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Topical Review

Lead Toxicity in Children: An Unremitting Public Health Problem

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ABSTRACT

Background: Lead is a pervasive environmental contaminant. Lead accumulates in the body, impairing a molecular level various cellular processes. Lead exposure during childhood causes adverse and permanent neurodevelopmental consequences, sometimes even with "low" blood lead levels. Symptoms are frequently silent, making lead exposure an often unrecognized and underestimated threat for pervasive neurocognitive disorders.
Methods: We identified articles focusing on childhood exposure to lead and neurodevelopment via a search of the electronic database PubMed (National Library of Medicine), including journal articles published from 2007 to 2019. These articles were used to evaluate the effect of environmental lead exposure and analyze whether control efforts over the past decades have altered the prevalence of exposed children.
Conclusions: Children are still being exposed to lead despite evidence of the adverse impact of exposure, even for children with blood lead levels below the currently recognized threshold for intervention. Legislative and educational efforts have reduced lead exposure but are not being followed universally. Primary prevention and identification of high-risk populations are the best cost-benefit interventions to fight this public health problem.

Background

Lead is a heavy, bluish-gray metal that is used in several industries. It is easily molded and very resistant to corrosion, does not degrade to other substances, and accumulates over time. Over the past century lead has contaminated the environment as a result of human activity. In the last several decades it became apparent that both acute and chronic exposure at any level is harmful, with adverse effects on neurodevelopment and cognition.

Chipping and dust from lead-based paint in older housing utits constitute an important source, especially in the pediatric population. Lead can accumulate in dust, soil, and water sediment, especially near urban areas and mining and industrial sites, where it can persist for years. Lead from lead pipes and solder can also be released into drinking water service lines when the water is acidic.[1] Lead and its alloys are still used in automobile batteries, pipes, fishing sinkers, ammunition, dyes and paints, ceramic glazes, some imported toys, and certain cosmetics or traditional remedies. Occupational or leisure activity exposure may also be a source through dust and particles settled on clothes and tools. Young children, who consume more water per unit of body mass than older people and who commonly engage in mouthing behaviors, are especially at risk for exposure. Chronic exposure in children younger than six years of age continues to be an environmental and public health problem.[2,3] Studies indicate an adverse effect of lead exposure even when the blood lead concentrations are low.[4-6]

Beginning in the 1970s, efforts were made to control lead concentrations in the environment, leading to a substantial decline, thanks to regulatory and public education initiatives.[2,3] However, because lead can never be completely removed from the environment, we must continue to monitor diligently.

A notorious incident that drew attention to lead contamination occurred when close to 100,000 residents of Flint, Michigan, were affected by changes in the drinking water quality after the water

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supply source was switched between April 2014 and October 2015. The later source lacked necessary corrosion control treatment to prevent lead from being released from pipes into drinking water. An advisory was issued because by-products of disinfectants were detected in the water, prompting studies that led to the detection of elevated blood lead levels (BLL) ≥5 μg/dL in young Flint children. A federal state of emergency was declared in 2016. Flint's water supply was switched back, but the state faced multiple lawsuits related to this public health crisis.[7] There also have been recent incidents of products marketed especially for children having high lead concentrations, including jewelry and toys imported from other countries.

Before 2012, children were identified as having a blood lead "level of concern" if the result was above 10 μg/dL. In May 2012, the Advisory Committee on Childhood Lead Poisoning Prevention from the Centers for Disease Control and Prevention (CDC) recommended a population-based reference value to identify children with BLLs greater than 97.5% of children aged one to five years, or the highest 2.5% children when tested for lead levels. This reference value, currently set at 5 μg/dL, is not a clinical reference level outlining an acceptable range or a toxicity threshold, but rather a tool to help identify the children in whom prevention efforts need to be targeted. This reference value may be decreased further in the future.[4,8]

Methods

We reviewed the literature related to lead exposure in childhood and its effects on health and the nervous system. This article reviews the epidemiologic and clinical features of lead toxicity in children based on a comprehensive literature review from MEDLINE electronic database using PubMed, with appropriate keywords to incorporate recent literature from 2007 or later. Keywords included lead, lead poisoning, lead toxicity, children, neurotoxicity, and neurodevelopment. Other keywords used included neurotoxicology and cognition. The included articles were derived primarily from human studies and focused on childhood exposure, interventions, and indicators of neurodevelopment. In addition, some animal model studies illustrate mechanisms of toxicity and support the neurobehavioral effects of lead exposure. A total of 40 sources were included, published in peer-reviewed journals and others available at the official websites from the CDC and the World Health Organization. We evaluated the effect of environmental lead exposure on the neurodevelopment of children by reviewing the literature and analyzing whether control efforts have had an effect on lead exposure.

In numbers

According to the World Health Organization and the Institute for Health Metrics and Evaluation, in 2017 lead exposure accounted for 1.06 million deaths and 24.4 million years of healthy life lost (disability-adjusted life years) worldwide due to long-term effects on health. The highest burden was in low- and middle-income countries. Lead exposure is estimated to account for over 60% of the global burden of idiopathic developmental intellectual disability, 10.3% of the global burden of hypertensive heart disease, 5.6% of the global burden of the ischemic heart disease, and 6.2% of the global burden of stroke.[9] Worldwide, lead exposure in childhood is estimated to account for almost 600,000 new cases of children with intellectual disabilities every year.[10]

The epidemiology of lead exposure in children has markedly changed over the past decades. In the 1970s approximately 13.5 million US children younger than five years had BLL ≥10 μg/dL. Thirty years later this decreased to about 250,000 children. Data from 2007 to 2010 and 2009 to 2015 showed that approximately 2.6% to 3% of US children younger than six years still had levels ≥5 μg/dL.[11,12] In the United States alone, an estimated loss of 23 million intelligence quotient (IQ) points has been attributed to lead, with 80% of those lost IQ points being in people with BLLs <5 μg/dL.[5] Certain subgroups have been identified to be at higher risk of exposure, including children from low-income families, non-Hispanic black children, and children living in older housing (built before 1950).[12-14] These demographic disparities have persisted over time.

There would be considerable benefit from preventing pervasive and neurocognitive disorders associated with lead exposure.[15] It has been estimated that each US dollar invested in controlling lead in paint resulted in a return of $17 to $221 or net savings of $181 to $269 billion when considering costs of health care, special education, and crime associated with elevated lead exposure.[16,17] This cost-benefit ratio has been compared with that of public health interventions such as vaccines.[2,11]

Toxicokinetics

Lead can be absorbed via inhalation of lead-containing dust and paint or through ingestion of contaminated water and food. Gastrointestinal absorption is higher in children. Red blood cells bind most of it, and only 1% to 2% lead can be found in plasma. Lead has a half-life of about 35 days, meaning that blood levels reflect only recent exposure. Lead is then distributed to soft tissues and eventually to bone, where it deposits and can persist for decades.[18,19] BLLs are more reflective of acute exposure, whereas bone lead levels better reflect cumulative exposure over time.[3] Bone turnover releases lead back into the bloodstream in pregnancy, menopause, and lactation. Lead can also cross the placenta and the blood brain-barrier in the developing fetus.[18]

Mechanisms of lead toxicity

The exact mechanisms underlying lead toxicity are still unclear, but multiple processes have been described in which lead has an adverse effect.

Lead can disturb cellular functions because it substitutes for calcium, and to a lesser extent, zinc, and activates processes reliant on calmodulin, a calcium-binding messenger protein.[19-21] Lead also binds to the sulfhydryl group of proteins, making it particularly toxic to multiple enzymes. Lead interferes with heme production by inhibiting the enzyme delta-aminolevulinic acid dehydratase and by altering the incorporation of iron by ferrochelatase, resulting in microcytic, hypochromic anemia. The vitamin D receptor has been also described to modulate lead uptake, because it is involved in intestinal calcium absorption and calcium storage in bone.[18] Gene variants of delta-aminolevulinic acid dehydratase and vitamin D receptor are in fact considered susceptibility markers of lead toxicity in humans.[22] In the liver, lead interferes with cytochrome P450 enzymes.[19]

Lead easily crosses cell membranes and exerts pro-oxidative effects within the cell with formation of reactive oxygen species, thereby activating processes of programmed cell death.[20,21,23] Lead can also deplete intracellular glutathione, an important antioxidant.[18]

Neurotoxicity

Neurotoxic chemicals such as lead can harm the sensitive and complex processes of central nervous system (CNS) development. Even a slight change in cell multiplication, differentiation, migration, and formation of synapses can trigger a cascade of

neurological dysfunction due to the very limited opportunities to repair and compensate for these changes.

Animal models[24-26] indicate that in the developing CNS, lead's strong resemblance to calcium is associated with adverse effects. Lead can impair dendritic spines and synaptogenesis; alter the release of neurotransmitters such as glutamate; disrupt GABAergic, dopaminergic, and cholinergic systems; and impair NMDA receptors. Prenatal exposure to lead in rodent models has been found to target dopamine and increase the myoinositol signal in the hippocampus, related to learning and memory, and thus affect neurodevelopment. Lead has also been shown to disrupt the tyrosine kinase receptor signaling system required for cell division in CNS progenitor cells.

Neurodegenerative diseases and amyloidogenesis can also be influenced by lead, with data from animal models suggesting that the pathogenesis of Alzheimer disease may be influenced by early life exposure. This further validates the idea that CNS development is a critical period that could increase future susceptibility to neurodegeneration.[18,24,27]

Clinical effects of lead

Signs and symptoms vary widely and depend on the length of exposure and cumulative amount of lead in the system. The developing child is particularly sensitive to lead exposure because of an immature blood-brain barrier, increased absorption, and usual mouthing behaviors at a young age. Comorbidities such as iron deficiency, common in infants and children, can enhance lead absorption.[2]

Studies have shown that prenatal exposure to lead, particularly in late pregnancy, is significantly associated with a reduction of the infant's growth, intensified in the presence of low maternal calcium intake.[28]

Symptoms of acute poisoning (BLL often >100 to 150 μg/dL) include nonspecific gastrointestinal symptoms like abdominal pain (lead colic) and vomiting, arthralgia, myalgia, muscle weakness, encephalopathy, ataxia, seizures, and peripheral neuropathy. With chronic exposure over months or years, lead interferes with calcium-dependent enzymes, heme synthesis, membrane integrity, and steroid metabolism. Lead accumulates, and lines can be found on gingival tissue at the base of the teeth (Burton lines) or incidentally on radiographs, usually on long bone metaphyses. Renal disease, hypertension, and degenerative diseases found in adults have been associated with childhood exposure to lead.[18,19,29]

Neurocognitive and neuropsychologic effects

Long-standing exposure to any amount of lead has been associated with intellectual disability in a dose-dependent manner, ranging from delay or loss of developmental milestones to reduced cognitive function and academic achievement. Other symptoms are shortened attention span, impaired executive function, delayed processing speed, and impairments in visual and verbal memory and visuospatial skills.[10,11,15,18,23,30,31]

Exposure to neurotoxins like lead can have pervasive and permanent effects in younger children. Lead exposure especially before age three years, even with only low levels of lead detected in the blood, has been associated with adverse effects on learning and behavior, persisting through childhood and adolescence.[6,19,32]

A recent study from 2015 that involved almost 60,000 children in Chicago found that 13% of reading failure and 14.8% of math failure can be attributed to exposure to lead, even after adjusting for gender, ethnicity, socioeconomic status, maternal education, and history of preterm birth or very low birth weight.[33] Another study that prospectively evaluated a cohort of Mexican children showed that BLL at age two years was predictive of decreased cognitive scores at age four years.[34]

Reduction in gray matter volume in adults has been associated with childhood lead exposure, especially in the prefrontal cortex, ventrolateral prefrontal cortex, and anterior cingulate cortex, structures that direct cognition and emotion.[21,35] Other areas include postcentral gyri and cerebellar hemispheres, which control fine motor tasks. Lead exposure during childhood has also been posited as a possible contributor to neurodegenerative disease, seen by a correlation between Folstein Mini-Mental Screening test scores and bone lead levels.[18]

Affective disorders such as anxiety and depression, as well as aggressive, criminal, and antisocial behaviors have been described with chronic lead exposure.[21,29,36]

Genetics and gender differences

The variability in neurological outcomes depends on genetic predisposition and interactions with the environment. Growing evidence suggests that environmental factors such as lead can impact the developing brain through epigenetic mechanisms[18,24] with long-lasting consequences and can even affect generations to come.

Gender differences have been well documented. A study that evaluated over five million BLLs in US children younger than six years from 2009 to 2015 showed a statistically significant larger proportion of high BLLs in boys than in girls,[13] findings confirmed by other studies.[14] Specific areas of the brain seem to develop differently under the influence of sex hormones and different genes in the sex chromosomes. Differences in toxicokinetics between genders may account for differences in neurotoxicity, with estrogen posited as a neural regulator with a role against neurotoxicants.[23-25]

Testing and screening

A lead level in venous blood is used for screening and diagnosis. Capillary samples need a confirmatory venous test. Other tests supporting lead toxicity include a complete blood count, which can reveal microcytic hypochromic anemia and occasionally basophilic stippling on a smear.[19] Bone lead concentration can be measured but is not the standard for screening.

In real life practice, questionnaires are commonly used as a screening tool despite evidence that questionnaires alone have failed to identify children who have elevated BLL.[37]

The CDC and American Academy of Pediatrics recommend testing children for lead, especially in high risk populations, that is, those living in older housing or in a community with high prevalence (greater than 5%) of elevated BLL (more than 5 μg/dL).[11,38] The American Academy of Pediatrics recommends testing in immigrant, refugee, and internationally adopted children. The CDC recommends screening refugee children aged six months to 16 years when they arrive in the United States and re-testing those younger six years three to six months later. A recent study from 2010 to 2014 of over 27,000 refugee children showed that nearly one in five has elevated BLLs.[39]

The Centers for Medicare and Medicaid Services require all children to receive blood lead screening at ages 12 and 24 months, or ages 36 to 72 months if they had no previous screening.[40] Each state has laws and regulations regarding blood lead tests that are then reported to the state health department.[4]

Treatment

No effective treatments have been proved to ameliorate the long-lasting neurodevelopmental effects of lead. Educating parents

and providing household cleaning supplies to decrease exposure failed to show significant reductions in children's BLL.[1] Similarly, despite a higher prevalence in children with iron and calcium deficiencies, supplementation of those minerals has not shown to be effective.

Chelation therapy is used to treat more acute lead toxicity and much higher BLL. Succimer (meso-2,3-dimercaptosuccinic acid) accelerates lead elimination from the body, but it is only marginally better than the complete cessation of lead exposure alone.[35]

Discussion: have the efforts been successful?

Over the past four decades, BLL among US children's blood lead concentrations have declined dramatically since the elimination of lead from gasoline, paints, and other consumer products:

- 1978: The US Consumer Product Safety Commission restricted the allowable content of lead in residential paint to 0.06% (600 ppm). In 2008, it was lowered to 0.009% (90 ppm).
- 1976 to 1980: Phase out of leaded gasoline. In 1994, the United Nations Commission on Sustainable Development called on all governments to eliminate lead from gasoline, and on January 1, 2000, the European Union banned leaded gasoline as a public health hazard.[19]
- 1990s: Use of lead solder in canned foods was banned in the United States.
- 1991: The US Environmental Protection Agency proclaimed the Lead and Copper Rule, which regulates tap water.
- 2008: Regulations to control lead content in toys and other consumer products.[14]
- 2011: Congress enacted the Reduction of Lead in Drinking Water Act.[19] Data from the National Health and Nutrition Examination Survey from 1988 to 2004 showed that the prevalence of elevated BLLs among children decreased from 8.6% in 1988 to 1991 to 1.4% in 1999 to 2004, an 84% decline.[13]

Despite the progress, there are still demographic disparities and BLLs continue to be higher in low-income children, non-Hispanic black children, and children living in older housing. Analysis suggests that the vast majority of US children still have some low-level exposure to lead.

A limitation on the objective assessment of the impact of the lead reduction efforts lies in the variability of exposure and the amount needed to show a definite BLL, given its nature to deposit in tissues. However, after adjusting for confounders, historical data have shown that long-standing exposure to any amount of lead is associated with detrimental neurodevelopmental outcomes in a dose-dependent manner. Interestingly, most estimated IQ points lost due to lead in the United States occur in individuals with BLL less than 5 μg/dL.[5] Reducing the number of children in the United States with elevated lead levels from 13.5 million to 250,000 would be expected to account for millions of dollars saved, and more importantly, millions of IQ points saved, and this needs to be studied further.

Screening for lead exposure has not been as successful as lead reduction efforts. Despite Centers for Medicare and Medicaid Services requirements, fewer than half of the children enrolled in Medicaid are being tested for lead.[2] We must not relax, because there is evidence that lead is still causing substantial harm to children. Primary prevention through identification and elimination of lead exposure is now widely recognized as the optimal strategy because of the irreversible effects of lead toxicity. A revision of the current guidelines as well as enforcement and promotion of screening tests should be implemented at the primary care level.

Nutritional deficiencies can increase lead absorption, so iron deficiency needs to be identified and treated along with ensuring adequate calcium and zinc intake to prevent predisposing factors.

A study concluded that states with laws to control lead were 43% to 79% less likely to have residential addresses with subsequent lead poisoning cases after identification of an index case.[40] This fact further provides evidence of the importance of enforcing policies to manage this important and preventable environmental and public health problem.

Conclusions

- Children are still being exposed to lead; this is a public health problem.
- Lead exposure in early childhood results in more severe and permanent neurological damage.
- No amount of lead exposure is deemed safe. Chronic exposure to even low levels of lead can lead to varying degrees of neurodevelopmental deficits, and in larger amounts, lead produces toxicity with multiorgan damage and even death.
- Childhood lead exposure remains a persistent problem in developing countries, where regulations like the ones established in the United States are insufficient or nonexistent. In recent years, refugee children have shown to be a high-risk population.
- Primary prevention is cost-beneficial. Because lead accumulates in the body, all sources of lead should be controlled or eliminated. Efforts cannot and should not be stopped.

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