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Evidence that cognitive deficit in children is associated not only with iron deficiency, but also with blood lead concentration: A preliminary study

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ABSTRACT

Objective: To investigate whether blood lead concentrations are elevated in iron-deficient children, and to examine the association between iron deficiency and/or elevated blood lead concentration and cognitive deficits in children.
Method: The present study is a component of the Mothers' and Children's Environmental Health (MOCEH) study, a multi-center birth cohort project in Korea that began in 2006. The study cohort consisted of 194 children who underwent testing of blood lead and serum C-reactive proteins (CRPs) and ferritin concentrations, and the Korean version of the Wechsler Preschool and Primary Scale of Intelligence, revised edition (WPPSI-R), at 60 months of age. In addition, the mothers' blood lead concentrations during pregnancy were included in the analyses. Multivariate linear regression analysis was performed to analyze the correlation between high blood lead and low serum ferritin concentrations, after adjustment for covariates, in children, as well as to analyze the association of verbal IQ with serum ferritin and blood lead concentrations.
Results: Lead and ferritin concentrations were inversely and significantly associated in children after adjustment for covariates. Moreover, both concentrations were associated with verbal IQ, after adjustment for covariates, and each was associated with cognitive deficits after adjustment for the other. Sobel test statistics showed that blood lead concentration was a significant partial mediator for the relationship between iron deficiency and verbal IQ.
Conclusion: Due to the results discussed in the present study, cognitive deficit in children seems to be associated not only with iron deficiency, but also with blood lead concentration.
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Introduction

Iron deficiency affects approximately one-third of the world's population [1]. Iron-deficiency anemia in children has been associated with poor cognitive and motor development and with behavioral problems [2–4]. Infants aged 6–24 months are at particularly high risk, but the entire preschool-age population may be vulnerable, especially in developing countries [5]. Moreover, a recent regional and country summary showed that iron deficiency anemia is widespread among children <5 y of age [6].

Lead from environmental sources can enter the body via inhalation or ingestion [7], and evidence has emerged that lead neurotoxicity occurs in children at lower levels of lead exposure than had been previously thought [8]. The Centers for Disease Control

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and Prevention (CDC) in the USA has set the reference concentration of lead in blood at 50 $\mu g\,L^{-1}$ [8]. Because body structures such as the nervous system are developing in children and are more sensitive to the effects of lead than structures in adults, levels of environmental exposure that do not affect health in adults may cause adverse effects in children [9–11].

Iron deficiency has been found to predispose animals to lead toxicity by increasing gastrointestinal lead absorption [12–14]. Although several studies have reported an association between iron status and blood lead concentration in children [15–24], other studies have found no association [25–30]. This study was therefore designed to assess (1) whether blood lead concentrations are elevated among iron-deficient children, and (2) whether iron deficiency and/or blood lead concentration is associated with cognitive deficits in children.

Subjects and methods

Subjects

The present study is a component of the Mothers' and Children's Environmental Health (MOCEH) study, a multi-center prospective birth cohort project involving 1751 pregnant women, which was conducted in South Korea from May 2006 to December 2010 [31]. The study cohort consisted of 194 children who underwent testing of blood lead and serum C-reactive proteins (CRPs) and ferritin concentrations, as well as the Korean version of the Wechsler Preschool and Primary Scale of Intelligence, revised edition (WPPSI-R), were measured at 60 months of age. In addition the mothers' blood lead concentrations during pregnancy were included in the analyses.

Parents of all participants were interviewed by trained personnel, using a detailed questionnaire, to obtain information about each child's demographic characteristics, socioeconomic status, residential characteristics, medical and reproductive history, exposure to occupational hazards, alcohol consumption, nutritional habits, and exposure to secondhand smoke in the home. Each questionnaire was completed on the day on which the blood sample was collected.

Laboratory testing

Heparinized venous blood samples were obtained from each child, and blood count, hemoglobin concentration, hematocrit, and serum ferritin and CRP concentrations were measured. To assess the association of blood lead with iron and anemia, serum ferritin was categorized into three levels: low (<15.0 $\mu g\,L^{-1}$), low normal (15.0 to <30.0 $\mu g\,L^{-1}$), and normal ($\geq$30.0 $\mu g\,L^{-1}$) [32].

Lead determination in whole blood

Blood lead concentrations were measured by graphite furnace atomic absorption spectrometry with Zeeman background correction (GFAAS) (Perkin Elmer AAS800, Perkin Elmer). The GFAAS temperature programs consist of five steps (Table 1). All samples were analyzed by the Neodin Medical Institute, a laboratory certified by the Korean Ministry of Health and Welfare. For internal quality assurance and control, commercial reference materials were used (Lyphochek® Whole Blood Metals Control; Bio-Rad, Hercules, CA, USA). The coefficients of variation were within 0.95–4.82% for the blood lead measurements of the three reference samples. The Neodin Medical Institute passed the German External Quality Assessment Scheme of Friedrich-Alexander University (Germany), both in the occupational and environmental medical ranges, the latter with much lower concentrations of toxic substances; as well as passing the Quality Assurance Program operated by the Korea Occupational Safety and Health Agency. The Neodin Medical Institute was also certified by the Ministry of Employment and Labor (Korea) as a designated laboratory for analysis of specific chemicals, including heavy metals and certain organic chemicals. The limit of detection (LOD) for blood lead concentration using this method was 2.07 $\mu g\,L^{-1}$. No tested blood sample had a lead concentration below the limit of detection. The limit of quantitation (LOQ) for blood lead concentration was 8.78 $\mu g\,L^{-1}$. Eighteen tested blood samples had lead concentrations below the LOQ.

K-WPPSI

The K-WPPSI is the Korean version of the Wechsler Preschool and Primary Scale of Intelligence, revised edition (WPPSI-R) [33,34], an instrument commonly used to measure intelligence in young children, aged 3 years to 7 years 3 months. The K-WPPSI consists of subtests of verbal skills (Verbal IQ) and performance skills (Performance IQ), as well as composite scores that represent Verbal IQ, Performance IQ, and Full Scale IQ. The verbal subtests include those on Information, Comprehension, Arithmetic, Vocabulary, Similarities, and Sentences, and the Performance subtests consist of those on Object Assembly, Geometric Design, Block Design, Mazes, Picture Completion, and Animal Pegs.

Statistical analyses

Blood lead concentrations were natural log-transformed because their distributions were skewed, and their geometric means (GMs) were calculated. Significant differences in mean of blood lead concentration and verbal IQ according to categorical variables were determined using Student's *t*-tests. Multivariate linear regression was used to analyze the association between blood lead and serum ferritin concentrations at 60 months of age, after adjustment for covariates (e.g., CRPs, sex, maternal blood lead levels, and breast feeding). Although iron deficiency has been defined as a serum ferritin concentration <15 $\mu g\,L^{-1}$, dichotomization around this concentration would lead to a decrease in patient numbers [32]. Therefore serum ferritin concentration was practically categorized into two levels: abnormal (<30.0 $\mu g\,L^{-1}$), and normal ($\geq$30.0 $\mu g\,L^{-1}$). Multiple linear regression analysis was used to assess the association of verbal or performance IQ with serum ferritin or blood lead concentration after adjustment for covariates (e.g., sex, educational level of both parents, family income, and CRP concentrations). Regression path analyses with Sobel test statistics were used to assess the significance of mediational effects of blood lead concentration between iron deficiency and IQ [35–37]. SPSS (18.0) software was used for all statistical analyses, with a *P* value <0.05 considered statistically significant.

Results

Table 2 shows blood lead concentrations and verbal IQ of the study participants by various categories. The GM blood lead concentration was significantly higher in male than in female children, but there was no difference in the arithmetic means (AMs) of verbal IQ. The GM of blood lead concentration and verbal IQ were significantly higher in the low and normal serum ferritin group, respectively. In contrast, performance IQ did not differ among the groups (data not shown). There were no differences in the GMs of blood lead and the AMs of verbal IQ when subjects were assorted by CRP concentrations, parents' educational level, family income, or the duration of breast feeding. To evaluate the association between blood lead and serum ferritin in multiple regression analyses, after controlling for covariates (e.g., CRPs, sex, maternal blood lead levels at pregnancy, and breast feeding), a beta coefficient and its 95% CI were calculated (Table 3). In models 1 and 3, the beta coefficient values of log-transformed blood lead concentrations for

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