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Prenatal and postnatal lead exposure and cognitive development of infants followed over the first three years of life: A prospective birth study in the Pearl River Delta region, China

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ABSTRACT

Purpose: Our pilot studies showed that there was a significant relationship between low cord blood levels and scores of neonatal behavioral neurological assessment. The study was further to probe the adverse cognitive effects induced by low-level lead exposure during prenatal and postnatal period.
Method: Totally 362 mothers with their infants located the PRD, Guangdong, China participated in the study during their stay in these center: 141 in the high lead group [umbilical-cord blood lead levels (UCBLLs) $\geq$ 3.92 μg/dl] and 102 in the low lead group (UCBLLs $\leq$ 1.89 μg/dl). The other 137 subjects failed to complete the study for a variety of reasons. Blood Lead levels (BLLs) were measured by atomic absorption spectrophotometry, equipped with a graphite furnace. The developmental functioning of infants and children was assessed with BSID-II. The children's birth outcome and the rest of information were obtained from their medical records or a comprehensive questionnaire from their parents, which contained demographic characteristics, lifestyle, mother's IQ and environmental lead sources, etc.
Results: Of 380, 243 newborns (63.95%) had complete data collection for all variables included at 6, 12, 24 and 36 months of age. The mean UCBLLs for high and low lead group were 5.63 $\pm$ 0.32 μg/dl and 1.35 $\pm$ 0.26 μg/dl, respectively. Significant inverse associations have been found between the UCBLLs and the MDI and the PDI. The associations might attenuate over subsequent years. BLLs at 24 months were significantly associated, in an inverse direction, with MDI at 24 and 36 months. The observed trend of cognitive deficit beginning at 6 months of life might persist, and even develop over the coming years. A positive significant effect of home nurture environment was observed on MDI scores at 12, 24, 36 months of age and PDI scores at 24 and 36 months of age.
Conclusion: Our study demonstrates that prenatal and postnatal lead exposure as low as 5 μg/dl has an adverse effect on neurodevelopment, best arrested by measuring UCBLLs and BLLs at 24 months of age, and suggest a reference for a blood lead critical value below 5 μg/dL. The collective evidence indicate that low lead exposure must be addressed appropriately by health policy makers and argues for an improvement of home nurture environment, i.e., reduce the burden of Pb on children and, strengthen the training of cognitive ability.

1. Introduction

Despite remarkable successes in recent decades in abating key sources and pathways of exposure, lead remains the important pediatric environmental health problem, contributing significantly to the burden of childhood disease in both developed and developing countries (Bellinger, 2013, 2008). The developing central nervous system is considered to be the principle target system for lead toxicity in children, and young children and fetus are more vulnerable to lead exposure (Bijoor et al., 2012).

Recent studies showed that no level of lead exposure appears to be 'safe' and even the current 'low' levels of exposure in children are associated with neurodevelopmental deficits (Bellinger, 2008). Cohort studies have revealed that blood lead level (BLL) as low as 1–2 μg/dl (Téllez-Rojo et al., 2006; Hu et al., 2006; Chen et al.,

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2012) can be associated with disturbances in early physical and mental growth and in later intellectual function, and in behavior in children who exposed to lead in fetus period and/or during early childhood (Surkan et al., 2007; Miranda et al., 2007; Kordas et al., 2006; Li et al., 2003; Lanphear et al., 2005). A pooled analysis (Lanphear et al., 2005) predicted a 9.2-point decline in IQ over the range of less than 1–30 μg/dl, two-thirds of this decline (6.2 points) was predicted to occur in the range of less than 1–9.9 μg/dl, with an additional 1.9-point decline between 10 and 19.9 μg/dl, and a 1.1-point decline between 20 and 30 μg/dl. This has led to emphasize the rationale for lowering the blood lead action level from 10 to 2 μg/dl (Gilbert and Weiss, 2006). To assess the developmental effects at very low lead exposure levels, more evidence is needed from cohort studies on neurocognitive deficits, especially from areas with race-based and relatively large child population and low lead exposure.

China is the largest populated country in the world, and there are about 130 million children aged 0–6 years old considered to be the most susceptible to lead toxicity. The Pearl River Delta region (PRD), situated in the southern Guangdong Province, is one of the most economically developed areas in China. Foshan, Shenzhen, and Zhuhai are three cities in the PRD with different economic structure, growth dynamics, degree of internationalization, and transport infrastructure. Zhuhai has enjoyed clean environment, Foshan is affected by mild pollution and Shenzhen suffers intermediate environmental contamination (Chen et al., 2012; Zhang et al., 2008). Our latest study found that fetal lead exposure as low as 5 μg/dl has an adverse effect on neurodevelopment during early pregnancy (Liu et al., 2014) However, the extent to which low lead exposures specifically during late prenatal and postnatal period affect neurodevelopment are unclear.

Therefore, the purpose of this study was further to probe the cognitive effects induced by low-level lead exposure during prenatal and postnatal period followed over the first 3 years of life in the Pearl River Delta Region, China. It was hypothesized that pregnancy and postnatal lead exposure would be related to cognitive developmental deficits of infants in the first 3 year of their life. To avoid the methodological limitations of retrospective studies, our present prospective study has the following advantages: the time sequence, a wide range of outcomes, a reduced recall and selection bias, i.e., a prospective birth study with majority populations and minority sample attrition were conducted in our present studies. Therefore, continuous concentrations of blood lead and parameters of cognitive development were obtained to assess cognitive development longitudinally by subsequent measurements done at 6 (baseline), 12, 24, and 36 months of age.

2. Materials and methods

2.1. Study subjects

Referring to the study design of Bellinger et al. (1987), between January 2009 and January 2010, mothers delivering in the Shenzhen Bao'An, Foshan, and Zhuhai Maternal and Child Health Center located the PRD, Guangdong, China were solicited to voluntary participate in the study during their stay in these centers. The following exclusion criteria were applied to the mothers: not a resident of city; planning to leave the area within 5 years; daily consumption of alcoholic beverages; addiction to illegal drugs; continuous use of prescription drugs; diagnosis of multiple pregnancy, preeclampsia, renal or heart disease, gestational diabetes, and use of corticosteroids. In addition, infants also had to satisfy the following criteria: absence of a medical condition considered to be a risks factor for development difficulty (e.g., Down's syndrome, cleft palate, gestational age <5 weeks; residence near the hospital (<5 km) in an area considered safe for home visitors, and maternal consent to be contacted. In recruiting our longitudinal sample from this population, all mothers were informed about the nature and the aims of the study and given information on ways to minimize lead exposure. All signed a letter of informed consent. The research protocol was approved by the Medical Ethics Committee of the four hospitals and Sun Yat-sen University. Trained staff screened the potential subjects for eligibility via structured face-to-face interview to ensure that they met the criteria. In the end, 2306 umbilical-cord blood samples were collected and measured. On the basis of distribution of umbilical-cord blood lead levels (UCBLLs): below the 25th percentile (low), and above the 75th percentile (high), the two exposure groups (high lead group: UCBLLs $\geq$ 3.92 μg/dl, n = 219; low lead group: UCBLLs $\leq$ 1.89 μg/dl, n = 161) were established. The other 1944 potential subjects whose mother had BLLs between 25th and 75th quartile were excluded from the following MDI and PDI test. Totally 362 infants were included in the final cohort: 141 in the high lead group and 102 in the low lead group. The other 137 subjects failed to complete the study for a variety of reasons: withdrew voluntarily (high, n = 15; low, n = 11), failure to locate and moving from the area (high, n = 21; low, n = 15), Chinese cultural practice (high, n = 19; low, n = 16); no apparent beneficial impact (high, n = 23; low, n = 17). Attrition subjects were 17,27,36 and 57 (high, n = 7, 14, 20, 37; low, n = 10, 13, 16, 20), respectively at 6,12,24 and 36 months. There was no difference in the dropout rate between low and high lead group at the same time point in the follow-up.

2.2. Blood sample collection and analysis

After delivery, approximately 10 ml of umbilical cord blood was collected by the obstetrician midwives in a lead-free, heparinized vacationer. Collection tubes were refrigerated and transported to the laboratory no later than 24 h after a sample was collected. The samples were deep frozen at −20 °C and analyzed to assess umbilical cord blood lead level (UCBLLs) within a week. Infants venous blood (2 ml) specimens at the follow-up four points (6, 12, 24, 36 months) were collected by trained pediatric nurses using a strict research protocol to avoid lead contamination and were frozen for lead analyses. Blood lead levels (BLLs) were measured by atomic absorption spectrophotometry, equipped with a graphite furnace (Varian AA-DUO). Our laboratory has participated successfully in a CDC-administered quality-control program (Blood Lead Proficiency Testing Program) for the measurement of lead in whole blood. Analysis of each specimen was conducted using a replication procedure, and the mean of the repeated measurements was taken as the final measure. Blood lead reference materials for quality control (QC) were provided by the Institute of Environmental Health Monitoring, Academy of Chinese Preventive Medicine. QC samples were inserted blindly among the study samples (one QC sample in every 10 study samples). The relative precision of the established method over a wide concentration range (0–40 μg/dl) is 5% (95% confidence limits).

2.3. Neurodevelopment testing

We used the second edition of Bayley Scales of Infant Development (BSID-II), a well-recognized test that assesses the current developmental functioning of infants and children. The scales have been translated into Chinese and locally standardized to become culture-appropriate. The reliability and validity of the standardized scales have been shown to be satisfactory, and test results are comparable with those of the original scales (Ling and Li, 2007). The BSID-II consists of three scales: the Mental Scale, Motor Scale, and Behavior Rating Scale. In this study, only the first two scales were administered, which are complementary in the evaluation of the child. The Motor Scale assesses control of gross