# Lead Poisoning: A Persistent Health Hazard-General and Oral Aspects

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## ABSTRACT

Because of the benefits of it's physio-chemical properties, the use of lead can be traced back to the times of Hippocrates. However, it still remains to be one of the most important and significant environmental toxicant. Toxic levels of lead has a multi systemic organ involvement which attributes to high levels of morbidity and mortality. Because of its non biodegradable nature and continuous use, lead poisoning continues to be an important public health concern. Accurate and timely diagnosis of lead poisoning should be made by thorough medical history and eliciting the spectrum of varied clinical signs and symptoms. Appropriate intervention and management by chelating agents are necessary to combat this dreaded entity.

**Keywords:** Lead, environmental toxicant, encephalopathy, anaemia, chelating agents.

## INTRODUCTION

During the early stages of evolution, medical science has used a wide range of metallic compounds. However, ongoing research on the toxic effects of these compunds has restrained their use. Unfortunately unintentional occupational exposure and ingestion of these heavy metals by industrial workers employed in paint, battery industry remains a major occupational threat. The commonly involved heavy metal agents in these occupational hazards are lead, mercury and arsenic[1]

Lead is a multitargeted environmental toxicant that is capable of causing numerous acute and chronic illnesses[2] The potential ill effects of lead can be traced back to the second century B.C., when Nikander, a Greek physician, described colic and paralysis that followed lead ingestion[3] However, lead continues to be commonly used due to its salient physio-chemical properties like softness, low melting point, malleability, ductility, poor conductibility and resistance to corrosion. It's continuous use and non- biodegradable property, leads to environmental accumulation and has significantly contributed to an increase in the prevalence related healh hazards[4] The clinical spectrum of lead toxicity ranges from subtle biochemical abnormalities to severe health emergencies. Due to it's multisystemic organ impact (Nervous system, renal system, cardiovascular system, reproductive system, haemopoietic system, gastrointestinal tract and oral cavity), lead poisioning significantly contributes to morbidity and mortality[2]

Preventive measures prove to be an integral component in the management protocol of lead poisoning. Chelating agents are the drug of choice and the specific agents are chosen in accordance to blood levels and presenting clinical manifestations[5]

**Sources of lead exposure**

Lead is a heavy metal that is both poisonous and a ubiquitous environmental toxicant. It is environmentally distributed in three forms: Metallic lead, lead salts, and organic lead containing carbon[6]

The various sources of exposure to lead are summarised in Table 1[4,7,8,9]

**Metabolism of lead**

Lead mainly enters the bloodstream via the gastrointestinal and respiratory tracts and less commonly through the skin and mucosa[10] Respiratory tract is the main route for absorption (30-70%) through which lead enter the body circulation. Gastrointestinal absorption in adults is generally less (10%), in children, gastrointestinal absorption amounts to 50% and, additionally along with inhaled lead the environment exposure is about four times higher than in adults. Lead absorption is commonly promoted by fasting states, iron deûciency and low dietary calcium[7] Only organic lead gets absorbed through the dermal and mucosal route, especially tetraethyl lead[11] After absorption, a major proportion of lead gets bound to various body tissues, like hard tissues (dense bone, hair. teeth. etc.), soft tissue (brain, kidney, bone marrow, etc ). plasma protein. and erythrocytes; while the rest is excreted with the urine, sweat, and feces[10] 99% of circulating lead is bound to erythrocytes after absorption, for approximately 30-35 days (1% of absorbed lead is found in plasma and serum) and is dispersed into the soft tissues – aorta, brain, lungs, spleen, teeth, bones, liver, renal cortex- over the following 4-6 weeks. Bones are the primary reserviour of lead content (95%) where half life of lead is decades long. Release of lead from the bones also serves as a persistant source of toxicity even after the cessation of any external source of lead toxicity[2]

**Clinical manifestations of lead poisoning**

The spectrum of clinical presentations differs in organic versus inorganic lead poisoning[11]

**Table 1: Various sources of lead**

| | |
|---|---|
| 1.Occupational | Smelting/refining lead<br>Battery manufacture<br>Plastics manufacture<br>Housing renovation<br>Lead crystal<br>Ammunition manufacture<br>Brass and bronze<br>plumbing<br>Radiation shields<br>Military equipments (jet turbines engine, military tracking systems)<br>Intravenous pumps and fetal monitors<br>Developing dental x ray films prior to digital x rays. |
| 2.Environmental | Lead paints/pigments<br>Drinking water containg<br>Lead piping and solder<br>Leaded petrol/gasoline<br>Ceramic lead glaze<br>Food eaten/stored in containers painted with lead based paints/lead containing glaze |
| 3.Recreational | Model soldier making<br>Home jewellery making<br>Indoor range firearm use<br>Ingestion of moonshine whisky<br>Petrol sniffing<br>Cigratte ash |
| 4.Others | Alternative medicines (especially south Asian)<br>Gunshot wounds<br>Mobilization of bone in hyperthyroidism<br>Eye shadow/cosmetics from developing nations<br>Lead in toothpastes |

Lead poisoning does not have pathognomic clinical manifestations, hence, making the diagnosis difficult, particularly in children[10]. Usually, most patients have a history of three to 6 months of lead intake before the onset of clinical presentation of lead poisoning. Subtle clinical effects are observed at blood lead levels of 30 to 50 PLg per 100 ml . Mild nonspecific signs and symptoms are seen at blood lead levels of 50 to 100 pg, and acute lead toxicity manifestations occur at higher blood lead levels. (greater than 80 pg per 100 ml)[9]

**Effects of lead on nervous system**

Effects of lead have the maximum predilection for the nervous system which happens to the most sensitive target for lead induced toxicity. Invlovement of the central nervous system as well as the peripheral nervous system is quite common in lead exposure. The involvement and effects on the peripheral nervous system are more commonly seen in adults while the central nervous system is far more involvement in children[12] There are several mechanisms by which lead exposure damages the human nervous systems. Direct effects on the nervous system are divided into morphological or pharmacological. When the effects are morphological in nature, they alter the nervous tissue development, specially in the prenatal to early childhood. This often involves disruption of important processes like neuronal migration and differentiation; interference with synapse formation, reduction in neuronal sialic acid production mediation; and premature differentiation of glial cells. Lead interferes with the calcium,zinc metabolisms and, also triggers processes reliant on calmodulin. Lead exposure also alters the release of neurotransmitters like the GABAergic,dopaminergic, and cholinergic systems as well asi nhibiting NMDA-ion channels during the neonatal period. In vitro studies prove that exposure to lead can activate protein kinase C in the capillary cells and inhibits Na+/K+-ATPase in the cell membrane, therefore causing interference with the energy metabolism. Within the cell, calcium from the mitochondria is affected, thus giving rise to formation of reactive oxygen species, which in turn results in mitochondrial self damage. Resulting in mitochondrial self-destruction through formation of the permeability transition pore, and priming activation of programmed cell death processes. Indirect effects on the nervous system result from interference with other body systems related to the nervous system function. Lead exposure has been found to increase risk of numerous conditions that may have adverse effects on nervous system function, including hypertension, renal insufficiency, thyroid metabolism, vitamin D deficiency, and premature birth[13]

Lead exposure can also result in encephalopathy, which presents with hallucinations, irritability, poor attention span, dullness, memory loss, muscular tremor, and headache. Increased levels of exposure resulted in encephalopathy like symptoms along with paralysis, delirium, coma, convulsions, ataxia, and lack of coordination. As children are more prone to develop neurological symptoms and tend to become hyperactive, easily irritated, and non-attentive even at the low level of exposure to lead. At higher levels of exposure, children often suffer with reduced intelligence, delayed growth and development, hearing loss and possessing only short-term memory ability. Permanent brain damage and even death might be a result of higher exposure to lead. [6]

Peripheral neuropathy, is the most common manifestation among adults with occupational exposure, Typically, involvement of extensor muscles, with very little sensory loss is often the presentation in peripheral neuropathy. A “wrist –drop” or a “foot- drop” is usually seen in case of radial and peroneal nerve induced neuropathy[14]

**Effects of lead on the hematopoietic system**

Lead has a direct effect on the hematopoietic system through two major mechanisms: a) downregulating the salient enzymes of heme synthesis, thus, limiting the synthesis of haemoglobin. b) Making the cell membranes more fragile and hence, reducing the circulating RBC’s life span[12] The resulting anemias are of two types: When blood lead levels are significantly increased for a prolonged duration, it results in Frank anemia. Hemolytic anemia is associated to a extremely high exposure to lead[6] Lead affects the heme synthesis pathway by inhibiting the three significant enzymes in a dose dependent manner. ä-aminolevulinic acid synthase (ä-ALAS) is a mitochondrial enzyme that facilitates the synthesis of ä-aminolevulinic acid synthesis (ä-ALA), starting from glycine and succinyl CoA. Two ä-ALA molecules forms porphobilinogen , in the presence of the cytosolic enzyme ä-aminolevulinic acid dehydratase (ä-ALAD). Mitochondrial enzyme ferrochelatase catalyzes the incorporation of a ferrous ion ($Fe2+$) into protoporphyrin IX to form heme[15]

Lead inhibits the cytosolic ALAD and prevents the porphobilinogen formation. The precursor 5-amino-laevulinic acid (ALA) accumulates in the plasma and triggers an oxidative stress response, as in acute intermittent porphyria. Inhibiting action of lead on mitochondrial ferrochelatase causes accumulation of free protoporphyrin IX and formation of metal chelate with zinc. (ZPP) Zinc protoporphyrin, thus, demonstrates lead exposure over the prior 3 months. Elevation of ZPP also occurs in iron deûciency anaemia, thalassaemia trait, haemoglobin E and protoporphyria[7].

The mechanism accountable for reducing the life cycle of erythrocytes is not completely clear[12] The activity of pyrimidine 5'-nucleotidase may be impaired by lead, thus, increasing the pyrimidine nucleotides in erythrocytes and averting the development of erythroid elements. The resulting effect is decreased red blood cell counts and ultimately anemia. Basophilic stippling and premature hemolysis of erythrocytes are significant biomarkers to illustrate the hematological effects of lead. However, these are not pathognomic for lead poisoning and can also be seen in other conditions. (benzene and arsenic toxicity, and in a genetically-induced, enzyme deficiency syndrome)[8]

**Effects of lead on kidneys**

Renal function abnormalities are generally associated with high levels of lead exposure (>60 ìg/dL), although damage can also occur at lower levels (~10 ìg/dL)[12] Early or acute nephropathy is mostly reversible and commonly observed in children[14] Degenerative changes in the tubular epithelium and the occurrence of nuclear enclosure bodies containing lead protein complexes forms the morphological characteristics of acute nephropathy, whereas impaired tubular transport mechanism shows the functional characteristics. This does not explain the presence of urinary proteins, although, it could be a reason for fanconi's syndrome. (Increased nonstandard secretion of amino acids, phosphates, and glucose)[6] Chronic lead nephropathy manifests mainly in adults and the effects are irreversible[14] The condition is characterized by altered tubulointerstitial and glomerular functions, causing hyperuricemia, hypertension and renal breakdown[6]

**Effects of lead on cardiovascular system**

Although the association between lead exposure and cardiovascular consequences can be traced back to more than 100 years, yet, the exact role of lead to cardiovascular disease is still ambiguous. The cardiovascular effects of lead are not only restricted to increased blood pressure and hypertension. The detrimental effect of lead is also associated with higher occurrence of clinical cardiovascular end points such as coronary heart disease, cerebrovascular accidents (stroke), and peripheral arterial disease and with other cardiovascular function anomalies such as left ventricular hypertrophy and variations in cardiac rhythm. Effect of lead on the cardiovascular system may be attributed to two major mechanisms of action. Calcium-facilitated control of vascular smooth muscle contraction and renal effects facilitated through renin-angiotensin system[16]

**Effects of lead on reproductive system**

Reproductive system in both men and women has been adversely affected by lead[12] According to study by Kafourou, diminished somatic growth in primary school children may be linked with elevated blood lead concentrations[14] Adverse effects on the male reproductive tissues are: reduced libido, abnormal spermatogenesis (reduced motility and number), chromosomal destruction, infertility, abnormal prostatic activity and alterations in serum testosterone[12] The effects of lead on the female reproductive tissues are more pronounced. Miscarriage, prematurity, low birth weight, and problems with development during childhood are the manifestations of toxic lead levels[11]

**Effects of lead on gastrointestinal system**

Severe colicky abdominal pain (dry belly ache) frequently occurs with persistent constipation, anorexia and metallic taste. Colic and constipation is usually an acute but late late manifestation of chronic plumbism. Profuse sweating and vomiting generally preceeds an attack of colic[2]

**Effects on respiratory system**

Recent studies have suggested an association between blood lead levels and childhood asthma. Although, blood lead levels are not significantly linked with a diagnosis of asthma, the higher blood lead levels may culminate to a more severe form of asthma in children. (due to eosinophilia and elevated immunoglobulin E levels)[5]

**Orofacial features**

Oral manifestations are usually seen in chronic lead poisoning. Ulcerative stomatitis, sialorrhea with swelling of the salivary glands, dysphagia, metallic taste, coated tongue, tremors of the tongue on extension[9] and gray spots on the buccal mucosa are the salient features[7] One of the earliest and consistent feature resulting from vasospasm is Facial pallor (predominantly around the mouth)[2] Gingival lead line or Burtonian line, first described by Grisolle in 1836 and later by Burton in 1840, is usually seen in 20 to 85 percent of individuals[9] The lead line typically manifests as a purple-blue line within gingival tissue or as a stippled bluish-black line at the junctions of the gums and teeth, more pronounced on the maxillary teeth. Burtonian line results from a reaction between circulating lead with sulphur ions released by oral bacterial action[1] However, this gingival pigmentation is not pathognomonic of lead poisoning and similar presentation may also be seen in other heavy metal toxicity (for example, bismuth and mercury). Gingivitis, physiological pigmentation, and discoloration due to an amalgam tattoo may also be given a place in the differential diagnosis. Disappearance of the line upon pressure by a glass slide will be seen in gingivitis. However, due to the ishemic effects of lead on the tissues, the line will get accentuated in lead poisoning. This line is not observed in the presence of meticulous oral hygiene, in the infant, or in the edentulous patient. It is rarely detected in children because of ready deposition of lead in bone tissue[9]

**Diagnostic methods**

Extensive medical history and knowledge of varied presenting manifestations is essential for a prompt and accurate diagnosis of lead poisoning.

**Hematology**

Evaluation of blood lead concentration is the most frequently available biological indicator of lead poisoning[14] A significant feature of lead poisoning is basophilic stippling (accumulation of aggregated ribosomes in red blood cells)[8] However, basophilic stippling is not pathognomic of lead poisoning and may be seen in other disorders. (Thallesemias and Iron deficiency anaemia)

Estimation of blood erythrocyte protoporphyrin (EP) is also an important diagnostic aid in lead poisoning[8] At high levels of circulating lead, EP increases, often with a delay of a few weeks. However, EP level alone is not sensitive enough to identify elevated blood lead levels below approximately 35ìg/dL. Because of the high threshold in detecting high levels of circulating lead, and the fact that iron deficiency anemia also projects increased level of EP, detection of EP levels is not used for diagnosis. Recent or current lead exposure can be detected in the blood, and is merely an indicator for recent exposure and not the actual amount of lead storage[4]

**Urine analysis**

Detection of urinary coproporphyrins is also a biomarker of lead toxicity by virtue of lead effect on heme biosynthesis. High levels of urinary coproporphyrins are usually indicative of severe cases, although, high levels of lead can also be detected in the body in the absence of coproporphyrins[9]

**Radiographic studies**

X-ray fluorescence is the most significant biomarker for measurement of total body lead and cumulative lead contact[4] Radiopaque densities or signs of paint chip intake may be demonstrated on radiographic abdominal analysis. Radiographic bone investigations reveal dense trasverse bands at the end of the long bones. These are “lead lines” which are mostly seen across the metaphyses of long bones and along the margins of ûat bones, as in the case of iliac crest. Lead line vary in their width, which depends on the level of lead deposition and also the duration of lead exposure. However radiological examination is not a sensitive diagnostic tool for acute lead poisoning[14]

Miscellaeous tests

Nerve conduction velocity testing- for cases where clinical manifestations are indicative of peripheral neuropathy.

Neurobehavioral testing- for cases where diminished cognitive function are seen and higher blood lead levels (above 80 µg/dl).

Sperm analysis is reserved for men with a history of lead contact and complaint of infertility[14]

**Prevention and treatment**

Although lead poisoning causes severe effects and is a matter of serious concern, yet importantly it is preventable. The The most important initial aspect of management of lead poisoning is the removal of the patient from the source of exposure[4] Parents should receive guidance about intervention as well as optimal nutrition. Nutritional interventions include iron and calcium supplementation, a reduced fat diet, and frequent meals, as all these measures are associated with reduced gastrointestinal absorption of ingested lead[14]

Chelating agents continue to be the mainstay of treatment for lead poisoning which forms complexes with lead, prevent its binding to cell constituents and, being hydrophilic. These drugs are metoblized and are eliminated in the urine[7] The most widely used chelating agents are Dimercaprol, also known as British Anti-Lewisite (BAL), Calcium Disodium ethylenediaminetetraacetate (EDTA), and Succimer (2,3-meso-dimercaptosuccinic acid or DMSA)[14]

**Advanced measures**

A new technique called nano-encapsulation of antioxidants (curcumin, beta carotene) may provide improved biodistribution and bioavailability of poorly soluble therapeutics through solubilisation.

A recent study on a cohort of workers occupationally exposed to lead found that worker's cohort treated with N-acetylcysteine (NAC) showed a significant reduction in the blood lead levels. Additionally, all groups receiving NAC showed a significantly elevated activity of glutamate dehydrogenase. Further, the treatment with NAC normalised the level of homocysteine and decreased oxidative stress. It can thus be concluded that NAC could be as an alternative therapeutic agent for chronic lead toxicity in humans[4]

## CONCLUSION

Lead poisoning is a serious but preventable health concern. Varied non- specific symptoms of lead poisoning make it difficult to diagnose, hence a timely diagnosis and management of the condition is of outmost importance. The general and Oral physicians should be familiar with the bizzare manifestations of the condition. The best approach is to avoid any possible exposure to lead. This can be achieved by identification of the lead sources in the environment and continued public health initiatives to remove lead from the environment.

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