Pediatric Environmental Illness: The Canary in the Coal Mine

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Pediatric Environmental Health Specialty Units

Western States PEHSU
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1-866-827-3478
National PEHSU System
www.pehsu.net 888-347-2632
Breathing rates calculated from inhalation rates (m³/kg-day) and body weights reported in Layton (1993); original data from NFCS (1977-78).

Breathing Rates by Age Group

- Breathing rates calculated from inhalation rates of pigs, chickens, and turkeys.
- Original data from NFCS (1977-78) except for pigs (1977-78).
Case

- Female infant
- Breastfed with formula supplement
- Normal 1 month checkup (mother notes acrocyanosis at 2 weeks)
- At 2 months pharmacist comments on cyanotic color

- Given progressively more formula made with well water
- At 2 months develops vomiting and severe diarrhea
- Rushed to physician - cyanosis doesn’t respond to oxygen / full arrest
- Chocolate-brown blood
- Well water 150mg/L nitrates

By Mike Blyth (Own work) [GFDL (http://www.gnu.org/copyleft/fdl.html), Commons]
Nitrates

- Preventable cause of methemoglobinemia in infants
- Over 2,000 cases reported with case fatality rate of 10%
- EPA drinking water standards nitrates < 10mg/L (10ppm)
- 4.5 million people served > EPA standard
  - 65,000 infants
  - 117,000 children via public systems

Infant Under 4 Months

- Hemoglobin F dominant – more readily oxidized
- Methemoglobin reductase activity low
- Single food source
- High fluid intake
- ↑ Gastric pH
  (↑ bacteria that convert nitrate to nitrites)
EXPOSURES DURING DEVELOPMENTAL PERIODS AND AT DOSES NOT ASSOCIATED WITH ADULT TOXICITY MAY RESULT IN IMPACTS UNEXPECTED BY ADULT EXPOSURE

Chlorpyrifos Impacts Neurodevelopment

- Detected in >64% of maternal and newborn blood samples
  - Follow up at 3 yrs. for 189 children
- Highly exposed
  - Delays in psychomotor and mental developmental indexes (Bayley)
    - PDI delays 5 times as great (MDI 2.4 times)
- Symptoms ADHD and PDD significantly more likely (child behavior checklist)
- Declines in working memory and full scale IQ at age 7

Rauh et al., Pediatrics 2006
Rauh et al., EHP 2011
Chlorpyrifos has Measurable Impact on Brain Structure (non-occupational)

Regional enlargements of the cerebral surface (primarily underlying white matter)

- Posterior middle temporal, inferior postcentral gyri bilaterally
  - Attention and receptive language
- Superior frontal gyrus, superior temporal gyrus, cuneus, and precuneus
  - Social cognition
- Gyrus rectus (related orbitofrontal regions)
  - Reward, emotion, and inhibitory control
- L superior frontal gyrus (dorsal and mesial surfaces)
  - Executive function
From Minamata
Eugene and Aileen Smith
H.R.W 1975
### Time Lines of Developmental Processes in Humans

<table>
<thead>
<tr>
<th>Prenatal Period (Months)</th>
<th>Postnatal Period (Years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Birth</td>
</tr>
<tr>
<td>1</td>
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**Cell Proliferation**
- Radial glia, neurons
- Glia

**Migration of Neurons**
- Brain, spinal cord
- Ext. granular layer cerebellum

**Subplate Neurons**

**Synapse Formation**
- MZ
- SP
- HP
- RF
- Visual cortex
- Association cortex

**Myelination**

*Key: MZ = marginal zone; SP = subplate; HP = hippocampus; RF = reticular formation*

### Specific processes disrupted by neurodevelopmental toxicants

<table>
<thead>
<tr>
<th>Process</th>
<th>Disruptive Substances</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proliferation</td>
<td>Radiation, ethanol, mercury, cholinesterase inhibitors</td>
</tr>
<tr>
<td>Migration</td>
<td>Radiation, mercury, ethanol</td>
</tr>
<tr>
<td>Differentiation</td>
<td>Ethanol, nicotine, mercury, lead</td>
</tr>
<tr>
<td>Synaptogenesis</td>
<td>Radiation, ethanol, lead, triethyl tin, parathion, PCBs</td>
</tr>
<tr>
<td>Gliogenesis &amp; myelination</td>
<td>Thyroid, ethanol, lead</td>
</tr>
<tr>
<td>Apoptosis</td>
<td>Ethanol, lead, mercury</td>
</tr>
<tr>
<td>Signaling</td>
<td>Ethanol, cholinesterase inhibitors, mercury, lead, PCBs</td>
</tr>
</tbody>
</table>
Cohort studies find lower dose effects:

loss of IQ points, decreased performance: memory, attention, language, and spatial cognition


Who is the canary?

✓ A day laborer goes to the ER for a work related injury.
✓ Working on demolishing a firing range - lead level is 74 mcg/dl after 3 days on this job.
✓ Four other workers tested between 57 and 98 (all worked less than 2 ½ weeks).
✓ None had previously worked with lead.

Hipkins KL, Materna Bt, Payne SF, Kirsch LC., Clin Pediatri 2004
What should be done next?

1. Perform X-ray fluorescence (XFR) on workers to evaluate cumulative exposure?
2. Inquire about use of traditional medicine?
3. Check for use of imported pottery.
4. Test the worker’s families for lead poisoning?

Occupational/Take Home Exposures

- 9 children of three workers tested between 13 and 34 mcg/dl. (highest 18 month old)
- Wife of one with symptoms and Pb level of 36 mcg/dl.
- Workers may bring home hazards on clothing, shoes, and body.
- In 2001-2002 year, 22% of California childhood lead poisoning cases had potential contribution from occupational sources.
Early Life Lead Exposure and Alzheimer’s Disease? (Barker’s Hypothesis)

- Plaque and neurofibrillary tangles
- β amyloid and APP make up plaques
- Expression of genes related to these upregulated by lead exposure in early childhood (10mcg/dl)
- Methylation patterns altered
- Monkeys exposed to lead in early life develop plaque and NFTs in old age

Wu et al., J Neuroscience 08

Transient Hypertonia in an Infant

- 7lbs. 14 oz. term female, jaundice peak bili 12.6
- NI. PE at 12 weeks except lower extremity hypertonicity
- Pediatric consult at 16 weeks - upper and lower extremity hypertonicity, ankle clonus with Dx of cerebral palsy
- Physical therapy begun
- No environmental hx was taken

Wagner SL, Orwick DL., Pediatrics 1994
Parents Ask if Symptoms Could be Related to Pesticide Spray? I Would Say:

1. Yes
2. No
3. Maybe (I have no idea)
4. Let’s call the National Pesticide Telecommunications Network (800.858.7378)

Transient Hypertonia in an Infant

- Diazinon 1% sprayed by unlicensed pesticide applicator
- Levels still high six months after spraying
- Serum cholinesterase normal
- Urine metabolites high
  - similar to post-shift urine of applicators
- Six weeks after removal from house muscle tone returned to normal
Children aren’t little adults?

Developmental origins of health and adult disease (DOHAD)

• Under-nutrition *in utero and infancy* resulted in changes in organ structure, function, and metabolism that were permanent
  • *adult lipid profiles* linked to high cholesterol and hypertension
  • *Impaired glucose regulation* (insulin resistance)
  • *Metabolic syndrome*
Morris Water Maze

- Test of memory and spatial learning (adults)
- LG babies do better
  - Non-LG babies raised by LG mom’s do better
- Adults born to mothers with prenatal stress but same postnatal environment do worse

It is a combination of genetics and pre/postnatal environment that determines function into adulthood.

**EFFECTS OF CROSS-FOSTERING**

<table>
<thead>
<tr>
<th>low LG and low LG mothers</th>
<th>low LG and high LG mothers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fearful offspring with brisk HPA stress response</td>
<td>Less fearful offspring with more modest HPA stress response</td>
</tr>
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Slide courtesy of Bob Wright – Mt. Sinai NYC
Genetics = Gene + Expression

GeneJcs = Gene + Expression

Epigenetics

Wikipedia commons

Demethylation of GR exon 1
Deacetylation of histones around GR exon 1

Permanent increase in GR expression in hippocampus

Increased NGF1-A activity in hippocampus

Increased Serotonin tone

Mother high licker groomer

pup

exploratory, less fearful and stress reactive more cognitively intact in old age.

Adult
High hippocampal GR levels
High licker groomer behavior

Mother high licker groomer

less methylation GAD1

Champagne and Meaney, Behavioral Neuroscience 2007
Champagne et al, Journal Neuroscience 2009
Zhang et al, Journal Neuroscience Sept. 2010
Prenatal Stress – Effects in Adult Female Offspring

- Exposures
  - Relationship hardship (e.g., Divorce)
  - Death/severe illness of someone close
  - Severe financial, car accident, refugee

- Impacts
  - Altered HPA axis response (Trier Social Stress and ACTH stimulation)
  - Bias to Th2, IL-4, IFN-\gamma, IL6, IL10 production

Entringer et al Dev Psychobiol 2008
Entringer et al Hormones and Behavior, 2009
Allostasis – active process for adaptation (brain – body)

Limbic Plasticity effected by
• Parental resources
• Education
• Exposures/nurturance

Costs: metabolic, cardiovascular, immune, behavioral dysregulation

Adapted from McEwen and Gianaros, 2010

Neural Mediators of Resilience

• Brain Derived Neurotrophic Factor (BDNF)
  – Necessary factor in plasticity
  – BDNF low in depression
  – Elevated by fluoxetine, regular physical activity
    • Reopen windows of plasticity (stroke and depression)
      – Combined with intensive physiotherapy or behavioral therapy

Karatsoreos and McEwen, Resilience and Vulnerability: A neurobiological perspective
Lead/Stress Act by Similar Mechanisms

- Learning and memory in hippocampus dependant on activation of NMDA glutamate receptors
- Stress or an environmental chemical (lead) impact same mechanism
- Both lead and stress impact HPA axis

Environmental enrichment enhances memory and learning /plasticity

- Early lead exposure results in decrease in learning, memory, NMDA r activity (BDNF)
- Enriched environment reduces leads cognitive impacts and normalizes NMDA r activity (BDNF)
Environmental enrichment effective in ameliorating neuro-cognitive effects

Social environment

- Lead – association cognitive deficit <10mcg/dl only in “less advantaged”, >10mcg/dl → effect attenuated for “advantaged”*
- PCBs – (prenatal) negative effect only in “less optimal” parenting and home characteristics. Breastfeeding protective of attention at school age.
- ETS – greatest cognitive effect in those with “unmet basic needs in the areas of food, housing, and clothing”

Weiss and Bellinger, 2005
Rauh et al., Neurotox Teratol, 2004
Vreugdenhil et al. EHP 2002
Bellinger, Neurotox Teratol, 1988*, Miranda et al. 2008**
Jacobson and Jacobson, 2003
AAP Grand Rounds 6:16-17 (2001)
© 2001 American Academy of Pediatrics

EPIEMIOLOGY

Oral Succimer for Lead Chelation
Does Not Lead to Better
Neuropsychological Outcomes
(children with 20 – 45 mcg/dl)

SOCIAL ENVIRONMENT / CHEMICAL ENVIRONMENT INTERACTION
Ozone - postnatal exposure (+/- HDMA)

- Results permanently alters bronchioles (monkeys)
  - Fewer branches
  - Longer
  - Smaller diameter
  - Altered muscle bundle orientation
  - Change in innervation

Plopper et al. 2007

Community/Home Violence Link to Decrease in Lung Function

- Girls with home conflict (highest tertile) had >5% decrease in FEV₁ and FVC (smaller decrease in boys)
- Boys with exposure to community violence (highest tertile) had >5% decrease in FEV₁ and FVC
  - Independent of SES, SHS, birth wt., respiratory illness history

Suglia et al 2007 Psychosomatic Med
Asthma – 
neurobiology underlying stress vulnerability

• Early life adversity (chronic stress) linked to:
  – Disturbed regulation of endocrine and autonomic processes
    • HPA axis; sympathetic adrenal medullary system
      – May permanently program for exaggerated stress response
    • Alterations in Th1/Th2 balance
    • Alterations in inflammatory cytokines, IgE

RJ Wright Biological Psychology 2010
Perinatal stress and early life programming of lung structure and function

Stress and Asthma 
Cohort Study on IPV

• 3,116 participants enrolled at birth
• Assess intimate partner violence impact on asthma Dx by 36 mos.
• IPV 2 fold increase
• Maternal child activity protects
  – IPV + housing hardship/disarray additive

Air Pollution and Exposure to Violence Synergistic Effects

- Birth cohort N=417
- NO$_2$ measured
- Lifetime exposure to violence surveyed
  - Association between air pollution and asthma only in those with above median ETV
  - For lifetime residents (most accurate exposure)
    asthma OR 2.4 (1.48-3.88) for higher air pollution + ETV

Clougherty et al EHP 2007: Shankardas et al PNAS 2009

Days exceeding CA standards for Ozone (1 hr) and PM10 (24 hr) (South Coast air basin Data California Air resources Board)

A portion of adult lung function is set by infancy

Up to 14% of adult lung function predicted by lung function at 2-3 mos
Stern 2007

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Western States Pediatric Environmental Health Specialty Unit

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Children may be canaries due to:

1. Exposures may be different or greater
2. Physiologic differences (pharmacokinetics)
3. Sensitive developmental windows (pharmacodynamics)
4. All of the above

Lung Function

1. In middle age is predicted in part by childhood lung function
2. In adults is not impacted by early life events
3. In children is reduced as a result of exposure to violence
4. Exposure to stress plus air pollutants are additive factors for asthma risk in children
5. 1, 3, 4
Critical Windows of Development

Include:

1. Time periods of rapid growth and development such as fetus, infancy, and adolescence.
2. Periods in which structure and function may be programmed and impact adult disease.
3. Times when programming can result in reduced risks.
4. All of the above.