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REVIEW ARTICLE

PHARMACOLOGY

# LEAD INDUCED ENCEPHALOPATHY: AN OVERVIEW

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## ABSTRACT

In behavioral neurosciences such as neurobiology and biopsychology, animal models enable investigation of brain– behavior relations, with the aim of gaining insight into human behavior and its underlying neuronal and neuroendocrinological processes. In spite of a considerable body of literature giving detailed descriptions of human autopsy material, the pathogenesis of lead induced encephalopathy is not well understood and the cause of neuronal damage is not clear. Lead is ubiquitous in our environment but has no physiologic role in biological systems. Its effects are pervasive yet often subtle, with consequences ranging from cognitive impairment in children to peripheral neuropathy in adults. Exposure of lead can take place either through inhalation of dust, fumes, vapors', or ingestion of contaminated foods or drinks. Because of its cumulative property it is capable of exerting toxic effects at any level of exposure. Toxic effect of lead on the body is known as Plumbism and it is now well recognized that inorganic lead produces not only clinically defined encephalopathies and neuropathies, but also various behavioral changes indicative of cerebral dysfunction.

## KEYWORDS

Lead encephalopathy, Neuropathies, Plumbism, Lead

## INTRODUCTION

It has been known since ancient times that lead may cause poisoning in man (1), but only within this century have extensive studies of the problem been focused. Lead is ubiquitous in our environment but has no physiologic role in biological systems. Its effects are pervasive yet often subtle, with consequences ranging from cognitive impairment in children to peripheral neuropathy in adults. Exposure of lead can take place either through inhalation of dust, fumes, vapors', or ingestion of contaminated foods or drinks. Because of its cumulative property it is capable of exerting toxic effects at any level of exposure. Toxic effect of lead on the body is known as Plumbism and it is now well recognized that inorganic lead produces not only clinically defined encephalopathies and neuropathies, but also various behavioral changes indicative of cerebral dysfunction. However, only within the past fifty years attention has been called to its effects in children (2, 3) in whom toxicity can easily be overlooked until clinically recognizable encephalopathy occurs (4). The brain is exceptionally sensitive to the effects of lead poisoning (5), and it is the young- from birth to about 7 years of age who show the most serious brain damage following lead poisoning. The clinical manifestations of lead poisoning are well defined and include headache, incoordination, tremor, twitching, convulsion, paralysis, coma and death (6). There is considerable knowledge about the histopathological condition of the brain tissue of those poisoned individuals who do not survive (7). In the brain, cerebellum was found to be most severely affected (8) accompanied by areas of focal cortical necrosis. Significant decrease in spine density (9) and reduction in the maximum width of the hippocampus (10) have also been reported. In spite of the seriousness of the clinical effects of lead on the central nervous system, less is known about lead-induced lesions of the nervous system than about renal (11) or hematopoietic (12) effects. Indeed, not all children dying of acute lead encephalopathy have discernible histologic changes. No apparent abnormality could be found by Pentschew (6) in three of twenty authopsied cases. In spite of a considerable body of literature giving detailed descriptions of human autopsy material, the pathogenesis of lead induced encephalopathy is not well understood and the cause of neuronal damage is not clear. In those poisoned individuals who do survive acute lead encephalopathy, the associated pathological changes may or may not be completely reversible (5). There is a high incidence of permanent brain damage which can lead to periodic convulsions, irritability, hyperactivity, retardation of normal development, emotional instability, behavioral disorders, low attention span, impaired motor development, and antisocial behavior.

In behavioral neurosciences such as neurobiology and biopsychology, animal models enable investigation of brain– behavior relations, with the aim of gaining insight into human behavior and its underlying neuronal and neuroendocrinological processes. The

most relevant information, of course, is derived from the study of humans, but this is not always possible. For example, behavioral dysfunctions and the underlying processes in the brain cannot be investigated in humans, except when they are assessed in a clinical setting with patients as subjects. Even then, it is difficult to evaluate the damage caused by accidents or by illness. The extent and location of the damage, and its 'history', are often unclear, and the neurobiological variables associated with behavioral dysfunctions cannot be controlled sufficiently. As a consequence, large samples are needed to achieve meaningful and interpretable results (13). While in human studies, it is, for example, very difficult to control for cohort differences between young and old subjects, especially with respect to health-related factors, but also with respect to education and events with a profound impact on the life of entire generations (14), such as war, these differences can be minimized in animal studies: breeding and housing conditions can be controlled, and the health status monitored. A comparative approach that relies on animal models could be used to answer questions about behavioral dysfunctions and their underlying neural substrate. Animals with a known and reproducible dysfunction or damage may help us to understand brain (dys) functions and their effects on behavior. Experimental manipulation of brain structures in one or more species (including humans, if possible) provides information about brain structures, function, behavior, and how they are related (15). This approach is based on the evolutionary theory and the assumption that fundamental aspects of the behavior of humans have a genetic basis with a common evolutionary trajectory, i.e., is shared with other animals (16, 17, 18). Species with behavioral or psychological repertoires similar to humans so that the results of experiments with these animal models may throw light on seemingly related behavior in human beings" (19). Thus, whereas animals are in most instances intended as model of humans, one animal species may also serve as model organism for another species. Studies, however, which explicitly compared behavior across species, are rare in neuroscience (20).

***PATHOPHYSIOLOGY***

Lead exerts numerous adverse mechanisms of toxicity.

a) Lead has a high affinity for sulfhydryl groups. It is therefore particularly toxic to multiple enzyme systems.
b) Many of lead's toxic effects also result from its inhibition of cellular function requiring calcium. Lead binds to calcium-activated proteins with much higher (105 times) affinity than calcium. The interaction of lead and calcium with cellular sites depends upon the concentration of free ions present ($Pb^{2+}$, $Ca^{2+}$). $Pb^{2+}$ and $Ca^{2+}$ compete at the plasma membrane for transport systems, which affect their entry or exit (ie, $Ca^{2+}$ channels and the $Ca^{2+}$ pump.) Intracellular $Ca^{2+}$ is buffered by proteins, endoplasmic reticulum, and mitochondria; $Pb^{2+}$ disturbs this intracellular $Ca^{2+}$ homeostasis. A ($Ca^{2+}$)-($Pb^{2+}$) interaction at the mitochondria have been described. $Pb^{2+}$ interacts with a number of $Ca^{2+}$ -dependent effector mechanisms, such as calmodulin (a $Ca^{2+}$ receptor protein, which couples to several enzymes, eg, phosphodiesterase, protein kinases), protein kinase C, $Ca^{2+}$ -dependent $K^{+}$ channels in the plasma membrane and neurotransmitter release.

***MOLECULAR MECHANISMS***

***The cellular, intracellular, and molecular mechanisms of lead neurotoxicity are numerous, as lead impacts many biological activities at different levels of control:***

1) At the voltage-gated channels, first, second, and third messenger systems
2) Lead impacts postnatal reorganization of brain through a number of recognized mechanisms: decreased oligodendrite density; myelin deposition; cortical synaptogenesis; induces precocious glial cell differentiation; blocks voltage-sensitive calcium channels; interferes with neurotransmitters; disorganized synaptic pruning; interferes with protein kinases.
3) Chronic occupational exposure led to atrophy and increased white matter lesions years after termination of the exposure. Total brain volume, frontal and total gray matter volume, and parietal white matter volume were found to be decreased. Higher measured bone levels were also associated with regionally diminished volumes in the cingulate gyrus and insula (21).
4) Lead also impacts the auditory nervous system. Lead exposure affects conduction in the distal auditory nerve and the auditory pathway in the lower brainstem. Subtle impairments of auditory processing could have profound effects on learning. Traditionally, the neuromuscular disorder associated with lead poisoning has been purely motor. However, patients may also note sensory and autonomic neuropathic features. It has been proposed that the traditional motor syndrome associated with subacute lead poisoning is more likely to be a form of lead-induced porphyria rather than a direct neurotoxic effect of lead. Toxic neuropathy caused by lead was a frequent phenomenon before 1925. In modern times, it is a distinct rarity.
5) Lead has an effect on heme biosynthesis, causing anemia at high blood levels; however, at low levels, $Pb^{2+}$ causes microcytosis (ie, decreased mean corpuscular volume [MCV] and mean corpuscular hemoglobin [MCH]) and a compensatory increase in number of red blood cells. Lead irreversibly binds to the sulfhydryl group of proteins, causing impaired function without any discernible threshold. The enzymes delta-aminolevulinic acid dehydratase, which catalyzes the formation of the porphobilinogen ring, and ferrochelatase, which inserts iron into the protoporphyrin ring, both are compromised by lead.

The inhibition of these enzymes may begin with lead levels as low as 5 mcg/dL. Ferrochelatase is the enzyme that catalyzes the incorporation of iron into the porphyrin ring. If the enzyme is inhibited (ie, lead toxicity) or inadequate iron is present, zinc is substituted for iron and zinc protoporphyrin concentrations increase. The major consequence of this effect is the reduction of circulating levels of hemoglobin. Basophilic stippling of erythrocytes may be present.

6) Lead poisoning inhibits the proximal tubular lining cells. Abnormalities that may be seen with lead toxicity include aminoaciduria, phosphaturia, and glycosuria (Fanconi syndrome). These effects are reversible. This acute from of nephropathy is more frequently reported in children. Gout secondary to lead-induced nephropathy is typically a long-term complication of occupational lead exposure. Chronic lead nephropathy, chronic tubulointerstitial nephritis on biopsy, occurs in the setting of long-term lead exposure and is often associated with hypertension and gout.

Diagnosis of chronic lead nephropathy is more difficult since the laboratory abnormalities seen with acute lead intoxication are not present with chronic lead exposure.

7) Association between blood pressure and blood lead; Nawrot et al published a meta-analysis focusing on the epidemiological reappraisal of the association between blood pressure and blood lead (22). Previous studies have reached divergent conclusions. In this meta-analysis, the association between blood pressure and blood lead was similar in both men and women. In the combined studies, a 2-fold increase in blood lead concentration was associated with a 1 mm Hg rise in the systolic pressure and with a 0.6 mm Hg increase in the diastolic pressure.
8) Lead toxicity has been associated with decreased fertility. Males with elevated lead levels have been found to have reduced sperm counts and impaired sperm motility. In females, increased infertility, stillbirths, and miscarriages have been reported in association with lead toxicity as well as reduced birth weight. Lead poisoning has also been associated with menstrual irregularity.
9) The accumulation of lead in bone cells may have toxic consequences for bone status itself. Skeletal development and the regulation of skeletal mass are ultimately determined by the 4 different types of cells: osteoblasts, lining cells, osteoclasts, and osteocytes. These cells, which line and penetrate the mineralized matrix, are responsible for matrix formation, mineralization, and bone resorption, under the control of both systemic and local factors. Systemic components of regulation include parathyroid hormone, 1, 25-dihydroxyvitamin D-3, and calcitonin. Local regulators include numerous cytokines and growth factors. Lead intoxication directly and indirectly alters many aspects of bone cell function.

a) First, lead may indirectly alter bone cell function through changes in the circulating levels of those hormones, particularly 1, 25-dihydroxyvitamin D-3, which modulate bone cell function.
b) Second, lead may directly alter bone cell function by inhibiting the ability of bone cells to respond to hormonal regulation. For example, the 1, 25-dihydroxyvitamin D-3–stimulated synthesis of osteocalcin, a calcium-binding protein synthesized by osteoblastic bone cells, is inhibited by low levels of lead. Impaired osteocalcin production may inhibit new bone formation as well as the functional coupling of osteoblasts and osteoclasts.
c) Third, lead may impair the ability of cells to synthesize or secrete other components of the bone matrix, such as collagen. Finally, lead may directly effect or substitute for calcium in the active sites of the calcium messenger system, resulting in loss of physiological regulation.

Compartmental analysis indicates that the kinetic distribution and behavior of intracellular lead in osteoblasts and osteoclasts occurs by perturbation of the calcium and cAMP messenger systems in these cells. A lead line refers to the metaphyseal line of increased radiodensity that occurs in lead poisoning. The histologic lesion consists of impaired resorption of calcified metaphyseal cartilage, depressed bone deposition on cartilaginous surfaces, and the accumulation of numerous multinucleate giant cells, some containing

lead inclusions. The lead line is the result of a lead-induced inability of cartilage-resorbing cells to degrade mineralized matrix, with a resultant impairment of metaphyseal cartilage resorption. The radiodensity of the lead line is due to persistent mineralized metaphyseal cartilage and not to a primary osseous change or lead itself.

10) Lead may also cause other signs and symptoms. Lead colic is a symptom of chronic lead poisoning and is associated with obstinate constipation. The Burton line or gingival lead line is a dark blue line along the gums, signifying lead poisoning. It occurs typically when lead poisoning is associated with poor oral hygiene.
11) Lead causes activation of protein kinase C (23) (PKC) and binds to PKC more avidly than $Ca^{2+}$, its physiologic activator. This further compound the problem with neurotransmitter release described above. Alteration of PKC function also compromises second-messenger systems within the cell, leading to further changes in gene expression and protein synthesis.
12) At higher blood levels, $Pb^{2+}$ disrupts the function of endothelial cells in the blood-brain barrier. This may lead to hemorrhagic encephalopathy, characterized by seizures and coma.

***DEVELOPMENT***

The development of encephalopathy is considered the most detrimental lead health hazard. The microvasculature of a child's developing brain is uniquely susceptible to high-level lead toxicity and is characterized by cerebellar hemorrhage, increased blood-brain barrier permeability, and vasogenic edema. Previous studies on the toxic effects of lead on the brains of young animals have shown damage to the blood-brain barrier, which in severe forms appears as a hemorrhagic encephalopathy.

***FREQUENCY***

Although no blood level of lead is considered safe, Centers for Disease Control and Prevention (CDC) have established 10 mcg/dL as the level of concern (24).

***MORTALITY/MORBIDITY***

***Essentially, 2 syndromes of lead poisoning exist, depending upon exposure;***

***1) Acute or Subacute High-Level Lead Exposure.***

With exposure to high levels of lead, patients develop lethargy, progressing to coma and seizures. Death is uncommon with appropriate medical management. Long-term sequelae depend on the duration, as well as the amount, of exposure.

***2) Chronic Low-Level Lead exposure.***

With chronic exposure to low or moderate levels of lead, subacute symptoms develop.

***AGE***

- Young children who are independently mobile are at greatest neurological risk from chronic exposure to low or moderate levels of lead.
- From the time children are able to crawl until they enter school, they are at risk of ingesting lead-containing dust. While this sometimes is associated with pica and intentional ingestion of paint chips, lead poisoning often occurs without such behavior.
- The long-term effect of lead exposure is maximal during the first 2 or 3 years of life, when the developing brain is in a critical formative stage.

***CLINICAL PRESENTATION***

The clinical presentation varies widely, depending upon the age at exposure, the amount of exposure, and the duration of exposure. Younger patients tend to be affected more than older children and adults, because lead is absorbed from the gastrointestinal tract of children more effectively than from that of adults.

- Most children with elevated blood lead levels demonstrate few, if any, symptoms that immediately suggest lead poisoning. For this reason, the Centers for Disease Control and Prevention (CDC) advocate obtaining blood lead levels in children at ages 1 and 2 if they meet ANY one of the criteria noted below. In addition, children aged 3-5 years who have not previously been tested and meet ANY one of the criteria below should also be tested.
  - Living in a ZIP code determined to be high risk based on age of housing and other factors
  - Living in or regularly visiting a house or daycare center built before 1950
  - Living in or regularly visiting a house built before 1978 with peeling or chipping paint or recent (within the last 6 mo), ongoing, or planned renovation
  - Living with or regularly visiting a sibling, housemate, or playmate with lead poisoning
  - Living with an adult whose job or hobby involves exposure to lead
  - Living near an active lead smelter, battery recycling plant, or other industry likely to release lead
- ***Furthermore, when the symptoms do occur, they are typically nonspecific. The symptoms are as follows:***
  - Temperamental liability, irritability, behavioral changes
  - Hyperactivity or decreased activity
  - Loss of developmental milestones, language delay
- ***More significant exposure to lead may cause symptoms in children that are more likely to lead to a medical evaluation. They are as follows:***
  - Abdominal pain, loss of appetite, vomiting, constipation
  - Headache, ataxia, somnolence
  - Lethargy, seizures, stupor, coma
- ***In adults, similar symptoms may develop, although cognitive changes may be discerned more easily, especially since exposures are more typically acute. In addition, adults with chronic exposure may develop other symptoms, such as the following:***
  - Weakness of extensor muscles (eg, foot drop, wrist drop)
  - Delirium, hallucinations
- ***A meticulous environmental history is necessary in patients with suspected lead exposure. Depending on whether it is tailored to children or adults, it should include the following information:***
  - Present and recent residences - Including location, age and condition of building, renovations, inspections, deleading programs; analysis of indoor and outdoor surfaces, water, and soil (if available)
  - Other potential sources of lead - Other homes where the child stays; parent working as painter or renovator or in a battery factory, shooting range, or other industry that uses lead; lead-based kitchen utensils, pottery, imported toys; lead-based folk remedies
  - Past medical history - Developmental milestones or delays; hygiene; pica; prior lead exposure
  - Occupations or hobbies - Activities of all adults in the home; practices concerning

changing of clothes; work areas in the home
- Siblings - Ages; developmental history and school performance; blood lead levels

***PHYSICAL CHANGES***

- Subtle changes in cognitive performance are not identified easily on physical examination.
- Careful mental status examination may detect changes in more severe cases, while formal neuropsychological testing may be needed to detect changes in other cases.
- Impaired fine-motor coordination[5] or subtle visual-spatial impairment may be seen.
- In adults, chronic distal motor neuropathy may be seen with decreased reflexes and weakness of extensor muscles. Sensory function is relatively spared.
- Cranial nerve involvement, particularly the optic nerve, is possible. Chronic lead exposure has been shown to cause optic neuritis and blindness (25).

***CAUSES***

All causes of lead poisoning are environmental; however, the source of lead is quite varied. Lead-based paint remains the single most significant source of lead exposure to children. Although lead in paint has been recognized as a source of neurotoxic effects for a century, not until 1977 did the Consumer Product Safety Committee mandate that lead would no longer be added to residential paint. However, this did not address problems of deteriorating paint in older homes and use of leaded paint for exterior surfaces. Flaking, dusting, and peeling lead paint is by far the number one source of lead exposure in children. However, other sources of lead in a child's environment may result in acute lead poisoning or contribute to an already elevated blood lead level.

- ***Work Environment:*** Adults may become exposed or bring lead dust home from their job on clothes, hands, hair, and shoes. Occupations with exposure to lead include house painting or wallpapering; home renovation; furniture refinishing; lead smelting or mining; firearms instruction; automotive repair; battery manufacturing or recycling; or bridge/tunnel/elevated highway construction.
- ***Hobbies:*** Certain hobbies may contaminate the home with lead dust or fumes, or contaminate the parent's clothes, hands, hair, or shoes. Examples include melting lead for homemade musket balls or fishing tackle; target shooting; making stained glass (artists may use lead solder and solid lead came, which wraps around pieces of glass and frames the artwork); and ceramics.

- ***Soil:*** Though lead was completely phased out of gasoline by 1995, lead particles emitted in engine exhaust still persist in some soil near major roadways. In addition, deteriorating exterior lead paint may contaminate the soil around old homes. Children who play in bare soil risk exposure to lead, and family members may track contaminated soil into the home on their shoes.

- ***Ceramics:*** Lead is used in some ceramic glazes because it produces certain colors and helps prevent cracking. Improperly fired glazes and deteriorating glazes may leach lead into food and beverages, especially following prolonged contact or if the food is hot or acidic. The Food and Drug Administration (FDA) has established leaching limits on commercially made or imported products, but handmade items are

not regulated. Ceramics bought in foreign countries and items not intended for food use may also leach high levels of lead.

- ***Folk Remedies:*** Some Hispanic, Indian, Asian, and Middle Eastern folk medicine practices consider heavy metals to be therapeutic. Certain folk remedies for digestive ailments have been found to contain very high levels of lead. Names include Azarcon, Alarcon, Coral, Pay-loo-ah, and Greta. The product is likely a capsule, or an orange or yellow powder, which is ingested.
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- ***Lead Solder:*** Solders with varying concentrations of lead are used in the electronics industry and in making stained glass. Though illegal, some people may use them to make fishing tackle or in home plumbing projects. Homemade moonshine stills may be soldered with lead, which can result in lead leaching into the drink (26). In 1995, the FDA banned lead-soldered food cans, but some may still occasionally be imported illegally into the United States, especially to ethnic grocery stores. Soldering is messy and creates tiny fragments and dust-sized particles of lead, as well as lead fumes.

- ***Drinking Water:*** Most public water sources are routinely tested and do not exceed the Environmental Protection Agency (EPA) lead limits of less than 15 ppb (for bottled water: <5 ppb). However, water may become contaminated if it encounters old lead-soldered pipes or lead-containing faucets inside old buildings. Lead levels are highest in water left standing in pipes for more than a few hours and in hot or acidic water. Lead levels in Washington DCs drinking water were recently found to be above EPA standards (27, 28).The cause was uncertain but may have been due to a change in water purification techniques.

- ***Fishing Tackle****:* Lead weights and sinkers are small and smooth and easily swallowed by curious children; especially when imitating adults who use their teeth to manipulate the tackle.

- ***Costume/Toy Jewellry:*** Cheap jewellry marketed to children, often sold in vending machines, and has been the source of several documented cases of acute lead poisoning. Children readily chew or suck on the items or unintentionally swallow them.

- ***Curtain Weights:*** Some are made of lead and are of swallowable size. They are sewn into the hem of curtains or drapes.

- ***Artist Oil Paint:*** One color of fine art oil paint, "flake white," contains lead carbonate. Many artists feel there is no substitute for this product, which enhances a painting's durability. They lobbied successfully for its exemption from the US Consumer Product Safety Commission's 1977 ban on lead paint.

- ***Vinyl Mini-Blinds:*** Vinyl mini-blinds made before 1997 may contain lead. Over time, exposure to heat and sunlight deteriorates the vinyl and lead dust forms on the surface. Blinds made with lead were recalled and banned by the Consumer Product Safety Commission in 1997, but prior to then millions of them were sold and are likely still in many US homes.

- ***Pool Cue Chalk:*** The use of lead as a coloring agent in pool cue chalk is often

denied by the industry. Nevertheless, one study in 1996 did conclude that 3 of 23 brands of pool cue chalk tested contained lead; one as much as 7000 ppm.

- ***Antique Toys:*** The Consumer Product Safety Commission continually screens newly produced toys for hazardous substances including lead or lead paint. Antique toys, however, may contain lead, especially toy cars, planes, or trucks; painted toys; and toy soldiers or other figurines.
- ***Glassware:*** Like ceramics, leaded crystal can leach lead into food or beverages, especially following prolonged contact or if the beverage is acidic. Experts advise against storing beverages in a lead crystal container or drinking from crystal routinely. Leaded crystal baby bottles should never be used.

- ***Kohl:*** Kohl is an ancient black cosmetic still used by some women in the Middle East, Asia, and Africa. It often contains ground galena, a metallic mineral and source of lead. Some cultures also put kohl on the umbilical stump of newborns, or decorate the eyes and faces of children.

- ***Mexican Candies:*** Studies have found high levels of lead in many Mexican candies, especially those with tamarind or chili powder as an ingredient. Ink used to print the wrappers has also been shown to contain dangerous amounts of lead.

- ***Projectiles (eg, bullets)****:* Lead has been used to make projectiles since the mid 15th century. Its widespread availability, malleability, and high density continue to make it ideal for this purpose. Today, most bullets for shotguns, handguns, and rifles are made of a lead core surrounded by a copper or steel jacket to protect the lead from changing shape at high speeds. Economical solid lead bullets are also available, as are traditional lead musket balls. Curious young children will readily swallow projectiles. Buckshot (small balls of lead used by hunters) may remain in cooked game and be unintentionally eaten. Also, lead from projectiles that remain lodged in the acidic synovial fluid of joints can be absorbed into the blood.

***IMAGING STUDIES***

- Neuroimaging (eg, MRI, CT) does not play an important role in the diagnosis of lead poisoning. However, cerebral edema and microhemorrhages may be seen in patients presenting with acute encephalopathy on both CT and MRI. With chronic exposure to lead, patchy calcifications may be seen. Atrophy and white matter changes may be present with chronic exposures. Atre et al reported a case of lead encephalopathy with MRI findings of symmetric occipital lobe lesions that were bright on T2-weighted and fluid-attenuated inversion recovery images and hypointense on T1-weighted images (29).These lesions disappeared after chelation therapy with clinical laboratory improvement.

- Classic findings of lead lines on radiographs of long bones are seen rarely, as most cases of lead poisoning in children are due to exposures to low or moderate amounts of lead. Obtaining radiographs in search of lead lines is not recommended by the CDC.

- In selected cases, abdominal radiographs may demonstrate lead-containing paint

chips or other lead-containing objects. Retained lead objects within the gastrointestinal tract are an acute emergency and should prompt referral for potential removal.

- EEG findings can be normal or show nonspecific findings and are generally not helpful in the diagnosis.

***OTHER TESTS***

Formal neuropsychological testing provides the best measure of a patient's cognitive impairment. This is effective in tracking improvement in attention, visual-spatial abnormalities, and memory as a result of treatment and in establishing the extent and nature of long-term impairment.

***MEDICAL CARE***

Medical treatment is one element of a comprehensive treatment plan for exposure to lead; removal of the source of lead exposure is more important. Interventions described below relate to chelation therapy for the most severe cases of lead poisoning. Chelation is of only transient benefit in the patient whose source of lead exposure has not been identified and removed.

- ***Succimer (Chemet)*** is a water-soluble, oral chelating agent that is appropriate for use with blood lead levels above 45 mcg/Dl (30).

- ***D-Penicillamine (Cuprimine)*** is a second-line oral chelating agent, although it is not approved by the US Food and Drug Administration (FDA) for use in lead poisoning.

- ***Calcium Disodium EthyleneDiamine Tetra-Acetate ($CaNa_2$ EDTA [calcium disodium versenate])*** is a parenteral chelating agent. It should never be used as the sole agent in patients manifesting with lead encephalopathy because this agent does not cross the blood-brain barrier and can potentially lead to exacerbation of lead encephalopathy. Dimercaprol, which does cross the blood-brain barrier, should be administered first. Life-threatening hypocalcemia has been reported when disodium EDTA was inadvertently substituted for calcium disodium EDTA.

- ***Dimercaprol (British AntiLewisite [BAL])*** is another parenteral chelating agent recommended as an agent of first choice for patients with lead encephalopathy. With high blood lead levels (ie, >100 mcg/dL), it is used in conjunction with $CaNa_2$ EDTA.

***OUTPATIENT CARE***

- After chelation, the blood lead level should be rechecked in 7-21 days to determine whether repeat chelation therapy is required.
- Do not discharge patients from the hospital until they can go to a lead-free environment.

***DETERRENCE/PREVENTION***

- ***In cooperation with local health departments, the physician should educate families about the following:***
  - Causes and effects of lead poisoning
  - Relationship between blood lead level and anticipated medical or neuropsychological problems
  - Importance of follow-up or serial blood lead level determinations to monitor effects of treatment and environmental lead abatement
  - Identifying and eliminating possible sources of lead exposure

- Increased lead absorption in patients with iron-deficiency anemia
- Local resources about lead exposure and treatment

- Each patient requiring treatment for lead toxicity should be reported to local health authorities, so that they may initiate appropriate environmental evaluation and lead abatement.

***PROGNOSIS***

- Lead poisoning in children has been associated with lower intelligence quotient (IQ) scores. Prospective cohort studies have demonstrated effects with blood lead levels as low as 10 mcg/dL. Cohort studies demonstrate an effect regardless of socioeconomic group and indicate a loss of 3 IQ points for every 10 mcg/dL blood lead level above 10 mcg/dL (31, 32, 33, 34).
- Impairment of attention also may result from lead poisoning, creating a clinical syndrome difficult to distinguish from attention deficit hyperactivity disorder.
- Fine motor coordination may be impaired, with one cohort study suggesting a dose-effect relationship between incoordination and lifetime postnatal lead exposure (35).
- Both receptive and expressive language may be impaired with lead poisoning. Verbal comprehension and auditory processing have been reported in affected children.
- With occupational exposure, progressive cognitive decline years after the exposure has terminated has been documented.

***MEDICOLEGAL PITFALLS***

- The primary medical legal pitfall is not considering lead as a potential cause of encephalopathy in a child or adult. Lead toxicity is a tremendous mimicker of other diseases.
- Another pitfall is failure to assess the source of lead. Children in particular should not be allowed to return to a lead-contaminated environment. Involvement of the local Health Department can assist in assessment of the source of lead.

***SPECIAL CONCERNS***

Lead can cross the placenta. Blood lead levels tend to remain constant throughout pregnancy in women who were exposed to lead previously, even if no additional exposure to lead is present. Further occupational exposure or ingestion of lead may result in harm to the fetus. This may range from delay in later cognitive development to stillbirth, depending on the extent of exposure.

***REGULATIONS***

***1) CPSC***

- Furniture articles for consumer use that bear paint with lead at levels greater than 0.06% of the total weight of the solid or dried paint film are banned Metal-cored candlewicks containing more than 0.06 percent lead by weight in the metal, and candles with such wicks, have been banned Paint or any other surface coating materials for consumer use may not contain lead at levels greater than 0.06%.
- Toys and other items for child use that bear paint with lead at levels greater than 0.06% of the total weight of the solid or dried paint film is banned.

***2) DOT***

- Lead, numerous specific lead compounds, and lead compounds not otherwise specified are all considered hazardous materials and requirements have been prescribed for shipping papers, package marking, labeling, and transport vehicle placarding for the shipment and

transportation of these hazardous materials.
- Numerous lead compounds are considered marine pollutants and requirements have been prescribed for marking the packaging and transport vehicles containing these materials.

***3) EPA***

- ***Clean Air Act***

***Mobile Source Air Toxics:*** Lead Compounds listed as a Mobile Source Air Toxic for which regulations are to be developed

***NAAQS:*** National primary and secondary ambient air quality standard = 1.5 µg/m3 (lead and lead compounds)

***NESHAP:*** Lead Compounds listed as a Hazardous Air Pollutant (HAP)

***NSPS:*** Manufacture of tetraethyl lead, tetramethyl lead, and tetra (methyl-ethyl) lead is subject to provisions for the control of Volatile Organic Compound (VOC) emissions. **Prevention of Accidental**

***Release:*** Threshold Quantity (TQ) = 10,000 lb (tetramethyl lead) **Urban Air Toxics Strategy:** Lead Compounds identified as one of 33 HAPs that present the greatest threat to public health in urban areas. Gasoline shall not be sold for use in motor vehicles, as defined by the Clean Air Act, which contains lead additives or contains lead at a concentration greater than 0.05 grams/gallon

- ***Clean Water Act***

***Biosolids Rule:*** *Ceiling concentration of total lead for land application = 840 mg/kg*
***Effluent Guidelines:*** Listed as a Toxic Pollutant (lead and lead compounds)

- ***Comprehensive Environmental Response, Compensation, and Liability Act***

Reportable Quantity (RQ) = 10 lb (lead, lead acetate, lead chloride, lead fluoborate, lead fluoride, lead iodide, lead nitrate, lead phosphate, lead stearate, lead subacetate, lead sulfate, lead sulfide, lead thiocyanate & tetraethyl lead); 1 lb (lead arsenate)

- ***Emergency Planning and Community Right-To-Know Act***

***Toxics Release Inventory:*** Lead and lead compounds are listed substances subject to reporting requirements.

- ***Federal Insecticide, Fungicide, and Rodenticide Act***

Registrations for most non-wood preservative uses of inorganic arsenicals, including lead arsenate, have been cancelled.

- ***Resource Conservation and Recovery Act***

***Characteristic Toxic Hazardous Waste:*** TCLP Threshold = 5.0 mg/L
***Listed Hazardous Waste:*** Waste codes in which listing is based wholly or partly on lead or lead compounds - F035, F037, F038, K002, K003, K005, K046, K048, K049, K051, K052, K061, K062, K064, K069, K086, K100, P110, U144, U145, U146

- ***Safe Drinking Water Act***

Treatment Technique, Action Level = 0.015 mg/L (lead)
Numerous requirements have been established to reduce exposure to lead in drinking water due to lead leaching from lead pipes and lead fittings

- ***Toxic Substances Control Act***

A seller must disclose to the purchaser of a home any known lead-based paint hazard where a lead hazard is defined, in part, as lead concentrations exceeding 40 µg/ft2on floors or 250 µg/ft2 on interior window sills (dust-lead); 400 ppm (soil in play area) or 1,200 ppm (bare soil in rest of yard)

Lead-Based Paint Poisoning Prevention Regulations stipulate that paint used in home renovations shall not contain lead at levels greater than 1.0 mg/cm2 or 0.5% by weight.

***4) FDA***

A permanent and conspicuous warning statement shall be applied, e.g., embossed on ornamental or decorative ceramic ware that contains lead that leaches in excess of levels permitted for ceramic food ware stating that the vessel is not for food use and may be harmful if used for such.

A number of food ingredients that are Generally Recognized As Safe (GRAS) are permitted for use in foods for human consumption providing maximum lead levels do not exceed concentrations which range from 0.1-10 ppm

Action levels for lead in ceramic flatware, hollowware, cups, mugs and pitchers range from 0.5-3.0 ug/mL of leach solution.

Lead acetate-containing hair coloring must provide warning labels and may be safely used in cosmetics intended for coloring hair on the scalp if lead levels do not exceed 0.6% (weight to volume)

Lead solder may not be used in food cans.

Lead specification limits in various color additives range from 5-70 ppm

Maximum permissible level of lead in bottled water = 0.005 mg/L

Select food additives are permitted for use in animal feed with maximum lead levels ranging from 10-30 ppm

Lead specification limits in various food additives range from 0.1 to 50 ppm (select items as specified by the regulation); from 0.5 to 2 mg/kg (select items as specified by the regulation); or up to a maximum of 0.002% (select item as specificed by regulation)

Select vitamin preparations are permitted for use in animal feed with lead levels not to exceed 10 ppm

Some drug substances and excipients have limits for heavy metals (including lead), generally 10 or 20 ppm. These limits are given in the U.S. Pharmacopeia.

***5) HUD***

A seller must disclose to the purchaser the presence of any lead-based paint in a home forsale, provide an EPA pamphlet on the health effects of lead, provide records on lead based paint used in home, and provide a 10-day period to conduct a home inspection.

***6) OSHA***

Permissible Exposure Limit (PEL) = 0.050 mg/m3 (metallic lead, inorganic lead compounds, organic lead compounds called "soaps")

“Comprehensive Standards” for occupational exposure to lead have been developed.

***GUIDELINES***

***1) ACGIH***

Threshold Limit Value - Time-Weighted Average Limit (TLV-TWA) = 0.05 mg/m3 (lead, inorganic lead compounds, lead chromate); 0.15 mg/m3 (lead arsenate, tetramethyl lead); 0.1 mg/m3 (tetraethyl lead)

***2) CPSC***

Requests manufacturers to eliminate the use of lead that may be accessible to children from

products used in or around households, schools, or in recreation. CPSC Recommends that, before purchasing products for resale, importers, distributors, and retailers obtain assurances from manufacturers that those products do not contain lead that may be accessible to children.

***3) NIOSH***

Immediately Dangerous to Life and Health (IDLH) = 100 mg/m3 (as metallic lead)
Recommended Exposure Limit (REL) = 0.050 mg/m3 (metallic lead, lead oxides, and lead salts (including organic salts such as lead soaps but excluding lead arsenate))
*No separate CAS registry number is assigned to lead compounds.

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