



A REVIEW ON PAEDIATRIC LEAD TOXICITY

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ABSTRACT

Lead is a metal which has been associated with human activities for the last 6000 years. In ancient civilizations, uses of lead included the manufacture of kitchen utensils, trays, and other decorative articles. However, lead is also toxic to humans, with the most deleterious effects on the haemopoietin, nervous, reproductive systems and the urinary tract. The main sources of lead exposure are paints, water, food, dust, soil, kitchen utensils, and leaded gasoline. The majority of cases of lead poisoning are due to oral ingestion and absorption through the gut. Lead poisoning in adults occurs more frequently during exposure in the workplace and primarily involves the central nervous system. Symptoms of haemopoietin system involvement include microcytic, hypochromic anaemia with basophilic stippling of the erythrocytes. Hyperactivity, anorexia, decreased play activity, low intelligence quotient, and poor school performance have been observed in children with high lead levels. Lead crosses the placenta during pregnancy and has been associated with intrauterine death, prematurity, and low birth weight. In 1991, the Centers for Disease Control and Prevention in the USA redefined elevated blood lead levels as those ≥ 10 $\mu\text{g}/\text{dl}$ and recommended a new set of guidelines for the treatment of lead levels ≥ 15 $\mu\text{g}/\text{dl}$.

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INTRODUCTION

Background

Lead is a widely used metal, but it is simultaneously a versatile, subtle, and persistent poison. Significant exposure to lead is an environmental threat to optimal health and to physical development in young children that affects all socioeconomic groups [1]. However, the deleterious effects of lead may be efficiently prevented by applying specific regulations to its use. Metallic lead has constituted a part of the human environment for over 5000 years [2]. The characteristic features of lead toxicity, including anaemia, colic, neuropathy, nephropathy, sterility, and coma, were noted both by Hippocrates and Nikander in ancient times [3]. In 370 BC, Hippocrates first described abdominal colic in a man who mined metals [2]. The effects of lead toxicity on young children were first described in 1892 in Brisbane, Australia [4]. Even though two thousand years have passed since Vitruvius chronicled the dangers of lead in water supplies, this threat to public health still remains with us [5]. Besides drinking water, paint and leaded gasoline have also been identified as major sources of lead exposure. Lead in household paint was recognized as a danger early in the 20th century [6].

In 1923 a General Motors chemist, Thomas Miggely, found that tetraethyl lead was an effective anti-knocking agent and boosted engine power. When this company began to manufacture tetraethyl lead, workers started to display signs and symptoms of psychosis, and much fatal causality. In spite of this, leaded gasoline continued to be used for almost 70 years. The removal of lead from gasoline in 1990, regarded by many as one of the major public health triumphs of the 20th century, was a major victory for the environment and had an immediate impact [7,8].

Absorption of Lead

Lead may enter the body by ingestion through the intestines, through the lungs by inhalation, through the skin, or by direct swallowing and ingestion [9]. Inorganic lead absorption takes place throughout the respiratory and gastrointestinal tracts. For adults with occupational exposure, the most significant route for absorption is through the respiratory tract [2,9]. Respiratory lead absorption is primarily dependent on particle size. The percentage of inhaled lead reaching the bloodstream is estimated to be 30-40% [2]. Rates of absorption through the gastrointestinal tract depend on the nutritional status and the age of the individual exposed. Therefore, while adults absorb an average of 10 to 15% of the ingested quantity, this amount can increase to 50% in infants, young children and pregnant women [2,9]. Absorption through the gut is the predominant route for children and increases when dietary intakes of iron, calcium, phosphorus, or zinc are low [2,9,10]. There is little transcutaneous absorption of lead when inorganic lead

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compounds, such as those found in paint, are applied to the skin. In contrast, organic (tetraethyl) lead, which is that found in gasoline, can be absorbed via the skin. This route may have contributed to the lead poisoning in chemical workers during the development of this gasoline additive in the 1920s [2,9,11].

Distribution of lead after absorption

Following exposure to lead, the element is absorbed into and transported by the bloodstream to other tissues. Once absorbed, lead accumulates in three compartments: blood, soft tissues, and bone. In blood, approximately 99% of the lead is found in the erythrocytes, leaving about 1% in the plasma and serum [12]. The concentration of lead in plasma is more significant than that in whole blood as the means of distribution to target organs, i.e. brain, lungs, spleen, renal cortex, aorta, teeth, and bones [2,13]. The kinetics of lead transfer from blood to soft tissues is low and takes approximately 4 to 6 weeks [2]. Lead in blood has an estimated half-life of 35 days [14], in soft tissue 40 days [15], and in bones 20 to 30 years [16]. The biological half-life of lead may be considerably longer in children than in adults [15]. Blood lead concentrations reflect the intake of only the previous 3 to 5 weeks and thus cannot be used as indices of chronic exposure [2,9,12]. The initial distribution of lead throughout the body is dependent on blood flow to the tissues. More than 95% of lead is deposited in skeletal bone as insoluble phosphate [2]. Autopsy studies have shown that 90 to 95% of the body's burden is present in cortical bone and teeth. In adults, some 80-95% of the total body burden of lead is found in the skeleton, compared with about 73% in children. The residence period of lead in bone is up to 30 years, with lead concentrations in bone and teeth increasing as a function of age. Bone lead may be regarded as two physiologically distinct pools: an inert pool, with a half-life of decades, and a labile pool that readily exchanges with lead present in blood or soft tissues [2,12]. It has been determined that lead crosses the placental barrier, with foetal uptake, beginning at 12 weeks gestation and continuing throughout development up to birth. Concentrations of lead in umbilical cord blood were found to be 80-100% of the maternal blood lead level [2,17,18]. Several conditions known to increase bone turnover, such as pregnancy, lactation, chemotherapy, tumour infiltration of the bone, or postmenopausal osteoporosis, may be associated with the mobilization of lead in bone stores, leading to chronic lead toxicity [18-21]. Although hyperthyroidism also increases bone turnover, it has only rarely been implicated in the pathogenesis of lead poisoning, with only two reported cases [19].

Excretion of lead

Inorganic lead is not metabolized; however, alkyl lead compounds are oxidized by the hepatic P 450 system. Generally, lead excretion is low, with the most significant route being via the urinary tract. The use of chelating agents can enhance lead excretion in urine and this constitutes the basis of the therapeutic approach to lead poisoning. Lead may also be excreted with bile through the gastrointestinal tract. Although minute amounts of lead are excreted through the sweat and the nails, these routes do not have any practical significance. In general, lead is excreted extremely slowly from the body, with its biological half-life estimated at 10 years, thus facilitating accumulation in the body [2].

Epidemiology of lead toxicity. Sources of lead toxicity

Lead is found in mineral deposits and is released into the environment from natural causes as well as through human industrial activity. It does not dissipate, nor is it biodegradable. Therefore, lead in dust becomes a long-term source of Review Article Med Sci Monit, 2005; 11(10): RA329-336 RA330 lead exposure. Because of its malleability, low melting point, and ability to form compounds, it has been used in hundreds of products such as pipes, solder, brass fixtures, crystal, paint, cable, ceramics, and batteries [2,9]. There are basically two routes for lead exposure: inhalation and swallowing. Worldwide, six categories of products account for most cases of lead exposure: gasoline additives, food-can soldering, lead-based paints, ceramic glazes, drinking water pipe systems, and folk remedies [9]. Inhalation of lead fumes or lead-containing dust is mainly a problem in occupational settings, such as smelting, recycling facilities, production of storage batteries, and lead-glazed ceramics. Swallowing of lead-containing particles, food or drinks is an important route for both occupational and environmental exposure to lead [22]. Airborne lead eventually settles on land, in water supplies, and on buildings, and thus can enter the food chain. Besides the settling of atmospheric lead, surface contamination also occurs from contact with industrial waste containing lead. Furthermore, lead may leach into drinking water from water pipes and solder [2,5]. Human beings are also exposed to lead from cigarette smoking [23]. Adult lead poisoning is primarily a result of exposure by inhalation of lead fumes or ingestion of lead particles during activities in the workplace which involve the production, extraction, or reclamation of lead [2,9]. Lead poisoning in children is a characteristic disease usually occurring between the second and third year of life as a result of ingestion of lead particles from household or outdoor environmental sources. Children are exposed to lead from a variety of sources and through various pathways, as well as via normal, repetitive hand-to-mouth activity, which is now recognized as a major contributor to the total body burden of lead in children. Lead-based paint was the most widespread and dangerous source of high-dose lead exposure in pre-school children, as paint in most homes in the late 1940s was, in essence, a crust of lead [9,24]. Moreover, many consumer products, including toys, have been made of, or painted with, lead.

Over the last 40 years, attempts have been made to remove lead from all these sources [2,9,24]. However, lead poisoning may also appear, although rarely, in the first year of life. In infancy it comes from unusual sources, such as in-utero transmission of lead from women exposed to lead poisoning, or, in infants, through formula prepared with lead-contaminated water [24]. Lead exposure in developing countries may have different sources from those in the Western World. In certain Asian and Latin American countries, populations with a low socioeconomic background may use lead-contaminated folk medicines. Known sources of lead poisoning in Arabian communities are traditional remedies for abdominal colic and early passage of meconium after birth [25], called "bint adh Dhahab" (Daughter of Gold), or a locally used teething powder in Saudi Arabia known as "Saott" and "Cebagin" prescribed by traditional healers [26,27]. Furthermore, "Kahal", a commonly used eye cosmetic in the Arabian Peninsula [27], involves a formula

prepared with lead-contaminated water, or in a lead-soldered samovar [24].

Effects of Lead

Lead is a poison that affects virtually every system in the body. Children are more vulnerable to lead exposure than adults because of the frequency of pica, hand-to-mouth activity, and a higher rate of intestinal absorption and retention. The most deleterious effects of lead are on erythropoiesis, kidney function, and the central nervous system [28,29]. Haemopoietin system. The adverse effects of lead appear even with blood concentrations as low as 10 µg/dl. The best understood toxic effects of lead involve heme synthesis, as lead inhibits three important enzymes participating in the process, i.e. delta aminolevulinic acid dehydratase, delta aminolevulinic acid synthase, and ferrochelatase [30]. It is suggested that the inhibition of delta aminolevulinic acid dehydratase starts at values as low as 5 µg/dl. At higher lead concentrations this inhibition is very pronounced, reaching 50% inactivation at blood lead levels of 16 µg/dl and 90% inactivation at 55 µg/dl, resulting in the accumulation of delta aminolevulinic acid in plasma and its excretion in urine. Because this enzyme is normally present in great quantities, the inhibition of its activity may pass unnoticed [30,31]. Ferrochelatase is the enzyme that catalyzes the incorporation of iron into the porphyrin ring. If, as a result of lead toxicity, the enzyme is inhibited and its pathway is interrupted, or if adequate iron is not available, zinc is substituted for iron, and zinc protoporphyrin concentrations increase. The critical target, however, seems to be the enzyme's heme synthesis, essential for the insertion of iron into the precursor, protoporphyrin IX [32,33]. The major consequences of this effect, which have been evaluated in both adults and children, are reduction of circulating levels of haemoglobin and the inhibition of cytochrome P 450-dependent phase I metabolism [32]. Lead clearly inhibits normal haemoprotein function in both respects, which results in basophilic stippling of erythrocytes related to clustering of ribosomes and microcytosis when blood lead levels are 20 µg/dl. Thus, microcytic hypochromic anaemia is often diagnosed in victims of lead exposure. Compared with adults, children, especially in their first year, develop certain toxic effects at lower blood lead levels, and lead induced anemia has been related to age [11,15,18,24-28].

Nervous system and neurodevelopmental sequelae Headaches, poor attention span, irritability, loss of memory, and dullness are the early symptoms of the effects of lead exposure on the central nervous system. The ability to think and reason is extremely sensitive to toxic metal assault. The developing nervous system of the child makes it more sensitive to lead-induced impairment. The most serious manifestation of lead poisoning is acute encephalopathy, the symptoms of which include persistent vomiting, ataxia, seizures, papilloedema, impaired consciousness, and coma. Lead encephalopathy rarely occurs at blood lead levels below 100 µg/dl. Poor attentiveness, impulsiveness, inability to follow sequences or directions, decreased play activity, low intelligence quotient, and poor school performance are neurobehavioral abnormalities observed in affected children whose blood lead levels are approximately 35 µg/dl. Similar abnormalities have appeared at even lower levels of lead exposure.

A growing body of evidence suggests, however, that the functional integrity of the central nervous system can be compromised at substantially lower levels of lead exposure, particularly in the human foetus and young child. Early post-natal neurobehavioral development is compromised by maternal or cord blood lead levels of somewhat Med Sci Monit, 2005; 11(10): RA329-336 Papanikolaou NC *et al* - Lead toxicity update... RA331 RA less than approximately 10 µg/dl (a level of lead not uncommon in the general population). Results of more recent cross-sectional and prospective studies indicate that postnatal lead exposure resulting in blood levels as low as 25 µg/dl, and probably lower, are also associated with deficits in intellectual attainment, achievement, and affect behaviour. Impaired hearing has been observed at blood concentrations of 10 to 20 µg/dl [29,33]. Peripheral neuropathy, on the other hand, is the most common manifestation among adults with occupational lead exposure, but it is rarely seen in children except for those with sickle cell disease. Typically, the peripheral neuropathy of lead toxicity is seen as involving the extensor muscles, with minimal sensory loss. Lead-induced neuropathy on the radial and peroneal nerve in adult lead toxicity results in the characteristic "wrist drop" and "foot drop". Gastrointestinal colic is caused by high lead exposure and may be associated with lead neuropathy [29,33,34].

Needleman and his associates summarized the observations of teachers that lead-exposed students exhibited behaviour characterized as distractible [35], not persistent, dependent, not organized, hyperactive, impulsive, frustrated, daydreaming, and unable to follow directions and sequences, with low overall functioning. The outcomes of four key studies of the neurobehavioral effects of low-level lead exposure in children were reviewed and analysed by Davis, who concluded from these data that impaired performance can be caused by lead levels of 10 to 15 µg/dl or lower [36]. Electrophysiological changes on sensory functioning occur in children at exposure levels below 10 µg/dl [37]. Furthermore, changes in cortical visual-evoked potentials have been reported in children aged 3 to 12 years associated with blood lead levels from 6 to 59 µg/dl [38]. Recently, Rothenberg and colleagues recorded the brainstem auditory-evoked response in children 5-7 years of age who had been exposed to lead prenatally and observed that a mean maternal lead level of 7.7 µg/dl at 20 weeks of pregnancy was associated with changes [39]. Although the functional significance of these changes is not clear, it may be relevant that increases in the auditory threshold have been reported with blood lead levels ranging from 6 to 18 µg/dl [40]. There are few symptoms of chronic lead poisoning and they are mostly non-specific, involving abdominal and muscle pain, arthralgia, irritability, depression, altered sleep, memory disturbances, and hyperactivity in children.

Needleman *et al.* also warned that childhood lead exposure is associated with deficits in central nervous system functioning that persist into adulthood. Long-term neurobehavioral effects of childhood lead poisoning were assessed in individuals 50 years after known exposure. The results of this long-term follow-up study indicate that a history of childhood plumbism is associated with cognitive dysfunction still evident in adulthood. The effects of chronic lead toxicity on psychological development were first described by Byers and Lord in 20 children who suffered lead poisoning during the

first two years of life from eating paint chips. These children were re-assessed during the primary school period, and a high frequency of educational and behavioural problems was noted.

The magnitude of the effects of blood lead on the IQ of young children has been estimated as an average loss of two to three points for lead levels averaging 20 µg/dl compared with lead levels averaging 10 µg/dl. A number of studies recently reviewed by the National Research Council found an association between lead levels and intellectual functioning in children. In one population, lead levels >30 µg/dl were correlated with an increase in the percentage of children with severe deficiency. (i.e. IQ)

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