Biol Trace Elem Res (2008) 123:41–46
DOI 10.1007/s12011-008-8099-6

Blood Lead Levels and Increased Bronchial Responsiveness

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Received: 11 December 2007 / Accepted: 21 January 2008 /
Published online: 20 February 2008

Abstract The immune system is one of the targets most sensitive to lead toxicity, and the association between lead exposure and serum immunoglobulin E (IgE) has been published. Recent studies also reported that lead caused the development of IgE-mediated allergy. To investigate whether blood lead levels contribute to other allergic conditions, we examined the effect of blood lead on bronchial responsiveness (BR) in the general population. We performed a cross-sectional study with adults aged 19 to 58 years in a Korean community. Blood lead level and the methacholine provocation test were performed. The overall mean blood lead level was 2.9 μg/dl, and the mean BR index was 1.14. The percent of subjects with clinically diagnosed asthma was 21 (4%) and there was no difference in blood lead level with and without asthma. In the multiple regression model, the elevation of blood lead level was related to the increase of BR after adjusting for age, sex, height, smoking status, and the presence of asthma. Blood lead level was significantly associated with increased BR that came from the elevation of the IgE level with lead exposure. Lead may contribute to the increase of asthma and other allergic conditions.

Keywords Blood lead level · Immunoglobulin E · Asthma · Immunotoxicity

Introduction

Lead is not biologically needed by humans [1]; however, when human organs absorb it, lead has the ability to disrupt biological systems and produce subclinical toxicity. The immune system is one of the targets most sensitive to lead toxicity at low levels. Exposure

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to lead at low to moderate levels can cause a major functional shift and decrease of host resistance to disease, at doses that are not cytotoxic to immune cells [2].

Previous studies have suggested that lead exposure alters immune system components and is associated with increased production of immunoglobulin E (IgE) [3–6]. For example, Lutz et al. [4] reported a significant positive relationship between blood lead level and serum IgE and suggested that this relationship is indicative of an increased predisposition to allergic disease later in life. Sun et al. [6] also reported that the serum IgE level was significantly associated with the blood lead level in girls. The relationship between the two was supported by the relationship between in utero lead exposure and cord blood total IgE [7].

Two recent reports inferred a connection between lead and the development of asthma, an IgE-mediated allergic disease [8–9]. It is of interest to investigate whether blood lead levels contribute to other allergic diseases. In this regard, we postulated that if the production of IgE and prevalence of asthma were increased as a result of the effect of lead on the immune system, the blood lead level might contribute to increased bronchial responsiveness (BR). Increased BR and serum IgE level are intermediate in allergic disease. Increased BR is associated with the IgE level and is present in almost all patients with clinically current asthma [10]. Therefore, this study examined the effect of blood lead on BR in the general population.

Materials and Method

Study Population

The study participants were middle-aged adults, and data were collected during health examinations at a district office in Seoul, Korea. Exclusion criteria were (1) difficulty completing the methacholine provocation test or blood collection and (2) failure to give consent or noncooperation. Five hundred twenty-five subjects participated in the study. The study group consisted of 274 males and 249 females, aged 19 to 58 years. All of the subjects completed the interview questionnaire and performed the methacholine and blood lead tests. Written informed consent was obtained from all subjects.

Blood Lead Measurement

Venous blood was drawn in a trace metal-free tube and sent to the Department of Clinical Pathology of Samsung Medical Center (Seoul, Korea) for lead content analysis. After digestion with nitric acid, the sample solutions were centrifuged, and the supernatant was analyzed using VG PlasmaQuad-induced, coupled plasma/mass spectroscopy (Fisons Instrument, UK). External quality control samples were provided by the College of American Pathologists.

Methacholine Provocation Tests

To examine BR, the methacholine provocation test was performed according to the modified Chai protocol [11]. The aerosolized particles were generated with a De Villbis 646 nebulizer (output, 0.125 ml/min), and methacholine concentrations of 2.5, 6.25, 12.5, and 25 mg/ml were prepared by dilution with buffered saline. Through a Rosenthal–French dosimeter (Laboratory for Applied Immunology, Baltimore, MD, USA), the subjects inhaled five breaths of increasing methacholine concentration, and the test was continued

until either a 20% drop in FEV_1 from the basal value or the highest concentration was reached. The BR index was calculated as the log [(% decline in FEV_1/log final methacholine concentration as mg/dl)+10] [12].

Statistical Analysis

Data was presented with the mean value (SD) and frequency (%) and examined the difference of blood lead levels in each group. The relationship between BR and blood lead level was shown with a graph.

Because of nonnormal distributions, blood lead levels were analyzed as logarithmic values. Multiple regression model was conducted to investigate the relationship between BR and blood lead level. Age, sex, height, smoking status, baseline FEV_1, and the presence of asthma were included as independent variables. Statistical analysis was performed with the SAS statistical software programs [13].

Results

Table 1 shows the characteristics of the study population. Subjects had a mean age of 40 years (range, 19–58 years), and 274 subjects (52%) were male. The overall mean blood lead level was 2.90 μg/dl, and there was a significant difference between male (3.3 μg/dl) and female (2.5 μg/dl). When compared to the nonsmoking group (59%), the smoking group had significantly higher blood lead level ($p<0.05$). The percent of subjects with clinically diagnosed asthma was 21 (4%), and there was no difference in blood lead level with and without asthma. The mean values of FEV_1 and BR index were 3.30 l and 1.14, respectively.

In the multiple regression model, age, sex, height, smoking status, baseline FEV_1, and the presence of asthma were included as independent variables, and the elevation of blood lead level was related to the increase of BR (Table 2). The plot of the association between BR index and blood lead level is shown in Fig. 1.

Table 1 Characteristics of the Study Population (N=523)

Variables	Mean or N	SD or %
Age (years)	39.78	9.59
Height (cm)	163.47	8.53
Weight (kg)	62.40	10.45
Bronchial responsiveness index	1.14	0.18
Blood lead level (μg/dl)	2.96	1.59
FEV_1 (l)	3.30	0.70
Sex		
Male	275	52.38
Female	250	47.62
Smoking status		
Current smoking	215	40.95
Nonsmoking	310	59.05
Asthma		
Asthma	21	4.00
Nonasthma	504	96.00

Table 2 Multiple Regression Model for BR

Variables	Estimate	SE	*p* value
Age (years)	0.00042	0.001	0.625
Height (cm)	0.00229	0.002	0.129
Blood lead level (μg/dl)	0.01797	0.007	0.015
FEV_1 (l)	−0.06718	0.021	0.0013
Sex			
Male	−0.07446	0.029	0.012
Female	Reference		
Smoking status			
Smoking	0.05277	0.024	0.026
Nonsmoking	Reference		
Asthma			
Asthma	0.04164	0.040	0.293
Nonasthma	Reference		

Discussion

This study assessed the effect of lead on BR. We found that an elevated blood lead level was significantly associated with an increased BR index in middle-aged adults, after adjusting for age, sex, height, smoking, and asthma diagnosis. This means that exposure to lead might increases BR.

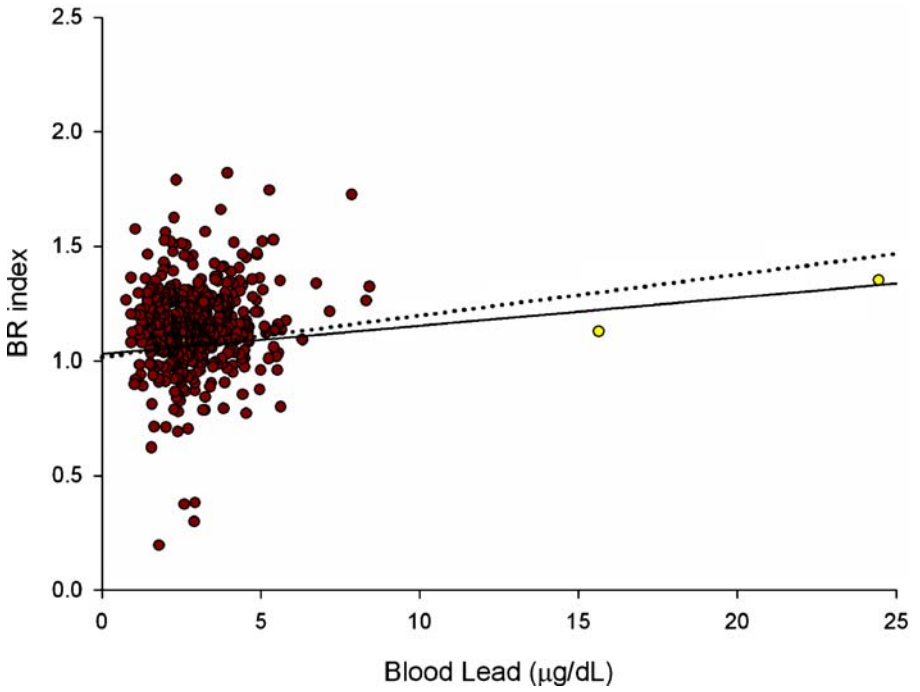

Fig. 1 Plots of BR index and blood lead level. The *solid line* includes two yellow outliers of blood lead levels (β=0.01239, p=0.017), and the *dotted line* excludes two outliers of blood lead levels (β=0.01797, p=0.015)

Although the mechanism responsible for this association is not clear, the result suggests that the increase in IgE caused by lead exposure might reflect a mechanism that increases BR. This is why IgE is a main independent factor influencing the occurrence of bronchial hyperresponsiveness (BHR) and a specific marker indicating lead-induced immunotoxicity [14–15].

For the effect of lead on the immune system, many studies showed that lead exposure affected T-dependent immune response and the alteration of immunoglobulin levels, such as IgA, IgM, and IgE [2, 5, 6]. The increased serum IgE level has been a central issue in lead-induced immunotoxicity because lead acts to increase the production of IgE through the direct or indirect stimulation of B cells or the binding [4–7], and B cell stimulation can cause increased and/or improper immune response [16]. IgE is also closely related to the expression of Th2 cytokines, such as IL-4 and IL-21 [17, 18].

There is convincing evidence that lead causes the development of IgE-mediated allergy. Snyder et al. [19] found that mouse neonates exposed to lead transplacentally or lactationally had a significantly higher serum IgE level and lower splenic white blood cell count than age-matched controls. Bener et al. [8] found that industrial workers (exposed) had a significantly higher blood lead level and prevalence of asthma and respiratory symptoms compared with nonindustrial workers (unexposed). Joseph et al. [9] studied blood lead levels and the development of asthma in 4,636 young African and Caucasian Americans. An elevated risk of developing asthma was associated with the blood lead level in Caucasian American children, whereas there was no association in African Americans.

An implication of our study is that a significant association between lead and increased BR show intermediate level of the occurrence of asthma and/or other allergic conditions caused by lead exposure. We also imply that such toxicity of lead is not limited to certain immune aspects in a susceptible population. So far, human studies concerning the immunotoxicity of lead have been focused on susceptible and high-risk groups, such as children and workers. However, there is no evidence that lead-induced immunotoxicity is uniquely associated with susceptible groups only, and all exposed to lead may eventually be affected, although their relative risk is small compared to the susceptible groups. For example, someone with increased BR, even within the normal range, is more likely to develop symptoms of allergic disease in response to sufficiently strong stimuli [20].

In our result, additionally, there was small increase, but not significant association between asthma and BR. This does not imply that subjects with asthma are less sensitive to BR, but their symptoms and lung function may be managed by medical treatments.

Several limitations of this study must be considered when interpreting the results. First, because we analyzed the health examination results of inhabitants in a certain area, the result cannot be generalized. In addition, our study was restricted by a lack of information on other risk factors for BR (e.g., family history) and by its cross-sectional design. Therefore, it was impossible to confirm causality between lead exposure and BR in this study.

In summary, we showed that the blood lead level was significantly linked to increased BR in the general population. This suggests that increased BR results from the elevation of the IgE level with lead exposure. Further studies are required to investigate the possible role of lead-associated toxicity in BR and other allergic conditions.

Acknowledgement This study was supported by the G7 grant from the Korean Ministry of the Environment.

Conflict of interest statement There is no conflict of interests. The first and second authors equally contributed to this study.

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