Effects of Prenatal Alcohol Exposure on the Developing Brain

Hannah C. Kinney, M.D.
Professor of Pathology
Department of Pathology
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Children’s Hospital Boston and Harvard Medical School
The Potential Spectrum of Disorders Associated with Prenatal Alcohol Exposure

Is the sudden infant death syndrome part of FASD?

Does serotonin link SIDS and cognitive/affective deficits in survivors of infancy?
SIDS in the Aberdeen Area Indian Health Service in the 1990’s

• SIDS: Sudden and unexpected death of an infant <12 months that remains unexplained after a complete autopsy and death scene investigation

• Leading cause of all infant deaths in Aberdeen Area

• Accounted for more than one half of postneonatal infants deaths
  – 1 month - 12 postnatal deaths
Risk Factors for Sudden Infant Death Syndrome Among Northern Plains Indians

Solomon Iyasu, MBBS, MPH
Leslie L. Randall, RN, MPH
Thomas K. Welty, MD
Jason Hsia, PhD
Hannah C. Kinney, MD
Frederick Mandell, MD
Mary McClain, RN, MS
Brad Randall, MD
Don Habe, MD
Harry Wilson, MD
Marian Willinger, PhD

JAMA 2002; 288: 2717-2723
Design of the Aberdeen Area Infant Mortality Study

• Cohort from the Aberdeen Indian Health Service
  – 10 tribes or tribal communities (SD, ND, Nebraska, Iowa)
  – 66% of the area population
• 4-year, retrospective, case-control study of infants who died after discharge from the hospital
• Review of infant care practices and sociodemographic, economic, medical, health care, and environmental factors
• Parental interviews
• Death scene investigations, autopsies, neuropathology studies, medical chart abstractions
• Surveillance system for infant deaths
# Prenatal Alcohol Exposure and SIDS

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SIDS (n=33)</th>
<th>Controls (n=66)</th>
<th>Adjusted Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 months before pregnancy</td>
<td>75.0%</td>
<td>59.7%</td>
<td>Not significant</td>
</tr>
<tr>
<td>Any time during pregnancy</td>
<td>78.8%*</td>
<td>57.6%*</td>
<td>3.4 (1.4,10.9)</td>
</tr>
<tr>
<td>Periconceptional use</td>
<td>65.6%</td>
<td>27.4%</td>
<td>6.2 (1.6-23.3)</td>
</tr>
<tr>
<td>Binging in 1st trimester</td>
<td>46.7%</td>
<td>19.4%</td>
<td>8.2 (1.9-35.3)</td>
</tr>
</tbody>
</table>

*National average, 12%*  

Iyasu S et al. JAMA, 2002
Serotonin neurons in the lower (caudal) brainstem are critical for the control of breathing and autonomic function during sleep.
Analysis of Neurotransmitter Receptors

- Neurotransmitters: Chemical messengers between nerve cells (neurons)
- Located pre- or post-synaptically
- Neurotransmitter binds to receptor of next neuron in circuit and stimulates or inhibits firing in the neuron depending upon receptor subtype
- MEASURE OF FUNCTION AND INTEGRITY OF NEURONS AND NEUROTRANSMISSION

Receptors=Major site of drug interactions with implications for therapeutic interventions
Reduced Serotonin Receptor Binding in the Arcuate Nucleus in SIDS

Hemisections of the Medulla Oblongata

Arcuate nucleus: Human Homologue of Chemosensitivity Zone in Animals—Regulates Response to CO₂
Serotonergic Receptor Binding (fmol/mg tissue) in the Arcuate Nucleus*

<table>
<thead>
<tr>
<th>Group</th>
<th>Northern Plains (n)</th>
<th>Boston Children’s Hospital (n)</th>
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<tbody>
<tr>
<td>SIDS</td>
<td>7 ± 1 (23)</td>
<td>6 ± 1 (50)</td>
</tr>
<tr>
<td>Control</td>
<td>13 ± 2 (5)</td>
<td>19 ± 1 (12)</td>
</tr>
<tr>
<td>p-value</td>
<td>0.003</td>
<td>0.0001</td>
</tr>
<tr>
<td>% Decrease</td>
<td>46%</td>
<td>68%</td>
</tr>
</tbody>
</table>

* Age-adjusted mean ± standard deviation

Arcuate Nucleus
Involved in response to carbon dioxide

Same binding abnormalities in other regions of lower brainstem also confirmed
Serotonin Receptor Binding in the Arcuate Nucleus and Prenatal Exposure to Smoking and Alcohol

Aberdeen Area Infant Morality Study
Multiple Abnormalities in Medullary Serotonin System in Four Independent SIDS Datasets (1985-2008)

1. Reduced 5-HT level
2. Reduced TPH2 level
3. Reduced 5-HT<sub>1A</sub> binding
4. Increased 5-HT Neuron density
5. Delayed maturation of 5-HT neurons
6. Relative decrease in 5-HT transporter binding
Prenatal Alcohol Exposure Effects upon Neurotransmitter System Development

Prenatal Alcohol Exposure

GABA  Glutamate  Serotonin  Norepinephrine  Dopamine
The Brain’s Serotonin (5-HT) System: 2 Components

**ROSTRAL 5-HT DOMAIN**
- Mood, Cognition, Arousal
- Abnormalities in temporal lobe epilepsy patients

**CAUDAL 5-HT DOMAIN**
- Breathing, Temperature, Blood Pressure
- Abnormalities in SIDS infants
Serotonin Hypothesis: Prenatal Alcohol Exposure Differentially Alters the Caudal versus Rostral Serotonin Domains

Modifiers: Genetic and Environmental Factors

ROSTRAL 5-HT DOMAIN
Cognitive and Affective (Depressive) Abnormalities of FASD

CAUDAL 5-HT DOMAIN
Homeostatic dysfunction and sudden infant death
Serotonin Abnormalities due to Prenatal Alcohol Exposure in Animal Models

• Decreased levels of serotonin in different brain regions at different postnatal ages

• Decreased number of serotonin neurons in rostral and caudal brainstem domains postnatally

• Decreased serotonin fibers projecting to forebrain postnatally

• Decreased 5-HT_{1A} receptors in different brain regions at different postnatal ages

• Mechanism of alcohol toxicity upon serotonin unknown
The Neuropathology of Human FAS

Microcephaly
Holoprosencephaly
Leptomeningeal heterotopia
Deficits of corpus callosum (agenesis)
Neuronal migration deficits
Hypoplasia of the cerebellum
Brainstem dysgenesis
Quantitative Tools for Cellular, Neurochemical, and Molecular Abnormalities in the Brain

Normal Looking Infant Brain

Probing Neurotransmitters

Tissue Receptor Autoradiography

Primary Visual Cortex (Cell Stain)
Phase I, 2003-2006: Development of hypotheses and protocols; pilot/feasibility studies

Phase II, 2006-2016: Performance of full-scale, hypotheses-driven studies (prospective and retrospective studies) in 12,000 pregnancies
The Safe Passage Study: 2007-2016

• Mission: To determine the role of prenatal alcohol exposure in the risk for SIDS and adverse pregnancy outcomes, including stillbirth and Fetal Alcohol Spectrum Disorder (FASD)
  – Populations at high risk for maternal drinking during pregnancy, SIDS, and stillbirth
    • Includes American Indians in Northern Plains and mixed ancestry (Cape Coloured) in Western Cape, South Africa
  – Target=12,000 maternal/fetal dyads
  – Prospectively collected information about demographics, prenatal drug exposures, fetal and infant physiology, placental pathology, nutrition, genetics, neurobehavioral development, and neuropathology
  – ~280 fetal and infant deaths projected, with request for consent for brain research in all of these cases
  – Brain analysis performed at Boston Children’s Hospital, MA
Prenatal alcohol exposure increases the risk for the sudden infant death syndrome (SIDS) and stillbirth.
## Study Populations in PASS

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Overall U.S.</th>
<th>Northern Plains</th>
<th>Cape Town</th>
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<tbody>
<tr>
<td>Any drinking during pregnancy</td>
<td>12%</td>
<td>47%*</td>
<td>57%*</td>
</tr>
<tr>
<td>SIDS rate</td>
<td>0.57/1000</td>
<td>3.46/1000</td>
<td>3.41/1000</td>
</tr>
<tr>
<td>Stillbirth rate</td>
<td>6.5/1000</td>
<td>8/1000</td>
<td>15/1000</td>
</tr>
<tr>
<td>FAS rate</td>
<td>0.5-3/1000</td>
<td>3.9-8.5/1000</td>
<td>40.5-46.4/1000</td>
</tr>
</tbody>
</table>

*Based upon Phase II data as of September, 2009*
Human Brain Development
Over the Second Half of Gestation

Midgestation (20 weeks)

Term (40 weeks)
7 Selected Brain Regions for Analysis

BA 39: Spatial Attention Network; Language; Reading; Sensory integration

BA 11: Self-regulation Network

BA 46: Working Memory

BA 24: Attention and Self-regulation Networks

Hippocampus: Learning and Memory

BA 17: Vision

BA 37: Facial Recognition

Mesulam, MM, 2000
5-HT$_{1A}$ Receptor Binding in BA 17 (Primary Visual Cortex)

Abbreviations: CS, Calcarine Sulcus
Different Binding Patterns in BA 17 Between 5-HT_{1A} Receptor and 5-HT Transporter

5-HT_{1A} Receptor

5-HT Transporter

5 postnatal months

5 postnatal months
Quantitative Analysis of Cerebral Cortical Binding Patterns

Questions PASS Brain Analysis can Begin to Address: Link of Prenatal Exposures with Human Neuropathology

- Is abnormal $5\text{-HT}_{1A}$ receptor binding associated with exposure to heavy, moderate, and/or low prenatal alcohol exposure?
- Is the pattern of $5\text{-HT}_{1A}$ receptor binding altered by exposure? In one functional network (attention)? In several networks (memory, language perception)?
- Does the level of pre- and/or postnatal $5\text{-HT}_{1A}$ receptor binding correlate with the number of drinks per week? Other quantitative alcohol measures?
- Does a combined history of smoking during pregnancy compound a $5\text{-HT}_{1A}$ receptor binding deficit related to alcohol exposure?
Is 5-HT$_{1A}$ binding low in areas from both the rostral and caudal serotonin domains? Is one part of FASD a Developmental Serotonopathy with different consequences based on whether rostral or caudal domain targeted?
Normal Adult Brain: 1200 grams

Fetal Alcohol Syndrome: 1050 grams

Fetal Alcohol Syndrome and Secondary Schizophrenia: A Unique Neuropathologic Study

1Stoos C, 1Nelsen L, 2Schissler KA, 1Elliott AJ*, 2Kinney HC*. 1Sandord Health, SD; 2Boston Children’s Hospital, MA. J Child Neurol 2014, in press.

• 34 year old woman with diagnosis of FAS in early childhood and development of schizophrenia in adolescence; sudden death due to pulmonary embolus as young adult.
Adult FAS Brain Study

BA 37: Facial Recognition
- FAS Case 5-HT$_{1A}$
- Control 5-HT$_{1A}$
- FAS Case 5-HT Transporter
- Control 5-HT Transporter

BA 28: Learning and Memory; Parahippo. Gyrus
- BA 28

BA 37: 5-HT Transporter
Human Brain Analysis through Collaborative Tissue Banks

- Delineate human morphological, cellular, and molecular factors
- No extrapolation from animal studies
- Species differences in anatomy, neurochemistry, modifying factors, genetics
Return of the AAIMS Remains
August 24, 2009 at Boston Children’s Hospital
August 26, 2009 Returned to the Black Hills

Gift of Tribes to Boston Children’s Hospital
Gift of AAIMS to Tribes
Acknowledgements

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• The Safe Passage Study (NIAAA, NICHD, NIHLDS)