

**Robert’s Program on Sudden Unexpected Death in Pediatrics (SUDP)**

Richard D. Goldstein, MD, Director; Hannah C. Kinney, MD, Associate Director; Robin L. Haynes, PhD, Laboratory Director

*Newsletter of Research, January 2018*

**The purpose of this Research Newsletter is to inform the families of the progress of the research in Robert’s Program in the last year. We are deeply grateful for the support of this work by all, and we are excited to inform you of its progress.** Please call us or email us if there are questions or comments:

***Telephone: (617) 919-4513; email: Robertsprogram@childrens.harvard.edu***.

**Background**. Sudden and unexpected death is an under-recognized but serious health concern affecting infants and children worldwide. A seemingly healthy child dies without warning or explanation, leaving parents and clinicians stunned and grief-stricken. Sudden unexpected death encompasses sudden infant death syndrome (SIDS), sudden unexplained death in childhood (SUDC), sudden cardiac death in youth (SCDY), and sudden unexpected death in epilepsy (SUDEP). Each year in the US, approximately 3,500 infants less than one year old succumb to SIDS—the disorder alone accounts for more deaths in children than pediatric cancer or cardiac disease. SUDC accounts for the largest percentage of sudden and unexpected deaths in children over one year of age—more than deaths attributed to known natural causes of unexpected childhood death, including infection and cardiac disease. The alarming severity and frequency of these disorders combined with the immense toll they have on families led to the establishment of Robert’s Program on Sudden Unexpected Death in Pediatrics (SUDP) at Boston Children’s Hospital.

Founded in July 2012 by Richard D. Goldstein, MD, and Hannah C. Kinney, MD, Robert’s Program is a first-of-its-kind initiative that takes a comprehensive and multidisciplinary approach to discovering the causes of sudden and unexpected death in children, and provides support and advocacy services for families. Dr. Goldstein, a pediatrician with community-based SIDS experience and an expert in palliative care and parental bereavement, and Dr. Kinney, a pediatric neuropathologist and expert in brain disorders of childhood, have devoted their medical careers to the study of sudden and unexplained death in children. **The mission of Robert’s Program is to translate basic research from a range of scientific and medical disciplines into helping families understand what happened to their child.** The program also seeks to provide emotional support to the parents and families in the wake of a devastating loss, with the goal of developing interventions to ameliorate grief and provide novel means for coping. We also aim to train early career scientists in SUDP research. Donations to the program have helped fund students at different levels who participate in and perform this research.

**Robert’s Program is comprised of a group of multidisciplinary investigators and trainees. Our team includes experts in neuroscience, neuropathology, neurology, biochemistry, pediatrics, pediatric pathology, cardiology, epilepsy, forensic pathology, genetics, neuroimaging, palliative care, and biostatistics working together in SUDP research**. Through collaboration, we perform the research projects that are ongoing in the laboratory and under the auspices of the Research Registry. Our work is funded by NIH grants, as well as grants from private SIDS foundations and individual donors. **Preventing sudden childhood death is our over-riding goal.**

1. **Translational Research through the Massachusetts Program**

**Our clinical cases allow for in-depth assessment, family based insights and potential findings of importance to parents and siblings.** Our first publication from the clinical program included a description of our approach to examining sudden death as a biological problem and not merely an accident. It included our initial case series. Explanations of our approach to genetics, the development of our gene panel, and our model of bereavement support are in development. We will also be announcing newly discovered genes that are proving to be important in SUDP.

1. **The Research Registry in Robert’s Program**

* **We have developed a Research Registry for analysis by the clinicians and scientists at Boston Children’s Hospital in the program to evaluate nationally and internationally referred cases of sudden and unexplained death in infants.** Detailed information is collected and reviewed by our multidisciplinary team. The Co-Directors of Research in Robert’s Program are Drs. Hannah Kinney and Susan Dymecki.
* **In the Research Registry in Robert’s Program, we take a different, more broad approach in which we cast a wide net to attempt to define causes of SIDS that may or may not involve the brain.** The major hypothesis in the research in Robert’s Program is that unexplained death in infants is caused by undiagnosed diseases, either completely undiscovered and extreme (lethal) diseases, or known diseases presenting in a previously unrecognized lethal fashion. Research is based on the premise that through careful characterization of individual cases, thoroughly reviewing patient medical records, collecting detailed family pedigrees, and performing pathological examination and genetic testing, underlying biological disorders will be discovered in a large percentage of cases. New rare diseases will be determined, as well as new presentations of known rare diseases. These new diseases likely include the disorders of the central homeostatic network in the brain that protects against life-threatening challenges (see below). Research in Robert’s Program relies on its case registry, which has an important role in the future testing of new hypotheses, and helps to accelerate discovery. Clinical subtypes discovered by examining human cases of SIDS generate hypotheses about its causes that can be studied in the basic science laboratory. Several different clinical patterns (phenotypes) of sudden unexplained infant death have begun to emerge in this research that are being actively pursued by Robert’s Program. To research the different hypotheses ongoing in the Research Registry takes time to accrue a sufficient sample to establish statistically meaningful relationships and patterns in SUDP. A single research project takes one to five years to complete. We have now registered almost 100 cases into the program, and we are open to continuous referrals for the program. Any findings that might affect medical or genetic care of the child’s family are reported to both the family and the family’s physician. Otherwise, the data are used for research purposes.
* **Grief Research**
* **Sudden unexpected death carries an enormous burden on the future lives of affected families. Robert’s Program aims to determine which parents carry an increased risk of more extreme and disabling grief**. Once the research accomplishes the means to identify those most at risk, Robert’s Program plans to develop interventions to assist identified families and bring new attention in aiding with the coping process. Dr. Goldstein in Pediatric Palliative Care directs this research. We have begun implementing parent support groups and will use research findings to directly help families cope with their loss.
* **Project**: **To determine if SIDS and SUDC infants with hippocampal pathology in the dentate gyrus have variants (mutations, polymorphisms) in genes that are related to epilepsy, including temporal lobe epilepsy, and/or hippocampal maldevelopment using whole exome sequencing.** We are examining the genetic basis of SIDS-HPM (hippocampal malformation) as an entity potentially related to epilepsy, treating each case as an undiagnosed disease with epilepsy-related neuropathology. Our colleagues in pediatric neurology, Dr. Ann Poduri, and genetics, Dr. Ingrid Holm, are involved in this work. Genomic DNA samples taken at autopsy from SIDS infants, as well as available living family members, are analyzed. Known genes linked to sudden death, epilepsy, temporal lobe epilepsy, and dentate gyrus development are analyzed for genetic variants. Variants deemed pathogenic or likely pathogenic in the SIDS-HP are confirmed using different sequencing techniques. The opportunity to combine strong clinicopathologic data from the infants in parallel with exome sequencing has future promise of being combined with functional analysis of identified mutations in experimental systems, the latter intended for future work by our group
* **Curated gene list. We developed a list of genes to be used in the screening of sudden unexpected death in any child, incorporating genes implicated in sudden death due to many causes.** This panel is the most comprehensive gene panel available, and will report critical information of potentially heritable factors involved in sudden death. We are in the process of determining the operating characteristics of the panel. Once achieved, we will make this panel available in the evaluation of all cases of sudden death in children. The panel has continuously been assembled and revised since the opening of Robert’s Program, and is used daily. It is continuously revised to incorporate new discoveries. This work is a joint effort of the investigative team of Robert’s Program.

**II. Ongoing SUDP research in the laboratory**

* **SIDS Research**
* **The mission of our SUDP research program in the laboratory is to determine the role of the brain in causing sudden, unexpected, and unexplained death in infants**. We are in search of brain abnormalities that contribute to sudden infant death, as well as their causes. Once the nature of the brain abnormalities and their cause(s) are determined, it will then be possible, we believe, to devise the means to: 1) identify living infants and children at risk with diagnostic tests, preferably in the newborn period; and 2) to develop interventions to prevent the deaths. Several of the projects are related to sudden unexplained death under a year (e.g., SIDS), some to sudden unexplained death over a year (SUDC), and some to both because in the latter circumstance, we have found shared hippocampal pathology in children dying before and over a year.
* **The overall hypothesis of our research in SIDS in the laboratory is that SIDS, or a subset of SIDS, is due to an abnormality in the network of brain circuits that protect against life-threatening stresses during sleep in a critical developmental period (the first year of life).** This brain network is called the “central homeostatic network”, and consists of multiple different structures in the brain that are integrated together by interconnecting pathways. This network orchestrates coordinated responses to dangerous bodily threats during sleep, such as low oxygen (hypoxia), high carbon dioxide (hypercarbia), hypoxia and hypercarbia combined (asphyxia), overheating, and sudden changes in blood pressure. These threats may complicate unsafe sleep environments, such as face down/prone sleep position, soft bedding, sofas, and adult beds.
* **The central homeostatic network acts like an internal   
  “alarm system” that is triggered by hypoxia or other stresses during sleep**. When triggered, this alarm system sets in motion protective defenses against the stressors. Such defenses are arousal from sleep and turning the head to the side for fresh air from the face down position in soft bedding. If an infant has a defect in this alarm system (that is, in the central homeostatic network), he/she may not be stimulated internally to wake up, but rather, may undergo repeated stresses and ultimately go on to die in his/her sleep from the progressive hypoxia or other stress.
* **Over the last two decades, our laboratory has provided compelling evidence of defects in SIDS cases in the two major components of the alarm system or central homeostatic network--the lower brainstem and the hippocampus (the latter structure located on each side of the cerebral hemispheres above the brainstem).** Our laboratory has provided evidence in four independent datasets of tissue defects indicating dysfunction of the neurotransmitter serotonin in the medulla oblongata (lower brainstem) involved in protective responses to life-threatening challenges during sleep in about 40% of SIDS infants. These serotonin defects include significantly *decreased* levels (~26%) of 5-HT itself in SIDS cases compared to age-adjusted controls, as well as abnormalities in serotonin receptors and serotonin’s biosynthetic enzyme. In 2015, we then reported a second new finding, from light microscope studies in a key portion of the hippocampus, called the dentate gyrus. The dentate gyrus defect was present in a major subgroup of SIDS cases (~40%). This structural abnormality in the dentate gyrus has been reported in some patients with temporal lobe epilepsy, suggesting the possibility that SIDS deaths may involve seizures originating in the hippocampus and affecting the autonomic nervous system as a major stress. The brainstem is interconnected with the hippocampus, and each structure influences the function and organization of the other, with brainstem influences upon hippocampal development as well. The laboratory work is done in a long-standing collaboration with the Office of the Medical Examiner, San Diego, CA, and the program coordinator of SIDS research there, Ms. Elisabeth A. Haas, MPH.
* **Our ongoing goal is to** discover potential new abnormalities in the brainstem and other brain sites that, in conjunction with serotonin, contribute to the chain of events that lead to sudden infant death in SIDS. We want to know the molecular and biochemical basis of the different serotonin abnormalities that we have reported on SIDS. We are currently using “omics” methodologies to simultaneously screen large numbers of messenger RNA (transcriptomics) and metabolites (metabolomics) for abnormalities in SIDS infants compared to control infants dying of known causes. Through the use of such screening techniques, we will gain insight into the molecules that cause the dysregulation in serotonin factors and into pathological changes beyond what we currently know of SIDS pathology. This information will provide new clues as to abnormal proteins, metabolites, and/or metabolic pathways that may ultimately serve as new targets for SIDS intervention. Dr. Haynes oversees this research.
* **SELECTED PUBLICATIONS**
* **WITH ROBERT’S PROGRAM INVESIGATORS AS AUTHORS**
* **In 2017**
* ***Haynes, HL, Frelinger AL 3rd, Giles IK, Goldstein RD, Tran H, Kozakewich HP, Haas EA, Germits AJ, Mena OJ, Trachtenberg FL, Paterson DS, Berry GT, Adeli K, Kinney, HC, Michelson SD. High serum serotonin in sudden infant death syndrome. Proc Natl Acad Sci USA 2017; 114; 7695-7700.***
* **One of our main goals is to discover a biomarker of infants at risk for SIDS due to brainstem serotonin and/or hippocampal defects.** Here, a **biomarker**, or **biological marker**, refers to a biochemical or molecular substance whose detection indicates a particular disease state. To be diagnostically useful, biomarkers are derived from readily accessible bodily fluids, such as serum or blood, even if the disease process is centered in another organ site, such as postulated in the brain in SIDS (see above). Work in our laboratory has established important differences in SIDS infants, consistent with an underlying vulnerability in the brainstem and hippocampus that makes certain infants susceptible to SIDS. There is also substantial evidence that death in SIDS is preceded by *undetectable* dysfunction in respiratory and autonomic control and sleep-wake pattern, including episodic apnea and bradycardia (decrease in heart rate). Currently, there are no biomarkers for SIDS risk in living infants. a major problem given that the death occurs suddenly, without warning, and unwitnessed in seemingly healthy infants. To reach this goal, an association of a candidate biomarker with a pathologic process must first be established. Here we demonstrate increased serum serotonin levels in a subset (31%) of SIDS infants compared with control infants. These findings suggest the potential of a high serum serotonin level as a forensic biomarker at autopsy to differentiate SIDS deaths with serotonergic defects from other causes of sudden death and, importantly, as evidence of a peripheral 5-HT abnormality in SIDS. Dr. Haynes oversees the biomarker research in the laboratory.

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

**This manuscript describes the rationale, goals, approaches, and initial findings in Robert’s Program.** 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 including abnormalities in the hippocampus seen both across the age ranges of SUDP 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. Undiagnosed disease 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. 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, abnormalities of the hippocampus, the predominantly natural manner of death, and sibling observations.

***Goldstein IS, Erickson DJ, Sleeper LA, Haynes RL, Kinney HC. The lateral temporal lobe in early human life. J Neuropathol Exp Neuol 2017; 76; 424-438.***

We have recognized abnormalities of the temporal lobe, including the lateral temporal lobe in SIDS and SUDC in a spectrum of temporal lobe abnormalities associated with sudden unexpected death. Yet, more normative data are needed for a better understanding of gyrification in this brain region. Here we establish initial guidelines for the analysis of the lateral temporal lobe in early life. We present quantitative methods for measuring gyrification at autopsy using photographs of the brain and simple computer-based tools in a cohort of 28 brains ranging from 27 to 70 postconceptional weeks (end of infancy). We provide normative ranges for different indices of gyrification and identify a constellation of qualitative features that should also be considered in these analyses. The ratio of the temporal area to the whole brain increased dramatically in the second half of gestation, but then decelerated after birth before increasingly linearly around 50 postconceptual weeks. Tertiary gyrification continued beyond birth in a linear process through infancy with considerable variation in patterns. Analysis of 2 brains with gyral disorders of the temporal lobe demonstrated proof-of-principle that the proposed methods are of diagnostic value. These guidelines are proposed for assessments of temporal lobe pathology in pediatric brains in early life, including in SIDS and SUDC.

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***MESSAGE FROM HANNAH KINNEY, MD***

I’d like to take this opportunity to announce my retirement on March1, 2018 at the age of 69 years. Robert’s Program will continue under the direction of Dr. Richard (Rick) Goldstein, and the Laboratory Director, Dr. Robin L. Haynes. The team members remain the same, with the addition of a promising neuropathologist who will continue and expand upon my work. I will continue in a consulting/counseling role as an emeritus professor.

Robert’s Program will continue to build upon the contributions of the group and myself. I am amazed by the new ideas and enthusiasm of our group, and feel confident about the future. We will depend as always on the continued insights of the families in Robert’s Program into the future. I thank all of you and others connected with Robert’s Program who have taught me so much, and whose courage has inspired me daily. Thank you for all your gracious and generous support and help over the years. I will continue to think about the problem of sudden death in children, and work in any way I can to help eradicate it.

Sincerely,

*Hannah*