Cord Blood Manganese and ADHD-Related Behaviors Among 8-Year –Old Children

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Manganese Exposure

Sources of Mn:
• Ubiquitous element
• Diet, water
• Production of steel, batteries, catalysts, glass, ceramics; mining; welding
• Organic forms: fungicides, MMT

Kinetics:
• Readily absorbed via inhalation, less so ingestion (Fe deficiency increases)
• $t_{1/2}$ blood short; longer in tissues
• Crosses placenta; potential enhanced fetal CNS uptake
Manganese and Neurological Function

- Essential element required for healthy neurodevelopment

- Neurotoxicity with heavy occupational exposure (Parkinsonian, dementia, ↓memory, emotional lability, aggression)

- Animal models alterations in dopaminergic function with prenatal/early postnatal exposure, behavior (hyperactivity), learning/memory

- CNS neuropathology: degenerative changes especially in basal ganglia
Attention Deficit-Hyperactivity Disorder

- Most common neurobehavioral disorder of children (6-12% worldwide)
- Risk factors poorly understood
- Clinical diagnosis (no specific test)
- Neuroimaging: ↓brain volume
- Mechanism: “dopamine deficit”
- Deficiencies:
  - vigilance-attention
  - cognitive control (working memory, impulse ctrl)
  - motivation
Biomarkers of Prenatal Mn Exposure and ADHD-Related Behavior

Preschool (3-5 yrs):

↑Behavioral disinhibition at 3 yrs (teeth)\(^1\)

↑Impulsive errors (CPT/Stroop) at 4.5 yrs (teeth)\(^1\)

↓Attention (McCarthy) at 3 yrs (cord blood)\(^2\)

School age (6-17 years):

↓Prosocial (♀), ↑Conduct probs (♂ > ♀) (water)\(^3\)

↑Internalizing, ↑Externalizing, ↑Hyperactivity (teeth)\(^1,4\)

No association clinical ADHD diagnosis (cord serum)\(^5\)

\(^1\)Ericson et al. Neurotoxicol Teratol 2007; \(^2\)Tasker et al. Neurotoxicology 2003; 
\(^3\)Rahman et al. EHP 2016; \(^4\)Mora et al. Environ Int 2015 (prenatal in ♂); 
\(^5\)Ode et al. Environ Res 2015
Study Goal

Assess associations of cord blood manganese levels (*in utero* exposure) with behaviors related to ADHD at age 8 years.
**New Bedford Cohort (NBC) Study**

- 788 newborns enrolled at birth 1993-1998
- Maternal residence in towns next to PCB-contaminated New Bedford Harbor
- Assess relation early life exposure to PCBs, OC pesticides and metals with child neurodevelopment and growth
Analysis Population

Birth

788 mother-infant pairs recruited

709 (90%) with cord blood manganese

8 yrs

607 (77%) children followed up

602 ADHD-related measure

540 with ADHD measure & blood manganese
Manganese Exposure Assessment

• Assessed in cord blood
  – Collected at delivery (Vacutainer™ trace metal tubes)
  – Whole blood analyzed with Inductively Coupled Plasma Mass Spectrometry (ICP-MS) at Harvard Trace Metals Laboratory
  – LOD 0.2 µg/L
Data Analysis

• Multivariable linear regression models (linear dose-response in penalized splines)

• Covariates:
  – Child: age, sex, and race
  – Mother: age, education, marital status, IQ, depression, prenatal smoking, prenatal alcohol consumption, illicit drug use
  – Household: income, HOME score, paternal education

• Sensitivity analyses:
  – Lead (cord blood, peak @ 12-36 months)
  – PCBs (cord serum sum of 4 congeners 118,138,153,180)
Unpublished Preliminary Findings
Removed
Outcome: Behavioral Rating Scale

• Conners Rating Scale – Teachers (CRS-T)
  – 59 item questionnaire, problem behaviors
  – Used in clinical dx, monitoring, research
  – Analyzed 4 subscales:
    • Conners’ ADHD Index
    • DSM-IV Inattention
    • DSM-IV Impulsivity-Hyperactivity
    • DSM-IV Combined
Unpublished Preliminary Findings
Removed
Outcome: Continuous Performance Test

- **Conners Rating Scale – Teachers (CRS-T)**
  - 59 item questionnaire, problem behaviors
  - Used in clinical dx, monitoring, research
  - Analyzed 4 subscales

- **Continuous Performance Test (CPT)**
  - Inattention and impulsivity assessed as:
    - Errors of omission (non-response, inattention)
    - Errors of commission (false response, impulsivity)
    - Mean response time
    - Response time variability
Unpublished Preliminary Findings

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Outcome: Psychometric Test

- **Conners Rating Scale – Teachers (CRS-T)**
  - 59 item questionnaire
  - Assesses problem behaviors in children
    - conduct, cognitive, emotional, ADHD
  - Used in clinical diagnosis (DSM-IV), treatment monitoring, research

- **Neurobehavior Examination System 2 Continuous Performance Test (CPT)**
  - Computer assisted test system
  - Inattention and impulsivity assessed with 3 outcomes:
    - Errors of omission (non-response)
    - Errors of commission (false response)
    - Response time

- **Wechsler Intelligence Scale for Children 3rd Edition (WISC-III)**
  - IQ Test
  - Components associated with ADHD (*a priori*):
    - Processing Speed
    - Freedom from Distractibility
Unpublished Preliminary Findings
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Thank you!

New Bedford Harbor