Review Article

Lead and Growth

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Abstract. Lead is highly toxic to the human body and children are much more vulnerable to lead toxicity than adults. Many studies have revealed that relatively low levels of blood lead can adversely affect human health, especially childhood growth and development. Blood lead levels (BLL) of children and adults have been decreasing recently almost all over the world, but a safety level for blood lead does not exist, and lead exposure is still a serious health problem especially for fetuses and children. Maternal lead burden causes fetal lead exposure and increases the risk of abortions, prematurity, low birth weight, and some minor anomalies. Infant BLL are inversely associated with weight gain. A negative relationship between somatic growth and BLL in children has been revealed. It has been suggested that lead exposure causes decrease of gonadotropin secretion of adolescents and delay of pubertal development. Several studies have revealed that children who are exposed to cigarette smoke have higher BLL than children who are not. Children should be protected from cigarette smoke for the purpose of avoiding the risk of increased BLL which might adversely affect their intellectual development and physical growth.

Key words: blood lead level, passive smoking

Introduction

Lead (Pb) is a major environmental pollutant, and is highly toxic to the human body. Since the earliest recorded times, lead has been widely used in human life. The metal has been smelted, applied as a cosmetic, painted on buildings, and glazed on ceramic pots (1).

On the other hand, lead may be the oldest recognized chemical toxin (2). Signs and symptoms of lead toxicity depend on blood lead level (BLL) and age, and children are much more vulnerable to lead toxicity than adults. Anorexia, lethargy, vomiting, and colicky abdominal pain are the most common symptoms of lead poisoning in children at BLL of more than 40 μg/dl. Blood lead of more than 80 μg/dl can cause encephalopathic symptoms in children. Irritability, lethargy, and ataxia may be early signs of acute encephalopathy, and convulsions and coma are the hallmarks. Other symptoms include bizarre behavior, ataxia, apathy, and memory loss. About 30% of children with encephalopathy have permanent neurological deficits (3). There have been a few patient reports of acute lead poisoning of children. Most cases were caused by accidental ingestion of lead products such as

fishing sinkers, and some of them were fatal with BLL of more than 200 μg/dl (4).

Apart from accidental ingestion, lead is absorbed daily from air and foods. Lead use and environmental pollution increased dramatically during the 20th century, especially with use of lead as a gasoline additive. Therefore, BLL of people was generally high in the 20th century.

However, owing to various governmental measures, for example banning of leaded gasoline use, serious lead poisoning cases have been decreasing recently almost all over the world. Many studies in recent years, however, have revealed the considerable harmfulness of low-level lead exposure to children. Lead exposure is even now a public health problem, especially for children.

In this paper, the effects of lead, mainly on growth and development of children, are discussed.

Blood Lead Levels of Children and Adults

Since the 1940s, many studies have been conducted to measure BLL of children and adults for the purpose of screening for chronic lead poisoning and/or evaluating the effects of relatively low levels of blood lead on human health. BLL is usually measured by atomic absorption spectrometry or inductively coupled plasma-mass spectrometry. Both are exact methods and there is no difference in the results from identical samples.

It was reported that the mean BLL of U.S. children aged 1 to 5 yr were 13.7 μg/dl for non-Hispanic whites and 20.2 μg/dl for non-Hispanic blacks in 1976 (5). The BLL of adult men and women in Switzerland in 1984 were reported as 12.2 and 8.5 μg/dl, respectively (6).

It had long been considered that blood lead of less than 20 μg/dl was almost harmless to the human body, because no clinical or biochemical effects had been recognized in such a condition until about two decades ago. Since then,

however, many studies have revealed that much lower levels of blood lead can adversely affect human health, especially childhood growth and development (7, 8). Scientific understanding of the health effects of lead has flourished over the past two decades. Advances in this area of research have spawned a series of efforts by governmental agencies to enhance the protection of public health from the adverse effects of lead (9). In Switzerland, for example, leaded gasoline was predominantly used before the 1980s, but unleaded gasoline use has been encouraged since the late 1980s. As a result, the mean BLL of adults in Switzerland decreased remarkably in only nine years, from 12.2 to 6.8 μg/dl in men and from 8.5 to 5.2 μg/dl in women (6). Decreases of BLL of children have also been observed in many industrialized countries (5). In Swedish children, for example, a dramatic decrease of BLL was found during the period 1978–2001, from about 6 to 2 μg/dl, which was considered to reflect the beneficial effect of gradual withdrawal of leaded gasoline (10).

A safety level of blood lead, however, does not exist, and lead exposure is still a serious health problem especially for fetuses and children. Many studies have demonstrated that lead exposure causes intellectual and behavioral impairment in children. Lead intoxication is still a hazard in the industrialized countries, and especially pregnant women and children are at high risk.

Absorption and Metabolism of Lead

Sources of ingested lead are food, water and air. Lead is absorbed from the gastrointestinal tract (approximately 5–10% of ingested dose in adults and as high as 40% in children) and lungs (approximately 50–70% of inhaled dose). Absorbed lead is temporarily in the bloodstream and about 95% of the lead exists in the red blood cells. The lead in erythrocytes has a half-life of 35 days and distributes into soft tissue or bone

stores (3).

Bones are the major depository for lead in the body, with about 90% of the total body lead burden existing in the skeleton. The half-life of lead in bone is 20–30 yr. Some equilibration between bone and blood lead does occur. Up to 70% of blood lead may derive from the bones, and during pregnancy and lactation more lead is mobilized from bone stores (11).

The Effects of Maternal Lead Burden on Fetuses and Neonates

Lead crosses the placenta, possibly by both passive diffusion and active transport, and accumulates in the fetus (12). It is suggested that lead might induce abortions, prematurity, and moreover some minor anomalies, for examples, hemangiomas, minor skin anomalies, hydrocele and undescended testicles (13). Therefore, maternal lead burden is a serious health problem for fetuses and neonates.

A considerable number of studies have been conducted to evaluate the influence of maternal lead burden on fetal and postnatal growth, and many of them have demonstrated the unfavorable effects of fetal lead exposure.

Bellinger *et al.* investigated the relationship between prenatal low-level lead exposure and fetal growth in a sample of 4,354 pregnancies in which the mean umbilical cord BLL was 7.0 μg/dl, and found that infants with BLL greater than or equal to 15 μg/dl had significantly higher risk of low birth weight (less than 2,500 g) than those with BLL less than 5 μg/dl (14).

Odland *et al.* collected maternal and umbilical cord blood specimens from 50 consecutive mother-infant pairs from hospital delivery departments in three Russian and three Norwegian communities, and measured the BLL. The corresponding maternal BLL were 2.9 μg/dl in Russians and 1.2 μg/dl in Norwegians. Both levels are relatively low, and maternal and cord BLL were strongly correlated. They found that

maternal BLL was a negative explanatory variable for birth weight, with or without adjustment for gestational age (15).

Sanin *et al.* investigated the effect of maternal lead burden on growth of breast-fed newborns (16). In lactating women, lead is transferred from bone to the bloodstream and then to breast milk. The authors measured lead levels among mother-infant pairs in umbilical cord blood at birth and maternal and infant venous blood at one month postpartum, and the maternal bone lead levels with a ^{109}Cd K-X-ray fluorescence instrument. They reported that the mean maternal and infant BLL at one month of age were 9.7 and 5.6 μg/dl, respectively, and the mean maternal bone lead levels were 10.1 and 15.2 μg of lead per one gram of bone mineral for the tibia and patella, respectively. They showed that infant BLL were inversely associated with weight gain, with an estimated decline of 15.1 g per 1 μg/dl of blood lead. Furthermore, weight gain of exclusively breast-fed infants was shown to decrease significantly with increasing levels of maternal bone lead. The multivariate regression analysis predicted a 3.6 g decrease in weight at one month of age per 1 μg of lead per gram bone mineral increase in maternal patella lead levels (16). Another study, however, could not confirm adverse effects of prenatal lead exposure on either neonatal size or subsequent growth (17).

There have been some clinical trials attempting to reduce the BLL of lactating women. Hernandez-Avila *et al.* conducted a randomized trial among lactating women in Mexico City to evaluate the effect of calcium supplementation (1.2 g of elemental calcium daily) on the decrease of BLL. They reported that calcium supplementation was effective at reducing lead in lactating women who had high bone lead levels, with an estimated reduction in mean blood lead of 16.4% (18). Further studies are required to assess the clinical effects of calcium supplementation on the BLL of lactating women.

Growth, Pubertal Development and Lead

There have been many studies investigating the relationship between BLL and the growth of children. Schwartz *et al.* examined about 2,700 children aged 7 yr and younger in the Second National Health and Nutrition Examination Survey (NHANES II) in the United States, and found an inverse correlation between BLL in the range of 5 to 35 μg/dl and body height. They concluded that low-level lead exposure could impair the somatic growth of children (19). Kafourou *et al.* also found negative relationships between growth parameters and BLL in Greek children aged 6–9 yr, an increase in BLL of 10 μg/dl being associated with a decrease of 0.86 cm in height, 0.33 cm in head circumference and 0.40 cm in chest circumference (7).

Vivoli *et al.* carried out a study evaluating the relationship between somatic growth and lead exposure in Italian adolescents aged 11–13 yr. The mean BLL of the boys and the girls were 8.5 and 7.0 μg/dl, respectively. Significantly negative relationships were found between BLL and stature in 13-yr-old boys and 12-yr-old girls. Also, negative relationships between BLL and serum concentrations of gonadotropins (LH, FSH) were found, but only in boys, with BLL higher than 9.0 μg/dl. The authors suggested that even for low lead exposure, this heavy metal might affect linear growth and gonadotropin secretion of adolescents (20). In animal experiments, a dose-dependent decrease in hypothalamic gonadotropin-releasing hormone and somatostatin was found in lead-treated guinea pigs and their fetuses (21).

Recently Wu *et al.* assessed measures of puberty in girls in relation to BLL to determine whether sexual maturation might be affected by current environmental lead exposure, using data from the Third National Health and Nutrition Examination Survey (NHANES III) in the United States. They found a negative relationship between BLL and attainment of menarche or

stage 2 pubic hair, which remained significant in logistic regression even after adjustment for race, age, family size, residence in metropolitan area, poverty income ratio, and body mass index. They concluded that higher BLL were significantly associated with delayed attainment of menarche and pubic hair among U.S. girls (22).

Selevan *et al.* analyzed the relations between BLL and pubertal development among girls aged 8–18 yr, including three ethnic groups, non-Hispanic white, non-Hispanic African-American and Mexican-American, also using data from NHANES III. They reported that BLL of 3 μg/dl were associated with significant delays in breast and pubic hair development in African-American and Mexican-American girls, but not in white girls for reasons which were not clear. They suggested that environmental exposure to lead might delay growth and pubertal development in girls, although confirmation was warranted in prospective studies (23).

Passive Smoking and Lead Exposure to Children

It has been suggested that children who are exposed to cigarette smoke have higher BLL than children who are not (24, 25). We measured BLL of Japanese children and evaluated the effects of passive smoking on BLL, and found that passive smoking increased BLL of preschool children. The mean BLL of preschool children who were exposed to cigarette smoke in their homes was 4.15 μg/dl, and those whose family never smoked was 3.06 μg/dl, a difference significant. We also found that passive smoking did not increase the BLL of school children. Regarding the reasons for the difference in the effects of passive smoking on the two groups of children, we speculate that preschool children might spend more time with their parents and might have more contact with cigarette smoke than school children, and additionally, young infants have limited ability to excrete lead from
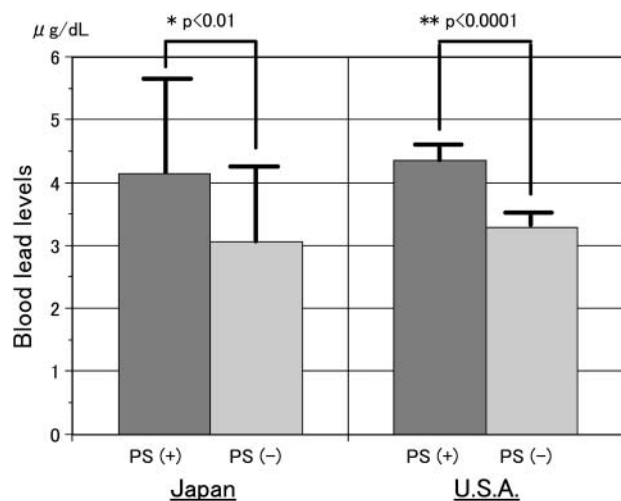
Fig. 1 Blood lead levels (mean ± standard deviation) of children who are exposed to cigarette smoke in their homes (PS(+)), and those who are not (PS(−)), in Japan (26) and the U.S.A. (27). PS: Passive smoking.

the body because of immaturity of the renal function (26).

Ballew *et al.* investigated the BLL of a total of 4,391 non-Hispanic white, non-Hispanic black, and Mexican-American children of the United States aged 1 to 7 yr, using data from NHANES III. They reported that the mean BLL of the children who had smoking families was 4.36 μg/dl and that of the children who did not was 3.29 μg/dl (27), very similar to the values reported in our study (Fig. 1). Stromberg *et al.* also found a significant effect of parental smoking habits on the BLL of Swedish children, an 18% increase on average (10).

The adverse effect of passive smoking on children's health is an universal problem in the world. Children should be protected from cigarette smoke for the purpose of avoiding the risk of increased BLL which might adversely affect their intellectual development and physical growth.

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