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Review Article

Heavy Metal Body Burden – Current Day Glimpse at Xenobiotic Lead

Jennifer Gantzer*

Department of Health Sciences, US

***Corresponding Author:** Jennifer Gantzer, Department of Health Sciences, US.

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Abstract

Lead exposure in neonates, infants, toddlers, and adults is physiologically detrimental with no biological role in the human body, yet accumulation occurs in a wide range of tissue including brain, kidney, teeth, bone, and a preference for red blood cells. Xenobiotic Lead is a neurotoxin associated with brain white matter lesions as well as demyelination centrally and peripherally seen as cognitive, behavioral, developmental, and motor impairments. It induces oxidative stress and depletion of Glutathione levels in many organ systems and at higher blood levels can cause irreversible damage. Understanding entry/exit of xenobiotic Lead is vital to understanding body burden toxic accumulation and modes of elimination. Natural solutions to reduce Lead body burden are discussed alongside Lead pathophysiology.

Keywords: Lead Poisoning; Heavy Metal; Neurotoxin; Neuropathy; Glutathione; Chelation; Natural Solutions

Introduction

Lead exposure in neonates, infants, toddlers, and adults is physiologically detrimental with no biological role in the human body, yet accumulation occurs in a wide range of tissue including brain, kidney, teeth, bone, and a preference for red blood cells [1-5]. Lead exposure in even small amounts during the developmental years acts as a significant neurotoxin and chronic exposure in children induces severe neurological and developmental encephalopathies with impaired intelligence [4]. Undiagnosed and untreated childhood Lead poisoning is linked to future criminal activity, and elevated blood Lead levels (BLL) have been found in criminal and/or destructive behaviors, aggression, and ADHD [2]. Neurological deficits occur in adults seen as fatigue and lethargy, cognitive impairments, and motor nerve problems [1-6]. Lead can penetrate the blood brain barrier and upon advanced imaging of the brain, MRI commonly demonstrates white matter lesions and demyelination with no discrimination for lobes or cerebellum [6]. Lead toxicity in males is associated with significant loss of brain volume, moreso then in females. Lead is also associated with nephritis, hypertension, and gout [2,7].

Over the last 30 years, there has been tremendous focus on improving Lead poisoning and/or exposure with great success in bringing awareness to the public as well as physicians and addressing ways to lower the allowed blood Lead levels (BLL) [2,3]. The prior standards were BLL of <10 mcg/dL, however it had been well documented that significant negative health effects and adverse growth and developmental problems still existed at that range. Current day objective focuses on prevention of Lead toxicity and exposure and exists under the Healthy People 2020 initiative to eliminate BLLs >10 mcg/dL in part governed by the CDC [1-3,5]. Today, the standard has the upper limit set at BLL of 5 mcg/dL and optimal range to be <5 mcg/dL. (2,3) Conjoined efforts with the CDC, the Agency for Toxic Substances and Disease Registry for environmental health and medicine education states, "No level of Lead in the blood is safe". They explained this lowered set limit as the level at which evaluation and intervention are recommended" [2]. Ettinger., *et al.* confirms the Healthy People 2020 incentive has a very large focus especially on preventing childhood Lead poisoning. Attaining the goal requires cooperation and improvements in the following areas: blood Lead testing, surveillance, population interventions, and processes to children with potential toxicity due to exposure with intervention strategies to follow [3].

Exposure, absorption, and excretion

In 1982 significant Lead contamination for infants and toddlers came from canned infant formulas and juices, as well as infant glassed food containers, and evaporated milk cans. After recognizing these as harmful sources from the 1970s and early 1980s efforts were successful in reducing Lead contamination from food sources

[5]. Several years later, it was determined that primary exposure shifted to airborne Lead from gasoline ejections and Lead dust and ingestion of Lb paint chips [1-5]. "Although Lead-based paint and dust in the home environment continue to be the predominant sources for Lead exposure in children, exposure also occurs from Lead in air, soil, water, and nontraditional sources including foods, folk remedies, and consumer products such as spices, toys, and cosmetics among others" [3]. Unfortunately, families of lower socioeconomic status present with the highest risk [1,2]. Lead paint dust and paint chips occur from deteriorating Lead paint walls from older houses most commonly in America prior to and including 1978. Renovated remediated houses can cause secondary exposure as recontamination. Another risk includes living next to industrial sites which can continue as a source even closure of the facility, which can be another source of Lead fumes and soil deposits [1].

Understanding entry/exit of Lead is vital to understanding body burden toxic accumulation and modes of elimination. Lead elimination occurs solely through excretion via the renal filtrate into urine [8] which poses a significant problem for infants and toddlers with developing renal system and lower excretion capacities [4,8,9]. Inhaled atmospheric Lead through the respiratory tract accounts for 30-70% of absorption [3] and virtually all inhaled Lead into the lower respiratory tract is absorbed [2]. Adult gastrointestional absorption is 10%-20% after a meal rising to 60-80% absorption on an empty stomach. For children, that figure rises to 50% gut absorption after a meal, and 100% on an empty stomach [2,8]. Fasting and empty stomach allow for the highest rates of absorption. Mafaffey explains, "most investigations of food restriction on absorption and toxicity of Lead indicate that diminished food intake increases Lead absorption" [8] therefore malnourished children are at a heightened risk upon Lead exposure [2].

Additional factors allowing enhanced gut Lead absorption are low Calcium and Iron deficiency [1,2,8]. Since dietary nonheme Iron depends on dietary Ascorbate (Vitamin C) for increased gastrointestinal absorption, Vitamin C deficiency also impacts malnutrition status and increased Lead exposure risks [10]. Diets low in Calcium promote Lead deposits into non-osseous tissue. During times of mobilized tissue Lead, under low Calcium diet status, instead of renal excretion the Lead is mobilized then redistributed back into non-osseous tissue [8]. Iron deficiency enhances upwards of a 5-fold increase of gastrointestinal Lead absorption due to gut divalent metal transporter [1]. It mechanistically then poses a dual risk. In addition to enhanced gut absorption, Iron deficiency also promotes an Iron-deficiency anemia (IDA) and one of the associated symptoms is that of pica, a symptom of cravings and desire for eating non-food stuff, an underlying cause of ingesting sweet-tasting paint chips shown to be prevalent in Iron deficient pregnant mothers exposing neonates and for ingestion of Lead-based paint chips in children [2,11]. The more chronic the Iron deficiency the worsening of Lead biotoxicity [1,2,8]. Furthermore, IDA presents with hypochromatic, microcytic anemia as does anemia of Lead poisoning. (4,8) Therefore, with a pre-existing IDA even low exposure to Lead can significantly exacerbate the IDA and Lead absorption.

BLL vs Total Body Burden

Blood Lead level (BLL) is the best indicator of recent exposure and accounts for the rapidly exchangeable form with 95% on RBC erythrocyte membranes with the remaining 5% in plasma; but this accounts for only 2% of Total Body Burden. The majority of Lead is stored in skin, muscle, and internal organs, but a stable pool of Lead exists in teeth and skeletal bone, where teeth and bone comprise 95% body burden with a half-life of up to 30 years [4]. Lead likes to accumulate in the epiphyses of long bones radiologically called Lead-bands [1,6]. Additionally, bone does not benignly store elevated levels simply as Lead sequestering sites. Natural mechanisms of bone cell turnover release regular amounts of Lead into the bloodstream. Then, any mechanism that increases bone turnover rates as seen in menopause, osteoporosis [8], and hyperthyroidism [4] for example can be a source of chronic Lead exposure. Low Calcium diets present with elevated femur (osseous) and kidney (non-osseous) deposits [1,8]. Blood levels drop after chelation therapy however accumulated body burden Lead in bone and soft tissue persist as an intrinsic toxic Lead source. Additionally, pregnancy and lactation are known mobilizers of bone and tissue-stored Lead [2,8]. Mahaffey further explains the concern for neonates, "Mobilization of long-term stores of Lead from the maternal skeleton may be a major determinant in transfer of Lead from mother to infant during pregnancy and lactation." [8].

Lead symptoms and pathophysiology

The following symptoms are some of the most common warning signs of Lead poisoning and can be recognized in both children and adults to include: unexplained lethargy, comatose, and other neurological/behavioral signs such as unexplained headaches, confusion, irritability, and hyperactivity [1,4]. Other important central nervous system signs to monitor are clumsiness and decreased interest and/or activities especially in young children [1]. Persistent GI symptoms are also common with abdominal pains, constipation, vomiting, and recent onset of anorexia and weight loss [1,2,4]. A recent change in pallor of skin, especially during occurrence of abovementioned symptoms in any combination [1] indicates extreme suspicion for acute Lead poisoning and the pallor is indication of

high BLL with severe onset anemia [1,2]. Hauptman states "cognitive, behavioral, and neuropsychological effects have been shown to be irreversible, especially with BLL 20-40 mcg/dL" and he referenced a medical report of a child dying of Lead poisoning in 2006 from ingestion of a Lead charm [1].

Lead neurotoxicity presents with cognitive and behavioral symptoms, developmental delays, and motor problems. Taking a deeper look at the pathophysiology, the neurotoxicity occurs in the central and peripheral nervous systems alike with mitochondrial dysfunction, vascular injury, disturbed blood brain barrier and neurotransmitter transmission [12,13]. Brain white matter lesions were observed in frontal, temporal, and occipital lobes, in the cerebellum, and demyelination was seen centrally in the brain white matter and peripherally in the nerves [6,12]. These underlying mechanisms of injury explain behavioral and cognitive deficits, developmental issues, and motor/coordination impairments. Adult encephalopathy has been reported to occur with seizures in addition to the other cognitive and motor symptoms [6,12]. Any child suspected of Lead exposure whom presents with neurological, cognitive, and/or behavioral symptoms should be taken to the emergency room and in children BLL > 45 mcg/dL is admitted to the hospital [1].

Lead toxicity is also highly associated with the diagnostic presentation of hypertension with gout [2,14,15] and hypertension alone has been correlated to disruptions in renal function and onset of essential hypertension [2]. Several reports of damage to the ocular system and lenses have been reported [16,17]. Lead exposure and accumulation can also present as colic and chronic gastrointestinal pains [1,4,12] As previously discussed, Lead can exacerbate an existing IDA. Both Lead toxicity and Iron deficiency inhibit the synthesis of heme via the common biochemical pathway of protoporphyrin IX and inhibition of Ferrochelatase, the final step of heme synthesis [4,8]. Additionally, Lead accumulation also inhibits an earlier heme synthesis enzyme, D-Aminolevulinate Dehydratase (ALAD) [1,4]. Lead-induced anemia occurs with significantly elevated BLLs [4] such as 50 mcg/dL and more commonly presents in children at these high BLLs, however tends to be rare for occupationally exposed adults according to the ATSDR [2,4]. Anemia of Lead poisoning is more typically late phase chronic Lead poisoning in adults and is associated with very high BLLS. In all populations, it presents with pallor of skin and basophilic stippling of RBC upon blood sampling evaluation [4]. Lead preferentially accumulates in the RBC and this induces oxidative damage altering membrane structure and shape, changes RBC osmotic balance, and ultimately shortens RBC life span [18].

Lead and free radical oxidative stress

Heavy metals are known to stimulate the generation of free radicals, and Lead is no exception [18-23]. Low and high levels of Lead exposure are associated with generation of free radicals and Lead-induced oxidative stress in virtually all body systems but especially brain, blood vessels, lung, liver, and reproductive organs [19]. In xenobiotic Lead metal toxicity, free radical formation has been shown to deplete Glutathione (GSH) stores, an important intrinsic free radical fighting molecule. It's utilized in the liver's xenobiotic biotransformation pathway for conjugation and elimination of toxic substances [24,25]. The enzyme Glutathione Transferase (GST) carries out the xenobiotic-Glutathione conjugation reaction [24]. Lead intoxication causes an increase in kidney GSH levels as an up-regulation [25]. also causes a decrease in liver GSH levels [16,25]. The liver demonstrated a 61% depletion of GSH upon Lead exposure and a rise in the free radical oxidative stress marker Malondialdehyde. The lowered levels of liver GSH resulted in a concomitant decreased activity of glutathione-requiring enzyme GST [25]. People demonstrating a polymorphism (SNP) in several known lines of GST have been shown to be at a higher rate of Lead-induced oxidative damage due to lowered activity of the SNP in their GST, even at very low Lead exposure levels [24]. Supporting the synthesis and recycling of GSH and activity of GST is vital.

Decreasing Lead Body Burden and Protection from Its ROS

It's important to take into account that many different physiological imbalances and disease states simultaneously occur thereby increasing the systemic load of inflammation and free radical generation including metabolic disorders like hypertension, hypercholesterolemia, hyperglycemia, diabetes, metabolic syndrome and each of these through different mechanisms induce endothelial dysfunction (and worsened hypertension) a known driver of oxidative damage and perpetual generation of both damaging ROS (reactive oxygen species) and RNS (reactive nitrogen species). Much of the population exist in a body habitus that possesses many of these ROS generators and adding heavy metal toxicity body burden only worsens their systemic presentation of chronically elevated inflammatory markers, worsening symptoms, biotoxicity, and disease presentation [26].

Avoidance of Lead exposure and toxicity is the mainstay for Lead poisoning prevention and is demonstrated in the governmental goals for the Healthy People incentive of 2020 [2]. Prevention follows to ensure addressing dietary deficiencies of the known contributors to increased Lead absorption and biotoxicity such as Iron, Calcium, and Vitamin C [8,10]. Additionally, dietary intake and

supplementation should also include a wide range of synergistic established potent free radical scavengers and/or ROS quenchers. These need to be combinations of antioxidants such as resveratrol, curcumin, quercetin, and EGCG, phytonutrients Spirulina and Chlorella, essential B1 and B6 vitamins, essential fat-soluble Vitamin E, and aforementioned essential water-soluble Vitamin C [26-30]. The essential minerals magnesium, manganese, selenium, and copper are needed to support enzyme function and fulfill cofactor roles for optimal biochemical reactions [29,30], many of which are known to be negatively effected by Lead exposure, and worsened by chelation therapy [1,16,27]. Sulfur and thiol-containing nutrients need to be included too such as the antioxidant alpha lipoic acid (31) and amino acids methionine and cysteine. The latter two have successfully been demonstrated to rescue Lead toxicity directly; methionine can chelate accumulated Lead [32] and cysteine supplemented as NAC restores depleted Glutathione levels [17,33,34].

For hospitalized Lead patients the common chelators are CaNa2EDTA or DMSA (Succimer). According to Division of Clinical Pharmacology and Medical Toxicology, the USA preferably uses oral DMSA for BLLs greater > 45 mcg/dL and this allows for a large portion of blood Lead to be eliminated within 24 hours of administration. The IV use of CaNa2EDTA in the hospital is preserved for BLLs > 70 mcg/dL but has been shown to mobilize body burden Lead and can actually induce a Lead encephalopathy [35]. The ATSDR states the use of a Lead-challenge elimination test with CaNa2EDTA is no longer recommended to assess Lead toxicity, which should not be confused with Na2EDTA [2]. Hauptman., *et al*. suggests the use of CaNa2EDTA can also cause the loss of essential minerals, and the use of DMSA is safer and tends to be more essential mineral sparing [1]. Alternatively, Vitamin C itself has been shown to safely increase excretion of body burden stored Lead in animal studies as well as human children/adults [18,36]. There was a dose response for higher amounts of Vitamin C supporting greater Lead excretion amounts, however Vitamin C chelation alone was not conducted in grossly elevated BLLs [36].

Conclusion

Occupational hazards for adults and malnutrition and/or low socioeconomic housing for infants and toddlers pose the greatest risks for lifestyle exposures. Xenobiotic Lead exposure and toxicity can be greatly avoided by ensuring an antioxidant-rich diet including all the essential minerals and vitamins, as well as heme and non-heme sources of Iron. This helps decrease ingested Lead and improve its excretion. Daily intake of antioxidant supplements help to combat Lead toxicity free radical oxidative stress, as well as other body habitus and lifestyle-induced sources of inflammation and oxidative stress which could be occurring alongside the Lead toxicity. Chelation therapy is available for both acute and/or chronic symptomatic Lead toxicity but should be administered under a hospital or licensed trained physician. Even with chelation therapy, there is risk of loss of essential minerals and existence of oxidative species, and therefore intake of antioxidants is again highly recommended.

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