudden unexpected death of a child with Arnold Chiari malformation (status postsurgical repair) associated with seizure disorder and sleep apnea	Natural
Living siblings					
NR	Surviving twin of 22-mo-old SUDP (above), both with history of febrile seizures	MRI with abnormally malrotated hippocampus and increased signal intensity consistent with deceased sibling's endfolium sclerosis	Neurology; complex febrile seizure aborted with early antiepileptic medication. Now on daily AED	NR	NR
NR	Sibling of SUDC	Onset of benign epilepsy with centrotemporal spikes. MRI with hippocampal asymmetry and inversion	Followed by neurology, on daily AED	NR	NR
NR	Sibling of SIDS	MRI with under opercularization of the bilateral Sylvian fissures and prominence of the extra-axial spaces in the frontal lobes bilaterally (also found in deceased sibling). Genetic testing for glutaric aciduria type 1 negative, as in deceased sibling	Ongoing periodic assessments in Robert's Program, in concert with general pediatrician	NR	NR

AED, antiepileptic drug; HFM-SUDP, hippocampal formation maldevelopment in SUDP; NR, not relevant; SUDC, sudden unexplained death in childhood; TLE, temporal lobe epilepsy; VUS, variant of unknown significance; —, not indicated.

[a] Medical examiner's and Robert's Program conclusions differ.

Unexpected deaths, especially in children, undergo mandated review by medical examiners. In Massachusetts, the Office of the Chief Medical Examiner (OCME) notifies the Center for Sudden Infant Death Syndrome, which in turn refers families to our program when abuse and neglect are not suspected in children <3 years of age. Collaboration between Boston Children's Hospital and the Massachusetts OCME begins once consent is obtained from parents (Fig 1). While the OCME conducts its independent autopsy and death scene investigation, clinicians in our program with expertise in neuroscience, neuropathology, neurology, pediatrics, pathology, cardiology, genetics, neuroimaging, palliative care, and bioinformatics work to diagnose diseases beyond those usually accessible through standard autopsy. Real-time collaboration circumvents many of the limitations of second opinions on completed autopsies and augments the technology and expertise available for the forensic evaluation. After a joint case conference with the OCME, a meeting is held with parents, the medical examiner, Robert's Program clinicians, and the child's general pediatrician to share conclusions. When consensus on the cause or manner of death is not achieved, differences in conclusions are explained to the parents. The medical examiner independently certifies the death. A strategy to address the family's ongoing support needs, including referrals for any medical findings, is developed. Our program is offered free of charge, with the intent of assuring the availability of advanced analytic methods based solely on need. Costs are supported by philanthropy and clinical departments because health insurance does not reimburse for deceased persons.

We investigate SUDP as the potential consequence of a number of extreme phenotypes of undiagnosed or potentially undiscovered diseases, which sometimes combine with environmental triggers and lead to death.[7] The assessment includes standardized autopsy and tissue sampling at the OCME, with an extensive neuropathology protocol. As the forensic investigation proceeds, we obtain an in-depth history with special attention to sudden death, including a comprehensive 3-generation pedigree and intensive medical record review. We sequence and analyze exomes of the deceased child and the parents, then screen

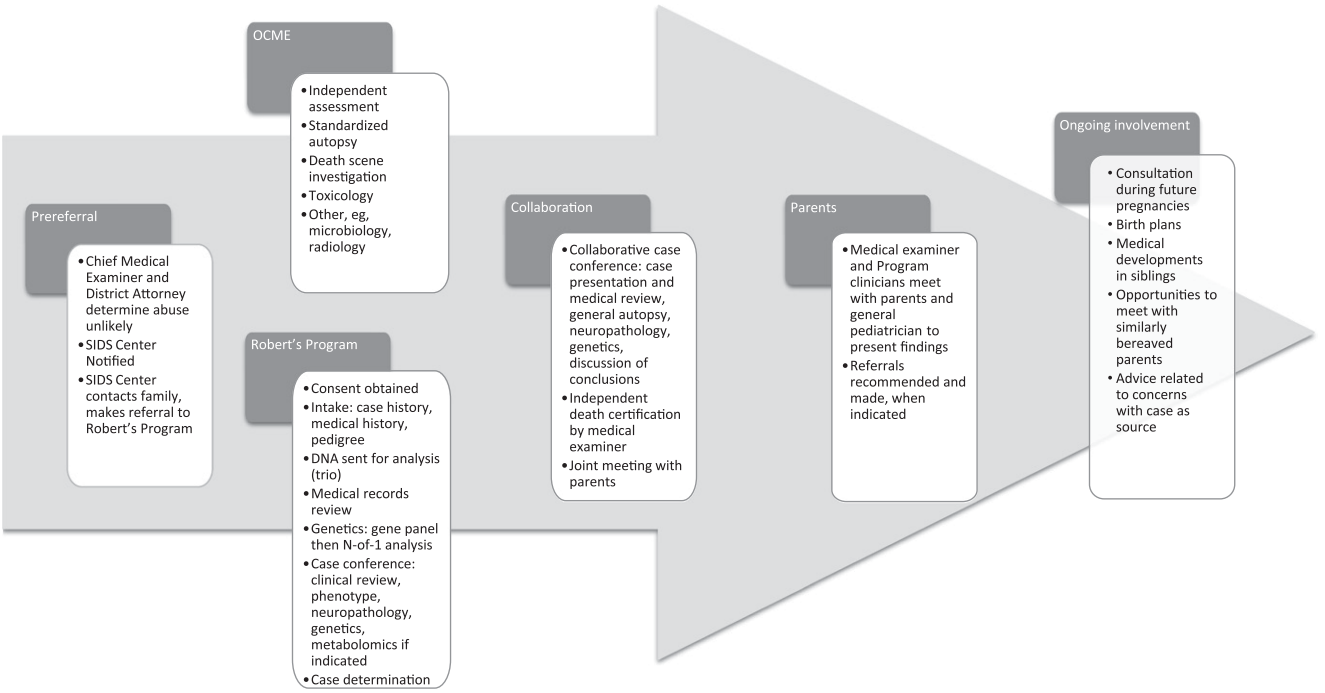

FIGURE 1
The services provided in Robert's Program and their sequence. OCME, Office of the Chief Medical Examiner.

the trios by using a formalized panel of genes and pathways previously validated as pathogenic and related to sudden death, for example, mutations implicated in cardiac arrhythmias, epilepsy, metabolic conditions, brain malformations, and other disease categories. Where indicated, imaging and advanced metabolomics are performed. The unique clinical findings, history, pedigree, and phenotype then guide additional analysis of exome trios. Plausible hypotheses for contributing vulnerabilities are considered as well as overt pathologic findings. Pathogenic variants in genes of interest are reported using American College of Medical Genetics guidelines.

Obtaining consent from acutely grieving parents during a period of unexpected loss is a difficult medical encounter at a difficult time. Parents do not want to "inflict more" on their child. The consent requirement to report any uncovered suspicions to authorities is especially complicated to introduce, given parental sensitivity to being suspected of foul play. Some parents complain that gaining a better explanation exposes them to additional legal risks at a time of strained trust, no matter how much participation is desired. Most importantly, however, parents desire to understand what has happened and whether anything may have prevented it and find the benefits of participation justify enrollment complexities.

Parents understandably seek reassurances about their other children. Consequently, we attempt to identify subclinical phenotypes identified through the deceased child, which was previously not possible. This aids the incremental evaluation of potentially contributing novel traits with new possibilities for in vivo detection, including potential biomarkers and MRI neuroimaging approximating the resolution of light microscopy. Imaging of siblings with interrelated concerns due to seizures, twinship, or incidental discoveries has been limited although highly informative when selectively performed.

Parents of these children are at extremely high risk for disordered grief, a problem largely unrecognized in pediatric offices in the aftermath of SUDP. Whatever our findings and determinations, the program encompasses a grief intervention as parents adapt to the physical absence of their child. Bereavement experiences and the medical investigation are intertwined and fluid, each influencing the other and a parent's ability to cope with their situation at any given time. Facts about how their child died and direct answers to their questions specifically address pressing concerns that complicate bereavement. Decreasing the despair and isolation that bereaved parents often report is an important therapeutic goal, and we provide opportunities to meet with other parents whose children have similarly died, while assisting those identified to be at heightened risk

for complicated bereavement. Our availability remains ongoing, and parents have reconsulted for advice at the births of subsequent children or for specific worries provoked by later infants, for example. Future research will examine outcomes.

The typical approach to SUDP rarely provides answers or capitalizes on the trusted relationships that are the hallmark of pediatrics. Our clinical interactions, if not definitive, provide important information and reassurance to families. We believe this new approach will increase the understanding of latent, biological risk and, ultimately, demonstrate benefits in disease diagnosis, risk assessment, and coping. Parents will benefit in learning results from an advanced investigation of the death, understanding the circumstances that contributed to it, and receiving counseling about prevention and support in its aftermath. We invite other clinical pediatricians and pathologists to consider our approach to this problem, in which our role is not generally considered and family needs are unmet.

ACKNOWLEDGMENTS

We thank the clinicians of Robert's Program and the Massachusetts medical examiners for their roles in creating and implementing the program. We also thank the families of Robert's Program. We thank the Massachusetts Center for Sudden Infant Death Syndrome for their assistance.

ABBREVIATIONS

OCME: Office of the Chief Medical Examiner
SIDS: sudden infant death syndrome
SUDP: sudden unexplained death in pediatrics

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Pediatrics; originally published online July 5, 2017;
DOI: 10.1542/peds.2017-0024

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OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

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