What’s New in SIDS Research?

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San Diego SIDS/SUDC Research Project

Objectives

• Certification of sudden unexpected infant death
• Neuropathology
• Newborn hearing screens and SIDS
• Cardiac causes of sudden infant death
• Other considerations
Sudden Unexpected Infant Death: SIDS - Or Not?

- SIDS
- Other Certifications Gaining Wider Currency
  - Sudden Unexpected Death In Infancy (SUDI)
  - Sudden Unexpected Infant Death (SUID)
  - Unclassified Sudden Infant Death (USID)
  - Undetermined
  - Unascertained

SIDS or Accidental Asphyxia?

- Choice between SIDS or asphyxia now centers on death scene findings
- Current scene investigative methods neither quantify nor determine the lethal certainty of potential asphyxia
- Autopsy reliably quantifying asphyxia are unavailable
- Therefore COD assignment for death certifiers is
  - An inevitable slippery slope
  - Ultimately a judgement call

SIDOr Accidental Asphyxia? Demonstration Of The Slippery Slope

- 5 pathologists blinded to one another’s reviews
- Used classification scheme estimating asphyxial risk at death scene in scene investigations descriptions
- Each pathologist assigned a cause of death (COD) to
  - Sudden infant death, cases 117
  - SIDS as Original Dx cases 83

SIDS Or Accidental Asphyxia

Results

• Death scene contributed to or caused death in

<table>
<thead>
<tr>
<th>GROUP</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>All study group cases</td>
<td>32 – 50 %</td>
</tr>
<tr>
<td>83 cases with SIDS as original Dx</td>
<td>40 – 59 %</td>
</tr>
</tbody>
</table>

• Among the 83 cases with SIDS as original Dx

<table>
<thead>
<tr>
<th>GROUP</th>
<th>RANGE</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIDS diagnosis decreased by</td>
<td>55 – 69 %</td>
</tr>
<tr>
<td>Another diagnosis plausible in</td>
<td>2 – 12 %</td>
</tr>
</tbody>
</table>


The Triple Risk Model for SIDS

0-12 Postnatal Months

Critical Developmental Period

Vulnerable infant

Exogenous Stressor

Intrinsic Risk Factors
- Male Gender
- Prematurity
- Genetic polymorphisms
- Perinatal exposure to tobacco and/or alcohol

Extrinsic Risk Factors
- Preterm birth
- Capsule position
- Bed-sharing
- Over-sleeping
- Soft bedding
- Foreseen


My Plea To Use SIDS As A Cause Of Death

• SIDS is preferable when asphyxia cannot be established with certainty and other causes ruled out
  – SIDS explicitly acknowledges the **multifactorial and simultaneous intersection** of potential asphyxia with extrinsic and intrinsic risk factors
  – SIDS does not require **precise quantification** of existent triple risk elements
• Alternative designations, e.g., SUDI, do not capture the complexity inherent in the mechanism(s) of death even though they may be exclusionary

Neuropathology and SIDS

Documented Neuropathological Abnormalities In SIDS Compared to Control Cases

- Increased serotonin (5-HT) neuron counts and density
- Decreased 5-HT levels
- Decreased 5-HT(1A) receptor binding
- Lack of excessive 5-HT degradation
- Lower tryptophan (TPH) and tryptophan hydroxylase (TPH2), a 5-HT biosynthetic enzyme, levels
- Lower 14-3-3 isoform proteins levels (influence TPH2 activity)
- Decreased γ-aminobutyric acid (GABA) receptor binding
- Lower dopamine levels
- Normal 3H-nicotine binding, except with increased ETOH consumption
Background

• SIDS
  – Heterogeneous causes
  – Intrinsic vulnerabilities and/or environmental factors
  – Numerous abnormalities already identified (vide supra)

• Neuropathology research generally focuses upon
  – Role of brain regions, particularly the brainstem, that regulate or modulate autonomic and respiratory control during sleep or transition to waking

• Hippocampus
  – Modulates autonomic and respiratory control via brainstem connections
  – Role in sudden infant death has received little attention
LEFT Hippocampal asymmetry in a 10-month-old infant boy dying suddenly

BELOW, PANEL C Focal granule cell bilamination (FGCB) in the dentate gyrus

Dentate Gyrus Abnormalities in SUID

_Hypothesis_

Focal granule cell bilamination (FGCB) in the dentate gyrus of the hippocampus is

• a variant of granule cell dispersion
• a pathologic marker in temporal lobe epilepsy
• associated with sudden unexplained infant death

Methods: Cases and Classification

• Sudden infant death cases 227
  – San Diego County Medical Examiner’s Office, 1991 - 2012
• Classification
  – Explained death cases
    • Acute hypoxic insult, e.g., drowning, intentional suffocation
    • Without acute hypoxic insult
  – Unexplained death cases
    • Death occurring in setting of safe sleep practices
    • Death occurring in the setting of unsafe sleep practices
    • Possible suffocation by history, but lacking autopsy evidence
Methods, continued

• Excluded cases
  – Dentate gyrus not orientated properly
  – Microscopic sections unsatisfactory

• Two pediatric neuropathologists
  – Hannah Kinney, Dawna Armstrong

• Blinded independent review of hippocampus
  – Cases with discordant observations reviewed together to achieve consensus

### Demographic Results

<table>
<thead>
<tr>
<th>Clinical Feature</th>
<th>Unexplained With Focal GCB, n = 47</th>
<th>Unexplained Without Focal GCB, n = 67</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Postnatal age, weeks</td>
<td>15.0 ± 7.5 (3.0–41.0)</td>
<td>16.3 ± 10.7 (4.0–51.1)</td>
<td>0.46</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>38.8 ± 2.3 (30–41)</td>
<td>37.5 ± 4.2 (25–42)</td>
<td>0.04</td>
</tr>
<tr>
<td>Postconceptional age, weeks</td>
<td>53.7 ± 6.3 (41.0–41.0)</td>
<td>53.8 ± 11.4 (37.0–91.1)</td>
<td>0.90</td>
</tr>
<tr>
<td>Male rate (%)</td>
<td>28/47 (59.6 %)</td>
<td>36/67 (53.7 %)</td>
<td>0.54</td>
</tr>
<tr>
<td>Premature birth (%)</td>
<td>5/47 (10.6 %)</td>
<td>20/67 (29.9 %)</td>
<td>0.02</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>19/47 (40.4 %)</td>
<td>32/67 (47.8 %)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>10/47 (21.3 %)</td>
<td>5/67 (7.5 %)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>10/47 (21.3 %)</td>
<td>18/67 (26.9 %)</td>
<td></td>
</tr>
<tr>
<td>Other/Unknown</td>
<td>8/47 (17.0 %)</td>
<td>11/67 (16.4 %)</td>
<td></td>
</tr>
<tr>
<td>Prone sleep position at discovery</td>
<td>21/39 (53.8 %)</td>
<td>25/57 (43.9 %)</td>
<td>0.63</td>
</tr>
<tr>
<td>Co-sleeping</td>
<td>13/47 (27.7 %)</td>
<td>26/65 (40.0 %)</td>
<td>0.18</td>
</tr>
<tr>
<td>Minor illness around time of death</td>
<td>12/47 (25.5 %)</td>
<td>13/64 (20.3 %)</td>
<td>0.52</td>
</tr>
<tr>
<td>Intrathoracic petechiae</td>
<td>16/47 (34.0 %)</td>
<td>57/67 (85.1 %)</td>
<td>0.25</td>
</tr>
</tbody>
</table>

### Neuropathology Findings

• Cases with ≥ 1 satisfactory hippocampal microscopic section
  – 157 of 227 | 69 %
  – Mean age | 2 ± 2.7 months
  – Age range | 2 - 358 days

• 4 of 157 cases with brain and/or somatic malformations excluded
  – Cases analyzed | 153

• Dentate Gyrus Focal Granule Cell Bilamination (FGCB)

<table>
<thead>
<tr>
<th>Group</th>
<th>Percent</th>
<th>n, N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unexplained</td>
<td>41.2%</td>
<td>47, 114</td>
</tr>
<tr>
<td>Explained</td>
<td>7.7%</td>
<td>3, 39 (p &lt; 0.001)</td>
</tr>
</tbody>
</table>

• FGCB often associated with other dentate developmental abnormalities reflecting defective neuronal proliferation, migration, and/or survival
Discussion

• FGCB 5½ times more common in *Unexplained* than in *Explained* SUDI cases

• FGCB may be a morphological marker of an impaired neuronal network that increases the risk of SUDI
  – due to instability of modulation of brainstem cardiorespiratory-related nuclei, or
  – by inducing a subclinical seizure in an infant predisposed to epilepsy but without a previous clinical seizure
  – may be a morphological marker that “identifies” the vulnerable infant within the SIDS triple-risk model

Discussion, continued

• Hippocampus
  – interconnected with sites in the limbic network (amygdala, insula, hypothalamus) as well as in the brainstem
  – mediates autonomic function and respiration

• Limbic network
  – very susceptible to seizure generation and propagation in temporal lobe epilepsy resulting in
  – life-threatening apnea, bradycardia SUDI
Conclusions

• Dentate lesions in many SUDI may represent a developmental vulnerability leading to
  – autonomic and respiratory instability
  – autonomic seizures
  – sleep-related death when challenged by homeostatic stressors

• FGCB recognizable in microscopic sections prepared in current forensic practice

• Future research necessary to determine the relationship between hippocampal and previously reported brainstem pathology in sudden infant death

Brainstem Serotonergic Abnormalities in SIDS

Multiple Serotonergic Brainstem Abnormalities In SIDS Compared To Controls

<table>
<thead>
<tr>
<th>Group</th>
<th>Mean ± SD</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIDS</td>
<td>148.04 ± 51.96</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Controls</td>
<td>72.56 ± 52.36</td>
<td></td>
</tr>
</tbody>
</table>

• Higher 5-HT neuron counts
• Higher 5-HT neuron density
• Lower 5-HT(1A) receptor binding site density
  – All 9 medullary nuclei involved in homeostasis
• 5-HT neuron immaturity

Paterson DS, et al. JAMA 2006;296:2124
Multiple Serotonergic Brainstem Abnormalities In SIDS Compared To Controls

- 5-HT(1A) receptor binding density in the raphé obscurus lower in male than female SIDS cases

<table>
<thead>
<tr>
<th>Gender</th>
<th>Mean ± SD, fmol/mg</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>16.2 ± 2.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Female</td>
<td>29.6 ± 16.5</td>
<td></td>
</tr>
</tbody>
</table>

- Does this explain higher SIDS male incidence?

Paterson DS, et al. JAMA 2006;296:2124

Serotonin Metabolites In Cerebrospinal Fluid In SIDS

Background

- Forensic biomarkers are needed to help differentiate SIDS from other SUDI cases
  - Such markers might have predictive value in living infants
- Multiple serotonergic (5-HT) abnormalities in brainstem nuclei that help mediate protective responses to homeostatic stressors
- But, these abnormalities can not currently be identified in living infants


Hypothesis

- Serotonin (5-HT)-related metabolites are abnormal in the cerebrospinal fluid (CSF) of SIDS infants compared with autopsy infant controls
Methods

• Cases N
  – SIDS 52
  – Non-SIDS infants 29

• CSF 5-HT levels can’t be reliably measured, < 10 pg/ml

• Therefore, CSF 5-HT related analytes were measured
  – Tryptophan (Trp), serotonin substrate
  – 5-hydroxyindoleacetic acid (5-HIAA), serotonin degradation product
  – Tyrosine (Tyr), dopamine substrate
  – Homovanillic acid (HVA), dopamine degradation product

Results

• Between the SIDS and non-SIDS groups, there were no significant differences in the levels of
  – Tryptophan (Trp)
  – 5-hydroxyindoleacetic acid (5-HIAA)
  – Tyrosine (Tyr)
  – Homovanillic acid (HVA)
Results

5-HIAA and HVA Levels Across All Groups Are Relatively Constant

- 5-HIAA - 5-hydroxyindoleacetic acid (5-HIAA), serotonin degradation product
- Homovanillic acid (HVA), dopamine degradation product
- PCA (w) – postconceptional age in weeks
- Solid circles, SIDS
- Open circles, non-SIDS group
- Resuscitated SIDS (RSIDS), grey shaded circles

Potential Study Limitations

- CSF was obtained at autopsy by two approaches, (lumbar puncture and cisternal tap)
  - Site not always specifically stated
  - Uneven concentration gradient in CSF metabolites reported in older children and adults, including at autopsy
  - Therefore, values may vary by rostral or caudal site
- Nevertheless, this putative gradient may not be present in infants, as a 5-HIAA and HVA gradient was not observed in six living infants who underwent neurosurgery for hydrocephalus

Conclusion

- 5-HIAA, HVA, Trp, or Tyr measurements can not be used at autopsy as CSF biomarkers of serotoninergic medullary pathology in SUDI
Newborn Hearing Screens and SIDS

Newborn Oto-acoustic Emission Hearing Screening Tests: Preliminary Evidence For A Marker Of Susceptibility To SIDS

OBJECTIVE
To compare the newborn transient evoked oto-acoustic emission (TEOAE) hearing screening tests of infants later diagnosed with SIDS

Dr. Daniel Rubens
Seattle Children’s Hospital
Seattle Children’s Hospital Research

METHODS
• Case-controlled study
  – 31 SIDS infants individually matched on gender, term vs. preterm age and NICU vs. well baby nursery
  – 31 newborn infants surviving first year of life
• Newborn TEOAE hearing screens compared retrospectively

Newborn Oto-acoustic Emission (TEOAE) Hearing Tests And Subsequent SIDS

RESULTS

• Right, but not left-side, TEOAE screens of SIDS infants demonstrated significantly decreased signal to noise ratios compared to healthy control infants
  – at 2000, 3000, and 4000 Hz (p<0.05)

Conclusions

• Simple non-invasive hearing screens may offer the opportunity to identify infants at risk of SIDS during the early postnatal period by revealing a unilateral difference in cochlear function

• The ability to implement preventative measures well in advance of a potential critical incident would be an important breakthrough

Newborn Hearing Screens and SIDS

Concerns

• How SIDS was diagnosed was not stated
  – 58% of a group of SIDS papers in 2005 either did not specify a SIDS definition, or used a non-standard definition
  Byard RW. J Forensic Leg Med. 2007;14:453

• Retrospective study, therefore, not predictive of risk

• Small number of SIDS and control cases

• Cochlear (hearing) function used as unproven surrogate for vestibular function
  – Vestibular, not cochlear, dysfunction might be related to SIDS

• Urged parents to follow Back To Sleep recommendations until future studies provide clarification

Krous HF, Byard RW. Early Human Dev 2008;84:371
### Hearing Screens and SIDS

**Michigan, 2004 - 2006**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Left Ear “Failure”</th>
<th>Right Ear “Failure”</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIDS</td>
<td>150</td>
<td>1.34%</td>
<td>0%</td>
</tr>
<tr>
<td>Liveborns</td>
<td>374,296</td>
<td>1.45%</td>
<td>1.18%</td>
</tr>
</tbody>
</table>

**Conclusions**

- SIDS and Liveborn infants were not significantly different
- Connection between SIDS and hearing loss unlikely
- **CDC Study Conclusion**: Relationship between SIDS and hearing screen results is uncertain; more study needed

*Farquhar LL, Jennings P. Early Hum Dev 2008;84:699*

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### Inner Ear Injury Ablates Arousal Responses To Hypoxia And Hypercarbia

**INTRODUCTION**

- Apparent association between hearing suppression on the newborn hearing test and subsequent SIDS death


- Subsequent study found that inner ear dysfunction precipitated a marked suppression of the hypercapnic ventilatory response (HCVR)


- Failure of arousal proposed as key component in SIDS

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### Inner Ear Injury Ablates Arousal Responses To Hypoxia And Hypercarbia

**OBJECTIVES**

- To assess whether inner ear dysfunction
  - weakens the hypercapnic response
  - plays a role in suppressing the arousal response to suffocating gas mixtures

*Allen T, et al. Neuroscience 2013;253:283-91*
METHODS

• Wild-type mice (n=28)
  – Intra-tympanic gentamicin (IT-Gent)
    • Bilateral or unilateral injections
    • To precipitate inner ear hair cell dysfunction
• Three control groups (n=22)
  – Intra-tympanic saline (IT-Saline)
    • Bilateral or unilateral injections
  – Intra-peritoneal gentamicin (IP-Gent)
• Hypercapnic ventilatory responses (HCVR) and arousal movements in response to severe combined hypoxia-hypercarbia (5% CO₂ in N₂) ventilation measured
  – Under light anesthesia 8 days after gent or saline


RESULTS

• Bilateral and unilateral IT-Gent-treated animals and controls behaved similarly

• Hypercapnic ventilatory response (HCVR) and arousal movements in response to severe hypoxia-hypercarbia (5% CO₂ in N₂) were suppressed in bilateral or unilateral IT-Gent-treated animals compared to saline-injected control animals


Normalized minute ventilation (nV̇min) during exposure to hypercarbia
(ratio of the peak minute ventilation compared to baseline)
Distance of arousal movements in response to severe hypoxia–hypercarbia stimulus in unilateral and bilateral IT-Gent-treated animals compared to corresponding IT-Saline and IP-Gent controls.

Representative path of movement (red lines) of individual subjects receiving either bilateral IT-saline (left) or bilateral IT-Gent (right).

Arousal onset time in response to severe hypoxia–hypercarbia stimulus in unilateral and bilateral IT-Gent-treated animals compared to corresponding IT-Saline and IP-Gent controls.
Postulated Vestibular Mechanisms And SIDS

• For balance adjustments, vestibular hair cells
  – Depolarize on the side toward which the head turns
  – Hyperpolarize on the other side

• Bilateral vestibular afferent depolarization occurring in response to severe hypoxia–hypercarbia during sleep might lead to ineffective body or head movement to escape suffocation

Brainstem Auditory Pathways and SIDS

Modified from Presentation By

David S. Paterson, PhD
Children’s Hospital Boston and Harvard Medical School

Transient Evoked Oto-acoustic Emission (TEOAE)

• Measurable response of the inner ear to acoustic stimuli of very short duration, e.g., clicks
• Produced by the cochlea, most likely as a result of the expansion and contraction of hair cells in response to sound
• Provides information on peripheral auditory system
Questions

• Is TEOAE a potential diagnostic test for SIDS risk?

• If so, how might inner ear dysfunction relate to mechanisms underlying SIDS?
  – i.e., what is the biological basis for auditory dysfunction as a marker for SIDS risk?

Peripheral Inner Damage

• Has many causes, e.g., antibiotics
• Can lead to neuronal loss secondary to trans-synaptic degeneration
• Degeneration can extend to the vestibular and cochlear nuclei in the brainstem

  Powell and Euliker, 1962
  Jean-Baptiste and Morest, 1975

Brainstem Auditory System and Cardiorespiratory Function

• Cochlear and vestibular neurons project to the pre-Botzinger complex (Pre-BotC) and paragigantocellularis lateralis (PGCL), cardiorespiratory sites that stimulate respiration in animals and humans

  Andrezik, 1981; Bellintani-Guardia 1996
  Nakazawa et al., 1997; Lopez et al., 1999
  Zec et al., 2001
Brainstem Auditory System and Cardiorespiratory Function

- Vestibular system injury in humans reduces respiratory rate
  Jauregui-Renauld et al., 2005
- Vestibular and auditory inner ear injuries cause reduced hypercapnic ventilatory responses in mice
  Allen et al., 2011

SIDS and the Pre-Bötzing Complex

- Brainstem abnormalities may alter the pre-Böt complex network and impair sigh and gasp generation, which may increase vulnerability to SIDS
- During prone sleep in the face down position, re-breathing exhaled air can increase CO2 and decrease O2 levels
- Altered blood gas composition initiates arousal response that begins with sigh generation during continued normal breathing
- Successful arousal results in head lift and repositioning, which restores blood gas levels to normal
- Arousal and autoresuscitation protect infants sleeping prone from SIDS
- Should an infant fail to both arouse and autoresuscitate, irreversible hypoxic insult leads to asphyxiation and SIDS

Respir Physiol Neurobiol 2013;189:10
**Hypothesis**

- Inner ear injury in a vulnerable infant, e.g., one with hippocampal dentate maldevelopment, may result in:
  - Brainstem-mediated cardiorespiratory dysfunction
  - Sudden death

**Hypothesis**

Thus, auditory brainstem (specifically olivochochlear) pathology may cause abnormal transient evoked oto-acoustic emission (TEOAE) (i.e., abnormal newborn hearing screens) in infants dying of SIDS

**Kinney Laboratory Studies**

Still in progress
Unpublished as of November 18, 2015
Keep watching for reports!

**Conclusion**

Potential relationship of newborn hearing screens, vestibulocochlear function and SIDS still worthy of ongoing research
Cardiac Causes of Sudden Unexpected Infant Death

- Ion channelopathies, e.g., long QT syndrome
  - Most are autosomal dominant with variable expressivity
  - Jervel and Lange-Nielson syndrome is autosomal recessive
- Catecholaminergic polymorphic ventricular tachycardia
  - Normal resting EKG and heart structure and function
  - Risk for exercise-induced syncope or sudden death
- Cardiomyopathies
  - Dilated, hypertrophic, and restrictive cardiomyopathies
  - Arrhythmic right ventricular cardiomyopathy
  - Left ventricular noncompaction cardiomyopathy
- Congenital heart disease
  - Obstructive left heart lesions
- Myocarditis

Cardiac Conduction System

Cardiac Cell, Membrane and Sodium Channel
Prolonged QTc, (Long QT Syndrome, LQTS) Caused by drugs, disease, congenital, acquired Increases possibility of severe ventricular arrhythmias and sudden death

Genetic Investigation Of 100 Genes Associated With Cardiac Diseases In SUID

Background
• Inherited cardiac diseases, mainly channelopathies, among causes of SUDI

Objective
• To investigate SUDI cases for potential lethal variants in 100 cardiac genes associated with inherited channelopathies and cardiomyopathies

Methods
• 47 SUDI cases evaluated

Results
• Variants in 47 SUDI cases
  – With likely functional effects in ≥ 1 genes 34%
  – In genes affecting ion channel functions 17%
  – In genes associated with cardiomyopathies 17%
• Possible effects of the variants not verified with family or functional studies

Conclusions
• Channelopathies are an important cause of SUDI
• Cardiac-disease-associated genes analysis in SUDI is valuable

Cardiac Channelopathies Associated With Infantile Fatal Ventricular Arrhythmias

BACKGROUND
• Fatal ventricular arrhythmias associated with cardiac channelopathies
• SIDS infants have provided evidence of this association

OBJECTIVE
• To assess the prevalence and functional properties of cardiac ion channel mutations in infantile fatal arrhythmia cases

METHODS
• 7 infants with potentially lethal arrhythmias at age < 1 year
  – 5 males, 2 females
  – age of onset 44.1 ± 72.1 days
• Analysis for KCNQ1, KCNH2, KCNE1-5, KCNJ2, SCN5A, GJAS, and CALM1


RESULTS
• In 5 of 7 patients, mutations in
  – SCN5A
  – KCNH2

CONCLUSION
• High prevalence of cardiac channelopathies
• Gain and loss of channel function in SCN5A and KCNH2 identified

Molecular Autopsy To Investigate Cardiac Conditions In Sudden Unexpected Death In Infancy And Early Childhood

OBJECTIVES
• Search for putative pathogenic genetic variants in a broad spectrum of cardiomyopathy, channelopathy, and aortic disease-associated genes that may increase the vulnerability to sudden cardiac death

DESIGN
• 41 cases of sudden unexplained infant and childhood death
• Search for 86 sudden cardiac death-related genes
• Molecular autopsy with massive parallel sequencing
• Literature review to prioritize putative pathogenic variants
**Broad-based Molecular Autopsy**

**RESULTS**
- 63 genetic variants identified in 35 cases
- Cardiomyopathy-associated genes comprised largest proportion
  - Expected more channelopathy-associated gene variants
- Subtle microscopic features of heart tissue may indicate early onset cardiomyopathy as a predisposing condition


**CONCLUSIONS**
- Cardiomyopathies deserve more attention than heretofore given in SUDI
- Further investigation of early onset inherited cardiomyopathies and myocardial dysfunction recommended
- Early detection of variants could unmask subtle forms of disease within relatives who would benefit from counselling

**QTc Interval Prolongation And Severe Apneas Associated With A Change In Infant Positioning**

- Clinical importance of prolonged QT interval
  - Surrogate marker for autonomic instability
  - Identify increased morbidity and mortality risk, including SIDS
- Case Report
  - Prolonged QTc interval developed after male infant changed from supine to prone position
  - Baseline QTc 413 ms (normal) increased to 500 ms (prolonged)
  - Sustained for 2 hours, associated with clinical apnea
  - Repositioning to supine position resulted in immediate decrease of QTc to baseline and termination of apneic events
**Rationale And Objectives For ECG Screening In Infancy**

**Background**
- ECG screening in infants who may be at risk of sudden cardiac death (SCD) is controversial
- Rational & emotional arguments given equal weight

**Objective and Methods**
- Build consensus among ourselves based on facts
- Provide unbiased review of relevant science and policies in favor of or against infant ECG screening

*Saul JP, Schwartz PJ, Ackerman MI, Triedman JK. Heart Rhythm 2014;11:2316*
Rationale And Objectives For ECG Screening In Infancy

Results
- Long QT syndrome (LQTS) satisfies several criteria that may make ECG screening worthwhile
  - Not rare (1 in 2000 births)
  - ECG diagnosis is feasible, can be used to trigger appropriate genetic testing
  - Causes approximately 10% of SIDS cases
  - Effective treatments are available
  - Diagnosis of affected infants may prompt identification of asymptomatic but affected individuals

Saul JP, Schwartz PI, Ackerman MJ, Triedman JK. Heart Rhythm 2014;11:2316

Screening ECG at 3-4 Weeks of Life

Conclusions
- Neonatal screening is cost-effective by conventional criteria
- Using a corrected QT (QTc) cutoff of 460 ms in 2 different ECGs, the number of false positives is estimated to be low (1 in 1000 births)
- Parents of newborn children should be informed about LQTS, a life-threatening but treatable disease of significant prevalence diagnosable by ECG

Saul JP, Schwartz PI, Ackerman MJ, Triedman JK. Heart Rhythm 2014;11:2316
Congenital Heart Disease

Normal Heart

Congenital Heart Disease
Left Heart Outflow Obstruction
Hypoplastic Left Heart Syndrome
Aortic Valvulopathy
Cardiomyopathy

Myocarditis
- Usually caused by viruses
  - Coxsackie virus
  - Adenovirus
- Death caused by
  - Arrhythmia
  - Cardiac failure

• Usually caused by viruses
  - Coxsackie virus
  - Adenovirus
• Death caused by
  - Arrhythmia
  - Cardiac failure
Other Selected Causes To Be Excluded By Scene Investigation, Complete Autopsy, And Ancillary Testing

- Suffocation/Asphyxia
- Metabolic Disorders
  - Fatty acid oxidation defects, e.g., MCAD deficiency
  - Carnitine palmitoyltransferase deficiency, type 2
- Infection
- Gastric aspiration
- Intoxication
- Accidental and Non-accidental trauma

Summary

- SIDS is the preferred and defensible diagnosis
- Neuropathology research continues to clarify why some infants are vulnerable to SIDS
  - Brain pathology is critical in the triple-risk model
- Hearing screens hold promise to be helpful in understanding some cases of SIDS
  - Much more research is necessary before recommendations can be made
- Numerous cardiac and other causes of SUDI

Thank You