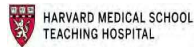


After SIDS, SUID, or Undetermined: A diagnostic service for parents wanting to know more

Richard Goldstein, MD, Ann Poduri, MD, MPH, Sanda
Alexandrescu, MD, Catherine Brownstein, PhD, Gerard
Berry, MD, Ingrid Holm, MD, MPH
Robert's Program on Sudden Unexpected Death in Pediatrics
Boston Children's Hospital, Harvard Medical School



Objectives

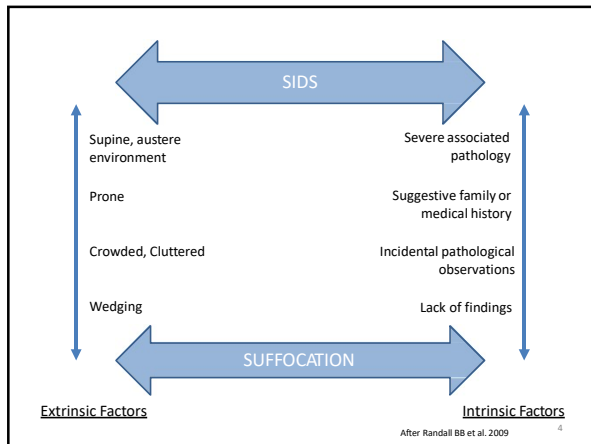
- Describe new developments in the explanation of sudden unexpected death in pediatrics
- Define the undiagnosed diseases diagnostic approach of Robert's Program for sudden, unexplained natural deaths in children and infants under age three years
- Understand case illustrations demonstrating undiagnosed genetic, neurologic, cardiac and metabolic diseases

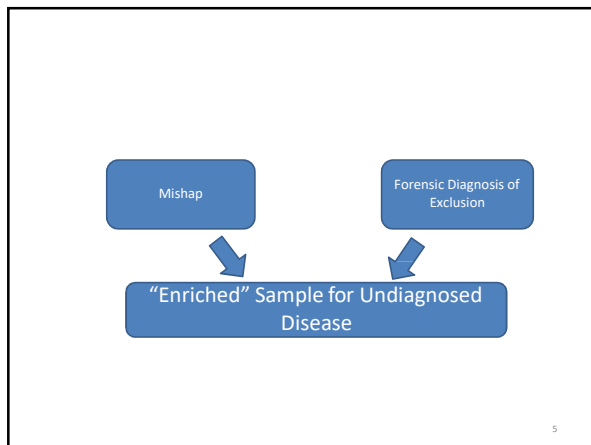
2

A 3-month-old boy was found dead in its crib, face up (supine). He was clad in a dry diaper and a thin blanket covered the body but not the head or face. The infant was born at term and there were no prenatal or postnatal medical conditions. The home was well cared for. There was nothing in the crib or at the scene that suggested a possible external cause of death or contributing factor. This was the parents' first child. A complete autopsy was performed which showed no abnormalities, histology showed normal organs, and toxicology tests for alcohol, drugs of abuse, and therapeutic drugs were negative. The office could not afford to have testing performed for genetic cardiac abnormalities. A routine metabolic screen was negative. (377 respondents)

a. SIDS	35.8%
b. SUID	33.4%
c. Undetermined	15.1%
d. Suffocation	0.5%
e. No response	6.3%
f. SIDS versus SUID	4.2%
g. Defer to pathologist	4.5%

Variations in Cause-of-Death Determination for Sudden Unexpected Infant Deaths,
Shapiro-Mendoza et al, Pediatrics 2017





Extreme phenotype: lethal presentation of sleep-associated death in a seemingly well infant

SUDP represents heterogeneous phenotypes expressing rare variants with severe negative selection pressure

6



- Sudden unexplained death as a clinical problem
- Collaboration between medical examiners and Robert's Program, sharing expertise and resources
- Comprehensive, state-of-the-art evaluation
- In depth phenotyping informs the genetic analysis of a heterogeneous, multifactorial condition
- Goal is explanation to the greatest degree possible

7

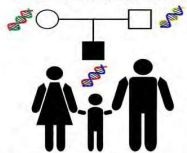
Robert's Program on SUDP – Undiagnosed Disease Network (UDN) Approach to SUDP



UDN Participants evaluated: 735
UDN Participants diagnosed: 198
27%

**Living patients typically sought
diagnosis for over 6 years**

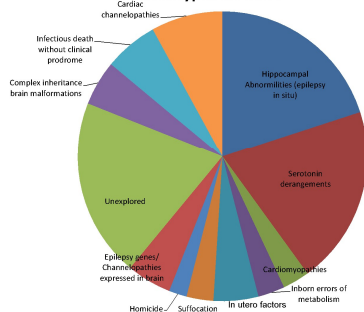
Human Genetics & Genomics



- ☐ Deep clinical phenotyping
- ☐ Next-generation sequencing
- ☐ Variant filtering, prioritization
- ☐ Search for matching cases

8

Phenotypes for SUDP



9

Beyond Determination of Manner of Death

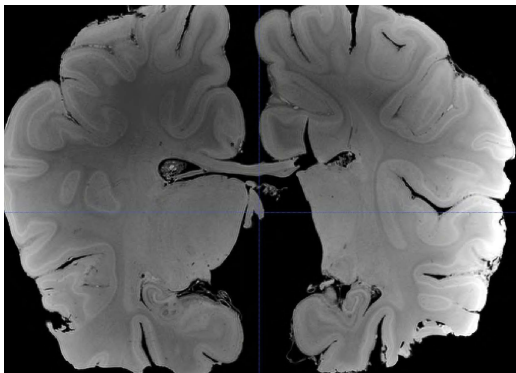
- Bringing advanced techniques to all cases:
 - In depth family/personal historical review
 - Consistent practice of obtaining pedigrees
 - Whole exome sequencing
 - In depth neuropathology with evaluation of brainstem and hippocampus
 - Autopsy review
 - Metabolomics when suggested

10

Available

- Proband
 - Gene panel with report
 - 254 gene panel to identify potential cause of death that is otherwise unexplained
 - Second opinions path/neuropath
- Parent-child triad
 - Medical and family history review (chart biopsy), pathology, neuropathology
 - Full genetic review with recommendations
 - “Likely suspects”, de novo, compound heterozygous, disease and history specific

11



12

- Novel presentations of known diseases
- New and rare conditions
- Estimation of heritable risk

13

Cases

14

Parents After SIDS

- Searching for a reason
 - Why did this happen?
- Searching for the logic
 - This doesn't make any sense, the baby was perfectly healthy
- Searching for meaning
 - What does this mean for my life from now on?

After Martin, 1998.

15



- Sudden unexplained death as a clinical problem
- Collaboration between medical examiners and Robert's Program
- Shared expertise and resources
- Comprehensive, state-of-the-art evaluation
- Goal is explanation to the greatest degree possible

16
