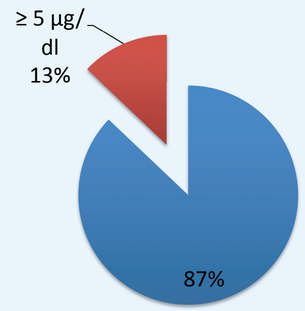
Lead Toxicity: What is it and How is it Happening?

Kimberly A. Parada, BA; Jay S. Schneider, PhD

Department of Pathology, Anatomy & Cell Biology, Jefferson Medical College of Thomas Jefferson University, Philadelphia, PA

EPIDEMIOLOGY

Lead poisoning accounts for 0.6% of the global burden of disease.

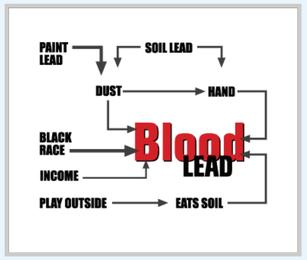


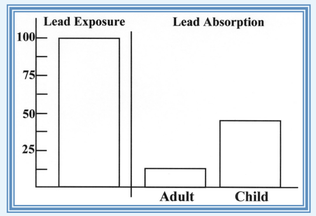
In Pennsylvania in 2010, 148,751 children under 72 months of age were tested for blood lead levels. Of those children, 19,176 had blood lead levels greater than 5 µg/dl.

- A lower socioeconomic status increases the chances for lead exposure.
- Lead toxicity is an under-appreciated problem that is entirely preventable.

HOW ARE WE EXPOSED TO LEAD?

The main pathway in which children are exposed to lead is through ingestion. Dust from deteriorated leaded paint in old homes is the major source of exposure in the U.S. This dust can get on the floor, clothing, toys etc. Most exposures occur during early childhood, between ages 1 and 3 years, when children begin moving around more on their own and exhibit a lot of mouthing behaviors. Children put the dust from these items into their mouths and it is absorbed through the intestines.

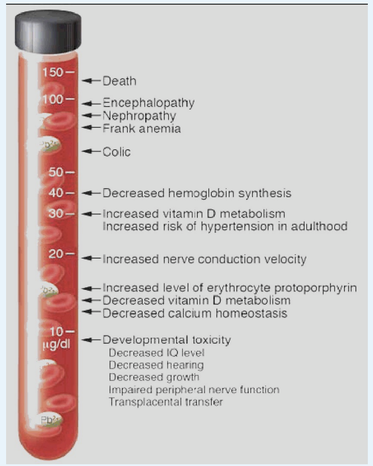




For a given exposure, more lead is absorbed in a child. Nutritional deficiencies will increase absorption.

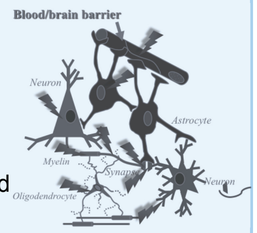
EFFECTS OF LEAD

The current lead reference level is 5 µg/dl.
Very high blood lead levels can cause anemia, encephalopathy, seizures, and death. However, lower blood lead levels can cause cognitive and behavior problems, affecting attention, working memory, and results in lower IQ.
Childhood lead exposure increases the risk of later life diseases including chronic kidney disease, high blood pressure and hypertension, Parkinson's disease, and Alzheimer's disease.



HOW DOES LEAD CAUSE BRAIN DAMAGE?

Lead can replace metals such as calcium and zinc, altering their homeostasis. It can also cause changes in neurotransmitter synthesis and release and receptor density. Lead can increase oxidative stress and inhibit superoxide dismutase activity. Lead damages the blood brain barrier, increasing permeability. Specific gene expression alterations have been identified in rat frontal cortex and hippocampus, including genes involved in learning and memory.



HOW ARE THE GENES BEING AFFECTED?

We hypothesize that long term affects and differential gene expression are related to early-occurring epigenetic changes. Epigenetic changes are modifications of DNA that can switch genes on or off without changing the DNA sequence. They can also be somatically inherited. If DNA methylation or histone acetylation are altered, a gene can become incorrectly silent or active, influencing cell health and function.

RESEARCH TO DATE

Preliminary studies have explored potential relationships between developmental lead exposure and epigenetic changes.

- Expression of DNA methyltransferases and methyl CpG binding proteins are altered in the brain following low level exposures.
- DNA extracted from human white blood cells showed 99 genes whose promoters were differentially methylated between children with different levels of lead exposure.
- Alterations in DNA methylation and histone acetylation are modified by factors including sex, developmental timing of exposure, level of exposure, and duration of exposure.

FUTURE RESEARCH DIRECTIONS

1. Compare the list of altered genes in the rat frontal cortex and hippocampus with the differentially methylated genes in the human white blood cells. Also determine if epigenetic changes in blood derived DNA reflects epigenetic changes occurring in the brain.
2. Further interrogate epigenetic changes in selected gene targets from the above studies. Specifically, I would choose ones involved in learning and behavior.
3. Verify changes in methylation status of selected genes using bisulfite conversion, pyrosequencing and ChIP-PCR.
4. Determine functional significance of lead-induced methylation changes.
   - Does the change in methylation status change gene expression?
   - Does the altered gene expression lead to changes in protein production?
   - How much of a change in methylation/gene expression/protein production is necessary to cause a change in behavior?
5. If there are defined epigenetic changes from lead exposure, can they be reversed?

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