Editorial

Lead Toxicity

In the recent past lead toxicity has emerged as an important global problem with public health consequences, particularly in children, due to its serious impact on brain function. There is in fact an urgent need for developing countries to generate data on the nature and extent of the problem so that appropriate steps can be taken to prevent lead toxicity. In this communication, we highlight certain important facets of lead toxicity.

Sources

The important sources of lead exposure include gasoline additives, food can solder, lead based paints, ceramic glazes, drinking water system, cosmetics and folk remedies, and battery/plastic recycling industry. In India, the main source of lead pollution is through automobile exhaust because of the use of unleaded gasolene. In developed countries like UK, the Royal Commission(1) on environmental pollutants has banned the use of leaded gasolene. In India, first National Emission standards for lead and other pollutants were issued in February 1990 through an Extraordinary Gazette of India. These standards were revised and promulgated in April 1996 and will be applicable till 2000-2001. However, these recommended permissible limits of lead (0.56 g/1) are still very high than the levels (0.013 g/1) in developed countries such as USA, UK and Germany(2).

Absorption and Metabolism

Lead is absorbed by. ingestion, inhalation and through skin. Absorption varies from individual to individual and depends on the chemical form of lead and type of exposure. The alimentary and respiratory tracts are the main portals of entry for lead into the body. It is estimated that 150-300 µg of lead is ingested through the oral route and about 10-20 µg is inhaled via the respiratory tract daily(3). The absorption of lead through oral route is 5-10% and 35-50% from respiratory tract in adults. Unlike adults, children absorb about 50% of ingested lead and retain 8% of dietary lead(4). The organic lead compounds like tetraethyl or trialkyl lead can be readily absorbed through the unbroken skin. Approximately 90% of absorbed lead is reported to be stored in the bone with a half life of 600-3000 days. The remaining 10% is stored in soft tissues like kidney, brain and liver. The half life of lead in these tissues ranges from 100-200 days(5). Lead passes through the placenta easily and fetal blood has almost the same lead concentration as maternal blood(6). Ninety per cent of the ingested lead is excreted in the stool and urine, whereas the inhaled lead is excreted through renal pathway. Lead is also eliminated through sweat and mother's milk.

Toxicity

Lead toxicity is termed as "plumbism" or "saturism". It is known to cause acute, chronic and sub-clinical toxicity.

Acute Toxicity

Acute poisoning is uncommon. It results from inhalation of large quantities of lead due to occupational exposure among industrial workers and in children through ingestion of large oral dose from lead based paint on toys. Acute lead toxicity is also noticed among children with pica. The clinical symptoms of acute lead

poisoning are characterized by metallic taste, abdominal pain, vomiting, diarrhea, anemia, oliguria, collapse and coma.

Chronic Toxicity

This is more common and can be described in three stages of progression: *(i)* The early stage is characterized by loss of appetite, weight loss, constipation, irritability, occasional vomiting, fatigue, weakness, lead line of gums and anemia; *(it)* The second stage is marked by intermittent vomiting, irritability, nervousness, tremors and sensory disturbances in the extremities, most often accompanied by stippling of red blood cells; and *(Hi)* A severe stage of toxicity is characterized by persistent vomiting, encephalopathy, lethargy, delirium, convulsions and coma(3).

Sub-Clinical Toxicity

Chronic low levels of lead exposure particularly through environment often do not result in overt manifestation of toxic symptoms but lead to chronic, slow, progressive and usually irreversible toxicity of hematopoietic, nervous, renal, gastrointestinal and reproductive system.

Effect on the Hemopoietic System: Biochemical effects of lead and its deleterious action on hemopoietic system is well known. As lead has very high affinity to bind to red cells, hypochromic microcytic anemia due to bone marrow depression is reported; but not all patients with lead poisoning are anemic(7).

Lead induces critical derangement in hemebiosynthesis and leads to increased excretion of porphyrins and its precursors into urine(3). Blood lead concentration at low levels (30-35 µg/dl) inhibits the enzyme, d-amino levulunic acid dehydratase (ALAD) which is responsible for coupling of two molecules of amino levulunic acid (ALA) to form porphobilinogen and further synthesis of hemoglobin.

Effects on the Nervous System: Lead is known to affect both peripheral and central nervous system. High lead exposure causes encephalopathy, the classical signs and symptoms of which are ataxia, coma and convulsions. Milder exposure may decrease peripheral nerve conductions which are indicative of involvement of nervous system. Chronic low exposure produces psychological disturbances such as learning difficulties, behavioral changes and intelligence defects especially in children. Peripheral damages range from paresis to slight functional impairment detectable only by electrophysiological techniques. The U.S. Environmental Protection Agency(8) declared lead as a 'neurotoxin' that causes encephalopathy, overt serious and potentially fatal and irreversible clinical disorders of nervous system. Recently, the Child Development Center (CDC) USA has reported that blood lead level around 10 (ig/dl can result in cognitive deficits in children(9).

Effect on Renal System: Lead is known to cause sub clinical kidney damage which is related to the extent of exposure. Histopathological studies in animals have demonstrated tubular damage. Clinical studies have also indicated ultra structural changes of proximal tubule at very low blood lead concentrations(10).

Effect on Gastrointestinal System: Lead poisoning causes loss of appetite, epigastric distress, nausea, indigestion, abdominal colic and constipation or diarrhea. The mechanism of lead colic is not clear but involves contraction of smooth muscle of intestinal wall. The gastrointestinal symptoms are reversible with chelation therapy. There is no definite evidence of liver toxicity due to lead(11).

Effect on Reproductive System: Lead causes sterility in males by damaging the germinal epithelium and also spermatocytes(3). In females, menstrual irregularities, still birth, preterm deliveries and unexplained sudden death of infants are also reported(11).

Toxicity in Children

In the last few decades, many epidemiological and experimental evidences point out that lead even at low levels of exposure can cause harmful effects specially at the crucial stages of brain development. Experimental evidences further suggest that lead retards synaptogenesis and reduces cortical connectivity which is responsible for behavioral changes at subcellular levels(12). The deleterious effects of lead poisoning on growth and development of nervous system of young children has also been documented^). Between 1940 and late 1970's several studies on lead exposure and cognitive deficit in children were reported(14). It is known to reduce IQ resulting in reading and learning disabilities, reduced attention span and produce hyperactivity and behavioral problems. The Surgeon General Report(15) estimates that 20,000 to 40,000 children in USA have elevated blood lead levels (> 40 µg/dl) and 1% of these develop brain damage and about 0.1% develop lead encephaiopathy. A group of studies(16) demonstrated the inverse associaton between psychological tests, such as neuropsychological, cognitive and behavioral assessments and dentile lead levels. The results of the animal experiments clearly indicate that astrocyte specific protein, which is important for brain development is inhibited by lead. Some of the recently conducted studies in USA suggest that chronic exposure to lead will inhibit the process of endochondrial bone formation in children.

We have observed high blood lead levels in 3 categories of children occupationally exposed to lead. It was alarming to note that in Indian children working in petrol bunks, the blood lead levels were high (35 µg/dl) while in children working in bangle making industry, the mean blood lead levels were 30 (µg/dl. In pica eating children, 47% had blood lead levels around 30 (µg/dl. Children with pica have retarded intellectual development as assessed by Raven progressive matrices(17). Higher hair blood lead levels (23 µg/g) have been observed(18) in hyperactive children as compared to normals (16.8 µg/g). Investigations in blood lead levels in various cities such as Mumbai revealed that in high traffic area, in 75% children the blood lead is > 10 µg/dl, while 10% adults in the vicinity of jewellery industry and 50% of occupationally exposed adults have levels >25 µg/dl(19). In another study, in children residing within 5 km of food packing industry, the blood lead levels were between 22-58 µg/dl and 62% had levels > 34 (µg/dl. There was a significant decrease in blood lead levels of children residing 5-20 km from the above industry(20). The Center for Disease control(9) recently revised their decision and declared that blood lead levels above 10 µg/dl in children and pregnant women are enough to be considered as neurotoxic.

Influence of Nutritional Status

There is scant information on the interaction of lead and nutritional status in the clinical situation. The intensity of changes seen in lead sensitive parameters like inhibition of certain enzyme systems, alteration in neurotransmitter levels, degeneration of myelin, glial and neural elements, impairment of fine and gross motor coordination and lower IQ were found to be aggravated in subjects with poor nutritional status. There are a few clinical reports indicating

that intake of high fat enhances the absorption of lead, whereas low protein levels increase the retention of lead in soft tissues. Lead is also known to cause deficiency of riboflavin, nicotinic acid and folic acid. Among the various micronutrients, calcium, selenium, zinc and iron deficiencies aggravate lead toxicity(21). In our country, micronutrient and energy deficiencies are major public health problems. It is even more important for us to examine these interactions.

Other Effects

There are a few reports indicating the effect of lead directly on cardiovascular system. A high incidence of hypertension with renal impairment among occupational workers exposed to lead has been reported. However, such effects are still debatable(22). Lead can also induce chromosomal aberrations(23).

Diagnostic Criteria for Assessing Lead Toxicity

During the past 50 years extensive attempts have been made to quantitate the impact of lead exposure on human health(11). The clinical diagnosis is difficult in the early stages as the symptoms are non specific while the late symptoms that are specific are too late for prevention *(Table I).* The advanced symptoms are observed only in established cases of lead poisoning with blood lead levels as high as 80 µg/dl.

Blood Lead Levels

The monitoring of blood levels does not always give an accurate estimate of total body burden of lead, duration of exposure and extent of sub clinical toxicity as 90% of lead is stored in bone. Therefore there is a difference of opinion among various international agencies on fixing the safe limits of blood lead levels *(Table II).* Nevertheless, blood lead levels indicate current ongoing exposures. The consensus today is that it **is** not only important to monitor the blood lead levels but also to detect sub-clinical damage specially at cellular level using reliable biochemical markers. Some of the biochemical markers that are reported to be

TABLE I–*Blood Lead Levels and Clinical Findings*

Blood lead levels (µg/dl)	Sub-cellular/ Clinical changes
10-25	Cognitive deficits in children No effect in adults Alterations in neuropsychological functions in children
25-50	– 50-60% inhibited ALAD activity – 4-8 fold increase enzymuria – Possible decrease conduction in peripheral nervous system
50-80	– Non-specific complaints – 50-60% inhibited ALAD activity – 4-8 fold increase enzymuria - Mild renal dysfunction – Reticulocytes and basophilic stipplings. – Decreased peripheral nerve conduction
≥ 80	– Colic, irritabiliy, nausea, vomiting, convulsions, coma – 50-60% inhibited ALAD activity – Fanconi Syndrome – Minimal to severe brain damage – Weakness/paralysis neuropathy – Minimal learning disability to profound mental and behavioral problems – Convulsions and blindness

Abstracted from Reference 3.

TABLE II–*Views of International Agencies on Blood Lead Levels*

Blood Lead Levels (µg/dl)	Effects	Comment	Source
80	Toxicity in children	Immediate medical attention required	US Surgeon General Report (1971)
< 80	No effects	Safe limit	National Institute of Occupational Safety, USA (1972)
50	Likely to develop toxicity in adults	Upper normal limit	Massachusetts Public Health Department (1973)
> 25	Cognitive deficit in children	Toxic range	Medical Research Council, London, UK (1983)
> 60	Likely to develop toxic effects on hemopoietic and nervous system in adults	Biological screening test required	WHO (1986)
50	Likely to develop toxic effects in workers	Compensation recommended	Workers' Compensation Board, USA (1986)
> 50	Likely to develop toxicity in workers	Change of work place adviced	US Occupational Safety and Health Dept (1991)
10	Neurotoxic effects in children	Toxic range	Center for Disease Control, USA (1991)

sensitive enough to detect such damages are enumerated here

Estimation ofd-ALAD in Blood

The toxic effects of lead on heme synthesis are very well documented The first step in the synthesis of heme is coupling of two molecules of d-ALA to form porphobilinogen m the presence of an enzyme ALAD The ALAD from most species have same molecular weight and number of sulfhydryl (-SH) groups which are responsible for its maximum activity Lead inhibits the ALAD activity by blocking the-SH groups The estimation of basal ALAD and its *in vitro* restoration (% stimulation) using dithiothereitol (DTT) is a measure of the extent of interference of lead in the process of heme system(24) The inhibitory levels of ALAD have been demonstrated even at blood lead concentrations of 30-50 M-g/dl which were considered to be safe a decade ago(25)

Estimation of Enzymes in Urine

Lead accumulates in the S_3 segment of renal proximal tubule The assessment of renal damage/injury based on serum creatinine/urea is insensitive However, low levels of lead exposure do not usually

result in overt nephrotoxicity, but causes ultrastructural damage of renal tissue(26). Since a decade the estimation of enzymes in urine (enzymuria) is gaining acceptence as a potential diagnostic tool to detect early renal damage. Among the various enzymes, the estimation of urinary N-acetyl beta-D-glucosaminidase (NAG) is a reliable, sensitive index of early renal injury(27). Enzymuria (enzymes in urine) indicating early renal injury has been documented in subjects with blood lead levels of 60-70 jig/dl(27). A clear dose-effect relationship between NAG and lead exposure is reported(28). In India, a significant correlation was documented between urinary NAG and blood lead levels in auto garage employees and monocasters(29).

Treatment and Prevention

The conventional treatment of this major prevalent disease of environment origin(30) involves the use of well known potent chelators like ethyline diamine tetra acetic acid (EDTA) and Aimercaprol (BAL). However these potent chelators have disadvantage including possible renal toxicity, pain at injection site and low absorption which preclude their routine use. Recently, the use of oral DMSA (Dimercapto succinic acid; Trade Name - Succimer) has been reported to be effective with a wide therapeutic index for treatment in children with blood lead levels above 20 µg/dl(31). However, it is an expensive treatment and the drug is riot marketed in India.

Recent data suggests that dietary factors decrease absorption of lead. The role of vitamins specially that of thiamin in treating/preventing chronic lead toxicity in animals has been explored(32). Our studies on therapeutic efficacy of thiamin in animal and human experiments also confirm its beneficial effects. A pilot study on monocasters suggests that the administration of thiamin not only restores 30-50% of the basal ALAD activity but reverses the urinary NAG activity and reduces 25-30% of blood lead levels in a span of 10 months. *In vitro* studies using NMR spectroscopy indicate that thiamin can chelate lead(33).

It is important to realize that lead has no physiological benefit and its intoxication is preventable. The only primary prevention is limiting exposure to lead in the environment. In developing countries such as India, it may be difficult to prevent the potential sources of exposures, namely gasoline additives, lead in paints, water pipes and batteries. Intervention requires a source specific approach. The Government should adopt and enforce regulation to control industrial air, water and other emissions. Cottage industries such as bangle making sectors should not employ children. Child labor in petrol and auto garages should be prevented. Occupational exposures or air level monitoring coupled with blood lead screening in workers should be made mandatory. Use of safer technologies, protective clothing and filters can bring down the exposure. Household traditional remedies need to be checked for lead content. A fresh look at lead content in drinking water and in building materials is the need of hour. Above all information needs to be generated on lead burden in different segments of the population for controlling exposure.

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